Funding Priorities in the Era of Enzyme Replacement Therapy: A Proposal for Grand Challenge Grants by the National MPS Society

October 14, 2011 (final 12/20/2011)

Future Directions Committee (in alphabetical order): Patricia Dickson, N. Matthew Ellinwood, Mark Haskins, Katherine Ponder, Mark Sands, Calogera Simonaro, Steven Walkley, Barbara Wedehase and Klane White

Since its inception in 1974, the National MPS Society has been extremely successful in achieving its mission for many of its members. In the beginning, there were few scientists researching MPS and related diseases, there was no corporate interest, and there were no effective therapies. Now, therapies are approved and available in the U.S. for MPS I, II, and VI, and clinical trials are ongoing for MPS IIIA and IVA. There are in addition experimental approaches that are being investigated, which may hold promise for other diseases. However, as more and more therapies reach clinical trials and come onto the market, the urgency to support MPS-related research becomes less evident. Also, as the NIH budget is unlikely to grow to match the increasing expense of performing research, rare diseases are more likely to face decreasing Federal funding. The risk is that, without a clear plan for the future, the National MPS Society may lose relevance, and fail to draw financial support and scientific interest, and not be able to promote and fund promising projects by young investigators to provide preliminary data important for NIH funding.With a careful strategy, this can be avoided. An example is the Cystinosis Research Network, which suffered from its own success when cysteamine therapy was developed. In 2007, though, they ran an awareness campaign, partnered with nephrology societies, and were able to continue to offer generous grant support[1].

[1] See http://cystinosis.org/uploads/file/docs/07annual.pdf.

The Cystinosis Research Network represents one disease, while the National MPS Society represents many. One challenge that the National MPS Society faces is to ensure that its funding priorities benefit its diverse membership. The Society has tried with little success to persuade families to support general rather than disease-specific funding priorities. The Society's current funding mission includes the statement that although it is tempting to direct the proceeds from an individual fund raiser towards the specific disease affecting the member's family, this is not necessarily the most efficient means of advancing science[2]. In addition, given the similarities among these diseases, there is a good chance that a new technology or a discovery in one disease will be applicable to other disorders. Directing a significant portion of the research funds to disease-specific projects reduces the amount of money available for more generalized and possibly innovative projects. In addition, it limits the ability of the Scientific Advisory Board to reward promising new ideas or investigators. As our knowledge of biological mechanisms increases exponentially, it becomes even more important to make resources available for new approaches and technologies regardless of the source.

However, the reality is that many families donating to the National MPS Society do so because they have a family member or are themselves affected by an MPS or related disease. A worrisome trend is the disaffection of families affected by specific MPS diseases for which there is no available therapy. In several instances families have left the Society to begin separate groups with the goal of having a more direct impact upon therapy development for their particular disease. Thus, while the availability of new therapies for some MPS diseases has been a life-changing and life-saving development, it has created major difficulties for the Society: 1) how to raise awareness that current treatments are not cures and that new and combination therapies need to be developed and evaluated, 2) how to work towards therapies for diseases without current treatment in an aggressive enough way that it keeps families under the umbrella of the National MPS Society, and 3) how to emphasize the importance of the

[2] http://www.mpssociety.org/research/sab-funding-recommendations/

Society's funding in the current climate of low success rates for federal research grants (e.g., National Institutes of Health).

We propose that the Society formulate a clear funding mission that will address these challenges. While it may be impossible to prevent families from preferring to donate to a specific disease, the Society must raise awareness of the importance of our collective power to improve the lives of individuals living with MPS and related diseases. Here, we propose the following funding priorities for the National MPS Society

Unmet Needs of the MPS Community:

The first step in defining goals for the Society as it moves forward is to define the unmet needs of the membership. These fall into three categories: 1) presently untreatable diseases, 2) neglected manifestations of treatable diseases, and 3) other services.

Untreatable diseases: These diseases can be defined as those without effective, clinically-available treatment to reduce lysosomal storage. In 2011, these include MPS IIIA, IIIB, IIIC, IIID; MPS IVA and B; MPS VII and ML II and ML III.

Neglected manifestations of treatable diseases: Current treatments exist for MPS I, II, and VI. However, disease manifestations that are not completely addressed by available therapies include: orthopedic (hips and other joints, spine, etc.), ophthalmologic (corneal clouding, retinal involvement), central nervous system (cognitive deterioration, hydrocephalus, spinal cord compression, and headaches), and cardiovascular (valvular heart disease, coronary artery narrowing, myocardial thickening and fibrosis) manifestations.

Other services: Other needs that remain unmet or under addressed in the MPS community include the lack of newborn screening or other means to enable early diagnosis (and avoid or shorten the

"diagnostic odyssey" that many families experience), the lack of clinically-relevant biomarkers of disease progression and treatment response, and supportive care.

Topics for Funding Consideration:

The Future Directions Committee proposes that the following topics be supported by the Society: development of new therapies, biomarkers, symptom management and palliative care, and the basic cell biology of the lysosomal system in health and in lysosomal disease.

Development of new therapies: The Society should emphasize the development of new therapies in its requests for funding applications. These would include therapies for untreatable conditions, better (combination) therapies for treatable conditions, and therapies with the potential to treat multiple conditions with an urgent emphasis on the need for new therapies for fatal conditions without current effective treatment. The Society must endeavor to make it clear to the community that it views the development of therapy for fatal, untreatable diseases as a critical imperative. The Society speaks proudly of "Living with MPS," which is a source of great support for many affected individuals and their families. However, it must address that a significant proportion of the membership is dying from MPS, and do not share the same experience.

Biomarkers: Biomarkers can be biochemical, protein, or RNA or other substances measured in blood, urine, cerebrospinal fluid, or skin samples. They may also refer to imaging markers, such as white matter hyperintensities [1-4]. Biomarkers are critical in a clinical trial to show efficacy in small populations, as is presently being pursued in the evaluation of oxysterols in the lysosomal disease known as Niemann-Pick type C [5]. Another potential use of biomarkers is to predict disease progression and, therefore, signal when specific types of interventions are needed, such as a biomarker for early brain involvement. Finally, biomarkers may someday be used to adjust the dose of available treatments.

Symptom management and palliative care: The effective treatments that are available nevertheless leave many disease manifestations unaddressed or insufficiently addressed. The Society should support research into combination therapies for the many disease manifestations not managed by current therapies. We expect that the majority of this research (such as the study of treatments for orthopedic issues) will span many MPS types.

Basic Cell Biology: Understanding the basic biology of the lysosomal system is critical to understanding lysosomal diseases and their impact on brain, bone, and other tissues. Greater knowledge of blood-brain barrier mechanisms holds the key to getting therapies to brain cells in need of treatment. The discovery of the mannose 6-phosphate receptor system that enabled hematopoietic stem cell transplantation and enzyme replacement therapy took place due to careful basic science investigations. Unquestionably, basic science is the wellspring for new therapeutic innovations for lysosomal diseases. The Society should continue to support basic science research that will provide a pipeline for new therapies, biomarkers, and tests for MPS conditions.

Newborn screening: As lysosomal storage diseases are by nature progressive, early treatment will result in better outcomes in nearly all cases. While the Scientific Advisory Board is generally supportive of newborn screening, this topic was felt to reside outside of the purview of research. The Society may wish to fund or otherwise support newborn screening efforts on an ad hoc basis, but these activities will not be described further here.

Funding Priorities: A Strategic Three-Year Plan for Grant Requests

To ensure that research dollars have the best chance of benefiting MPS affected individuals, we would like to provide our opinions regarding the funding priorities for the Society moving forward. Our recommendations are based on the best available published evidence as of October, 2011. Limitations

include our lack of information on proprietary therapeutics, diagnostic tests, and biomarkers that are currently in development at biotechnology companies or in academic laboratories.

Priority #1: Therapy Development for MPS and Related Disorders without Clinically Available Treatments. There are no therapies currently for MPS III (all types), MPS IV (A and B), MPS VII, or ML (all types). Enzyme replacement therapies for MPS IIIA and IVA are in clinical trials, leaving MPS IIIB, C, and D, ML II, III and IVB, and MPS VII (it appears likely that a clinical trial may begin for MPS VII). These can be ranked in terms of prevalence: MPS IIIB > ML II/III > MPS IIIC > MPS VII > MPS IIID (incidence of MPS IVB is unknown). There are other criteria which could be employed to prioritize MPS and ML diseases. Diseases could be ranked in terms of "treatability," i.e. the theoretical "ease" with which the disease may be corrected. For example, ML diseases and MPS IIIC may be more challenging to treat definitively than are diseases due to deficiency of a soluble enzyme. An unbiased measure of a disease's "treatability" would be the preclinical evidence for disease reversal in animal models. A PubMed search for each of these MPS and ML types shows that successful treatment of animal models has been established for MPS VII [6-12]; and IIIB [13-17]. In addition, there are case reports of partial improvement in the phenotype of MPS VII (one patient) and ML II (two patients) following early bone marrow transplantation [18-20]. However, in both cases the transplant was incompletely successful, and the numbers are too small to determine the likelihood of clinical efficacy of bone marrow transplantation for these diseases.

While the ultimate goal is to produce effective therapies for all types of MPS and ML diseases, we recommend prioritizing the following (in order of importance): 1) Translational development of therapies with success in animal models, particularly MPS IIIB (more prevalent) followed by MPS VII (less prevalent); 2) Novel and translational therapy development for diseases that are currently untreatable and lack preclinical efficacy assessments, including ML, MPS IIIC, and MPS IIID; 3) Novel therapy

development for currently untreatable diseases with therapies in clinical trials (MPS IIIA and IVA) and with therapies in the clinic (MPS I, II, and VI). For number 3, precedence should be given to new therapies that address or circumvent shortcomings of available therapies, such as continued disease burden (see "Priority #3" below), invasive or inconvenient delivery system, adverse effects, and cost.

Priority #2: Biomarker Development. Biomarkers that may be used in clinical trials as surrogate endpoints include neuroimaging and biochemical markers of disease progression. Early stages of biomarker development include demonstration that the marker is associated with the disease, while later studies must establish clinical relevance, sensitivity, and specificity in patients. Both should be supported, with the latter taking precedence, as these types of studies are needed to develop the markers as surrogate endpoints for clinical trials.

Priority #3: Therapy Development for Neglected Manifestations of Treatable Diseases. The development of treatments for orthopedic, cardiovascular, and other manifestations of treatable diseases should be the second funding priority for the Society because in many cases, these types of adjunct therapies may have benefits across several MPS types.

Basic science: Basic science investigations into MPS diseases are more challenging, in that there is no immediate "pay-off" for funding in these areas. Yet, it is important to recognize that basic science provides new discoveries that may lead to new avenues for treatment or new biomarkers, etc. Basic science is less expensive than clinical and translational science, and the Society can provide small "seed" funding that investigators can use to generate preliminary data for NIH support. The Society should make basic science funding parallel with the priorities listed above.

Funding Strategy: We propose a funding strategy consisting of three types of offerings.

1. Grand Challenge Grants: The Society should offer one grant per year (or every two or three years) based on priority topics #1-3 above. These "grand challenge" grants should be as large as is financially feasible (such as $200,000 over a one to two-year period). The SAB suggests that the first Grand Challenge Grant be issued for treatments and clinically-relevant biomarkers for Sanfilippo syndrome. This grant would be issued to the most meritorious application that would study either a therapy or a biomarker that has passed the proof-of-concept stage but requires further pre-clinical or clinical testing. Biomarkers must be potentially useful in monitoring the therapeutic response in the central nervous system in clinical trials. The request for applications would also consider proposals for therapies or biomarkers for other types of MPS and related disorders, provided that these could also be applicable to Sanfilippo disease. The competition would be open to corporate entities as well as academic research laboratories.

2. Basic science and preclinical proof of concept proposal grants: The Society should offer one grant per year (or every two years) for basic science. Proposals should be hypothesis-driven, but may focus on any area related to MPS. The Society should continue to support early-stage investigators to promote interest in MPS research.

Partnering for a Cure: Building Alliances with other Groups to Achieve Enhanced Funding

To facilitate a new and expanded approach to funding, particular for the Grand Challenge Grants, it is proposed that the National MPS Society seek out specific partnerships with other foundations and interest groups with a focus on therapy for MPS and other lysosomal disease, and if applicable, with industry, small biotech companies, and so forth, as a means to raise the additional funds to make such studies viable on the larger scale.

References

1 Gabrielli O, Polonara G, Regnicolo L, Petroni V, Scarabino T, Coppa GV, Salvolini U: Correlation between cerebral MRI abnormalities and mental retardation in patients with mucopolysaccharidoses. Am J Med Genet A 2004;125A:224-231.

2 Vedolin L, Schwartz IVD, Komlos M, Schuch A, Azevedo AC, Vieira T, Maeda FK, Marques da Silva AM, Giugliani R: Brain MRI in mucopolysaccharidosis: Effect of aging and correlation with biochemical findings. Neurology 2007;69:917-924.

3 Vedolin L, Schwartz IVD, Komlos M, Schuch A, Puga AC, Pinto LLC, Pires AP, Giugliani R: Correlation of MR Imaging and MR Spectroscopy Findings with Cognitive Impairment in Mucopolysaccharidosis II. Am J Neuroradiol 2007;28:1029-1033.

4 Manara R, Priante E, Grimaldi M, Santoro L, Astarita L, Barone R, Concolino D, Di Rocco M, Donati M, Fecarotta S, Ficcadenti A, Fiumara A, Furlan F, Giovannini I, Lilliu F, Mardari R, Polonara G, Procopio E, Rampazzo A, Rossi A, Sanna G, Parini R, Scarpa M: Brain and spine MRI features of Hunter disease: frequency, natural evolution and response to therapy. J Inher Metab Dis 2011;34:763-780.

5 Porter FD, Scherrer DE, Lanier MH, Langmade SJ, Molugu V, Gale SE, Olzeski D, Sidhu R, Dietzen DJ, Fu R, Wassif CA, Yanjanin NM, Marso SP, House J, Vite C, Schaffer JE, Ory DS: Cholesterol Oxidation Products Are Sensitive and Specific Blood-Based Biomarkers for Niemann-Pick C1 Disease. Sci Transl Med 2010;2:56ra81.

6 Taylor R, Wolfe J: Decreased lysosomal storage in the adult MPS VII mouse brain in the vicinity of grafts of retroviral vector-corrected fibroblasts secreting high levels of [beta]-glucuronidase. Nat Med 1997;3:771-774.

7 Liu G, Chen YH, He X, Martins I, Heth JA, Chiorini JA, Davidson BL: Adeno-associated Virus Type 5 Reduces Learning Deficits and Restores Glutamate Receptor Subunit Levels in MPS VII Mice CNS. Mol Ther 2007;15:242-247.

8 Sands MS, Vogler C, Kyle J.W., Grubb J.H., Levy B, Galvin N, Sly WS, Birkenmeier EH: Enzyme replacement therapy for murine mucopolysaccharidosis type VII. J Clin Invest 1994;93:2324-2331.

9 Vogler C, Sands M, Higgins A, Levy B, Grubb J, Birkenmeier EH, Sly WS: Enzyme replacement with recombinant beta-glucuronidase in the newborn mucopolysaccharidosis type VII mouse. Pediatr Res 1993;34:837-840.

10 Frisella WA, O'Connor LH, Vogler CA, Roberts M, Walkley S, Levy B, Daly TM, Sands MS: Intracranial injection of recombinant adeno-associated virus improves cognitive function in a murine model of mucopolysaccharidosis type VII. Mol Ther 2001;3:351-358.

11 Daly TM, Vogler C, Levy B, Haskins ME, Sands MS: Neonatal gene transfer leads to widespread correction of pathology in a murine model of lysosomal storage disease. Proc Natl Acad Sci USA 1999;96:2296-2300.

12 Herati RS, Knox VW, O'Donnell P, D'Angelo M, Haskins ME, Ponder KP: Radiographic evaluation of bones and joints in mucopolysaccharidosis I and VII dogs after neonatal gene therapy. Mol Genet Metab 2008;95:142-151.

13 Heldermon CD, Ohlemiller KK, Herzog ED, Vogler C, Qin E, Wozniak DF, Tan Y, Orrock JL, Sands MS: Therapeutic Efficacy of Bone Marrow Transplant, Intracranial AAV-mediated Gene Therapy, or Both in the Mouse Model of MPS IIIB. Mol Ther 2010;18:873-880.

14 Fu H, Kang L, Jennings JS, Moy SS, Perez A, DiRosario J, McCarty DM, Muenzer J: Significantly increased lifespan and improved behavioral performances by rAAV gene delivery in adult mucopolysaccharidosis IIIB mice. Gene Ther 2007;14:1065-1077.

15 McCarty DM, DiRosario J, Gulaid K, Muenzer J, Fu H: Mannitol-facilitated CNS entry of rAAV2 vector significantly delayed the neurological disease progression in MPS IIIB mice. Gene Ther 2009;16:1340-1352.

16 Fu H, Samulski RJ, McCown TJ, Picornell YJ, Fletcher D, Muenzer J: Neurological correction of lysosomal storage in a mucopolysaccharidosis IIIB mouse model by adeno-associated virus-mediated gene delivery. Mol Ther 2002;5:42-49.

17 Fu H, DiRosario J, Kang L, Muenzer J, McCarty DM: Restoration of central nervous system alpha-N-acetylglucosaminidase activity and therapeutic benefits in mucopolysaccharidosis IIIB mice by a single intracisternal recombinant adeno-associated viral type 2 vector delivery. J Gene Med 2010;12:624-633.

18 Yamada YF, Kato KF, Sukegawa KF, Tomatsu S FAU - Fukuda, Fukuda S FAU - Emura, Emura S FAU - Kojima, Kojima S FAU - Matsuyama, Matsuyama TF, Sly WS FAU, Kondo NF, Orii T: Treatment of MPS VII (Sly disease) by allogeneic BMT in a female with homozygous A619V mutation. Bone Marrow Transplant 1998;21:629-34

19 Grewal S, Shapiro E, Braunlin E, Charnas L, Krivit W, Orchard P, Peters C: Continued neurocognitive development and prevention of cardiopulmonary complications after successful BMT for I-cell disease: a long-term follow-up report. Bone Marrow Transplant 2003;32:957-960.

20 Imaizumi M, Gushi K, Kurobane I, Inoue S, Suzuki J, Koizumi Y, Suzuki H, Sato A, Gotoh Y, Haginoya K, Kikuchi M, Aikawa J, Narisawa K, Ohunuma A, Ohmura K, Shintani H, Tanaka A, Tada K: Long-term effects of bone marrow transplantation for inborn errors of metabolism: A study of four patients with lysosomal storage diseases. Pediatr Intl 1994;36:30-36.