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The Power of Science is Collaboration: Understanding the knowledge sharing practices of rare disease non-profit organizations in regard to repurposing sirolimus

Ania Korsunska
Syracuse University

ABSTRACT

Purpose: This dissertation investigates the knowledge sharing practices and inefficiencies among Rare Disease Nonprofit Organizations (RDNPs) engaged in drug repurposing efforts, particularly focusing on the drug sirolimus. The goals of this research are to provide an understanding of the knowledge-sharing practices and challenges for RDNPs and to contribute to the academic discourse in knowledge sharing theory by applying it to a unique and practical use case. The motivation behind this research stems from the pivotal role RDNPs play in the rare disease treatment landscape. Given the limited financial incentives for pharmaceutical companies to invest in rare disease treatments, RDNPs are often at the forefront of innovative approaches like drug repurposing. However, the lack of centralized knowledge-sharing mechanisms among these organizations leads to significant inefficiencies.

Design & Methodology: This research adopts a multi-method qualitative approach including thematic transcript analysis, network analysis, and detailed case studies of RDNPs. This approach allows for a comprehensive examination of both the micro-interactions of knowledge sharing and the broader organizational structures that support or inhibit these practices.

Findings: The findings reveal that while RDNPs are pivotal in advancing drug repurposing initiatives, they face significant barriers in knowledge sharing due to the decentralized, volunteer-based nature of their operations and lack of systematic processes. Specifically, inefficiencies arise from a lack of centralized resources, varied levels of experience among RDNPs, and insufficient formal mechanisms for collaboration and information dissemination. These factors lead to duplicated efforts and missed opportunities for leveraging collective knowledge in drug repurposing.

Originality & Value: This research contributes to the field of knowledge management by applying Nonaka's Theory of Dynamic Organizational Knowledge Creation (Nonaka, 1994) in the novel

context of rare disease nonprofits and drug repurposing and suggesting a framework of factors that affect the knowledge sharing practices from Yang and Maxwell (2011). It highlights the critical role of structured knowledge sharing practices and the potential of organized, systematic efforts to enhance the effectiveness of drug repurposing projects. The dissertation provides a theoretical framework for understanding interorganizational knowledge sharing among small nonprofit organizations and offers practical insights that can help RDNPs improve their operational strategies and enhance collective impact on drug development for rare diseases.

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By
Ania Korsunska
B.A., Bilkent University, 2012
M.A., University of Chicago, 2015

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Syracuse University

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TABLE OF CONTENTS

List of Figures

List of Tables

CHAPTER 1: BACKGROUND

1.1 Scale and Burden of Rare Diseases

Even by very conservative estimates, around 473 million people world-wide could be affected by a rare disease, constituting around 6.2% of the general population (Ferreira, 2019). Estimates of the number of rare diseases also vary greatly, ranging anywhere from 800 up to over 9 thousand[1] (Ferreira, 2019), though most estimates settle on the range between 5,000 - 8,000 (The Lancet Neurology, 2011; Zuccato et al., 2019). These numbers are further complicated by the fact that there are several def-i-nitions of rare or "orphan" diseases and these def-i-nitions differ between countries. In the US, congress passed the Orphan Drug Act in 1983 which established a disease as "rare" if it affects less than 200,000 people in the US (Orphan Drug Act, 1983). To contrast, in Japan, rare diseases are defined as those with a prevalence in Japan of less than 50,000, or one in 2,500, and with no known cause or cure (Shuichiro & Umeda, 2008). Utilizing the Orphan Drug Act definition, about 8-12% of the US population, or 25–30 million people in the US are diagnosed with a rare disease. Thus, rare diseases, though individually rare, when taken together constitute a substantial burden on the world both socially (through disease-related suffering), and economically, in both direct (medical) and indirect costs (loss of productivity) (Angelis et al., 2015). In addition, a large portion of rare diseases, nearly 70%, are exclusively childhood onset, and a further 18% have

[1]This wide range is in part due to the lack of standardization as to how to count rare diseases which have many subtypes.

onset spanning both childhood and adulthood. This means that up to 88% could first present in childhood (Nguengang Wakap et al., 2020; Michaels-Igbokwe et al., 2021). Though rare diseases in all ages can be devastating, children with rare genetic disorders undoubtedly lose out the most in all areas of life, with a high possibility of debilitating functional impairment or disability, reduced cognitive and reproductive capability, as well as decreased life expectancy (Michaels-Igbokwe et al., 2021).

Unfortunately, due to a variety of systemic and institutional factors, people diagnosed with rare diseases suffer disproportionately compared to those with more common diseases, as both diagnosis and treatment of rare diseases are filled with unique challenges. The first of these challenges is commonly referred to as the "diagnostic odyssey" of a rare disease patient. This is the series of appointments, tests, biopsies, and surgical procedures, as well as time and resources spent in pursuit of a diagnosis, which is often significantly longer and more complex compared to more common diseases (Michaels-Igbokwe et al., 2021). A EURORDIS survey found that 25% of rare disease patients waited between 5 to 30 years from onset of symptoms for a diagnosis, and in 40% of instances the initial diagnosis was inaccurate (EURORDIS, 2007). It is also worth mentioning that even despite extensive testing and doctor's visits, a substantial proportion of rare disease patients may never even receive a diagnosis, either due to lack of funds for increasing medical expenses, insurance issues, travel and caregiving needs, poor communication between medical providers or institutions, misplaced medical records, lack of awareness (on the doctor's side) of new diagnostic criteria, lack of support or rare disease non-profit organization and, of course, illness severity (meaning the patient may pass away before

receiving a diagnosis) (Taliangis & Baynam, 2020). Even when the patient has been diagnosed correctly, they may find that there are very few or even no treatment options available, as, according to some estimates, up to 95% of rare diseases currently have no FDA-approved therapy (Miyamoto & Kakkis, 2011; Pushpakom et al., 2019). The only remaining options are to receive off-label treatments with little to no safety or efficacy data for their condition, participation in clinical trials with all the associated risks and low likelihood of treatment success, or settling for symptom management while hoping that additional research and drug development is underway. This latter approach of "hoping that additional research and drug development is underway" can be referred to as the "Santa Claus theory of civilization", in other words - the hope that for every problem in the world, there are people diligently working to solve it (Fajgenbaum, 2019).

For rare diseases often little is known, and little is being done to better understand the diseases and develop new treatments, and the reasons for this lack of attention are well known in the industry. In order for a compound to be discovered and developed into an effective treatment, a combination of stakeholders and interests need to come together, namely sufficient basic research into both diseases and potential drug compounds from researchers (academic or industry), sufficient technological innovation, and significant amount of funds to support the entire drug development and clinical trial process, which can cost $2-3 billion and take 13-15 years per treatment, on average (Nosengo, 2016; Pushpakom et al., 2019). Additionally, the regulatory space must be favorable, and the market promise of return on investment must be enough to warrant the pursuit of a certain drug rather than another, as well as intellectual

property protections for long enough to recoup the costs of investment. Rare diseases, being heterogeneous, often idiopathic, and, by definition - rare - do not often present an enticing project to support neither in a research sense, nor a commercial one. The Orphan Drug Act did create certain incentives for the investment into rare diseases, namely 1) federal grants for research, 2) tax credits for the costs of clinical trials and 3) 7 years of market exclusivity for new orphan drugs or previously FDA-approved drugs with new orphan indications (Orphan Drug Act, 1983). Nevertheless, issues of identifying promising drugs for rare diseases and shepherding them through the various stages towards FDA approval are filled with roadblocks, and even with the Orphan Drug Act incentives, the pharmaceutical company might never recover the costs of investment, let alone make a profit on the orphan drug. In fact, the Orphan Drug Act uses this as part of its definition for rare diseases, as ones in which "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (Orphan Drug Act, 1983).

1.2 Benefits and Complexities of Drug Repurposing

Given these obstacles for novel drug development for rare diseases, drug repurposing (DR) provides a potential solution. Drug repurposing is a strategy of identifying new uses for approved or investigational drugs outside their original medical indication. Due to the fact that many diseases share the same underlying causes, the same treatments can often be used to treat multiple diseases. While this process is faster and less expensive than new drug development and repurposed treatments are sometimes found serendipitously, a number of

barriers prevent this from happening systematically. Thus, repurposing existing FDA-approved drugs to treat rare diseases is a promising approach to help patients as quickly as possible. Similarly, drugs developed for one condition but proven ineffective or unsafe and thus never approved for the intended condition can also be used in another disease. Because the basic research and preliminary safety studies on the compound have already been completed, drug repurposing and repositioning is able to skip many steps and costs. Additionally, because the repurposed drug has already been proven safe and effective in another disease, it has a higher likelihood to succeed in clinical trials, compared to new, untested compounds (Stone, 2020). Despite the increasing popularity of drug repurposing as an alternative to novel drug development, no common definition has been identified in the literature (Langedijk et al., 2015), and it is often used interchangeably with related terms such as drug repositioning or reformulation. In this project, I utilize the following definition: “Drug repurposing is a process of research to identify potential treatments that are already FDA-approved or in development for one disease, for use in another disease by gathering data and analyzing efficacy in order to improve treatment guidelines and access".

There are a number of notable examples of drugs that have been repurposed to save rare disease patient lives, such as sildenafil for pulmonary arterial hypertension (originally for erectile dysfunction) (Ghofrani et al., 2006), thalidomide for multiple myeloma (originally for leprosy) (Latif et al., 2012), and sirolimus for Castleman disease (originally for transplant rejection) (Fajgenbaum et al., 2019). Given these success stories, there is tremendous enthusiasm and interest in how to repurpose existing drugs for rare diseases, particularly from

rare disease nonprofit organizations, whose mission is to support patients with a specific rare disease or set of diseases. However, the process and steps for how a rare disease nonprofit organization can effectively support a drug repurposing project has never been formalized into a guidance document by any entity, nor has there been any data to illustrate the state of drug repurposing, nor the paths, roadblocks and opportunities involved in the process.

The basic idea of drug repurposing is that once a treatment has been FDA-approved for one condition, it can be re-approved, or repurposed, to treat other conditions. The same goes for drugs developed for one condition but proven ineffective or unsafe and thus never approved for the intended condition; they can be repurposed and approved to treat a different condition (this is sometimes referred to as “drug rescue”). The repurposing process, in most cases, is able to skip typical drug development steps, because the basic research on the properties of the compound has already been completed, as well as preliminary safety clinical trials. Depending on the new indication and how different it is from the original in both the target disease, population, dosages and modes of administration, drug repurposing could start from Phase II or Phase III clinical trials, and thus it becomes a faster (only 1-3 years to implementation, comparing to the 13-15 years for new drug development) and cheaper ($300 million, compared to $2-3 billion for new drug development (Pushpakom et al., 2019) option to get treatments to patients. Additionally, because the repurposed drug has already been proven safe and effective, it has a higher likelihood to succeed in future clinical trials, compared to new, untested compounds - 1/10 success rate vs the 1/10,000 for new drug development (Stone, 2020). Thus, redirecting more funding and research towards maximizing the utility of existing

treatments, rather than focusing solely on the expensive, time-consuming and risky development of novel drugs, is potentially one of the fastest and most effective ways to get treatments to patients with rare diseases.

However, the process has not received enough interest from relevant stakeholders or funding organizations, and most prior drug repurposing efforts are a result of serendipitous discovery rather than a systematic, intentional pursuit (Pushpakom et al., 2019). Relying on serendipity isn't enough to help cover the needs of the millions of rare disease patients that have no FDA-approved treatment options.

1.3 Role of Rare Disease Non-Profit Organizations (RDNPs)

Among the stakeholders involved in the drug repurposing process, rare disease non-profit organizations (RDNPs) stand out as a potentially powerful intermediary between the patients, researchers, physicians, government agencies, and pharmaceutical companies. The primary role of RDNPs is their roles as a network creator and facilitator. Not many (if any) RDNPs are willing to or able to employ researchers and conduct research in-house. Thus their power to make any significant progress in the research and treatment of their rare disease(s) or focus is twofold: 1. Their personal passion and perseverance against all odds to help the patients (often it's themselves, their spouses or children) suffering from the rare disease and 2. The networks they are able to create and leverage with their patients, researchers, physicians and external contacts (members of the pharmaceutical industry, government agencies, biotech, etc.) Their power to drive action is to create series of these relationships with people who will - often for

free or at a reduced rate - engage with their mission and push forward process for their rare disease (e.g. pharmaceutical company “champions'' who help shepard applications along internally, patients who serve as fundraisers as well as educators and advocates, data companies donating their time and staff to work on a specific problem for the RDNP, etc.) Because of their network and the trust they hold as their central “node” stakeholder, RDNPs are very well placed to drive forward drug repurposing efforts for their rare disease(s). But, the effort of making drug repurposing into a systematic pursuit suffers from a series of compounding problems. The one I focus on understanding in this project is that of knowledge sharing: the lack of information on how RDNPs can efficiently support drug repurposing.

1.4 Problems with Knowledge Sharing in Drug Repurposing

One potential explanation for the lack of widespread adoption of drug repurposing research projects within RDNPs is either a lack of or inefficiencies in the transfer of knowledge regarding how to do drug repurposing. The rare disease space is an interesting case - in which most of the rhetoric is on “coming together”, sharing insights, data and experience as the biggest disadvantage with rare diseases is the small population size. This is evidenced by the official slogan of the National Organization for Rare Disorders (NORD) “Alone we are rare. Together we are strong” and such programs as the “Rare As One” (RAO) Project from the Chan Zuckerberg Initiative (CZI) and the tagline of Rare Disease Day “Rare is many. Rare is strong. Rare is proud.” Within such an atmosphere of sharing and coming together, we should expect there to be existing mechanisms of widespread and efficient knowledge sharing, especially in regard to

something as promising as drug repurposing, as it could drastically improve the speed of getting treatments to rare disease patients.

Though there have been notable examples of RDNPs that have helped to spearhead or support drug repurposing opportunities, and an ongoing call for better collaboration (Denton et al., 2021, 2022) their gained experience is not centralized or widely available to share between the stakeholders, and no centralized "top down" guidance or resources exist to help new RDNPs navigate the drug repurposing landscape. This leaves individuals and organizations to independently "reinvent the wheel" over and over, and not always successfully. It seems that there is much value to be gained from newer, less experienced RDNPs learning from the more experienced RDNPs, and for the more experienced RDNPs to share this knowledge and establish partners and collaborations. RDNPs do actively participate in workshops, events, conferences (including, notably, FindACure's annual Drug Repurposing conference) and projects such as CZI's RAO are working on bringing RDNPs together for knowledge sharing and collaboration. But still, the understanding of current knowledge sharing practices of RDNPs as well as ways to improve them remains elusive on three fronts:

1. who is sharing information and with whom

2. what kind of information/knowledge they are sharing and how

3. where are the inefficiencies in this process

Thus, in this project I will focus on understanding the knowledge sharing practices and challenges of RDNPs in regards to drug repurposing, as well as considering ways in which this

process could be made more clear and efficient. The focus on "inefficiencies" is derived from preliminary evidence from the ROADMAP survey data **(see Chapter 4, section 4.2)**, which I will discuss in a later section, which shows that some knowledge sharing processes are indeed occurring, and the desire for them to occur exists. From this I make the conclusion that it is not a complete lack of knowledge sharing that is the issue here, but inefficiencies within the existing processes. By focusing on identifying and exploring solutions to the existing "roadblocks" for more efficient knowledge sharing, I can start to explore the implications for solutions through the creation of spaces to facilitate knowledge sharing in the rare disease space. In order to focus the project further and eliminate a vast amount of variance from the analysis, I propose to focus this study on repurposing projects on one specific drug called Sirolimus (also known as rapamycin and sold under the brand name Rapamune).

1.5 The sTORy[2] of sirolimus

Sirolimus offers an interesting lens to the study of rare disease drug repurposing. Sirolimus, originally discovered in a soil sample from Easter Island, has transcended its initial antifungal designation to become a cornerstone in the field of rare disease treatment. Its journey from an obscure natural compound to a critical therapeutic agent exemplifies the potential hidden in natural sources and the transformative power of drug repurposing. In the context of rare diseases, where research and development are often hindered by limited financial incentives, sirolimus stands as a testament to the untapped possibilities that exist within existing

[2] In reference to mTOR, the mechanistic target of rapamycin pathway.

compounds. This case not only underscores the importance of innovative approaches in pharmacology but also highlights the need for a more concerted effort in exploring repurposing opportunities as viable pathways for addressing the complex challenges of rare diseases.

Discovery & Initial Research

In 1964, an expedition from Canada, embarking from Halifax aboard the HMCS Cape Scott (Figure 1), set sail for Easter Island (Rapa Nui), a Chilean territory. This island, a subject of fascination for explorers for over a century, faced potential ecological disruption due to the planned construction of an airport in 1966. To document the unique biosphere and population of Easter Island before these changes, Dr. Stanley Skoryna, a surgeon and gastroenterologist from McGill University, along with Georges Nogrady, a microbiologist, organized a medical expedition (Hobby et al., 2022).

Figure 1: The HMCS Cape Scott, a vessel of the Royal Canadian Navy that carried the expedition to Easter Island (Hobby et al., 2022)

During this expedition, Nogrady collected soil samples which were later transported back to Canada. These samples were then entrusted to Suren Neth Segal (Figure 2) at the Ayerst Laboratory in Montreal, as part of a quest to discover new antibiotics from natural sources (Hobby et al., 2022).

Figure 2: Surendra (Suren) Nath Sehgal, a mycologist who played a pivotal role in discovering sirolimus from a soil sample in Easter Island's Vai Atare region in 1972 (Kahan, 2003)

Sehgal, originally from a small village in present-day Pakistan, was a trailblazer in pharmaceutical microbiology, following his father's footsteps in the field. After earning his academic credentials in India and the UK, Sehgal joined the Ayerst-McKenna-Harrison Corporation in Montreal (Kahan, 2003). Samples in hand, Sehgal and his team identified a specific strain of Streptomyces hygroscopicus in a soil sample taken from the Vai Atare area of Rapa Nui. In tests designed to detect antifungal capabilities, this strain demonstrated notable properties. The active compound was extracted from the mycelium of the Streptomyces (Figure 3). Following purification, this compound crystallized into a material with strong antifungal effectiveness. This newly discovered antibiotic was christened “rapamycin”, a name derived from 'RAPA' (short for Rapa Nui) and the suffix '-mycin', commonly used for antibiotics (Sehgal, 2003).

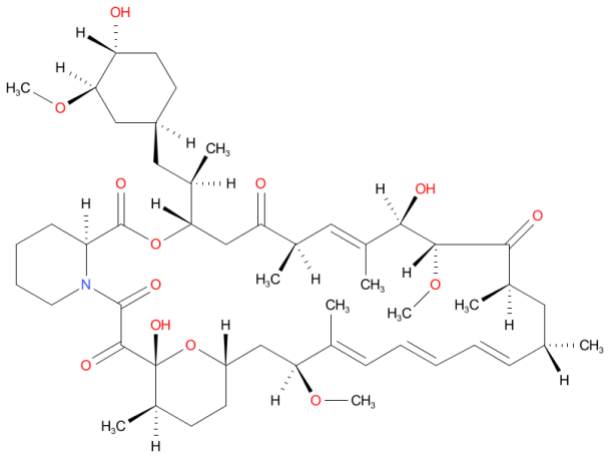


Figure 3: Chemical structure of sirolimus (DrugCentral: Sirolimus, n.d.)

Sehgal's extensive work on sirolimus, from developing its fermentation process to uncovering its antimicrobial and antiproliferative properties, marked a significant advancement in medical science. Dr. Sehgal received a Lifetime Achievement Award from the Indian Society of Organ Transplantation in 1997. He was diagnosed with metastatic colon cancer in 1998 and he was treated with sirolimus. He passed away in 2003 after 40 years of active research and saving countless lives (Kahan, 2003; Debopam, 2017).

How sirolimus works

Sirolimus acts on the mechanistic target of rapamycin (mTOR) pathway, which is a central pathway in cellular regulation. The mTOR pathway is a critical cellular signaling pathway that plays a vital role in regulating various cellular processes, including cell growth, cell proliferation, protein synthesis, and autophagy - the process by which cells degrade and recycle their components. This pathway comprises two distinct complexes: mTORC1 and mTORC2. mTORC1,

which is sensitive to rapamycin, primarily regulates protein synthesis, while mTORC2, less sensitive to rapamycin, is involved in cell survival and cytoskeletal organization. The regulation of the mTOR pathway is complex, integrating signals from diverse sources such as nutrient availability, oxygen levels, the energy status of the cell, and growth factors, thereby controlling both anabolic and catabolic processes within the cell. Sirolimus, a key drug in this context, operates by forming a complex with the protein FKBP12 (FK506-binding protein 12). This complex then directly binds to and inhibits mTORC1, leading to a reduction in cellular proliferation, growth, and survival by decreasing protein synthesis and other processes regulated by this complex (Sehgal, 1998).

Approvals & Repurposing

Although sirolimus was initially explored for its antifungal properties, the focus rapidly transitioned to its potential in other therapeutic areas, driven by the discovery of its potent immunosuppressive and antiproliferative effects (Kahan, 2004). For renal transplant rejection, sirolimus was approved in the US in September 1999 (FDA, 1999), and in November 2000 by the European Medical Agency (EMA, 2000). Japanese research on the potential for sirolimus to treat lymphangioleiomyomatosis, a rare lung disease, led Nobelpharma to seek manufacturing and marketing approval for this new indication, which was approved by the FDA in July 2014 (FDA, 2015). Based on this research, the use of sirolimus expanded to other Lymphatic anomalies, a group of diseases involving systemic dysplasia of lymphatic vessels, including Gorham–Stout disease (Ozeki et al., 2019).

Over the subsequent decades, its activities have been widely investigated and it has been found to be an exceptionally versatile molecule in that it possesses antifungal, immunosuppressive, and anticancer activities. Recognition of rapamycin's anti-tumor target of the mTOR pathway led to the development of analogues of rapamycin as chemotherapeutic agents against solid tumor types, including breast cancer (Seto, 2012). In 2021, the Food and Drug Administration approved sirolimus protein-bound particles for injectable suspension for adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumors (FDA, 2021). Under the name "Hyftor", sirolimus was approved for treatment of facial angiofibroma. Studies have also suggested its efficacy in potentially lowering the risk of atherosclerosis (Liu et al., 2019), treating systemic lupus erythematosus (Oaks et al., 2016) and Graft-versus-host disease (Blazar et al., 1998). In 2022 the FDA has approved HYFTOR (sirolimus topical gel 0.2% formulation) as the first topical treatment indicated for facial angiofibroma, a rare benign tumor, associated with tuberous sclerosis complex (Nobelpharma, 2022), later also approved in the EU in May 2023 (EMA, 2023). Recently, QTORIN, a 3.9% topical sirolimus formulation received FDA Breakthrough Therapy Designation (Andrus, 2023). During the recent pandemic, sirolimus was proposed to prevent or reduce the cytokine storm seen in very serious cases of COVID-19 (Husain & Byrareddy, 2020).

Sirolimus also has shown potential for widespread use as a longevity-promoting drug, with evidence pointing to its ability to prevent age-associated decline of cognitive and physical health. In the lab, it was shown to inhibit and slow aging in worms, yeast, and flies, and then to improve the condition of mouse models of various diseases of aging (Bitto et al., 2016).

According to CEO of TORnado therapeutics Dr Joan Mannick: “There is no therapeutic that’s better validated than Rapamycin for targeting aging and extending lifespan” (Sullivan, 2022).

Why sirolimus?

Sirolimus represents a critical intersection between pharmacology and cell signaling pathways. Its role in targeting the mTOR pathway has vast implications in both clinical medicine and research, offering insights into treating various diseases that involve aberrant cell growth and proliferation. Now being off-patent, it is an easy drug to repurpose and utilize off label - it is cheap, widely available, has a long-standing safety profile with few serious side effects (since renal transplant patients have been on it for decades, there is data on long term safety and efficacy), and a well-understood mechanism of action. The pathway it targets (mTOR) is a very important one for various functions in the body, and so it is potentially a target for a wide variety of rare diseases. There is even some animal model research to show that it may slow the effects of aging, and depending on the dose may either increase immune function (with obvious benefits) or decrease immune function (which is beneficial in cases of an immune system going into life-threatening cytokine storm disorders, such as Castleman Disease or even COVID-19). Though it seems very beneficial for RDNPs to be engaging in knowledge sharing in regards to <u>any</u> drug repurposing experience for all the benefits of drug repurposing in general discussed prior, drug repurposing efforts by different rare disease organizations in regards to the same drug seem of incredible value for several reasons.

- Additional data of the effects of the drug on different patient populations (with different rare diseases) may help clarify both how the drug works, as well as help

inform how different types of patients will react to different treatment regimens, dosages, and how the drug might impact different body functions over time (fertility, etc.)

- By combining or comparing data from different rare disease patients, each individual rare disease might gain additional knowledge about the mechanisms of their rare disease of focus and even might help support future hypothesis building as to new treatment pathways .
- By merging efforts, gaining researcher or pharmaceutical company support might be very beneficial for each rare disease non-profit. One might imagine that researchers could focus on multiple diseases when running experiments, or advocacy efforts in engaging pharmaceutical companies might be easier if multiple disease groups are putting pressure on them at the same time; also, there have bee cases in which clinical trials were able to move forward because rare disease non-profit organizations were able to partner and both better financially support the trial (pooling funding) and enroll more patients (pooling patients). Thus, because of its widespread utilization off label for rare diseases and common focus of repurposing, RDNPs which are repurposing Sirolimus stand to benefit from knowledge sharing, perhaps more so than organizations focused on different drugs.

There are, though, also reasons for why knowledge sharing in regards to the same drug may also not be beneficial for rare disease organizations. First of all - rare diseases vary greatly by

their severity, mechanism of action, affected populations, etc etc. so adding more variables to the equation may detract, rather than add value to any research process; it might muddy an already muddy water in which effective treatments are few and far between. Also - by partnering with other RDNPs, each individual RDNP does relinquish some control over the process and then has to engage with more actors, which opens them up to slow-downs and more potential for conflict over funding decisions, timelines, research direction, and so on.

CHAPTER 2: RESEARCH PROBLEM STATEMENT

2.1 Research Goal & Motivation

The primary goal of this research is twofold: to provide an understanding of the knowledge-sharing practices and challenges for Rare Disease Nonprofit Organizations (RDNPs) and to contribute to the academic discourse in knowledge sharing theory by applying it to a unique and practical use case. The motivation behind this research stems from the pivotal role RDNPs play in the rare disease treatment landscape. Given the limited financial incentives for pharmaceutical companies to invest in rare disease treatments, RDNPs are often at the forefront of innovative approaches like drug repurposing. However, the lack of centralized knowledge-sharing mechanisms among these organizations leads to significant inefficiencies. This research aims to dissect these inefficiencies, understanding the barriers to effective knowledge exchange and proposing solutions to enhance collaboration and efficiency. By focusing on sirolimus, the study provides a targeted exploration of knowledge sharing in a specific context, offering insights that are both deep and broad in their implications.

From an academic perspective, this research is anchored in Ikujiro Nonaka's Theory of Dynamic Organizational Knowledge Creation (1994), applying it to the case of rare disease drug repurposing and suggesting a set of factors that might drive the creation of knowledge and it's subsequent sharing within this context (Yang and Maxwell, 2011). This theoretical framework is used to analyze and understand the interorganizational knowledge sharing among decentralized, volunteer-driven RDNPs, a context that presents unique challenges and opportunities for knowledge management. The study not only contributes to the practical field of rare disease treatment and drug repurposing but also advances our theoretical understanding of knowledge sharing in complex, multi-actor environments.

The ultimate aim is to bridge the gap between theory and practice, enhancing the capacity of RDNPs in drug repurposing efforts and contributing to the broader mission of improving health outcomes in the rare disease community. This research, therefore, holds significant value for both practitioners in the field of rare disease treatment and academics in the field of information science and knowledge management.

2.2 Key Terms

1. **RDNP (Rare Disease Non-profit Organizations):** These are non-profit organizations focused on rare diseases. They typically engage in activities such as supporting research, advocating for patients, raising public awareness, and facilitating access to treatments. RDNPs often play a crucial role in bridging gaps between patients, healthcare providers,

researchers, and policymakers, especially in areas where the market and public health systems may not adequately address the needs of those with rare diseases.

2. **Drug Repurposing:** the process of research to identify potential treatments that are already FDA-approved or in development for one disease, for use in another disease by gathering data and analyzing efficacy in order to improve treatment guidelines and access. Drug repurposing is seen as a cost-effective and time-efficient strategy in drug development, particularly beneficial for treating rare diseases, which may not be the focus of mainstream pharmaceutical research due to lower financial incentives (Pushpakom et al., 2019).
3. **Rare Disease:** A rare disease, also known as an orphan disease, is a condition that affects a small percentage of the population. Each country may define "rare" differently, but it generally refers to diseases affecting a small number of people compared to the general population. These diseases are often chronic, progressive, and life-threatening, and they can pose significant challenges in terms of diagnosis, treatment, and research due to their low prevalence.
4. **Knowledge:** Knowledge is the understanding, awareness, or familiarity gained through experience or education. It encompasses the theoretical or practical understanding of a subject, and it's more than just a collection of facts; it includes insights, contextual understanding, and the synthesis of information into a coherent whole (Bates, 2005).
5. **Knowledge Sharing:** This is the process by which individuals, groups, or organizations exchange information, skills, and expertise. The purpose of knowledge sharing is to spread knowledge across different parts of an organization or between different

entities, enhancing understanding and capability. It's a key component of knowledge management and is crucial for learning, innovation, and problem-solving.

2.3 Research Questions

In this project I will focus on understanding the knowledge sharing practices and challenges of RDNPs in regard to drug repurposing for a specific drug (sirolimus), as well as considering ways in which this process could be made more efficient in regards to knowledge sharing. the three main research questions for the current project are

RQ1: How is sirolimus being repurposed in the context of Rare Disease Nonprofit Organizations (RDNPs), and what are the characteristics of this process from their perspective?

RQ2: Who are the key participants involved in the repurposing of sirolimus within the Rare Disease Nonprofit Organizations (RDNPs) network, and what influences their collaboration and interaction dynamics in this process?

RQ3: What are the prevailing barriers in the sirolimus repurposing process, and how can these obstacles be addressed to enhance efficacy and outcomes?

2.4 Overview of Research Design

This dissertation explains the knowledge-sharing practices and challenges inherent within RDNPs, particularly in the context of repurposing sirolimus. This inquiry is based on the premise

that optimizing these practices could significantly enhance the efficiency in the repurposing process via knowledge sharing. The research is centered around three themes:

(1) Identifying the Participants: Who is engaged in the knowledge sharing, and what are the dynamics of their interactions?

(2) Nature of Knowledge Exchange: What types of information or knowledge are being shared, and through what channels or stakeholders does this exchange occur?

(3) Locating Inefficiencies: Where are the barriers in this knowledge-sharing process, and what factors contribute to these inefficiencies?

Given the multifaceted nature of these research questions, I utilized a multimethod research approach:

1. **Case Studies**: In-depth examination of specific stories of repurposing, with a special focus on collaborations and knowledge sharing practices (see Chapter 6).
2. **Network Analysis:** Analysis of the structure and dynamics of the knowledge-sharing networks or lack thereof (see Chapter 7).
3. **Thematic Analysis:** Qualitative analysis of interview transcripts with RDNPs to gain their insider perspectives on the process, barriers and attitudes related to drug repurposing (see Chapter 8).

This dissertation aims to utilize Nonaka's theory of knowledge creation (1994) and map it to the rare disease repurposing landscape and the rare disease nonprofits engaged in sirolimus repurposing. In order to explain what drives knowledge sharing or lack thereof, I adapt the

factors from Yang and Maxwell (2011) into a 12 factor framework. In order to illustrate which factors are driving knowledge creation in the rare disease repurposing landscape, I conducted a qualitative analysis of 3 in depth case studies, engaging with the temporal parameter of Nonaka's knowledge creation theory - mapping the experience of an early, middle and late stage repurposing RDNP to Nonaka's theory and highlighting which factors are at play, driving the decision-making of these RDNPs.

I also visualized and analyzed the rare disease repurposing landscape through both RDNP-RDNP and bipartite RDNP-actor network analysis. Finally, I conducted thematic analysis of the interview transcripts, mapping the themes extracted from the transcripts to the 12 factor framework (Yang & Maxwell, 2011).

This dissertation also incorporates findings from a related research project, called the ROADMAP (*ROADMAP Project*, 2022). Although not directly within the scope of this study, the ROADMAP project offers critical background information and data that are instrumental in informing decision-making processes throughout this research. The ROADMAP **(see Chapter 4, section 4.2)** involved a survey and interviews, and I will briefly discuss the methods and findings as they are relevant to this dissertation. The inclusion of these findings is intended to provide a comprehensive understanding of the complexities involved in knowledge sharing among RDNPs in the context of drug repurposing (see **Chapter 5**).

2.5 Epistemological Stance

This dissertation adopts a qualitative approach to explore the knowledge-sharing practices of RDNPs involved in drug repurposing. Qualitative methods such as in-depth interviews, case studies, and thematic analysis are employed to capture the nuanced and multifaceted nature of knowledge sharing among RDNPs. These methods allow for a detailed exploration of the motivations, relationships, and practices that quantitative methods might overlook. A qualitative research approach also provides the flexibility to adapt to emerging themes during data collection and analysis. This adaptability is crucial for studying the dynamic interactions within RDNPs. The depth of qualitative analysis allows for examination of specific cases as well as overarching themes, revealing insights that are not easily quantifiable.

The primary aim of this qualitative research is to generate a deep understanding rather than statistical generalization. This approach allows for an in-depth exploration of the specific, often unique, circumstances of each RDNP, capturing the richness and diversity of their knowledge-sharing practices. Thus, limited quantitative metrics are reported in this study.

Specific Methods Employed

- In-depth interviews are conducted to gather detailed insights from RDNP stakeholders. This method allows participants to share their experiences and perspectives in their own words, providing rich, qualitative data.
- Three case studies (Smith-Kingsmore Syndrome Foundation, Pachyonychia Congenita Project, and The LAM Foundation) are used to illustrate different stages of the drug

repurposing process. Case studies provide a detailed contextual analysis of each organization's knowledge-sharing practices and challenges.

- Thematic analysis is used to identify and analyze patterns within the qualitative data. This method helps in understanding the key themes and factors influencing knowledge sharing among RDNPs.
- Network analysis is employed to visualize and analyze the structure and dynamics of the knowledge-sharing networks among RDNPs. Network analysis complements qualitative data by revealing patterns of collaboration and knowledge dissemination that might not be immediately apparent through narrative accounts alone.

Conclusion

The qualitative stance and methods employed in this research are well-suited for studying knowledge sharing among RDNPs, especially considering that this process is not occurring as efficiently or often enough to be able to study it quantitatively. The approach taken in this dissertation allows for a nuanced understanding of the complex and context-dependent phenomena, providing valuable insights into the practices and challenges faced by RDNPs in drug repurposing efforts. By generating deep understanding rather than statistical generalization, this research can develop targeted strategies to enhance knowledge management in the rare disease nonprofit sector and set the groundwork for further, more quantitative research in the future.

2.6 Expected Contributions

The expected outcomes of this dissertation will contribute in two ways: First, there is an expected contribution to knowledge management theory. The application of case studies, network analysis, and interviews in this research is designed to construct a map of the knowledge-sharing ecosystem within RDNPs engaged in sirolimus repurposing. This endeavor will delineate the roles and interactions of diverse stakeholders but also provide an in-depth analysis of their collaborative dynamics. The resulting framework will offer insights into how knowledge is shared and co-created in a decentralized, multi-actor setting and can serve as a comparative model for understanding knowledge sharing in other sectors. Such an analysis is invaluable for advancing our theoretical understanding of knowledge networks and their dynamics.

Second, this dissertation offers practical knowledge. Through analyzing the nature and mechanisms of knowledge exchange in the context of drug repurposing. By examining the types of information shared, the channels used for this exchange, and the effectiveness of these channels. This aspect of the research is particularly significant for knowledge management theory, as it offers insights into the practical applications and challenges of knowledge dissemination and utilization in a specialized field. The findings from this analysis will not only contribute to the optimization of drug repurposing efforts but also provide a blueprint for effective knowledge management practices in similar complex, multi-stakeholder environments.

In summary, by employing a multimethod approach, this research focuses into the intricacies of knowledge sharing within the specific context of rare disease drug repurposing, offering a unique case study that enriches our theoretical understanding of knowledge dynamics in complex, multi-stakeholder environments and also provide actionable strategies for improving knowledge management practices in similar contexts.

CHAPTER 3: THEORETICAL FRAMEWORK

The theoretical framework of this project is centered around Ikujiro Nonaka's Theory of Dynamic Organizational Knowledge Creation (Nonaka, 1994). Nonaka provides a high level framework that helps us understand both each individual RDNPs' actions, as well as its interactions with other RDNPs and other types of stakeholders within the rare disease ecosystem. Furthermore, to understand the factors that help drive the knowledge sharing practices described by Nonaka, I adapt the framework of Yang and Maxwell (2011) into a set of 12 internal and external factors.

In this chapter, I will first posit this theoretical framework in the greater context of the knowledge management literature. Then, as the concept of knowledge is closely related to the concepts of information and data, and the transformation from one to the other is closely related to Nonaka's theory, I will first define these terms utilizing information science literature and discuss the idea of transformation of information into knowledge as a part of the knowledge creation process. Next, I will describe Nonaka's Theory of Dynamic Organizational

Knowledge Creation in detail, including all the different layers and elements. Then, I'll discuss how this project aims to expand Nonaka's theory in several ways, namely moving it into the interorganizational space and into a decentralized organizational environment. I will introduce my own theoretical contributions, in how the existing theoretical frameworks are able to give rise to several factors that affect organizational capacity, and how this affects the knowledge sharing process. I will further discuss the framework of factors involved in interorganizational knowledge sharing by Yang and Maxwell (2011), and my adaptation into a set of 12 internal and external factors.

3.1 Introduction to Knowledge Management

This research primarily contributes to the space of knowledge management (KM). Broadly defined, knowledge management is a field of study that focuses on the processes involved in capturing, distributing, and effectively using knowledge (Girard & Girard, 2015; Koenig, 2018). This domain has traditionally centered its attention on organizational contexts, fostering an environment where knowledge sharing emerges as a pivotal component within the KM process. Both industry leaders and researchers in related fields agree that knowledge is becoming important sources of competitive advantage for organizations (Stewart, 1997; Burciu & Kicsi, 2015; Vrdoljak Raguž et al., 2017). A large emphasis has been placed on the value of tangible knowledge in the form of data (social media use, purchasing preferences, geolocation, even DNA-related data through services such as 23&me). However, a less tangible knowledge base, such as innovative thinking and insider "know-how" is also a crucial, albeit sometimes undervalued resource for organizations and industry leaders worldwide. Insider knowledge is a

combination of prior experience, individualized expertise, creative vision, organizational mission and relationships with external stakeholders. It is often not formally written down and sometimes not even something the organization is aware of until it is put in contrast with other similar organizations. This insider knowledge is less tangible than data and so it can't be easily quantified and sold as a commodity. Internally, it may not even be seen as an asset, and thus not valued both internally nor shared externally. Importantly, in the knowledge economy, where growth and performance are driven by the quality, quantity, and accessibility of information rather than traditional production factors, positions knowledge as a primary asset (Brinkley, 2006; Powell & Snellman, 2004). In this state, leveraging knowledge and intellectual capital becomes crucial for innovation and competitive advantage, some would even say this "insider knowledge" is the most important asset of organizations (Stewart, 1997) and that "an organization's competitive advantage lies in the knowledge residing in the head of its employees and the capability to harness the knowledge for meeting its business objectives" (Tan et al., 2009, p. 18). But how does an organization take an experience or a set of experiences and make that into something more than the sum of its parts, something with value and something that can be both archived as an organizational knowledge asset and also shared externally?

3.2 Transformation from Information to Knowledge

The distinction between tangible and intangible assets for a company mirrors the distinction made in information science between (1) data, (2) information and (3) knowledge. These three concepts can be seen as points on a spectrum, which transform and evolve from one to the

other over time. The question is then, how does data become information, and information become knowledge? There have been many different attempts to conceptualize different levels of information. Here I will briefly discuss two, from Bates (2005) and Buckland (1991).

Bates (2005) has a framework rooted in the theory of evolution, with "modes of information perception, processing, transmission, and storage that developed as a part of the general [process of] evolution" (p.1). In this view, information is a vital way of organizing our understanding of the world, recognizing patterns and forming heuristic shortcuts to help us navigate an ever-changing landscape of data. Bates (2005) distinguishes two levels of information: information 1 and information 2, the first being a pattern of organization of matter and energy, and the second – the same pattern, which has been then given meaning by a living being. When these emergent patterns with meaning are integrated into a greater framework of understanding, this, according to Bates, is when information becomes knowledge. In this view, information is a vital way of organizing our understanding of the world, recognizing patterns and forming heuristic shortcuts to help us navigate an ever-changing landscape of data. But new information needs to be given meaning and integrated into the existing landscape of other information to become knowledge. Buckland (1991) on the other hand, conceptualizes information in three facets: "information as thing", "information as process" and "information as knowledge". "Information as thing" denotes objects that are informative, such as data and documents. "Information as process" denotes the act of informing or spreading of new information. "Information as knowledge" denotes information which is intangible, personal, subjective and conceptual; it is what is spread by "information as process".

Between both conceptualizations, we can see a hierarchy, in which as patterns get organized into larger systems, they become increasingly complex and this corresponds to the change from data, to information, to knowledge. In Nonaka's theory of knowledge creation which I will discuss next, Nonaka distinguishes between tacit and explicit knowledge. Tacit and explicit knowledge seem to be subtypes of both Bates's definition of knowledge as well as Buckland's "information as knowledge" as both describe information as a process or information as being transformed from one form to another. In Nonaka's terms, information turns into knowledge when it becomes an externalized knowledge asset. In this project, I will focus on the transformation of tacit knowledge to explicit knowledge and vice versa.

3.3 Nonaka's Theory of Dynamic Organizational Knowledge Creation

The theoretical landscape of knowledge management was long dominated by the information-processing model for organizations. Similar to Shannon's (1948) mathematical theory of communication which defined interpersonal communication as the transference of information from sender to receiver, in the information processing model the organization is viewed as a machine that takes in and processes information from the environment in order to solve a problem and adapt to the environment (Simon, 1973). Both theories were later criticized for being too mechanistic and as viewing the actors as being too passive (Chandler, 1994; Carey, 2007). Though information processing certainly takes place for both individuals and organizations (e.g. answering emails, project management meetings, etc.) when we are looking at the context of innovation or knowledge creation, the organization does not simply process information, but create something new, something which is greater than the sum of its parts:

“Instead of merely solving problems, organizations create and define problems, develop and apply new knowledge in order to solve these problems, and then further develop new knowledge through problem-solving activities”; this knowledge creation process works through “action and interaction” (Nonaka et al., 2003, p. 492).

Nonaka’s Theory of Dynamic Organizational Knowledge Creation (Nonaka, 1994) was proposed as an alternative to the dominant theories which viewed organizations as either information-processing machines, or as passive actors, ignoring the dynamic dimension of knowledge creation and learning. Nonaka’s theory consists of three parts: (1) the Socialization, Externalization, Combination and Internalization (SECI) model, (2) the space for knowledge creation (the “ba”) and (3) the organization’s knowledge assets. Nonaka describes movement and transformation both within each for the three elements through “knowledge spirals”, as well as between them (see Figure 4). Each of the three elements is made up of four types: SECI consists of 4 modes of knowledge creation (Socialization, Externalization, Combination and Internalization), there are 4 types of “ba” (originating “ba”, dialoguing “ba”, systemizing “ba”, and exercising “ba”) and 4 types of knowledge assets (experiential, conceptual, systematic, and routine). Each of the 4 types of the three elements correspond to each other and fit within the “knowledge creation spiral”, where knowledge is constantly created and recreated as it passes through each mode, each “ba” and each type of knowledge asset.

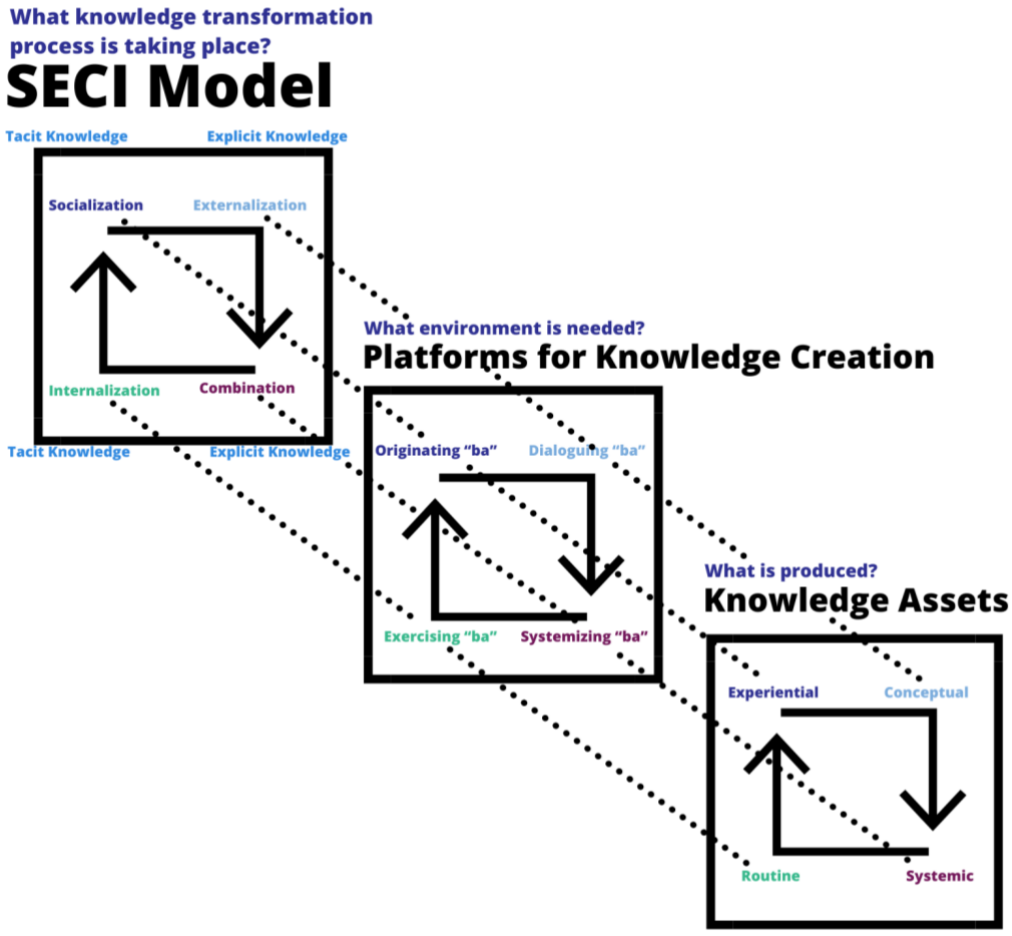


Figure 4: The three layers of the knowledge-creation process (adapted from Nonaka et al., 2003, p. 493)

I will first explain these elements and their subtypes; then I will illustrate how all these elements are interrelated and finally, I will discuss how this project will expand this theory on several dimensions.

3.3.1 The SECI Model of Knowledge Creation

As briefly mentioned prior, according to Nonaka there are two types of knowledge: tacit and explicit. Explicit knowledge is knowledge that is already or can easily be expressed in a formal and systematic way, such as data, manuals, guidelines, scientific formulas, etc. Tacit knowledge,

on the other hand, is highly personal and not easily expressed or quantified, such as subjective insights, insider "know how", personal expertise, hunches, subconscious routine actions, etc. Tacit knowledge is deeply ingrained in intangibles such as culture, emotion, routine, mission, ideals, values, etc. In this project, tacit knowledge is each organization's experience with drug repurposing, including why they are pursuing it (or why not), what has been their process, what roadblocks they have encountered on the way and how they have moved forward (or whether they have given up on the project). It is also highly contextual to time and place, so it is difficult to articulate and share as an asset (Nonaka, 1994, 1998; Nonaka et al., 2003). In this project, each RDNP's experience with drug repurposing is highly contextual to two types of factors: (1) characteristics of the RDNP itself and (2) characteristics of the rare disease itself; more on that in later sections.

There are 4 modes of knowledge creation in the SECI (socialization, externalization, combination and internalization) model and they correspond to the transformation of tacit and explicit knowledge: from tacit to tacit, from explicit to explicit, from tacit to explicit and from explicit to tacit (See **Figure 5**).

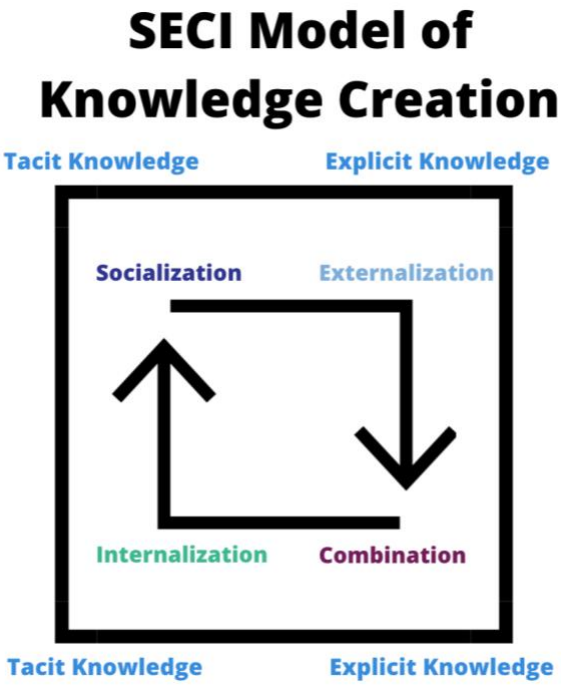


Figure 5: The SECI model of Knowledge Creation (adapted from Nonaka et al., 2003, p. 493)

Socialization is the process of taking tacit knowledge from one person and spreading it to another still in tacit form. Traditionally this was done through apprenticeships; nowadays it can be done through internships or through social activities between colleagues. It is a process of learning without a formal system or manual, but by observing in context and shared experience. For example, when medical students follow a doctor on "rounds" to see patients and discuss diagnoses; they learn by doing and also watching others; learning the tips and tricks that nobody teaches explicitly. Similarly, within the medical research setting in academia, young researchers often work in labs focused on a variety of projects, in which they are encouraged to contribute in a variety of ways to the projects of the lab, and thus are trained in both "soft" skills on how to conduct research and "hard skills" such as how to work the equipment and run analyses. This know-how is also applicable to drug repurposing research, where identifying

potential drug target candidates is a collection of skills and insider knowledge which may be difficult if not impossible to articulate in a manual.

Externalization is the process of articulating tacit knowledge, making it explicit. This mode, according to Nonaka, is key for new knowledge creation: "When tacit knowledge is made explicit, knowledge becomes crystallized, at which point it can be shared by others and can be made the basis for new knowledge" (Nonaka et al., 2003, p. 495). Within medical research, externalization is often done through publication or presentation, where a new conceptualization, algorithm or research technique is made available for others to utilize.

Internalization is the opposite of externalization; it is the process of conversion of explicit knowledge into tacit through routine or practice. This corresponds to the traditional learning model, in which something that has been systematized and formalized becomes ingrained in practice.

Combination is the process of taking knowledge already explicit and connecting it with other explicit knowledge. This can be done in two ways - (1) by taking disconnected pieces of knowledge and organizing them into a larger system or (2) by breaking complex concepts down into workable, smaller subsets. Both of these approaches can also lead to new discovery through sorting, adding, combining, categorizing, seeing higher levels trends and patterns.

With this framework in mind, we can now refine RQ2 to be more specific. When I refer to "types of knowledge sharing processes", I am referring to the SECI processes, of tacit and explicit knowledge conversion. Nonaka states that while each of the four modes of knowledge conversion in the SECI model can create new knowledge independently, the dynamic interaction between the different modes of knowledge conversion is vital (i.e. the knowledge spiral). In other words, knowledge creation centers on the creation of both tacit and explicit knowledge and on the transformation of one into the other. Though Nonaka primarily focuses on individuals within an organization as knowledge creation catalysts, the SECI process is not limited only to individuals or even organizations. In fact, the knowledge spiral can also move in between different levels - through the individual level up to community level and even beyond the organization's boundaries. The latter, the interorganizational level of knowledge creation and sharing, will be of primary interest in this project.

3.3.2 Knowledge Assets

Knowledge assets are both inputs and outputs of the knowledge creation process. They are what is produced by each knowledge creation process in the SECI model, and what then serves as the input of the next step in the knowledge spiral. Nonaka divides these into 4: experiential, conceptal, systematic, and routine, each one also corresponding to the appropriate mode of knowledge creation: Socialization, Externalization, Combination and Internalization. Knowledge assets form the basis of the knowledge creation process which flows from one mode to another via the SECI model.

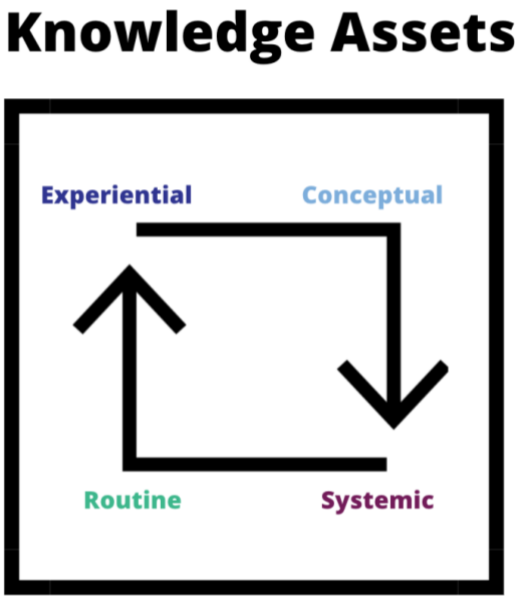


Figure 6: Knowledge assets (adapted from Nonaka et al., 2003, p. 493)

Experiential knowledge assets are defined as tacit knowledge assets which are created through hands-on experience between people or organizations. As they are tacit, they are hard to grasp, evaluate, assess the value of or share. They are also incredibly context specific and difficult to abstract out for sharing.

Conceptual knowledge assets are created when explicit knowledge is articulated as a concept, either written down or illustrated with images or models. They are built through the process of externalizing experiential knowledge assets, making that knowledge more practical, easier to articulate and share.

Systemic knowledge assets are systematized explicit knowledge (through combination and collaboration). This type of knowledge is formalized as documents, patents or data.

Routine knowledge assets are tacit knowledge assets which become embedded within the actions and practices of an organization through the process of internalization.

3.3.3 The "ba": Platforms for Knowledge Production

An important aspect of Nonaka's model is the idea of "ba", or "place". In simplest terms, a "ba" is a space where new knowledge is created, and a framework in which knowledge becomes a resource. It answers the question - what kind of environment is needed for the particular process (be it **S**ocialization, **E**xternalization, **C**ombination or **I**nternalization) to take place efficiently? It can be a physical, virtual, or a mental space in which individuals and ideas can be expressed, combined and amplified.

"Ba" (or "basho") is based on a concept introduced by Japanese philosopher Kitaro Nishida (Nishida, 2012) "ba" is a space in which knowledge is shared, created, and utilized (Nonaka & Konno, 1998). This relates back to the idea of action and interaction mentioned previously - knowledge is not created in isolation but requires context and interaction. It is proposed in this model that the interaction of people and their ideas is a vital process of knowledge creation. "Ba" functions both as an encouragement for interaction as well as a concentrated resource of

knowledge - both a time and space for knowledge to concentrate and be harnessed as a resource. Nonaka breaks down the concept of “Ba” into 4 types: originating “ba”, dialoguing “ba”, systemizing “ba”, and exercising “ba”, each of which are the appropriate environment for the corresponding knowledge creation processes of the SECI model to take place

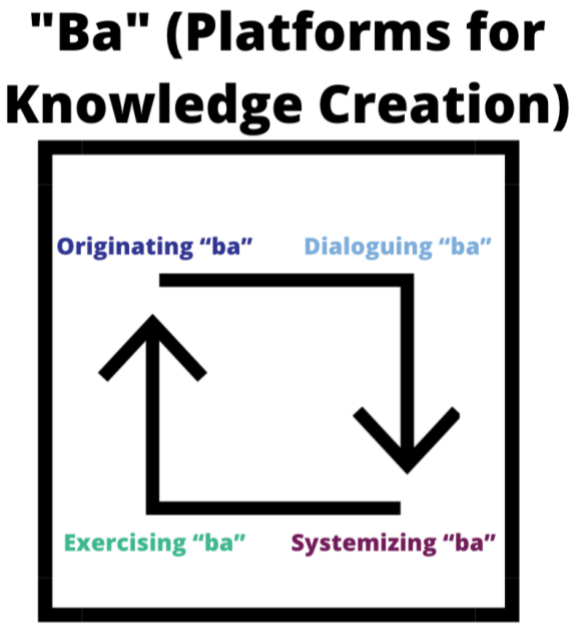


Figure 7: Platforms for knowledge creation (adapted from Nonaka et al., 2003, p. 493)

Originating “ba” is the space of tacit knowledge sharing (socialization), where people share feelings, experiences and mental models normally through physical, face to face interaction, where things like trust and commitment are established and the knowledge creation is sparked. In an organization, this may be the office space, meeting space, or after work events in which colleagues gather to celebrate milestones and get to know each other.

Dialoguing "ba" is the space where these mental models are externalized, i.e. converted into explicit knowledge systems through the creation of common terms, concepts, models, documents, etc. These could be physical spaces for working groups to collaborate, or virtual spaces where ideas can come together for a project or publication.

Systemizing "ba" corresponds to the mode of combination; Nonaka states that this is typically a virtual, collaborative environment where explicit knowledge can be easily shared to large groups of people and learned. In an organization, this may be an organization's intranet system, communications platform, data sharing platform or project management software.

Exercising "ba" is a space where the newly acquired explicit knowledge is converted into tacit knowledge through the mode of internalization; through things like on the job training and active participation in activities, newly acquired knowledge becomes part of the persons or organizations routine. In an organization, this may be internal meetings, team retreats or training offered to advance skills and stay compliant to changing regulatory requirements for both data protection and research integrity.

Just like the SECI model, Nonaka states that "ba" is also not limited to an individual or organizational but also exists on various levels - the "ba" of teams, the "ba" of departments, the "ba" of organizations or the "ba" of entire industries. Overall, these three layers - SECI, "ba" and knowledge assets constitute the dynamic organization knowledge creation process. The key to keeping the knowledge creation process going, Nonaka says, is to manage the three

layers effectively. An organization that can master that is a “knowledge creating company” (Nonaka, 1998; Nonaka et al., 2003).

No organization is an effective knowledge creation organization, according to Nonaka, without the right management style. Nonaka posits that the traditional top down and bottom-up management styles do not allow for the flexibility of the knowledge creation process: “In the top-down model, there is the danger of depending too much on a few top managers. In the bottom-up model, because knowledge creation depends on the patience and talent of a particular individual, knowledge creation tends to be much more time-consuming than in the top-down model” (Nonaka et al., 2003, pp. 504–505). Thus, Nonaka proposes the middle-up-down management style, which emphasizes the role of middle management in supporting organizational knowledge creation. While top management provides direction, middle managers work as knowledge producers, translating these visions into more concrete concepts, which are then passed down to low-level managers and then workers. In this way, the “ba” are created and energized and the spiral of knowledge is allowed to flow through the various levels within an organization.

One of the theoretical contributions of this project is to explore how Nonaka’s theory of knowledge creation can be applied to an alternate organizational context. This contribution is twofold:

1. The expansion of the Nonaka’s Theory of Dynamic Organizational Knowledge Creation to the interorganizational space

2. The expansion of the Nonaka's Theory of Dynamic Organizational Knowledge Creation to the rare disease non-profit case, in which organizations are decentralized and use volunteer, crowdsourced labor

3.4 Knowledge sharing at an interorganizational level

Nonaka discusses knowledge creation as occurring on multiple levels - both within close groups of people within a certain department or project and vertically throughout the various levels of the organization. Though Nonaka does acknowledge the role the external environment plays in shaping organizational knowledge creation - discussing the role that technology, customers, suppliers, competitors, etc. play in an organization's process of knowledge creation - the theory mainly focuses on fostering knowledge sharing within an organization (on the "intra-organizational" level). Nevertheless, the theory is able to transcend the boundary of any individual organization. Next, I will introduce the concept of a knowledge economy and the role of organizational networks. Later I will describe how Nonaka's theory applies to the interorganizational space.

Interorganizational knowledge sharing is becoming increasingly important in the knowledge-based economy, as organizations are facing more complex and uncertain environments, with systems and tools that require collaboration. The knowledge economy refers to an economic system in which knowledge and intellectual assets are effectively utilized for economic growth and competitiveness and social development (Machlup, 1962; Drucker, 1969; Andersson & Dahlman, 2001; Hepworth et al., 2005; Brinkley, 2006). It is characterized by the production,

distribution, and utilization of knowledge and information as key drivers of innovation, productivity, and economic development (Powell & Snellman, 2004). In the knowledge economy, organizations and individuals are increasingly reliant on knowledge-based activities such as research and development, innovation, education, and training. This economic system emphasizes the centrality of theoretical, intellectual property, human capital, and creativity as key drivers of innovation and success, and often relies on technology to facilitate the exchange of knowledge and ideas (Bel, 1973; Powell & Snellman, 2004). Related, the "new growth theory" literature in economics also stresses the importance of knowledge in economic growth (Aghion & Howitt, 1990; Romer, 1990). In the knowledge economy, knowledge is considered an asset that can be leveraged to create value for the organization. There are no physical outputs in knowledge production, and knowledge assets are inexhaustible, they grow and increase through sharing and use, and they need ongoing stimulation to avoid becoming obsolete (Passerini, 2007). Thus, the proper management of these intangible assets is critical to enable organizations to create, capture, share, and utilize knowledge to stay competitive, as well as the increased demand for "knowledge workers" to facilitate this process (Machlup, 1962). What distinguishes knowledge assets from traditional assets is that they grow in both quantity and value through utilization and application (Alavi & Leidner, 2001). A knowledge economy grows when knowledge grows, through repeated cycles of the knowledge spiral (Nonaka et al., 2003; Passerini, 2007). The lifeblood of a knowledge economy are organizational networks, which act as the actors involved in creating, sharing and growing knowledge.

The current project pushes this concept further and looks at how knowledge creation is occurring in the interorganizational space of RDNPs, and what complexities does having a heterogeneous pool of actors introduce to the theory. I will refer to this interorganizational space of organizations as an "organizational network". I will use a broad definition of a network as "a structure where a number of nodes are related to each other by specific threads" (Håkansson & Ford, 2002) and, given the lack of an agreed upon definition of an organizational network (Bergenholtz & Waldstrøm, 2011), I will be conceptualizing an organizational network quite broadly as a set of interconnected organizations. Knowledge in organizational networks flows through the network structures via its nodes (organizations) and edges (links between organizations) (Håkansson & Ford, 2002). My organizational network will include RDNPs focusing on sirolimus, regardless of whether they are partners or competitors. The connections between them will be defined as knowledge transfer channels, "channels that diffusely and imperfectly direct transfers between nodes, facilitating information spillovers" (Owen-Smith & Powell, 2004).

Networks provide the opportunity for each organization to enlarge the flows of resources, to access new ideas (Kleinknecht & Reijnen, 1992) and access knowledge which can improve an organization's innovation and performance (Marchiori & Franco, 2020). The "network" aspect underlines that the relationship (the exchange of knowledge in this case) between organizations is central: "small-scale interaction becomes translated into large-scale patterns, and that these, in turn, feed back into small groups" (Granovetter, 1973, p. 1360). By analyzing the organizational network, we see how behavior of each organization can help shape macro-

level patterns (knowledge sharing within the rare disease space), and the role that weak ties (ties not heavily invested in by the nodes) and bridges (nodes connected by a single tie) play in network dynamics (Granovetter, 1973).

3.4.1 Nonaka in The Organizational Network Space

Exploring the SECI model within organizational knowledge networks provides a valuable lens for understanding how interorganizational knowledge sharing can be enhanced through the creation of "interorganizational ba" spaces. Organizations, seen as part of a larger whole akin to departments within a single company, act as nodes connected by various channels. This perspective enables the knowledge spiral to function across organizational boundaries, highlighting the dynamic exchange of tacit and explicit knowledge facilitated by shared spaces. In support of this notion, Nonaka and Toyama (2003) emphasize that the boundaries of an organization do not confine these knowledge-sharing domains. Most organizations are not isolated “islands” (Håkansson & Snehota, 1989), as they require external services, resources or people in order to function. Hakansson & Snehota (1989) also suggest looking at the organizational-environment interface, in which there is a complex network of interdependencies between different actors. Through this interaction, knowledge and capabilities are revealed and developed in mutual dependence. In Nonaka’s terms, the context or space in which these interactions take place are “ba”. In this way, “ba” is not limited to the frame of a single organization but can and does easily transcend organizational boundaries (**See Figure 8**).

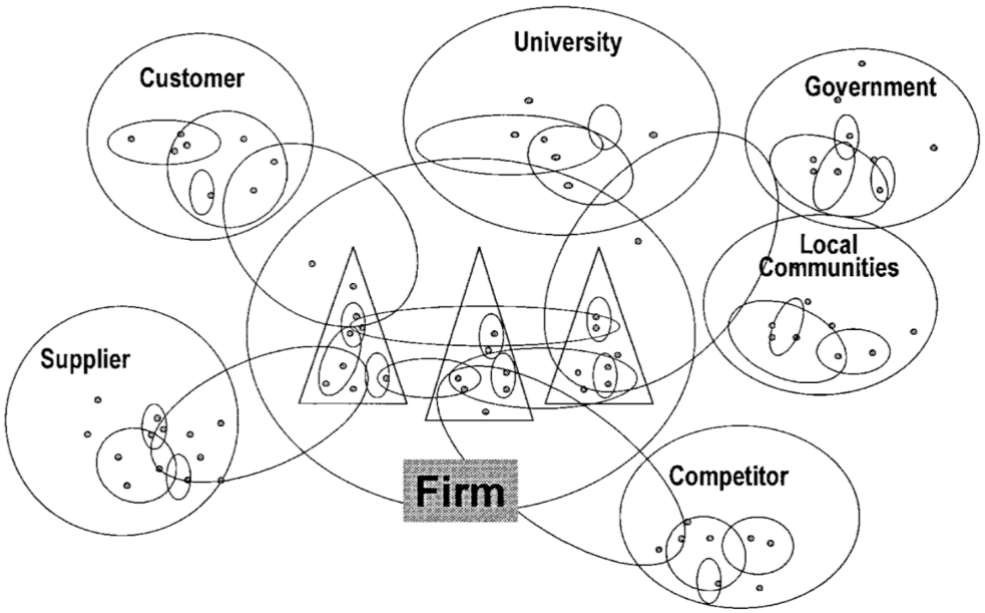


Figure 8: Nonaka & Toyama's (2003) conceptualization of an organization as an organic configuration of "ba" spaces

"Ba" spaces can be built through joint ventures with a supplier or distributor of goods, through cooperation with other organizations, through interaction with customers, and so on. Through the creation of these various levels of "ba" spaces, Nonaka & Toyama describe a network of interconnected "spaces" of various hierarchies. Some "ba" need to be built within the company because they will co-create knowledge that will give the firm a competitive advantage. Especially important for a company is a "ba" that gives the company the capability to synthesize. Knowledge creation is a dynamic human process, and managers and workers grow in such a process. Managers become leaders and grow their capability to synthesize various "ba" through their experience of participating in ba" (Nonaka & Toyama, 2003, pp. 8–9). Such initiatives can help establish a network of interconnected spaces that foster collaborative learning and innovation, much like the environments described by Swan et al. (1999). They note that effective networking practices not only build trust and reduce barriers to knowledge

exchange, but also foster a common language among stakeholders, thereby enhancing the collective capacity for innovation.

Innovation in medical fields, particularly in drug repurposing, requires a distributed approach involving collaboration between multiple sectors and actors. Ramlogan et al. (2007) emphasize that partnerships among academic institutions, healthcare providers, and industry can fuel groundbreaking medical innovations. By establishing multidisciplinary collaborations, RDNPs can enhance their knowledge bases and improve their drug repurposing efforts. These partnerships provide access to specialized knowledge and innovative ideas that can significantly broaden the scope and effectiveness of medical treatments. Mohan et al. (2007) further clarify that medical research produces "fragmented knowledge," comprising both explicit and tacit insights, and advocate for networks that promote comprehensive knowledge exchange. Their approach aligns with the findings of Wang et al. (2014) who emphasize that network diversity and strategic partnerships are crucial for fostering exploratory innovation. By connecting diverse clusters and creating an environment that encourages the flow of non-redundant information and complementary skills, RDNPs can build a more innovative and responsive ecosystem for drug repurposing.

In regard to the impact of the structure of knowledge networks on innovation, Phelps et al. (2012) illustrate from their review that the density of networks can either support or inhibit collaboration. For RDNPs, strategically balancing network density with the inclusion of bridging actors is crucial. Such actors can optimize collaborative learning and enhance innovation by

ensuring that networks are neither too sparse to inhibit connection nor too dense to stifle novel inputs.

Thus, Nonaka's "ba" concept, enriched by insights from these studies, illustrates the importance of well-structured, interconnected networks in facilitating effective knowledge sharing among RDNPs. By fostering strategic partnerships and creating spaces that transcend traditional organizational boundaries, RDNPs can significantly enhance their collaborative efforts and drive innovative solutions in the realm of drug repurposing. A question remains, though, is what factors actually drive or halt the knowledge sharing spiral across knowledge sharing networks?

3.4.2 Factors Involved in Interorganizational Knowledge Sharing

A review of interpersonal, inter-organizational and intra-organizational information sharing by Yang & Maxwell (2011) illustrated three main perspectives on information sharing: the organizational and managerial, the technological and the political and policy, and synthesized the factors within each perspective that are relevant to the public sector (see **Figure 9**). They also found that even though there are some differences between the factors that play a role in inter-organizational and intra-organizational information sharing models, most of the factors fall into similar categories (see **Figure 10**).

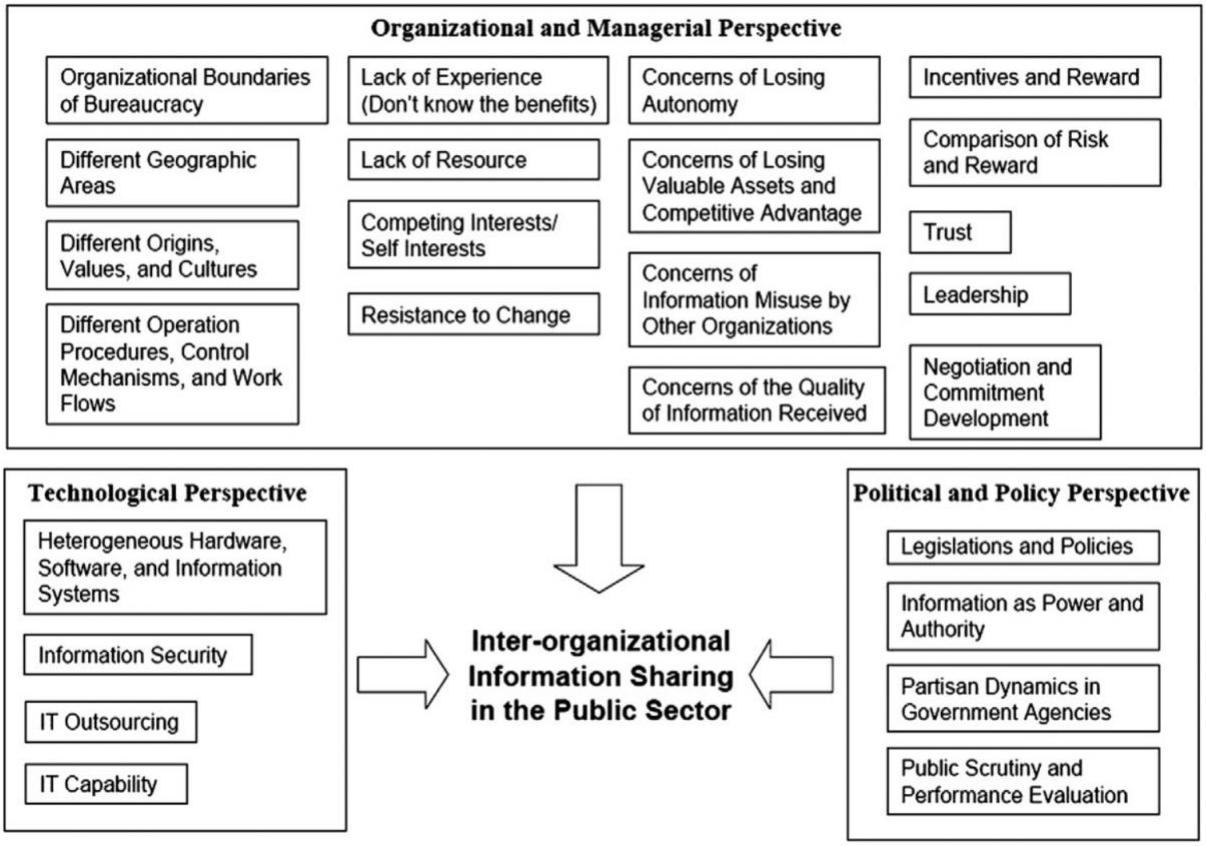


Figure 9: Factors affecting inter-organizational information sharing (Yang & Maxwell, 2011, p. 169)

These similarities help support the assumption that theories that were primarily designed for the intra-organizational context can be applied to the inter-organizational context, while the differences provide exciting avenues for exploration and theory expansion.

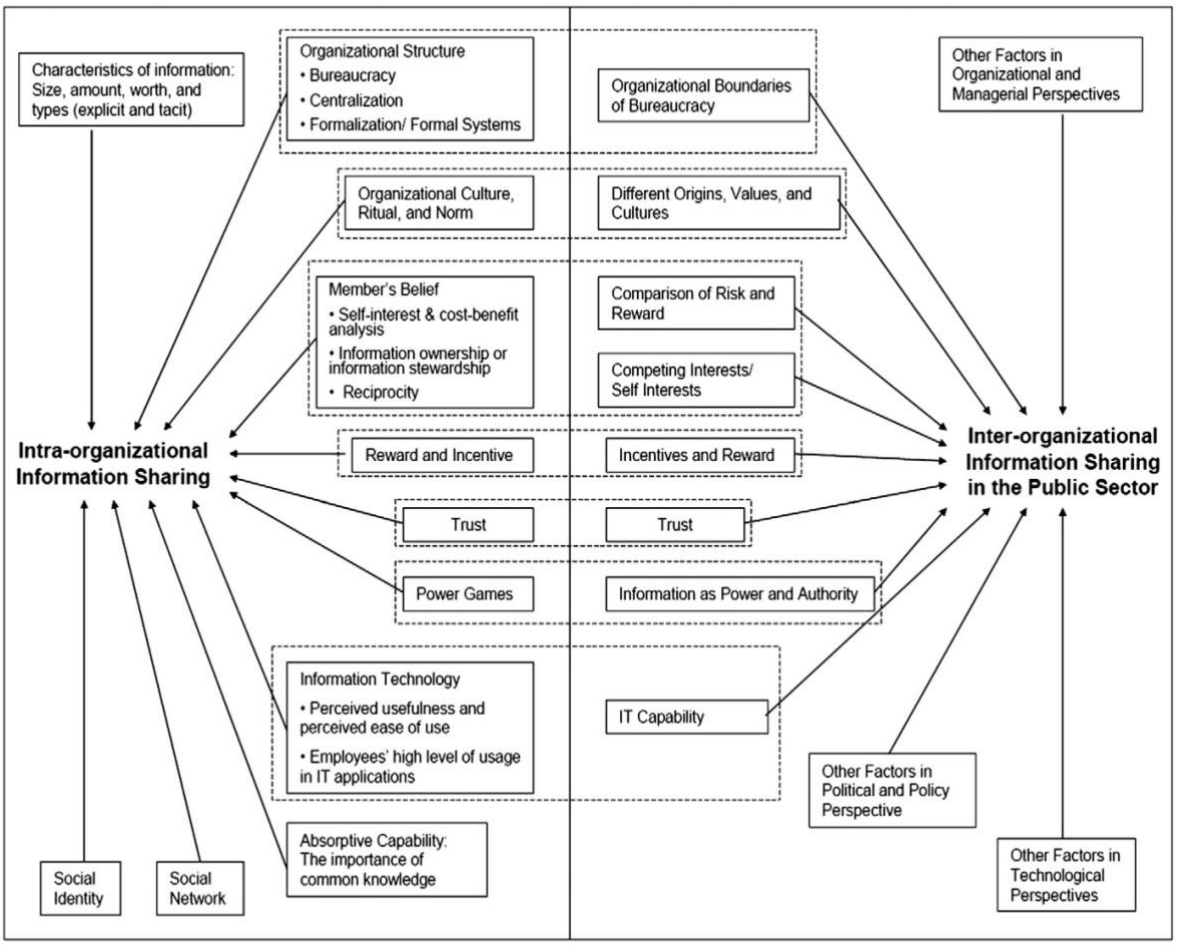


Figure 10: Intra-and inter-organizational factors for information sharing (Yang & Maxwell, 2011, p. 172)

Yang and Maxwell (2011) state that information sharing has been recognized as a key driver for enhancing organizational efficiency and performance. Though their review focuses primarily on the public sector, the same principles could be applied to the nonprofit sector. In particular, there are certain factors that play a critical role in interorganizational knowledge sharing within both contexts.

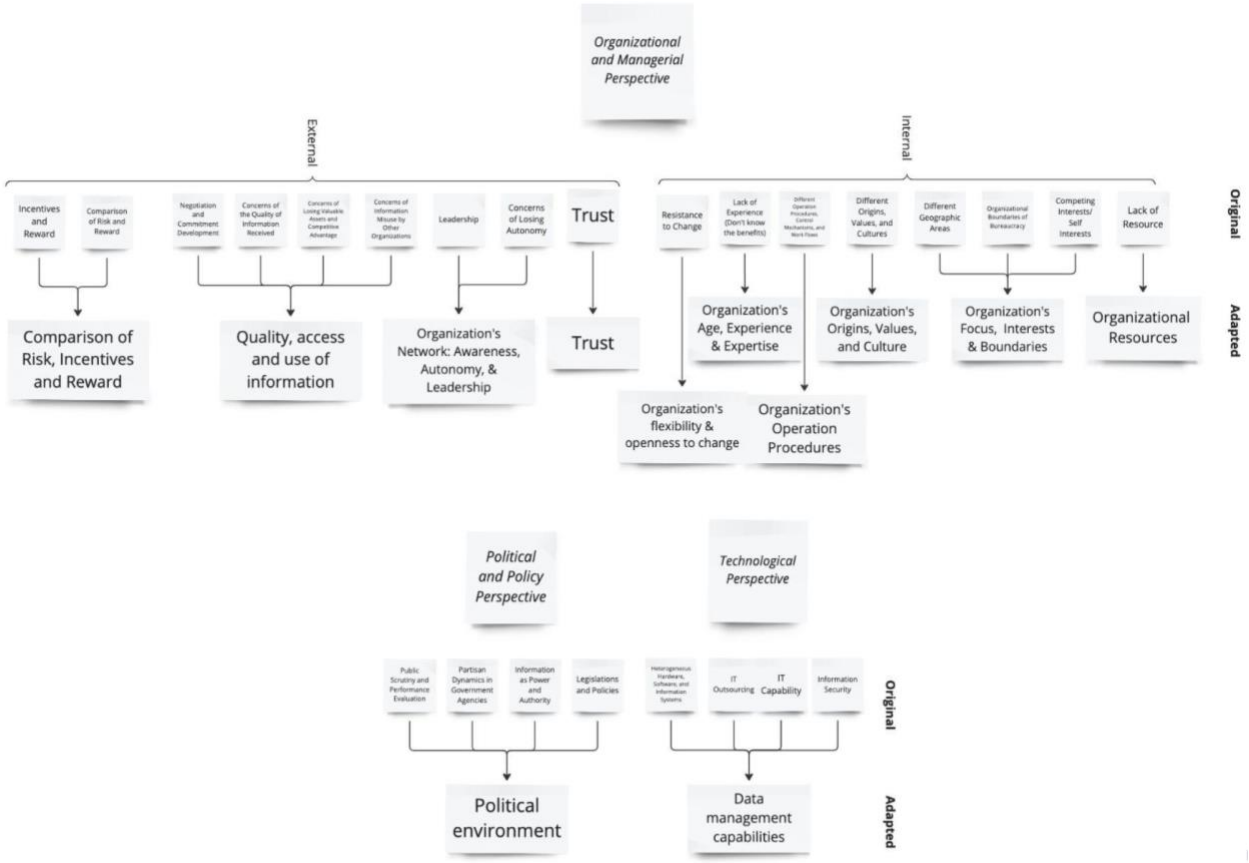


Figure 11: Illustration of the synthesis of Yang and Maxwell (2011) framework into 12 factors

By synthesizing the Yang and Maxwell (2011) framework and adapting it to the nonprofit landscape, I have developed 12 factors that can affect an organization's knowledge sharing capacity, which ultimately determine its participation in and the ultimate continuation or cessation of the knowledge sharing process. See **Figure 11** for an illustration of the synthesis process and **Table 1** for a description of each of the 12 factors.

Table 1: 12 factors adapted from the Yang and Maxwell (2011) framework

	FACTOR	DESCRIPTION
Internal	Organizational Resources	Related to an organizations' funding, staff size, or other organizational constraints, the development and/or utilization of research tools such as a NHS/NHR, biobank, etc, Also includes references to the utilization of networks of researchers, physicians, etc.
	Organization's Focus, Interests & Boundaries	Related to an organizations' rare disease of focus, mission statement (types of activities they support) and where the boundaries are (do they look at other rare diseases or other organizations within the space). Includes physical boundaries as well, such as different geographic foci.
	Organization's Origins, Values, and Culture	Related to an organizations' values (collaboration, open sharing, etc.) and cultural values
	Organization's Operation Procedures	Related to an organizations' workflows, such as the existence of specific staff or guideline documents to form external collaborations for knowledge sharing, to discussions of specific knowledge sharing events.
	Organization's Age, Experience & Expertise	Related to an organizations' age and expertise levels regarding drug repurposing
	Organization's flexibility & openness to change	Related to an organizations' stance openness to change their position as to knowledge sharing
External	Trust	Related to an organizations' trust in other organizations; seeing them as valuable partners rather than competitors/threats
	Organization's Network: Awareness, Autonomy, & Leadership	Related to an organizations' position in the rare disease organizational network; level of embeddedness, awareness of their role, desire to take a leadership role in bringing people/organizations together, and their level of independence in taking on their own mission. Includes mentions of awareness/lack thereof of the network itself.
	Quality, access and use of information	Related to an organizations' attitudes towards the quality of knowledge they receive/give, access to their knowledge and understanding/concerns as to how it will be utilized
	Comparison of Risk, Incentives and Reward	Related to an organizations' conceptualization of the value of sharing and receiving knowledge vs the risks/costs related to this (time/money/effort/etc).

	FACTOR	DESCRIPTION
	Political environment	Related to an organizations' understanding of and involvement in the political roadblocks and opportunities
	Data management capabilities	Related to an organization's capabilities to interpret information (IT capability, security, information systems, etc.); includes any technical resources or capacity issues that affect their participation in knowledge sharing events, etc.)

These factors can either facilitate or impede the knowledge sharing process, and their relationship with each other remains to be explored. Furthermore, it is essential to understand when these factors become relevant and how they influence the knowledge spiral timeline, as they can initiate, sustain, or even terminate the spiral at different stages or levels.

3.4.3 Factors Driving Interorganizational Knowledge Sharing via SECI model

One way to examine the influence of these factors is to map them to Nonaka's SECI process (Socialization, Externalization, Combination, Internalization) in an interorganizational context:

Socialization

- *Internal Organizational Resources:* Adequate resources could enable organizations to engage more effectively in face-to-face interactions, workshops, and shared spaces, facilitating tacit knowledge exchanges.
- *Trust:* Trust among organizations is foundational for sharing tacit knowledge informally, as it fosters open communication and reduces barriers to social interaction.

Externalization

- *Organization's Focus, Interests & Boundaries:* Clearly defined focus and boundaries can help organizations articulate their tacit knowledge into explicit forms that align with their core mission and activities.
- *Organization's Operation Procedures:* Established procedures and guidelines aid in formalizing tacit knowledge into explicit documentation, such as collaborative research findings or shared best practices.

Combination

- *Data Management Capabilities:* Strong capabilities in handling data allow organizations to systematically integrate and synthesize diverse explicit knowledge from various partners.
- *Quality, Access, and Use of Information:* High-quality and accessible information supports effective combination of knowledge, ensuring that explicit knowledge integrated from different sources is reliable and usable.

Internalization

- *Organization's Age, Experience & Expertise:* More experienced organizations might internalize combined knowledge more effectively, translating it into improved practices or innovative approaches.
- *Organization's Flexibility & Openness to Change:* Organizations open to change are more likely to adapt and internalize new knowledge and practices learned from interorganizational collaborations.

Other factors may contribute to either several stages, or the overall context in which the knowledge spirals are embedded in, such as:

- *Organization's Origins, Values, and Culture:* The cultural alignment regarding collaboration and knowledge sharing can significantly influence all stages of SECI by shaping how knowledge is perceived and valued across organizations.
- *Organization's Network: Awareness, Autonomy, & Leadership:* Awareness of one's position in the network and the autonomy to act within this network may facilitate all phases of SECI, enhancing the effectiveness of knowledge sharing and creation.
- *Comparison of Risk, Incentives, and Reward:* Organizations need to assess the risk and rewards associated with sharing and receiving knowledge. This can particularly impact the stages of externalization and combination, where explicit sharing and integration of knowledge occur.
- *Political Environment:* The broader political context can affect all stages of SECI by influencing the regulatory and funding environment, thereby shaping the feasibility and scope of interorganizational knowledge sharing.

By linking these factors to the SECI model, we can illustrate the complex interplay between organizational characteristics and knowledge management processes in a multi-organizational landscape. The combination of the factors derived from Yang & Maxwell (2011) and Nonaka's theory (1994) can help us understand how RDNP collaborations in drug repurposing can be optimized by addressing specific challenges and leveraging strengths in each phase of the SECI process.

In summary, understanding the factors that influence interorganizational knowledge sharing within the nonprofit context is critical for enhancing organizational efficiency and performance. It is essential to recognize that various factors play a crucial role in initiating, sustaining, or terminating the knowledge sharing spiral, and that the process itself is dynamic, with knowledge evolving over time as it is impacted by other factors.

3.5 Knowledge sharing in rare disease non-profit organizations

As mentioned prior, among the stakeholders involved in the drug repurposing process, RDNPs stand out as a potentially powerful intermediary between the patients, researchers, physicians, government agencies, and pharmaceutical companies. RDNPs also provide an interesting company type to analyze through the lens of the knowledge creation theory, as they are very different from the multinational corporations that Nonaka based his theory on, such as Honda (Nonaka, 1988). Compared to Honda's hundreds of thousands of employees, the average RDNP has 1-2 full time members of staff, and, in some cases, there are no paid employees at all[3]. It is difficult to discuss management styles where the 1-2 full time employees play the roles of both top, middle, low-level managers as well as workers at times. In order to fulfill their mission, RDNPs employ a team of volunteers and external collaborators to execute work day to day and strongly rely on their communities (patients, loved ones, physicians and researchers) to help fulfill their mission, be it fundraising, spreading disease awareness, creating a research agenda

[3] Out of the 147 organizations in the ROADMAP survey data, 52 have said they have 0 full time staff; 55 said they have 1 or 2.

or executing research studies. In terms of theory, we can say this is a difference between a centralized, hierarchical organizational structure and a decentralized, alternative organizational structure.

While for profit organizations such as the multinational corporations Nonaka focused on are accountable to their shareholders in regard to their innovation activities and knowledge asset production, non-profit organizations are accountable to their board and community members. As their community members are also a part of their unofficial workforce, helping to fulfill their mission as discussed above, it becomes a collaborative organizational structure. In the medical RDNP setting, this can be described as the patient-centered model (Korsunska, 2021). Within the RDNP setting, the rare disease patients are not only the center of the organization's mission and unofficial members of staff (in charge of fundraising, awareness, education, outreach, support, etc.) but also a source of data for RDNPs that focus on research. Patient data collected through natural history registries or natural history studies becomes an invaluable resource to identify trends in the rare disease of interest and flag off label drugs which may be helping patients in order to pick them up for drug repurposing research. Additionally, some RDNPs, such as the Castleman Disease Collaborative Network, actively survey their patient and loved one populations (as well as researchers and physicians) to generate research ideas to then prioritize and fund as a part of their international research agenda (Korsunska, 2021). In this way, the "crowd", in this case a RDNPs community, becomes an integral part of both creating knowledge and furthering the mission of the organization. In Nonaka's model, there is no space

for members of the general public to participate in the knowledge creation process of an organization, except perhaps as consumers of the products.

The idea of understanding knowledge sharing efforts and developing solutions to combat inefficiencies has been pursued in other industries. A notable example is the efforts to share and reuse knowledge generated during construction projects (Tan et al., 2007, 2009). Due to concerns over the level of knowledge sharing in the construction industry, knowledge transfer frameworks have been developed which encourage organizations to transfer knowledge between projects more efficiently (Carrillo et al., 2006). In construction, projects are undermined by the loss of important insights and knowledge due to the delay in capturing knowledge, contractor staff turnover, and reluctance of workers to share knowledge. To address this, Tan et al (2007) propose for knowledge to be captured "live" in a collaborative environment while the project is still being executed and presented in a format that will facilitate its reuse. Their research uses a case study approach to investigate the worker's requirements for the live capture system, as well as the shortcomings of current knowledge sharing practices.

In summary, in order for knowledge creation and transformation to occur, many factors need to come together, namely three: a desire to share knowledge, a platform or space ("ba") where knowledge sharing takes place and the successful creation of knowledge assets. Due to the vast, disconnected network of RDNPs and their limited resources, it is likely that there are inefficiencies in the knowledge sharing process regarding drug repurposing, and, without any

formal guidance on how to do drug repurposing from any government organization or regulatory body, this may be one of the reasons that RDNPs have not been able to overwhelmingly take the lead on driving drug repurposing initiatives as of yet.

CHAPTER 4: RESEARCH DESIGN

4.1 Methodology Overview

This dissertation aims to explain the knowledge-sharing practices and challenges inherent within Rare Disease Nonprofit Organizations (RDNPs), particularly in the context of drug repurposing of the same drug (sirolimus). This inquiry is based on the premise that optimizing these practices could significantly enhance the efficiency in this vital process. Central to this exploration are three themes:

(1) Identifying the Participants: Who is engaged in the knowledge sharing, and what are the dynamics of their interactions?

(2) Nature of Knowledge Exchange: What types of information or knowledge are being shared, and through what channels or stakeholders does this exchange occur?

(3) Locating Inefficiencies: Where are the barriers in this knowledge-sharing process, and what factors contribute to these inefficiencies?

Given the multifaceted nature of these research questions, I utilized a multimethod approach:

1. **Case Studies**: In-depth examination of specific stories of repurposing, with a special focus on collaborations and knowledge sharing practices (see Chapter 6).

2. **Network Analysis:** Visualizing and analyzing the structure and dynamics of the knowledge-sharing networks or lack thereof (see Chapter 7).
3. **Interviews:** Conducting interviews with RDNPs to gain their insider perspectives on the process, barriers and attitudes related to drug repurposing (see Chapter 8).

In this context, the dissertation will focus on answering the following research questions:

RQ1: How is sirolimus being repurposed in the context of Rare Disease Nonprofit Organizations (RDNPs), and what are the characteristics of this process from their perspective?

This research question focuses on:

- Identifying and characterizing RDNPs Involved in sirolimus repurposing: Which RDNPs are actively engaged in repurposing sirolimus or had been involved in repurposing sirolimus previously, and what are their defining attributes and motivations?
- Examining the stages of their repurposing journey: At what stages in the drug repurposing process are these RDNPs currently? What are their planned next steps?
- Understanding the extent of their engagement: What is the role of RDNPs in the repurposing process?

Method:

The initial list of RDNPs focused on sirolimus, as well as some basic characteristics about them, will be sourced from the ROADMAP project data (**see section 4.2**). Then, the majority of the analysis for this research question will be through case studies based on interview data**,** which will provide an in-depth examination of specific instances of sirolimus repurposing. Focusing on

the detailed narratives of select RDNPs, the case studies will uncover the unique characteristics, strategies, and challenges specific to each organization's approach to repurposing sirolimus.

RQ2: Who are the key participants involved in the repurposing of sirolimus within the Rare Disease Nonprofit Organizations (RDNPs) network, and what influences their collaboration and interaction dynamics in this process?

This research question focuses on:

- Identifying key participants: Who are the primary researchers and other RDNPs involved in sirolimus repurposing? What roles do these entities play, and what drives their involvement in this process?
- Analyzing their collaboration: How do these participants collaborate and interact during the repurposing process? What are the mechanisms and channels of their interaction?
- Assessing external influences and support: To what extent is the repurposing process conducted independently by RDNPs, and how much is influenced or supported by external forces such as other RDNPs, external resources, or broader networks?

Method:

The data on who is involved in the collaboration networks will be elicited through interviews, as well as the nature of their involvement. Then, network analysis will be utilized visualizing and analyzing the patterns of collaboration and interaction within the RDNP network. It will reveal how different entities are connected and the structure of the relationships that facilitate the repurposing process, identifying key nodes and gaining a more holistic understanding of the ecosystem dynamics.

RQ3: What are the prevailing barriers in the sirolimus repurposing process, and how can these obstacles be addressed to enhance efficacy and outcomes?

This research question focuses on:

- Identifying and analyzing barriers: What specific challenges and hurdles are RDNPs facing in the repurposing of sirolimus? This includes both internal organizational obstacles and external environmental factors.
- Evaluating efficacy: Assess the current practices in sirolimus repurposing – what aspects are functioning effectively, and which are not? This involves a critical examination of the methods and strategies employed.
- Proposing solutions: Based on the identified barriers and inefficiencies, what potential strategies or interventions could be implemented to optimize the repurposing process? This seeks to provide actionable recommendations for enhancing overall effectiveness.

Method:

Conducting interviews with individuals in RDNPs will provide direct insights into the barriers encountered during the repurposing process. Interviewees can offer perspectives on inefficiencies and suggest potential improvements, providing a rich source of qualitative data for thematic analysis.

Table 2 below summarizes how each method provided data to answer each research question. I will next cover each method in detail.

Table 2 Research Questions and Methods

Research Question	Primary Method	Primary Data	Analysis	Additional Method/Data	Method Strengths	Method Limitations
RQ1: How is sirolimus being repurposed in the context of Rare Disease Nonprofit Organizations (RDNPs), and what are the characteristics of this process from their perspective?	Case Study	Interview Transcripts	Narrative and Comparative Analysis	ROADMAP survey data (Utilized for interviewee selection and general RDNP characteristics)	Narrative analysis provides deep insights into individual experiences and perceptions, capturing the nuanced characteristics of the process. Comparative analysis allows the identification of common patterns and differences across various organizations.	Narrative analysis can be highly subjective, as it relies on personal accounts and experiences. This might lead to biases and a lack of generalizability. Comparing narratives can be challenging due to their qualitative nature and the unique context of each story. The choice of cases to compare can introduce bias, as cases may be selected that are not fully representative of the broader population of RDNPs.
RQ2: Who are the key participants involved in the repurposing of sirolimus within the Rare Disease Nonprofit Organizations (RDNPs) network, and what influences their collaboration and interaction dynamics in this process?	Network Analysis	Network Node and Edge lists	Network Statistics Analysis and Visual Network Interpretation	Interview Transcripts	Network data enables visual and statistical analysis of the RDNP's knowledge sharing network and the identification of network overlap between different RDNP networks, a variety of different stakeholder types	Gathering network data through interviews allows for interviewee memory error and bias. Network analysis shows only a high level of interaction; does not capture detail on the context and knowledge sharing practices within each interaction. The data gathered will not allow for dynamic relationship analysis over time.

Research Question	Primary Method	Primary Data	Analysis	Additional Method/Data	Method Strengths	Method Limitations
					(researchers, physicians, etc) and the identification of important nodes.	
RQ3: What are the prevailing barriers in the sirolimus repurposing process, and how can these obstacles be addressed to enhance efficacy and outcomes?	Interviews	Interview Transcripts	Qualitative Thematic Transcript Analysis	ROADMAP data (Utilized for interviewee selection and general RDNP characteristics)	Thematic analysis enables the identification of common themes and patterns across different interviews, which is valuable for understanding prevalent barriers and potential solutions. It allows for a nuanced understanding of the issues.	The research is constrained by the limited number of organizations that can be interviewed. The research is subject to biases from interviewees, who may provide responses based on personal perspectives that might not align with broader trends or issues. The process of thematic analysis of these interviews is inherently subjective, influenced by the researcher's perspectives.

4.2 ROADMAP Project: Research Design Overview

In my role at the CDCN, I was project lead of the ROADMAP project, completed in February 2023, with the final deliverable being a data-driven “roadmap” of how RDNPs can more efficiently pursue drug repurposing projects by leveraging their aggregated lived experiences.

The ROADMAP project was the first and largest project known to date that set itself the goal to identify the paths that can be taken to repurpose drugs for any rare disease, highlight the roles of various stakeholders, and centralize information on how to do this most effectively through an interactive tool (*ROADMAP*, 2023). In order to understand the most effective paths for rare disease drug repurposing, we first obtained data on the paths taken by rare disease stakeholders and the roadblocks they are facing. We achieved this through a 6-phase process, leading up to the final tool launch (**Figure 12**).

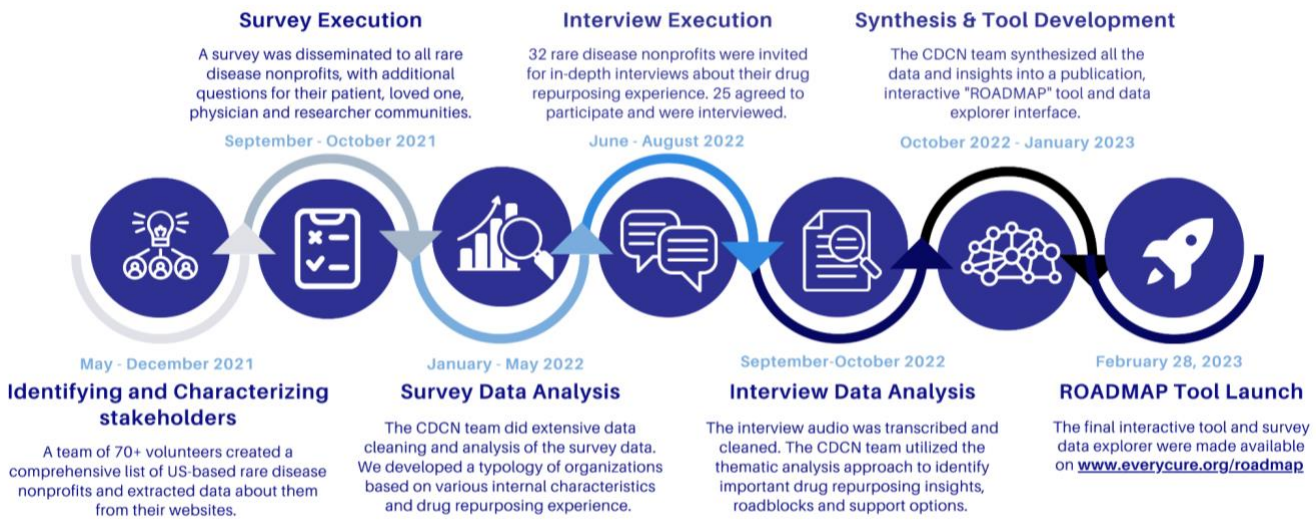


Figure 12: Six-phase project plan for ROADMAP project execution

Identifying and Characterizing Stakeholders

The ROADMAP project team initiated the research by aggregating lists of US-based RDNPs from various existing databases and conducted supplementary searches to ensure comprehensiveness. Over a seven-month period, a dedicated team of more than 70 volunteers analyzed these organizations' websites. This effort aimed to gather a wide range of information,

including each organization's founding year, founders' details, and available resources such as conferences, research agendas, biobanks, and registries. Additionally, the team sought information on drug repurposing initiatives, including specific drugs targeted and any noted collaborations or partnerships, to paint a full picture of each RDNP's scope and engagement in repurposing efforts. As a result, 711 rare disease nonprofit organizations were identified in the US.

Survey Execution

We designed a comprehensive survey using the Qualtrics platform, which included sections for several different stakeholder types: (1) rare disease nonprofit organization leaders, (2) rare disease patients, (3) rare disease patients' loved one (parent, spouse, friend, sibling, etc. of a rare disease patient), (4) physicians who treat rare diseases, (5) rare disease researchers. Any member of the leadership team of a US-based rare disease-focused nonprofit organization was able to participate in this research project. They were then invited to directly reach out to their US-based patient, loved one, physician, and researcher network and invite them to take the survey. Since rare diseases predominantly affect children, we allowed participants under 18 to participate in the project through an adult loved one who provided informed consent and took the survey. Additionally, since many rare diseases cause physical and cognitive disabilities, we allowed those patients to also participate in the survey through a loved one, regardless of the patient's age. Also, we included an option for patients and loved ones to participate in Spanish, in order to be as inclusive as possible. We focused our questions on potentially unique insights from each stakeholder. For rare disease nonprofit organization leaders: organizational

characteristics (age, funding, staff size, etc.), level of resources (biobank, patient registry, natural history study, scientific advisory board, etc.), the rare disease state of research (availability of treatment guidelines, diagnostic criteria, ICD code, biomarkers, etc.), information on any FDA or off-label drugs being utilized, and drug repurposing experience, including challenges they've encountered, the support they need, and who was in their collaboration network. We conducted 10 preliminary semi-structured interviews with a selection of rare disease nonprofits, in order to receive feedback to refine the survey and project communication materials. We distributed the survey to all US-based rare disease organizations for which we could gather contact information. The survey was launched on September 29, 2021 and remained open for data collection until January 6, 2022.

Data Cleaning and Analysis

The project team undertook a thorough data cleaning process, primarily utilizing R studio. We meticulously removed entries that did not meet specific inclusion criteria, such as non-compliance with 501c3 status, lack of support for a rare disease, or incomplete survey responses. We also resolved any contradictions and inconsistencies between entries that we identified. In total, 1,324 entries (out of an original 1,929) were removed due to not meeting inclusion criteria or removed as a result of deduplication, leaving 605 entries that qualified to remain in the final dataset.

We reviewed and cleaned all manually-inputted job titles, specialties, organization names, disease names, and drug names. Two participants who met our inclusion criteria completed the

Spanish-language version of the survey. To ensure that their data would be represented in our analysis, we translated their survey responses into English. In cases where translations of participant-entered text were required, two Spanish speakers (one native speaker, and one non-native speaker) reviewed each translation for accuracy. For the purposes of analysis and visualization, we created new variables that were used to classify existing data. Such as creating new categories for existing questions based on responses provided in the "other" sections, classifying drug repurposing stages, status, and progress, etc. Additionally, some response categories were renamed, merged, and/or removed based on team expertise and consensus.

We made changes, corrections, and updates to our data on an ongoing, case-by-case basis. For example, in the rare case when a drug status change was identified among our list of 147 rare disease nonprofits since (e.g., a new drug being targeted for repurposing; a drug receiving FDA approval), we updated all survey question data corresponding to that drug. Except for these major changes, we did not make updates based on any other status updates that were discovered throughout the research and interview process, and the dataset provides a snapshot of the state of drug repurposing as of survey date completion and some of the data may be or soon will be outdated.

We performed descriptive statistics analysis to report basic quantitative statistical data about the ROADMAP survey. Examples include frequencies, measures of central tendency, and correlations. The overarching goal of this descriptive analysis has been to characterize the rare disease nonprofits who participated in the ROADMAP survey (their characteristics, resources,

etc.). We formulated specific questions about our data. While our general interest was to assess the relationship between organizational characteristics, drug identification methods, and stage(s) of progress, specific research questions included (but were not limited to): How many organizations had how many drugs in what stages currently? How each drug was identified and what stage is it in currently? How/Whether each organization's characteristics are related to the drug identification method used? How/Whether the drug identification method is related to the various types of "success" endpoints? To answer these questions, we developed cross-tabulations of our data, which involved breaking the data into subgroups in order to look for patterns, trends, or other noteworthy observations. We did not perform any kind of inferential or predictive statistics using our data; we focused on reporting raw frequencies, proportions, and percentages, and we used these numbers to help describe, characterize, and summarize our drug repurposing data, as well as answer the specific research questions outlined above.

Another important outcome of the ROADMAP project was a comprehensive understanding of all the "menu" items in the drug repurposing process, namely all the steps involved and all the options that a researcher can pursue or a representative of a rare disease nonprofit can support. This categorization was done through an ongoing manual, collaborative visualization exercise. Additionally, we built a network dataset, which allowed us to gain a better understanding of the types of relationships going on between different rare disease nonprofit organizations, as well as their external links to research institutions, pharmaceutical companies and government organizations.

Interview Execution

From the pool of surveyed RDNPs, the team selected 32 organizations for in-depth interviews, based on a variety of characteristics and their experiences with drug repurposing. 25 consented to participate. These interviews, conducted via ZOOM, look into each organization's repurposing journey, uncovering the steps taken, challenges faced, and the strategies that led to success or failure. This phase not only provided a qualitative depth to the research but also captured a wide array of experiences across the repurposing spectrum, from early exploration to achieving treatment milestones. Even though 25 organizations were interviewed, we were able to capture the experiences of repurposing 75 drugs since many organizations had experience with several different drugs.

Synthesis and Tool Development

Integrating the insights from both the survey and interviews, the ROADMAP project team developed an interactive tool and data explorer interface. Hosted on GitHub Pages and built using Jekyll for ease of use and accessibility, this tool serves as a comprehensive resource for navigating the complexities of drug repurposing within the rare disease sector. It offers stakeholders a detailed guide through the repurposing process, informed by real-world experiences and data-driven insights, thereby enhancing the collective effort to find new treatments for rare diseases. It is available open source at www.everycure.org/roadmap.

4.3 Insider Research Approach

Throughout my dissertation research, I was closely associated with the Castleman Disease Collaborative Network (CDCN), first as a volunteer in summer 2020 and then employed as the biomedical leadership fellow from February 2021 to March 2022. My embeddedness in the rare disease community gave me an incredible opportunity of gaining important contextual knowledge of the inner workings of rare disease nonprofit organizations and the drug repurposing process in rare diseases. In ethnographic work, specifically in discussions of 'backyard ethnography', it has been discussed that "both too much familiarity and too little familiarity can be blinding" (Treitler, 2016, p. 93). Too much familiarity with both the subjects and the subject matter presents opportunities for bias and overlooking some findings due to them being too obvious or familiar within the context. On the other hand, if there is no or too little prior knowledge, i.e. "no cognitive hooks on which to hang new knowledge", then the researcher is unable to understand and contextualize important aspects of their findings (Treitler, 2016, p. 102). In some conceptualizations, the level of "insiderness" is seen on a spectrum, where the researcher could be a partial insider or a partial outsider, depending on the distance or detachment from the community (Chavez, 2008).

Although this project is not an ethnography, many factors align with ethnographic work in this aspect, such as the level of embeddedness and access to both resources and insider knowledge; this undoubtedly has led to a deeper understanding of the project subject matter, enabling me to be better prepared for the current analysis compared to an outsider to the space. In order to

minimize the possibility of bias and take advantage of my level of access and insights, I utilized several approaches:

- **Avoid assumptions and overfamiliarity:** All interviews were treated with the same level of rigor and followed the same outline, reiterating things even if they seemed obvious and have been discussed before. Furthermore, by reiterating what was already known or had been previously discussed in a new context actually opened up the opportunity to revisit assumptions for both interviewer and interviewee on what we discussed prior, and the reasons behind these shared assumptions, as well as provide updates to previous conversations.
- **Emphasize the value of various opinions:** Both in my email communications and during the interview, I reiterated that we are looking to hear from different organizations, with different perspectives and approaches, and that no insight can be deemed as "not valuable". I also encouraged participants to disagree with or clarify anything I articulated back to them (e.g. So what I'm hearing you say is this. Am I understanding correctly? "
- **Providing options on a spectrum rather than dichotomies:** Being an insider provided me the opportunity to contextualize my questions in the RDNPs' experience. Instead of asking them if they thought knowledge sharing was valuable, I instead focused them on the spectrum of which knowledge sharing is more valuable, when is it more valuable to them on a timeline of the drug repurposing journey, or with whom do they deem it most valuable. This provided the opportunity for organizations to prioritize certain collaborations over others without necessarily explicitly needing to state that certain actors or types of interactions were deemed not worth their time.

- **Clarification:** Oftentimes I became aware of certain assumptions I could make based on prior knowledge of the organization and their drug repurposing experience. Also, because I had spoken to many of these organizations previously, we had already had a shared understanding of what I knew and what was discussed prior. I utilized this to clarify certain points and question certain assumptions during the interviews. Many times - I was surprised by the answers and my assumptions were challenged.
- **Triangulating findings:** In the process of the interviews, as certain themes emerged I consciously started to not only start to articulate them to the interviewees as they emerged, but also mention these preliminary findings in subsequent interviews to others in order to continue to test assumptions and gain additional insights. To avoid prompting the interviewee to agree with whatever I offered up as a preliminary finding, open to discussion and contradiction.
- **Data-driven decisions:** I made decisions during the data cleaning and analysis based on the data, rather than my level of familiarity with certain organizations, both CDCN and the others that I have worked with and interacted with over time. For example, CDCN is too much of an outlier case to be included as a case study for this project. Being lead by a founder who is also a patient, researcher, physician all in one is a rare and unique case, which enabled CDCN to avoid many of the roadblocks usually faced by RDNPs - such as how to find researchers filling to take on a rare disease for research and conducted analyses on their patient data, or how to identify other experts in the field and connect with them. So even though it would have been an easy choice for selection, I instead chose organizations that better captured the more typical experiences and

struggles of RDNPs in space, enabling me to apply the theory and factors driving decision-making without having to make exceptions for extraordinary confounding factors.

This balanced approach between insider knowledge and methodological rigor allowed me to navigate the potential biases inherent in researching a field where I am deeply embedded, ensuring the validity and reliability of my findings. The embeddedness was able to provide me with scaffolding in order to be able to ask the right questions and understand the incentives and constraints with which the RDNP landscape.

4.4 Justification of method selection

Interview data served as the primary source of data for thematic analysis, case studies and network analysis in this dissertation. Conducting interviews about the knowledge sharing practices of these actors and inquiring about these hidden processes is the best choice of method for several reasons, both practical and philosophical. In a practical sense, since knowledge sharing in regard to drug repurposing can happen over years or even decades, and between organizations and partners which are geographically dispersed throughout the US or even internationally, it is not something that can be directly observed or measured by other methods. Some of the processes I am interested in are inherently hidden (tacit knowledge, lack of collaboration, etc.) there is no way to observe them directly or find them through analyzing published literature or other content. Many of these organizations are so early in their repurposing journey, there is no “paper trail” at all to follow, and if there was - a vital part

would be missing - their experiences of the process, the reasons for engaging in or avoiding certain projects or collaborations. Due to the nature of experiential (tacit) knowledge, the only way to bring it to the surface is through externalization, in this case through semi-structured interviews.

Interviews also support my philosophy that the engagement of participants is not only just a part of the approach to gathering data, but the essence of the methodology, based in the co-creation of knowledge. This dovetails perfectly with the insider research approach discussed earlier, as when we take a co-creation of knowledge approach, we allow both the participant and researcher to play a role in creating knowledge. In this way, the deeper connection between researcher and subject is a benefit that allows a conversation to take place in which knowledge is produced. Kvale and Brinkmann (2008) describe this distinction with a metaphor: a researcher could be a "miner" or they could be a "traveler." The "miner" "finds" information and does their best to not "contaminate", whereas a traveler accepts the role they play in shaping knowledge. These two metaphors represent two approaches of knowledge, whether it is seen as something that is given (the miner) or constructed (the traveler)" (Kvale & Brinkmann, 2008, pp. 58–59). The "miner" typically view their participants as either data points in themselves, having possession of data that can be extracted or creating content that becomes data. With these approaches, there is traditionally little room for participant co-creation of knowledge, as the participants are only involved in the research in a limited capacity, often do not see the finished product, and sometimes are not even aware that their data become data points from which researchers draw conclusions about their subject of study.

The “traveler” conception is nearer to the traditions from anthropology, in which the researcher is not a cold, objective observer, but a co-participant in the process. Kvale & Brinkmann (2008) argue that interviews “attempt to understand the world from the subjects’ points of view, to unfold the meaning of their experiences, to uncover their lived world prior to scientific explanations” (p.10). Thus, interviews were the most suited method for data collection for this dissertation due to their ability to create a space of co-creation of knowledge and surfacing tacit, experiential knowledge to the surface.

Case Studies

The utilization of case study analysis in this dissertation enables a nuanced exploration of the organizational adaptation and innovation over time, providing rich insights into the complex interplay between stakeholders, their strategic decisions, challenges and successes encountered, providing a grounded perspective that quantitative methods alone might overlook. Furthermore, leveraging case studies facilitates the generation of insights into the tacit dimensions of knowledge management and innovation, resonating with the principles outlined by Nonaka and colleagues in their Organizational Knowledge Creation Theory, which emphasizes the social interaction and context-specific dynamics critical for knowledge creation and innovation (Nonaka, 1994) This theoretical lens underscores the importance of narratives and stories in understanding how knowledge is shared, created, and utilized within organizations, an aspect that case studies can richly capture and convey. By selecting cases that represent various stages of the drug repurposing process, this dissertation is able to contribute valuable insights into the strategies that drive successful drug repurposing efforts, the barriers

that impede progress, and the potential pathways to overcoming these challenges. Therefore, case study analysis emerges as a highly appropriate and powerful method for exploring the multifaceted nature of drug repurposing by RDNPs, offering both depth and breadth in understanding the critical factors that influence innovation in the rare disease domain.

Network analysis

Network analysis allows us to map and examine the patterns of interaction between various RDNPs and their stakeholders. Through this lens, we gain insights into how knowledge flows within and between these entities, identifying both central and peripheral participants in the network. Network analysis is a natural choice of method for the study of knowledge sharing as knowledge sharing is a process that happens in between two or more actors with some sort of relationship in an environment. Since social networks have been shown to be important to "increase an organization's effectiveness, efficiency and opportunities for innovation" (Cross & Parker, 2004, p. 8), by looking at RDNPs in a network structure, we can gain insights into how effective it is at drawing on the expertise of its network partners, and their partners. We can also gain an understanding of the collaborations an organization is or can be facilitating, and uncover the importance of certain connections by looking at their locations within the network. In the case of this project, the environment of focus is the rare disease non-profit organizations' network space. In this space there are various actors: other rare disease non-profit organizations, pharmaceutical companies, government institutions, biotech companies, universities, hospitals, patients, physicians, researchers, etc. Through interviews with the RDNP leadership team members I will gather rich, qualitative data on the RDNP's knowledge sharing

behavior, I will utilize network analysis to identify who else is within their network and this will help guide subsequent interviews.

This is similar to Howard's (2002) 'network ethnography' approach, in which he describes utilizing network analysis to help justify case selection and complement qualitative interview data with contextual network data. Another related reason for the selection of network analysis as a method for this research is that, as mentioned prior, the primary role of RDNPs in drug repurposing is their roles as a network creator and facilitator. The networks they are able to create and leverage with their patients, researchers, physicians and external contacts (members of the pharmaceutical industry, government agencies, biotech, etc.) ensure that these actors engage with their mission and push forward processes such as drug repurposing initiatives for their rare disease(s). They can do this in many ways: engage the patient population in donating medical records, tissue or blood samples for research, coordinate the storage, shipment, access and analysis of these samples, enroll in clinical trials, etc., engage the network of researchers and physicians to conduct the research and help facilitate clinical trials, and facilitate collaboration with a set of external actors, namely the pharmaceutical company who owns the patent rights to the drug (and if the drug is off patent - generic manufacturers, etc.) and any regulatory bodies involved as to data requirements for approval.

Furthermore, network analysis provides a quantitative and qualitative framework for evaluating the efficiency and effectiveness of knowledge sharing practices. By identifying key actors and understanding their roles and connections, we can uncover bottlenecks and opportunities for

enhancing knowledge dissemination. This approach aligns with the theoretical foundations laid out in Nonaka's Theory of Dynamic Organizational Knowledge Creation, specifically in terms of understanding how knowledge is transformed and circulated within the network. Network analysis enables the identification of patterns that can either facilitate or hinder effective knowledge exchange, providing a basis for suggesting ways of optimizing the collaborative efforts of RDNPs in the drug repurposing landscape.

Thematic Analysis

Thematic analysis is employed in this dissertation to uncover patterns and themes within the qualitative data collected from all RDNPs in the sample. This method involves a systematic process of coding and categorizing data to identify key themes related to knowledge-sharing practices. Thematic analysis is particularly well-suited for this research as it provides a deep, context-rich understanding of the experiences and perspectives of RDNPs. This depth is essential for capturing the complexity of their interactions, motivations, and challenges in the context of drug repurposing efforts.

By focusing on narrative data rather than quantitative summaries of theme counts, thematic analysis allows for the exploration of nuanced insights that might be overlooked by quantitative methods. This approach helps to reveal the underlying reasons and motivations behind specific practices and decisions, offering a comprehensive view of the factors influencing knowledge sharing. The rich, detailed insights generated through thematic analysis are crucial for

developing effective and targeted knowledge-sharing strategies, ultimately enhancing collaboration and efficiency among RDNPs in the rare disease nonprofit sector.

4.5 Data Collection: Overview

The ROADMAP project provided vast information about RDNPs and their repurposing projects. By analyzing data from the ROADMAP, I identified 16 RDNPs as having potentially pursued sirolimus drug repurposing or its off-label use **(see Table 3)**. The core sample consisted of 8 RDNPs, all of which I have previously interviewed and validated their involvement with sirolimus drug repurposing as a part of the ROADMAP project:

1. Castleman Disease Collaborative Network (CDCN)
2. Cure HHT
3. Hannah's Hope Fund
4. LAM Foundation
5. Lymphangiomatosis & Gorham's Disease Alliance (LGDA)
6. Pachyonychia Congenita Project (PC Project)
7. Smith-Kingsmore Syndrome Foundation (SKS Foundation)
8. RUNX1 Research Program

Additionally, four other RDNPs have identified sirolimus to be promising for their rare disease (it is being utilized off label for their patient populations), but did not state that they are actively pursuing a repurposing project as a part of the ROADMAP project survey:

1. CLOVES Syndrome Community
2. MEPAN Foundation
3. PTEN Hamartoma Tumor Syndrome Foundation
4. Myositis Support and Understanding Association

Four additional RDNPs were identified from the crowdsourced dataset, which also suggested sirolimus or related mTOR inhibitors for drug repurposing or off label use, namely:

1. Klippel-Trenaunay Support Group
2. The FAVA Foundation
3. Progeria Research Foundation
4. Project 8p

Combining the three lists, then, I anticipate the full population size of RDNPs which have supported or are currently supporting sirolimus drug repurposing efforts or at least its off-label use, to the best of my knowledge, is 16 (See **Table 3**).

Table 3: RDNPs repurposing sirolimus

	Category	RDNP	Rare Disease(s)	Data Source	Invited for interview	Outcome
1	PRIMARY: Actively repurposing	Lymphangiomatosis & Gorham's Disease Alliance (LGDA)	Complex Lymphatic Anomalies	ROADMAP Survey	yes	Interview completed November 29, 2022
2		Pachyonychia Congenita Project (PC Project)	Pachyonychia congenita	ROADMAP Survey	yes	Interview completed December 6th
3		Castleman Disease Collaborative Network (CDCN)	Castleman disease	ROADMAP Survey	yes	Interview completed November 28, 2022

	Category	RDNP	Rare Disease(s)	Data Source	Invited for interview	Outcome
4		Cure HHT	Hereditary hemorrhagic telangiectasia	ROADMAP Survey	yes	Interview completed November 15, 2022
5		Smith-Kingsmore Syndrome Foundation (SKS Foundation)	Smith-Kingsmore syndrome	ROADMAP Survey	yes	Interview completed November 16, 2022
6		RUNX1 Research Program	RUNX1 mutations	ROADMAP Survey	yes	Interview completed December 1, 2022
7		Hannah's Hope Fund	Giant axonal neuropathy	ROADMAP Survey	yes	No response
8		LAM Foundation	Lymphangioleio myomatosis	ROADMAP Survey	yes	Interview completed Nov 30, 2022
9	SECONDARY: Identified as promising	CLOVES Syndrome Community	CLOVES syndrome	ROADMAP Survey	yes	Unable to schedule
10		MEPAN Foundation	MEPAN syndrome	ROADMAP Survey	yes	Declined
11		PTEN Hamartoma Tumor Syndrome Foundation	PTEN hamartoma tumor syndrome	ROADMAP Survey	yes	No response
12		Myositis Support and Understanding Association (MSU)	Idiopathic inflammatory myopathies	ROADMAP Survey	yes	Interview completed November 27, 2022
13	TERTIARY: Potentially Promising	Klippel-Trenaunay Support Group		RDNP website	yes	Declined
14		Project FAVA		RDNP website	yes	Interview completed Nov 22, 2022
15		Progeria Research Foundation		RDNP website	yes	No response
16		Project 8p		RDNP website	yes	Use other mTOR inhibitors, not sirolimus

As I already had obtained their contact information from the ROADMAP project, all 16 RDNPs were invited to participate directly via email. 3 RDNPs declined to be interviewed. 3 RDNPs did not respond, and I sent follow up requests twice in two-week intervals before labeling them as

unresponsive. 10 RDNPs consented to participate in the study: 7 out of 8 (87.5%) from my primary sample, 2 out of 4 (50%) from my secondary sample, and 1 out of 4 (25%) from my tertiary sample, overall giving me a response rate of 62.5%. Because of time zone issues, CLOVES Syndrome Community was not able to schedule an interview, bringing the total of RDNP interviews conducted to 9. Additionally, through the interview I identified a researcher who seemed to play a pivotal role in the repurposing projects for several organizations (Denise Adams), so I conducted one additional contextual interview.

In the period between November 15, 2022, until January 12, 2023, I conducted nine 60-minute semi-structured interviews with leaders of these RDNPs, and one 45 minute contextual interview with the researcher noted prior. The interviews were scheduled through Calendly software and conducted remotely through ZOOM. Consent documents were provided ahead of time to the participants and time was given in each interview prior to starting the recording in which I was able to answer any questions or address any concerns the interviewees had about the project or their participation. I recorded the interviews utilizing the ZOOM once I had verbal consent from the interviewees. The interview materials and consent form are available for review in **Appendix C**.

The interview protocol for the RDNPs consists of three sections: (1) knowledge assets, (2) organizational network characteristics and (3) knowledge sharing. The knowledge assets section asked the RDNP to walk me through their process of repurposing Sirolimus as well as their attitude towards the value of their experience; in Nonaka's terms, this would be a question of

whether they are aware of or value their tacit, “experiential” knowledge assets. This was important to establish as a baseline because the awareness of an existing knowledge asset will affect subsequent knowledge sharing behavior (or lack thereof), since if you do not think you have anything of value to share, you will not engage in knowledge sharing and thus the knowledge spiral will come to a standstill. I also asked general questions about their level of awareness of other RDNPs repurposing Sirolimus as well as their awareness of how common sirolimus repurposing is in general. Important to now, I had already spoken to many of these organizations about their experience with drug repurposing drugs from the ROADMAP interview process.In the organizational network characteristics section, the focus was their collaboration network. The questions focused on their level of interest and ability of collaborating with other RDNPs in general, what are incentives and roadblocks to collaborating, as well as what kind of RDNPs they think are of most value to them as collaborators (e.g. RDNPs focused on the same/similar rare diseases, RDNPs of the same/similar age/funding as them, RDNPs which are more experienced, etc.).

Finally, in the knowledge sharing section, we focused on sirolimus drug repurposing specifically, listing all the actors which they collaborated with, what their value is and what the drawbacks are. Though many of the actors they listed were not RDNPs, but researchers, that was also of great value as one way RDNPs may be connected indirectly is through the same researchers or through the same institutions. So, by listing everyone that was vital in their sirolimus drug repurposing process, I was able to capture both direct RDNP-RDNP collaboration as well as potentially build “weak tie” connections through other institutions. When direct RDNP-RDNP

collaboration was mentioned, we explored in detail how these connections came about, what kind of value they brought to both sides of the collaboration and discussed any difficulties that arose from the various types of knowledge sharing that were brought up. The interviews concluded with a general discussion of what the interviewees felt that needed to be done to accelerate the process of greater RDNP-RDNP knowledge sharing and whether they think there is value in connecting with other RDNPs that are repurposing sirolimus on a larger scale than they already had. Through these questions I was able to identify any issues in knowledge sharing processes, either existing issues affecting ongoing collaborations or roadblocks for new collaborations to be created in the future. I elicited ideas as to what is causing these issues or roadblocks, and asked the interviewees if they have any ideas of what kind of solutions they would like to see implemented which could help solve some of these issues. For the full interview protocol, please see **Appendix D**. The audio of the interviews was utilized for transcription and analysis. I utilized a tool called Dovetail to preliminary clean the transcripts, then I completed a manual review of each one to ensure data quality. The data generated from the interviews helped inform both the case study, thematic analysis and network analysis.

4.6 Data Analysis Overview

Transcript data analysis: Thematic Analysis and Case Study Data

For the analysis of the interview transcript data, I conducted a thematic analysis using the online software “Dovetail”. This platform facilitated the transcription, tagging, and categorization of themes. Through this process, an initial list of 51 preliminary themes was generated. The iterative nature of the thematic analysis involved a process of synthesis, where

themes were combined or divided as required to best represent the data. This approach adhered to the principles outlined by Braun & Clarke (2006), emphasizing the flexibility and recursive nature of identifying patterns within qualitative data. Subsequently, the themes were refined further. A second coding pass was undertaken to ensure comprehensive coverage of the data, bringing to light additional themes previously overlooked or those that did not align with the initial set. The Yang and Maxwell (2011) framework provided a structured approach to organize the themes into a coherent and meaningful analysis. The final distillation of the data resulted in 20 themes across 10 categories that encapsulate the rich diversity of the data collected (see **Chapter 8, Table 5**).

For the case study analysis, the transcripts were utilized to map the RDNPs across a continuum of early, mid, to late-stage in their drug repurposing journey. This timeline-based selection strategy allowed for a diverse representation of RDNPs at different stages in their repurposing efforts, ensuring a breadth of experiences and perspectives were considered. This combination of iterative thematic analysis and case study selection underpins the robust qualitative methodology employed in this research, seeking to provide a rich, multidimensional understanding of the RDNPs' experiences in drug repurposing efforts.

Network data analysis

To conduct the analysis of the networks of RDNPs, I extracted the names and relationships of each stakeholder mentioned in the interview transcripts into a spreadsheet. This extraction process focused on identifying direct mentions of collaboration and affiliations, resulting in a

preliminary list of nodes (actors) and edges (relationships). The extracted data formed the basis of a bipartite network dataset, which included two types of nodes: individuals and organizations. Additional searches were conducted for each mentioned external actor to capture "weak" ties and affiliations, such as researchers to institutions or physicians to medical institutions. This helped in identifying indirect relationships and expanded the network dataset. Next, each node was categorized based on the actor type, such as RDNP, researcher/physician, pharma/biotech, etc. This classification allowed for a more nuanced analysis of the network structure. With the comprehensive data collected, two key lists were prepared: a node list detailing the attributes of each actor and an edge list outlining the connections between nodes. This process was done for both the original network (direct mentions in transcripts) and the enhanced network (including weak ties and affiliations of all actors involved). This resulted in two networks and two sets of node and edge lists.

Gephi, a network visualization and analysis software, was chosen for its capabilities in handling complex network data. The node and edge lists were imported into Gephi for visualization and analysis. Initial visualizations were generated to get an overview of the network's structure. Different layout algorithms were applied to find the most insightful representation of the network. Various network metrics, including degree centrality, path analysis, and density, were calculated to assess the network's connectivity, identify key actors, and understand the overall network structure. Additionally, modularity algorithms were used to detect communities within the network, highlighting groups of nodes that are more densely connected to each other than to the rest of the network. The results were interpreted in the context of the specific network,

looking for patterns, central nodes, and isolated clusters. This iterative process involved refining the data and applying different analytical approaches to deepen the understanding of the network dynamics.

CHAPTER 5: THE STATE OF RDNP DRUG REPURPOSING

This dissertation incorporates findings from a related research project I completed, called the ROADMAP. Although not directly within the scope of this study, the ROADMAP project offers critical background information and data that are instrumental in informing decision-making processes throughout this research. The ROADMAP involved a survey, interviews and network analysis, and I briefly discuss the methods and findings as they are relevant to this dissertation. The inclusion of these findings is intended to provide a comprehensive understanding of the complexities involved in knowledge sharing among RDNPs in the context of drug repurposing.

5.1 State of rare disease nonprofits in the US

From our crowdsourcing initiative, 711 rare disease nonprofit organizations were identified in the US and basic information was extracted from organizations' websites. Interestingly, 56% of these organizations were founded between 2011-2021. 430 (60.5%) organizations focus on a single rare disease and its subtypes, while 264 focus on multiple rare diseases (some organizations were very broad, focusing on either all rare diseases or both rare and common diseases). 416 (41.9%) of the organizations were started by loved ones of patients (parents,

spouses, siblings, etc.) and 206 (20.8%) were started by the patients themselves. Utilizing the organization's websites, our team of extractors identified how many stated that they utilize certain resources that may be important for an organization to be able to successfully support research projects in the future, such as: 423 (59.5%) organizations had a scientific advisory board, 335 (47%) had a formalized research agenda, 291 (41%) had a natural history study or registry, 234 (33%) mentioned formalized treatment guidelines for their rare disease of focus, and 142 (20%) had a biobank. Interestingly for this project, drug repurposing initiatives, off-label use or treatment guidelines that included repurposed drugs were found on 135 (19%) organizations' websites.

5.2 ROADMAP Survey insights

In total, we received 1,923 total survey responses (completes and incompletes), which, after data cleaning and deduplication, included 723 total respondents (605 unique): 147 organization representatives, 340 patients, 170 loved ones, 23 physicians, and 43 researchers. Based on our search for rare disease nonprofit organizations, there are 711 active rare disease nonprofit organizations in the US. This means that we gathered data from approximately 20.7% of the total sample, which is notable. Though there is an obvious selection bias to organizations who are interested or pursuing drug repurposing to take our survey, review of the characteristics of these organizations suggests that we captured a variety of organizations.

Drug Repurposing: General Findings

Among the 147 organizations surveyed, 127 support research. 58 organizations are currently pursuing drug repurposing projects and another 58 are not yet, but are interested in doing so. Out of the 58 which are pursuing drug repurposing, only 40 organizations provided a specific drug of focus. This may indicate that the remaining 18 organizations are in preliminary stages and have not yet identified a specific drug yet. From the drug point of view, there were 94 (76 unique) drugs which are in the process of being repurposed by 40 organizations. Out of these 40 that already have one or more drugs for repurposing, 14 have met at least one endpoint. There is a wide range in terms of what organizations selected as their success endpoint goal: "Drug to provide significant reduction in symptoms" (48 selected this endpoint - 17 reported that is has been met), "Drug to provide significant improvement in quality of life" (48 selected - 11 met), and "Drug to be freely available to patients off-label with safety / efficacy data" (47 selected - 2 met). While 5 drugs have made it to FDA approval, only 40 (43%) of drug repurposing projects in our data even set FDA approval as their success endpoint goal. Thus, getting an FDA approval for the drug to be used in a new disease area is often less of a goal of interest than demonstrating it is effective and helping patients, which can be accomplished without an FDA approval (as long as it is approved for another disease and widely available).

In our dataset, 36 drugs have reached an outcome (FDA approval / off-label use / unsuccessful) of interest. Only 5 drugs have so far made it to FDA approval for their new rare disease indication but 18 are being used off-label and having some sort of positive effect on the patients despite not having official FDA approval. 13 drugs were reported to have been

abandoned. Most drugs (58) are still in process, and have not yet achieved any of the defined endpoint categories.

Note: due to some overlap between the stage and the outcome categories, the number of drugs in the stages does not add up exactly to the ones marked as in progress in the outcome

Pursuit of multiple projects

Among the 58 organizations which reported to be currently pursuing or have pursued drug repurposing projects in the past, 19 organizations have pursued multiple drugs for repurposing, with an average of 3.84 projects per organization (range of 2 - 7); most organizations only pursued two projects at a time, likely due to the financial limitations of supporting multiple complex projects.

Off-label data use tracking

“Off-label drug use” refers to when a drug is prescribed for a disease that it is not specifically approved for. Out of the 58 organizations that are pursuing drug repurposing projects (or have in the past), only 17 systematically track off-label drug use in their patient population. This is important to highlight since tracking off-label drug use is an important way to assess whether a repurposed drug is effective. Data on off-label drug use can also be used as a way to identify a drug for potential further repurposing research. In fact, data analysis of off-label drug use was the third most reported method for identifying a repurposed drug, helping 14 organizations to identify 25 drugs as promising for their rare diseases. Though the majority do not track off-label

drug use at this time, 66% stated that they are interested in tracking this information in the future.

Identifying a promising drug for repurposing

The most common method for identifying promising drug repurposing opportunities was preclinical/translational research (66 drugs). This category can also be described as pathogenesis targeting, whereby the researcher identifies a potential problem underlying a disease (e.g., mTOR activation is increased in Castleman disease) and then matching a drug to reverse the problem (e.g., using an mTOR inhibitor to treat Castleman disease), which is then studied further in the laboratory. The other top choices were looking at drugs used in similar diseases (29), off-label use data analysis (25), high throughput drug screening (HTDS) (21) and literature review/meta-analysis (16). The least common option was machine learning/artificial intelligence approaches (2), which may speak to the novelty of this approach and its slow integration into the existing research/repurposing processes or that it is mostly being utilized without the involvement of rare disease nonprofit organizations. It is also important to mention that more than one identification method was employed to identify 57 drugs. The most common combinations of methods were: 1) HTDS and Preclinical/Translational research (11 cases); and 2) looking at drugs used in similar diseases and Preclinical/Translational (9 cases). It is also interesting to point out that 11 drugs were identified as promising by multiple organizations using different drug identification methods. This speaks to the value of pursuing multiple avenues at once and triangulating the findings from one method with another.

Success outcome: FDA Approval

Out of our 94 (76 unique) drugs, only 5 have made it to FDA approval:

1. Dupilumab // Eosinophilic diseases
2. Selumetinib // Neurofibromatosis
3. Alpelisib // CLOVES syndrome
4. Rituximab // Pemphigus, Pemphigoid
5. Sirolimus // Lymphangioleiomyomatosis

Looking closer at the 5 organizations which have had a repurposed drug make it to FDA approval, they are on average 25.8 years old (range: 11 - 44); their annual funding ranged from $100,000 to more than $5,000,000 (the most common selection was "$1,000,000 and $2,000,000"); and they have the following characteristics: all 5 have an SAB/MAB, 3 have a natural history study, 3 have a formal research agenda, 3 already have an FDA approved drug prior to pursuing drug repurposing, 2 have a patient registry, and 1 has a biobank. One of these organizations has no full-time staff, relying entirely on volunteer or part-time staff to achieve their success, while the other four have anywhere from 1 to 40 full-time staff. The amount of time that passed between initial FDA approval and repurposing approval ranged greatly, from 3 up to 21 years. Also worth mentioning that Selumetinib was a case of drug repositioning, as it was being explored as a potential drug for several indications, but was not pursued all the way to FDA approval; instead, it was identified as promising for an alternative use and received its first FDA approval for Neurofibromatosis. It is important to note that there are very many factors that affect whether a drug can ever get FDA approval that do not depend on its safety,

efficacy and are beyond the control of a researcher or a rare disease nonprofit organization supporting a drug repurposing project. Notably the most important of these is whether the pharmaceutical company who developed the drug is interested in investing the time and money into supporting the FDA approval application for a new disease when it is already approved for another disease. Furthermore, FDA approval for the new disease is not always necessary in order to have a drug be able to reach patients in need (the primary purpose). Thus, we consider FDA approval to be one of many metrics of success.

Success outcome: Off-label use with some subjective measure of benefit

As an alternative success outcome to FDA approval, we can consider off-label, with some subjective measure of benefit, such as being freely available to patients off label with safety / efficacy data, providing significant reduction in symptoms, improvement in quality of life, increase life expectancy / decrease in mortality, provide cure of disease, provide prevention of relapse. If we look at organizations that fit this criteria for at least one drug, we end up with 12 organizations. They are on average 17.6 years old (range: 2 - 44); the majority (4 organizations, 33.33%) reported annual funding between $100,000 and $500,000; and they have the following characteristics: 11 (91.67%) have an SAB, 6 (50%) have a natural history study, 7 (58.33%) have a formal research agenda, 6 (50%) have a patient registry, 5 (41.67%) have a biobank, and 3 (25%) already have an FDA-approved drug prior to pursuing drug repurposing (one organization has two FDA-approved drugs). Interestingly, 6 (50%) have no full-time staff, relying entirely on volunteer and/or part-time labor to achieve their success.

Among these 12 organizations, there are 44 unique drugs being repurposed. The most common drugs among these organizations were Sirolimus (3 organizations), Trametinib, Everolimus, and Bevacizumab (2 organizations each). The most common identification method for these drugs was Preclinical/Translational research (30), closely followed by data from similar diseases (17) and off-label use (17). Most of these drugs are currently in early stages or clinical trials, specifically in recruiting patients for clinical trials (18). Their respective rare diseases have the following characteristics: 11 (91.67%) have animal models, 8 (66.67%) have cell lines developed, 9 (75%) have an identified genetic mutation, 8 (66.67%) have an ICD code, 7 (58.33%) have treatment guidelines, 5 (41.67%) have a clear understanding of etiology or disease pathogenesis, and 3 (25%) have predictive biomarkers.

Sirolimus

Another outcome of the ROADMAP project was the unexpected identification of sirolimus (Rapamyacin) as the most common drug for rare disease drug repurposing **(see Appendix F, Figure 1 and Table 1)**. In the ROADMAP survey, sirolimus was listed by 8 RDNPs as being actively repurposed. An additional 4 RDNPs listed sirolimus as a drug which is promising but not FDA-approved for their rare disease, but did not say they are actively pursuing repurposing. Through analysis of the crowdsourced data, an additional 4 RDNPs were found to have mentioned sirolimus as being potentially promising for repurposing. Thus, there were a total of **16 RDNPs** across all of the ROADMAP data. During the ROADMAP project research, I interviewed 9 of these organizations:

1. Cure HHT: Conducting a Phase II trial of sirolimus for moderate or severe epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT) patients.
2. Lymphangiomatosis & Gorham's Disease Alliance (LGDA): Using sirolimus off-label for complex lymphatic anomalies (CLAs).
3. RUNX1 Research Program: Developing a clinical trial for sirolimus in RUNX1 familial platelet disorder.
4. Pachyonychia Congenita Project: Partnering with Palvella Therapeutics for a Phase III trial of QTORIN™, a topical sirolimus, for Pachyonychia Congenita (PC).
5. Castleman Disease Collaborative Network: Using sirolimus off-label for idiopathic multicentric Castleman disease (iMCD) and unicentric Castleman disease (UCD), with ongoing Phase II trials.
6. Smith-Kingsmore Syndrome Foundation: Using sirolimus off-label for intractable seizures in patients with Smith-Kingsmore syndrome (SKS).
7. Myositis Support and Understanding Association: Conducting a Phase 3 trial for sirolimus in inclusion body myositis (IBM), with some patients using it off-label.
8. Project FAVA: Using sirolimus off-label for fibro-adipose vascular anomaly (FAVA), with ongoing studies for potential full FDA approval.
9. LAM Foundation: FDA-approved sirolimus for Lymphangioleiomyomatosis (LAM) in 2015.

5.3 ROADMAP data implications for knowledge sharing

As illustrated by this data as well as mentioned prior as to well-known success stories, there have been notable examples of RDNPs that have been successful in supporting drug repurposing projects. Despite these successes, a major challenge remains: the lack of knowledge on how to best navigate the process of drug repurposing, including overcoming various types of hurdles such as regulatory, legal, fundraising, etc. This information is not centralized or widely available to share between the stakeholders, and no resources exist to help them navigate the drug repurposing process.

Are RDNPs engaged in or interested in knowledge sharing?

In the ROADMAP survey, the participant RDNP representatives were asked to list the top 5 organizations with whom they collaborate. Then, they were asked to select what kind of activities the RDNPs taking the survey engage in with these collaborator organizations. When aggregated for all selected organizations, the top choice of activity was “Sharing prior experiences that can inform future decision making” (n=274). See **Figure 13** below.

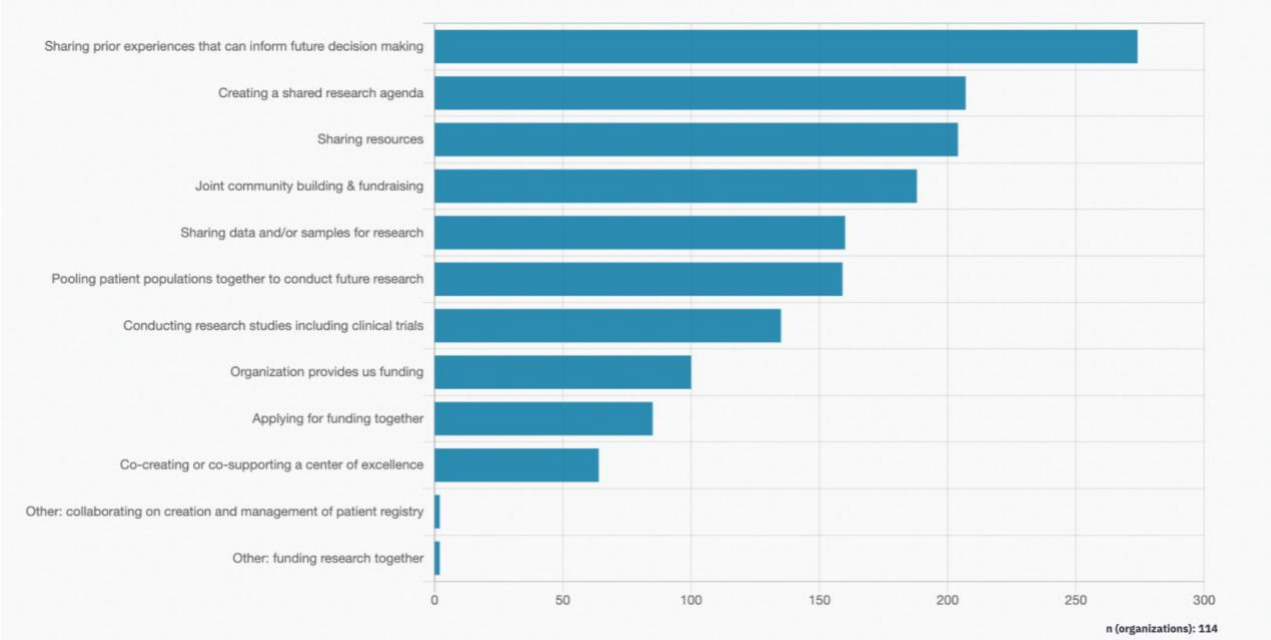


Figure 13: ROADMAP survey results to the question "What kinds of activities do you engage in with these organizations [top 5 collaborator organizations entered in a previous question]?" (ROADMAP Project, 2022)

*Note: this question merges data from 1-5 collaborator organizations, listed per ROADMAP participating organization. These numbers vary by how many organizations answered each question and how many collaborators they listed

From this it is evident, that at least among closely collaborating organizations, knowledge sharing is the main activities RDNPs engage in, along with sharing resources, creating a shared research agenda and joint community building.

Is there a widespread understanding of the steps involved in drug repurposing?

In the ROADMAP survey participant RDNPs were asked if they have been involved in a drug repurposing project in the past, and for those that marked "no", they were then asked the reasons for why not. Out of 147 organizations who have taken the survey, 78 have said they have not been involved in drug repurposing, and 35 (45%) of them listed the "lack of understanding of the steps for successful drug repurposing" as their reason for non-pursuit. It is

the second top selected choice, right after the inevitable “lack of financial resources''. Also notably, 5 organizations stated that they have never heard of drug repurposing before.

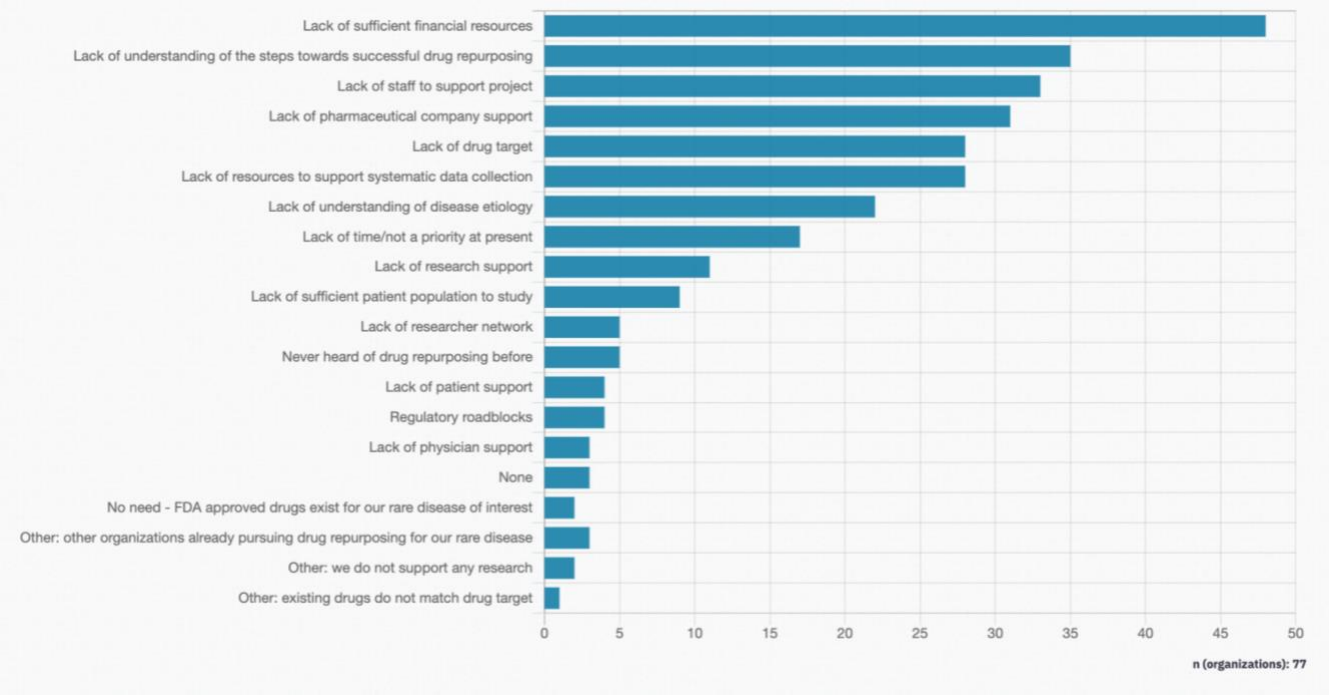


Figure 14: Preliminary ROADMAP survey results to the question “What are some reasons for why your organization has not supported drug repurposing?” (ROADMAP Project, 2022)

Thus, we can see with this data that this gap in understanding is one of the top reasons for why RDNPs chose to not support drug repurposing, often leaving this fast and affordable option of getting treatments for their patient populations aside. Together, these two findings from the ROADMAP survey data support the assumption that despite best efforts, knowledge sharing in the rare disease space is inefficient, in the way that it is not being aggregated into a useful format to help guide future decision making.

5.4 Limitations

Though the ROADMAP project met and surpassed the planned project goals, there are several notable limitations. First, with such an extensive survey and with as many important research questions as we were pursuing, it would have been helpful to include the data analysts who performed the analyses early in the process of survey design. Second, while the team aimed to collect as much data as possible, some respondents may have been overwhelmed by the survey's length and complexity, potentially leading to inaccurate or incomplete data. Doing iterative testing of the survey with respondents before its full launch to determine the optimal length could have been beneficial. Third, conducting a separate survey for different stakeholders to reduce survey-taking time and stakeholder overlap would have ensured that each stakeholder group's unique needs and perspectives were adequately captured without overwhelming respondents. Fourth, the results may not be representative beyond the surveyed population. For example, the ROADMAP project focused only on US-based RDNPs, which may limit the generalizability of the findings to other countries. We also did not include pharmaceutical or biotech company representative perspectives in our dataset, so it is not clear how their repurposing processes are different or similar from our conceptualization. Similarly, we were not able to interview representatives of the FDA or any other regulatory bodies to get more detailed perspectives on how rare disease organizations can best support an FDA approval process. Finally, we completed data collection in October 2021 and our dataset provides a snapshot of the state of drug repurposing at that time. Since drug repurposing efforts are ongoing, the data in the survey could be continuously updated, perhaps every 3-5

years, in order to continue to provide an accurate assessment of the state of rare disease drug repurposing as well as the major obstacles that hinder progress.

CHAPTER 6: CASE STUDIES

This chapter utilizes case study analysis to explore the organizational adaptation and innovation of Rare Disease Nonprofit Organizations (RDNPs) involved in drug repurposing. By examining detailed case studies, we gain rich insights into the complex interplay between stakeholders, strategic decisions, and the challenges and successes encountered over time.

6.1 Introduction

In this chapter, I present a detailed analysis of three RDNPs engaged in the repurposing of sirolimus for their respective rare diseases. The focus of this analysis will be to utilize three case studies to answer **RQ1:** How is sirolimus being repurposed in the context of Rare Disease Nonprofit Organizations (RDNPs), and what are the characteristics of this process from their perspective? The chosen case studies represent different stages in the drug repurposing journey: early, middle, and late stages, offering a temporal perspective on the evolutionary dynamics of organizational innovation and adaptation within the RDNP landscape. The case studies chosen reflect a spectrum of activity and challenges in the sirolimus repurposing process. For the early stage, we look at the Smith-Kingsmore Syndrome Foundation (SKS Foundation), focusing on off-label use for treating intractable seizures. The middle stage is

represented by the Pachyonychia Congenita Project (PC Project), actively involved in a Phase III clinical trial for a topical sirolimus formulation. Lastly, the late-stage organization is the LAM Foundation, which has successfully navigated the FDA approval process for sirolimus in treating Lymphangioleiomyomatosis (LAM). Each case study will begin with a historical background and an overview of the RDNP's journey with sirolimus, from discovery to current status. We will then explore various aspects of each organization's experience, supported by direct quotes from interview transcripts. The discussion will utilize and expand upon Nonaka's theory of knowledge creation and a discussion of each organization's approach to knowledge sharing and challenges encountered.

6.2 Methods

As described in **Chapter 4.4**, by analyzing data from the ROADMAP project, I identified 16 RDNPs as having potentially pursued sirolimus drug repurposing or its off-label use. The core sample consisted of 8 RDNPs, all of which I have previously interviewed and validated their involvement with sirolimus drug repurposing as a part of the ROADMAP project; four other RDNPs listed sirolimus to be promising for their rare disease (it is being utilized off label for their patient populations), but did not state that they are actively pursuing a repurposing project; four additional RDNPs were identified from the ROADMAP crowdsourced dataset, which also suggested sirolimus or related mTOR inhibitors for drug repurposing or off label use. I interviewed 9 of the 16 RDNPs for this project. In order to trace the dynamics of organizational adaptation and innovation on a temporal parameter, I selected three case

studies to explore further in depth, each exemplifying an early-stage, middle-stage, and late-stage repurposing organization.

Stages of Drug Repurposing

This analysis is strengthened by the strategic selection of case studies that represent different stages of repurposing efforts, providing a comprehensive view of the evolutionary dynamics of RDNP adaptation and innovation over time. First, I will define the stages and which organizations from the entire interview sample fall into which category (see **Figure 15)**.

Figure 15: RDNPs repurposing sirolimus on a timeline or early, mid or late stage in the repurposing process

Early Stage

These organizations are in the early stages of repurposing sirolimus for their respective rare diseases. They are currently exploring the potential of sirolimus, either using it off-label or considering its application for clinical trials. Their efforts are focused on gathering preliminary data, building infrastructure, and raising awareness.

- Smith-Kingsmore Syndrome Foundation (SKS Foundation): Engaged in using sirolimus off-label.. The focus is on collaboration, infrastructure building, and raising awareness rather than actively pushing for clinical trials.
- Project FAVA: Sirolimus is currently being used off-label. Attention has shifted towards other treatments targeting the PIC3CA mutation, which seem more promising.
- RUNX1 Research Program: In the preclinical stage, identifying sirolimus as promising and currently developing a clinical trial.
- Myositis Support and Understanding Association (MSU): Prior clinical trials did not meet primary endpoint, but still had some promising signs. A phase 3 trial in Australia is currently ongoing, but it is still considered an experimental drug and is not integrated into treatment guidelines.

Mid Stage

Organizations in the mid-stage are actively engaged in clinical trials or have completed some form of preliminary study with some positive early signs, whether or not they are pursuing FDA approval or not. This stage illustrates a commitment to pursuing research for further drug repurposing beyond off-label use recommendation.

- Pachyonychia Congenita Project (PC Project): Conducting a Phase III clinical trial with FDA Orphan Drug and Fast Track designation for a topical sirolimus formulation through a partnership with Palvella Therapeutics.
- Cure HHT: Sirolimus is undergoing a Phase II clinical trial specifically for HHT patients at the University of Toronto.

- Castleman Disease Collaborative Network (CDCN): Sirolimus is being used off-label for patients with iMCD and UCD, and is currently being studied in a Phase II clinical trial at the University of Pennsylvania.

Late Stage

Late-stage organizations have made significant progress in the repurposing of sirolimus. This includes organizations that have successfully completed clinical trials, and/or received FDA approvals. Their efforts are now focused on expanding access, understanding long-term effects, and exploring further therapeutic indications of sirolimus within their patient subpopulations.

- LAM Foundation: Sirolimus was FDA approved for LAM in 2015, after several years of facilitating the collaboration of the scientific community, industry, pharma and government.
- Lymphangiomatosis & Gorham's Disease Alliance (LGDA): A large phase II trial recently concluded, reaffirming sirolimus's efficacy and acceptable side-effect profile. However, the pathway to FDA approval appears stalled, leaving sirolimus to be used off-label as the primary treatment method.

For the in-depth case study analysis, I have chosen one organization in each of the three stages. These three organizations were chosen not only because they represent the three different stages of the drug repurposing process, but also based on their collaborative approach, active interest in sirolimus, and representativeness of other organizations in the sample. Though all 9 RDNPs could provide interesting case studies, the vascular anomaly-focused RDNPs in the

sample (e.g. Project FAVA, LGDA) are currently more focusing on an alternative drug repurposing target and are not actively pursuing sirolimus, while others are too much of an outlier to focus on them as a case study within the scope of this research (e.g. CDCN). For a more detailed overview of all 9 RDNPs that were interviewed, please see **Appendix E**. All 9 RDNPs are included in the thematic analysis in **Chapter 8**.

The three case studies selected for this research are:

Early Stage - Smith-Kingsmore Syndrome Foundation (SKS Foundation)

The SKS Foundation is in the early stage of drug repurposing, focusing on using sirolimus off-label for treating intractable seizures in patients with Smith-Kingsmore syndrome (SKS). Their efforts are primarily centered on building infrastructure, raising awareness, and expanding their patient registry. The foundation's current status reflects a stage of exploration and initial adaptation, where the primary focus is on leveraging existing treatments and resources efficiently without actively seeking new drug repurposing opportunities or clinical trials due to various internal and external limitations.

Mid Stage - Pachyonychia Congenita Project (PC Project)

The PC Project is at a mid-stage of drug repurposing, conducting a Phase III clinical trial to evaluate QTORIN™, a 3.9% topical sirolimus formulation, in partnership with Palvella Therapeutics. This stage is characterized by active clinical development and regulatory engagement, with the drug having received FDA Orphan Drug and Fast Track designation. The project's involvement in advanced clinical trials and partnerships with pharmaceutical

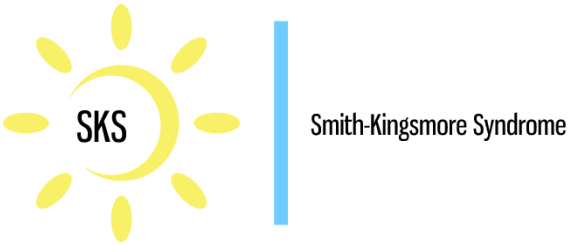
companies signifies a deeper level of organizational adaptation and innovation aimed at achieving regulatory approval and bringing new treatments to patients.

Late Stage - The LAM Foundation

The LAM Foundation represents a late stage of drug repurposing, having successfully facilitated the FDA approval of sirolimus for Lymphangioleiomyomatosis (LAM) in 2015. This accomplishment exemplifies the culmination of the drug repurposing journey, where the focus shifts towards maximizing patient access to approved treatments, ongoing research for dose optimization and side effects management, and international collaboration to improve care standards globally. The foundation's strategic external relations and advocacy efforts underscore a sophisticated level of organizational innovation and adaptation, leveraging the success of sirolimus repurposing to foster broader impacts within and beyond their immediate community.

Within each case study, I will first provide a historical background and overview of the RDNP formation, discovery of sirolimus and later research (if any), until present day. Then, I will discuss several interesting aspects of each case study, supported by direct quotes from the interview transcripts. Next, I will discuss each case study with the lens of Nonaka's theory of knowledge creation and highlight the driving factors, from the adapted Yang and Maxwell (2011) framework. I will conclude with a summary of the insights gained from each case study.

6.3 Case Study: Smith-Kingsmore Syndrome Foundation



- **Founded in 2020**
- **Rare disease of focus:** Smith-Kingsmore syndrome (SKS)
- **FDA Approved Drugs:** There are no FDA-approved drugs for SKS
- **Current status of sirolimus repurposing:** Sirolimus is currently being used off label by 8 patients with SKS.

General Case Study Description

Historical Background

The discovery of sirolimus as a potential treatment for Smith-Kingsmore Syndrome (SKS) and the subsequent establishment of the SKS Foundation was initiated by a family in search of answers for their child's rare condition, a phenomenon quite common in the rare disease space[4]. SKS is a rare, neurodevelopmental genetic disorder, which impacts the digestive, endocrine, metabolic and nervous systems. Patients with SKS have various medical, intellectual, and behavioral disabilities resulting in different clinical outcomes, the most common of which are intellectual disability, developmental delay, large brain size and seizures (Gordo et al., 2018; Smith et al., 2013) With the diagnosis of SKS, the family embarked on a search that led them to

[4] As described in Chapter 5, from the ROADMAP crowdsourced data, we know that out of 711 RDNPs that were identified in the US, 416 (41.9%) of the organizations were started by loved ones of patients (parents, spouses, siblings, etc.) and 206 (20.8%) were started by the patients themselves (*ROADMAP Project*, 2022)

connect with experts and researchers in the field, as well as the search for other families on the same journey. Their search led them to Dr. Laurie D. Smith who first described the disorder in 2013 (Smith et al., 2013). She suggested trying sirolimus, an mTOR pathway inhibitor. At the time, Dr. Smith had not yet used sirolimus as treatment on any SKS patients but knew that the mTOR pathway was involved in SKS. Despite the lack of precedent or clinical evidence for sirolimus in SKS, the family navigated through the challenges of several doctors (including a geneticist) across several hospitals. The doctors they consulted with had used sirolimus for tuberous sclerosis, but never yet for SKS, so the treatment was experimental. They decided to try sirolimus, closely monitoring its effects and managing side effects, particularly severe sleep disturbances, with the support of Cincinnati Children's Hospital.

The experience with sirolimus not only opened new avenues for managing SKS symptoms but also highlighted the need for a dedicated platform to support research, connect families, and raise awareness about the syndrome. Motivated by their journey and the lack of organized support, the family joined 3 others also with children diagnosed with SKS and founded the SKS Foundation. At the time, they were able to identify only 44 other SKS patients through social media, which has grown to about 200 at the time of the interview. The foundation has filled a crucial need to bridge the information gap, foster a community for SKS families, and catalyze research efforts.

Sirolimus treatment for SKS remains in an early, experimental phase, characterized by cautious optimism and a personalized medicine approach due to the variability in patient responses and genetic variations. The initial use of sirolimus in SKS saw mixed results, with noticeable

improvements in certain symptoms, albeit with significant sleep cycle disturbances. These anecdotal outcomes spurred wider interest within the SKS community, leading to more families to consider trying sirolimus, guided by the founding family's experience and the medical team's support at Cincinnati Children's. Currently, the incentives to pursue something as complex and expensive as a clinical trial, or the pursuit of FDA-approval just do not make sense as a focus for the SKS Foundation.

Limited resources lead to strategic prioritization

The SKS Foundation has played a pivotal role in advancing the understanding of SKS and spearheading sirolimus repurposing. Its efforts are geared towards raising awareness, supporting research for better understanding and treatments, and fostering a global community of families and researchers. By prioritizing foundational research, patient registry expansion, and international collaboration, the organization aims to lay the groundwork for more informed and effective treatments in the future, with a long-term vision of improving quality of life for individuals with SKS. Balancing internal RNDP limitations in staff capacity and funding, they need to prioritize only the highest impact research directions:

> "There are so many different opportunities, and we are such a tiny organization. We just hired our first executive director who's also a parent who happens to have operational experience [...] **There's so many good opportunities, it's like a fire hydrant and there's so few of us that are able to take part in them**."

Nevertheless, the SKS Foundation has initiated foundational research, including supporting a study at the University of Florida funded by an NIH grant. The focus remains on gathering more clinical and genetic data to inform future treatment strategies, with an emphasis on precision medicine and exploring potential beyond sirolimus, including new drugs or therapies that could offer better outcomes or fewer side effects.

> "When it comes to this [sirolimus repurposing], with all the other, all the other stuff that we are trying to want to do, [...] it also goes down to capacity. So, we have a treatment, such as it is, **I don't see what FDA approval is going to really give us**, especially since in the United States, sirolimus is 100% covered by Medicaid. So [...] why would we bang our head against the wall and go through that process? [...] So yeah, so we're good enough right now, but maybe five years from now, when there's more information out there, and maybe that might change."

> "Yeah, **the urgency [isn't there].** We have something, families are aware of it. We have that mentioned in the patient brochure, not in a 'oh, it works for everybody' but kind of like 'this is one treatment option'. So we, I mean, for us, **our priority is awareness building for medical providers and to find an adult population**. [...] our priorities from a science perspective is to try to build a population and encourage those families to participate in the patient registry, expand our translation services to, to get more of that data."

Taking a "potluck" approach

SKS Foundation is looking to collaborate with other rare disease organizations that focus on the mTOR pathway. They recognize that their patient population is small and want to work smarter to use their resources efficiently. The group aims to supplement the work of other, larger organizations and be a network creator across other rare diseases, so that knowledge sharing is able to happen for mutual benefit:

> "[...] we're trying to make connections so that people are aware, because I recognize there's **a lot of silos in rare diseases** and in research. And we don't want to reinvent the wheel, especially when our wheel is not going to be so great, because we're so tiny."

Currently focused on building their infrastructure and raising awareness for their cause rather than partnering with other organizations. While they are open to collaborating with other organizations, their priority is on building their patient registry and expanding translation services to gather more data. While they are open to exploring other drugs, they are not actively seeking them out at the moment. They want to be clever in leveraging their small population size, and make an impact where they can, especially for larger research fields in which they have a unique insight:

> "I like to think of it as like a potluck that we could be like, because our issue seems to be that people [researchers] **who've been the most interested have been the sleep researchers because of the circadian element**. So like for studies of sleep, we can bring that, like the side dish, we can bring the mac and cheese to the potluck. We're not going to bring the main protein but you know, we could bring something".

> "We joke that **we're tiny but mighty**. We're not the biggest, or the most funded, but we try to be clever in how we use our resources."

Through the Lens of Nonaka's Theory of Knowledge Creation & Driving Factors

Though the focus of this research is primarily interorganizational knowledge sharing, interorganizational knowledge sharing was not a primary focus for the SKS foundation. This "early stage" case study starts even before the organization was officially formed, as it was establishing its core functions and resources. Consequently, the analysis of interorganizational knowledge sharing during these initial stages is limited. Because of this, I think it's very important to highlight the SKS Foundation as a case study, as it illustrates the very initial phases of knowledge discovery and setting up the infrastructure to progress on their own journey, while creating the network that will later support further knowledge sharing. Nevertheless, we are able to trace the SECI knowledge sharing spiral, the factors that were most relevant at each step, the creation of "ba" spaces, and knowledge assets in this case study. This case study illustrates that early stage RDNPs have limited capacity to engage in knowledge sharing with other RDNPs, due to various compounding factors.

The SKS Foundation's repurposing journey began with the tacit knowledge exchanged between the founding family and the team of physicians and researchers, corresponding to the *socialization* stage of the SECI model. The family's quest for understanding and treating SKS through sirolimus was driven by them sharing their lived experiences, insights, and intuitions about the disease on one side, and the potential benefits of sirolimus based on its action on the mTOR pathway from the researcher/physician side - both tacit knowledge assets. These groups

of stakeholders came together, sharing their understandings and experiences in a manner that wasn't codified but deeply rooted in personal experience and expertise. The "originating ba" space is where individuals share experiences and mental models during the process of socialization. For the SKS Foundation, the doctors' offices and informal gatherings with researchers served as this "originating ba." Here, the tacit knowledge from the family's experiences with SKS and the clinicians' expertise with the mTOR pathway and sirolimus was shared. This exchange is characterized by direct interactions, where feelings, emotions, and shared experiences create a mutual understanding — a necessary precursor to developing new, explicit knowledge about potential treatments for SKS. Even though some of these initial steps were taken before the official RDNP formation, I would still consider them to be a part of the preliminary stages of the RDNPs' knowledge sharing spiral, primarily involving interactions between the family, their physicians, and researchers.

In the *externalization* phase, the tacit knowledge held by the founding family began to be systematically articulated when they formed the SKS Foundation. The creation of the Foundation itself was a significant step in converting individual experiences and understandings into an organized, collective entity. It provided a formal structure where the shared experiences with sirolimus could be documented, analyzed, and disseminated. The outreach efforts through conferences and social media further expanded the scope of this knowledge sharing, establishing a "dialoguing ba" that fostered interaction and learning among stakeholders. This expansion was crucial in moving the shared understanding of SKS from a confined group to a

wider audience, allowing for more diverse inputs and collaboration in the management and research of the syndrome.

In the *combination* phase, the SKS Foundation combined various pieces of explicit knowledge to create new knowledge. This involved synthesizing information from medical research, patient experiences, and treatment outcomes to understand better and manage SKS. The collaboration with Cincinnati Children's Hospital and the University of Florida to support foundational research and the NIH-funded study exemplifies the systematic combination of existing explicit knowledge to generate new insights into SKS and potential treatments, in a systemizing “ba” space. The development of patient brochures and the establishment of a patient registry were key initiatives that the Foundation undertook, serving to inform and educate and also act as repositories of explicit knowledge. They collected and centralized information, making it accessible for the entire SKS community including patients, researchers, and physicians, thus facilitating a broader sharing of knowledge.

The *internalization* phase is where the explicit knowledge generated through the RDNP’s activities is absorbed and transformed back into tacit knowledge through its application in real-life contexts by SKS community as well as other RDNPs. This application is witnessed as families and healthcare providers incorporate insights from the patient registry and brochures into their daily decision-making and care practices for SKS, and when other RDNPs take the insights and data from SKS’s experience and apply it to their own organizational infrastructure or repurposing approach.

Through this framework, the SKS Foundation's experience with sirolimus repurposing is an example of early stage knowledge creation and management in the context of rare disease repurposing. By fostering environments conducive to the sharing and generation of knowledge, the SKS Foundation has facilitated the dynamic interaction between tacit and explicit knowledge, critical for the continuous evolution of understanding and treatment approaches for SKS. This case study also illustrates how various factors can impact an RDNP's ability to engage in knowledge sharing with other RDNPs.

Knowledge sharing as to sirolimus repurposing

Though they are in ongoing collaborations for various purposes with other RDNPs, some of which are also repurposing sirolimus, this has not come up in conversation. There seems to be a lack of incentives to move forward with further steps with sirolimus repurposing, as well as a general lack of capacity to internalize the learnings of other, very different RDNPs. In this case, considering the amount of effort it would take to adapt external knowledge to their own situation, especially considering the lack of incentives to further pursue sirolimus as a viable treatment - pushes the cost to benefit ratio towards the cost side. The collaboration between SKS and other RDNPs has instead focused on either infrastructure or research in a broad sense. Their collaboration strategy is under constraints of a three-year grant period, necessitating a prioritization of infrastructure development to ensure long-term sustainability. As one representative from SKS explains:

> "**We're trying to focus on our infrastructure** because the grant period is only three years and we need to get on in order to be able to make an impact, we need to be able to create a funding system that is going to sustain us beyond. [...] if we just totally, just 110% focused on building those connections with the other rare organizations for science, we like the funding would run out and we wouldn't and then we'd have to stop."

However, there is a recognized value in data sharing among researchers investigating the mTOR pathway across rare diseases. SKS envisions a collaborative approach that centers on the pathway rather than the drug itself, which offers a more logical starting point for collaboration. This perspective is driven by the belief that newer mTOR inhibitors, which may be more targeted and financially appealing to pharmaceutical companies, could provide more promising avenues for repurposing and potentially easier paths to FDA approval compared to sirolimus. As one SKS representative notes:

> "Our dream is to, like, lock all the mTOR researchers in a room. And, you know, like that, you know, beyond SKS and, and just, and just have them kind of work through and just kind of, like, let each other know what they're doing, like, high level [...] It's such a small world. We joke that it does seem like sirolimus is, for rare diseases, that's like the go to drug. And we recognize that our population is so small, so we try to collaborate. It's great that we have Dr Krueger who is very heavily involved with tuberous sclerosis, and they're way bigger and more established than we are. And **trying to connect with**

organizations on the MTOR pathway to have a logical starting point, as opposed to, 'hey, we all have rare diseases and we know each other.'"

Thus, this is case study highlights several interesting reasons for the lack of interorganizational knowledge sharing among SKS and other RDNPs in the context of sirolimus drug repurposing:

- **Limited Incentives:** For SKS, the incentives of pursuing further repurposing itself affects their desire to invest time and effort into connecting with other organizations on the subject. For a drug that was providing more benefit to their patient population, the case might be different.
- **Lack of Capacity:** Early stage RDNPs struggle to find the capacity to internalize and adapt the learnings from other RDNPs, especially when the knowledge is from very different contexts (i.e. different rare diseases).
- **Cost-Benefit Imbalance:** The effort required to adapt external knowledge to their own situation, coupled with the lack of incentives for drug repurposing, can make the cost-benefit ratio unfavorable.
- **Focus on Infrastructure:** Organizations like SKS prioritize building their infrastructure and securing sustainable funding over specific research collaborations, due to limited grant periods.
- **Pathway vs. Drug Approach:** SKS sees more value in collaborating on the research of biological pathways, such as the mTOR pathway, rather than focusing on specific drugs like sirolimus. This approach can bypass constraints related to drug repurposing, such as

lack of interest from pharmaceutical companies in supporting research on off-patent drugs.

Overall, this case study sheds light on the multifaceted challenges that an early stage RDNP faces in fostering interorganizational collaboration for drug repurposing. While the repurposing of sirolimus is not currently a central focus for SKS, there is a shared interest in exploring the broader mTOR pathway as a foundation for future collaborative efforts and potential drug repurposing initiatives.

6.4 Case Study: The Pachyonychia Congenita Project

- **Founded in 2003**
- **Rare disease of focus:** Pachyonychia Congenita (PC)
- **FDA Approved Drugs:** There are no FDA-approved drugs
- **Current status of sirolimus repurposing:**
    - Palvella therapeutics is currently conducting a Phase III clinical trial to evaluate QTORIN™, a 3.9% topical sirolimus."
    - This trial is being conducted in partnership with PC Project, utilizing their patient registry of genetically confirmed patients.
    - Palvella has been awarded both FDA Orphan Drug and Fast Track designation.

General Case Study Description

Historical Background

The story of the PC Project began with the founder Mary Schwarz's personal connection to pachyonychia congenita (PC) through her daughter-in-law, who was diagnosed with the condition. PC is an ultra-rare, chronic, debilitating skin disorder which causes lifelong limited mobility and severe pain through painful calluses, blisters, cysts, and thickened nails. Through a collaboration with Dr. Sancy Leachman, a dermatologist at the University of Utah School of Medicine who emphasized the need for a community of researchers to tackle PC, Mary convened a meeting of twenty-three top scientists and researchers, most of whom remain involved with the PC Project to this day.

The PC Project's journey with sirolimus began when a researcher funded by the organization, Dr Roger Kaspar, discovered that the mTOR pathway was activated in PC. This finding led to a small oral study of sirolimus, which showed potential benefits but negative gastrointestinal side effects (Hickerson et al., 2009). Recognizing the need for a different approach, the focus shifted to developing a topical formulation of the drug. Wes Kaupinen, the founder of Palvella Therapeutics, took a chance on PC when no other companies were interested in drug development for this rare disease. Palvella conducted a phase 2 clinical trial for a topical sirolimus formulation called QTORIN rapamycin, leading to a full phase 3 trial after some initial challenges with the trial design. Pfizer agreed to provide rapamycin for the study. The current goal is to determine QTORIN’s efficacy for PC, with the hope that it will be approved by the

FDA. Because this is a new formulation, it is not available off label to patients until it is approved for any disease by the FDA.

Palvella is testing QTORIN in various diseases, including Gorlin Syndrome Alliance, Basal Cell Carcinoma, and Microcystic Lymphatic Malformations. In 2023 Palvella received FDA Breakthrough Therapy Designation for the treatment of microcystic lymphatic malformations (*Palvella Therapeutics*, 2023). This FDA designation is intended to expedite the development and review of drugs that show substantial improvement over existing therapies for serious or life-threatening conditions, making the drug eligible for a more streamlined development process, and faster review times. This is a positive development for PC as well since it sets a precedent for off-label use and insurance coverage, increases disease awareness for better diagnosis, and offers opportunities for collaboration and learning in the use of sirolimus for rare skin-related conditions. To the best of my knowledge, the results of the clinical trial are yet to be announced.

Throughout this process, the PC Project played a crucial role in patient recruitment, support, and advocacy. The organization's commitment to finding a treatment for PC was unwavering, even in the face of regulatory and scientific hurdles. As they await the results of the phase 3 trial, the hope is not only for the approval of the topical sirolimus but also for the broader impact it could have on disease awareness and diagnosis.

Not all eggs in one basket

The PC Project has formed a collaboration with Palvella Therapeutics, facilitating a rich exchange of data and knowledge between their researchers. This strategic partnership has granted Palvella access to the PC Project's patient registry, among other resources, thereby enhancing the research and development efforts for topical sirolimus. Given the novelty of the Sirolimus formulation, Palvella's strategy to target multiple rare diseases simultaneously is particularly advantageous. This approach not only broadens the potential impact of their research but also mitigates the risk inherent in drug development, where the success of clinical trials can be uncertain. By diversifying their research focus, Palvella enhances the likelihood of achieving a breakthrough in at least one area, which could, in turn, benefit the broader community of patients with rare diseases, including those affected by Pachyonychia Congenita. If QTORIN gets approved for anything by the FDA, it will become available off label for other diseases.

> "I think that makes them a little more successful. Because **if one of their trials doesn't work for PC**,[...] if for any reason it doesn't get passed [by the FDA] for us, if it gets passed for one of these other rare diseases, then maybe **we can still have access to it**."

There is also an anticipation that if approved, Palvella's marketing efforts of this novel sirolimus formulation would significantly enhance disease awareness among dermatologists—thus aiding in the diagnosis of undiagnosed cases of PC. This is a very interesting aspect of this case, as it may be the only situation in which sirolimus (off patent and available off label in oral form) becomes an on patent and potentially profitable drug again.

> "If it gets passed, Palvella will go in and do so much more disease awareness among dermatologists. You know, like I said, we have this registry, but most of the patients come to us without a diagnosis. So we're not just trying to find treatments. We're trying to help patients even get a diagnosis in the first place. And **if this drug gets approved**, I know Palvella is going to go to the dermatology clinics and **find people that have patients and sell them the drug**. But they've got to find them [the patients] first and we are so undiagnosed. So I want that to happen."

Through the Lens of Nonaka's Theory of Knowledge Creation & Driving Factors

The Pachyonychia Congenita (PC) Project's exploration into the potential of sirolimus as a treatment began with the foundational *socialization* stage, rooted in the tacit knowledge exchange between PC Project founder Mary Schwarz and a dedicated network of researchers and clinicians. This stage was characterized by the sharing of deep personal experiences with PC and insights into the scientific aspects of the disease. Through meetings and exchanges of data and knowledge this collective of individuals shared their tacit knowledge in a natural, unstructured manner, laying the groundwork for the project's focused efforts on developing and testing a topical formulation of sirolimus. The unawareness of similar repurposing efforts restricts the flow of this invaluable tacit knowledge between RDNPs. It limits the opportunities for collaborative learning and shared understanding that could emerge from discussions and interactions among researchers and practitioners working across different rare diseases but facing similar challenges.

Next, the PC Project's efforts to articulate the findings from preliminary studies on sirolimus, including its potential benefits and side effects, and the development of a topical formulation, drove *externalization* of knowledge. Publishing results, presenting at conferences, and applying for regulatory approvals are ways in which the tacit knowledge embedded within the project's early work was formalized and shared with the wider scientific and patient communities, setting the stage for further research, collaboration, and innovation in the treatment of PC.

The PC Project's collaboration with Palvella Therapeutics to conduct phase 2 and phase 3 clinical trials of the QTORIN rapamycin formulation can be seen as an example of *combination*. By integrating findings from previous studies with new data from clinical trials, the project aimed to develop a comprehensive understanding of sirolimus's efficacy for PC. This phase also involves organizing, categorizing, and systematizing knowledge to build a structured repository that can be easily accessed and utilized by all stakeholders involved. By organizing this explicit knowledge into structured formats such as detailed reports, updated clinical guidelines, and databases, the PC project facilitated the broader dissemination and application of the findings. Without awareness of other sirolimus repurposing endeavors, RDNPs miss critical opportunities to compare methodologies, results, and patient responses. This lack of comparative insight can lead to a narrower scope of combined knowledge, potentially omitting alternative perspectives or complementary findings that could refine and enhance the collective understanding of sirolimus's application across various rare conditions.

The final internalization phase involves converting explicit knowledge back into tacit knowledge through practical application. As the PC Project and its partners await the results of the phase 3

trial, there is an opportunity for internalization. Through this process, the explicit information about drug efficacy, application methods, and patient outcomes becomes part of the individuals' tacit knowledge base, influencing clinical practices, patient care strategies, and even shaping future research directions. This phase exemplifies how structured, explicit knowledge can be integrated back into the everyday practices and experiences of those involved, completing the knowledge creation cycle and setting the foundation for new cycles of knowledge generation in the ongoing fight against rare diseases like PC.

Though successfully creating knowledge within the RDNP and PC community and network more broadly, the lack of awareness of other RDNPs repurposing sirolimus hinders the effective sharing and leveraging of tacit and explicit knowledge across organizations. Without a clear understanding of parallel efforts, the potential for enriching the knowledge base through collaborative insights and experiences is significantly reduced. Such gaps in the knowledge sharing process can lead to missed opportunities for innovation and the development of more effective treatment strategies for rare diseases. By not fully exploiting the collective wisdom and learnings from across the spectrum of sirolimus repurposing activities, RDNPs might slow the pace of discovery and limit the potential impact of their work on patient outcomes. Thus, enhancing communication and awareness among RDNPs is crucial for a more integrated and efficient knowledge creation and sharing process, ultimately benefiting the broader rare disease community.

Knowledge sharing as to sirolimus repurposing

The PC Project offers a very interesting case study of a mid stage repurposing organization, with a unique incentive towards pursuing sirolimus drug repurposing. Despite being in the midst of clinical trials, the PC Project has shown a readiness to share their process and findings hypothetically. They recognize the value in their experiences, stating, "some of the things we did were smart," yet they also express concern about the limited time and resources available to engage more broadly. Though they are “close friends” with the other RDNPs in Palvella’s QTORIN clinical trials, they have not discussed sirolimus with them specifically. They had lacked awareness of how common this drug was and did not even consider searching for other RDNPs focused on repurposing this specific drug. Described by representative of PC Project in this way:

> “Before I talk to you. I had no idea there were so many companies or so many diseases that were interested in sirolimus. **I had no idea**. I knew Palvella was dealing with those other two diseases, but I had no idea. And when I learned about David Fajgenbaum[5], I heard about him, but I never realized that it was - until I talked to you - I knew he had found his own cure, but I had no idea it was this drug. So yeah, I think you've educated me more than anybody**. I thought it was just a drug that only people with transplants used**. That was it. I mean, I had no idea. I never even knew to even think about it. “

This illustrates an issue in the rare disease research ecosystem - RDNPs often work in isolation, unaware of parallel efforts that could benefit from shared insights. It also relates back to the RDNP’s capacity to look beyond its immediate mission, with limited staff, time and money,

[5]Reference to Dr David Fajgenbaum from the CDCN, who discovered sirolimus for the treatment of Castleman Disease.

collaborations with other rare diseases seem at odds with the RDNPs focus on their own rare disease. As noted by a PC Project representative:

> "It wasn't even on my radar to think about other organizations. You get **so focused on your mission**. And, yeah, bandwidth is always limited. I would imagine, I'm not special in this rare disease world. I'm buried all the time. You know, I work insane hours. Nobody really has time to Google. Or even it didn't even occur to me to say, oh, who else is using sirolimus? All I knew is like I said that it was for transplant rejection. It just didn't even occur to me. I wasn't, you know, thinking thoughtfully or broadly about it. You know, you're just so in your own space, but it is really I admit, it's really interesting to me now to just know that there's all of these diseases out there that are exploring the possibilities. [...] I just don't think I've thought about collaborating with others, because they weren't, **it wasn't even on my radar to even think that there might be others out there**."

This is a very interesting case study, as instead of the incentives to push forward sirolimus driving RDNP-RDNP knowledge sharing, we see that an external actor - the biotech Palvella Therapeutics - has taken on this role. But their role as a knowledge gatekeeper has been very much shaped by the PC Project:

> "We basically put Palvella in touch with our researchers. [...] We just really tried **to be collaborative and introduce them to the right people.** You know, we want people who know about the disease to be running a trial. And even with Palvella, you know, we've spent a lot of time with them talking about patients, they've come to our patient

support meetings, they've come to our scientific meetings, you know, just so that they get the message, right? **They know what's important to patients**, what they care about and kind of win their hearts a little bit too, you know."

Now in this role, Palvella has pooled both funding and patient populations for the potential benefit of all rare diseases, effectively eliminating the need for the RDNPs to connect directly.

This case study highlights several interesting reasons for the lack of direct interorganizational knowledge sharing among PC Project and other RDNPs in the context of sirolimus drug repurposing:

- **Limited Awareness:** The PC Project's lack of awareness about the commonality of sirolimus in rare disease research highlights a broader issue of RDNPs working in isolation, unaware of parallel efforts that could benefit from shared insights.
- **Resource Constraints:** Limited time, staff, and financial resources restrict the PC Project's ability to engage more broadly in knowledge sharing activities.
- **Narrow Focus:** The intense focus on their specific mission and the overwhelming workload can lead RDNPs like the PC Project to overlook potential collaborations with other organizations working on sirolimus repurposing.
- **Knowledge Gatekeeper:** While Palvella Therapeutics has facilitated knowledge sharing by pooling resources and patient populations, it also acts as a knowledge gatekeeper, potentially limiting direct interaction and collaboration between RDNPs.

In summary, this case study sheds light on interesting mid stage RDNP faces in driving forward repurposing efforts and balancing incentives, resource constraints and network gatekeepers. In this case, interorganizational knowledge sharing is happening, but facilitated by an external actor, who was put there in part by the RDNP itself. In a way, this is a solution to the resource constraints of a small RNDP and a very smart, strategic move. On the other hand, it does create information and knowledge silos, in which for profit biotech companies are facilitating interorganizational knowledge sharing, which can create problematic dynamics due to different priorities between for profit companies and RDNPs.

6.5 Case Study: The LAM Foundation

- **Founded in 1995**
- **Rare disease of focus:** Lymphangioleiomyomatosis (LAM)
- **FDA Approved Drugs & Current status of sirolimus repurposing:** Sirolimus was FDA approved for LAM in 2015.

General Case Study Description

Historical Background

The LAM Foundation was established in 1995 to address the lack of research and understanding surrounding lymphangioleiomyomatosis (LAM), a rare lung disease that predominantly affects women. The disease is characterized by the abnormal growth of smooth muscle cells,

particularly in the lungs, lymphatic system, and kidneys, leading to a loss of lung function, fluid accumulation, and tumor growth.

Founded by Sue Byrnes who was faced with her daughter's diagnosis of LAM, found little information or hope in medical literature. Determined to save her daughter, Sue, her husband and Dr. Francis McCormack, a University of Cincinnati pulmonologist, started the LAM Foundation. The foundation became a global leader in LAM research, focusing on educating women with LAM, organizing annual conferences to develop a research agenda, and successfully lobbying for a National Institutes of Health (NIH) intramural program and a National LAM registry.

There was no specific decision to repurpose a drug, that's where the science led them. Dr. McCormack pulled together a loose network of people studying the disease, and they became interested in sirolimus because it regulated LAM cell growth in the laboratory and in animal models. In 2007, they launched the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial, funded by the NIH Office of Rare Diseases, which showed that sirolimus was effective for the treatment of LAM.

The LAM foundation played a central role in bringing together and facilitating the collaboration of the scientific community, industry, and government to get sirolimus approved by the FDA. Originally Pfizer did not want to support the approval process, but through pressure from the LAM community, they changed their position. It was approved in 2015 after four years of effort, which included a 2562 page clinical study report that was required for the FDA filing. Since

then, they are still very active in both continuing research, patient advocacy and support and knowledge sharing with other organizations.

Through the Lens of Nonaka's Theory of Knowledge Creation & Driving Factors

The LAM foundation offers a more complete view at knowledge creation through mapping to Nonaka's work, and also how it was able to embed itself into the wider RDNP ecosystem and engage in interorganizational knowledge sharing. This case illustrates the foundation's approach to tackling both a specific rare disease and their commitment to fostering a culture of learning and sharing within and beyond the rare disease community.

Initially, the foundation's story begins with the tacit knowledge shared among its founders—Sue Byrnes, her husband, and Dr. Francis McCormack. This sharing of personal experiences and insights about LAM set the stage for the foundation's creation. The foundation's engagement in various conferences and rare disease events further exemplifies socialization, where tacit knowledge is exchanged through *socialization* - direct interactions, fostering a sense of community and shared understanding among patients, researchers, and practitioners.

Next, the LAM foundation's efforts to articulate their tacit knowledge into explicit forms are evident in their organization of annual conferences, development of research agendas, and presentations to organizations like NORD, through the *externalization* process. These activities helped crystallize their experiences and insights into accessible knowledge, such as strategies for repurposing sirolimus, forming registries, and establishing patient advocacy organizations.

This stage is crucial for making tacit knowledge available for broader dissemination and understanding.

In the *combination* phase, The LAM Foundation's role in synthesizing diverse pieces of explicit knowledge comes to the forefront. Through collaboration with the scientific community, industry, and government, the foundation combined research findings, clinical trial data, and regulatory insights to support the approval of sirolimus. Their efforts to share and integrate knowledge through peer-reviewed journals and formal research channels further demonstrate the combination of explicit knowledge to create new, comprehensive insights that advance the field.

Finally, the LAM foundation's initiatives enable the LAM community and other rare disease organizations to *internalize* the shared explicit knowledge, turning it into tacit knowledge. This process enriches the collective understanding and capabilities of individuals and organizations in managing diseases, conducting research, and advocating for patient rights. The foundation's strategic external relations, as part of the CEO's evaluated responsibilities, ensure that this knowledge sharing is not only sustained but also actively pursued, emphasizing the importance of learning from and contributing to the broader rare disease community.

The LAM Foundation's story demonstrates a continuous cycle of knowledge transformation and sharing that extends beyond the organization to influence the wider field of rare disease research and advocacy. Their commitment to collaboration, even when it involves navigating

challenges and stepping out of comfort zones, underscores the belief in the power of collective action and knowledge sharing to drive scientific progress and improve patient care. This expanded engagement with other organizations, even those at different stages or focusing on different rare diseases, allowed The LAM Foundation and its partners to leverage collective insights, experiences, and resources, thus accelerating scientific advancements and patient support initiatives beyond what could be achieved in isolation.

Knowledge sharing as to sirolimus repurposing

LAM Foundation is incredibly interested in sharing their experience, as well as learning from other organizations, regardless of stage or rare disease type. They are very active through various conferences and rare disease events, as well as through formal research channels, such as peer review journals. They also have collaboration formalized as a part of the CEO's job, and it is something they are evaluated on. This was unique across all the RDNPs I've interacted with, with a formal expectation to reach out beyond the LAM Foundation network and play a role in the bigger rare disease community.

> "When we do our annual plan for the LAM Foundation, we always have **a component of the CEO's job, which is strategic external relations** and that so it is an expectation of mine. And when I have my job review, it's - who did you reach out to externally? And I can say, well, we were at the CZI presentation and we presented at NORD and we had our annual meeting with the NHLBI and we sit on PAR at ATS. So I think there is an

> expectation that you have to do it. [...] seeking out those next level of collaborations is always an expectation."

Even though they are clearly a success story, FDA approval is not the end of their journey with sirolimus. Looking globally, the approval systems in different countries mean that many LAM patients worldwide still do not have access to sirolimus. Also, the research is never finished - they are still exploring different doses and treatment regimens, as well as studying different patient subtypes as to specific side effects, etc. Importantly, due to the advances in technology, LAM Foundation also sees collaboration as an important vehicle to learn from others trying different and new approaches. They believe that there are "nuggets" of learning that can only be gained through interaction and discussion, things that are not formalized into peer review publications. As a representative from the LAM Foundation put it:

> "Everything moves so quickly now that a patient organization that might appear to be part of the earlier in the timeline, **they can leapfrog you in a minute**. Right? And because of the technology and the processes, they can do something that **when we were at that phase, the same technology didn't exist.** So it took us a whole different way to do something. [...] The only way that patient advocacy work gets done is by sharing. When you hoard information doesn't help anybody."

Even though collaboration was in the fabric of their organization, they still had to make the case for the value of it to their board. There is a delicate balance between internal hyperfocus on a specific rare disease and patient population, and the power of collaboration:

> "The more people who have brains on this, the faster the science is going to move. [...] So I think that as we would make the case, it was that same philosophy that **the power behind science is collaboration**."

The LAM Foundation has tried to embody collaboration even in organizing patient conferences. Though it felt uncomfortable and may have caused some issues with different priorities between various actors, ultimately everyone seemed to benefit:

> "On a practical level, hosting rare lung disease conferences instead of just our own [LAM conference] was really hard for a small patient advocacy group, but **it opened so many opportunities.** And we were able to raise more money. I hate to say that but you've got more industry interest with potential targets in the pipeline and they're going to want to be there with this wide group of scientists and clinicians. It's rewarding and energizing for the scientists and the clinicians themselves to be interacting, to be in these workshops, looking at trials, looking at what's next, how is that not, you know? It's something we didn't do all the time, but we know that it was helpful to us and it inspired more clinics, it inspired more reach for LAM. It inspired more education."

They also discussed engaging in fundraising efforts with other organizations being involved, which felt risky and uncomfortable, but ultimately the collaboration made them able to raise more money than they could have alone.

That all being said, they were not able to list specific RDNPs that they have advised as to their drug repurposing journey, but have just been very active in general as to facilitating various

types of collaborations with different types of actors across rare diseases, countries, industries, etc.

Overall, this case study highlights several interesting reasons for why the LAM Foundation has been more active in pursuing interorganizational knowledge sharing compared to the other case studies:

- **Strategic Vision and Leadership Commitment:** The LAM Foundation has institutionalized the concept of interorganizational collaboration and knowledge sharing into their operational model.
- **Culture of Generosity and Sharing:** The foundation operates on a fundamental belief in the power of sharing and generosity, driven by an understanding of the common struggles faced by rare disease communities.
- **Recognition of the Value in Diverse Perspectives:** By actively learning from and sharing with other organizations, regardless of their stage or focus, the LAM Foundation acknowledges that insights can come from various sources. This openness has allowed them to benefit from “nuggets” of learning that are not readily available in formal literature, underscoring the importance of dialogue and interaction over mere data exchange.
- **Continuous Learning and Engagement:** Despite achieving FDA approval for sirolimus, the LAM Foundation continues to engage in research and patient advocacy. This ongoing commitment underscores an understanding that the journey doesn't end with a drug's approval; there are always new challenges to address, from varying international

regulatory landscapes to evolving treatment protocols and the advent of new technologies.

The LAM Foundation's approach to interorganizational knowledge sharing is multifaceted, incorporating strategic planning, a culture of generosity, an embrace of global collaboration, continuous engagement in research and advocacy, and an openness to innovation. This comprehensive strategy not only enhances their effectiveness in advocating for LAM treatment but also contributes significantly to the broader rare disease community by fostering an environment of mutual learning and support.

6.6 Findings, Discussion & Limitations

The case studies of the Smith-Kingsmore Syndrome Foundation (SKS Foundation), Pachyonychia Congenita Project (PC Project), and The LAM Foundation provide insights into the dynamics of knowledge sharing in the context of drug repurposing within RDNPs, analyzed through the lens of Nonaka’s SECI model.

The SKS Foundation, in its early stage of drug repurposing, illustrates the challenges and strategies of knowledge sharing at the outset of an organization's journey. Limited by capacity and resources, the foundation's approach to knowledge sharing is focused on building a foundational understanding of their rare disease and establishing a network for future collaboration. Their "potluck" approach to collaboration, where they aim to contribute specific insights to a larger pool of knowledge, reflects a strategic use of their limited resources to maximize impact. This approach supports Nonaka’s socialization and externalization processes.

By sharing tacit knowledge through direct interactions and externalizing this knowledge into formal reports and materials, the SKS Foundation aligns with the initial stages of the SECI model. However, the foundation's limited capacity challenges the combination and internalization processes, as they may struggle to integrate diverse explicit knowledge sources and internalize this knowledge within their community.

The PC Project, at the mid-stage of drug repurposing, highlights the role of strategic partnerships in facilitating knowledge sharing. Their collaboration with Palvella Therapeutics not only advances their own research but also opens avenues for knowledge exchange with other organizations involved in Palvella's clinical trials. However, the PC Project's experience also underscores the potential limitations of knowledge sharing when organizations are unaware of parallel efforts in drug repurposing. The PC Project's strategic use of partnerships exemplifies Nonaka's combination process, where explicit knowledge is integrated from various sources. However, the project faces challenges in socialization and internalization, as the knowledge gained from collaborations may not fully permeate their organizational culture and practices.

The LAM Foundation, at the late stage of drug repurposing, exemplifies the benefits of a proactive and strategic approach to knowledge sharing. Their commitment to strategic external relations and their culture of generosity have enabled them to embed themselves within the wider RDNP ecosystem. By actively engaging in interorganizational collaboration and sharing their experiences and insights, the LAM Foundation has not only advanced their own mission

but also contributed to the broader rare disease community's understanding and capacity for drug repurposing. This proactive approach aligns with all stages of Nonaka's SECI model, demonstrating effective socialization, externalization, combination, and internalization processes. The LAM Foundation's success in knowledge sharing challenges the notion that resource limitations are insurmountable barriers, showing that strategic vision and a culture of generosity can overcome these obstacles.

Thus, we can see that by analyzing RDNPs at different stages of drug repurposing, we found that they also correspond to different stages of Nonaka's SECI model. Early-stage RDNPs, like the Smith-Kingsmore Syndrome Foundation, are primarily engaged in the initial phases of the SECI model, focusing on socialization and externalization. This emphasis is crucial for building a foundational understanding and establishing a network for future collaboration. Mid-stage RDNPs, such as the Pachyonychia Congenita Project, exemplify the combination phase of the SECI model. They integrate explicit knowledge from various sources through strategic partnerships and collaborative projects, pivotal for progressing drug repurposing projects and enhancing the organization's overall knowledge base. Late-stage RDNPs, like The LAM Foundation, demonstrate the full cycle of the SECI model, including the internalization phase. They have established robust networks and infrastructure for knowledge sharing, allowing them to internalize explicit knowledge into tacit forms through continuous application and practice. Their advanced stage of knowledge sharing highlights the importance of sustained efforts and strategic vision in embedding new knowledge into the organization's routine practices and culture.

These observations underline the critical importance of continuous development and enhancement of knowledge-sharing infrastructure over time. As RDNPs progress through the stages of drug repurposing, their focus on different phases of the SECI model evolves, necessitating ongoing efforts to support and facilitate these knowledge conversion processes. The case studies illustrate that building and maintaining effective knowledge-sharing mechanisms is an iterative process that requires long-term commitment and adaptation.

Applying Nonaka's framework to these case studies reveals both strengths and limitations in the SECI processes. While the SECI model provides a robust framework for understanding knowledge creation and sharing, its application in the context of RDNPs highlights **several challenges:**

- Socialization: The informal and often ad-hoc nature of socialization in early-stage RDNPs can limit the depth and breadth of tacit knowledge exchange.
- Externalization: Resource constraints may hinder the ability of RDNPs to effectively externalize tacit knowledge into explicit forms.
- Combination: The integration of diverse explicit knowledge sources is often challenged by limited awareness of parallel efforts and strategic partnerships.
- Internalization: The ongoing internalization of explicit knowledge into organizational practices requires continuous education and training, which can be resource-intensive.

These limitations suggest that while Nonaka's framework is valuable for understanding knowledge dynamics within RDNPs, its full implementation requires addressing the unique constraints and contextual factors of these organizations. Future research should explore strategies to enhance each phase of the SECI model, tailored to the specific needs and capacities of RDNPs engaged in drug repurposing

Limitations and Future Research

Despite the insights gained from these case studies, there are limitations to consider. The experiences of these organizations may not be fully generalizable to all RDNPs due to differences in disease focus, organizational structure, and resources. The case studies primarily reflect the perspectives of the organizations' representatives and may not capture the full complexity of the challenges and dynamics of knowledge sharing in drug repurposing. The research was not longitudinal, and therefore, it was not able to trace the development of knowledge-sharing practices over time within each RDNP. This limitation means that while the case studies provide a snapshot of the knowledge-sharing dynamics at different stages, they do not capture the evolution of these processes over time. Future research should aim to conduct longitudinal studies to observe how RDNPs develop and refine their knowledge-sharing practices over extended periods, providing a more comprehensive understanding of the continuous and dynamic nature of knowledge creation and sharing in the context of drug repurposing. Additionally, the evolving landscape of rare disease research and drug repurposing may introduce new challenges and opportunities for knowledge sharing that are not addressed in these case studies. As the field continues to advance, ongoing research and analysis will be

necessary to fully understand the implications of these developments for interorganizational knowledge sharing among RDNPs.

CHAPTER 7: NETWORK ANALYSIS

In this chapter, I employ network analysis to map and examine the patterns of interaction between RDNPs and their various stakeholders during the drug repurposing process. This method provides a high-level view of the interactions between RDNPs in this dissertation, as well as potential knowledge flow paths between them.

7.1 Introduction

The ecosystem of rare disease research and drug repurposing presents a unique and complex landscape for collaboration and knowledge sharing. This chapter focuses on the network analysis of RDNPs and their interactions with various stakeholders in the specific context of sirolimus drug repurposing efforts. The ecosystem of rare disease research and drug repurposing presents a unique and complex landscape for collaboration and knowledge sharing. According to Nonaka (1994), knowledge sharing networks are dynamic entities influenced by the relationships between individuals and organizations, the flow of information, and the context in which interactions occur. This chapter is focused on the network analysis of RDNPs and their interactions with various stakeholders in the specific context of sirolimus drug repurposing efforts.

Specifically, this chapter aims to address **RQ2:** Who are the key participants involved in the repurposing of sirolimus within the Rare Disease Nonprofit Organizations (RDNPs) network, and what influences their collaboration and interaction dynamics in this process? While the primary focus is on knowledge sharing between RDNPs, the broader ecosystem of collaboration, encompassing other organizations and stakeholders, is also included in the analysis. This is predicated on the understanding that these external entities not only contribute to but also facilitate the flow of knowledge, potentially acting as intermediary nodes that enrich the network of drug repurposing efforts. By elucidating the dynamics of social structures in knowledge sharing, we can gain insight into the interconnectedness of RDNPs and other stakeholders. Additionally, we can explore how organizational structures affect the mechanisms of knowledge sharing within and between organizations.

Inter-organizational networks play a critical role in facilitating knowledge sharing and collaboration across various entities. The dynamics of these networks and their impact on knowledge flows have been extensively studied, drawing upon principles from social network theory and organizational theory. Granovetter's (1973) concept of "the strength of weak ties" underscores the importance of bridging ties in networks, which are instrumental in accessing novel information and resources from distant parts of a network. This notion is particularly relevant in inter-organizational networks, where weak ties between different entities can facilitate the flow of knowledge and innovation across the network. Particularly interesting is the concept of gaps in the network, where different parts of the network are disconnected.

Burt (1995) discusses this under the concept of “structural holes”, arguing that individuals or organizations that act as brokers between disconnected groups in a network can leverage these positions for innovation and competitive advantage. This perspective highlights the strategic importance of network positions in facilitating or impeding knowledge sharing.

The internal network structures of organizations significantly influence knowledge flows. Tsai (2001) emphasizes the role of internal social capital in facilitating knowledge sharing within and across organizational boundaries, suggesting that cohesive relationships and trust within organizations enhance the willingness and ability to share knowledge. Cross-functional teams represent a critical mechanism for integrating diverse knowledge bases within organizations. Edmondson and Harvey (2018) discuss the role of team-based structures in fostering organizational learning and innovation, highlighting the importance of cross-disciplinary collaboration in addressing complex problems.

With this lens, this chapter aims to shed light on the complex network of collaborations that drive knowledge sharing in the domain of rare disease drug repurposing.

7.2 Methods

As per the research design outlined in **Chapter 4** of the dissertation, I conducted a series of interviews with 9 representatives of RDNPs repurposing sirolimus, and one researcher (Denise Adams) who was identified as an important actor in several of the RDNP’s repurposing networks. The primary aim was to explore the experiences of these organizations with the drug

repurposing process for sirolimus, emphasizing the exploration of collaborative networks that emerged throughout this journey. The interview protocol was designed to prompt respondents to provide a narrative of their drug repurposing journey with sirolimus, with special emphasis was placed on identifying all relevant stakeholders involved, categorized as researchers, collaborators, data providers, consultants, advisors, and so forth.

Interviews were conducted via ZOOM, ensuring a comprehensive record of the discussions. Subsequently, the recordings were transcribed and analyzed utilizing the software Dovetail, facilitating the extraction of detailed information regarding the names and relationships of each mentioned actor. To manage the complexity of the data, I partitioned the information into several distinct datasets, each serving a different analytical purpose.

First, extracted each mention of an external actor that was involved in the sirolimus repurposing story from the transcripts. This created a preliminary node-edge list of direct mentions. I also created a "node attributes" list, in which I labeled each node as to which category of actor it represented:

1. RDNP
2. RDNP leader
3. Researcher/Physician
4. Pharma/Biotech
5. Hospital/University/Research Center
6. Consortium/Alliance/Network

7. Government
8. Other

The resulting node and edge lists became the primary network dataset which was used for the analysis. The names of the RDNP representatives were combined with their affiliate RDNPs in order to be able to clearly visualize RDNP-RDNP collaboration, except in the case of Dr. David Fajgenbaum, as he was representing not only CDCN as the founder, but also a researcher and physician associated with University of Pennsylvania.

Second, I noticed that when the interviewees described their collaboration with other actors such as researchers, they mentioned individual actors instead of the organization. This provided an opportunity to expand the network. Because I was also interested in exploring "weak" ties between RDNPs, so I conducted additional searches for each mentioned external actor and created an "affiliation" node-edge list, in which I noted these types of connections:

- Researcher - Research institution
- Research Center - Research institution
- Founder - Organization
- Physician - Medical institution

For the many researchers and physicians who had multiple affiliations, or were at a prior institution when they were involved in sirolimus repurposing and have since moved on, I created an edge related to each affiliation. This created a second node-edge list set, including these affiliate connections. In this way, even if not directly mentioned, we would be able to visualize a more complete view of the collaboration networks in the rare disease space.

7.3 Visualization & Analysis of Networks

Using Gephi software for network visualization (see **Figure 16**), initial analyses focused on identifying the most connected nodes through degree centrality metrics, understanding network connectivity via path analysis and density calculations, and detecting community structures through modularity analysis. This multifaceted approach enabled the identification of key actors and clusters within the network, highlighting potential pathways for knowledge sharing and collaboration. Iterative analyses were conducted to refine our understanding, utilizing various metrics such as betweenness centrality to pinpoint nodes that act as critical bridges within the network. Similarly, closeness centrality and harmonic closeness centrality distributions offered insights into the network's overall connectivity and the efficiency of information spread among nodes.

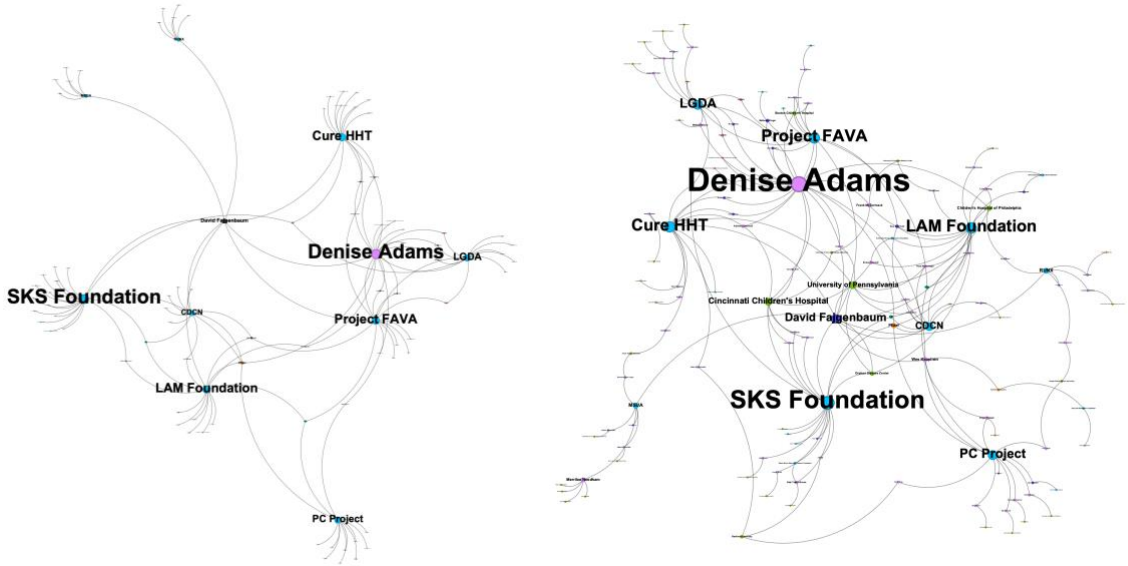
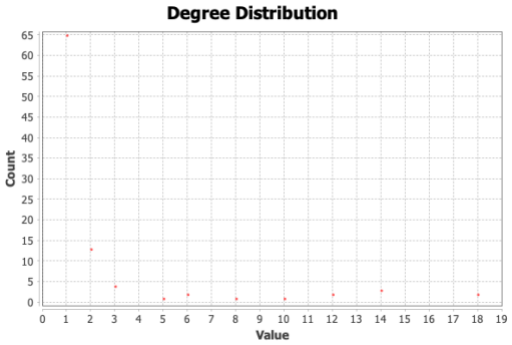
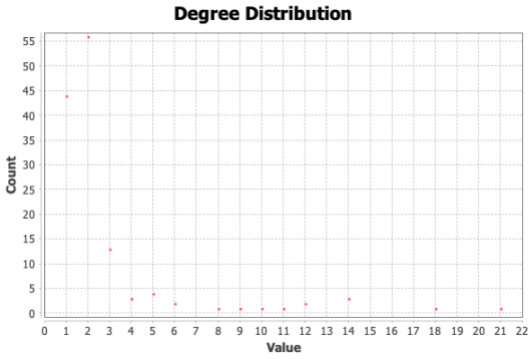
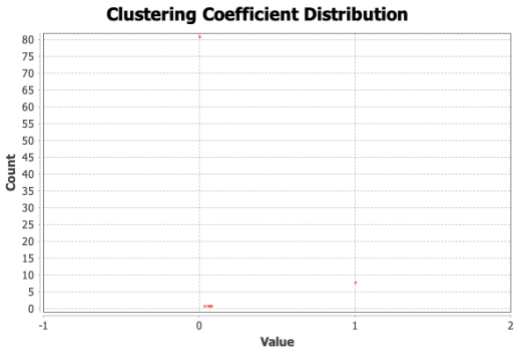
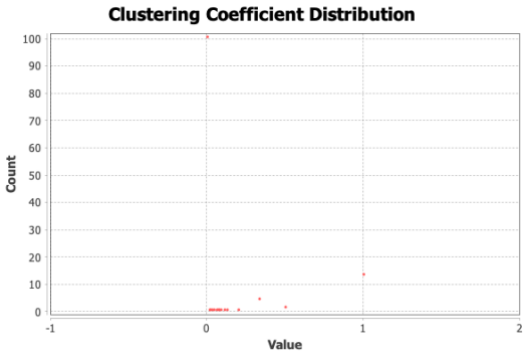
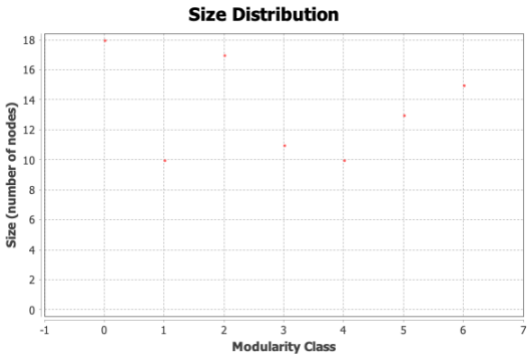
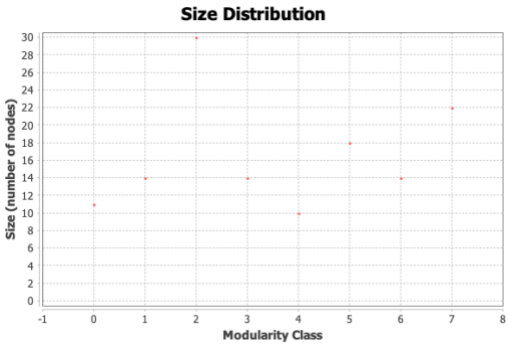
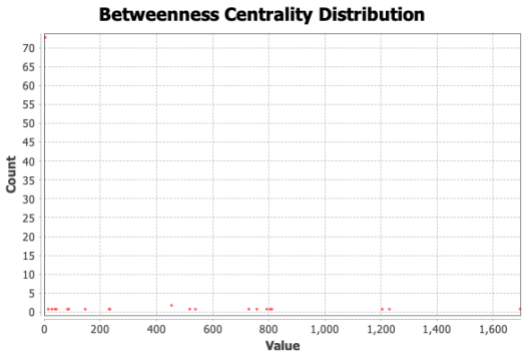
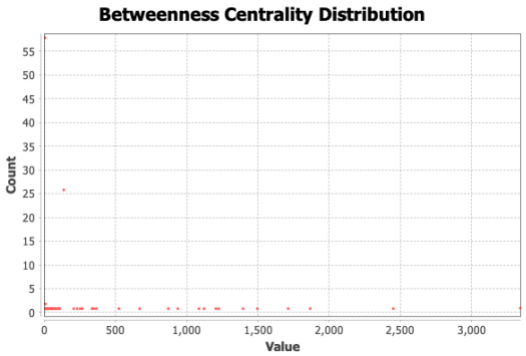


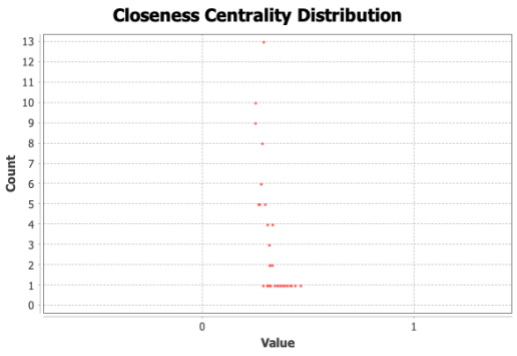
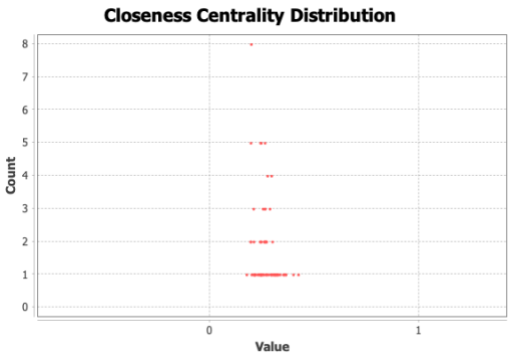
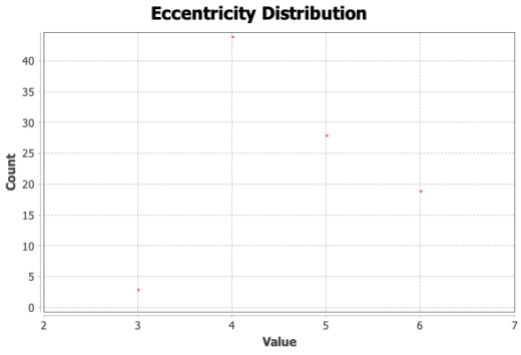
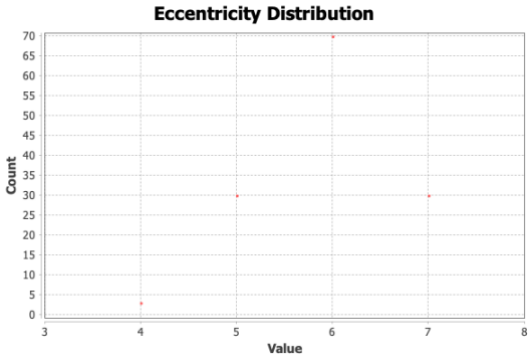
Figure 16: Network visualizations - Direct mentions (left), Direct + affiliate (right); (Force Atlas layout, color by type of node, node size and label size by degree, undirected edges)

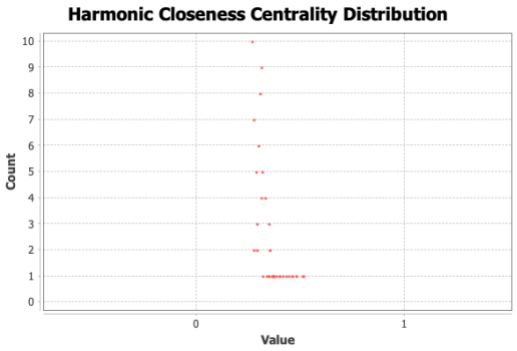
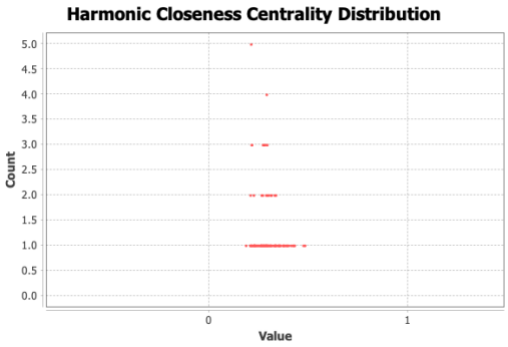
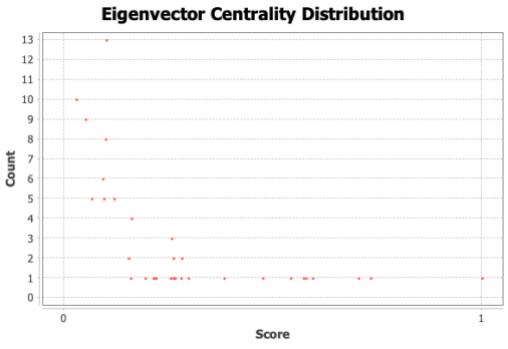
Table 4 below summarizes the quantitative aspects of the network analysis for both networks. The statistics presented indicate the structure and dynamics of the network and provide valuable insights into its characteristics and the role of its nodes.

Table 4: Network statistics, Gephi

	Direct Mentions Data only		**Direct Mentions + Affiliate Data**	
Degree	Average Degree: 2.553 		Average Degree: 2.872 	
Top 5 Nodes: Degree	Denise Adams	18	Denise Adams	21
	SKS Foundation	18	SKS Foundation	18
	Project FAVA	14	Project FAVA	14
	Cure HHT	14	Cure HHT	14
	LAM Foundation	14	LAM Foundation	14
	LGDA	12	LGDA	12
Density	Density: 0.027		Density: 0.022	
Graph Distance	Diameter: 6 Radius: 3 Average Path length: 3.47609242736216		Diameter: 7 Radius: 4 Average Path length: 4.005240373661426	

Clustering Coefficient Metric	Average Clustering Coefficient: 0.286 Total triangles: 11 		Average Clustering Coefficient: 0.197 Total triangles: 26 	
Modularity	Modularity: 0.602 Modularity with resolution: 0.602 Number of Communities: 7 		Modularity: 0.624 Modularity with resolution: 0.624 Number of Communities: 8 	
Betweenness Centrality Distribution				
Top 5 Nodes: Betweenness centrality	David Fajgenbaum	1694.98314	David Fajgenbaum	3339.36165
	SKS Foundation	1226.42027	Denise Adams	2442.64742
	Denise Adams	1200.94117	SKS Foundation	1859.94655

	PC Project	807.663636	PC Project	1705.63436
	Project FAVA	801.476252	Cure HHT	1488.75994
Closeness Centrality Distribution				
Top 5 Nodes: Centrality Distribution	David Fajgenbaum	0.460396	David Fajgenbaum	0.421725
	Denise Adams	0.434579	Denise Adams	0.39759
	Pfizer	0.41704	Pfizer	0.361644
	Project FAVA	0.411504	Project FAVA	0.360656
	SKS Foundation	0.397436	Wes Kaupinen	0.354839
Eccentricity Distribution				
Top 5 Nodes (lowest): Eccentricity Distribution	Denise Adams	3	David Fajgenbaum	4
	Project FAVA	3	Denise Adams	4
	SKS Foundation	3	Wes Kaupinen	4
	David Fajgenbaum	4	Pfizer	5

	Pfizer	4	Project FAVA	5
Harmonic Closeness Centrality Distribution				
Top 5 Nodes: Harmonic Closeness Centrality	Denise Adams	0.514337	Denise Adams	0.479798
	David Fajgenbaum	0.508065	David Fajgenbaum	0.472222
	Project FAVA	0.478495	SKS Foundation	0.427652
	SKS Foundation	0.478495	Project FAVA	0.425126
	Pfizer	0.460573	Cure HHT	0.418813
Eigenvector Centrality	Network Interpretation: undirected Number of iterations: 100 Sum change: 0.005634240068659327 		Network Interpretation: undirected Number of iterations: 100 Sum change: 0.006359983671615063 	
Top 5 Nodes: Eigenvector Centrality	Denise Adams	1	Denise Adams	1
	Project FAVA	0.73381	David Fajgenbaum	0.758607
	David Fajgenbaum	0.704625	Project FAVA	0.647548

	Cure HHT	0.594887	SKS Foundation	0.578719
	LGDA	0.579306	Cure HHT	0.561901

Direct Mention Network

The average degree of 2.553, signifies that, on average, each node has about 2.553 connections to other nodes. This measure reflects the average connectivity within the network, suggesting a moderate level of interaction among the nodes. The density of the network stands at 0.027, indicating a sparse network wherein only 2.7% of all possible connections are actualized. The graph's diameter—the longest shortest path between any two nodes—is 6, and the radius—the shortest maximum distance from any node to all others—is 3. These distances imply that while some nodes are well connected, others may be quite distant within the network structure. The average path length of 3.476 suggests that it takes approximately three and a half steps to travel from one node to another, on average. The average clustering coefficient is 0.286, with a total of 11 triangles identified. These metrics indicate the presence of local clustering within the network, where a subset of nodes forms a tightly-knit group, enhancing the potential for localized knowledge sharing and collaboration.

The network has a high modularity of 0.602, which reflects a strong division into seven distinct communities (see **Figure 17**). This high level of modularity implies that the network is likely to have dense connections within communities while connections between different communities are less frequent.

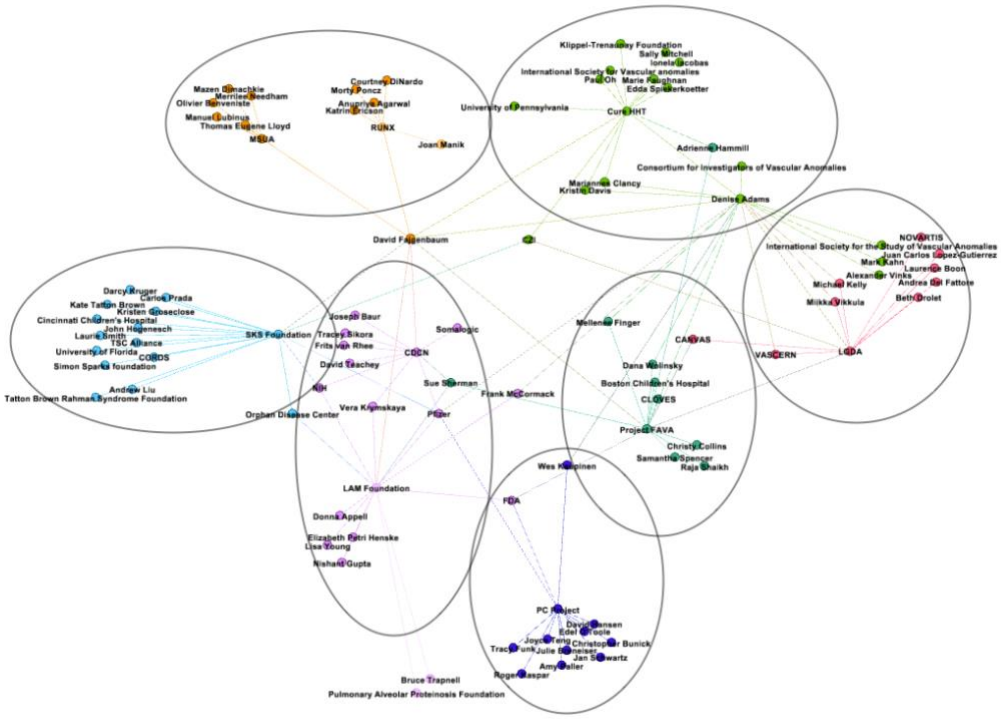


Figure 17: Direct Mention Network, colored by modularity. Circles added to illustrate the 7 communities identified

The distribution of centrality measures gives us insight into the most influential nodes within the network:

- **Betweenness Centrality:** David Fajgenbaum leads with the highest betweenness centrality of 1694.98314, followed by SKS Foundation, Denise Adams, PC Project, and Project FAVA. This measure indicates these nodes act as significant bridges within the network, facilitating the flow of information between other nodes.
- **Closeness Centrality:** David Fajgenbaum also has the highest closeness centrality score of 0.460396, signifying that he is, on average, closer to all other nodes in the network. Denise Adams, Pfizer, Project FAVA, and SKS Foundation follow, indicating they are also central within the network's structure.

- **Eccentricity Distribution:** Denise Adams, Project FAVA, and SKS Foundation have the lowest eccentricity, showing that they are among the nodes closest to all others in the network. David Fajgenbaum and Pfizer follow, with slightly higher eccentricity scores.
- **Harmonic Closeness Centrality:** This measure takes into account the reachability of a node and is useful in larger or more disconnected networks. Denise Adams leads with the highest harmonic closeness centrality, suggesting her pivotal role in maintaining network coherence and reach.
- **Eigenvector Centrality:** This measure takes into account not only the number of connections a node has but also the centrality of the nodes to which it is connected. Denise Adams scores the highest, indicating her significant influence within the network due to being connected to many well-connected nodes.

Direct + Affiliate Network

In the expanded network analysis that includes both direct mentions and contextual data, we observe nuanced changes in the network's structure and connectivity. This network represents a more comprehensive picture by incorporating indirect connections which may not be evident through direct mentions alone. The following section explains the findings from this broader perspective.

The average degree increases slightly to 2.872 from 2.553 when contextual data is added. This indicates that, on average, nodes have more connections, suggesting that the network is more interconnected when considering indirect relationships. The density of the network decreases

slightly from 0.027 to 0.022. Although this change seems counterintuitive given the increase in average degree, it can occur because the number of possible connections increases more than the number of actual connections when contextual data is added, reflecting a broader but sparser network. The diameter of the network increases from 6 to 7, and the radius increases from 3 to 4, suggesting that the network has become larger and possibly more complex. The average path length also increases from 3.476 to 4.005, indicating that, on average, the shortest paths between nodes are longer, which could suggest less efficient communication across the network. The average clustering coefficient decreases from 0.286 to 0.197, with the total number of triangles increasing from 11 to 26. This indicates that, while there are more closed loops of three nodes (triangles), the overall tendency of nodes to cluster tightly with their immediate neighbors has reduced. This could reflect a network where nodes form broader connections rather than limiting themselves to tight-knit clusters.

The modularity of the network increases from 0.602 to 0.624, and the number of identified communities increases from 7 to 8. This suggests that the network's structure has become more segmented into distinct clusters or groups, which might be more internally cohesive due to the inclusion of contextual links.

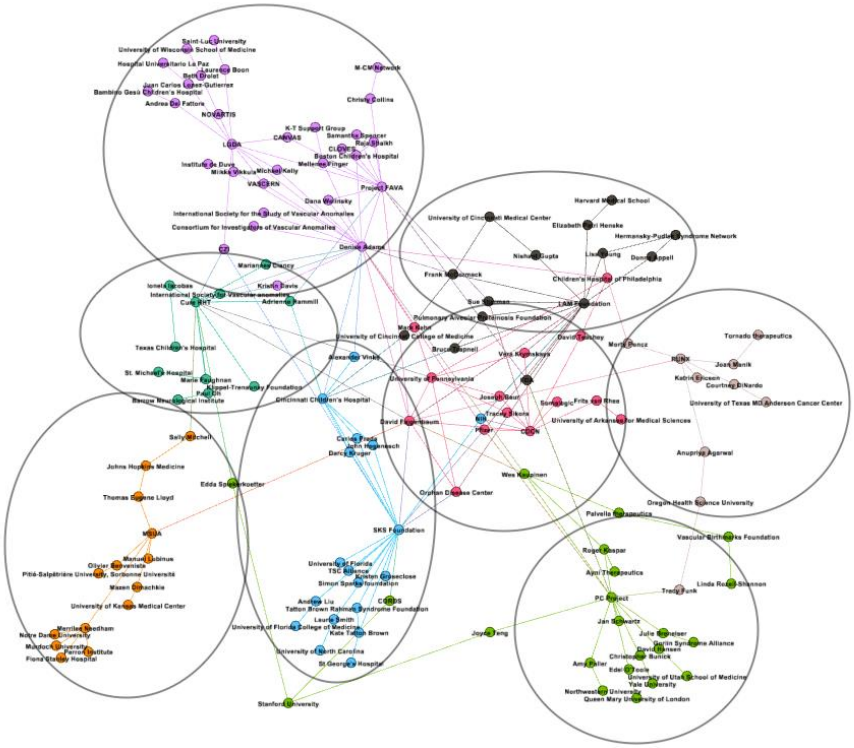


Figure 18: Direct Mention + Affiliate Network, colored by modularity; Circles added to illustrate the 8 communities identified

These findings suggest that the addition of contextual data has made the network more complex, with a greater number of connections and communities, but slightly less dense and with a reduced tendency for tight clustering. The structure suggests a network with broader scope and a more diverse set of connections, which could lead to new insights and opportunities for knowledge sharing, albeit with potential challenges in maintaining cohesion and efficiency in communication across the expanded network.

Now, looking at how the centrality measures have changed with the addition of the new nodes:

- **Betweenness Centrality:** David Fajgenbaum stands out with a significantly increased betweenness centrality score of 3339.36165, up from 1694.98314 in the direct mentions

only network. This suggests that his role as an intermediary has become even more central with the addition of contextual data.Denise Adams and SKS Foundation also see increased betweenness centrality scores, indicating their strengthened roles as connectors within the expanded network structure.

- **Closeness Centrality:** David Fajgenbaum continues to have the highest closeness centrality (0.421725), denoting that he remains relatively close to all other nodes in the network even after the inclusion of contextual data. Denise Adams and other top nodes like Pfizer and Project FAVA also maintain high closeness centrality scores, albeit slightly decreased, indicating their persistent ability to spread information efficiently across the network.
- **Eccentricity:** Denise Adams, Project FAVA, and SKS Foundation maintain the lowest eccentricity in the network, implying their central positioning within the network remains after considering the contextual data.
- **Harmonic Closeness Centrality:** Denise Adams has the highest harmonic closeness centrality (0.479798), suggesting her pivotal role in maintaining network coherence and reach remains strong. David Fajgenbaum and other key nodes also score high in this measure, underscoring their importance in the network's connectivity.
- **Eigenvector Centrality:** Denise Adams achieves the highest eigenvector centrality score of 1.000000, indicating her significant influence within the network due to connections with many well-connected nodes. David Fajgenbaum and other top nodes like Project FAVA and SKS Foundation also have high eigenvector centrality scores, reinforcing their influential status within the network.

In summary, the addition of contextual data to the network's analysis has amplified the roles of certain nodes as central connectors, efficient spreaders of information, and influential entities.

7.4 Findings, Discussion & Limitations

Discussion and Findings

The network analysis conducted provides an overview of the current state of connectivity among RDNPs and other key actors involved in the sirolimus repurposing process. By integrating Nonaka's theoretical framework on knowledge sharing spirals and the role of knowledge activists, we can gain deeper insights into the dynamics of interorganizational connectivity. This integration not only enhances our understanding of how knowledge is created and shared within these networks but also offers potential solutions to improve collaboration and information flow, addressing existing challenges in the network structure.

Network Spareness and Lack of Shared “ba” Spaces

The sparseness of the direct mention networks is a key finding, illustrating that direct connectivity through shared “ba” spaces between RDNPs is a significant factor that limits knowledge sharing related to drug repurposing. According to (Nonaka & Konno, 1998) the concept of “ba” is crucial for knowledge creation. These spaces can be physical, virtual, or mental contexts where interactions occur, and knowledge is shared and created. In the context of RDNPs, the sparseness of the direct mention networks illustrates that there are few shared spaces where knowledge can be actively created and exchanged. This lack of “ba” directly

impacts knowledge flow and collaboration efforts, resulting in duplicated work and significant underutilization of collective knowledge across organizations. With already constrained funding and workforce, this duplication represents a critical inefficiency in resource use.

Community Structures and Knowledge Silos

The network analysis identifies distinct community structures that foster knowledge silos within RDNP networks. Despite their shared goals, RDNPs often cluster within internally cohesive groups, limiting cross-community knowledge sharing. This segmentation aligns with Burt's (2004) concept of structural holes, where gaps between communities hinder collaboration and innovation. According to Nonaka (1998), the dynamic interaction between tacit and explicit knowledge is crucial in the knowledge creation process. Within these communities, tacit knowledge is often shared through direct, personal interactions, while explicit knowledge is documented and disseminated through more formal channels. Silos can thus hinder the sharing of explicit knowledge due to a lack of connectivity across rare diseases. Bridging these silos requires mechanisms to convert tacit knowledge into explicit forms. Activities such as strategic networking could transform the RDNP's effectiveness in facilitating drug repurposing initiatives.

Bridging Structural Holes and Leveraging Weak Ties

In line with Burt's (2004) concept of structural holes, our analysis identifies gaps within the RDNP knowledge sharing networks that represent missed opportunities for collaboration and innovation. Bridging these structural holes through strategic networking could transform the RDNP's effectiveness in facilitating drug repurposing initiatives. Weak ties, as Granovetter

(1973) suggests, are instrumental in providing non-redundant information across network segments. For RDNPs, these less frequent, casual connections can help identify novel opportunities for drug repurposing and facilitate the rapid dissemination of innovative ideas. Employing these bridging actors, who strategically connect otherwise distant clusters, amplifies RDNPs' collaborative efforts and resource mobilization.

We can even illustrate this in the data: by comparing the direct vs direct + affiliate networks, we can see potential knowledge-sharing paths among RDNPs through indirect connections **(Figure 19)**.

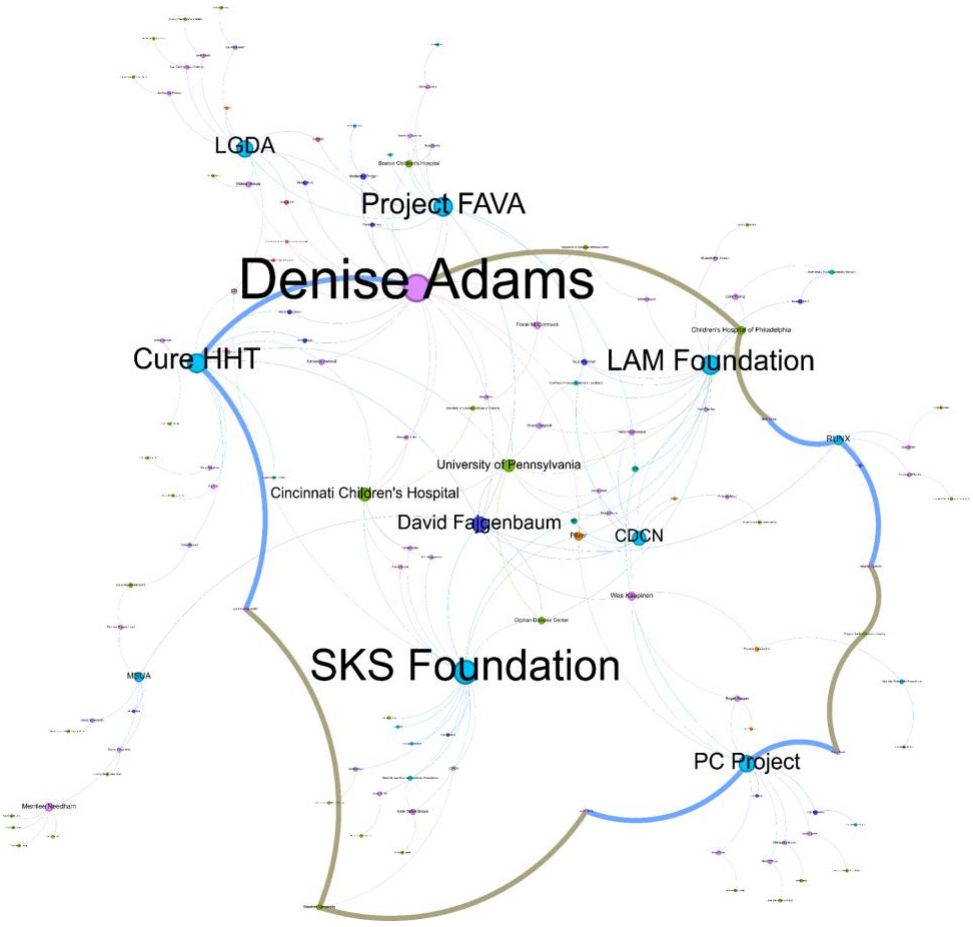


Figure 19: Illustration of a hypothetical path through all the major clusters in the network from the Direct + affiliate network (Force Atlas layout, color by type of node, node size and label size by degree, undirected edges).

These connections are established via shared researchers or institutions involved in the drug repurposing process. This aspect is crucial for understanding how RDNPs, which may not have direct collaborations, could still be linked in a broader network of knowledge exchange through other collaborations, such as ones between researchers or between physicians - connections the RDNPs may or may not be aware of. This two-network approach helps in understanding the nuanced landscape of RDNP interactions and highlights the importance of indirect ties in facilitating knowledge dissemination and collaboration across the field of rare disease drug repurposing.

Key Nodes and Strategic Network Development

Our analysis highlights a consistent set of nodes across both networks: Denise Adams (degree of 18), SKS Foundation (18), Project FAVA (14), Cure HHT (14), and the LAM Foundation (14). Using Nonaka's terminology, we can consider key nodes as actors which can create opportunities for "ba" spaces, convergence points where diverse knowledge from different parts of the network comes together. These nodes can facilitate the continuous creation and dissemination of knowledge by acting as central connectors within the network. Nonaka, von Krogh and Ichijo (1997) refer to these actors as "knowledge activists" – individuals who actively promote and facilitate the sharing and creation of knowledge within and across organizations. Their role is crucial in identifying and connecting knowledge sources, fostering an environment conducive to knowledge exchange. Key influential individual nodes in our data, like Denise Adams and David Fajgenbaum, have access to multiple network segments and align with the

definition of knowledge activists. Their prominence underscores that those connected to well-linked individuals can facilitate broader knowledge dissemination.

The emergence of the SKS Foundation as a significant RDNP node shows that even early-stage RDNPs can quickly establish strategic connections if they are proactive and methodical in their networking efforts. Their approach of identifying key partners early on underscores the importance of purposeful relationship-building from the outset. Conversely, the LAM Foundation, theoretically a 'super connector,' does not prominently feature in this data, which could be attributed to several factors, including network recall bias due to its longer history in repurposing.

These connections are often established via shared researchers or institutions involved in the drug repurposing process. Even RDNPs that may not directly collaborate could still be linked through a broader network of knowledge exchange involving researchers and physicians.

Limitations and Future Research

Several limitations are worth noting in this analysis. Firstly, there is potential over-reporting of Dr. David Fajgenbaum due to the context of the interviews. My prior affiliation with the CDCN may have influenced respondents' responses, suggesting caution in interpreting the centrality of CDCN-related nodes. Additionally, since Denise Adams was also interviewed, she could directly provide several context nodes, possibly leading to her increased centrality.

Additionally, earlier-stage RDNPs, like the SKS Foundation, may report a more extensive array of connections compared to older organizations, such as the LAM Foundation, which could only recall the most pivotal actors. This network data is thus constrained not only by the respondents' memory but also by the organization's size, age, and experience.

To mitigate these biases, future research could incorporate additional data sources, such as published articles and social media networks, to obtain a fuller picture of external actors in drug repurposing projects. This would provide a more holistic view and reduce biases related to personal recollection. While the network analysis provides valuable insights, it's crucial to interpret the findings within the context of these limitations. Longitudinal network studies are recommended to observe the evolution of RDNP networks and understand collaboration dynamics. By incorporating data from various sources, such as published articles and social media networks, researchers can build a comprehensive understanding of RDNP networks and reduce biases from personal recollection.

Solution Recommendations

To overcome the issue of sparse networks and enhance knowledge sharing, RDNPs could actively develop shared research platforms and collaborative funding mechanisms. Initiating more structured opportunities for interaction, such as regular workshops, joint research projects, and virtual “'ba” — online spaces conducive to collaboration, which would foster denser and more interconnected networks. These initiatives can incentivize regular and

structured interactions that foster trust, mutual understanding, and more impactful drug repurposing efforts.

Strategic network development requires the mapping of relationships to identify strategic partners and bridging actors. Knowledge activists can play a vital role in overcoming silos by actively promoting the sharing and creation of knowledge across different communities. By identifying and connecting disparate knowledge sources, knowledge activists help bridge gaps within the network, facilitating broader collaboration and innovation. Empowering knowledge activist actors with formal roles and resources can help them enhance knowledge dissemination between different clusters. Network mapping tools will be essential in visualizing collaboration opportunities and highlighting potential gaps in the network.

A balance between localized and broader collaboration is essential to maintaining network coherence and maximizing the flow of knowledge. Supporting actors who can disseminate knowledge beyond local clusters will provide cohesion across different RDNP groups and sustain network effectiveness.

Conclusion

In summary, understanding and addressing network sparseness among RDNPs is crucial for enhancing knowledge sharing and collaboration. By integrating knowledge activists into these networks, RDNPs can foster more robust and interconnected relationships, which are essential for streamlining drug repurposing efforts and improving outcomes for rare disease patients.

Knowledge activists are instrumental in identifying and connecting disparate knowledge sources, promoting a culture of collaboration, and bridging structural holes that hinder information flow. Their efforts not only facilitate the exchange of innovative ideas but also ensure that valuable insights are effectively disseminated across the network. Additionally, knowledge activists help build trust and mutual understanding among different stakeholders, creating an environment conducive to continuous learning and adaptation. Addressing these challenges through the strategic deployment of knowledge activists will lead to more efficient and impactful advancements in drug repurposing, ultimately accelerating the development of new treatments for rare diseases.

CHAPTER 8: THEMATIC TRANSCRIPT ANALYSIS

This chapter focuses on thematic analysis to uncover patterns and themes within the qualitative data collected from RDNP stakeholders. Through systematic coding and categorization, we map key themes related to knowledge-sharing practices of RDNPs.

8.1 Introduction

In studying RDNPs and their drug repurposing efforts, thematic analysis offers clear insights into how they share knowledge, work together, and face challenges. This analysis aims to tackle a **RQ3:** What are the prevailing barriers in the sirolimus repurposing process, and how can these obstacles be addressed to enhance efficacy and outcomes?

Thematic analysis in this dissertation serves as a way to understand the deeper workings of how organizations interact, share knowledge, and navigate the obstacles in drug repurposing. Through the detailed stories of those involved, this analysis sheds light on the collaborative network within RDNPs, emphasizing the critical role of sharing knowledge to push forward drug repurposing projects.

Contrary to what one might expect—that a competitive environment and scarce resources might hinder collaboration—the interviews from this study reveal a different scenario. There was no sign that RDNPs are unwilling to share knowledge or collaborate in principle. Instead, their readiness to work together is affected by a complex mix of factors, showing that the dynamics of knowledge sharing and collaboration are intricate. The themes discussed here focus on the various internal and external challenges RDNPs encounter.

8.2 Methods

The data for this study were collected through a series of structured interviews, discussed in **Chapter 4.4.** Following the completion of the interviews, the recordings were transcribed using Dovetail, which provided a platform for transcription, tagging, and categorization of data into preliminary themes.

The thematic analysis of the interview transcripts was conducted in accordance with the principles outlined by Braun & Clarke (2006). This approach emphasizes the importance of a flexible and recursive process in identifying patterns and themes within qualitative data.

Initially, the analysis through Dovetail resulted in the identification of 51 preliminary themes. This list was subject to an iterative process of synthesis, including the combination and division of themes to more accurately reflect the nuances of the data. Then, themes were refined through a second coding pass, which was critical for uncovering additional themes that were either previously overlooked or did not align with the initial thematic framework. To structure the thematic analysis further and ensure a coherent organization of the identified themes, the themes are matched to the adapted version of the Yang and Maxwell (2011) framework, as discussed in **Chapter 3.4**. The process of synthesis resulted in a consolidated list of 20 themes across the 10 factor categories (see **Table 5**). There was not sufficient mention of any factors relating to the political environment or data management capabilities, so these factors were excluded from the analysis.

Table 5: Themes extracted from transcript analysis

	FACTOR	FACTOR DESCRIPTION	THEMES
Internal Factors	Organizational Resources	Related to an organizations' funding, staff size, or other organizational constraints, the development and/or utilization of research tools such as a NHS/NHR, biobank, etc, Also includes references to the utilization of networks of researchers, physicians, etc.	Staff
			Funding
			Time
	Organization's Focus, Interests & Boundaries	Related to an organizations' rare disease of focus, mission statement (types of activities they support) and where the boundaries are (do they look at other rare diseases or other organizations within the space). Includes physical boundaries as well, such as different geographic foci.	Mission
			Rare Disease(s)
			Priorities
			Passion & Dedication

	Organization's Origins, Values, and Culture	Related to an organizations' values (collaboration, open sharing, etc.) and cultural values	Attitude towards collaboration
	Organization's Operation Procedures	Related to an organizations' workflows, such as the existence of specific staff or guideline documents to form external collaborations for knowledge sharing, to discussions of specific knowledge sharing events.	Organizational structure
			Events
	Organization's Age, Experience & Expertise	Related to an organizations' age and expertise levels regarding drug repurposing	Assessment of successfulness
	Organization's flexibility & openness to change	Related to an organizations' stance openness to change their position as to knowledge sharing	Approach to learning
External Factors	Trust	Related to an organizations' trust in other stakeholders and organizations; seeing them as valuable partners rather than competitors/threats	Collaboration vs Competition
	Organization's Network: Awareness, Autonomy, & Leadership	Related to an organizations' position in the rare disease organizational network; level of embeddedness, awareness of their role, desire to take a leadership role in bringing people/organizations together, and their level of independence in taking on their own mission. Includes mentions of awareness/lack thereof of the network itself.	Lack of network awareness
			Role in the network
			One rare disease, many RDNPs
			Network size & maturity
	Quality, access and use of information	Related to an organizations' access to information, attitudes towards the quality of knowledge they receive/give, and understanding/concerns as to how it will be utilized	Lack of data sharing

	Comparison of Risk, Incentives and Reward	Related to an organizations' conceptualization of the value of sharing and receiving knowledge vs the risks/costs related to this (time/money/effort/etc).	Balancing complexities of different rare diseases
			Too many initiatives, not enough leadership

Quote Selection

In the sections that follow, I present direct quotes from the interviews. These quotes have been minimally edited for clarity, with filler language and personal details removed to maintain anonymity. The intent is to focus on the insights provided rather than the identities of the speakers or their organizations. This approach facilitates an open discussion, particularly on the more sensitive topics within these themes.

Quotes were selected to accurately represent each category. Initially, interview transcripts were thoroughly read, and relevant segments were coded. These codes were then grouped into broader themes. Quotes were chosen based on their relevance, and ability to illustrate the themes. Due to the natural interweaving of themes, some quotes include multiple themes. Thus, I have bolded the sections of the quotes most relevant to each theme. To the best of my ability, I have evenly sampled quotes across all 9 RDNPs involved in the analysis, ensuring a balanced representation of perspectives.

Theme Frequency

The frequency of each theme's occurrence is not discussed. This decision is rooted in the understanding that the interviews with RDNPs in this research offer only a snapshot of the

broader RDNP experience. Consequently, even themes mentioned infrequently are considered with the same weight as those more commonly noted. As discussed in Braun & Clarke (2006) the 'keyness' of a theme is not necessarily dependent on quantifiable measures, but rather on whether it captures something important in relation to the overall research question. As further illustrated by Clarke & Kitzinger (2004) - key themes were not necessarily the most prevalent themes across the data set, but illustrate theoretically important experiences from the data. This approach acknowledges the value of each unique experience, ensuring a comprehensive and respectful examination of the themes.

8.3 Internal Factors

Organizational Resources

In the rare disease space, organizational resources act as the foundation upon which both medical innovation processes can be conducted, and knowledge sharing can be executed. In this section, I discuss how funding levels, staff, and time constraints shape the RDNP's internal capacities and potential for collaboration.

Staff

From the ROADMAP data, we know that many RDNPs operate with a lean workforce, often relying on a mix of part-time staff, volunteers, and sometimes even individuals who are themselves affected by the rare diseases in question. The dual reality of operating with a minimal staff and the complex, multifaceted nature of rare disease advocacy and research necessitates that those within RDNPs wear multiple hats, juggling administrative duties with

research, fundraising, and advocacy. While this adaptability is also the reason why so much innovation and creative problem solving happens in the rare disease space, it also inherently limits the capacity for expansive program development or the pursuit of multiple parallel initiatives.

> "We're on a budget of what, $300 to $400,000 max in a year. **I work for free**. **I have one full time staff member and a bookkeeper**."

But it is not only the quantity of staff, but also their expertise and background that are important to note. Many are founded by parents of children with the rare disease or rare disease patients themselves, who have passion and dedication to lead the RDNP to success, but may lack a medical, scientific background often needed to spearhead research initiatives or collaborations. This grassroots origin is both a strength and a challenge; it ensures a deep commitment to the cause but can also present a steep learning curve and skill gaps in critical areas necessary for organizational management and growth. Compounded by funding limitations, RDNPs may struggle to bridge the gap between their transformative vision for rare disease research and the practicalities of operational management, advocacy and research support. In response, these organizations often adopt a pragmatic approach, focusing on achievable goals that align with their competencies, while progressively building their internal capacity and seeking external expertise to enhance their impact.

> "We **just hired our first executive directo**r who's **also a parent**, who happens to have operational experience [...] she has a daughter with a condition. So it was perfect for us.

> [...] **We don't have a scientific advisor** at this point yet. Because we're still building our organization."

This lack of staff speaks to a related huge problem that most RDNPs encounter - of not having an in-house research team, or having enough expertise to cultivate a research network to push the research forward. Without a scientific director, or anyone with research experience on staff it is often difficult for an RDNP to first, pull these networks together and then - to keep them engaged. This brings us to funding.

Funding

Funding is the lifeblood of any organization, but especially vital for small RDNPs with ambitious goals and urgent needs. One reason funding can make or break an RDNP's mission is its necessity to be able to entice a researcher to help them pursue research for their rare disease. Researchers and physicians have their own sets of incentives and constraints, and they do not always align with the needs of the RDNP or their patients.

> "It's also a question of **the driver or the incentive**. [..] **Every researcher is going to need some sort of carrot or stick**, right? If you want them to do sirolimus work, there aren't many sticks in research because like, I mean, you can't really punish people that much and they're just going to go on to another disease. But you can give carrots, and that's funding. [...] you need both a researcher who is capable of having activity, but you also need some sort of a carrot to get them on that treadmill".

Another aspect of funding in the RDNP context is that, at least in the early stages, it is almost entirely sourced as donations from the patient population itself. For ultra-rare diseases in which there are maybe ~200 cases world wide, this is an especially difficult roadblock, when research costs of something like a clinical trial are extremely high. Although pooling patients together sounds like a potential solution, due to the high costs per patient, pooling funds doesn't work in practice.

> "There's a cost per patient, and adding more patients or **adding more groups is unlikely to lower the cost on a per patient basis**. [...] Clinical trials have really high marginal costs. So for each additional patient that you enroll, if we're going to add patients, we need more money for those patients. It's not like there's sort of like a synergy that comes from grouping together."

Additionally, pooling funds together brings with it a certain risk, and requires a high level of trust. Funds raised from rare disease patient families are extremely precious and are subject to reporting back to the patient population as to how the funds were spent and how that is bringing them tangible benefit. This makes collaboration that involves financial aspects difficult, as the outcome might end up benefiting one patient population more than the other.

> "Everyone's, you know, **laser focused on their rare disease**. And so the last thing anyone wants to do is spend their [rare disease research] dollars on, you know, samples from a related disease"

Time

Time, as a resource, is often overshadowed by the more tangible assets of funding and staffing, yet its scarcity as a resource has significant effects on the capabilities of RDNPs. These entities frequently encounter the challenge of maximizing their impact with very limited time, frequently due to the lack of full-time dedicated personnel. Many of those involved in RDNPs are managing the organization, having other full time jobs, and also providing care for a child or children with the rare disease that the RDNP is focused on.

> "I was pretty much like the person who was able to **dedicate the most amount of time**. There are other board members, but they also have children with the condition and they have a lot going on. [...] he spends a lot of time too, but **he also works a full time job**."

This situation necessitates a strategic approach to prioritize initiatives. RDNPs are thus compelled to meticulously select their projects and collaborations, ensuring that their limited time is invested in endeavors that align closely with their mission and have the highest potential for impactful outcomes. The consequence of this prioritization is a landscape where strategic choices, rather than the breadth of activities, define the success and progress of these organizations in advancing rare disease research and support.

> "Q: What do you think is the biggest roadblock to kind of prevent collaboration from happening?

A: Time. Time. [...] We have meetings, we discuss great ideas and it's like - nothing happens. And, I'm at fault just like everybody else, **it just becomes a real time sink to dive into that with limited capacity**, to dive into these interesting questions and collaborations."

"There was one initiative that I recall that was to put together a pretty extensive tool kit. And after maybe eight or nine months of meeting, I just felt like **it wasn't bringing value** to where we were and what I could contribute. There are some days when you wake up and, and **you see on your calendar, another group that's trying to organize people** in a different way [...] I think you try to ask a few questions and figure out what might bring you value. And sometimes it works, sometimes it doesn't. So I don't know that I have a clear answer to that, except to stay open and, and look at different opportunities because, you know, you really can't know what's going to gain traction and what is not."

Organization's Focus, Interests & Boundaries

This theme category explores the unique characteristics of organizations focused on rare diseases, specifically examining their mission statements, the types of activities they support, and their operational boundaries. It looks at how these organizations define their scope—whether they concentrate solely on a specific rare disease or extend their efforts to other conditions and collaborate with different entities in the rare disease space. Additionally, it considers the geographical reach of these organizations, including any physical boundaries that may influence their activities and collaborations. This theme illustrates how organizations

navigate the complexities of the rare disease landscape, balancing their missions with the need for collaboration and the challenges of operating across diverse geographic regions.

Mission

The mission statement serves as the cornerstone for all activities undertaken by a RDNP, guiding its focus and priorities. Organizations with missions that highlight collaboration, innovation, and a wider operational reach may be more open to sharing knowledge and resources within the rare disease community. Typically, RDNP missions are crafted with a keen focus on supporting specific rare disease patient populations, aiming to enhance their quality of life. However, this focus also means that activities beyond the immediate scope of their specified rare disease—or beyond direct advocacy and patient support, such as engaging in research—require careful consideration to determine alignment with their core mission. This strategic alignment ensures that their efforts remain concentrated on their primary objectives while evaluating the potential to broaden their impact within and beyond their immediate community.

> "I think in the beginning, when we defined that part of our mission - **the mission is supporting people** - so I think we are able to do the patient-centered research based on that mission of support [...] it's just **getting our board to understand that some of the patient research is necessary** for us to continue the support that we provide to the patient."

For some RDNPs, the collaboration more naturally aligns with RDNPs focused on the same rare disease. In some cases, there are several RDNPs focused on the same rare disease or rare disease category within the US, or even more often - globally. This is a natural extension of the mission, as building out this collaborative network is in direct service to the mission, even though it involves external collaboration.

> "The idea is for us to **collaborate with other [same rare disease] organizations or associations around the world** [...] we have monthly coalition meetings, to work on papers together, surveys, for example, like a burden of disease surveys. We try to also include the other partners, so every time they need something, they can come to us as well."

The mission also determines the overall goal of research and the urgency with which research is pursued, naturally coupled with the severity and nature of the rare disease itself. If the goal of research is to find a cure within the lifetime of the current patients, that facilitates a very different research roadmap than if the goal is to better understand the disease, so that in the future, there can be better treatments.

> "The ultimate goal is precision medicine and that someday down the road, it could be maybe treated in utero. So that way, perhaps intellectual disability can be prevented from happening. But **I know for our community now, we didn't start this to find a cure for them**. We're just trying to **create meaning from our experience and hopefully help the next generation**."

Rare Disease(s)

The specific characteristics of a rare disease—its type, severity, and the demographics it affects—significantly influence how a RDNP approaches both drug repurposing and knowledge sharing. RDNPs focused on diseases with higher severity or those impacting a more vulnerable or specific population segment may prioritize urgent drug repurposing efforts and foster a more collaborative environment for sharing research, data, and strategies.

> "There's a bunch of factors that complicate this because yes - **we did some outreach, but we didn't do a ton** because there's **so much urgency** in terms of when you talk about the timeline between like identification [of the drug] and use. There was no outreach in that two week window between "looks promising" and "let's try it". But if you're talking about the, now what's been an eight year window between "let's try the drug for the first person" and "let's make sure it's advanced for other people. There have been, you know, there's obviously been a lot more time and there has been a lot more outreach."

On the other hand, if the networks required for collaboration would take too much time or effort - the severity of the disease might force the RDNP to move more quickly and independently. It also depends on whether the collaboration is around an urgent matter and/or the first ever use of the drug, or more long term, strategic decision-making.

> "I don't have clinical evidence to recommend it, at the same time it's available [off label]. [...] I don't know if I should be inviting other people to take the drug before we have enough data related to it. [We focus on] **a chronic disease**. Not like – if you don't take it today, you will die. So it's a different approach."

Another aspect to consider is that collaboration among RDNPs in research that could potentially benefit multiple rare diseases simultaneously embodies the principle of leveraging shared knowledge, resources, and experiences to overcome common obstacles - even if it is not evident in the moment

> "I can say - I may not have been successful, but **I set it up for the next generation** of people to take over. And that maybe in my small way, there could be a **ripple effect** that could move science forward in a marginal way or make it easier for another organization to have a breakthrough. Like maybe the information they have will lead to a breakthrough in [another rare disease]. Who knows? And so sometimes that has to be good enough."

Priorities

For RDNPs, the prioritization of efforts, resources, and research directions plays a crucial role. This is especially evident when the urgency of medical needs intersects with the strategic goals of RDNPs. In some cases, if the drug they are repurposing isn't seeming very promising, the incentives to focus on it are also missing, in which case the tacit knowledge of the repurposing experience loses its status as an important knowledge asset.

> "You are laser focused on the drug that is going to save either of your child or you as an adult. In other cases, [...] **sirolimus is just one another player** on the list of different things that have failed in the past. So it's just not the only thing that people are thinking about."

While the discovery of drugs for repurposing remains a hopeful prospect, the realities of resource limitations and the need for a strong foundation of patient data and collaboration dictate a more measured approach

> "So **our priorities** from a science perspective is to try to build up our [patient] population and encourage those families to participate in the patient registry, expand our translation services to get more of that data. And, and **less on trying it, like trying to find other drugs** [for repurposing]. I mean, if a drug fell into our lap, absolutely, we would explore, but we're not."

Organization's Origins, Values, and Culture

The origins of RDNPs are rooted in a response to a perceived lack of attention and resources dedicated to rare diseases in the broader medical and research communities. RDNPs adopt an approach focused on patient-centricity, collaboration, innovation, and transparency. Patient-centricity ensures that the initiatives and projects undertaken are deeply aligned with the needs and well-being of the patients. Collaboration is essential in overcoming the complexities and resource limitations inherent in rare disease research and advocacy. Innovation arises from the necessity to explore novel solutions and approaches, particularly in drug repurposing and treatment strategies. Transparency fosters trust and strengthens community engagement, essential for collective action and support

Passion & Dedication

RDNPs are founded on a deep commitment to addressing the unmet needs of patients with rare diseases. This commitment often stems from personal connections to the diseases, driving a mission-focused approach to research, advocacy, and community support.

> "The level of **altruism and generosity** across all of those groups was really extraordinary and I don't know how you bottle that up and share it. Was it a moment in time? Was it in extraordinary individuals? [...] I heard **the same passion and the same desire** to say - there's a problem here and we need to fix it. I'm always inspired by that fundamental motivation of people who are pulled into science and clinical care. It might not be as rare as we think, right? They just believe that people want to make a difference for the right reasons versus maybe what the media tells us about the world today."

Attitude towards collaboration

Organizations with missions that emphasize open collaboration and knowledge sharing may be more inclined to engage in inter-organizational knowledge sharing activities. For example, an RDNP focused on advancing research through collaborative efforts is likely to be more engaged in knowledge sharing than one with a narrow focus on a specific patient population without emphasizing collaboration. There needs to be an organizational value to be collaborative to justify that it is worth spending precious time and even money going outside the scope of ones' rare disease, and to believe that the value of sharing will also come back and benefit you in the future.

> "On a patient advocacy side, **we're always sharing**, whether it's related to how we repurposed sirolimus or whether it's how to, how do we form a registry or how to get a

> patient advocacy organization started. And I think there's just that **general sense of sharing and generosity** because **we've all been there**."

Another important aspect is to consider the question – which collaborations are most valuable? For example, if an RDNP has staff with enough expertise to be able to navigate the scientific literature and understand what exactly is needed to make progress, oftentimes talking to another RDNP as an intermediary doesn't make practical sense.

> "Though I was not engaging with Rare Disease organizations, I was going directly to the source, which is the [researcher], which to your point, you may need to go through the organization to get to them if you're, if I don't feel comfortable reaching out to them, I don't find them through pub med. Then maybe we would say [...] hey, can you connect us with someone and then they do connect us with the same people that I was going to directly and then there is value from that you know, shared learning. But I think that in our case, I was sort of **going more direct to the source without the intermediary**. [...] But if you can't go directly to the source, the intermediary is important."

Organization's Operation Procedures

RDNP operation procedures are pivotal in shaping their effectiveness and impact. Operation procedures typically encompass certain workflows, such as the presence of specific staff roles dedicated to forming external collaborations for knowledge sharing and organizing knowledge sharing events, as well as the general hierarchy of staff roles in the RDNP.

Organizational structure

The organizational structure of any organization can significantly influence their agility and capacity to respond. For RDNPs, the integration of specific roles or teams dedicated to research, patient registries, and external collaborations can streamline operations and foster innovation within the organization. Luckily, as discussed prior - RDNP teams are small so they do not suffer from the same issues as multinational corporations. On the other hand, limited staff size and funding means that there is usually no dedicated staff focused on fostering external collaborations.

> "**It's just me. I do 99% of the work**. So, I don't know if I have the resources to apply for [CZI grant] or to take advantage of what everything you would need to do once you get a half a million dollars. Yeah, I was, I was told [by another RDNP founder] when I first got started.. I said, oh, I said, oh, look at your website, you've done this, you've done that - so many things. And she said, OK, you're starting out. **Start small**, pick one thing and it will grow and learn from everybody and look around. So I've been using the last, you know, however many years really to learn and grow and see what works and what doesn't work. And so I feel like one day we will get bigger and we'll get to that point, but we're not, we're not there yet"

Events

Events can serve as vital platforms for knowledge sharing, community engagement, and strategic collaboration. Within the operational framework of RDNPs, events can range from scientific conferences and educational workshops to community awareness programs and fundraising activities.

> "We converted our own conference into a rare lung disease conference. And on the research side, we brought together an agenda that had topics even broader. [...] So then that really **just planted seeds of collaboration and trials and relationships**. [...] We were able to invite like a handful of patients and representatives from these other [rare disease] organizations."

> "When **we met in person,** we had so many synergies and they learned that we learned about their bio tissue repository … just conversations that lead in from one conversation to another to another. And I think that's really important and that's why I'm really grateful to have been a grantee because I can't imagine where we would have been without it."

Organization's Age, Experience & Expertise

The age and accumulated expertise of an RDNP play critical roles in its approach to drug repurposing and its overall impact on the rare disease community. Organizations with a longer history in the field tend to have established networks, a deeper understanding of the drug repurposing landscape, and a track record of navigating regulatory and research challenges. This experience translates into a richer knowledge base and a more nuanced understanding of effective strategies for advancing treatments for rare diseases.

Assessment of successfulness

Success or lack thereof in the context of RDNPs is multifaceted, often measured by advancements in drug repurposing, patient support, and advocacy achievements. Evaluating success involves not only considering the direct outcomes of drug repurposing efforts but also the broader impact on the rare disease community's knowledge and resource landscape.

> "What is success? **Sometimes success means that I figured out why this didn't work**. And sometimes when, especially from a disease organization perspective, you're not gonna like to take a ton of time to figure out why something didn't work. You're just gonna pivot and move to the next drug or project that looks like it's making progress towards something, right? So negative finding are unfortunately… I don't wanna say that we don't always seek the truth. But it's like, oh, it doesn't feel like there's something here, let's pivot, you know. Yeah, it is a huge, huge issue for sure."

> "You don't have to be perfect, you just have to be **good enough.** And when it comes to this with all the other stuff that we are trying to want to do, it also goes down to capacity."

Organization's flexibility & openness to change

Flexibility and openness to change are essential qualities for RDNPs, given the rapid pace of scientific discovery and the evolving needs of the rare disease community. Organizations that are receptive to new ideas, willing to pivot their strategies in response to emerging evidence or opportunities, and open to exploring innovative collaboration models are better positioned to

advance their missions. This adaptability is crucial for navigating the uncertainties inherent in drug repurposing and for fostering a culture of continuous learning and improvement.

Approach to learning

An RDNP's approach to learning is fundamental to its ability to grow, innovate, and effectively contribute to the rare disease field. Organizations that prioritize learning from both successes and failures, actively engage with the latest research, and embrace knowledge sharing within and beyond their immediate network can significantly enhance their impact.

> "I think that you know, again, **collaboration and really learning from one another** and from different patient populations, I think **is very worthwhile**. So, when we start looking at sirolimus and, you know, one of the keys to sirolimus is not only do patients respond but do they tolerate it? tI has several significant side effects. And so understanding those side effects over a broad population, I think would be really important and maybe we can start figuring out why certain patients respond really well and tolerate it really well and why certain patients don't."

> "I think there's **a lot of value**, not in terms of efficacy because you know, if it works for you guys, it might not work for us. But in terms of safety, I mean, safety is a huge issue. It's 50% of the issue. There'd be **a huge value in learning what others have found** in their own research in terms of the safety of the medication."

8.4 External Factors

Trust

The trust variable encompasses an RDNPs' confidence in the reliability, integrity, and competence of other stakeholders and organizations within the drug repurposing ecosystem for rare diseases.

Collaboration vs Competition

Within the trust theme, RDNPs described a shift from thinking about other organizations as competitors to recognizing them as invaluable partners in a shared mission. This perspective is foundational for fostering collaborative environments where knowledge sharing and joint efforts are not hindered by concerns over competition but are propelled by a collective aim to accelerate drug repurposing and enhance patient care.

> "So knowing that there are commonalities, I think that we as a team will not take away from any other disease. Sometimes, **if you're competing for the same dollars – I don't think that's the case as much anymore**. Especially if there's an unmet clinical need. So that's where I come down on this different dosages question. **We can all learn from each other**. What dosage, what, what's the maintenance, you know, have you done imaging? What kind of result? So there's just a lot that can be, I think, gleaned and benefit every organization."

> "So when that was proposed in 2014 – **super uncomfortable**. Wait a minute, we're gonna raise money as a patient advocacy group and we're gonna funnel that money to

another organization? **That took some trust** and some – let's just take baby steps and see how it goes and now we can look back and say that's generated almost another million dollars of research [for us]."

This illustrates the practical benefits of trust among organizations in the rare disease sector, emphasizing that collaboration, even when initially uncomfortable, can lead to substantial mutual gains.

Organization's Network: Awareness, Autonomy, & Leadership

An important factor to consider is the impact of how deeply an RDNP is integrated into the greater rare disease landscape, its self-awareness regarding its role within the broader network, its aspiration to lead collaborative efforts, and the degree of independence it maintains in pursuing its mission – and how that affects its knowledge creation and sharing behavior. The themes in this category underscore the varying degrees of network awareness among organizations, highlighting that while some actively seek leadership roles to unite different entities, others may be less aware of the broader network's existence or their potential role within it. The theme also reflects on the balance between collaboration and autonomy, suggesting that effective leadership within the network often requires a nuanced understanding of when to lead, when to partner, and when to independently forge ahead with specific initiatives.

Lack of network awareness

A critical challenge within the RDNP landscape is the limited visibility and understanding of the broader organizational network engaged in similar or complementary efforts. RDNPs, when deeply focused on their specific missions and constrained by resource limitations, often operate in isolation, unaware of potential collaborative opportunities with others working towards similar goals, such as sirolimus repurposing, or facing similar challenges. The theme underscores a gap in the ecosystem—a need for mechanisms or platforms that can enhance interorganizational visibility, thereby fostering collaboration, knowledge sharing, and more efficient advancement towards shared objectives in the rare disease space. Some RDNPs are able to leverage the existing network and engage in collaboration and knowledge sharing:

> "We're like, hey, it's a small world. We joke it does seem like **sirolimus is the - for rare disease - that's like the go to drug**. And so we recognize that **our population is so small and try to collaborate**. And so, it's great that we have [a partnership with another RDNP] they're way bigger and more established than we are. And trying to look, you know, trying to **connect with organizations on the MTOR pathway** to have a logical kind of a logical starting point."

Others are unaware of the existence of other RDNPs focused on the sirolimus repurposing or are unaware at the size of the network, how to access it and/or it's potential:

> "**I wouldn't even know how to search who's investigating sirolimus across the rare disease world**. So I think right there, that's a huge insight, right? Like if I want to find people who are working on this, that would just be painstaking to try to figure that out.

The lack of network awareness is not a deficiency in motivation, though, but a systemic gap in connectivity and information sharing across the sector. While RDNPs exhibit high levels of dedication towards advancing treatments and supporting their communities, the absence of a centralized platform or database significantly hampers their ability to identify and engage with other organizations pursuing similar objectives.

> "**The connections aren't made**. The connections aren't made. They really aren't. And it's really the advocacy organizations that are really motivated to get these answers now. [...] It's full steam ahead, 100%. I absolutely agree."

> "**It wasn't even on my radar** to think about other companies. You know, get so focused on your mission and yeah, bandwidth, like talked about that earlier is always limited."

Role in the network

RDNPs can serve diverse functions internally to their own rare disease community, as well as in the bigger rare disease ecosystem, ranging from leaders spearheading collaborative initiatives to followers benefiting from shared knowledge and resources. This dynamic underscores the importance of understanding and strategically leveraging one's position within the network to maximize impact on rare disease research and patient support.

> "And, and so for us, that's why **we've been not a leader, more of a complimentary follower.** You give me a survey, I can fill out a survey, but don't know enough about our condition to be able to push for things [...] we don't have the capacity to do it. We don't have a scientific advisor at this point yet. Because **we're still building our organization.**"

Within the network of RDNPs, the decision as to their role in the network – to lead or follow – is significantly influenced by the presence of connectors within the network. These connectors play a pivotal role in fostering collaborations and enhancing the network's cohesiveness. An example of such impact is reflected in how one individual, by virtue of organizing and introducing patient groups to one another, catalyzed a domino effect of networking and collaborative efforts.

> "She's [Denise Adams] was the one that **really organized and introduced all of us as patient groups**. [...] She gave me the names of other patient groups. And so I reached out to them and then they gave me the names of more patient groups and it just went on and on from there. So she's really been instrumental in organizing the groups together. She introduced us to pharmaceutical companies. [...] I think she's on all of our medical advisory boards. [...] So we have a really good network of patient groups."

One rare disease, many RDNPs

The complexities and dynamics of interorganizational collaboration are especially highlighted when there are multiple RDNPs focused on the same condition. This scenario often necessitates a delicate balance between cooperation and competition, especially considering the limited pool of patients and funding resources.

> "I've seen other organizations **struggle with having multiple organizations.** There are a lot of political issues that are involved and you have different researchers aligning with different organizations and different agendas."

The nature of the relationships and collaborations among RDNPs and researchers becomes pivotal in such contexts. An active researcher network, effectively sharing samples and information, can alleviate some of the pressures on individual organizations to spearhead the research or advocacy efforts. In situations where such a collaborative network is lacking or the disease is not well-known, patient organizations may find themselves in the critical role of bridging gaps and initiating collaborations. This is especially important on the global scale - considering the needs of different patient populations around the world, varied access to drugs, different medical and insurance systems, etc.

> "There are different organizations around the world [focused on our disease]. Depending on the organization, they may include other conditions as well, but **we talk to each other and we collaborate**. For example, we're collaborating right now on an editorial on why the patient voice needs to be heard more often than before. [...] We haven't worked yet in the repurposing of drugs. It's more about **having a single voice in partnerships with different player**s, at the academic level and also at the political level.

This interplay underscores the importance of incentives in motivating research and collaboration. While personal motivation can drive significant contributions to drug repurposing efforts, as noted in the case of sirolimus and mTOR repurposing work, broader engagement

often requires strategic incentives to encourage collaboration and knowledge sharing among diverse stakeholders.

Network size & maturity

An important factor to consider is the baseline existing research and medical community around a specific rare disease engagement, which determines – to a certain extent – the effectiveness of RDNP in catalyzing research and collaboration. When these networks are pre-existing and active (mature), sharing resources and information seamlessly, RDNPs may find their role more about facilitating existing connections rather than having to initiate or incentivize collaboration.

> "We're really lucky because **we do have this network of doctors** that are going to the FDA and getting money – there's researchers and there's doctors and they're really doing it all. So, as **a patient advocacy group, one of our main purposes is to be able to connect the doctors to the patients**, right? Because I don't have the amount of money that they need and they've been pretty successful at getting money from the FDA. So when they meet with us and talk to us a lot of it is – We have research. Number one, can you help us and look at it so we could formulate research and surveys that, you know, patients will understand. And then number two, once we put the research together, then can you help connect us to the patients? So that's **one big role I see for our organization to have**."

Conversely, in less mature networks where connections are sparse or non-existent, RDNPs face the challenge of not only identifying potential collaborators but also providing the necessary incentives to foster interest and engagement in their cause.

Quality, access and use of information

RDNP's perspectives on the caliber of knowledge they exchange, their ability to access this information, and concerns regarding its application can affect both data sharing practices, as well as broader knowledge sharing and collaboration within the rare disease research community.

Lack of data sharing

The lack of a centralized, user-friendly platform for knowledge exchange can present a significant barrier to effective collaboration.

> "I think a well organized platform where we can kind of see what other people are doing [is needed]. [...] If there was some easy way to sort of, you know, generate a platform that **we could all contribute to** and, you know, and really **see what each other are doing**, I think that would be incredibly helpful".

There are potential benefits of such a platform for drug repurposing specifically, which underscores the need for a more structured approach to information sharing, enabling organizations to easily see, learn from and contribute to each other's work.

> "I think that one thing that would be really valuable for drug repurposing specifically [...] I don't know how many clinical studies have been done with sirolimus that have yet to be published. [...] some patients are taking this drug off label and it's not even within a study and to me, somehow **sharing and capturing the safety and adverse events profile could and would be incredibly powerful**. And I know that's sort of like a big question and I don't really know how one would tackle that. But **I think that will make the path to drug repurposing so much easier if we're all sharing what's happening to our patient populations with these drugs.** Well before publication, because it just takes so long to get things published. And it's, it's a shame when that data can't be shared sooner, especially, you know, in the rare disease world."

This sharing could accelerate the drug repurposing process, a task made challenging by the traditional delays in publishing clinical studies. Together, these insights call for the creation of mechanisms that facilitate the immediate sharing of crucial data, thus enhancing the quality, accessibility, and utility of information within the RDNP ecosystem.

Comparison of Risk, Incentives and Reward

When considering the trade-offs between the value derived from sharing and receiving knowledge against the potential risks and costs involved, RDNPs weigh the benefits of contributing to and accessing a shared knowledge base against the inherent costs of resources (time, money, data, etc). The challenge lies in navigating these dynamics to foster a

collaborative environment that maximizes the collective impact on rare disease research and patient care while safeguarding individual organizational interests and resources.

Balancing complexities of different rare diseases

RDNPs are formed with a patient-centered mindset, which prioritizes the needs, well-being, and perspectives of their own rare disease patients above all else. This orientation shapes the mission, strategies, and activities of RDNPs, guiding them to operate with a deep commitment to directly addressing the unique challenges faced by individuals with rare diseases. In regards to external collaboration, this necessitates not only the forging of connections with other groups but also the ability to assimilate and apply external insights to their specific context. Given the often limited foundational knowledge about many rare diseases, coupled with significant variability in symptoms, affected organs, disease severity, and patient demographics, the effort required to learn from and adapt the experiences of others can be substantial.

> "So I think **it's hard**. Vascular anomalies are not just one disorder. I know Castleman's can be complicated as far as the phenotypes of Castleman's. We don't just take care of not just one disorder. We have been collaborating amongst all of these groups. And so **it's a little harder to then reach out there and collaborate** with someone else because it's like, it takes a lot of energy to collaborate amongst ourselves."

These "complex calculations" of determining the value of external collaboration against the backdrop of rare disease intricacies mean that, in some cases, the investment of time needed to benefit from shared knowledge may not justify the potential rewards. This dynamic

underscores the need for strategic considerations in how RDNPs engage with and contribute to the broader rare disease community, balancing the imperative to advance their missions with the practicalities of resource allocation and the specific challenges of their disease focus areas.

> "When we have a patient conference, we were able to invite like a handful of patients and representatives from these other organizations. But they said – we can't begin to bring our full or merge our full patient conference into your patient conference just because **the needs are so incredibly different**. You got different demographics, you've got different symptoms. [...] I mean, their patients have albinism, they have blindness, they have all of these radically different things. And it doesn't necessarily correlate with the patient's experience as much as it correlates with the clinical and scientific parallels between these things that affect the lung."

Too many initiatives, not enough leadership

Amidst the enthusiasm for collaboration and the sharing of successes and learnings, there's an acknowledgment of the operational realities that sometimes hinder these efforts. Initiatives aimed at consolidating knowledge or creating tools for collective use, while well-intentioned, can fall short of their intended impact due to changes in leadership, shifting priorities, or simply the rapid pace at which relevant information evolves. In some cases, there are numerous initiatives and good intentions, yet a lack of clear leadership and direction can lead to fragmented efforts that may not fully capture or utilize the wealth of knowledge within the community.

> "There was one initiative that I recall that was to put together a pretty extensive tool kit. And after maybe eight or nine months of meeting, I just felt like **it wasn't bringing value to where we were and what I could contribute**. And I felt like once this tool kit was created the way that they had done it, I felt like either a was gonna be partially outdated by the time we got it all put together or it was going to be posted on a website in such a way that I wasn't really sure how or who would ever use it. So **a lot of good intentions and a lot of work** but it's that – what you just referred to is the power of that quarterback."

8.5 Findings, Discussion & Limitations

This thematic analysis provided a structured approach to understanding the qualitative data collected in this study. The iterative and reflective nature of this process ensured a deep engagement with the data, leading to the identification of meaningful patterns and themes that underpin the research findings. This analysis reveals a strong inclination towards collaboration among RDNPs, not hindered by competition or resource scarcity. This disposition is influenced by a complex interplay of factors, including organizational resources, focus, and culture, as well as external trust and network dynamics. The analysis highlights the critical role of knowledge sharing in navigating the drug repurposing process, with RDNPs demonstrating a readiness to work together despite the varied challenges.

Internal factors such as staffing, funding, and time constraints are significant barriers, reflecting the operational realities of RDNPs working in the rare disease space. These organizations often operate with lean teams, balancing multiple roles and responsibilities, which can limit their capacity for expansive program development and collaboration. Moreover, the grassroots origin of many RDNPs, while a source of passion and dedication, sometimes translates into gaps in scientific expertise necessary for advancing research initiatives. Externally, the trust in and collaboration with other stakeholders, including researchers, healthcare professionals, and other RDNPs, are essential for overcoming the siloed efforts in rare disease research. However, the study notes challenges in network awareness and leadership, indicating a need for more robust mechanisms to facilitate collaboration and information sharing across the rare disease ecosystem.

Limitations and Future Research

This analysis is not without its limitations. The thematic analysis is based on a set of structured interviews, which, although rich in insights, represent a limited snapshot of the broader RDNP experience. The decision not to quantify the frequency of theme occurrence means that the analysis prioritizes depth over breadth, potentially overlooking the prevalence of certain challenges or strategies across RDNPs. Furthermore, the reliance on self-reported data from interviews may introduce bias, as participants might highlight successes over challenges or may not fully disclose competitive tensions.

Additionally, the study's cross-sectional design limits the ability to observe the evolution of knowledge-sharing practices and collaborative efforts over time. A longitudinal approach would provide a more dynamic understanding of how RDNPs adapt their strategies and overcome barriers in the long term. Future research could consider employing mixed-method approaches, combining qualitative insights with quantitative data to capture a more comprehensive picture of RDNP activities and impacts.

Despite these limitations, the study offers valuable insights into the collaborative dynamics and challenges faced by RDNPs in drug repurposing efforts. It underscores the importance of fostering a supportive ecosystem that encourages knowledge sharing, collaboration, and innovation to advance the development of treatments for rare diseases. Future research could explore the development of digital platforms and standardized protocols to enhance inter-organizational knowledge exchange, as well as the impact of regulatory frameworks and funding mechanisms on RDNP activities. By addressing these areas, future studies can further support the effectiveness and sustainability of RDNP initiatives.

CHAPTER 9: DISCUSSION, LIMITATIONS & CONCLUSION

This research has illustrated the significant role of RDNPs within the drug repurposing ecosystem for rare diseases and the fragmented knowledge landscape that RDNPs pursuing repurposing navigate.

9.1 Summary of Findings

RDNPs are inherently complex entities that could significantly benefit from strategic design and structured approaches to enhance their operations. The complexity of RDNPs stems from their multifaceted roles, limited resources, and the diverse array of stakeholders they engage with, including patients, researchers, healthcare providers, and industry partners. By adopting strategic frameworks and management practices, RDNPs can streamline their activities, optimize resource allocation, and enhance their overall efficacy. Implementing structured knowledge management systems and fostering an organizational culture that values continuous learning and adaptation are crucial steps toward realizing these improvements. Such strategic design not only addresses the internal challenges RDNPs face but also positions them better to leverage external collaborations and partnerships effectively.

Furthermore, the findings underscore the immense promise and potential of knowledge sharing within the RDNP ecosystem. Effective knowledge sharing can transform more RDNPs into powerful hubs of innovation and collaboration, enabling them to overcome the inherent challenges of working with rare diseases. The potential for impactful outcomes increases exponentially when RDNPs engage in collaborative efforts, sharing insights, data, and best practices across organizational boundaries. This collaborative approach can lead to significant advancements in drug repurposing and patient care, illustrating that when RDNPs work together, their collective impact far surpasses the sum of their individual efforts. The dissertation highlights that fostering a collaborative culture, supported by robust knowledge-sharing platforms and strategic partnerships, is essential for RDNPs to maximize their potential

and drive meaningful change in the rare disease landscape. Representatives from RDNPs, often unaware of the broader applications and interest in sirolimus across various rare diseases, find themselves in a unique position to connect disparate pieces of tacit knowledge, transforming them into explicit, actionable insights for themselves as well as others in the space.

I will now summarize the key findings related to each research question in turn.

Sirolimus Repurposing in RDNPs: Characteristics and Processes (RQ1)

RQ1: How is sirolimus being repurposed in the context of Rare Disease Nonprofit Organizations (RDNPs), and what are the characteristics of this process from their perspective?

This research question focuses on:

- Identifying and characterizing RDNPs Involved in sirolimus repurposing: Which RDNPs are actively engaged in repurposing sirolimus or had been involved in repurposing sirolimus previously, and what are their defining attributes and motivations?
- Examining the stages of their repurposing journey: At what stages in the drug repurposing process are these RDNPs currently? What are their planned next steps?
- Understanding the extent of their engagement: What is the role of RDNPs in the repurposing process?

In addressing RQ1, the dissertation identified and characterized 16 RDNPs potentially involved in sirolimus drug repurposing or its off-label use. The 9 RDNPs that consented to be included in this study were in the early (4), middle (3), and late stages (2) of the repurposing process, representing a diverse spectrum of engagement in both sirolimus repurposing activities and

related collaboration. Early-stage organizations are exploring sirolimus's potential, focusing on gathering preliminary data and building infrastructure. Mid-stage organizations are actively engaged in clinical trials or preliminary studies, showcasing early positive results regardless of their pursuit of FDA approval and late stage are focused on fine tuning sirolimus use through additional research, expanding access, understanding long-term effects, and exploring further therapeutic indications of sirolimus within their patient subpopulations.

The RDNPs play a crucial role in the drug repurposing process, primarily acting as network creators and facilitators. While they generally do not conduct research directly, their unique position enables them to connect various stakeholders—patients, researchers, physicians, government agencies, and pharmaceutical companies. This connection is driven by a deep personal commitment to addressing the diseases affecting them or their close ones and leveraging their networks to drive action. The case studies highlight several key reasons for the varying levels of interorganizational knowledge sharing among RDNPs in the context of sirolimus drug repurposing. For SKS, limited incentives, lack of capacity, cost-benefit imbalance, focus on infrastructure, and a preference for pathway research over specific drug repurposing hinder knowledge sharing. The PC Project's limited awareness of similar efforts, resource constraints, and narrow focus, coupled with the role of a biotech company as a knowledge gatekeeper, restrict their engagement in broader collaboration. In contrast, the LAM Foundation's success in interorganizational knowledge sharing is attributed to their strategic vision, culture of generosity, recognition of the value in diverse perspectives, and continuous engagement in research and advocacy. These findings underscore the importance of strategic

leadership, cultural openness, and a commitment to ongoing learning for effective knowledge sharing in rare disease research.

Key participants and interaction dynamic (RQ2)

RQ2: Who are the key participants involved in the repurposing of sirolimus within the RDNPs network, and what influences their collaboration and interaction dynamics in this process?

This research question focuses on:

- Identifying key participants: Who are the primary researchers and other RDNPs involved in sirolimus repurposing? What roles do these entities play, and what drives their involvement in this process?
- Analyzing their collaboration: How do these participants collaborate and interact during the repurposing process? What are the mechanisms and channels of their interaction?
- Assessing external influences and support: To what extent is the repurposing process conducted independently by RDNPs, and how much is influenced or supported by external forces such as other RDNPs, external resources, or broader networks?

The key participants in sirolimus repurposing span a network that includes researchers, medical professionals, patients, and other RDNPs. The network analysis demonstrates that RDNPs form a network with moderate connectivity, as indicated by average degree metrics. The inclusion of affiliate data expands the network's complexity, slightly increasing connectivity but also introducing a broader, albeit sparser, network structure. This suggests that indirect connections play a crucial role in facilitating knowledge exchange and collaboration, even among RDNPs

that may not directly interact. The centrality analyses consistently identify specific researchers as central nodes that act as significant bridges within the network. Their roles are pivotal in facilitating the flow of information and connecting disparate parts of the network, underscoring their importance in the collaborative efforts towards drug repurposing. High modularity scores in both network analyses indicate a strong division into distinct communities, suggesting that the network comprises tightly-knit clusters that may focus on specific aspects of drug repurposing. Some RDNPs have been instrumental in bridging connections, though the extent of engagement and success varies.

Barriers and Solutions (RQ3)

RQ3: What are the prevailing barriers in the sirolimus repurposing process, and how can these obstacles be addressed to enhance efficacy and outcomes?

This research question focuses on:

- Identifying and analyzing barriers: What specific challenges and hurdles are RDNPs facing in the repurposing of sirolimus? This includes both internal organizational obstacles and external environmental factors.
- Evaluating efficacy: Assess the current practices in sirolimus repurposing – what aspects are functioning effectively, and which are not? This involves a critical examination of the methods and strategies employed.
- Proposing solutions: Based on the identified barriers and inefficiencies, what potential strategies or interventions could be implemented to optimize the repurposing process? This seeks to provide actionable recommendations for enhancing overall effectiveness.

Based on the thematic analysis, there is a demonstrated strong inclination towards collaboration among RDNPs, which is not hindered by competition or resource scarcity. This desire for cooperation is driven by a variety of factors, including its mission, scope, cultural framework it operates within, and the dynamics of trust and networking in the external environment. Knowledge sharing stands out as a pivotal activity in the drug repurposing process, with RDNPs showing a readiness to collaborate despite facing a variety of challenges.

The analysis identifies significant internal barriers, such as staffing, funding, and time constraints, which reflect the operational realities for RDNPs in the rare disease sector. These entities often function with small, multitasking teams, which constrains their ability for broad program development and collaborative efforts. Furthermore, the grassroots origin of many RDNPs, while imbuing them with passion and dedication, can lead to a lack of scientific expertise critical for propelling research initiatives. Externally, building trust and collaboration with researchers, healthcare professionals, and other RDNPs is crucial to break through the isolated efforts that often characterize rare disease research. Nonetheless, the study acknowledges the existence of hurdles in network awareness and leadership, hinting at the necessity for more effective mechanisms to enable collaboration and information sharing within the wider rare disease ecosystem.

9.2 Expanding Nonaka's Framework to Inter-Organizational Contexts

While Nonaka's SECI model primarily focuses on intra-organizational knowledge creation, this dissertation extends the framework to encompass inter-organizational dynamics. By doing so, it provides a more comprehensive understanding of how knowledge is created, shared, and utilized across multiple organizations, particularly in the context of small nonprofit organizations like RDNPs.

Socialization in Inter-Organizational Networks

In the inter-organizational context, socialization involves the exchange of tacit knowledge between different organizations through direct interactions among organization leaders and key stakeholders at workshops, conferences, and during collaborative projects. These interactions create new "ba" spaces—environments conducive to knowledge sharing—facilitating the initial phase of knowledge conversion. By engaging in these shared experiences, RDNPs can enhance trust and mutual understanding, which are critical for effective collaboration. For instance, rare disease conferences and joint workshops serve as platforms where tacit knowledge about disease management and treatment strategies can be exchanged, thereby laying the groundwork for deeper, more integrated collaborative efforts.

Externalization Across Organizations

Organizations externalize tacit knowledge into explicit forms through joint documentation efforts, shared databases, and collaborative publications. This process involves articulating the implicit insights and experiences of various stakeholders into codified knowledge that is

accessible to a broader audience. By documenting best practices, research findings, and patient outcomes collectively, RDNPs can create a rich repository of explicit knowledge that can be leveraged by all participating organizations. This collective knowledge base not only enhances individual organizational capabilities but also fosters a shared understanding and coordinated action across the network, significantly advancing the field of drug repurposing for rare diseases.

Combination of Explicit Knowledge

The combination phase involves integrating explicit knowledge from various organizations through shared digital platforms and joint research initiatives. RDNPs can pool their explicit knowledge—such as research data, clinical trial results, and regulatory information—into centralized repositories or collaborative tools. This integration facilitates the synthesis of new insights and the development of comprehensive resources that drive innovation and improve drug repurposing efforts. For example, a shared database that aggregates clinical data from multiple RDNPs can provide a foundation for identifying new therapeutic applications of sirolimus, or potential side effects in specific subpopulations, thereby accelerating the pace of research and development.

Internalization in a Multi-organizational Environment

Internalization occurs when explicit knowledge is applied and internalized by stakeholders within and across organizations, transforming it back into tacit knowledge through practice and experience. Training programs, practical applications, and continuous education are essential

for embedding this new knowledge into the routine practices of multiple RDNPs. Joint training initiatives and workshops can help disseminate explicit knowledge widely, ensuring that it is absorbed and utilized effectively by all members of the network. For instance, training healthcare providers from various RDNPs on new treatment protocols for sirolimus not only enhances their individual capabilities but also standardizes practices across the network, leading to better patient outcomes and more cohesive inter-organizational collaboration.

By extending Nonaka's SECI model to include inter-organizational dynamics, this dissertation highlights the critical importance of strategic partnerships, shared "ba" spaces, and collaborative platforms in facilitating knowledge creation and sharing across organizational boundaries. This expanded framework can provide a valuable lens for understanding and optimizing the complex knowledge ecosystems of small organizations, ultimately enhancing their capacity to drive innovation and achieve their mission objectives.

9.3 Small vs. Large Organizations

As discussed in Chapter 3, Nonaka's framework was developed with large organizations in mind, where hierarchical structures and extensive resources support formal knowledge management practices. In contrast, RDNPs are typically small, decentralized, and rely heavily on volunteer-based efforts. This difference has several implications, across three main key areas:

Reduced Internal Distance and Communication

In large organizations, internal distance can hinder communication and hierarchical structures can lead to the formation of knowledge silos internally, but formal structures are in place to manage knowledge flow. The reduced distance in small RDNPs facilitates rapid internal communication but can create challenges in maintaining the same level of connectivity with external partners - leading to knowledge silos. RDNPs need to establish robust external communication channels to ensure seamless knowledge flow across organizations. Virtual collaboration tools and regular inter-organizational meetings can help bridge these gaps.

Resource Constraints

Extensive resources in both staff and funding in large organizations support comprehensive knowledge management practices. Limited resources in small RDNPs constrain their ability to implement sophisticated knowledge management processes. RDNPs should prioritize resource allocation for inter-organizational knowledge sharing by collaborating with external partners, leveraging their network connections and engaging with “knowledge activist” connector nodes that can work across rare disease spaces.

Flexibility and Adaptability

Large organizations often have rigid structures that can slow down knowledge sharing and adaptation. RDNPs are more adaptable and can quickly pivot their knowledge-sharing strategies. This flexibility can be leveraged to rapidly adapt to new collaborative opportunities and integrate new knowledge-sharing practices. Establishing agile inter-organizational networks

can enhance their collective responsiveness to emerging challenges and opportunities. By understanding these dynamics, RDNPs can better navigate the challenges and opportunities of inter-organizational knowledge sharing.

9.4 Additional Reflections

Though the prior chapters provide a comprehensive overview of all the key and relevant findings related to the research questions, two other aspects seem important to mention:

For one, this dissertation focused on sirolimus as the primary common thread uniting RDNPs in their drug repurposing efforts. Several interviewees suggested that the focus on the drug may be too specific, and rather the pathway that sirolimus inhibits in the body – the mechanistic target of rapamycin (mTOR) pathway – might be a more meaningful focal point for collaboration and research. The emphasis on sirolimus alone overlooks the potential contributions and insights from research on other mTOR inhibitors, such as everolimus, and potentially significantly limited the sample size of RDNPs. A broader approach focused on connecting rare diseases that have been linked to the mTOR pathway may have had potential for more comprehensive insights. This reorientation towards the mTOR pathway also acknowledges the complexity and diversity of the diseases RDNPs are tackling and the treatments they are exploring. Sirolimus's effectiveness and limitations in treating certain conditions underscore the necessity of exploring a wider array of therapeutic options within the mTOR signaling framework. For example, some participants noted that while sirolimus offers

benefits, it does not universally serve as a "miracle drug" for all patients, prompting a search for alternatives that might offer improved outcomes or fewer side effects.

Another unexpected aspect of this research was my role as an information broker, which emerged during the interviews. For instance, one participant shared, "Before I talked to you, I had no idea that there were so many companies or so many diseases that were interested in sirolimus. [...] I thought it was just a drug that only people with transplants used. I think you've educated me more than anybody." Another participant admitted that they only found out about the prevalence of sirolimus repurposing from me – “Only from you! I remember talking to you and you're like, gosh, it seems like there's a lot of organizations that are looking into sirolimus. So, yeah, you were the only one that sort of mentioned that.” This indicates a role I played in not just gathering information, but also disseminating it among the RDNP community, acting as a conduit for sharing knowledge that was previously tacit or unconnected. In Nonaka’s terms – the process of conducting these interviews became a form of "externalization", facilitated within a “dialoguing ba,” a space where shared understanding develops through interaction. My interviews served as this “dialoguing ba”, bringing to light the experiences of collaboration and knowledge sharing among RDNPs, many of whom were not actively aware of the broader network of sirolimus interest or the collaborative networks they were part of or could potentially join. In a way, I was part of the solution of bridging silos in the rare disease space.

9.5 Limitations

The potential limitations of this dissertation arise from both methodological constraints and the scope of the study. The main limitation is obvious - studying a process that is not occurring is inherently challenging. Though this dissertation illustrated what is intuitively known in the rare disease space – that there is not enough collaboration – the lack of this collaboration made illustrating the path of knowledge sharing between organizations difficult if not impossible at times. Through employing a multi-method approach and looking at the limited data from different angles, the present study aimed at illustrating what we can see from the current practices, and within the scope of the present study and its limitations, but further research is needed to assess any alternative avenues for knowledge sharing taking place, such as longitudinal analysis or widening the types of stakeholders interviewed.

The reliance on interview data as the primary source of data for both case studies, thematic analysis and network data collection presents inherent limitations, as it depends on the recollection and subjectivity of the participants, potentially leading to memory lapses or biases. Consequently, the accounts provided may not fully represent the multiplicity of experiences and views within the broader RDNP community. The non-quantitative approach of not measuring theme frequency further limits the breadth of understanding, possibly overlooking the extent to which certain challenges or strategies are prevalent across RDNPs.
Focusing exclusively on sirolimus also has its drawbacks. It narrows the research to a single drug repurposing effort, which may limit the applicability of findings across different drugs or diseases. This specificity might overlook the varied dynamics and challenges encountered in

other drug repurposing scenarios, thereby constraining the generalizability of the conclusions drawn.

While most RDNPs are at different stages in the repurposing process, several have concluded their major initiatives years prior, sometimes under the leadership of individuals no longer affiliated with the organization. This temporal gap can affect the accuracy and relevance of the information provided, as the landscape of drug repurposing, including the key players and the state of research, evolves over time. Additionally, this research was not longitudinal, and therefore, it was not able to trace the development of knowledge-sharing practices over time within each RDNP. This limitation means that while the case studies provide a snapshot of the knowledge-sharing dynamics at different stages, they do not capture the evolution of these processes over time.

The analysis also does not include data from pharmaceutical or biotech companies, regulatory bodies like the FDA, or perspectives from outside the United States, which restricts the applicability of findings to these other critical segments of the drug repurposing landscape. Furthermore, the rapidly evolving field of rare disease research and repurposing activities suggests that the landscape might have changed since data collection, underscoring the need for continuous updates to the dataset to maintain relevance.

Future research to address these limitations could involve iterative survey testing to optimize length and complexity, diversifying respondent pools beyond the U.S., and incorporating data

from additional stakeholders like pharmaceutical companies and regulatory bodies, and additional data sources, such as peer review publications from the relevant repurposing research studies. Such enhancements would contribute to a more holistic view of RDNP collaboration networks and improve strategies to enhance the efficacy of drug repurposing endeavors.

9.6 Conclusion

RDNP engagement in sirolimus repurposing activities is a complex process, marked by enthusiasm for collaborative efforts yet hindered by systemic inefficiencies and a lack of centralized support mechanisms. This dissertation identified a lack of centralized platforms or specialized actors for knowledge sharing among RDNPs. Despite these challenges, there exists a palpable potential for enhancing knowledge exchange, particularly where less experienced RDNPs can glean insights from their more seasoned counterparts, and occasionally, vice versa. Presently, workshops, conferences, and collaborative projects serve as the primary conduits for such exchanges, though not without their own set of inefficiencies and challenges.

Focusing on a commonly repurposed drug sirolimus, this study provides a unique window into the drug repurposing process. The collective endeavor in repurposing sirolimus across various rare diseases could significantly enrich the understanding of its effects, dosage optimization, and potential impacts on different body functions. However, the diversity of rare diseases introduces variables that could complicate research efforts rather than streamline them.

Moreover, collaborative ventures and knowledge sharing, while promising, are often too time and resource intensive for smaller, earlier stage RDNPs to undertake.

Major Takeaways

1. **Complexity and Need for Strategic Design in RDNPs:** RDNPs are complex and resource-limited entities that require strategic design and structured approaches to maximize their effectiveness. The research highlights that these organizations can benefit significantly from adopting more formalized collaboration frameworks and leveraging strategic actors, which can help streamline their operations and enhance their capacity to address the multifaceted challenges of drug repurposing.
2. **Promise and Potential of Knowledge Sharing for the RDNPs:** There is immense potential in enhancing knowledge sharing among RDNPs, which can transform these organizations into powerful hubs of innovation and collaboration. Effective knowledge sharing can lead to faster and easier drug repurposing, enabling the RDNPs to leverage collective insights, data, and best practices to accelerate the development of new treatments for their rare diseases.
3. **Impact of Collaborative Efforts:** Collaborative efforts among RDNPs can significantly deepen understanding and expedite drug repurposing processes. The dissertation emphasizes that collective action, facilitated by strategic partnerships and shared platforms, can lead to greater overall impact than isolated efforts. RDNPs working together can overcome resource constraints and amplify their influence on the rare disease landscape as a whole.

Theoretical Contributions

Grounded in Ikujiro Nonaka's Theory of Dynamic Organizational Knowledge Creation (Nonaka, 1994), this dissertation extends the framework to encompass inter-organizational dynamics. By doing so, it provides a more comprehensive understanding of how knowledge is created, shared, and utilized across multiple organizations in the context of small nonprofit organizations. This extension underscores the importance of knowledge as a source of innovation in a knowledge ecosystem, highlighting the value of both tangible data and the less tangible, yet crucial, insider knowledge such as creative vision and expertise. It also proposes a focus on various factors that affect the creation of and drive the continued existence of the knowledge spiral by adapting the Yang & Maxwell (2011) framework to this use case. Further studies in similar complex environments can build on this work as to what are the drivers of knowledge creation in different inter-organizational contexts.

Practical Solution Recommendations

This dissertation underscores the nuanced interplay among RDNPs at various stages of the sirolimus repurposing journey, emphasizing the potential of collaborative efforts to deepen understanding and expedite the drug repurposing process. It highlights the importance of a strategic approach to knowledge sharing, urging RDNPs to navigate and manage the complexities inherent in rare disease research carefully. Addressing the identified barriers and optimizing knowledge-sharing processes can enable RDNPs to leverage drug repurposing

initiatives more effectively, ultimately enhancing health outcomes for those affected by rare diseases.

Specifically, RDNPs can:

1. **Foster Collaborative Culture and Strategic Partnerships:** Encourage an internal culture of collaboration and establishing formal partnerships with other RDNPs, research institutions, and pharmaceutical companies can enhance knowledge sharing.
2. **Implement Structured Opportunities for Interaction:** Create and participate in more structured opportunities for interaction among RDNPs through regular workshops, joint research projects, and virtual 'ba'—online spaces conducive to collaboration. Structured interactions can foster denser and more interconnected networks, incentivizing regular and impactful knowledge exchange. This approach helps in overcoming the challenges posed by the isolated efforts and limited interaction typical in the rare disease research ecosystem.
3. **Identify and Empower Knowledge Activists:** Identify key individuals within and across organizations who can act as knowledge activists—those who actively promote and facilitate knowledge sharing. Provide them with formal roles and resources to enhance their ability to disseminate knowledge and connect different organizational clusters. Knowledge activists can play a critical role in bridging gaps between different RDNPs and other stakeholders, ensuring that valuable knowledge flows across the network. Empowering these actors can help overcome the fragmentation and isolation often observed in the rare disease research ecosystem .

Reflecting on the broader implications, over 30 million individuals in the U.S. alone face the disproportionate burden of rare diseases (Haendel et al., 2020). Drug repurposing emerges as a promise to deliver effective treatments more swiftly and economically than traditional drug development pathways. Yet, the path is full of challenges—chiefly, the inefficiencies in knowledge sharing among key stakeholders, including RDNPs, researchers, physicians, government agencies, and pharmaceutical companies. This research has sought to illustrate these challenges and propose pathways to overcome them, focusing on sirolimus as a case study to limit variance and capture the essence of knowledge sharing in drug repurposing endeavors.

In sum, this dissertation illustrates the significance of interorganizational knowledge sharing in the knowledge-based economy, where innovation, productivity, and economic development increasingly depend on the collective knowledge of networks rather than individual organizations. The theoretical implications lie in refining our understanding of knowledge sharing and creation in multi-actor, decentralized settings, while the practical recommendations aim to enhance the efficacy of collaborative efforts in the rare disease sector and beyond. This study reveals the multifaceted nature of knowledge sharing among RDNPs, enriching the existing literature on knowledge management and laying the groundwork for future initiatives aimed at resolving identified inefficiencies. As the rare disease landscape continues to evolve, this dissertation marks a step toward understanding and enhancing the role of RDNPs in the drug repurposing ecosystem.

APPENDIX

Appendix A: ROADMAP Survey Protocol

IRB submission and Review

The survey protocol, questions, translated materials and communication and recruitment materials were submitted to an external IRB service Advarra for review and approval. The Syracuse University IRB was notified since some of this data will be utilized for my dissertation and the Syracuse University IRB has agreed to defer to the external IRB service for the execution of this project.

Survey Participants

The ROADMAP survey focused on five different stakeholder populations: representatives of rare disease non-profit organizations (RDNPs), their patients, loved ones, researcher and physician communities. It is one survey, with a section for each stakeholder population. In addition to the general introduction, inclusion and consent questions, there are four sections, as there is no separate survey for loved ones, as the loved ones were asked to take the patient survey on behalf of a patient. The ROADMAP survey also provided a Spanish consent form and translated patient/loved one survey section for Spanish-speaking US-based patients, as we anticipated that Spanish-speaking patients would represent a significant portion of patients for certain rare disease non-profit organizations.

Target Population and Accrual

Rare Disease Non-profit Organizations (RDNPs)

Most of the research questions focus on exploring the role and characteristics of RDNPs. For this we had compiled a comprehensive list of US-based rare disease organizations. We were aiming to at least a 20% response rate for the survey. We made it clear in the communication materials that the person to answer the survey questions needs to be someone in a leadership role in the RDNP as they will be the most complete source of deep knowledge of the RDNPs activities and strategy.

Rare Disease Patients and Loved Ones

We asked the participating RDNPs to send the survey to their rare disease patients and their loved one community. We asked the patient themselves to take the survey. If the patient was either a minor or was unable to take the survey themselves, we allowed their loved one (parent, spouse, sibling, etc.) to take the "Patient's loved one, taking survey for a patient" survey.

Rare Disease Researchers & Researchers

We asked the participating RDNPs to send the survey to their rare disease researcher and physician networks. These are researchers whose work relates in some way to the RDNPs mission and physicians who treat the rare disease the RDNP is focused on.

Key Inclusion Criteria:

Any US-based rare disease-focused non-profit organizations, as well as their affiliated US-

based rare disease patients, loved ones, researchers, and physicians were able to participate in this research project.

Key Exclusion Criteria:

Organizations that are not based in the US, not focused on rare diseases, and/or are for-profit companies will not be included in this study, as well as participants that don't fit into our categories (government officials, representatives of pharmaceutical companies, etc.).

Subject Recruitment and Screening

Participating organizations were selected through a method of aggregating various existing lists of RDNPs and asking each of them to then distribute the survey to their patient, loved one, researcher, and physician populations.

Vulnerable Populations

This survey may include a variety of vulnerable populations.

- **Participants under 18** are not directly included in the study, but their experiences may be included in the study through the "Patient's loved one, taking survey for a patient" survey through an adult loved one.
- **Participants with either physician or cognitive disabilities** are able to participate in the study through the "Patient's loved one, taking survey for a patient" survey through an adult loved one.
- **Pregnant women** may be included in the study, but we neither capture this data nor anticipate any higher risk with neither the survey nor the interviews for pregnant

women compared to the general population.

- Because of the nature of the project, all vulnerable populations in relation to health status (**terminally ill, hospitalized, and HIV positive**) are likely to be a part of the patient and loved one populations, but we do not capture data on these characteristics specifically.
- Other vulnerable populations, such as **prisoners, military personnel, nursing home residents** and **economically disadvantaged persons** may be included in the study if they are patients, loved ones, researchers, or physicians associated with our RDNPs, but we do not capture data on these characteristics.

Risk & Benefit Assessment for Participants

There are no direct financial benefits to participants for their involvement. We hope to develop a tool that RDNPs and their affiliates can follow for their own drug repurposing ROADMAP in the future. Participants may feel a sense of accomplishment that they are actively contributing to research that can benefit rare disease care in the US. The survey does not involve the deception of participants. There are few risks to participants. The only potential discomfort or risk associated with this study for participants may be privacy concerns. Participants' privacy, confidentiality and/or anonymity will be maintained to the highest degree permitted by the technology being used by the researchers, and all reasonable precautions will be taken, such as password protection and deidentification of data and sharing only in aggregate form.

Additionally, some people may feel uncomfortable when answering questions about their

quality of life and/or the medications they are taking. Individuals may skip any questions that make them feel uncomfortable. If this research is published in any academic or media platforms (journals, blogs, newspaper articles, etc.) individual participants will not be mentioned by name and all data will be described in aggregate. RDNPs may be named if they consent first. This includes the final version of the ROADMAP tool, which will be made available freely online.

Confidentiality of Data

- Paper-based records will be minimal, but if any identifiable information will be printed, it will be kept in a secure location and only be accessible to those involved in the study.
- Computer-based files will only be made available to those involved in the study through the use of access privileges and passwords.
- Prior to access to any study-related information, those involved in the study will be required to agree to protect the security and confidentiality of identifiable information.
- Whenever feasible, identifiers will be removed from study-related information.
- Precautions are in place to ensure the data is secure by using passwords and encryption because the research involves web-based surveys.

Compensation

Subjects will not be financially compensated for their participation.

Consent Process

All survey participants had to read and acknowledge understanding the requirements of the study via an online informed consent form prior to taking the survey. There were various levels of consent included after the general survey consent:

- Option to consent for optional follow-up interviews in the future (participants enter their email)
- Option to consent to disclose the names of the participating RDNP as a part of the survey process, to be displayed on the website, in any project-related reports or publications, and in the network mapping visualizations.
- Optional consent for the patient, loved one, physician, and researcher communities to make their de-identified aggregate data and findings gathered from the surveys available for the organization they are a member of.

Survey Distribution

The survey utilized the Qualtrics platform for survey execution. We set up multiple channels of distribution:

- Asking the Chan Zuckerberg Initiative to distribute to their RDNP member networks on our behalf
- Sending RDNPs an email directly.
- Emailing the survey link directly to CDCN's patient, loved one, physician and researcher communities

The instructions for participation was twofold:

1. For a leadership representative of the RDNP to take the survey on behalf of their organization
2. For the RDNP to distribute the survey link to their patient, loved one, physician, and researcher networks

Survey Data Analysis

The data analysis was broken down into three sections: Quality Analysis, Descriptive Analysis and Subgroup Level Analysis.

1. **QUALITY ANALYSIS**

Goal: to check the level of completeness/reliability/representativeness of the dataset

- Data cleaning (removing duplicates, errors, spelling errors, etc.
- Data checks:
    - Check that all organizations are US based, rare disease based and are non-profits (meet inclusion criteria)
- Consolidating discrepancies:
    - Multiple organization representatives took the survey and they have different answers
    - Consolidating incompletes and skipped answers (potential sources of data - which questions were often skipped, where did people drop off the survey)
    - Outstanding decisions as to threshold for data aggregation for patients/loved ones/physicians where there are not a lot of responses

- Standardize data:
    - Make sure all drug names are consistent (generic)
    - Make sure all organization names are accurate

2. **DESCRIPTIVE ANALYSIS**

Goal: to check basic assumptions and get big picture data

- Organizations (verified RDNPs)
    - Interest in drug repurposing
        - How many orgs expressed high/very high interest in drug repurposing?
        - How many orgs expressed low/very low interest in drug repurposing? What reasons do they give?
        - How familiar are these orgs with drug repurposing?
    - Pursuit in drug repurposing
        - How many orgs are actively pursuing drug repurposing projects? What stages are they in?
        - Are orgs pursuing more than one drug repurposing project at once? How do the stages of these projects compare?
        - What are the biggest roadblocks in drug repurposing?
    - Success in drug repurposing
        - How many orgs consider that they've successfully completed a drug repurposing project?
        - How do orgs define success? What kinds of success endpoints have they set for their projects?
        - What do orgs state could help them be more successful?

3. **SUBGROUP ANALYSIS LEVEL**

Goal: to get a deeper understanding of the factors that impact big picture data points

- How each of the data points from the "big question analysis level" are impacted by:
  - RDNP characteristics:
    - RDNP focus (disease and types of activities)
    - RDNP resources (biobank, patient registry, natural history study, scientific advisory board, etc)
    - RDNP level of funding, funding distribution and sources
    - RDNP age (year of founding)
  - Rare disease characteristics:
    - Disease state of research (availability of treatment guidelines, diagnostic criteria, ICD code, biomarkers)
  - Drug repurposing indicators:
    - Existence of FDA approved drugs for the RDNP's rare disease and their efficacy and availability
    - Existence of off label drugs for the RDNP's rare disease and their efficacy and availability
    - Existence of other actors who are pursuing drug repurposing
    - Prior drug repurposing experience (positive/negative)
  - Collaboration indicators:
    - Types of collaboration/knowledge sharing activities the RDNP is involved in
    - Which RDNPs/other types of organizations does the RDNP collaborate with and why/why not

Outcomes of Survey

We were aiming to have the following outcomes:

- A typology of RDNPs based on basic organizational and disease characteristics, levels of knowledge sharing/collaboration and interest/success in drug repurposing into a typology for in-depth interviews and case studies

- A preliminary understanding of the associations between certain characteristics and interest or success in drug repurposing
- Foundational insights as to RDNPs' understanding of and interest in drug repurposing
- Preliminary data on where RDNPs are in the process of drug repurposing
- Data on the experiences of other stakeholders (patient, loved one, physician and researcher) as to drug repurposing.

Appendix B: ROADMAP Survey Text

Q1

Welcome to the Repurposing Of All Drugs, Mapping All Paths (ROADMAP) initiative, led by the Castleman Disease Collaborative Network (CDCN) and supported by the Chan Zuckerberg Initiative. Thank you so much for helping us to better understanding drug repurposing for rare diseases and to revolutionize the field! Please confirm your language preference below.

Bienvenido a la iniciativa Reutilización de Todos Los Medicamentos, el proyecto "ROADMAP", dirigido por Castleman Disease Collaborative Network (CDCN) y apoyado por la Iniciativa de Chan Zuckerberg. ¡Muchas gracias por ayudarnos a comprender la reutilización de fármacos para enfermedades raras y a revolucionar la disciplina! Por favor confirme su preferencia de idioma abajo.

- ○ Continue in English (4)
- ○ Continuar en Español *opción disponible solo para pacientes y seres queridos del paciente* (5)

Start of Block: Consent Form

Q2 **Thank you for considering taking part in the ROADMAP Project. The purpose of the below consent form is to provide you with information about participation in the research study and offer you the opportunity to decide whether you wish to participate. You can take as much time as you wish to decide and can ask any questions you have now, during, or after the research is complete.**

Informed Consent Form for Adult Subjects, Legally Authorized Representatives of Adults Unable to Provide Consent and Parents/Legal Guardians of Minors

Study Sponsor: The Castleman Disease Collaborative Network (CDCN)

Study Title: ROADMAP (Repurposing Of All Drugs, Mapping All Paths): Understanding the role of rare disease non-profits in accelerating data-driven drug repurposing

Principal Investigator: Dr. David Fajgenbaum, MD, david@castlemannetwork.org

Co-Investigator: Ania Korsunska, PhD candidate at Syracuse University and Biomedical Leadership Fellow at the Castleman Disease Collaborative Network (CDCN), ania@castlemannetwork.org

Address: Perelman School of Medicine (University of Pennsylvania) and Castleman Disease Collaborative Network (CDCN), PO Box 3614, Paso Robles, CA, 93447, USA

You are being asked to participate in a research study being run by researchers at the Castleman Disease Collaborative Network.

What is the purpose of this research study?

The purpose for this research study is to understand the experience different stakeholders (representatives of non-profit organization representatives, rare disease patients, loved ones [defined as any person performing the role of caretaker in regard to the health of a patient, including but not limited to parents, spouses, siblings, or formal legal guardians with no direct family connection], researchers and physicians) have with drug repurposing for the rare diseases. The data from this study will inform a ROADMAP tool that rare disease organizations can use to guide their drug repurposing efforts in the future.

What does participation in this study involve?

You are being asked to participate in an online survey that will take approximately 20 minutes. You may also choose to indicate that you are interested in participating in optional interviews to be held at a later time. The interviews will be conducted online via Zoom or a similar online platform. You may indicate if you consent to being contacted for follow up interviews on the next page.

This research study may involve subjects who may or may not have the capacity to consent to take part in the study. When the subject cannot legally consent to take part, pronouns "you" and "your" should be read as referring to the subject rather than the person (legally authorized representative) who is signing and dating this form for the subject. If you are the parent or legal guardian of a child, when you appears in this form, it refers to your child except where it says otherwise.

Participation in this study is voluntary. There is no cost to you for participating. You may refuse to participate or discontinue your involvement at any time without penalty or loss of benefits. You may choose to skip a question or opt out of any part of the study.

If you are an employee of this study site, you are under no obligation to participate in this study. You may withdraw from the study at any time and for any reason, and neither your decision to participate in the study, nor any decision on your part to withdraw, will have any effect on your performance appraisal or employment at this study site. You may refuse to participate or you may withdraw from the study at any time without penalty or anyone blaming you.

The study investigator or the sponsor can stop your participation at any time without your consent for the following reasons:

- If you fail to follow directions for participating in the study
- If it is discovered that you do not meet the study requirements
- If the study is canceled
- For administrative reasons

There are no direct financial or any other benefits to you by participating in the research survey. You will not be paid for your participation in this research. However, we hope that the knowledge that your participation will be helpful for rare diseases in the future is beneficial to you. This study is for research purposes only. Your only alternative is to not participate in this

study. Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be provided to you.

Are there any potential risks in participating?

All research data collected will be stored securely and confidentially. The only potential discomfort or risk associated with this study for you may be privacy concerns. Your privacy, confidentiality and/or anonymity will be maintained to the highest degree permitted by the technology being used by the researchers, and all reasonable precautions will be taken, such as password protection and deidentification of data in aggregate. It is important for you to understand that no guarantees can be made regarding the interception of data sent via the internet by third parties. However, you will not be asked to provide your name at any point and providing your email address is optional.

Additionally, some people may feel uncomfortable when answering questions about their quality of life and/or the medications they are taking. As a subject in this study, you have the right to skip any questions on the surveys or end the survey for any reason at any time. You may also withdraw from the study at any point, for any reason. There are no consequences for stopping your participation in the study.

As part of this research, you may be required to use a website (Qualtrics) in order to participate in the survey. You may participate via computer, phone or other electronics device (e.g.iPad). While using these, no information about you will be collected outside of your answers to the research questions, and no information about you will shared with people outside of the study without your consent. If you wish to review the Qualtrics Terms of Service you may do so at https://www.qualtrics.com/terms-of-service. While the Terms of Service may include statements limiting your rights if you are harmed as a result of your use of the site in this study, you do not release the study investigator, sponsor, institution, or agents for responsibilities

from mistakes. You also do not waive any of your rights as a research subject.

If this research is published in any academic or media platforms (journals, blogs, newspaper articles, etc.) you will not be mentioned by name and all data will be described in aggregate. This includes the final version of the ROADMAP tool, which will be made available freely online. The researchers do not plan to monetize or financially benefit from any data collected or insights gained from the research.

Who do I contact if I have any questions?

During the study, if you have questions, or concerns about the study, please contact the study co-investigator at ania@castlemannetwork.org.

If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact the IRB. An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects.

Contact by mail: Study Subject Adviser, Advarra IRB, 6100 Merriweather Dr., Suite 600, Columbia, MD 21044 Contact by phone (toll free): 877-992-4724

Contact by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: **Pro00055201.** Please print a copy of this consent form if you would like to keep it for your records.

- ○ I consent to participate in this research study. I certify that I am 18 years of age or older, and understand what my participation in this research involves.
- ○ I do not consent to participate in this research study.

Skip To: End of Survey If Q2 = I do not consent to participate in this research study.

Q3 Which rare disease organization provided you with this survey link (emailed directly or posted on social media)? Please type out full name of the organization, avoid acronyms.

_____

Q301 Which rare disease organization do you represent (for rare disease non-profit representatives) or are a part of (for patients, loved ones, physicians and researchers?) Please type out full name of the organization, avoid acronyms.

_____

Q4 Is the organization you represent or are a part of based in the US?

- ○ Yes
- ○ No

Display This Question:

If Q4 = No

Q5 Is this organization pursuing drug repurposing in the US?

- ○ Yes
- ○ No

Q6 We are currently only focusing on organizations in the US or those that are pursuing drug repurposing in the US. In future iterations of the ROADMAP project, we hope to include organizations in other countries. Thank you for your time!

Skip To: End of Survey If Q6 Is Displayed

Q294 Are you personally based (live/work) in the US?

- ○ Yes
- ○ No

Display This Question: If Q294 = No

Q295 Do you personally have experience with repurposing drugs in the US?

- ○ Yes
- ○ No

Q297 We are currently only focusing on participants based in the US or those who have experience with drug repurposing in the US, due to the difference in approved drugs and approval procedures in different countries. In future iterations of the ROADMAP project, we hope to include the experiences of in other countries. Thank you for your time!

Skip To: End of Survey If Q297 Is Displayed

Q7 What stakeholder group(s) do you represent? (Select all that apply)

- ☐ Rare disease non-profit organization representative
- ☐ Rare disease patient
- ☐ Rare disease patient's loved one (parent, spouse, sibling, etc.)
- ☐ Rare disease physician
- ☐ Rare disease researcher
- ☐ Other stakeholder (pharmaceutical company, regulatory agency, etc).

Display This Question:

If If What stakeholder group(s) do you represent? (Select all that apply)

q://QID55/SelectedChoicesCount Is Greater Than 1

Q8 **If you represent multiple stakeholder categories**, please perform the survey that aligns with your primary stakeholder role.

If you are able to, please consider taking additional surveys to capture your other various perspectives. You can select all the surveys you wish to take below, complete as much as you are able to now, and then come back and complete the remaining survey questions at a later time.

Display This Question:

If Q7 = Rare disease patient's loved one (parent, spouse, sibling, etc.)

Q9 **If you are a loved one of a rare disease patient** - this includes family members, caregivers, spouses, etc. - where the patient is either a minor or is unable to take the survey themselves - please take the "Rare disease patient's loved one, taking survey for a patient" survey. It is the same as the patient survey.

Display This Question:

If Q7 = Rare disease patient

And Q7 = Rare disease patient's loved one (parent, spouse, sibling, etc.)

Q300 If you are both a rare disease patient AND a loved one of a rare disease patient who is a minor or unable to take the survey themselves - feel free to only take the "Patient" survey. The questions are the same in the "Patient" and "Patient's loved one" survey.

Q10 If you received this survey from **multiple rare disease organization**s, please fill out the survey for the rare disease that you most closely associate yourself with. If you are able to, please consider taking the survey additional times for each rare disease as your perspective and experience may differ. Which survey or surveys would you like to participate in? (Hover over each answer choice for more information)

Display This Choice: If Q7 = Rare disease non-profit organization representative (CEO, founder, executive director, etc.)

☐ Rare disease non-profit organization representative

Display This Choice: If Q7 = Rare disease patient

☐ Rare disease patient

Display This Choice: If Q7 = Rare disease patient's loved one (parent, spouse, sibling, etc.)

☐ Rare disease patient's loved one, taking survey for a patient

Display This Choice: If Q7 = Rare disease physician

☐ Rare disease physician

Display This Choice: If Q7 = Rare disease researcher

☐ Rare disease researcher

Display This Question: If Q10 = Rare disease non-profit organization representative

Q11 For research purposes, do you consent for your organization's name to be listed as a participating organization on the CDCN website, on any future ROADMAP project-specific website that may be built in the future and in any reports or publications associated with this research? Any associated data will only be reported in de-identified, aggregate form, unless further consent is given for in depth case study analysis of my particular organization for further research. **This is optional and will not impact your participation in the project.**

- ○ Yes, I consent for my organization's name to be listed as a ROADMAP initiative participating organization.
- ○ No, I prefer for my organization's name to NOT be listed as a ROADMAP initiative participating organization.

Q12 We are interested in following up with a select group of rare disease organizations, patients, loved ones, researchers and physicians for 30-60 minute interviews regarding their experience with drug repurposing, including challenges faced and brainstorming solutions. These interviews will be **incredibly valuable** as they will provide vital information for us to use for the ROADMAP tool. This tool will help rare disease organizations better understand the prerequisites, steps, challenges and success outcomes of drug repurposing and will be open to use for the entire rare disease community. We hope it will be a step towards making drug repurposing easier and more accessible for more rare diseases.

Please indicate below if you're interested in participating in these interviews. **This is optional and will not impact your participation in the project.** (Note: consenting below does not

guarantee that you will be contacted. At the time of contact, you will be given another consent form and can change your mind about participating in the interviews at any time.)

- ○ I consent to being contacted by the study researchers for follow up interviews.
- ○ I prefer to not be contacted by the study researchers for follow up interviews.

Display This Question:If Q12 = I consent to being contacted by the study researchers for follow up interviews.

Q13 Please enter your email address where the study authors may contact you for follow up interviews:

_____

Display This Question:

If Q10 = Rare disease patient

Or Q10 = Rare disease patient's loved one, taking survey for a patient

Or Q10 = Rare disease physician

Or Q10 = Rare disease researcher

Q14 We have reached out to over 800 rare disease non-profit organizations and asked them to participate in this project by taking the survey and distributing it to their patient, loved one, physician and researcher communities, which is how it got to you!

One huge benefit to participating in this project for the organization you're a member of is to be able to learn from the data you provide for this project. So, in addition to utilizing your data to inform the ROADMAP project, we are allowing you the option to consent for **your data to be shared with the organization directly**. If you consent, your data will be de-identified before

being shared, so your responses will be anonymous. **This is optional and will not impact your participation in the project.**

- ○ I consent for the data I provide in this survey to be shared with the rare disease organization I'm a part of.
- ○ I prefer for the data I provide NOT be shared with rare disease organization I'm a part of.

Q15 The following questions pertain to you primarily as a **rare disease organization representative**. These questions should take ~20 minutes to answer. If you represent multiple stakeholders and have opted to participate in multiple sets of questions, those sections will come later in the survey.

Q16 What rare disease or rare disease area does your organization focus on? (Please type in full rare disease name(s), avoiding acronyms.)

_____

Q17 What is your official title in your rare disease organization (e.g. executive director, founder, etc.)?

_____

Q18 What year was the organization founded?

_____

Q19 How many full time staff members do you currently have?

_____

Q20 What kind of activities does your rare disease organization do? (Select all that apply)

- ☐ Patient education (e.g. flyers, patient education conferences)
- ☐ Patient community development (e.g. communication, community connection)
- ☐ Patient financial support (e.g. financial assistance for medical travel, expenses, genetic testing, etc.)
- ☐ Disease awareness
- ☐ Newly diagnosed patient support (e.g. connecting patients to physicians)
- ☐ Patient data collection (e.g. natural history registry, biobank)
- ☐ Developing centers of excellence and disease area guidelines
- ☐ Basic research
- ☐ Translational research
- ☐ Novel drug development
- ☐ Drug repurposing
- ☐ Fundraising efforts
- ☐ Policy development and advocacy
- ☐ Other, please specify _____

Q21 Out of these activities, which are the top 3 most important that the organization focuses on?

- ☐ Patient education (e.g. flyers, patient education conferences)
- ☐ Patient community development (e.g. communication, community connection)
- ☐ Patient financial support (e.g. financial assistance for medical travel, expenses, genetic testing, etc.)
- ☐ Disease awareness
- ☐ Newly diagnosed patient support (e.g. connecting patients to physicians)
- ☐ Patient data collection (e.g. natural history registry, biobank)
- ☐ Developing centers of excellence and disease area guidelines
- ☐ Basic research
- ☐ Translational research
- ☐ Novel drug development
- ☐ Drug repurposing
- ☐ Fundraising efforts
- ☐ Policy development and advocacy
- ☐ Other, please specify

Q22 In what way is your organization involved in supporting research in your rare disease space? (Select all that apply)

- ☐ We currently do not fund or direct research, and do not plan to do so in the future
- ☐ We currently do not fund or direct research, but are interested in doing so in the future
- ☐ We fund the most promising research grants that we receive through our requests for proposals (RFP) program
- ☐ We provide additional non-financial support to researchers (i.e. help researchers procure laboratory supplies, animal models, biospecimens and or patient samples for research)
- ☐ We find and fund researchers to study the questions that are important to our disease
- ☐ Our organization directs researchers and studies in our disease space
- ☐ Other, please specify _____

Q23 What is the average annual funding that your organization has had in the past 3 years (both raised internally and received from external grants and philanthropists)?

- ○ Less than $5,000
- ○ Between $5,000 and $10,000
- ○ Between $10,000 and $50,000
- ○ Between $50,000 and $100,000
- ○ Between $100,000 and $500,000
- ○ Between $500,000 and $1,000,000
- ○ Between $1,000,000 and $2,000,000
- ○ Between $2,000,000 and $5,000,
- ○ More than $5,000,000

Display This Question:

If Q22 != We currently do not fund or direct research, and do not plan to do so in the future

And Q22 != We currently do not fund or direct research, but are interested in doing so in the future

Q24 What percentage of this funding goes towards supporting research?

Not Applicable

0 10 20 30 40 50 60 70 80 90 100

Percentage of funding that supports research ()	

Display This Question:If Q22 != We currently do not fund or direct research, and do not plan to do so in the future

Q25 What kind of fundraising activities is your organization involved in to be able to fund research (now or in future)?

- ☐ Grassroots / Patient-led fundraising
- ☐ Organization-led events
- ☐ Grant-writing / Applying for grants
- ☐ Engaging with corporate/ industry donors
- ☐ Engaging with major private donors / philanthropists
- ☐ Employer matching
- ☐ Family foundation / creating a trust
- ☐ Other, please specify _____

Q26 Does your organization currently have the following resources:

	Yes	No, but we are interested in developing in the future	Not yet, but we are actively developing	No, and we are not interested in developing	N/A
Contact registry (i.e. database of contact information for patients and loved ones)	○	○	○	○	○
Community discussion space (e.g. Facebook group)	○	○	○	○	○
Patient & Loved one community gatherings	○	○	○	○	○
Patient community navigator (i.e. person on staff that is in charge of patient support)	○	○	○	○	○
Research Conferences	○	○	○	○	○
Fundraising events	○	○	○	○	○
Scientific or medical advisory board	○	○	○	○	○
Patient registry (i.e. database where patients or family members provide information about their disease)	○	○	○	○	○
Natural history study (i.e. research study utilizing long-term tracking of patient outcomes and response to treatment)	○	○	○	○	○
Patient reported outcomes (PRO) assessments	○	○	○	○	○
Biobank to collect patient samples (e.g. blood, tissue, etc.)	○	○	○	○	○
Research strategy or research agenda	○	○	○	○	○

Display This Question: If Q26 = No, and we are not interested in developing

Carry Forward Selected Choices from "Q26"

Q27 Please select the reasons you're not interested in developing {RESOURCE NAME}?

	Other organizations focused on the same/similar rare disease or genetic mutation as your organization already developed or is developing (1)	Academic or industry partners have already developed (2)	Not feasible to develop (based on rare disease characteristics) (3)	Not enough funding (4)	Not enough people (staff, researchers, patients, etc.) (6)	Not enough data or knowledge about rare disease (8)	Lack of academic or industry collaboration, partnership, or support (9)	Not interested (5)
Contact registry (i.e. database of contact information for patients and loved ones) (x9)	☐	☐	☐	☐	☐	☐	☐	☐
Community discussion space (e.g. Facebook group) (x4)	☐	☐	☐	☐	☐	☐	☐	☐
Patient & Loved one community gatherings (x5)	☐	☐	☐	☐	☐	☐	☐	☐
Patient community navigator (i.e. person on staff that is in charge of patient support) (x16)	☐	☐	☐	☐	☐	☐	☐	☐
Research Conferences (x6)	☐	☐	☐	☐	☐	☐	☐	☐
Fundraising events (x7)	☐	☐	☐	☐	☐	☐	☐	☐
Scientific or medical advisory board (x8)	☐	☐	☐	☐	☐	☐	☐	☐
Patient registry (i.e. database where patients or family members provide information about their disease) (x10)	☐	☐	☐	☐	☐	☐	☐	☐
Natural history study (i.e. research study utilizing long-term tracking of patient outcomes and response to treatment) (x11)	☐	☐	☐	☐	☐	☐	☐	☐
Patient reported outcomes (PRO) assessments (x12)	☐	☐	☐	☐	☐	☐	☐	☐
Biobank to collect patient samples (e.g. blood, tissue, etc.) (x13)	☐	☐	☐	☐	☐	☐	☐	☐
Research strategy or research agenda (x14)	☐	☐	☐	☐	☐	☐	☐	☐

Q28 Regardless of your organization's involvement in developing them, does your rare disease of focus currently have the following?

	Yes (1)	No, and not planned (2)	No, but in progress (3)	Unknown (4)	N/A (5)
Clear understanding of etiology or disease pathogenesis (1)	○	○	○	○	○
Treatment guidelines / Standard of Care guidelines (4)	○	○	○	○	○
Diagnostic Criteria (5)	○	○	○	○	○
A specific ICD-10 code (6)	○	○	○	○	○
Predictive biomarkers (i.e. to help to predict who likely to benefit from one treatment or another) (7)	○	○	○	○	○
Identified genetic mutation (8)	○	○	○	○	○
Animal models (9)	○	○	○	○	○
Cell lines (10)	○	○	○	○	○

Q29 Are there any FDA-approved drugs for your rare disease or diseases of focus?

- Yes
- No
- I don't know

Display This Question: If Q29 = Yes

Q30 Please list this/these drug(s) here. (Drugs which are FDA-approved for your rare disease)

- Drug 1 _____
- Drug 2 _____
- Drug 3 _____
- Drug 4 _____
- Drug 5 _____
- Drug 6 _____
- Drug 7 _____
- Drug 8 _____
- Drug 9 _____
- Drug 10 _____

Q31

	0 10 20 30 40 50 60 70 80 90 100
What percentage of your rare disease patient population benefits from {DRUG NAME}? ()	

Q32 For those patients that benefit from it, how effective is {DRUG NAME} at:

	Not effective	Neutral or no effect	Slightly effective	Moderately effective	Very effective	Unknown benefit
	1	2	3	4	5	
reducing the overall symptoms associated with your rare disease of focus for at least some of your patient population? ()						
preventing worsening of your rare disease of focus for at least some of your patient population? ()						
completely addressing all challenges associated with your rare disease of focus for at least some of your patient population? ()						

Q33 What roadblocks does your patient population have in getting access to {DRUG NAME} ? (Select all that apply)

- ☐ Insurance coverage / approval issues
- ☐ Affordability issues (even with insurance
- ☐ Physician won't prescribe it
- ☐ Accessibility (e.g. drug is not available in some hospitals)
- ☐ Other, please specify _____
- ☐ No roadblocks

Q34 Would you consider ${{DRUG NAME} to be a "cure" at least for some of your patient population? (Here, "cure" is defined as having no evidence of disease and no longer needing to take medication.)

- ○ Yes
- ○ No

Questions 31-34 REPEATED FOR ALL DRUGS LISTED IN Q30

Q35 Have any other drugs (drugs which have **not** been FDA approved for your rare disease of focus), been identified as promising for your rare disease of interest?

- ○ Yes
- ○ No
- ○ I don't know

Display This Question: If Q35 = Yes

Q36 Please list this/these drug(s) here. Drugs which are promising but not FDA-approved for your rare disease)

- ○ Drug 1 _____
- ○ Drug 2 _____
- ○ Drug 3 _____
- ○ Drug 4 _____
- ○ Drug 5 _____
- ○ Drug 6 _____
- ○ Drug 7 _____
- ○ Drug 8 _____
- ○ Drug 9 _____
- ○ Drug 10 _____

Q37

	0 10 20 30 40 50 60 70 80 90 100
What percentage of your rare disease patient population benefits from {DRUG NAME}? ()	

Q38 For those patients that benefit from it, how effective is {DRUG NAME} at:

	Not effective	Slightly effective	Neutral or no effect	Moderately effective	Very effective	Unknown benefit
	1	2	3	4	5	
reducing the overall symptoms associated with your rare disease of focus for at least some of your patient population? ()						
preventing worsening of your rare disease of focus for at least some of your patient population? ()						
completely addressing all challenges associated with your rare disease of focus for at least some of your patient population? ()						

Q39 What roadblocks does your patient population have in getting access to {DRUG NAME} ?(Select all that apply)

- ☐ Insurance coverage / approval issues
- ☐ Affordability issues (even with insurance)
- ☐ Physician won't prescribe it
- ☐ Accessibility (e.g. drug is not available in some hospitals)
- ☐ Other, please specify _____
- ☐ No roadblocks

Q40 Would you consider {DRUG NAME} to be a "cure" at least for some of your patient population? (Here, "cure" is defined as having no evidence of disease and no longer needing to take medication.)

- ○ Yes (1)
- ○ No (2)

Questions 37-40 REPEATED FOR ALL DRUGS LISTED IN Q36

Q41

○ Unknown

	0 10 20 30 40 50 60 70 80 90 100
Overall, what percentage of your patient population are currently helped with a drug, FDA approved or not?	
Out of the above percentage of patients which are being helped with a drug, FDA approved or not, **how much** have these patients improved? (0% - not improved at all, 100% - improved to the extent of having no evidence of disease, regardless of whether they continue to take medication or not.)	
Among all patients with your rare disease, what percentage of patients have had a reduction in the burden of their disease from **a treatment that your organization supported** in some way, through funding, research, resources, or otherwise?	

Q42 Does your organization systematically track off-label drug use in your patient population?

- ○ Yes
- ○ No

Display This Question: If Q42 = Yes

Q43 How do you track this off label use?

- ☐ Patient registry
- ☐ Direct email communication
- ☐ Natural history study
- ☐ Reports from the rare disease physician community
- ☐ From the published scientific literature (
- ☐ Other, please specify _____

Display This Question: If Q42 = No

Q44 Are you interested in tracking this information in the future?

- ○ Yes
- ○ No

Q45 **This project is interested in understanding your experience with drug repurposing. There are many different definitions of drug repurposing being used. For the purposes of this survey, we are utilizing a broad definition of drug repurposing:** "A process of research to identify potential treatments that are already FDA-approved or in development for one disease, for use in another disease by gathering data and analyzing efficacy in order to improve treatment guidelines and access". This includes the following:
Repurposing: taking an FDA-approved drug and using it for another disease from the one that it is approved for.
Repositioning: taking a drug with some safety and/or efficacy data in one disease and modifying its structure for use in another disease.
Reformulation: taking a drug with some safety and/or efficacy data in one disease and modifying its method of administration or dose for use in another disease.
Rescue: taking a drug that's not FDA-approved for any diseases due to complications in either safety and/or efficacy in the originally intended disease and trying it for another disease while maintaining the same structure and method of administration.

Q46 Please rate your familiarity with drug repurposing prior to this survey.

- ○ Not familiar at all
- ○ Slightly familiar
- ○ Moderately familiar
- ○ Very familiar
- ○ Extremely familiar

Q47 Please rate your level of interest in pursuing drug repurposing prior to this survey.

- ○ Not interested at all
- ○ Slightly interested
- ○ Moderately interested
- ○ Very interested
- ○ Extremely interested

Q48 Has your organization been involved in any drug repurposing efforts for your rare disease of interest?

- ○ Yes
- ○ No

Display This Question: If Q48 = Yes

Q49 Which drugs have you been involved in repurposing?

- ○ Drug 1 _____
- ○ Drug 2 _____
- ○ Drug 3 _____
- ○ Drug 4 _____
- ○ Drug 5 _____
- ○ Drug 6 _____
- ○ Drug 7 _____
- ○ Drug 8 _____
- ○ Drug 9 _____
- ○ Drug 10 _____

Q50 Has any drug repurposing initiatives been done for your rare disease of interest without your organization's involvement (i.e. efforts by other rare disease organizations focused on the same rare disease, by pharmaceutical companies, etc.)?

- ○ Yes
- ○ No

Display This Question: If Q48 = No

Q51 Would you be interested in pursuing drug repurposing for your rare disease of interest in the future?

- ○ Yes
- ○ Maybe / Not sure
- ○ No

Display This Question: If Q48 = No

Q52 What are some reasons for why your organization has not supported drug repurposing? (Select all that apply)

- ☐ Never heard of drug repurposing before
- ☐ No need - FDA approved drugs exist for our rare disease of interest
- ☐ Lack of understanding of the steps towards successful drug repurposing
- ☐ Lack of understanding of disease etiology
- ☐ Lack of drug target
- ☐ Lack of pharmaceutical company support
- ☐ Lack of sufficient financial resources
- ☐ Lack of sufficient patient population to study
- ☐ Lack of patient support (i.e. patients won't enroll in clinical trials)
- ☐ Lack of research support (i.e. researchers aren't interested in our rare disease of focus)
- ☐ Lack of researcher network (i.e. can't locate researchers working on our rare disease of focus)
- ☐ Lack of physician support (i.e. physicians aren't interested in being PIs for our clinical trial)

- [ ] Lack of staff to support project
- [ ] Lack of resources to support systematic data collection (i.e. patient registry, natural history study, etc)
- [ ] Lack of time/not a priority at present
- [ ] Regulatory roadblocks
- [ ] None
- [ ] Other, please specify _____

Q53 What was your organization's involvement in the repurposing process for {DRUG NAME}?

(Select all that apply)

- [ ] Funded preclinical research
- [ ] Provided research ideas that led towards drug repurposing
- [ ] Facilitated national or international researcher collaboration
- [ ] Gathered and shared patient samples for research
- [ ] Supported the development of a clinical trial (e.g. secured funding, identified PI, etc.)
- [ ] Supported patient recruitment into a clinical trial
- [ ] Support utilization of the drug off label
- [ ] Support compassionate use during ongoing experimental clinical trials
- [ ] Tracked off label drug usage in a patient registry, provided this data for research
- [ ] After FDA approval, informed patient and physicians of the results
- [ ] After FDA approval, worked with insurance companies to ensure coverage and promote patient access to the new drug.
- [ ] Other, please specify _____

Q54 Through which process was {DRUG NAME}? identified as promising? (Select all that apply)

- [ ] High throughput drug screening being conducted (i.e. testing existing drugs on cell lines)
- [ ] Utilizing AI / ML to identify potential repurposed treatments
- [ ] Preclinical research
- [ ] Translational research
- [ ] Analyzing patient's medical data to identify drugs that look promising based on off-label use
- [ ] Literature analysis / Meta-analysis

- [ ] Looking at similar diseases and what drugs are utilized or are promising for that patient population
- [ ] Other _____

Q55 What stage is the repurposing process currently for {DRUG NAME}? Select multiple if this drug is simultaneously in multiple stages.

- [ ] Securing funding
- [ ] Testing existing drugs in mouse or other animal models
- [ ] Recruiting patients for clinical trials
- [ ] Running Phase I clinical trials
- [ ] Running Phase II clinical trials
- [ ] Running Phase III clinical trials
- [ ] Analyzing clinical trial data
- [ ] Use of the drug in patients off label (i.e. without getting FDA approval)
- [ ] Submitting to FDA for approval
- [ ] FDA approval granted
- [ ] Abandoned
- [ ] Other, please specify _____

Q56 What roadblocks have you encountered in the process of repurposing of {DRUG NAME}? if any? (Select all that apply)

- [ ] Lack of pharmaceutical company support
- [ ] Lack of sufficient financial resources
- [ ] Lack of sufficient patient population to study
- [ ] Lack of patient support (i.e. patients won't enroll in clinical trials)
- [ ] Lack of research support (i.e. researchers aren't interested in your rare disease of focus)
- [ ] Lack of researcher network (i.e. can't locate researchers working on your rare disease of focus)
- [ ] Lack of physician support (i.e. physicians aren't interested in being PIs for your clinical trial)
- [ ] Lack of staff to support project
- [ ] Lack of resources to support systematic data collection (i.e. patient registry, natural history study, etc)

- [ ] Lack of understanding of the steps towards successful drug repurposing
- [ ] Lack of time / not a priority at present
- [ ] Regulatory roadblocks
- [ ] None
- [ ] Other, please specify _____

Q57 What was / were the success endpoint(s) you are aiming for the repurposing of {DRUG NAME}? (Select up to three)

- [ ] Drug to receive FDA approval for your rare disease
- [ ] Drug to be freely available to patients off label with safety / efficacy data
- [ ] Drug to be freely available to patients off label, even without safety / efficacy data
- [ ] Drug to provide significant reduction in symptoms
- [ ] Drug to provide significant improvement in quality of life (QOL)
- [ ] Drug to increase life expectancy / decrease in mortality
- [ ] Drug to provide cure of disease
- [ ] Drug to provide prevention of relapse
- [ ] Other, please specify _____

Carry Forward Selected Choices - Entered Text from "Q57"

Q58 Have this/these success endpoint(s) for the repurposing of {DRUG NAME} been achieved as of today?

	Yes	No
Drug to receive FDA approval for your rare disease	○	○
Drug to be freely available to patients off label with safety / efficacy data	○	○
Drug to be freely available to patients off label, even without safety / efficacy data	○	○
Drug to provide significant reduction in symptoms	○	○
Drug to provide significant improvement in quality of life (QOL)	○	○
Drug to increase life expectancy / decrease in mortality	○	○
Drug to provide cure of disease	○	○
Drug to provide prevention of relapse	○	○
Other, please specify	○	○

Questions 50-58 REPEATED FOR ALL DRUGS LISTED IN Q49

Q59 What additional support could help improve the speed or efficiency of your rare disease drug repurposing work? (Please select all areas where more resources or more collaboration could be helpful)

	More Resources	More Collaboration	More data / Information	N/A
Developing or utilizing infrastructure and models (e.g. Biobanks, cell lines, and mouse models)	☐	☐	☐	☐
Identifying a drug target (i.e. understand biology of the disease)	☐	☐	☐	☐
Identifying the ideal drug (i.e. performing drug screen, understanding toxicity)	☐	☐	☐	☐
Conducting preclinical work to show the drug is beneficial	☐	☐	☐	☐
Developing definition of outcomes measures that are meaningful and robust	☐	☐	☐	☐
Developing clinical trials (i.e. creating relationships with pharmaceutical company, funding, patient recruitment, execution)	☐	☐	☐	☐
Information on how to support drug repurposing (i.e. experiences of other researchers, explanations of the benefits, intellectual property protection, etc.)	☐	☐	☐	☐
Collaboration with other organizations with a similar disease pathway or treatment target	☐	☐	☐	☐
Understanding of the natural history of the disease	☐	☐	☐	☐
Improved patient access to drug (off-label)	☐	☐	☐	☐
Other, please specify	☐	☐	☐	☐

Q60 Would you like to share anything else with us about your organization's experiences with drug repurposing or are there any questions or concerns you have about drug repurposing?

_____

_____

Q61 You have now completed the main part of the survey, focused on your organizational characteristics, rare disease state of research and interest in / experience with drug repurposing. Additionally, we are also interested in your collaboration network. These questions will take ~5 minutes.

Q62 How many organizations do you collaborate with on a regular basis for either research or community-centered projects? These can include non-profit organizations, pharmaceutical companies, biotech companies, academic institutions, research labs, hospitals, "umbrella" organizations in which you are a member (NORD, Global Genes), any consortiums, alliances or networks you are a part of, etc.

- ○ 1-5 organizations
- ○ 5-10 organizations
- ○ 10-20 organizations
- ○ 20-50 organizations
- ○ 50 or more

Q63 Which organizations would you say are your closest collaborators or partners?

- ○ Organization 1 _____
- ○ Organization 2 _____
- ○ Organization 3 _____
- ○ Organization 4 _____
- ○ Organization 5 _____

Carry Forward Entered Choices - Entered Text from "Q63"

Q64 What kinds of activities do you engage in with these organizations?

	Sharing data and/or samples for research	Applying for funding together	Organization provides us funding	Creating a shared research agenda	Pooling patient populations together to conduct future research	Sharing prior experiences that can inform future decision making (e.g. research processes, drug repurposing steps, etc.)	Sharing resources (e.g. funding, staff, expertise, etc.)	Joint community building & fundraising (e.g. events, education initiatives, etc.)	Co-creating or co-supporting a center of excellence	Conducting research studies, including clinical trials	Other
Organization 1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Organization 2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Organization 3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Organization 4	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Organization 5	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Display This Question: If Q64 = Other

Q65 You selected "other" in the previous question - Please specify:

_____

Q66 Are there organizations focusing on the same rare disease or genetic mutation as your organization (in the US or internationally)?

- ○ Yes
- ○ No

Display This Question: If Q66 = Yes

Q67 Do you collaborate with these organizations (organizations focusing on the same rare disease or genetic mutation as your organization) on a regular basis for either research or community-centered projects?

- ○ Yes
- ○ No

Display This Question: If Q67 = No

Q68 What are some factors that contribute to the lack of collaboration with these organizations? (Select all that apply)

- ☐ Limited financial resources
- ☐ Limited time
- ☐ Limited staff and/or resources
- ☐ Personal disagreements
- ☐ Don’t know how best to collaborate
- ☐ Limited patient population - collaboration would mean pulling resources away from our focus
- ☐ No tangible benefit or reason for collaboration
- ☐ Difference in organizational focus or strategy
- ☐ Different viewpoints on next steps
- ☐ They are no longer active / defunct
- ☐ Other, please specify _____

Q69 Have you merged with or separated from any other rare disease organizations?

- ○ Yes
- ○ No

Display This Question: If Q69 = Yes

Q70 Please briefly describe which organizations you merged with or separated from. If in this process the name of your organization changed, please include this information.

_____

_____

Q71

Did you have any significant issues with the survey that you would like to share or anything else about this project that you would like us to know?

_____

Appendix C: Dissertation Interview Materials

Participation Materials

Dear [NAME],

Thank you again for your participation in this project! We are doing some additional interviews and analysis, this time focusing on organizations who have pursued sirolimus drug repurposing. This data will be utilized for my PhD dissertation research, so your time is very much appreciated.

The purpose of this interview is to explore your organization's experience with drug repurposing sirolimus specifically, diving into your collaboration network and how you share information with them in regards to your drug repurposing experience. Specifically, we're interested in any issues you have faced in this process and thinking through some potential solutions.

Interview Format

The interview (approximately 60 minutes) will be conducted via ZOOM. If needed, the interview may be broken into multiple sessions for your convenience. For the sole purposes of transcription and data analysis, I ask that we record the interview. This recording will be kept private and only shared with the research team, and will be deleted upon completion of the project. The information that you provide will be de-identified and not attributed to you directly in any form without specific permission from you.

Next Steps

If you agree to participate in interviews, please utilize this Calendly link [LINK] to schedule for a time that works best for you.

I really appreciate your time and willingness to share your experience! Thank you! Please let me know if you have any questions. The consent form for this research is attached, please review. We will also discuss these items in the interview prior to recording.

Informed Consent Form

You are being asked to participate in a research study being run by researchers at Syracuse University. The purpose of this form is to provide you with information about participation in a research study and offer you the opportunity to decide whether you wish to participate. You can take as much time as you wish to decide and can ask any questions you have now, during, or after the research is complete.

Purpose of the research

The purpose for this research study is to understand the knowledge sharing practices and challenges of rare disease nonprofit organizations in regards to the repurposing of a specific drug (Sirolimus), as well as considering ways in which this process could be made more clear and efficient.

The data from this study aims to contribute to the body of research in information studies, specifically the literature related to knowledge management. The researchers plan to submit the results to academic conferences and peer review journals to inform the field about this research. Approximately 15-20 participants will participate in this study.

Participation

Specifically, you are being asked to participate in an interview (approximately 60 minutes), which will be conducted virtually via ZOOM. If needed, the interview may be broken into multiple shorter sessions for your convenience. The interview will be conducted by the co-investigator Ania Korsunska.

Participation in this study is voluntary. There is no cost to you for participating. You may refuse to participate or discontinue your involvement at any time without penalty or loss of benefits. You may choose to skip a question during the interview or opt out of any part of the study.

The study investigator, co-investigator or the sponsor can stop your participation at any time without your consent for the following reasons:

- If you fail to follow directions for participating in the study
- If it is discovered that you do not meet the study requirements/inclusion criteria
- If the study is canceled or
- For administrative reasons.

This study is for research purposes only. Your only alternative is to not participate in this study. Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be provided to you.

Benefits

There are no direct financial or any other benefits to you by participating in the research survey. You will not be paid for your participation in this research. However, we hope that the knowledge that your participation in this research will be helpful for a better understanding of the knowledge sharing practices and challenges of rare disease nonprofit organizations in regards to drug repurposing is beneficial to you.

Recording and Data Privacy

For the sole purposes of transcription and data analysis, we ask that we record the interview (both audio and video). The recordings will be done via ZOOM and the interviewer will verbally let you know when the recording is started and stopped, and it may be paused at any time during the interview if necessary. If something is said during the interview, which you prefer to be removed, you may let the interviewer know during or after the interview and anything

requested may be redacted or removed from the transcript. The audio will be transcribed using an automated tool and then later manually cleaned by the co-investigator or research assistant. The interviewer will be using a visualization during the interview, for which the recording of the video will be helpful for later data analysis. Both audio and video recordings will be kept private and only shared with the researchers on this project and will be deleted upon completion of the project. The information that you provide will be de-identified and not attributed to you directly in any form.

All research data collected will be stored securely and confidentially. The only potential discomfort or risk associated with this study for you may be privacy concerns. Whenever one works with email or the internet there is always the risk of compromising privacy, confidentiality, and/or anonymity. Your privacy, confidentiality and/or anonymity will be maintained to the highest degree permitted by the technology being used by the researchers, and all reasonable precautions will be taken, such as password protection and deidentification of data in aggregate. It is important for you to understand that no guarantees can be made regarding the interception of data sent via the internet by third parties. You will not be asked to provide any personally identifiable information during the interview recording.

At any time, if you feel uncomfortable about answering any question for any reason, do not hesitate to let us know, we can move on to the next question, or end the interview at any time. There will be no penalty of any kind in declining to answer or ending the interview at any time.

If this research is published in any academic or media platforms (journals, blogs, newspaper articles, etc.) you will not be mentioned by name and all data will be described in aggregate. The researchers do not plan to monetize or financially benefit from any data collected or insights gained from the research.

Optional consent for organization to be mentioned as a participant

Because this research concerns rare disease nonprofit organizations and their practices, you have the option to consent for the name of your organization to be listed as a participating organization in any reports or publications associated with this research. Any associated data will only be reported in de-identified, aggregate form, unless further consent is given for in depth case study analysis of my particular organization for further research. This is optional and will not impact your participation in the project.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you have questions, concerns or complaints about the study, please contact the study investigator at the email listed on the first page of this consent document.

If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact the IRB. An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects.

SYRACUSE UNIVERSITY
INSTITUTIONAL REVIEW BOARD
Office of Research Integrity and Protections 214, Lyman Hall
Syracuse, New York, 13244-1200
Phone: 443-3013
orip@syr.edu

Please print a copy of this consent form if you would like to keep it for your records.

- I certify that I am 18 years of age or older, understand what my participation in this research involves, and agree to participate in this research study.
- I consent to the recording of both the audio and video of the interview session.
- (optional) I consent to the name of my organization to be mentioned as a participant in this study.

Appendix D: Dissertation Interview Protocol

Study Title: "Understanding the knowledge sharing practices of rare disease nonprofit organizations in regards to drug repurposing"

Principal Investigator: Dr. Carsten Østerlund
E-mail: costerlu@syr.edu
Address: 309 Hinds Hall, Syracuse University School of Information Studies

Co-Investigator: Ania Korsunska
E-mail: akorsuns@syr.edu

Interview Questions (semi-structured)

Introduction & Confirming Consent [read out loud]

Thank you so much for agreeing to participate in this interview! My name is Ania, I'm a PhD candidate at the Syracuse University information science and technology program.

For this project, we are interested in what is happening in the rare disease space in regards to drug repurposing. As you may know, though there have been notable examples of rare disease nonprofit organizations that have helped to shepherd and garner resources for drug repurposing opportunities in the US, there are various information-based challenges that they face. One of these challenges is simply how to navigate the process of drug repurposing, including overcoming various types of hurdles such as policy, legal, funding, etc. This information is not centralized or widely available to share between the stakeholders, and no resources exist to help stakeholders navigate the drug repurposing landscape. From preliminary ROADMAP survey data analysis, we know that out of 151 organizations who have taken the survey, over 50% have said they have not been involved in drug repurposing, and out of those, 46% marked the "lack of understanding of the steps for successful drug repurposing" as one of the top three reasons for why they have not pursued it, though this "sharing prior experiences that can inform future decision making" knowledge sharing was the top selected choice for collaborator organizations. This gap in understanding leaves individuals and organizations to independently reinvent the wheel over and over, and not always successfully, or avoid the challenge altogether, focusing instead on seemingly more achievable or clear goals.

Thus, the purpose of this interview is to explore your organization's collaboration network and how you share information with them in regards to your drug repurposing experience. Specifically, I'm interested in any issues you have faced in this process and thinking through some potential solutions as well.

I will reference the data you provided in the survey throughout the interview and allow you to elaborate and fill in any detail we may not have captured, feel free to let me know if any information is outdated or incorrect. Throughout the interview, we will utilize a visualization tool on my iPad, enabling me to visualize your collaborators and the type of collaboration activities you listed. Since this interview is being recorded, do not worry if I do not capture every detail on the visual.

At any time, if you feel uncomfortable about answering any question for any reason, do not hesitate to let me know, we can move on to the next question, or end the interview at any time.
Do you have any questions or concerns? Is it OK if I record? [start recording]

General - knowledge assets

1. In your organization, how do you conceptualize your knowledge value assets? Do you produce or help to produce data or knowledge, which you then consider to be organizational value assets?

2. Do you consider your experience in things like drug repurposing to be of value to share with other organizations?

a. If yes - which aspects do you consider to be of value?

Organizational network characteristics

3. How important is it to your organization's mission to connect with other rare disease non profit organizations?

4. Is this something you specifically focus on (have dedicated staff for?) or does it just naturally happen?

    a. If the former, who is in charge of this (what is their title), how much time do they devote to this?

    b.If the latter, when/where/how do these connections typically take place?

5. Is connecting with other rare disease non profit organizations more or less important to your organization's mission than connecting with other types of organizations (academic institutions, pharmaceutical companies, etc.)?

6. Is this something you specifically focus on (have dedicated staff for?) or does it just naturally happen?

    a. If the former, who is in charge of this (what is their title), how much time do they devote to this?

b. If the latter, when/where/how do these connections typically take place?

7. You said you [are/aren't] aware of other rare disease non profit organizations supporting your rare disease.

   a. If yes - Can you tell me a little about that relationship? In the survey you said you [do/do not] collaborate?, can you tell me more about that?

8. Do you think it's beneficial or detrimental for your rare disease of focus for there to be multiple organizations supporting it?

   a. If no - Do you think it's beneficial to have just one organization or would you prefer to have multiple?

9. Are there other rare diseases that are perhaps similar to the one you focus on that you get information or inspiration from?

   a. If yes - Do you collaborate with their associated organizations? How did you find and connect with them?

Knowledge Sharing

10. In the survey, we had a space for you to list your 5 closest collaborators or partners, but you said that in general you collaborate with [#] organizations on a regular basis. Tell me about these organizations - how do you build these relationships? Are they project-based or ongoing partnerships?

11. In the survey, we offered many different options on types of activities you were able to engage in with these organizations:

   a. Sharing data and/or samples for research

   b. Applying for funding together

   c. Organization provides us funding

   d. Creating a shared research agenda

   e. Pooling patient populations together to conduct future research

   f. Sharing prior experiences that can inform future decision making (e.g. research processes, drug repurposing steps, etc.)

   g. Sharing resources (e.g. funding, staff, expertise, etc.)

   h. Joint community building & fundraising (e.g. events, education initiatives, etc.)

i. Co-creating or co-supporting a center of excellence

j. Conducting research studies, including clinical trials

k. Other

For this interview, I'm especially interested in the organizations you listed as ones you listed under "sharing prior experiences that can inform future decision making (e.g. research processes, drug repurposing steps, etc.)". It was the most selected choice across all organizations which took this part of the survey, which is interesting.

12. Tell me how you interpreted this option choice. What does "sharing prior experiences that can inform future decision making" look like to you?

l. How often does it happen?

m. In which format?

n. Is it bi-directional or is there a hierarchy between you and these other organizations as to who shares more?

13. For this interview, let's call this "sharing prior experiences that can inform future decision making" knowledge sharing for short. Let's look at the organizations which you listed as having engaged in this knowledge sharing.

o. How did these collaborations come about? When did you first connect? How did you connect?

p. What have you learned from them in regards to drug repurposing steps or general things as to how to support research in the rare disease space?

q. How often do you meet or talk?

r. What format do these conversations take place in? (email, virtual, in person, at events?)

s. Have you faced any difficulties in knowledge sharing with these organizations?

t. Have you faced any difficulties in learning from their experiences and implementing them?

14. What do you feel like are the greatest barriers to more of this knowledge sharing happening?

15. What would help solve some of these challenges?

16. Now let's look at the organizations which you listed as NOT having engaged in this knowledge sharing, but they are still within your list of top 5 collaborators.

    u. Why are these organizations not once you share or receive knowledge from?

    v. Have you faced any difficulties in knowledge sharing with these organizations?

    w. Have you faced any difficulties in learning from their experiences and implementing them?

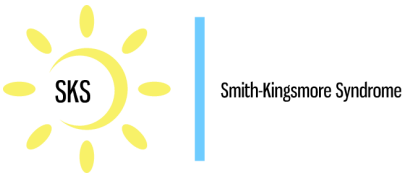
    x. What do you feel like are the greatest barriers to more of this knowledge sharing happening?

    y. What would help solve some of these challenges?

Thank you! [stop recording]

Appendix E: Overview of all 9 RDNPs

Smith-Kingsmore Syndrome Foundation



- **Organization Website:** Smith-Kingsmore Syndrome Foundation
- **Rare disease of focus:** Smith-Kingsmore syndrome (SKS)
    - SKS is a rare, neurodevelopmental genetic disorder, which impacts the digestive, endocrine, metabolic and nervous systems.
- **FDA Approved Drugs:** There are no FDA-approved drugs for SKS
- **Current status of sirolimus repurposing:**
    - Sirolimus is currently being used off label for patients with SKS to treat intractable seizures.

Historical Context: The interest in sirolimus as a treatment for Smith-Kingsmore Syndrome (SKS) began with a family's initiative after their son was diagnosed. They learned about sirolimus, an mTOR inhibitor, from Dr. Laurie Smith, and initiated treatment with the support of Cincinnati Children's Hospital, marking the start of off-label use for SKS without the backing of clinical trials specific to the syndrome.

Community Adoption and Research: This initial case led to increased interest within the SKS community, with more families exploring sirolimus for their children, guided by anecdotal improvements and medical advice. This collective experience fostered a sense of community and drove the establishment of a nonprofit organization to support research and connect families.

Current Status and Future Directions: Sirolimus treatment for SKS is in an exploratory phase, with ongoing research focused on understanding its effects and identifying better treatment options. The nonprofit plays a crucial role in funding research, raising awareness, and advocating for precision medicine approaches.

Organizational Focus: The organization founded by the family emphasizes research, community support, and collaboration to improve understanding and treatment of SKS, aiming for long-term advancements in patient care and quality of life.

The Pachyonychia Congenita Project

PC Project
Pachyonychia Congenita
Research & Patient Support Project

- **Organization Website:** Pachyonychia Congenita Project
- **Rare disease of focus:** Pachyonychia Congenita (PC)
    - PC is an ultra-rare, chronic, genetic autosomal dominant skin disorder, which causes lifelong limited mobility and severe pain.
- **FDA Approved Drugs:** There are no FDA-approved drugs for PC.
- **Current status of sirolimus repurposing:**
    - Palvella therapeutics is currently conducting a Phase III clinical trial to evaluate QTORIN™, a 3.9% topical sirolimus."
    - This trial is being conducted in partnership with PC Project, utilizing their patient registry of genetically confirmed patients.
    - Palvella has been awarded both FDA Orphan Drug and Fast Track designation.

Historical Context: The story of sirolimus for Pachyonychia Congenita (PC) began with Roger Casper's initial experiments on the mTOR pathway. Wes Kaupinen founded Palvella Therapeutics to focus on PC, leading to the development of a topical sirolimus formulation.

Currently, this formulation is undergoing Phase 2 and Phase 3 clinical trials, with a 3.9% efficacy observed in mini pigs.

Community Adoption and Research: PC Project connected their researchers with Palvella, facilitating data and knowledge sharing. They provided access to their registry and connected with other rare disease organizations working with Palvella on topical sirolimus. However, they had not previously considered broader collaboration with other organizations using sirolimus.

Current Status and Future Directions: The FDA has approved the topical formulation for a full Phase 3 clinical trial. Palvella is also exploring the use of sirolimus topical gel for other diseases like Gorlin Syndrome Alliance, Basal Cell Carcinoma, and Microcystic Lymphatic Malformations. The organization is now more curious about collaboration and the different formulations and side effects of sirolimus.

Organizational Focus: The organization is willing to share its process and knowledge, despite being in the clinical trial stage. They are open to connecting with other rare diseases, especially those focusing on skin diseases or using topical sirolimus. However, they are concerned about bandwidth and time constraints.

The LAM Foundation

- **Organization Website:** LAM Foundation
- **Rare disease of focus:** Lymphangioleiomyomatosis (LAM)
    - LAM is a rare lung disease that almost exclusively affects women; it's characterized by an abnormal growth of smooth muscle cells, especially in the

lungs, lymphatic system and kidneys. Unregulated growth of these cells can lead to loss of lung function, accumulation of lymph rich-fluid in the chest and abdomen and growth of tumors in the kidneys.

- **FDA Approved Drugs &** Sirolimus was FDA approved for LAM in 2015.

Historical Context: The LAM Foundation was established in 1995 with limited research or understanding of the disease. Frank McCormack, the volunteer scientific director, formed a network to study the disease. The foundation advocated for NIH protocols, leading to the CAST and MILES trials. Sirolimus was proven effective for LAM and approved by the FDA in 2015 after a four-year effort, including a patient petition and a 2,600-page report.

Community Adoption and Research: The foundation facilitates research by awarding grants and building a scientific network. Collaboration is emphasized, with a focus on sharing expertise and experiences. The foundation has a 35-member US-based clinic network and 65 global clinics for trials Funding was provided by the NIH's RDCRN, promoting collaboration among diseases.

Current Status and Future Directions: Global collaboration has intensified post-pandemic, with a shift towards a global initiative for care and treatment. The foundation continues to share its repurposing experience and learn from others. There is interest in connecting rare disease organizations working on similar pathways.

Organizational Focus: The foundation prioritizes building a scientific network and investing in research grants. There is a tension between focusing on the disease and collaborating with

other rare disease organizations. The foundation aims to balance patient support with scientific research and global collaboration. In summary, the LAM Foundation has played a pivotal role in advancing research and treatment for LAM through collaboration, advocacy, and a focus on scientific research. The foundation continues to engage in global collaboration and learning to improve access to care and treatment.

Cure HHT

- **Organization Website:** Cure HHT
- **Rare disease of focus:** Hereditary Hemorrhagic Telangiectasia (HHT)
    - HHT is a genetic disorder that causes malformed blood vessels and can affect multiple organs of the body.
    - The disorder is also sometimes referred to as Osler-Weber-Rendu (OWR).
- **FDA Approved Drugs:** There are no FDA-approved drugs for HHT
- **Current status of sirolimus repurposing:** Currently, sirolimus in a Phase II clinical trial for patients with HHT that are experiencing moderate or severe epistaxis (nose bleeds).

Historical Context: Cure HHT's journey with sirolimus began with an insight from a speaker at one of their conferences, who highlighted the potential of sirolimus for their patient community. This led to further exploration and eventual initiation of a Phase II clinical trial in Toronto, focusing on patients with moderate to severe epistaxis (nosebleeds), a common symptom of Hereditary Hemorrhagic Telangiectasia (HHT).

Community Adoption and Research: The clinical trial's launch marks a significant step in adopting sirolimus for HHT treatment. This effort was facilitated by collaboration with vascular anomalies experts and organizations, highlighting the importance of cross-organizational knowledge sharing and collaboration. Notably, Cure HHT worked closely with Denise Adams from CHOP, a key figure in vascular anomalies, to leverage her expertise and connections in this field.

Current Status and Future Directions: Currently, sirolimus is undergoing a Phase II clinical trial specifically for HHT patients at Toronto's HHT center. This trial is closely watched by the HHT community and represents a potential new therapeutic pathway for managing HHT symptoms. The outcomes of this trial will likely guide future research directions and potential broader application of sirolimus within the HHT patient population.

Organizational Focus: Cure HHT has positioned itself as a leader in fostering collaborations and exploring new treatment avenues for HHT. By establishing a therapeutic arm and engaging with various stakeholders, including biotech and pharmaceutical companies, Cure HHT demonstrates a strategic approach to advancing HHT treatment options. Their involvement in the broader vascular anomalies community and efforts to bridge connections with other rare disease organizations reflect a commitment to leveraging collective knowledge and resources for the benefit of HHT patients.

Lymphangiomatosis & Gorham's Disease Alliance (LGDA)

- **Organization Website:** Lymphangiomatosis & Gorham's Disease Alliance (LGDA)
- **Rare disease of focus:** Complex Lymphatic Anomalies
    - CLAs are a group of rare diseases that are characterized by abnormal growth of lymphatic vessels that may involve multiple organ systems, including lung, spleen, soft tissue and bones
- **FDA Approved Drugs:** There are no FDA-approved drugs for CLAs.
- **Current status of sirolimus repurposing:**
    - Sirolimus has shown efficacy in phase II clinical trials and is being used off label
    - It is currently one of the frontline agents for patients with complex lymphatic anomalies.

Historical Context: LGDA's interest in sirolimus originated from a phase II trial conducted by the University of Cincinnati, which explored the efficacy of sirolimus in treating various vascular anomalies, including lymphatic anomalies. Despite weak basic science backing at the time, clinical results showed symptom-based improvements in patients with lymphatic anomalies, despite not demonstrating significant radiographic improvements.

Community Adoption and Research: Following the trial, sirolimus saw increased usage across both the US and European consortia (CANVAS and VASCERN, respectively) for patients with lymphatic anomalies, positioned as a frontline medical therapy. Despite its adoption, there was a lack of concerted effort to pursue FDA approval for this specific indication, primarily due to pharmaceutical disinterest from Novartis.

Current Status and Future Directions: Currently, sirolimus remains a frontline agent for treating complex lymphatic anomalies, utilized off-label following demonstrated efficacy in phase II clinical trials. A large phase II trial recently concluded, reaffirming sirolimus's efficacy and acceptable side-effect profile. However, the pathway to FDA approval appears stalled without pharmaceutical support, leaving sirolimus to be used off-label as the primary treatment method.

Organizational Focus: The LGDA has been instrumental in promoting sirolimus within their community, yet there exists a broader potential for collaborative efforts across rare disease organizations. Such collaboration could enhance understanding of sirolimus's side effects, patient tolerance, and overall efficacy across different patient populations. An example highlighted was an unexpected observation regarding dental health issues in young patients on sirolimus, underscoring the value of cross-population insights. However, time constraints and the lack of a centralized platform for information exchange have been significant barriers to broader collaborative efforts.

RUNX1 Research Program

- **Organization Website:** RUNX1 Research Program
- **Rare disease of focus:** RUNX1 familial platelet disorder
    - RUNX1 FPD is a hereditary blood disorder causing bleeding, bruising, inflammatory conditions and a 40-50% lifetime risk of developing blood cancer.
- **FDA Approved Drugs:** There are no FDA-approved drugs for RUNX1-FPD.
- Current status of sirolimus repurposing:

- Preclinical data identified sirolimus as promising
- RUNX1 is currently developing a clinical trial.

Historical Context: Sirolimus was identified as a promising therapeutic candidate for RUNX1 familial platelet disorder (RUNX1 FPD) through a project funded by the organization. The discovery stemmed from single-cell RNA sequencing of patient samples, revealing elevated mTOR1 signaling among other pathways.

Community Adoption and Research: Following the identification of sirolimus as a potential treatment, a panel of inhibitors, including sirolimus and its variants, was tested. This research aimed at addressing hematopoietic dysfunction, with sirolimus emerging as one of the best candidates for rescuing blood function abnormalities.

Current Status and Future Directions: The program has since moved towards developing a comprehensive preclinical package to support clinical translation. Conversations with clinicians and experts in clinical trials have laid the groundwork for a pilot study, aimed at cancer prevention and interception among high-risk individuals without cancer. This approach benefits from sirolimus' extensive data supporting its use in immune function improvement and life-span extension, particularly in the anti-aging field.

Organizational Focus: The RUNX1 Research Program is actively working on translating preclinical findings into clinical applications, with a focus on developing a clinical trial for sirolimus. The involvement of patient leaders in advisory roles and the collaboration with

specialists in the field highlight an inclusive and forward-thinking strategy towards drug repurposing. The organization's efforts are also informed by insights from the broader scientific and patient communities regarding the potential of mTOR pathway modulation in treating rare diseases, including RUNX1 FPD.

The Castleman Disease Collaborative Network (CDCN)

- **Organization Website:** Castleman Disease Collaborative Network
- **Rare disease of focus:** Castleman Disease (CD) and it's subtypes
    - CD is a group of rare disorders that involve enlarged lymph nodes and a broad range of inflammatory symptoms and laboratory abnormalities. In CD, the cells of the immune system become hyperactivated, overproduce cytokines and other inflammatory compounds, and fail to return to a surveillance mode.
- **FDA Approved Drugs:** CD has one FDA-approved drug, siltuximab (Sylvant), which is effective for about 30-50% of CD patients.
- **Current status of sirolimus repurposing:**
    - Dr. Fajgenbaum discovered the potential for treating CD with Sirolimus in 2014.
    - Sirolimus is currently being used off-label for patients with iMCD and UCD, and is being studied in a Phase II clinical trial .

Historical Context:

CDCN identified the potential of sirolimus for treating Castleman Disease (CD) in 2014. Sirolimus has since been used off-label for patients with iMCD and UCD and is under study in a Phase II clinical trial. This discovery underscores the innovative approach of CDCN towards drug repurposing within the rare disease landscape.

Community Adoption and Research:

CDCN is a unique case in drug repurposing effort for several reasons. Firstly, the discovery of sirolimus as a treatment for CD was an incredible story in itself. CDCN's founder Dr. Fajgenbaum was diagnosed with CD while in medical school and after conventional treatments failed and facing near-certain death several times, he started conducting research to save his own life using his own samples, which finally led to the discovery of sirolimus as a treatment for CD (Fajgenbaum, 2019). Since then, dozens of patients have been successfully treated with sirolimus. Secondly, due to the fact Dr. Fajgenbaum,that holds a unique status as an RDNP leader, CD patient, physician, and researcher all in one, CDCN has unique accesses information directly from researchers and physicians, as well as its own research lab at the University of Pennsylvania, called the Center for Cytokine Storm Treatment & Laboratory (CSTL). This serves as a direct line to knowledge without the need to gather information through intermediary sources, such as other RDNPs, as well as the ability to push forward both data collection, fundraising and clinical trial research with one team, removing barriers such as lack of incentives or data-sharing.

Current Status and Future Directions:

CDCN's strategy focuses on advancing sirolimus through clinical trials to establish its efficacy and safety for CD patients, but is not aiming for FDA approval. The CDCN is also actively pursuing other repurposing opportunities, as through further research it has become clear that sirolimus does not work for all CD patients, and other drugs seem more promising.

Organizational Focus:

CDCN has streamlined its approach to drug repurposing and collaboration into a model called the “Collaborative Network Approach”, which prioritizes patient voices in driving research questions, and enables effective collaboration across researchers, physicians and patients (Zuccato et al., 2019). Spearheading efforts like the ROADMAP project aim to disseminate knowledge and foster knowledge sharing beyond CD and to other rare disease organizations.

Myositis Support and Understanding Association (MSU)

- **Organization Website:** Myositis Support and Understanding Association
- **Rare disease of focus:** Idiopathic Inflammatory Myopathies (IIM)
    - IIM, commonly referred to as myositis, are a group of rare, sporadic, systemic autoimmune diseases including dermatomyositis, inclusion body myositis (IBM), and necrotizing myositis. While myositis is classified as a muscle disease, it can also affect the skin, lung, heart, and joints and can be associated with cancer.
- **FDA Approved Drugs:** There are limited FDA-approved therapies for some forms of myositis outside corticosteroids and IV-IG. However, no treatment is available for IBM.
- **Current status of sirolimus repurposing:**
    - A randomized, double-blind, placebo-controlled, proof-of-concept, Phase 2b clinical trial was completed in 2020, which showed no evidence of sirolimus efficacy in IBM based on the primary end-point; however, the researchers found enough evidence of benefit in certain secondary outcomes to suggest conducting a phase 3 trial, which is now being financed by an Australian government grant and currently in the recruiting phase
    - Some patients are using sirolimus off-label, but it is not currently integrated into treatment guidelines.

Historical Context: MSU's engagement with sirolimus began with an initiative led by Dr. Benveniste in Paris, who explored its use in a Phase I/II study for myositis, specifically inclusion body myositis (IBM), due to its potential impact on T-cell involvement and neurodegeneration.

Despite the lack of pharmaceutical financing due to sirolimus being a generic medication, the initial findings showed promising trends in secondary endpoints, although the primary endpoint was not met. This discrepancy highlighted the challenges in selecting appropriate functional performance measures for rare diseases.

Community Adoption and Research: The initial study, conducted around 2017-2018 and published in the Lancet in October 2020, revealed sirolimus's potential, despite no significant progress towards a Phase III study due to financial constraints. This situation underscores the broader issue of funding and interest in advancing research for repurposed drugs in rare diseases. Subsequently, an Australian group secured funding for a Phase III study, including participants from Johns Hopkins and Kansas in the United States, focusing on a broader patient cohort within the myositis spectrum.

Current Status and Future Directions: The ongoing Australian-led Phase III study represents a significant step forward, funded entirely by non-U.S. sources. This international collaboration highlights the challenges and opportunities in drug repurposing research for rare diseases like myositis. MSU's role in this context is more about advocacy and patient support rather than direct involvement in the study, reflecting on the broader landscape of rare disease research where collaboration across borders and disciplines is crucial yet complex.

Organizational Focus: MSU's focus remains on supporting patients and leveraging patient-centered research to inform and improve treatment options. While actively engaged in

understanding and potentially advocating for sirolimus use in myositis, MSU confronts the realities of drug repurposing in the rare disease field—navigating financial, regulatory, and research hurdles to bring potentially beneficial treatments to their community. Their work emphasizes the importance of collaborative networks, patient advocacy, and the need for innovative funding models to advance research on off-patent drugs like sirolimus for rare conditions.

Project FAVA

- **Organization Website:** Project FAVA
- **Rare disease of focus:** Fibro-adipose vascular anomaly (FAVA)
    - FAVA is a rare vascular anomaly occurring when the body's own tissue infiltrates a muscle, creating a tumor-like mass typically found in one or more limbs.
- **FDA Approved Drugs:** In April, 2022, the FDA granted approval on an accelerated basis for Novartis's Vijoice (alpelisib) to treat FAVA and other conditions under the PROS umbrella, with studies continuing to potentially lead to full approval.
- **Current status of sirolimus repurposing:** Sirolimus is currently being used off-label.

Historical Context: The use of sirolimus for vascular anomalies within the FAVA community dates back to around 2007, initiated by a doctor who, faced with a lack of effective treatments for a patient, decided to experiment with sirolimus based on its use in another study at their center. Initial success with one patient led to a trial with five patients, yielding positive results, which subsequently led to a larger research project funded by the FDA, involving around 60 participants across two vascular anomaly centers.

Community Adoption and Research: Sirolimus quickly became recognized as an effective treatment for various vascular anomalies due to the collaboration and information sharing among a network of doctors at vascular anomaly centers in the US. It started with specific malformations but expanded to include others, including FAVA, due to observed similarities and successes. By the time Project FAVA was established in 2018, sirolimus was already well-recognized and used off-label for FAVA patients, notably at Boston Children's Hospital, which has seen significant success in its application.

Current Status and Future Directions: While sirolimus is widely used and accepted as a de facto treatment for FAVA and similar conditions, there does not appear to be a push for FDA approval specifically for FAVA at this time. Attention is shifting towards other treatments targeting the PIC3CA mutation, which is related to vascular anomalies. Alpelisib, a drug that targets PIC3CA instead of mTOR (the pathway inhibited by sirolimus), is gaining prominence, with discussions at medical conferences and meetings now focusing more on Alpelisib, especially following its FDA approval for related conditions.

Organizational Focus: Project FAVA, as a patient advocacy group, aims to connect patients with medical professionals and facilitate research. Although the organization was founded after the initial research on sirolimus, it supports research in a broad sense, focusing on areas that promise the most benefit for the FAVA community. This includes genetic research and potentially treatment-related studies that arise. The organization plays a crucial role in linking researchers with patients for ongoing and future studies.

Appendix F: Additional ROADMAP Data

Figure 1: Count of drug listed for repurposing, ROADMAP data

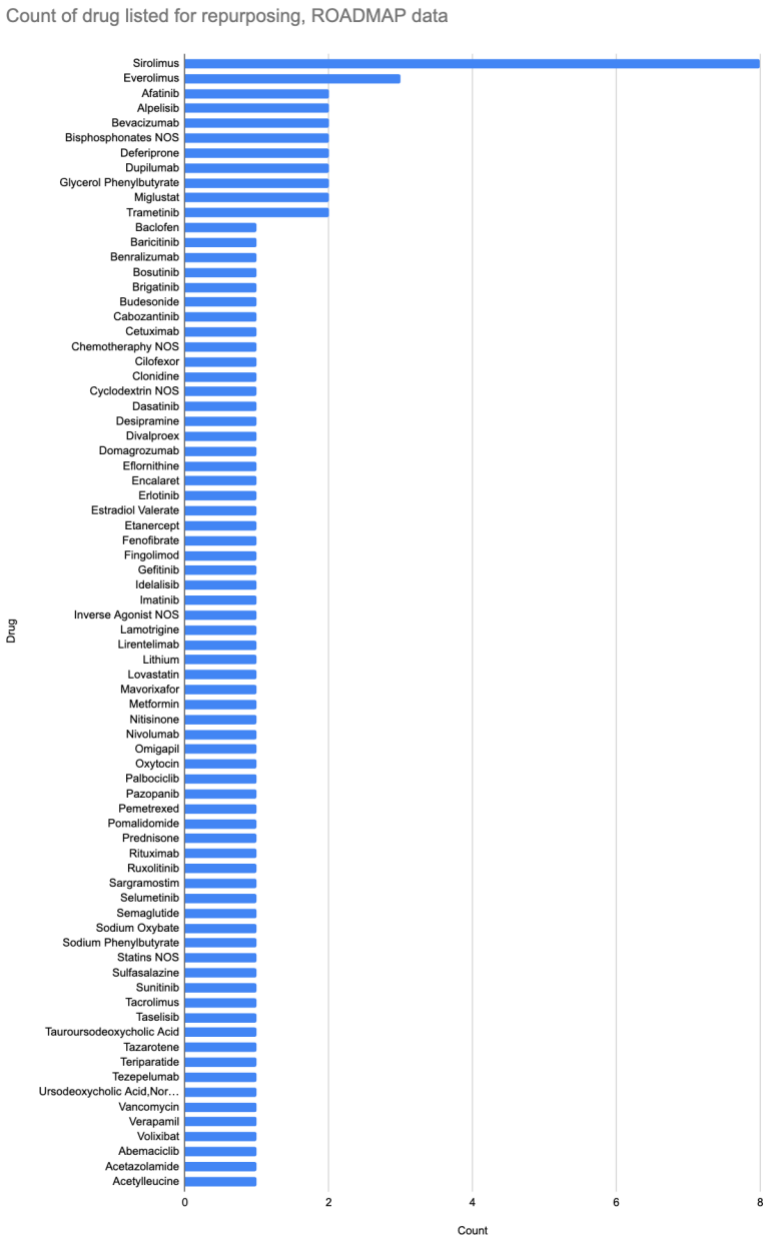


Table 1: Count of drug listed for repurposing, ROADMAP data

Drug	Count
Sirolimus	8
Everolimus	3
Afatinib	2
Alpelisib	2
Bevacizumab	2
Bisphosphonates NOS	2
Deferiprone	2
Dupilumab	2
Glycerol Phenylbutyrate	2
Miglustat	2
Trametinib	2
Baclofen	1
Baricitinib	1
Benralizumab	1
Bosutinib	1
Brigatinib	1
Budesonide	1
Cabozantinib	1
Cetuximab	1
Chemotheraphy NOS	1
Cilofexor	1
Clonidine	1
Cyclodextrin NOS	1
Dasatinib	1
Desipramine	1
Divalproex	1

Domagrozumab	1
Eflornithine	1
Encalaret	1
Erlotinib	1
Estradiol Valerate	1
Etanercept	1
Fenofibrate	1
Fingolimod	1
Gefitinib	1
Idelalisib	1
Imatinib	1
Inverse Agonist NOS	1
Lamotrigine	1
Lirentelimab	1
Lithium	1
Lovastatin	1
Mavorixafor	1
Metformin	1
Nitisinone	1
Nivolumab	1
Omigapil	1
Oxytocin	1
Palbociclib	1
Pazopanib	1
Pemetrexed	1
Pomalidomide	1
Prednisone	1
Rituximab	1
Ruxolitinib	1

Sargramostim	1
Selumetinib	1
Semaglutide	1
Sodium Oxybate	1
Sodium Phenylbutyrate	1
Statins NOS	1
Sulfasalazine	1
Sunitinib	1
Tacrolimus	1
Taselisib	1
Tauroursodeoxycholic Acid	1
Tazarotene	1
Teriparatide	1
Tezepelumab	1
Ursodeoxycholic Acid,Norursodeoxycholic Acid	1
Vancomycin	1
Verapamil	1
Volixibat	1
Abemaciclib	1
Acetazolamide	1
Acetylleucine	1

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CURRICULUM VITAE

EDUCATION

08/2019 – 06/2024
Ph.D., SYRACUSE UNIVERSITY
Information Science and Technology (iSchool)
Concentration: Human-Computer Interaction, Science Studies

09/2017 – 05/2019
TEMPLE UNIVERSITY (transfer)
Lew Klein College of Media and Communication, Ph.D. Program
Concentration: Health Communication,

08/2014 – 08/2015
M.A., UNIVERSITY OF CHICAGO
Master of Arts Program in the Social Sciences (MAPSS)
Concentration: Medical Sociology

09/2009 – 06/2012
B.A., BILKENT UNIVERSITY
Department of Communication and Design
Concentration: Journalism

08/2008 - 06/2009
IZMIR UNIVERSITY OF ECONOMICS (transfer)
Department of Public Relations and Advertising, B.A. program

PUBLICATIONS

Korsunska, A., Repasky, M., Zuccato, M., & Fajgenbaum, D. C. (2023). A model for crowdsourcing high-impact research questions for Castleman disease and other rare diseases. Orphanet Journal of Rare Diseases, 18(1), 75. https://doi.org/10.1186/s13023- 023-02678-6

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Introne, J., **Korsunska, A.,** Krsova, L., & Zhang, Z. (2020). Mapping the Narrative Ecosystem of Conspiracy Theories in Online Anti-vaccination Discussions. In *International Conference on Social Media and Society* (pp. 184-192). https://doi-org.libezproxy2.syr.edu/10.1145/3400806.3400828

Korsunska, A. (2019). The Spread and Mutation of Science Misinformation. In N. G. Taylor, C. Christian-Lamb, M. H. Martin, & B. Nardi (Eds.), Information in Contemporary Society (pp. 162–169). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-15742-5_15

CONFERENCE PRESENTATIONS

Korsunska, A., (2021) *Research Agenda-Setting in Medicine: Shifting from a Research-centric to a Patient-centric Approach.* Short Research Paper. iConference 2021. Virtual format due to COVID-19.

James, W. M., **Korsunska, A.** (2020) *Regime Complex in Sustainable Finance.* Paper will be presented at ISA 2021 Annual Convention April 6-9, 2021. Virtual format due to COVID-19.

James, W. M., **Korsunska, A**. (2020) *Regime Complex in Sustainable Finance.* Paper presented at ISA Midwest Conference. November 20, 2020. Virtual format due to COVID-19.

James, W. M., **Korsunska, A**. (2020) *Regime Complex in Sustainable Finance.* Paper presented at ISA Northeast Conference, Nov 7, 2020; S2CC: Environmental Governance and Climate Change Panel. Virtual format due to COVID-19.

Gupta, S., Bolden, S. E., Kachhadia, J., **Korsunska, A**., Stromer-Galley, J. (October, 2020). *PoliBERT: Classifying political social media messages with BERT.* WIP paper presented in 2020 SBP-BRiMS (International Conference on Social Computing, Behavioral-Cultural Modeling & Prediction and Behavior Representation in Modeling and Simulation). Virtual format due to COVID-19.

Introne, J., **Korsunska, A.,** Krsova, L., & Zhang, Z. (July, 2020). *Mapping the Narrative Ecosystem of Conspiracy Theories in Online Anti-vaccination Discussions.* Social Media & Society Conference. Virtual format due to COVID-19.

Gupta, S., Bolden, S. E., Kachhadia, J., **Korsunska, A.**, Stromer-Galley, J. (July, 2020). Classifying political social media messages with BERT. Poster presented at the 6th International Conference on Computational Social Science (IC2S2). Virtual format due to COVID-19.

Korsunska, A. (April, 2019). The Spread and Mutation of Science Misinformation. Short Research Paper. iConference 2019. Washington, DC.

Phillips, C., **Korsunska, A.** (November, 2018) Blurred Boundaries: Fake News Discussion and Conflict in Journalism. National Communication Association (NCA), Salt Lake City, UT.

SYMPOSIUM/FORUM PRESENTATIONS

Stromer-Galley, J., McKernan, B., Hemsley, J., **Korsunska, A.**, Bolden, S. E. (March, 2020) Communicating the Facebook Political Ad Library: Data and Design Challenges, Accepted for the Computation + Journalism 2020 Symposium. Boston, MA.

Korsunska, A., Introne, J. (October, 2019) Tracing misinformation back to its sources: Where do anti-vaxxers get their information?, Poster presented at -----iSchool Research Day. Syracuse, NY.

Wermer-Colan, A., Antsen, J., **Korsunska, A.**, Lemire-Garlic, N. (April, 2019) Social Media Debates about the Trump Wall, Digital Scholarship Center web-scraping working group project. Presented at Borders, Boundaries, Walls Symposium, Center for the Humanities at Temple University (CHAT). Philadelphia, PA.

Korsunska, A., Castonguay, J., Henninger, N. M. (March, 2019) Shining Light on the 'Middle Man': A Review of Health Related Press Releases. Temple Graduate Research Forum, Panel "Tenuous Relationships: Organizations, Practice and Mind". Philadelphia, PA.

Korsunska, A. (March, 2019) Changing the News at The New York Times: a NewsDiffs and DiffEngine Analysis. Temple Graduate Research Forum, Panel "News, Attitudes and Media Effects". Philadelphia, PA.

Korsunska, A. (April, 2018) Citing Misinformation: A lifecycle Case Study, Digital Scholarship Program Project. DSC/CHAT Digital Research Lightning Round Presentations. Philadelphia, PA.

Korsunska, A. (April, 2018) Why does it seem like everything causes cancer?. Temple Graduate Research Forum, Gatekeeping and Institutions Division. Philadelphia, PA.

RESEARCH & LEADERSHIP WORK EXPERIENCE

FOUNDER & CEO

Zemlia, PBC, 04/2023 – present

- Driving the mission to empower sustainable living through inclusive, positive, data-driven solutions, steering away from guilt-based tactics and focusing on user-friendly resources.
- Building partnerships across various sectors to enhance Zemlia's impact, integrating diverse insights and resources for comprehensive sustainability solutions.
- Managing teams across various product MVP roadmaps

COMMUNITY LEAD

Climate Vine, 07/2023 – 12/2023

- Spearheading the implementation of personalized experiences for community members by leveraging data analysis and taxonomy creation
- Facilitating knowledge sharing within the community by curating content and creating strategic networking opportunities.
- Managing and analyzing of member data to inform community growth strategies and enhance user experience.

BIOMEDICAL LEADERSHIP FELLOW & ROADMAP PROJECT LEAD

Castleman Disease Collaborative Network, 02/01/2021– 03/31/2023

- Leading the Repurposing of All Drugs, Mapping All Paths (ROADMAP) project. This project has implemented a mixed methods (interview/survey) approach to create a foundational dataset and interactive tool describing the process of drug repurposing for rare diseases to help solve some of the critical challenges rare disease organizations are facing in helping lead initiatives to get more treatment options for their patients.
- Coordinating tasks to both a small team of staff and a large (~60) and varied team of remote volunteers
- Improving the speed and efficiency with which projects go from concept to implementation through project management tasks: setting timelines, leading meetings, coordinating tasks, leading quality control of deliverables.
- Activating the entire network of Castleman disease patients, loved ones, researchers, and physicians to gather ideas for CDCN's international research agenda through the "AIM" crowdsourcing effort.
- Supporting the CORONA (COvid19 Registry of Off-label & New Agents) Project through various tasks related to data selection, data collection, data aggregation and database management. CORONA was set up in March 2020 to identify and track all treatments reported to be used for COVID-19 in an open-source data repository.
- Assisting with fundraiser event planning, patient education and engagement, communications.
- Growing the reach and influence of CDCN's approach to help support research in other rare disease areas.
- Leading report and paper writing on drug repurposing and crowdsourcing efforts.
- Supporting CDCN's grant management activities through Salesforce CRM
- Representing the CDCN in conferences, workshops and media outreach efforts (podcasts, blogs, etc.)
- Designing impactful and accurate communication materials (data graphs and visualizations, infographics, social media posts, logos, etc.)

CLIMATEBASE FELLOW & CAPSTONE PROJECT LEAD

Climatebase Fellowship, 2nd cohort, 08/2022– 10/2022

- Attended and participated in educational sessions to get up to speed on the latest in the climate solution space.
- Facilitated the creation of a capstone project group of 12 fellows of various interests, backgrounds, and experiences.
- Leading a capstone project, focused on the creation of two deliverables: 1. a comprehensive database on all individual action for climate change mitigation, with data on their impact, cost, effort, co-benefits, etc. and 2. a community-based tool designed to turn individual action into systemic change, and provide a "roadmap" through data-driven guidance and educational resources on how to succeed (project ongoing).

GRADUATE RESEARCH ASSISTANT

Center for Computational Data Science, mentorship of Dr. Jennifer Stromer-Galley, 08/15/2019 – present

- Providing research support for the Illuminating project, the goal of which is to provide an interactive online dashboard for journalists to easily and quickly track what the public is being told by presidential candidates and interest groups in their paid ads.
- Involved in a variety of tasks including conducting journalist interviews, thematic transcript analysis, website design work, creating website mockups, and user-experience testing.
- Trained for and participated in annotation of Twitter and Facebook campaign messaging data; helped manage the adjudication meetings for the team of undergraduate annotators.
- Responsible for some project management aspects of the project, such as organizing and leading the machine learning team meetings, taking notes and following up on action items.

Syracuse University, Center for Computational Data Science (CCDS), 05/29 – 08/14/2019

- Worked on the 'Cuse Grant project to experiment with ways to mitigate conspiracy thinking.
- Duties included developing and testing survey and experimental stimuli, and data cleaning and helping with basic statistical analysis of survey data.

DATA EXTRACTOR for COvid Registry of Off-label & New Agents (CORONA)

Castleman Disease Collaborative Network and the Center for Cytokine Storm Treatment & Laboratory at the University of Pennsylvania, 07/23/2020- present

- As a part of its volunteer data extractor team in Phase 2, I'm helping extract data from published articles regarding COVID19 treatments, which are being aggregated into the CORONA registry. This registry is open source and can be used by physicians to treat patients and prioritize drugs for trials.

DIGITAL SCHOLAR & GRADUATE ASSISTANT

Temple University, Digital Scholarship Center, 09/2017 – 06/2019

- Selected for participation in the Digital Scholarship Program and awarded research stipend to pursue work in the digital methods field 09/2017-06/2018
- From 09/2018 employed as a Graduate Assistant, providing support for digital scholarship projects, utilizing textual analysis, web scraping, GIS, VR and network analysis.
- Participated in a web-scraping workgroup and helped lead a series of workshops related to various approaches to web-scraping (data scraping, content and network analysis).

MEDICAL EDITOR

Discovery USA, Publicis Groupe, 04/2016-09/2017

- Analyzed and reviewed scientific articles used in the creation of healthcare marketing materials
- Maintained scientific accuracy and confirmed consistency of claims/references between projects
- Consistently monitored independent research to discover relevant information/claims for all brands

USER EXPERIENCE RESEARCHER

Growth from Knowledge | GfK Global Market Research Institute, 01/2016 – 04/2016

- Conducted usability studies through a combination of ethnographic research, strategy, and design for various medical devices prior to their submission for FDA approval, as well as various websites and apps

RESEARCH ASSISTANT

National Opinion Research Center (NORC) at The University of Chicago, 09/2015 – 01/2016

- Utilized multiple advanced locating techniques to verify identity and education information of sample members for the Survey of Doctorate Recipients (SDR)

TEACHING EXPERIENCE

TEACHING PRACTICA

Syracuse University, 08/2019-12/2020

- Assisted in the creation of assignments for IST 800 Social Network Analysis with Dr. Joshua Introne.

-Assisted in updating the readings list for a “special topics” section for IST649: Human Interaction with Computers with Dr Bryan Semaan.

-Independently led two synchronous virtual sessions of IST 618: Information Policy with Dr. Caroline Haythornthwaite, one session on information policy ethics and one on information economics.

TEACHING ASSISTANT

Temple University, 08/2017- 05/2019

- Reinforced lessons presented by teachers by reviewing material with students for exams and quizzes

- Assisted Professors with tracking attendance and grading assignments and exams, leading small-group study sessions.

ENGLISH TEACHER

Ihsan Dogramaci Primary School (Ankara, Turkey), 08/2012 – 06/2014

- Implemented a diverse curriculum in all English-language subjects for Turkish students ages 6-7

LANGUAGES

English – fluent, Ukrainian – fluent, Russian – fluent, Turkish –intermediate, Japanese – beginner.

SKILLS

R (beginner), Adobe Photoshop (intermediate), Adobe Illustrator (intermediate), Final Cut Pro (intermediate), Gephi (intermediate), Excel (intermediate), Tableau (beginner), InVision (intermediate), HTML (basic), Atlas.ti (intermediate).

HONORS, SCHOLARSHIP, AWARDS AND CERTIFICATES

- Future Professionals Program (FPP) by Women in Science and Engineering (WiSE) 09/2020-06/2022
- Teaching in Higher Education Certificate, Center for the Advancement of Teaching, 05/2019
- Graduate Student Association (GSA), Vice-President, 08/2018 – 05/2019
- Temple University Digital Scholarship Program 09/2017-06/2018
- University of Chicago, one third tuition scholarship, 08/2014-08/2015
- Certificate in Teaching English to Speakers of Other Languages (CELTA), International House Kyiv, Issued by University of Cambridge Local Examinations Syndicate, 06-07/2013
- Bilkent University, Diploma with High Honor, full tuition scholarship, 08/2009-06/2012