

TAY-SACHS GENE THERAPY CONSORTIUM

*A 3-year roadmap to a gene therapy clinical trial for
Tay-Sachs Disease*

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Summary

Tay-Sachs Disease (TSD) is an inherited neurological disease that severely affects the nervous system, and causes premature death. Children with the most common and severe form of Tay-Sachs Disease develop normally for the first months of life, but slowly deteriorate until death, usually by age 5. Juvenile and Late Onset forms are also devastating conditions. Although TSD was first described in the 1880's, this disease remains untreated. In recent years, outstanding therapeutic results have been achieved in mouse models of TSD using state-of-the-art gene therapy systems known as adeno-associated viral (AAV) vectors. Translation of these findings from mice to humans is a significant challenge that requires a considerable amount of research.

The Tay-Sachs Gene Therapy (TSGT) Consortium is an international collaborative group of scientists committed to translating current results from animal experiments into a human clinical trial within the next 3 years. The TSGT Consortium consists of physicians and scientists experienced in gene therapy and basic disease research, from four institutions: Auburn University, Boston College, Cambridge University (U.K.), and the Massachusetts General Hospital/Harvard University.

To accomplish the stated goal, a 2-year research plan has been developed and is currently under way. These 2 years will be used to prepare a natural history of Tay-Sachs and Sandhoff diseases which will inform the clinical trial design, and to optimize and test in large animals the AAV-based gene therapeutic approaches already shown to work exceptionally well in mice. Significant progress is already being made in all aspects of the tasks proposed for Year 1. The TSGT research goals are:

- 1) Prepare a standardized disease severity scale to determine the likelihood of benefit for each individual patient based upon disease stage.
- 2) Optimize critical components of AAV vector, such as vector serotype
- 3) Identify the optimal method of AAV vector delivery, such as injection into the cerebrospinal fluid or directly into the brain (both commonly employed procedures in current medical practice)
- 4) Evaluate the therapeutic efficacy of optimized vectors and delivery methods using mouse and cat models
- 5) Evaluate potential adverse responses to treatment, such as inflammation or tumors induced by the treatment

A number of tasks will be conducted during Year 3 in preparation for the clinical study: manufacturing clinical-grade vectors, performing necessary toxicity studies, and preparing/submitting applications to obtain permission for human clinical trials from American and European regulatory agencies. Physicians experienced with human clinical trial preparation and implementation will be involved in every step of the process to ensure the integrity of clinical trials.

The TSGT Consortium is closely associated with supporters and parents of TSD patients, as well as with the National Tay-Sachs and Allied Diseases Association, Inc (NTSAD). This group of committed individuals has aligned with the Consortium to raise the necessary funds for this ambitious task (~\$500,000 for Project Year 1 alone). Therefore, the TSGT Consortium is confident that each necessary component is in place to reach its goal of initiating human clinical trials for TSD within 3 years. Already the Consortium has been awarded a \$50,000 grant from NTSAD, and government grants will be sought for manufacturing, toxicity studies and the clinical program.

Development of a successful gene therapy treatment for Tay-Sachs will teach us how to safely deliver therapeutic proteins (treatment) to the whole brain – a technology that could be utilized to treat many neurological diseases that remain untreatable at present. It is estimated that in the US alone there are 44 million people affected by a neurological disease. **Therefore the impact of the TSGT Consortium project is likely to go well beyond Tay-Sachs Disease.**

A. Background

Tay-Sachs and Sandhoff diseases are closely related neurodegenerative diseases characterized by enzyme deficiencies and subsequent accumulation of GM2-ganglioside in the brain. These rare genetic diseases, also known as GM2-gangliosidosis (GM2), are parsed into three categories depending on the age of onset: Infantile, juvenile and late onset. The infantile form is the most common. Babies affected by Classic Infantile GM2 develop normally for the first 3-6 months of life. At this time development slows and then begins to regress. By age two, affected children suffer from frequent seizures, swallowing difficulties, respiratory infections, and loss of all motor control. Death typically occurs before the fifth birthday. Late Onset GM2 is the 2nd most common form, but because early symptoms are common to other diseases, affected adults often are misdiagnosed for 10+ years. Symptoms typically include speech difficulties, muscle weakness, tremor and ataxia. Manic-depressive or psychotic episodes are present in about 30% of affected persons. The majority of Late Onset patients are wheelchair-bound by age 30-40. The juvenile forms vary greatly in severity from case to case, but all juvenile forms of GM2 are fatal.

Tay-Sachs disease is caused by inherited mutations in a single gene (*HEXA*) resulting in production of beta-hexosaminidase enzyme with reduced or absent activity (depending on the mutation). This enzyme performs a single task in the recycling of cellular materials that takes place in lysosomes. These cellular recycling centers contain a large number of enzymes that participate in the 'disassembly' process. Deficiency in any one of these enzymes leads to a build up (storage) of specific materials in lysosomes causing one of 40 separate disorders and syndromes, collectively known as lysosomal storage diseases (LSDs). As a group, LSDs are the most common type of childhood genetic disorders, with an estimated combined frequency of 1 in 7700 live births [1], and thus represent a significant worldwide health problem.

It is estimated that 60% of all LSD cases present some degree of neurological involvement (neuronopathic). Currently there is no treatment for this large subgroup of LSDs. Presently, gene therapy is the best option to devise highly effective treatments for these and other devastating neurological diseases. Neurological diseases are a major worldwide health problem. As an example, a recent study of only 10 common neurological conditions (including Alzheimer's and Parkinson's Disease, stroke and epilepsy) concluded that >44 million Americans suffered from these disorders in 2005 [2]. Gene transfer technology has evolved quite dramatically in the last 5-10 years with development of safe and highly efficient vectors for delivery of therapeutic genes to the brain. Adeno-associated virus (AAV) vectors have emerged as the safest and most effective vectors for this application [3, 4].

Research in Tay-Sachs disease has been pioneering in many ways. Tay-Sachs disease was among the first diseases for which metabolic alterations were shown to be caused by an enzymatic defect [6]. A reliable biochemical diagnosis was established soon after, and Tay-Sachs disease became the first disease for which carrier screening and prenatal diagnosis were widely used in populations at risk. This created the need for genetic counseling, which has become an integral part of modern genetic medicine. Once again research in Tay-Sachs disease has the opportunity to perform a pivotal role in the evolution of genetic medicine with the development of an effective gene therapy treatment for this disease. **We anticipate that, as before, an approach first developed for Tay-Sachs disease (therapeutic this time) will be rapidly deployed in other LSDs, and numerous other neurodegenerative diseases.**

A1. Present Therapeutic Approaches

Generally, clinical symptoms of a lysosomal storage disease do not occur unless genetic mutations lead to a >90% reduction in the activity of the affected enzyme. Thus, a surprisingly low "critical threshold" of activity is needed to prevent/ reverse storage in patients. Even a small increase in patients' enzyme levels can dramatically enhance the length/ quality of their lives [7]. Lysosomal enzymes released by normal cells have been shown to be taken up and correctly targeted to the lysosomes of diseased cells, leading to correction of lysosomal storage [8, 9]. **This cross correction mechanism is the basis for ERT and gene therapy strategies for treatment of LSDs.** Enzyme replacement therapy is the most common and effective form of treatment for non-neuronopathic Gaucher Disease [15] and is now available, or is in different stages of clinical development, for a number of non-neuronopathic LSDs. Enzyme replacement therapy (ERT) consisting of regular intravenous infusion of active lysosomal enzymes is reasonably effective in treating LSDs without neurological involvement (non-neuronopathic) but ineffective in treating the neurological component of LSDs

due to the blood brain barrier. Moreover ERT is prohibitively expensive with costs ranging from \$175,000-\$1,500,000/year/patient. Therefore there is a pressing need for development of efficient and cost effective treatments for LSDs with neurological features.

Other therapies, such as bone marrow transplantation and umbilical cord transplantation rarely provide a reversal of clinical disease and have a high rate of complications. Embryonic stem cells are likely to be years away from any clinical applicability.

A.2 Gene Therapy

In general terms, the goal of gene therapy is to introduce genes into diseased cells to correct defects caused by genetic mutations, or kill tumor cells. LSDs are particularly suitable for gene therapy since they are caused by single gene defects. Moreover lysosomal enzymes are secreted from genetically modified cells, and taken up by enzyme-deficient cells where they correct lysosomal storage. Viral vector-mediated gene delivery to the brain holds great potential for the treatment of neuronopathic LSDs since the genetic modification of relatively small numbers of cells has proven to be sufficient to deliver corrective levels of enzyme to large regions of the brain in animal models of LSDs [4].

The track record of gene therapy has been disappointing given the high expectations generated by the rapid developments and sensational experimental results in its beginning more than 20 years ago. Most gene therapy clinical trials performed to date have failed. Due to the development of safer and more efficient vector systems for gene delivery, better understanding of delivery techniques and immune responses, gene therapy is entering a new chapter with several clinical trials showing positive results for treatment of genetic diseases, cancer, and neurodegenerative diseases.

A2.1 Adeno-associated virus (AAV) vectors have become the vectors of choice for gene delivery to the brain because of their exceptional efficiency in transducing neurons where they promote long-term expression of therapeutic genes with no apparent toxicity, and limited inflammation at the site of injection [3]. Direct infusion of AAV vectors into the brain parenchyma has shown remarkable efficiency in achieving complete correction of lysosomal storage throughout the brain in a large number of animal models of LSDs [4], including GM2 gangliosidosis [5]. Also delivery of AAV vectors into the cerebrospinal fluid (CSF) via the lateral ventricles [18] or intrathecally [19] appears to be a viable alternative to direct injection of AAV vectors into the brain. High-level expression of lysosomal enzymes in the CSF has a significant therapeutic effect [18, 19].

AAV vectors are being, or have been used in human clinical trials to treat at least 12 distinct diseases [20], with 38 approved trials to date (Genetic Modification Clinical Research Information System - <http://www.gemcris.od.nih.gov/>). Recently published results from an AAV-based gene therapy clinical trial for Parkinson's disease offer the first glimmer of hope for an effective treatment for this disease affecting millions of patients worldwide [25]. Current gene therapy vectors are safer and more effective than ever before due to an enormous amount of research and development that has taken place over the past decade. Data recently published attests to their safety in the human brain [24, 25].

B. Tay-Sachs Gene Therapy Consortium

B.1 Purpose. The Tay-Sachs Gene Therapy (TSGT) Consortium was formed with the goal of initiating a state of the art clinical trial for Tay-Sachs disease (and possibly Sandhoff disease) in the next 3 years. The TSGT consortium is composed of scientists from four (4) institutions (Auburn University, Boston College, Cambridge University-UK, and Massachusetts General Hospital/Harvard Medical School) that have been working on experimental gene therapy approaches to treat LSDs. In the last 3-5 years, laboratories in the TSGT Consortium, and others, have obtained exceptional therapeutic results with AAV vectors in mouse, cat, and dog models of different neuronopathic LSDs [4], including GM2-gangliosidosis [5] (Laboratory of Dr. Timothy M. Cox, Consortium member). The TSGT consortium is organized to foster 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 go into the clinical trial.

B.2 TSGT Consortium members. The members of this Consortium share the same common goal of performing a clinical gene therapy trial for Tay-Sachs in a short time frame (3 years). To accomplish this ambitious goal they will pool their resources and extensive experience in experimental gene therapy to devise the most effective AAV-based gene therapy approach to treat Tay-Sachs disease and bring it into simultaneous clinical trials in the US and UK. The Consortium is closely associated with parents/supporters

and the National Tay-Sachs and Allied Disease Association, Inc (NTSAD). Members of the TSGT Consortium are (NIH format *curriculum vitae* in will be provided upon request):

- . **Henry J. Baker**, DVM, is a Professor of Pathobiology at the Auburn University College of Veterinary Medicine and the Scott-Ritchey Research Center. Dr. Baker discovered and has maintained the feline models of gangliosidosis for 35 years. He has studied numerous therapeutic options for these diseases, including ERT, stem cell transplantation and gene therapy. He has published approximately 100 peer-reviewed articles on molecular characterization and therapy of a variety of animal disease models.
- . **Begona Cachon-Gonzalez**, PhD, is senior research associate in the Department of Medicine, Cambridge University, UK. After biologically training at the University of León, Spain, Dr. M. Begoña Cachón-González was awarded a PhD in Molecular Genetics at the Galton Laboratory, University College London. She mapped and characterised the hairless gene while working at NIMR, Mill Hill London. For the last ten years, while at Cambridge University Department of Medicine as a Senior Research Associate, her scientific research has concentrated on the treatment of inborn errors of metabolism where she has pioneered the successful treatment of experimental Tay-Sachs and Related Disorders. Her outstanding therapeutic results with AAV gene therapy appear in a recent issue of Proceedings of the National Academy of Sciences, USA (July 5, 2006).
- . **Nancy R. Cox**, MS, DVM, PhD, is an Associate Professor of Pathobiology at the Auburn University College of Veterinary Medicine and Interim Director of the Scott-Ritchey Research Center. Dr. Cox is a neuropathologist with 25 years experience evaluating disease progression in the feline gangliosidosis models. In conjunction with Dr. Baker, she performs intracranial injection of AAV vectors for the current project. She also directs the Necropsy and Histopathology laboratories of the Scott-Ritchey Research Center.
- . **Timothy M. Cox**, MD, is Full Professor of Medicine at the University of Cambridge, England, where he is head of department and director of the MB/PhD programme. He trained in cell biology and pathology is a practising internist and Metabolic Physician with a particular interest in the biochemical genetics of nutritional diseases – identifying mutant aldolase B in hereditary fructose intolerance and contributing to the mapping of juvenile hemochromatosis. Latterly he has investigated the genetics, pathogenesis and treatment of lysosomal disorders and initiated clinical development of the first licensed substrate-reducing agent for glycosphingolipid disorders as well as a novel biomarker for Gaucher disease - now in widespread use. He established the first government-funded National specialist center for the treatment of Lysosomal disorders in the UK at Cambridge University NHS Foundation Hospital Trust at Addenbrooke's hospital, which will serve as the focus for the proposed gene therapy programme for neurodegenerative lysosomal diseases.
- . **Florian S. Eichler**, MD, is a child neurologist in the Department of Neurology at the Massachusetts General Hospital, and an Assistant Professor in Neurology at Harvard Medical School. He is also Director of the leukodystrophy clinic at the Massachusetts General Hospital where he sees patients with a variety of white matter disorders. His clinical focus has been on diagnosis and identification of potential treatments for patients with leukodystrophies. His research focus is on the genetics of peroxisomal disorders, lipid metabolism, and spatial aspects of nuclear magnetic resonance spectroscopy.
- . **Douglas R. Martin**, PhD, is an Assistant Research Professor at the Auburn University College of Veterinary Medicine and the Scott-Ritchey Research Center. Dr. Martin's doctoral dissertation, entitled *Gene Therapy of the Gangliosidoses*, was completed in 1999 and focused on retroviral gene therapy for the gangliosidoses. Dr. Martin has 15 years' experience with the feline gangliosidosis models and will be primarily responsible for coordination, implementation and analysis of experiments in the current proposal.
- . **Miguel Sena-Esteves**, PhD, is an Assistant Professor in Neurology in the Departments of Neurology and Neuroscience at the Massachusetts General Hospital and Harvard Medical School, respectively. He is an expert in vector design, and vector-mediated gene delivery to the brain. His research focuses on developing gene therapeutic interventions for lysosomal storage diseases using G_{M1}-gangliosidosis as a model disease, brain tumors, and other neurodegenerative diseases.

. **Thomas N. Seyfried**, PhD, is a Full Professor of Biology in the Biology Department at Boston College. His laboratory has worked on glycosphingolipids and lipid diseases for more than 30 years. His objective over the last 10 years has been to develop an effective life long therapy for ganglioside storage diseases.

B.3 Gene Therapy for Tay-Sachs Disease – Projects and Progress

The TSGT Consortium has been established, and it is now a working group with progress being made in all 5 projects:

Project 1 - The Natural History of Tay-Sachs Disease

Investigator: Florian S. Eichler, M.D. (*Massachusetts General Hospital / Harvard Medical School*)

Dr. Florian Eichler ([Project 1](#)) in collaboration with the National Tay-Sachs and Allied Diseases Association (NTSAD) has identified contact information of 214 patients with Tay Sachs disease and 27 patients with Sandhoff disease. Surveys for families of patients are currently being prepared and will help define the clinical progression and optimal timing of intervention. Dr. Cynthia Tiffit, a geneticist at Children's National, Washington, and Dr. Kendra Bjoraker, a neuropsychologist at the University of Minnesota, are providing their expertise in the design and assessment of the surveys. The group has decided on separate surveys of the various clinical phenotypes (infantile, juvenile, adult) and is actively discussing validation instruments

Project 2 - AAV-mediated Gene Therapy for Tay-Sachs Disease: Vector Selection for Pre-clinical Development

Investigator: *Miguel Sena-Esteves (Massachusetts General Hospital / Harvard Medical School)*

Dr. Sena-Esteves' laboratory investigates vector design and different approaches to achieve global distribution of lysosomal enzymes in the adult brain. His laboratory has produced optimized versions of the human hexosaminidase α - and β -subunit genes with the intent of increasing their efficiency of expression. These optimized genes are being compared to their natural counterparts for efficiency of expression. They are working with Drs. Martin and Cachon-Gonzalez in testing different types of AAV virions (particles) for their efficiency of gene delivery to the brain in mice and cats. This joint effort between 3 labs will identify the AAV type that will be used in cat studies and in the clinical trial. Recently this laboratory has obtained exceptional results on lysosomal enzyme distribution in the brain after infusion of AAV vectors into the cerebral lateral ventricles of adult mice. This gene delivery approach resulted in exceptionally high levels of a lysosomal enzyme throughout the brain.

Project 3 - Pre-Clinical/Clinical Research Program: Tay-Sachs and Related Diseases

Investigators: *Timothy M. Cox / M. Begoña Cachon-Gonzalez (Cambridge University, UK)*

Drs. T. Cox and M.B. Cachon-Gonzalez ([Project 3](#)) have shown that AAV vectors injected directly into the brain of adult GM2 mice have a remarkable therapeutic effect [5]. Hexosaminidase activity was restored to levels up to 15 times normal throughout the entire brain. Moreover AAV treatment increased their lifespan from 121 days to 323 days, with 3 of 7 animals living >425 days (3-times the life span of untreated mice). The videos of AAV-treated and untreated GM2 mice illustrate the therapeutic potential of this approach. These videos can be found in the included CD or on the website of the National Tay-Sachs and Allied Diseases Association, Inc. (www.ntsad.org).

Project 4 - Pre-Clinical Studies of AAV Gene Therapy in Feline GM2 Gangliosidosis

Investigators: *Douglas R. Martin / Henry J. Baker / Nancy R. Cox (Auburn University)*

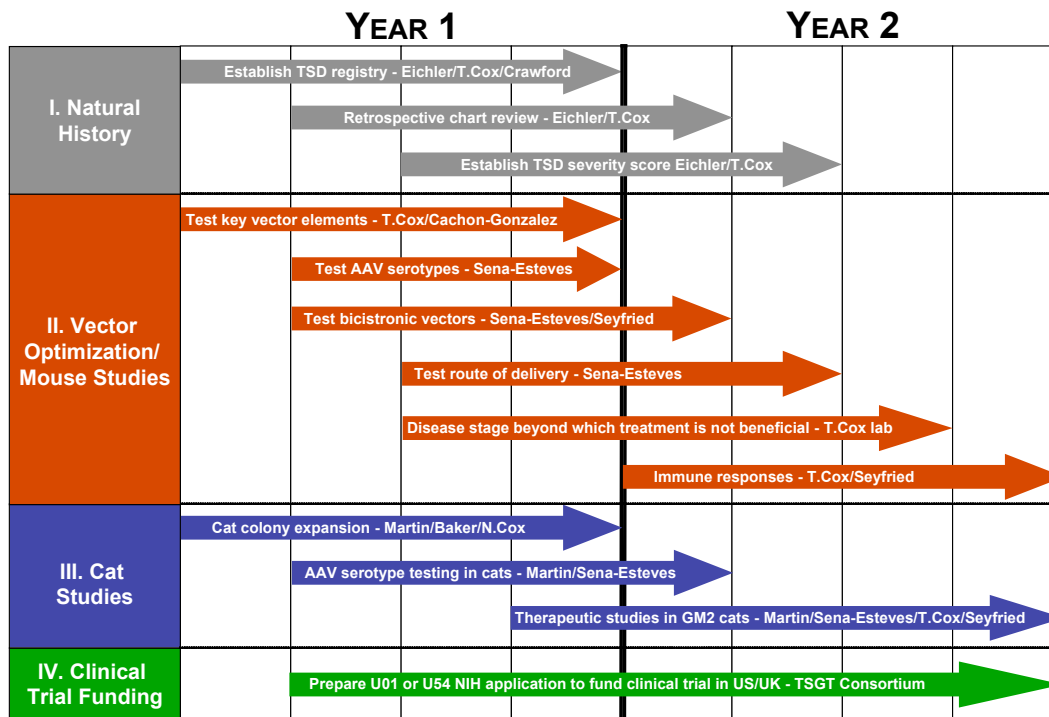
Dr. Martin has injected AAV vectors (same used to treat GM2 mice) into the brain of 6 week-old GM2 cats ([Project 4](#)), and shown that hexosaminidase activity was restored throughout the injected hemisphere to levels up to 175% of normal, and G_{M2}-ganglioside storage was reduced at the injection site. The GM2 feline model was co-discovered by consortium member Dr. Henry Baker in 1977 [28]. Affected cats display clinical and histopathological features typical of human GM2 gangliosidosis, with a slight head and body tremor beginning at 11 ± 1 weeks that progresses to inability to walk, use the litter box or eat without assistance from care givers by 21 ± 2 weeks of age. Stereotypical disease progression provides an excellent opportunity to evaluate therapeutic benefit in treated animals. Membranous cytoplasmic bodies, meganeurites and ectopic neurites are histopathological features common to both human and feline GM2 [29].

Project 5 - Neurochemical and Immunological Evaluation of AAV Gene Therapy Strategies

Investigator: *Thomas N. Seyfried (Boston College)*

Dr. Seyfried's laboratory (Project 5) has analyzed the ganglioside profile in GM2 brains of mice, cats and humans. These studies have shown that, as models of human ganglioside disassembly, mice and cats provide a continuum of similarity to humans, with cats closer in similarity to humans than are mice. Dr. Seyfried's recent studies further confirm the utility of the cat model in therapeutic studies of GM2 gangliosidoses.

B.4 Timeline of Experiments



B.5 Project Milestones/Goals

Year 1

- 1) Prepare clinical history for Tay-Sachs disease (and possibly Sandhoff disease) - develop clinical scoring scale/s
- 2) Optimization of AAV vector design and efficacy testing in GM2 mice
 - 2.1 Identify the AAV serotype most likely to work in the human brain for intraparenchymal and CSF delivery
 - 2.2 Compare the therapeutic efficacy of intraparenchymal vs CSF delivery of AAV vectors in mice
 - 2.3 Characterize the immune-response to AAV vector, and vector encoded genes
- 3) Expand GM2 cat colony
- 4) Initiate communications with FDA
- 5) Initiate communication with NIH/NINDS

Year 2

- 1) Compare the therapeutic efficiency of intraparenchymal vs CSF delivery of AAV vectors in cats
- 2) Evaluate the therapeutic efficacy of AAV vector injection before and after onset of symptoms in GM2 cats
- 3) Evaluate immune response to AAV vector and human hexosaminidase α - and β -subunits in cats
- 4) Provided that results are positive the following steps towards the clinical trial will be initiated in year 2:
 - 4.1 Evaluate different manufacturing facilities/options
 - 4.2 Conduct pre-IND meeting with FDA
 - 4.3 Prepare toxicity protocol required by FDA and European authorities
 - 4.4 Organize clinical study committee and develop clinical protocol

4.5 Initiate preparation of IND

Year 3

- 1) GMP-grade vector production
- 2) Acute toxicity studies required by FDA and European authorities
- 3) Prepare and send NIH/OBA submission for RAC review
- 4) IND submission to FDA
- 5) IRB submission in participating hospitals
- 6) Preparation of all aspects of human studies

B.6 Risk

AAV vectors have been used in 38 human clinical trials in the US (Source: Genetic Modification Clinical Research Information System, version 4.0 - <http://www.gemcris.od.nih.gov/>), and there have been no reports of serious adverse events [20]. Direct injection of AAV2 vectors into the human brain appears to be well tolerated and no significant adverse events have been reported [24, 25]. The TSGT Consortium brings together clinicians and scientists with exceptional combined experience in GM2-gangliosidosis at the clinical level and experimental gene therapy for lysosomal storage diseases. Although risk can never be eliminated from experimental treatments, we are confident that our studies in GM2 animals will provide ample information on safety, efficacy, and immunology to guide our design of a safe and effective clinical trial for Tay-Sachs disease (and possibly Sandhoff disease) within 3 years. Consultants to assist the Consortium in the preparation of clinical protocol and IND application for submission to RAC, FDA, and institutional IRBs have been identified and will be brought into the group as needed.

B.7 Fundraising

Two sub-project proposals (Martin, and Sena-Esteves) have been peer-reviewed and partially funded by the National Tay-Sachs and Allied Diseases Association Inc (NTSAD) research initiative (\$50,000). Additional \$450,000 will be needed for the year 1 to conduct research and meet project goals. It is expected that activities in year 2 will require \$300,000-\$400,000. Ninety percent of the money raised will be used for research activities, and 10% will be used to cover overhead costs in each institution involved in this project. The TSGT consortium will seek federal support for GMP-grade AAV vector preparation, conducting vector toxicity studies, and clinical trial in the US and UK.

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