Families and Researchers Collaborate in Advancing Therapy: The Role of NTSAD, Together with Parents, in Driving Toward Treatments

Susan R. Kahn*
National Tay-Sachs & Allied Diseases Association, Boston, Massachusetts.

“IS THERE A TREATMENT?” are always the first words uttered when a parent or relative of a newly diagnosed child contacts National Tay-Sachs & Allied Diseases Association (NTSAD) upon hearing the devastating news that their loved one was diagnosed with one of the life-limiting diseases supported by NTSAD. The simple answer is always the same: “There are no treatments.” But first we try to inject hope by telling them about the ongoing research, especially in gene therapy, as it has received much NTSAD research grant support for a number of years and has produced promising results in animal models. Investigational new drug (IND)-enabling studies are in process; we remain optimistic for reaching the next major milestone and then hopefully demonstrating efficacy in affected children or adults.

EXECUTIVE SUMMARY

As much has changed and progressed in the field of gene therapy in recent years, there are many good reasons to believe that gene therapy will be an effective treatment for the diseases affecting our families. NTSAD is proud to have played a role in this progress. NTSAD made its first grant for gene therapy in 2002, the year that NTSAD initiated a formal research grant process. This article will discuss the role that NTSAD and related family foundations have played in advancing gene therapy for our diseases, with a focus on the formation of and collaboration with the Tay-Sachs Gene Therapy Consortium (“Consortium”), and their work in Tay-Sachs and Sandhoff diseases (collectively “GM2”).

An international team of scientific and clinical experts formed the Consortium in 2007 with the explicit goal of advancing early stage gene therapy research to a clinical trial. From the first discussions, NTSAD played a key role on this team. The contribution of NTSAD and partnering families has brought much to support the dedicated and persevering research team, including:

1. Bringing value through funding
   - NTSAD, together with family foundations and families, provided the initial funding to help advance the research from early stage work. It allowed the Consortium to apply for and receive essential U01 funding from the National Institutes of Health (NIH) to develop the research to the point of IND filing.
   - Subsequent grants have been made for critical research that was not covered in the NIH grant or were subsequently required for additional studies, for example natural history studies, maintenance for animal models, IND-enabling studies (toxicology, animal studies).

2. Bringing value through leveraging our network, disease knowledge, and trusted connections to patients
   - Important insights and data about how the diseases affect children and adults have been documented in natural history studies. This work was funded by NTSAD, and these connections to the families were made through NTSAD. The scientific team has also gained first-hand and personal
knowledge about these diseases by participating in NTSAD's Annual Family Conferences.

- Through NTSAD's network, the Consortium has connected to other scientists, clinicians, and biotech companies who have brought meaningful expertise and funding sources. One of these connections led to filing Orphan disease designation applications, which were subsequently approved.

It's been a long road, with progress made possible by the strength of this collaboration.

BACKGROUND

NTSAD is one of the earliest patient advocacy groups in genetic diseases. For many years, it was a broad umbrella organization, but with the advent and need for more disease-specific groups, today NTSAD focuses on funding research and supporting families affected by four diseases: forms of the gangliosidoses (Tay-Sachs, Sandhoff, and GM-1) and Canavan disease (a leukodystrophy), all of which are monogenetic neurodegenerative diseases. Today these diseases have no treatments. They are fatal in children and progressively debilitating in adults.

As a 60-year-old patient group, NTSAD has always had its families’ interests and needs at the heart of its focus. After pioneering Tay-Sachs community carrier screening in the 1970s and 1980s, NTSAD started taking a more active interest in advancing research in our diseases as the science advanced and treatments became available for some lysosomal storage diseases (LSDs). The gangliosidoses are all LSDs.

The blood–brain barrier has long been the major hurdle in the development of an effective therapy for the diseases supported by NTSAD. In 1991, the landscape of LSD treatment changed with the Food and Drug Administration approval of Ceredase, an enzyme replacement therapy for Gaucher Type I. However, it quickly became clear that this breakthrough only applied to non-neurological symptoms because the enzyme, a large molecule, could not pass the blood–brain barrier. The vast majority of LSDs have significant neurological presentation. Gene therapy offers the potential of cure because it is not constrained by the blood–brain barrier.

Development of an effective gene therapy approach to progressive neurological genetic diseases has wide-ranging implications not only for the many devastating LSDs, but also as a model for treatment for many other diseases limited by the blood–brain barrier. As I write this article today, there are a number of clinical trials for LSDs, including a number in gene therapy, for example forms of Batten, metachromatic leukodystrophy, Sanfilippo type A, and other types of mucopolysaccharidosis diseases. We celebrate all successes, with the understanding that the learning curve is cumulative across diseases.

TAY-SACHS GENE THERAPY CONSORTIUM FORMATION AND EARLY DAYS

The international team that came together and self-formed in 2007 under the Tay-Sachs Gene Therapy Consortium brought complementary knowledge making up the pieces to advance their early-stage development to a clinical trial. They brought enthusiasm for a bold 3-year plan and a sincere interest in collaboration. They advocated for a free exchange of ideas and efficient optimization of vectors and delivery strategies conducive to the rapid development of the most effective gene therapy approach to treat Tay-Sachs and Sandhoff diseases.

The members of this team, with their institutions and expertise noted in parentheses, are Miguel Sena-Esteves, PhD (Massachusetts General Hospital, then UMass Medical School; vectors), Doug Martin, PhD (Auburn University; animal models), Professor Tim Cox and Begoña Cachón-González, PhD (Cambridge University, United Kingdom; early mouse studies), Tom Seyfried, PhD (Boston College; biochemistry assays), and Florian Eichler, MD (Massachusetts General Hospital; pediatric neurologist). Later, Ed Kolodny, MD (New York University; neurologist) joined the group. He discovered the Jacob sheep model of Tay-Sachs disease, which is complementary to the Sandhoff feline model discovered at Auburn.

The participants in the Consortium agreed that initial funds would be raised through the joint efforts of NTSAD, interested individuals, and other sources (grant money if applicable). They drafted a Memo of Understanding stating that “involvement of NTSAD is considered to be an essential component of this effort to disseminate project results to the patient community and coordinate the distribution of funds raised for this project.”

RESULTS AND PROGRESS

Each of the Consortium members wrote a grant proposal as part of a unified budget and plan, which was submitted to NTSAD. Following scientific reviews, collectively the Consortium members were awarded approximately $600,000 in grant funding from NTSAD in 2007 for their research projects. This investment paid off, as the NIH awarded the
Consortium a $3.5 million, 4-year U01 grant award in August 2009.

The animal studies produced the hoped-for impressive results in extending the life of affected GM2 cats, with an inability to distinguish unaffected from treated cats in videos. Even though this grant didn’t specifically fund GM1 research, this work proceeded in parallel with GM1 cats, and the results were similar. The results were so strong that the Consortium investigators met with NTSAD and the Funders in May 2012 to see if the work could be accelerated so that a clinical trial could be started in September 2012, rather than September 2013. In order to speed up the start of human trials, toxicity studies would need to be undertaken, along with additional animal studies and vector manufacturing not covered by the NIH grant. By this point in time, while not scientists, the family members were quite knowledgeable about gene therapy and what was needed to get to clinical trial. They understood the challenges and were driven to push this work forward as fast as possible so that children could be helped as soon as possible. NTSAD and its family foundation affiliates soon pledged $900,000 of the $1.2 million in additional funding that was needed.

Subsequently, there was a huge setback in early 2013 when toxicity was found in late-stage animal safety studies. Later, it was understood to be caused by the overexpression of enzyme in the neurons that then triggered cell death. It took several years to generate and identify new vectors that could meet the safety and efficacy requirements. Once more, NTSAD and the family foundations took the big step to commit to funding this unexpected but necessary research. At each step, NTSAD conducted scientific reviews of the grant proposals to ensure that sound grant decisions were being made. As of 2015, a new vector was identified and IND-enabling studies were outlined. These studies are ongoing and have been partially funded by NTSAD and other Funders.

THE FUNDERS AND THE ROLE OF FOUNDATION FINANCIAL SUPPORT

While thousands of donors and family members have raised the funds for this research, the majority of the nearly $3 million in non-NIH funding has come through family foundations focused on playing a leading role in advancing research. These family foundations include two long-time NTSAD-affiliate foundations started by families in honor and memory of their children who passed away from Tay-Sachs: the Cameron & Hayden Lord Foundation and the Mathew Forbes Romer Foundation. In addition, the Cure Tay-Sachs Foundation, which was founded by a dad whose daughter was affected by Juvenile Tay-Sachs disease, has been a fundraising force for research. NTSAD’s New York Area chapter is the one non-family group that also played a significant role in funding. Sophia Pesotchinsky, whose daughter is affected with Late Onset Tay-Sachs, has been working with NTSAD and the Consortium for >10 years to identify promising research and to play a role in advancing and funding it. For example, through her connections Sophia was instrumental in identifying a vector manufacturing source. The Consortium refers to this group of foundations and parents as “the Funders.”

Clearly, the money that NTSAD and the Funders brought to the Consortium was a catalyst for advancing the gene therapy. Since 2007, NTSAD has awarded grants totaling $1.9 million to the Consortium investigators, which is >50% of NTSAD’s total research grants made since the advent of our research grant program in 2002. This is a significant commitment from NTSAD, as the total annual budget is about $1 million, with family services and education aspects of its mission to support as well. To fund additional (non-Consortium) research, NTSAD has an annual request for proposal process, which we stayed committed to during this time, even while often prioritizing the Consortium, because GM2 gene therapy has been the closest to clinical trial of any other research. We decided to fund only Consortium grants instead of an open request for proposals (RFP) just once, as we have taken the long view in our approach to funding research. We thought that if we closed our RFP process to other scientists for >1 year, we would lose connection with our scientific network and lose opportunities to invest in other promising research. We decided that we needed to diversify our risk as well as pay attention to our other diseases. At various times, however, the challenge of prioritizing research funding opportunities created tension with some of the Funders who felt that we should be dedicated only to gene therapy and the Consortium.

IT’S NOT JUST ABOUT THE MONEY

NTSAD and its family foundations have added other meaningful value to the work of the Consortium, some of which are listed below.

NTSAD enlisted Inspire, a pro bono consulting arm of a local life-science consulting firm, to develop a partnering and funding strategy in 2012,
just before we anticipated the initiation of a clinical trial. Fast forward a few years, and after the Consortium started the IND-enabling studies, NTSAD re-engaged Inspire to update their 2012 study and learn more about possible strategies to get gene therapy to patients, whether through company formation, strategic partnering, or other avenues. This work would have cost any other client tens of thousands of dollars. While NTSAD was Inspire’s client, the goal was to add value to the institutions who employ the expert investigators and who hold the intellectual property.

As a 60-year-old organization, NTSAD has a strong brand in the patient community plus a broad network encompassing government, advocacy organizations, biotech/pharma, scientists, and clinicians. Between this network and my network developed through my past career in diagnostics and biotech, we have introduced the investigators to a number of companies and investors. While no business deals have yet been signed as a result of these networking introductions, it has been valuable to establish relationships and explore various types of collaborations.

Through NTSAD’s network, we were fortunate enough to identify a pro bono resource at the Keck Graduate Institute, who, with the supervision of an experienced regulatory professional, worked with the Consortium investigators to submit Orphan disease designation applications for Tay-Sachs and Sandhoff disease. At the time, it was very unusual to have a patient group such as NTSAD sponsor the designation at the time of our application. Subsequently, both Orphan designations were approved in the United States.

NTSAD enabled access to families and other important players in the network, primarily through the Annual Family Conference that gave an opportunity for everyone (scientists, clinicians, families, Funders) to gather in person for updates, planning, brainstorming, and building relationships. (Note: our language uses the words “families,” children, or adults rather than referring to patients.)

NTSAD updated its research strategy several years ago to include clinical trial readiness, which means investing in biomarker research, newborn screening (NBS), natural history studies, and animal models. One ongoing NTSAD grant is funding a pilot assay for Tay-Sachs NBS. NBS will be essential for diagnosing children earlier, so that treatments can be more effective.

NTSAD funded both retrospective and prospective GM2 natural history studies that are relevant for defining the clinical trial outcome measures. In addition to providing grant funds, NTSAD was the liaison for the retrospective study between families and the investigators. Kim Kubilus, NTSAD’s Family Services Director at the time, was part of the team that designed the patient questionnaire. She also played a key role in communicating with the families about the survey to encourage them to fill it out, and then she held the numerical key which matched patients and surveys because of the need to keep the responses anonymous.

CHALLENGES

All the clichés come to life when telling the story of NTSAD and the Consortium, for example “The road is long,” “It takes a village.” Collaboration and patience are key. However, parents who have dying children and adults with progressively debilitating diseases are passionate about speed not patience. Any diversion from the planned timeline or technical setback is taken hard by families. That makes it difficult for these extremely dedicated and bright scientists. Many of the challenges revolve around high hopes and expectations versus the challenge of developing treatments with evolving technologies.

With no treatments for these fatal diseases (in children), the families, their friends, and their network pay extremely close attention to what’s happening in Research. The NTSAD Annual Family Conference provides opportunities for the families to learn about the gene therapy program directly from the scientists. In meeting the families and the affected children and adults, the scientists are naturally drawn in emotionally to this drive for a treatment. The close relationships that develop between scientists and the families are positive but have some risks. The emotion motivates and sustains them, but then it is difficult to manage when the timeline slips because of various technical challenges or when the question is raised about who will be in a clinical trial or when the clinical trial will start.

The Consortium investigators now acknowledge, having learned much since embarking on this path in 2007, that 3 years was too ambitious when they set their original goals. That’s understandable to many, but it’s been difficult for the families to ride the many waves of good news and not-so-good news, especially when the initial animal studies were so promising. It is an ongoing challenge to sustain hope, enthusiasm, and support from the patient community when there are technical setbacks. I think that among all the people involved, we have managed to sustain interest, although
while the families were once driven mostly by emotion, there are more questions now and a natural and rational interest in investigating other therapeutic approaches.

The investigators are the experts. However, as the research has progressed, new areas of needed expertise have emerged, such as toxicology, manufacturing, regulatory, to mention just a few. In 2013, NTSAD established a Corporate Advisory Council (CAC), made up of biotech executives experienced in bringing rare disease drugs to patients. One of the roles of the CAC is to advise NTSAD about some of their research projects around issues such as feasibility for clinical development, possible regulatory challenges, biomarker strategies, and so on. Therefore, on behalf of NTSAD, the CAC has taken an interest in the Consortium and has met with some of the investigators to understand and to offer advice as they get involved in the regulatory process and get closer to market. While instructive, it has been a challenge to connect NTSAD’s corporate advisors with the academic investigators who have lived and breathed this research for many years. Ultimately, each will learn from the other; it just takes time.

At the inception of the Consortium, the investigators’ and NTSAD’s interests were aligned 100%.

It was clear that our funding support was needed to advance the program in order to go after the NIH funding necessary to then move toward an IND filing. Our interests are still aligned; we’re aiming to reach a treatment for our families. Yet, there are more points of divergence at this stage, and NTSAD’s role has changed vis-à-vis the Consortium. For example, what is the patient group’s role in exploring next steps and possible strategies in getting this research to patients? Who is involved in decision making? Who is in control? So many aspects of the relationship that were straightforward in the early days are not as clear now.

Everyone involved has worked hard to communicate and have a positive working relationship. There has been much to celebrate in our collaboration, and disappointments as well, but we are sticking together in partnership and hope.

ACKNOWLEDGMENTS

I want to thank all the investigators, family members, family foundations, and countless others who are part of this story. Hopefully, very soon, we will be looking back and reviewing it from the perspective of having successfully treated affected individuals.

REFERENCES

