THE LEGACY OF ANGELS FOUNDATION

2020 ANNUAL REPORT

The Legacy of Angels
FOUNDATION

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FROM THE DESK OF THE CO-FOUNDER

The introduction of COVID-19 into the world has made it a challenging year and a half for everyone. Even though life as we knew it is gone, we still had hope through it all; people dug in and adapted to address the impacts of the pandemic. For example, auto manufacturers stopped making cars and started making ventilators, a dormant printing plant was reopened and turned into a production facility for making hand sanitizer, and people stayed home on the advice of health care officials. Everyone did what he/she could to help stop the spread, treat the sick and look for an answer to the problem at hand. Doctors, nurses, and health care providers, dug in extra deep and even isolated from their own families while they provided care for the sick and dying. Our scientists and researchers dropped what they were doing to help uncover a vaccine as quickly as possible.

Similar to the motivation of scientists to find a vaccine for COVID-19, the response of the scientific Krabbe Community is also driven by the hope of making a significant difference in the lives of those affected by an illness. The only difference is that in this case, they are dealing with a genetic disorder and not a virus.

The Krabbe disease (KD) community looks forward to seeing two to three new treatments available to patients by mid-2022. This is a significant accomplishment. The new treatments will utilize gene therapy to replenish the missing enzyme, galactocerebrosidase, which is responsible for developing healthy myelin. However, these new treatments must be vetted through the FDA clinical trial process. Clinical trials can take years to fine-tune the therapy to achieve the achieve the best clinical outcomes for patients living with KD.

Thus, we must all do our part. While researchers play an important role, we can all do our part. We can sponsor research, talk with our government representatives, help with fundraisers, or support families impacted by Krabbe disease or Cystic Fibrosis. We can all help make a difference.

Until 2008, I never thought that my wife and I could make an impact on Krabbe disease or Cystic Fibrosis. Circumstances proved me wrong. We won the lottery. My wife, Sue, and I were happy without the lottery. However, winning the lottery allowed us to advance the treatment options for Krabbe disease and Cystic Fibrosis.

There will come a time when I choose to step back and honor my wife and the dream we had to travel, travel, travel. For now, though, I am committed to working hard for our mission. I am incredibly grateful for everyone who has given and continues to give of their time, resources, and talents to move the research and treatment forward for Krabbe disease and Cystic Fibrosis.

Warm regards,
Paul G Rosenau
Co-Founder and President

ABOUT TLOAF

With these attributes, we can collectively change the outcome for those impacted by Krabbe disease and Cystic Fibrosis.

BOARD OF DIRECTORS

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A LITTLE HISTORY

The Legacy of Angels Foundation (TLOAF) is a private family 501(c)(3) foundation established in 2008 by Paul and the late-Sue Rosenau after winning the Powerball on May 4th, 2008. Paul and Sue spent nearly a year organizing a strategic plan to institute a mission for Krabbe disease and Cystic Fibrosis; two rare diseases that affect the Rosenau family genetics. The Co-Founders, in the HOPE of finding a cure for Krabbe disease and Cystic Fibrosis, are passionate about research, newborn screening, and education that supports their mission.

TLOAF'S GRANT PROGRAM

The foundation's grant program drives the organization's mission forward. The foundation is committed to identifying grants, with the assistance of a strong scientific advisory board, to help advance research, newborn screening, and education for Krabbe disease and Cystic Fibrosis. The foundation's grants have grown significantly in size, scope, and stature, allowing the foundation to showcase many products from more than a decade of accomplished grants.

TLOAF'S MISSION

The foundation formed to improve the lives of children by working to promote the expansion of newborn screening, and to further education, awareness, and research of Krabbe disease and Cystic Fibrosis. With these attributes, we can collectively change the outcome for those impacted by Krabbe disease and Cystic Fibrosis.

TLOAF AWARDS ANOTHER MILLION DOLLARS IN GRANT FUNDING FOR THE 10TH CONSECUTIVE YEAR

Each year, The Legacy of Angels Foundation, along with the Scientific Advisory Board, selects grants that advance the work and mission of the foundation. Each grant goes through a thorough evaluation and must meet the following requirements: (1) the scope of the project must work to advance newborn screening, therapeutic advances, or disease awareness in Krabbe disease or Cystic Fibrosis, (2) the impact of the project works to make a significant contribution to the Krabbe disease or Cystic Fibrosis space, and (3) the merit of the team carrying out the project must be comprehensive. The 2020 grants awarded their initial year of funding are as follows:

Generation of Krabbe Mouse Model to Enable Regulated Expression of Therapeutic GALC Enzyme
Ernesto Bongarzone, Ph.D.
University of Illinois

Brain Connectome as a Novel Biomarker of Krabbe Disease
Li Ou, Ph.D.
University of Minnesota

NDRD Krabbe Disease Patient Care and Research
Maria Escolar, M.D.
Children's Hospital of Pittsburgh

Vesicular Delivery of GALC for ERT of Krabbe Disease
Maria Irene Givogri, Ph.D.
University of Illinois

Multi-year grants go through an annual review to ensure the principal investigator has met yearly milestones and to certify that funds are being distributed properly. The grants receiving their next year of funding are as follows:

Development of Pharmacological Chaperone Therapy for Krabbe Disease
Chris Lee, Ph.D.
Biomedical Research Institute of New Jersey

Studies of GALC Correction Stability after AAV Gene Therapy for Krabbe Disease
Ernesto Bongarzone, Ph.D.
University of Illinois

Lastly, at times, grants require additional time to carry out the remainder of their project. The additional time may be needed to complete additional testing, to synthesize data, to publish; at times it can even be due to an unforeseen circumstance such as a pandemic. The term used for projects requiring additional time but not requiring additional funds is known as a no-cost extension. The projects awarded a 1-year no-cost extension are as follows:

Development of High Throughput Screening Assay for Acid Ceramidase and UGT8 Inhibitors
Michael Gelb, Ph.D. – *University of Washington*

Developing a Target-Assay for Substrate Reduction Agents for Krabbe Disease
Gustavo Maegawa, M.D., Ph.D. – *University of Florida*

Assessing the Added Value of Whole Genome Sequencing in Cystic Fibrosis Newborn Screening
Philip Farrell, M.D., Ph.D.
University of Wisconsin, Madison

In 2020, The Legacy of Angels Foundation funded $1,398,663 in grants!

The Legacy of Angels Foundation Supports Newborn Screening Awareness and Improved Diagnostic Tools for Krabbe Disease and Cystic Fibrosis

CYSTIC FIBROSIS

For the past 10 years, newborns are screened for being at risk of Cystic Fibrosis by way of the newborn screening test. In the newborn screening test, newborns with low levels of a protein called cyclic adenosine-5'-monophosphate (AMP) are flagged as being at risk. However, further confirmatory tests must occur to confirm or disprove a diagnosis of Cystic Fibrosis

KRABBE DISEASE

10 states are currently testing newborns for Krabbe disease. Krabbe disease is identified by measuring an enzyme called Galactocerebrosidase or GALC for short. When GALC is low, a sample of the newborn screening blood spot is sent to a lab for further analysis to confirm the disease. Further analysis consists of identifying the mutation in the GALC gene or measuring the level of psychosine to confirm or disprove Krabbe disease.

KRABBE DISEASE

In the U.S., the incidence rate is 1 in every 100,000 individuals.

Psychosine is a highly toxic lipid that accumulates in the body as a result of a deficiency in the GALC enzyme.

NEWBORN SCREENING

Began in 1965.

All 50 states provide newborn screening however, not all states test for the same diseases and/or conditions.

Many babies' lives have been saved as a result of the newborn screening test.

CYSTIC FIBROSIS

The sweat test is the next step in confirming or disproving a positive newborn screening for Cystic Fibrosis.

According to the data collected by the Cystic Fibrosis Foundation, approximately 1,000 patients are diagnosed with Cystic Fibrosis each year.

The Legacy of Angels Foundation's Decade of Work to Help Improve the Lives of Those Diagnosed with Krabbe disease

Krabbe disease, also known as Globoid Cell Leukodystrophy, is a rare genetic neurological disorder causing a mutation on the 14th chromosome. This genetic mutation causes a shortage of an important metabolic enzyme called galactocerebrosidase or GALC. GALC is responsible for forming healthy myelin and is vital for brain well-being. Myelin is the thin coating around each of a human being's approximately 7 trillion nerves. This specialized coating allows for proper nerve condition to occur throughout your body. Without healthy myelin, the body is unable to send and receive messages properly to the brain, spinal cord, and organs. Consequently, many patients diagnosed with Krabbe disease experience severe delays in gross and fine motor skills, have trouble swallowing anything orally, and often develop seizures in addition to many other debilitating neurological symptoms.

Upon a Krabbe disease diagnosis, feelings of uncertainty plague the impacted family; however, "positive" change is happening. Research funded by TLOAF over the past decade has sparked the interest of several biotech companies, which has resulted in added education, increased awareness, and the exciting possibility of new treatments for Krabbe disease. However, working with biotech companies is not enough. The Krabbe disease community will need to band together and work diligently with the families of today and with the families who have lost loved ones to this disease. Patient and caregiver engagement along with non-profit funding and resources, is the only way that forward momentum will continue. To meet needs TLOAF will continue to build out their existing portfolio, strengthen community partnerships, and work diligently to disseminate knowledge until all Krabbe patients have access to a beneficial life-sustaining therapy. We encourage those impacted recently and those impacted 5, 10, or even 20 years ago to rally to help ensure that a Krabbe disease diagnosis does not remain a death sentence in the future!

TLOAF'S MOST NOTABLE ACCOMPLISHMENTS:

Contributed grant funds to advance research which has produced more than 30 peer reviewed journal publications acknowledging TLOAF as a funder

Fostered collaboration, education, and resource-sharing through the Annual Krabbe Translational Research Network Meeting

Supplied grant funding to help a group of collaborators develop a novel treatment, combining umbilical cord blood transplantation and gene therapy, to treat Krabbe disease. Forge Biologics is now enrolling patients in this combination therapy clinical trial.

Helped establish a Virtual Medical Home at the NDRD clinic in Pittsburgh to assist patients diagnosed with Krabbe disease throughout the world where they can virtually access experts to navigate the disease virtually.

Provided 13 years of direct support to Krabbe patient families at the NDRD clinic in Pittsburgh to help relieve transportation costs that accompany treatment and evaluation visits.

Miraculous New Therapies for Cystic Fibrosis

Philip M. Farrell, MD. PhD

The most significant development in cystic fibrosis during the 21st century has been the discovery of effective therapy aimed at the basic defect— an advance that seemed impossible prior to the era of molecular genetics. In fact, the combination of early diagnosis through newborn screening (NBS) and more effective treatments has transformed lives of patients with this relatively common genetic disorder. Such advances seemed impossible to even dream about when I took care of my first patient with CF in 1966— an 8 y/o girl who suffocated on her respiratory secretions. That experience during my 3rd year of medical school convinced me that no child should suffer such a frightening fate and that much more research was needed on this mysterious genetic disease. Fortunately, as molecular genetics emerged during the next two decades, teams of basic researchers made an elusive dream come true.

The transformation began in 1989 when the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) was discovered with identification of the principal CF-causing mutation, known at the time as ΔF508 and now commonly as F508del. This gene codes for the *CFTR* ion channel protein, which plays an important part in the transport of chloride and bicarbonate ions and secondarily water in vital organs like the lungs and pancreas. Once the *CFTR* gene was sequenced, many more CF-causing mutations were identified and their pathologic mechanisms defined as summarized in the accompanying illustration.

In addition to quickly applying this knowledge to improve diagnoses during infancy, researchers began immediately to investigate new strategies of treatments targeting the genetic defect. Initial efforts focused on gene replacement techniques that aim to provide a correct copy of the *CFTR* gene. Early exuberance and proof of concept about this “cure all” possibility was followed by three decades of disappointments. In retrospect, gene replacement therapy targeting the respiratory system is less appealing than subsequent therapeutic options because CF is a generalized ion channel disorder. Yet, successes with other genetic disorders stimulated much gene therapy research until a tragic death occurred in 1999 after an adenovirus-based trial for another genetic disease discouraged CF researchers and it became recognized that carriers (vectors) of replacement genes presented greater barriers than anticipated.

On the other hand, the visionary President/CEO of the CF Foundation, Dr. Robert Beall, embarked on a productive venture to develop what has become known as *CFTR* Modulator Therapy. Bob’s scientific background, passionate, relentless drive and willingness to invest funds wisely in a startup pharmaceutical company has led to incredible dividends. Bob recognized that high throughput screening procedures for drug development applied to cultured cells would facilitate assessing candidate compounds as potentiators for effectiveness in opening the *CFTR* channel at the cell surface to increase ion transport.

After evaluation of over 100,000 potentiator candidates, a drug eventually named ivacaftor was identified and soon studied successfully in international randomized clinical trials with patients having the Class III gating mutation G551D— leading to FDA approval in 2012. Now, this *CFTR* modulator is approved for other Class III and IV mutations and for children as young as 4 months old. Its impact includes both lung disease benefits and partial restoration of pancreatic function to enhance nutrition.

With *CFTR* Modulator Therapy now available during infancy, early diagnosis through NBS and concurrent determination/classification of genotype has become increasingly important. Another President/CEO of the CF Foundation, Dr. Preston Campbell, recognized this and engaged the CDC in a critical review of the evidence in favor of benefits as well as assessing risks. CDC then endorsed screening for CF in 2004, and by 2010 programs were underway nationwide. More research has been needed, however, to improve CF NBS, so fortunately The Legacy of Angels Foundation stepped forward and has contributed vital funding for projects that have advanced screening technologies and follow up programs as well as supporting valuable conferences.

Recent therapeutics research has been directed at the most common CF-causing mutation, F508del. Although traditionally listed in Class II, this oversimplifies the flaws of *CFTR*-F508del because abnormal gating (Class III) and shortened *CFTR* protein survival as in Class VI exacerbate the cellular processing defect. Initial drug discovery efforts focused on correctors— drugs that help the defective *CFTR* protein fold properly so that it can move to the cell surface. Applying rational drug design integrated with high throughput screening then led to multidrug strategies with corrector-potentiator combinations that provide genotype-specific, highly effective *CFTR* Modulator Therapy in this new era of personalized, precision medicine.

Class I *CFTR* mutations are a remaining challenge. Overcoming premature termination codon variants that interrupt *CFTR* production will probably require genetic engineering with emerging technologies like CRISPR to repair the underlying DNA sequence defect. Because “success breeds success,” optimism prevails among the teams studying such *CFTR* tools as the pace of discovery accelerates and more miracles are sought.

Dr. Philip Farrel- author of article

Insights From the Finance Director

Without a doubt 2020 has been one of the most challenging years of our lifetime. It was financially challenging as global stocks suffered one of the quickest declines on record. This rapid market decline in the first quarter caused TLOAF's portfolio to drop 15.94 percent leaving our assets at $27.7 million!

Regardless of the fluctuations in the market, however, the IRS still requires private foundations to distribute 5% of their assets fair market value each year. The 5% distribution requirement is an investment-planning and grant-making challenge that is unique to private foundations. This requirement can cause concerns for our sustainability since TLOAF relies heavily on the investment income to fund research.

In order for TLOAF to remain sustainable, their investment portfolio must earn a long-term rate that exceeds both the inflation rate as well as the 5% distribution rate. If addressed reactively and without forethought, this requirement has the potential to complicate our grant-making process and in turn, impact our research community. However, if addressed proactively we can satisfy our distribution requirements while providing consistent, reliable assistance to those we serve.

During these stressful times, challenging decisions need to be made about where to focus. Throughout the year, TLOAF assesses the impact and financial viability of each program the foundation supports, we consider the impact of each grant and fund the highest impact programs first. In addition, the foundation assesses what assets TLOAF was originally invested in and how those have changed over the years from holding annuities to more traditional investments. This analysis and revision process in ongoing.

With everything that happened in 2020, TLOAF's portfolio recovered at the end of year with net assets of $31,460,175. A reminder in order to create better investment outcomes, we need to align our portfolios with plans and purposes, harness the markets, avoid predictable disappointments, advance with science, and embrace uncertainty.

STATEMENT OF FINANCIAL POSITION

ASSETS	
Cash and Investments	$ 516,284.00
Life Insurance	$ 4,372,195.00
Annuities	$ 3,537,131.00
Corporate Stocks	$ 23,408,833.00
Total Assets	$ 31,834,443.00
LIABILITIES	
Accounts Payable and Accrued Expenses	$ 150.00
Grants Payable	$ 374,118.00
Total Liabilities	$ 374,268.00
NET ASSETS	
Capital Stock, Trust Principal, or Current Funds	$ 28,068,467.00
Retained Earnings, Accumulated Income, Endowment, or Other Funds	$ 3,391,708.00
Total Net Assets	$ 31,460,175.00
Total Liabilities and Net Assets	$ 31,834,443.00

Heather Techmeier,
Finance Director

A Nationally Recognized Leader in Newborn Screening for Cystic Fibrosis Receives The Sue Rosenau Legacy Award

The Legacy of Angels Foundation (TLOAF) is forever grateful for the efforts and contributions of Co-Founder and Chief Operating Officer, Sue Rosenau. Sue, a remarkable and driven wife, mother, and rare-disease advocate lost her 3-year battle with ovarian and serous endometrial cancer in July of 2018. To keep Sue's legacy alive within the foundation and community-at-large, TLOAF recognizes an inspirational leader who collectively creates lasting change and measurable differences in one or more areas of our mission. The individual honored must deliver extraordinary contributions, work to propel progress towards better treatments, and continuously gives altruistic support to the patient community; a replica of the late-co-founder, Sue Rosenau.

The individual selected for the 2020 award has an extensive history of accomplishments but is most notably recognized as an expert both on newborn screening for Cystic Fibrosis and on the ancient origin of Cystic Fibrosis throughout Europe and the Bronze Age. The admirable Dr. Phillip Farrell was presented virtually with the Sue Rosenau Legacy Award. His dedication to advancing research in Cystic Fibrosis newborn screening is directly tied to an encounter he had during his time as a medical student with an 8-year-old girl diagnosed with Cystic Fibrosis. Dr. Farrell's passion is a result of this 8-year-old girl he met in 1966 who died suffocating from this debilitating lung disease.

Cystic Fibrosis is the most common rare disease of European descent. CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator or *CFTR*. The *CFTR* is an important protein in the human body. It's responsible for regulating the viscosity, or in layman's terms, the stickiness of mucus, that lines the ducts of several organs. The extra mucus clogs passageways or ducts, especially in the lungs and pancreas, triggering a breeding zone for infections.

Dr. Philip Farrell was a top contender for the 2020 legacy award because his four decades of research efforts in Cystic Fibrosis have directly advanced early identification of CF through newborn screening. Dr. Farrell leads the Wisconsin Cystic Fibrosis Neonatal Screening Project, leads national research efforts in NBS quality improvement for Cystic Fibrosis (a collaborative effort with the CF Foundation and the CDC), leads an international interdisciplinary team investigating the ancient origin of CF, and so much more. His current project, funded by TLOAF, "Assessing the Added Value of Whole Genome Sequencing in Cystic Fibrosis Newborn Screening," hopes to prove that genome sequencing can offer medical personnel additional insight on the compatibility of medicines for a patient's unique genetic variants. Results of this project should be available to the public in late 2021.

Utilizing a Pandemic to Evaluate, Assess,

Many of us are all too familiar with the following keywords as a result of the pandemic: pivot, zooming, unprecedented times and, "you're on mute." Yes, this is just a fraction of the words trending since the entire world has borne witness to COVID-19. With no travel on the books for a year or more, the pandemic did provide our organization with additional time. The Legacy of Angels Foundation (TLOAF) utilized this valuable time to evaluate its mission and decade of work in advancing research, education, and newborn screening for two rare diseases: Krabbe disease and Cystic Fibrosis.

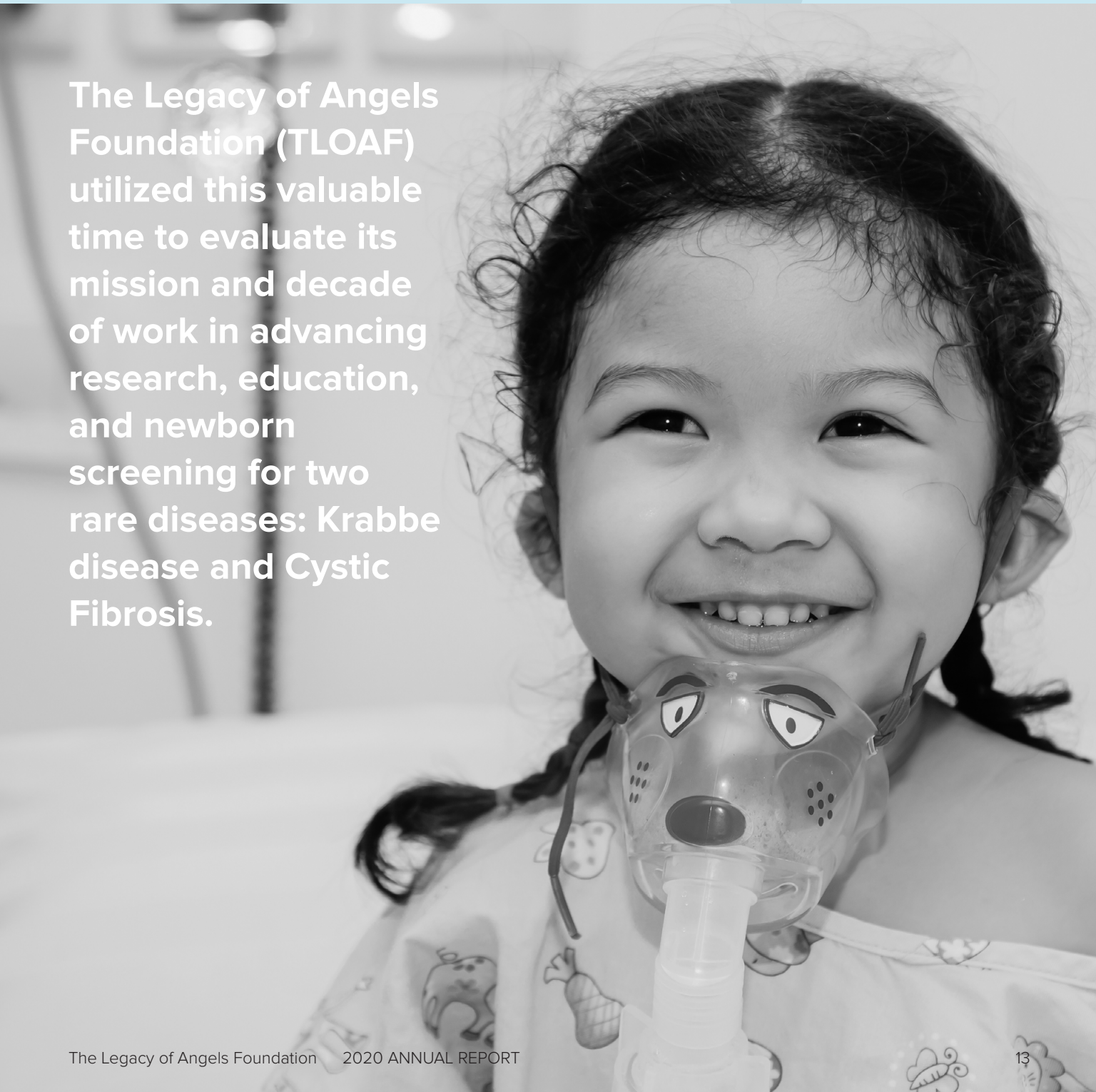
In February of 2020, TLOAF hired a coach to help evaluate, challenge, and encourage forward momentum for our organization. It's easy to hit the repeat button each year, continuing the work and efforts as any other given year, especially when you're reluctantly forced to say farewell to one of the pillars of the organization. Yes, I am talking about Sue Rosenau, Chief Operating Officer and Co-Founder of TLOAF, who lost her battle to cancer in July of 2018. Although we prefer to not experience a change of this nature anytime soon, it was apparent our organization was ready for a tune-up.

Complacency is easy and change is not. Yet, working with a non-profit coach was refreshing. It allowed our foundation to evaluate what is working and what is not, helped us gain community perspective on our accomplishments, informed us on the importance of diversifying our board, and confirmed the need for a Medical Director. You may have noticed some changes already. My title has transitioned from Director of Programs and Administration to Executive Director. Heather Techmeier's title is now Finance Director and Paul Rosenau continues to hold the President position.

As you stumble upon our social media pages or poke around our website from time-to-time, you will likely notice some significant changes over the next year with one being a complete reconstruction of our website. We're also going to do a better job of telling our story and streamlining our robust grant program. I believe the most important item you can count on from TLOAF is that we will continue to pave the way for new therapies in Krabbe disease and Cystic Fibrosis to be developed.

Stacy Pike-Langenfeld, Executive Director and author of this article

and Strategize for the Future of TLOAF



The Legacy of Angels Foundation (TLOAF) utilized this valuable time to evaluate its mission and decade of work in advancing research, education, and newborn screening for two rare diseases: Krabbe disease and Cystic Fibrosis.

2020 CALENDAR

ATTENDED CONFERENCE

World-Symposia

03/10-13/2020

This scientific meeting showcased presentations on current research in the lysosomal-disease space

SPONSORED EVENT

The Krabbe Translational Research Network Meeting

04/22-24/2020 (CANCELLED DUE TO PANDEMIC)

The KTRN meeting brings together a global network of cohorts to present and discuss recent research in biology, chemistry, physics, and related therapeutic technologies to advance the treatment of those diagnosed with Krabbe disease.

SPONSORED EDUCATION THROUGH TLOAF

Cystic Fibrosis Awareness Month

05/2020

This social-media campaign's intent was to raise awareness for Cystic Fibrosis.

SPONSORED EVENT

Paul Fernhoff Lecture Series

09/09/2020

This annual lecture celebrated Paul M. Fernhoff's life by focusing on advancements in infant and child health through early detection.

SPONSORED EDUCATION THROUGH TLOAF

Newborn Screening Awareness Month

09/2020

This social-media campaign's purpose was to raise awareness about one of the greatest public health initiatives, the newborn screening test.

SPONSORED EDUCATION THROUGH TLOAF

Leukodys-trophy Awareness Month

09/2020

This social-media campaign's objects was to raise awareness of Krabbe disease, a type of leukodystrophy.

OF EVENTS

SPONSORED EDUCATION THROUGH TLOAF

Cystic Fibrosis Awareness Month

05/2020

This social-media campaign's aim was to increase awareness of Cystic Fibrosis.

ATTENDED CONFERENCE

Hunter's Hope Family Symposium

07/21-24/2020

A family conference that works to bring individuals together impacted by a leukodystrophy. The conference focused on providing information, resources, and opportunities to network with others impacted by a leukodystrophy.

SPONSORED EVENT

Krabbe-Connect "A Million Dreams" Gala

10/10/2020

This event expanded awareness of and raised funds to #curekrabbe.

ATTENDED CONFERENCE

APHL Newborn Screening Symposium

10/10&11/11/2020

This symposium addresses state, national, and international newborn screening, genetic testing and policy issues important to public health newborn screening systems.

SPONSORED EVENT

Patient Focused Drug Development Meeting for Krabbe disease

10/29/2020

This virtual meeting with the FDA showcased the impact and burden of Krabbe disease through patient and caregivers stores.

SPONSORED EVENT

Cystic Fibrosis "Breath of Life" Gala

12/05/2020

This event worked to expand awareness and to raise funds until CF stands for Cure Found.

Co-Founders Paul and the late-Sue Rosenau

THE LEGACY OF ANGELS FOUNDATION
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