Rosenau Family
Research Foundation

2024 Annual Report

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From the Desk of the Executive Director


Gabriel Cohn, MBA
Executive Director

The 2024 Annual Report highlights Rosenau Family Research Foundation's (RFRF) unwavering commitment to advancing research and improving the lives of those impacted by Krabbe disease and Cystic Fibrosis. The foundation's efforts in research, advocacy, and collaboration continue to pave the way for a brighter future. In 2024, we evolved with the goal of enhancing the foundation's impact by expanding our reach, introducing cost-effective operational efficiencies, and maintaining fiscal discipline—without ever compromising our vision, mission, or core values.

Notable accomplishments included hosting a successful KTRN meeting that attracted many first-time attendees, implementing a new semi-annual grant cycle to help accelerate innovation, launching a new grants management platform to streamline the submission and administration of grant applications, and demonstrating an ongoing commitment to supporting new and talented investigators. Furthermore, we awarded five innovative grants that promise to enhance knowledge and improve clinical practice. Our engagement with advocacy partners for Cystic Fibrosis and Krabbe disease remained steadfast, including our support of collaborative efforts that, in 2024, led to the landmark recommendation to include Krabbe disease in newborn screening panels nationwide.

I am deeply grateful for your invaluable support, the indefatigable dedication of the foundation's co-founder, Paul Rosenau, the insights of the RFRF board, the tireless work of the RFRF staff, the thoughtful and meticulous efforts of our Scientific Advisory Committee and Investment Committee, and our outstanding team of legal and financial experts. Without these contributions, none of this would have been possible.

Rosenau Family
Research Foundation

Our Vision

Improving the lives of people impacted by Krabbe disease and Cystic Fibrosis through research funding and disease advocacy

Our Mission

Living a life undefined by Krabbe disease and Cystic Fibrosis

Our Values

Collaboration
Ethical Decision-Making
Science-Driven

2024 TEAM


Gabriel M Cohn, MD, MBA
Executive Director &
Medical Director


Heather Techmeier
Finance Director


Renea Muellerleile
Fractional Operations Director,
Hood & Associates


Mary Kay Delvo
Strategist, Certified Coach &
Facilitator, INspiring SIGHT


Heidi Carrozzella
Fractional Marketing Leader,
Zella Marketing


Rachel Jackson
Fractional Marketing
Director


Paul Rosenau
President and Co-Founder


Amanda Post
Secretary


Marci Sontag
Chair


Phil Christianson
Chair-Elect


Gillian Hauboldt
Treasurer


Heather Techmeier
Director


Li Ou
Director


Karlita Blackwell
Director


Julie McCarrier
Director


Gabriel M Cohn, MD, MBA
Director

WITH SUPPORT FROM

BelinMcCormick
ATTORNEYS AT LAW

Technology
BY DESIGN

ArcStone

FOSTER
GROUP

Dufault CPA
CERTIFIED PUBLIC ACCOUNTANT

Ellis International
MEETINGS • EVENTS • PRODUCTION • STRATEGY

The Evolution of the RFRF Board in 2024


Marci Sontag
RFRF Board Chair

The Rosenau Family Research Foundation's (RFRF) board is proud to oversee the scientific grant portfolio's growth and the staff development to support the activities of the foundation. The board has also continued to grow, and a significant development in 2024 was the formation of an Executive Committee, designed to streamline decision-making processes and ensure that the foundation's vision is executed effectively. This new committee will play a pivotal role in guiding our strategic direction and enhancing our operational effectiveness as we move forward. In September, RFRF held a productive board retreat that laid the groundwork for our future initiatives and reinforced our commitment to advancing RFRF's mission. During this retreat, board members engaged in meaningful discussions, brainstorming innovative strategies to enhance our research impact and community engagement.

In 2024 we bid farewell to Mary Kay Delvo, the consultant from Inspiring Sight who has helped to shape RFRF over the past five years. Mary Kay provided invaluable guidance that has significantly empowered our board members to operate with greater independence and confidence. Through her mentorship, we have cultivated a strong foundation of governance that emphasizes collaboration and innovation. As we celebrate this transition, we are excited about the future of RFRF and are committed to sustaining the momentum gained during this transformative period. Together, we are poised to advance our mission, fostering groundbreaking research that makes a meaningful difference in the community.

Hellos and Goodbyes

In the spring of 2024, we welcomed Amanda Post as the new Secretary of our Board of Directors! Amanda is a project manager at WCG Clinical. She works with pharmaceuticals and device companies to provide research solutions for active clinical trials, giving her experience in oncology, vaccine, neuro, and rare diseases.

Amanda has extensive experience designing and executing practical ways to connect patients to treatment options and supporting them along the way. We are excited to have her on our team!

In the fall of 2024, Board Director Julie McCarrier fulfilled the maximum number of terms with RFRF's Board of Directors.

In addition to Julie's industry expertise, her six years include serving originally on The Legacy of Angels Foundation board, experience working with board members and staff, and commitment to the foundation's mission She provided invaluable leadership through a critical transition period and evolution to where it is today. We are incredibly grateful for Julie's time with RFRF and are looking forward to following her endeavors moving forward.

From the Desk of the Finance Director

Heather Techmeier
Finance Director

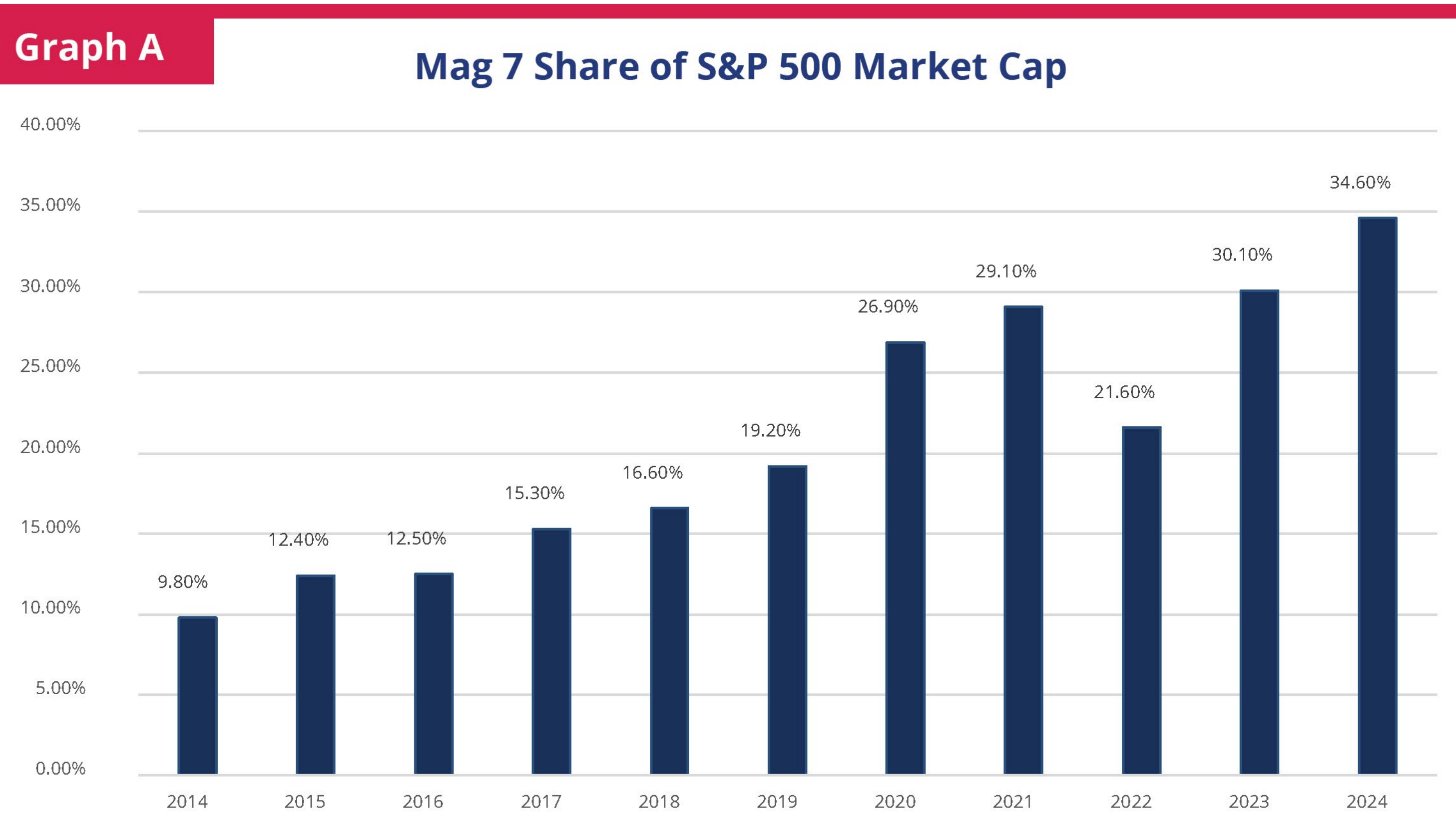
Entering 2024, numerous economists provided forecasts for the year, ranging from the most pessimistic (JP Morgan – Decline of 12%) to the most optimistic (Yardeni Research – Increase of 13%) (Source: MarketWatch). Various factors influenced these predictions, including the election year. Despite expectations of significant volatility, this did not materialize. Another key factor under consideration was inflation – whether it would continue its downward trend observed in recent years. Indeed, inflation decreased, prompting the Federal Reserve to implement four interest rate cuts throughout 2024.

While 2024 was a year of strong performance in the equity markets, it was also marked by concentrated growth, with a few key sectors driving the majority of gains. The Magnificent Seven – compromising Alphabet, Amazon, Apple Inc., Meta, Microsoft, Nvidia, and Tesla - continued their dominance. Meta and Tesla experienced growth exceeding 60%, while NVIDIA soared by over 170%, an impressive feat (Source: Koyfin). However, the increasing size and market share of these companies raise concerns. Currently, they represent one-third of the S&P 500 (see Graph A). Comparing the Magnificent Seven to other countries' market capitalization, Apple alone ranks among the top five (see Table A). Combined, Apple and NVIDIA's market capitalizations would rank second as a country, prompting the question of how much larger these companies can grow.

Magnificent 7

Market Capitalization Over Time

Graph A



Market Capitalization = Total number of shares X present share price
Source: https://www.visualcapitalist.com/

Magnificent 7

Market Capitalization as of January 2024

Table A

Rank	Country	Market Cap
1	United States	$60.366 T
2	China	$6.734 T
3	Japan	$4.914 T
4	India	$4.184 T
5	United Kingdom	$3.417 T
6	Canada	$2.910 T
7	France	$2.725 T
8	Saudi Arabia	$2.704 T
9	Germany	$2.330 T
10	Switzerland	$2.276 T

Company	Market Cap
Apple	$3.586 T
NVIDIA	$3.348 T
Microsoft	$3.143 T
Alphabet (Google)	$2.388 T
Amazon	$2.319 T
Meta (Facebook)	$1.583 T
Tesla	$1.270 T
Total	~$17.6 T

Market Capitalization = Total number of shares X present share price
Source: https://companiesmarketcap.com/

As a result of the market performance in 2024, Rosenau Family Research Foundation's investment portfolio increased by 9.72% as of December 31, 2024. This performance along with additional cash contributed to an increase in the investment portfolio from over $32 million on December 31, 2023, to over $38 million on December 31, 2024, while also providing over $1.7 million in grants to researchers – an extraordinary accomplishment!

While 2024 was a remarkable year in the market, it highlighted the importance of maintaining a well-diversified portfolio. As we approach 2025, RFRF will continue to evaluate protocols for risk management within our investment portfolios. We will also assess our asset allocation to ensure it aligns with our objectives. Consistently, one principle stands true for the foundation: Patience and diversification invariably yield positive outcomes.

Rosenau Family Research Foundation Balance Sheet

As of December 31, 2024

ASSETS	TOTAL
Current Assets	**$35,784,383.21**
Life Insurance	$2,307,315.43
TOTAL ASSETS	**$38,091,698.64**
LIABILITIES AND EQUITY	
Liabilities	
Current Liabilities	$6,319.51
Total Liabilities	**$6,319.51**
Equity	
Retained Earnings	$32,091,088.91
Net Income	$5,994,290.22
Total Equity	**$38,085,379.13**
TOTAL LIABILITIES AND EQUITY	**$38,091,698.64**

Investment Management Firm Request for Proposal

Heather Techmeier
Finance Director

In 2024 Rosenau Family Research Foundation (RFRF) initiated a Request for Proposal (RFP) for investment management services, as recommended by the Investment Committee (IC). The primary goal of the RFP process was to invite comprehensive and comparable proposals from qualified investment managers and to evaluate these proposals impartially and methodically. The RFRF Board of Directors (BOD) recognizes the significance of prudent asset management. After thorough deliberation, the BOD selected Foster Group to manage the Foundation's assets. Foster Group is a **reputable, privately held, independent, fee-only** financial management and investment management firm. Their fee-only compensation model mitigates potential conflicts of interest, **ensuring that advice provided is consistently aligned with the client's best interests.**

Grants

TWO Grant Cycles: Spring & Fall

On May 1, 2024, Rosenau Family Research Foundation (RFRF) announced the addition of a spring grant cycle! With our original fall grant cycle still in place, operating with two grant cycles enables RFRF to expand and provides an opportunity for applicants working on projects with varying schedules and needs. We are energized by the passion represented by the number of Letter of Intent submissions we received between both grant cycles in 2024 and are encouraged by the progress made to improve the lives of patients impacted by Krabbe disease and Cystic Fibrosis.

The table below lays out our updated grants schedule. You can visit the Grant Process Page on our website to learn more about our grant process.

Please send any questions to grants@rosenaufoundation.org.

Grant Management Process – Fall & Spring Grant Funding Cycles

FALL GRANT FUNDING CYCLES	KEY DATES
Call for LOI	11/1
LOI Submission Deadline	1/31
LOI Award/Denial Notification	2/16
Grant Application Deadline	6/1
Application Award/Denial Notification	Early Oct
Funding Agreement Executed	12/1
Funding Distribution	12/31

SPRING GRANT FUNDING CYCLES	KEY DATES
Call for LOI	5/1
LOI Submission Deadline	7/31
LOI Award/Denial Notification	8/16
Grant Application Deadline	12/1
Application Award/Denial Notification	Early April
Funding Agreement Executed	6/1
Funding Distribution	6/30

GRANT RECIPIENT REPORTING***	
May Progress & Financial Reports	5/1
November Progress Report	11/1
December Financial Report	12/1

*** Grants funded in both Fall and Spring grant funding cycles are required to submit progress and financial reports bi-annually on the same schedule

Grants Funded in 2024

ELUCIDATING THE METABOLIC SIGNATURE OF KRABBE DISEASE PLASMA, DRIED BLOOD SPOTS, AND CEREBROSPINAL FLUID USING UNTARGETED METABOLOMICS AND METABOLIC FLUX ANALYSIS

New Investigator: *Rachel Wurth — Mayo Clinic*

MODULATING OLIGODENDROGLIAL NFKB AS A THERAPEUTIC STRATEGY FOR KRABBE DISEASE

Daesung Shin, PhD — SUNY Buffalo

DISCLOSURE OF NEWBORN SCREENING RESULTS FOR KRABBE DISEASE IN PENNSYLVANIA

Laura Kirkpatrick, MD — University of Pittsburgh

EVALUATION OF IN UTERO GENE THERAPY IN CANINE KRABBE DISEASE

Allison Bradbury, MS, PhD — Nationwide Children's Hospital

GENOKRABBE: A COMPREHENSIVE GENOTYPE-PHENOTYPE DATABASE FOR KRABBE DISEASE

Paul Orchard, MD — University of Minnesota Medical School

The mission and vision of Rosenau Family Research Foundation (RFRF) is improving the lives of patients impacted by Krabbe disease and Cystic Fibrosis through research funding and disease advocacy, and helping individuals live life undefined by Krabbe disease and Cystic Fibrosis.

To support this mission and vision, the foundation considers grant funding for basic science research, translational research, and clinical research that can lead to or enhance treatments and cures for Krabbe disease and Cystic Fibrosis. Programs that promote, through education and awareness, the expansion of newborn screening, Krabbe disease, and Cystic Fibrosis are similarly considered.

"The 2024 funded grants continue a legacy of excellent research being done in the fields of Krabbe disease and Cystic Fibrosis," said RFRF Executive Director, Gabriel M Cohn, MD, MBA. "Our grant recipients also include one new investigator, which is exciting to us as an organization as we work to recruit greater participation in rare disease research."

CLICK HERE TO LEARN MORE ABOUT THE 2024 GRANT RECIPIENTS AND THEIR WORK

Grant Management Platform Development

Renea Muellerleile
Fractional Operations Director

As Rosenau Family Research Foundation (RFRF) continues to successfully grow and work toward achieving its mission to improve the lives of patients impacted by Krabbe disease and Cystic Fibrosis, we are committed to maintaining efficient, streamlined and cost-effective grant management operations.

Toward this goal, the foundation launched a new online grant management system in November 2023, automating the Letter of Intent (LOI) and grant application submission processes in 2024. This system incorporates enhancements to improve and expand the quality grant information available for objective evaluation of the LOIs and applications, including:

- Planned scientific methodology
- Hypothesis, research plan
- Milestones
- Detailed budget information along with referential data, investigator and organization background information

The online grant management system enables RFRF to administer blinded (scientific merit) reviews and unblinded (feasibility) reviews by our Scientific Advisory Committee at the LOI and application stages in the grant process. This ensures a fair and constructive funding opportunity for all who are interested in applying, and focused support of solid scientific practice and innovation.

With the online grant management system, we were able to quickly configure and manage the LOI and application submission processes for an additional grant cycle launched in May 2024 and recently completed the first full grant cycle, with funding agreements execution in December 2024. We are excited to continue to build out additional features and functionality to increase the efficiency of the overall grant management process and administration of ongoing funded grants. This will include automation of progress and financial reporting submissions and review processes that are easy for our grantees to use, and which will provide RFRF with the necessary information to responsibly oversee the grants. Initially, we will start with reporting from grant recipients that were included in the grant cycles started in the online grant management system and continue with the transition of grantee reporting on grants funded prior to the system implementation.

What is RFRF Looking For in a Grant Application?

Gabriel Cohn, MBA
Executive Director

The mission of Rosenau Family Research Foundation (RFRF) is to improve the lives of patients impacted by Krabbe disease and Cystic Fibrosis through research funding and disease advocacy, and to help individuals live life undefined by Krabbe disease and Cystic Fibrosis. RFRF Marketing Director, Rachel Jackson (RJ) spoke with RFRF Executive Director, Dr. Gabriel M. Cohn (GMC), to learn more about the foundation's research funding.

RJ: How does RFRF fund research?
GMC: RFRF has a competitive grants program that is vital to the foundation's mission of improving the lives of those impacted by Krabbe disease and Cystic Fibrosis.

RJ: What types of research proposals are considered for funding?
GMC: We will consider research proposals in basic science research, translational research, and clinical research that align with our mission. As such, grants that can lead to a better understanding of Krabbe disease or Cystic Fibrosis or that can enhance treatments and cures for Krabbe disease and Cystic Fibrosis will always be our highest priority. In addition, programs that promote, through education and awareness, the expansion of newborn screening, Krabbe disease, and Cystic Fibrosis, will be similarly considered.

RJ: Who is eligible to receive funding?
GMC: Currently, only organizations that meet 501(c)(3) tax-exempt status or 509(a) status, are eligible to receive funding through our program. In addition, we provide funding for established investigators of such organizations as well as new investigators (those that are either still in school or in training).

RJ: When and how can someone who is interested in receiving a grant apply?
GMC: In the past we solicited grants on an annual basis. This year, we've successfully transitioned to a semi-annual application cycle, one in the fall and another in the spring. We've noticed a 70% increase in grant application interest, which is very exciting!

> *"We've noticed a 70% increase in grant application interest, which is very exciting!"*

The grant application cycle begins with completion of our online Letter of Intent (LOI) form, a link to which can be found on our website. The fall grant funding cycle begins with a call for LOIs on November 1. The deadline for LOI submission is January 31. The spring grant funding cycle begins with a call for LOIs on May 1 with a deadline for submission of July 31. Following review of the LOIs, some applicants will be invited to submit a full grant application. Notification to submit the full grant application is 16 days after the LOI submission deadline: so, February 16 for the fall funding cycle and August 16 for the spring cycle. The full application is then due approximately 3.5 months later: so, June 1 for the fall cycle and December 1 for the spring funding cycle *(see table on RFRF Grant Process Page)*.

What is RFRF Looking For in a Grant Application?

RJ: What is the applicant expected to provide in the LOI form?
GMC: The LOI form asks that the applicant describe the purpose of the project, key hypothesis, specific aims, key experiments, anticipated outcomes, annual objectives, timelines, and budget. We ask about the relevance of the findings if the proposed hypothesis is confirmed and the significance of the findings if the findings are not supportive of the proposed hypothesis.

RJ: How is the LOI reviewed by the foundation?
GMC: Each LOI is reviewed by a member of the foundation's Scientific Advisory Committee (SAC). To limit any potential bias, the reviewer is blinded to the applicant's name and institution, so the reviewer sees and evaluates the content of the LOI that is specific to only the proposed project itself. The reviewer then scores each section from 0-2 with 2 being satisfactory, 0 being unsatisfactory, and 1 being somewhat satisfactory. A total score is then generated along with any reviewer comments and recommendations for or against inviting the applicant to submit the full grant application. Applicants whose LOIs received the highest scores along with recommendations to proceed to the full application phase are then invited to submit the full grant application. The full application, like the LOI, consists of an online form.

RJ: What is the difference between the LOI and the full application?
GMC: The LOI serves as more of a high-level summary of the proposed project whereas the full application asks the applicant to elaborate upon each section and provide greater detail, particularly in areas related to background and experimental approach and design.

RJ: Is the review of the full grant application similar to the review of the LOI?
GMC: There are similarities and differences.

- The key similarities between the LOI and full application are first, they both include a blinded scientific review. The scientific reviewer is blinded to any of the applicant's identifiers as we want to make this process as free as possible from any potential bias. Secondly, both review processes are standardized, meaning that each LOI and each full grant application is reviewed and evaluated against the same set of criteria and standards. By applying the same set of standardized criteria in the review of each application and by blinding the identifiers in the scientific review, we hope to make this process as fair, objective, and impartial as possible.

- Beyond these two similarities, there are some very significant differences. Unlike the LOI review, which is a single review, the full application review involves several steps:

    - Initially, the full grant application is reviewed for scientific merit in a blinded fashion. An SAC member is asked to review the content specific to the proposed project itself while being blinded to any of the applicant's identifiers. The reviewer provides a score for each section of our scientific review scorecard.

What is RFRF Looking For in a Grant Application?

- Once the blinded scientific review is completed, that evaluation is locked, and the SAC member performs a feasibility review. This consists of a review of the applicant's qualifications, the qualifications of any collaborators, mentor support if applicable, and the approval and support for the proposed project by the applicant's institution and relevant departments, such as animal safety, IRB etc. In addition, timelines, budget, and budget justification are also reviewed. As with the scientific review, the reviewer provides a score for each section of the feasibility review scorecard.

- The scientific review score represents 65% of the weighting while the feasibility review score represents 35% of the weighting. While both elements are critically important, it is essential that each funded application be scientifically robust.

- Once all the grants have gone through the formal review and scoring process, the SAC convenes to further review and discuss each proposal in detail. Based on those discussions, grants are ranked and prioritized along with recommendations relative to funding. Copies of the LOIs, the full grant applications, the LOI and grant application evaluations, as well as the SAC's ranked list and SAC recommendations are disseminated to the foundation's Board of Directors (BOD). The BOD meets and discusses each cycle's grant applications and the SAC recommendations and provides the final determination as to which grants will receive funding and whether any adjustments to the grant or budget are required.

RJ: How do the reviews by the foundation's SAC and BOD differ?
GMC: The SAC is comprised of individuals with expertise spanning biochemistry, newborn screening, basic science, translational medicine, clinical development, clinical trials, clinical practice, clinical genetics, drug development, genetic therapeutics, public health, Krabbe disease and Cystic Fibrosis. Their backgrounds also include work in academia, the biotech industry, governmental agencies, and the non-profit sector. As such, this group is invaluable in providing the expertise required in the technical review of the grant applications from both a scientific and feasibility standpoint. In addition, the SAC also provides perspectives as to how a particular proposal fits within the disease landscape and fits in relationship to the foundation's mission. The RFRF BOD, with its more diverse background, views the grant applications and SAC recommendations from a broader perspective, finalizing prioritization based not only on the SAC reviews and recommendations, but also on the foundation's mission, strategic and functional priorities, as well as the foundation's financial standing.

What is RFRF Looking For in a Grant Application?

RJ: What should those interested in applying for an RFRF grant know about the foundation's funding priorities and chances of getting approved?
GMC: Applicants should be aware of several considerations that can significantly improve their chances of receiving funding. First, the goals of the application must align with the foundation's mission. Second, given the backgrounds of the members of our SAC, the scientific and feasibility reviews are incredibly rigorous. This means that the background supporting a given hypothesis must be well substantiated and that the proposed experimental design and methodology be meticulously detailed to demonstrate to our reviewers that the proposed project is appropriately designed to confirm or reject the proposal's hypothesis. Unlike NIH grants, we do not require volumes of preliminary data, however some preliminary data based on prior publications, and/or some investigator generated findings, along with sound arguments in support of the rationale for the proposed hypothesis is required. Third, as we view the funding of these competitive grants as an investment in improving lives, the applicant must demonstrate sufficient care in the handling of these funds by identifying potential risks to the successful conduct of the study and should also be able to articulate risk mitigation strategies. Furthermore, as with any well thought out study, the results of a proposal, whether supportive of the proposed hypothesis or not, should lead to enhanced knowledge and move the field forward. The applications that provide the highest return on our research funding investment and are most deserving of funding are the ones that can clearly articulate how the lives of those impacted by Krabbe disease or Cystic Fibrosis will be enhanced regardless of the study's outcome. Finally, it is critical that the application include documentation supporting the investigator's and the collaborators' qualifications to perform the planned project and provide documentation of the institution's support for the proposal. In the case of new investigators (individuals still in school or in training) support from a qualified mentor is also essential.

RJ: Do you have any final thoughts you'd like to share?
GMC: What makes our grants program unique and exciting is that we fund new and innovative projects that are scientifically rigorous but require initial funding not typically available through such organizations as the NIH. If successful, the data generated from these programs can lead to funding which will allow such programs to fully develop and mature. This approach has led to several successful research programs including two gene therapy products that are being investigated in clinical trials, improvements in newborn screening for Krabbe disease and Cystic Fibrosis and studies that have led to a deeper understanding of both Cystic Fibrosis and Krabbe disease. In addition, our program also supports the research of new investigators in these fields with the hope that they will become the research leaders of tomorrow. This is truly an investment in the future, and one that's worthy of consideration by all those who work in these fields.

Click for more information about our Grant Process

Research & Labs

Psychosine Profiling and Evaluation of 1-Deoxygalactonojirimycin as a Therapeutic for Krabbe Disease

About the Study

Dr. Chris Lee, from the Biomedical Research Institute of New Jersey (BRInj), began a study in 2023 to characterize how GALC genetic mutations observed in patients with Krabbe disease impact disease onset and severity. Specifically, Dr. Lee and his team set out to create a standardized assay to test the functional consequences and molecular characteristics of disease-related mutations in order to provide the research community with a robust tool to more easily study Krabbe disease. Using this assay, they also planned to evaluate whether an FDA-approved, oral medication used to treat Fabry disease, can be repurposed to treat Krabbe disease.

2024 Progress

A human cell-based assay was established that reliably uses Krabbe disease biomarkers (GALC enzyme activity and psychosine levels) to report on the impact of disease mutations. The results show that the assay predictably identifies which mutations are most severe and forecasts the age of symptom-onset. The findings suggest that the assay could be a valuable resource in the field, particularly for analyzing probable Krabbe disease cases identified through newborn screening.

Looking Forward

The addition of infantile Krabbe disease to the Recommended Universal Screen Panel (RUSP) is a milestone for the Krabbe disease community. As Krabbe disease is added to newborn screening programs in more states, a large number of genetic variants with uncertain significance (VUS) will emerge, leaving some infants with uncertain clinical prognoses. To this end, Dr. Lee and his team will use their optimized cell-based assay to evaluate and assign clinical severity to VUS identified through newborn screening. The results from this study will also support future application to include later-onset Krabbe disease in RUSP.

> *"As an investigator at a small, non-profit research institute, funding support received from Rosenau Family Research Foundation has enabled us to explore high value Krabbe disease research with translational applications. The results and publications from this funded research, strengthens opportunities for NIH-funded awards, and maximizes benefits for the Krabbe disease community."*

Dr. Chris Lee
Biomedical Research Institute of New Jersey

Research Spotlight

Cystic Fibrosis

Enriching CF Newborn Screening Outcomes through a precision personalized medicine strategy

Uncovering Immune Mechanisms Shaped by Early-Life Events

Dr. Hara Levy's research program is pioneering a new direction in cystic fibrosis (CF) by investigating how early-life immune cell programming shapes susceptibility to chronic lung infections. This work is poised to transform the identification and intervention in disease progression for individuals diagnosed at birth.

Although CF is routinely identified in infancy through newborn screening (NBS), early diagnosis alone does not ensure a predictable health trajectory. Children with CF display striking variability in their risk for respiratory infections, long-term clinical outcomes, and responses to treatment. Emerging evidence reveals that this variability is further compounded by racial and ethnic disparities. Approximately 20% of individuals diagnosed with CF in the United States are African American, Hispanic, or from other underrepresented communities. Yet, these populations experience delays in diagnosis, are less likely to benefit from standard CFTR mutation panels, and often endure more severe pulmonary outcomes at a younger age.

These disparities highlight a critical need to modernize newborn screening practices—not only to broaden genetic coverage, but also to integrate functional and immune-based assessments that can better predict disease severity across diverse populations.

Dr. Hara's study focuses on evaluating immune cells from individuals with CF who carry a range of CFTR mutations, including those more prevalent among Black and Hispanic individuals (e.g., A559T, 3120+1G>A, and 3849+10kb C>T). By comparing immune responses among those with differing genetic backgrounds, her team aims to uncover why some individuals remain vulnerable to chronic infection despite early diagnosis and access to treatment.

"RFRF's support is instrumental in advancing our novel, high-risk research direction at a critical juncture in this work. Traditional funding mechanisms often overlook projects that challenge established paradigms; your investment enabled us to explore the uncharted role of neutrophil epigenetics and metabolic programming in CF pathogenesis.

This line of inquiry not only redefines early risk prediction in CF but also addresses persistent health disparities by focusing on immune biomarkers beyond CFTR genotype—an approach particularly relevant for underrepresented populations who are often missed by current newborn screening panels.

No other group is investigating this intersection of immune dysregulation, infection trajectory, and health equity in CF. RFRF's visionary support has laid the groundwork for a more inclusive, mechanistically-informed framework for early intervention.

We are deeply grateful for their partnership. Their investment continues to drive impactful science while advancing more equitable outcomes in CF care."

Hara Levy, MD, MMSc
- *Professor Pediatric Pulmonology and Sleep Medicine*
- *Department of Pediatrics*
- *University of Wisconsin School of Medicine and Public Health*

Scientific Premise and Data

Leveraging the power of newborn screening (NBS) cohorts, Dr. Levy and her team are well positioned to identify factors underlying the heightened susceptibility of some children to cystic fibrosis (CF) lung disease following early diagnosis. Their research is among the first to explore how early-life immune cell programming—particularly within neutrophils—shapes divergent clinical outcomes in CF. Although neutrophils are essential for host defense, in CF they frequently exhibit functional impairments and aberrant activation, leading to excessive pulmonary infiltration, sustained inflammation, and proteolytic tissue damage.

Preliminary findings from Dr. Levy's lab and collaborators reveal that macrophages in CF are impaired in their ability to clear pathogens, and importantly, this dysfunction is not corrected by CFTR modulator therapies. They further found that these dysfunctional macrophages influence neutrophil development and programming early in life. This novel insight reframes neutrophil dysfunction as a root cause—rather than a downstream effect—of chronic infection in CF.

Using next-generation epigenomic profiling (CUT&RUN), they observed reduced H3K4me3 enrichment at promoters of critical metabolic genes (Hexokinase 1, Fumarate hydratase) in neutrophils from individuals with chronic Pseudomonas aeruginosa (Pa) infections. This suggests that neutrophil metabolism is epigenetically reprogrammed in infection-prone individuals, leading to long-term immune dysfunction. Additional transcriptomic analyses reveal suppressed immune gene expression, further implicating a tolerance-like state that may allow pathogens to persist.

Collectively, these data support a new model in which early immune cell programming—particularly at the level of epigenetic and metabolic regulation—determines susceptibility to chronic infection and poor outcomes in CF.

This work, represents a promising step toward equitable and personalized care for all individuals with CF, regardless of their genetic background or community of origin.

Future Directions: Toward Early, Personalized Intervention

While CFTR modulators have dramatically improved CF care, chronic lung infections—particularly Pseudomonas aeruginosa—remain a leading cause of morbidity and mortality. Dr. Levy's research suggests that immune modulation, beyond CFTR restoration, may be critical to halting disease progression and improving long-term outcomes.

In their next phase of research, Dr. Levy and her team aim to leverage functional analysis and epigenomics to uncover novel therapeutic targets and provide more equitable, personalized care. Specifically, they will pursue three interrelated goals:

1. Map the epigenetic landscapes that drive neutrophil dysfunction in CF, identifying how early-life immune programming contributes to persistent infection susceptibility.
2. Investigate why current therapies fail to address immune dysfunction in CF, even when CFTR function is restored, to better understand the limitations of existing treatments.
3. Identify biomarkers of early immune dysregulation to facilitate risk stratification and preemptive, personalized interventions, particularly for marginalized populations who may not benefit fully from standard treatments.

Their ultimate goal is to shift the CF care model from reactive symptom management to proactive, precision medicine—enabling early intervention tailored to an individual's genetic, immune, and environmental profile—before irreversible lung damage occurs. This approach aims to not only advance therapeutic options but also address health disparities, ensuring equitable access to personalized, cutting-edge care for all individuals with CF.

Lab Highlight: Dr. Ernesto Bongarzone

In February of 2024, Rosenau Family Research Foundation (RFRF) sent a film crew to Dr. Ernesto Bongarzone's lab at the University of Illinois, Chicago to document the work of our four grant recipients there and talk to them about how RFRF funding has helped with their research projects. We spent the day touring the lab, capturing investigators and students at work, and conducting interviews to learn about the goals and progress of each of the four grants given to the investigators in the lab, and compiled the footage into a mini documentary.

Watch the Documentary:

The trip was part of a larger program, started in 2024, aimed at showcasing the work of RFRF grant recipients as they use their grant funding to advance their research in the fields of Krabbe disease and Cystic Fibrosis. This program will be further developed in 2025 to include grant recipient "hubs" on our website, video and written interviews with investigators, research updates and publications, and more.

If you are interested in participating in this program, please contact RFRF's Marketing Director, Rachel Jackson, at racheljackson@rosenaufoundation.org.

Partnerships & Awards

KTRN
Krabbe Translational Research Network
2024 Meeting

PRESENTED BY
Rosenau Family
Research Foundation

Gabriel Cohn, MBA
Executive Director

The 2024 KTRN Meeting was held on March 19-21, 2024, in Bloomington, Minnesota. This event featured a welcome reception with poster presentations by new investigators and scientific sessions on Krabbe disease pathophysiology, therapeutic advancements, clinical research, newborn screening, and evolving trends. There were many outstanding speakers who highlighted the significant role of inflammation and the immune system in contributing to Krabbe disease pathology, the potential overlap between the genetics associated with Krabbe disease and the biology and genetics of other neurodegenerative disorders such as Alzheimer's disease, the potential of new investigational therapeutic modalities including cell therapy, gene therapy, and gene editing, and progress in advancing Krabbe disease newborn screening to panels throughout the United States. Below are more technical, high-level summaries of just a few of the presentations:

1. Preclinical Research Insights (Cell and Animal Models):

- STING signaling contributes significantly to inflammation in Krabbe disease and other lysosomal storage disorders.
- GALC deficiency increases myelin vulnerability in post-myelinating adult oligodendrocytes and prompt metabolic stress in macrophages which may precipitate macrophage dysfunction by reducing metabolic fitness and inducing the expression of genes related to immune response, cell stress, metabolism, and cell death.
- Local accumulation of undegraded psychosine at the synapse is sufficient to interfere with synaptic function and alters synaptic structure in the hippocampus.
- Depletion of pathogenic CD8+ T cells improved myelin pathology and clinical outcomes, highlighting a potential therapeutic approach.
- Evidence may suggest potential links between Krabbe disease and Alzheimer's disease, with overlapping genetic mutations affecting amyloid-beta levels when present in gene carriers.

2. Emerging Therapeutic Approaches

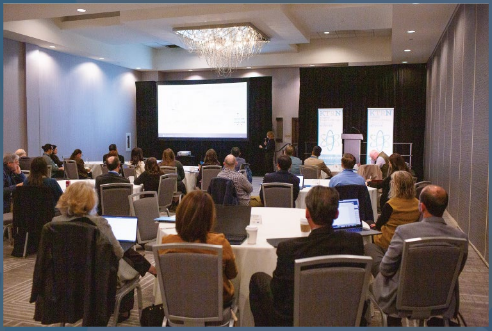
- Innovative therapies under development include microglia replacement, umbilical cord blood-derived cell therapy, AAV9-mediated gene therapy administered to the CSF via an intra-cisterna magna route, and ex-vivo, CRISPR/Cas9-based hematopoietic stem cell editing.
- An increase in mannose-6-phosphate levels in manufactured enzymes showed promise for therapeutic enhancement in lysosomal storage disorders, including Krabbe disease.

3. Clinical Advances

- A brain biorepository established in 2015 now holds 21 donations, contributing critical insights into Krabbe disease pathology and treatment.

- Results reported from five participants in the REKLAIM Phase 1b trial of FBX-101 demonstrated improved enzyme activity, reduced psychosine levels, and enhanced motor function in participants who received a low dose of the investigational gene therapy product, FBX-101.

4. Newborn Screening (NBS) Developments



- On January 30th, 2024, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) recommended to the US Secretary of Health and Human Services to add “Infantile Krabbe disease as defined by low GALC activity and psychosine (PSY) ≥10 nM for inclusion as a core condition on the RUSP” (Recommended Uniform Screening Panel). It wasreported that as of February 26, 2024, Krabbe disease became part of newborn screening.

- NBS is currently available in 12 states representing 34% of US live births. Eight states include PSY into their NBS strategy and outcomes. Strategies incorporating PSY measurements improve diagnostic accuracy.

- Advocates suggested prioritizing NBS expansion in six states with impactful newborn screening systems: Iowa, Massachusetts, Michigan, Oregon, Washington, and Wisconsin.

- Lessons learned from Cystic Fibrosis NBS diagnosis and care, include the importance of equity, health care provider education and knowledge, and parental understanding of newborn screening.

Honors and Awards

- Dr. Ernesto Bongarzone delivered a heartfelt memorial tribute to Dr. Laura Feltri.

- Dr. Mark Sands received the Sue Rosenau Legacy Award for his inspirational leadership and contributions to Krabbe disease research; Dr. Ernesto Bongarzone accepted it on his behalf.

The meeting successfully promoted collaboration and showcased significant progress in addressing Krabbe disease. Notably, nearly 20% of the speakers were new investigators, and over 40% of the speakers were first-time participants in the KTRN meeting. Attendees rated the program’s speakers and content, as well as the overall value to the field of Krabbe disease, very highly, with an average score of 4.8 out of 5 on the post-meeting survey (scale: 1-5: 1 = lowest, 5= highest).

Ongoing Collaboration with National Organization for Rare Disorders

NORD®
National Organization for Rare Disorders

In 2024, Rosenau Family Research Foundation (RFRF) partnered with NORD's Student for Rare program to introduce our network of researchers and help students explore the opportunities that come along with research grant funding.

Students for Rare unites students of all disciplines to spread awareness of rare disease and explore future opportunities working with the rare disease community.

RFRF participated in the program by sending our Executive Director, Dr. Gabriel Cohn, to NORD's annual 2024 Rare Diseases and Orphan Products Breakthrough Summit in Washington DC, where he provided an overview of the foundation's history, mission, and vision and announced our intention to work with NORD to develop and sponsor a summer internship program for students to gain healthcare or research-related exposure and experience in rare diseases. This program will be launched in the summer of 2025.

Moving forward, we hope for our collaboration with NORD to include sending more of our researcher network to more events, both in-person and virtual, as well as offering additional mentorship and internship opportunities to students and helping to expand the program by connecting students with our network at various educational institutions.

In February 2024, Dr. Gregory Grabowski was announced as the inaugural recipient of the Rosenau Family Research Foundation (RFRF) Award.

The RFRF Foundation Award is a staff-nominated award which honors a person whose contributions have been invaluable to the success of RFRF and have had an incredible impact on our community.

Dr. Grabowski has been directly involved in supporting RFRF for many years and has been instrumental in laying the groundwork necessary for RFRF's success. His career has spanned decades, and his research on the basic and clinical sciences of lysosomal storage and genetic diseases has been published in over 360 scholarly works, all while he has maintained active clinical and treatment programs for genetic diseases.

We can't think of someone more deserving of this award than Dr. Grabowski. It has been an honor to partner with him and his extensive knowledge and research, and we are lucky to have him as part of our community.

Dr. Mark Sands was named the recipient of the Sue Rosenau Legacy Award at the 2024 KTRN meeting in March.

The Sue Rosenau Legacy Award recognizes an inspirational leader who has collectively created lasting change and measurable differences in one or more areas of RFRF's mission.

Dr. Sands was the unanimous selection of the committee, which includes peers in industry, showing that his science speaks volumes to those who matter and choose to listen.

Ernesto R Bongarzone, PhD accepted the award on behalf of Dr. Sands, who was unable to attend the KTRN meeting.

Connect With Us!

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