Several specific therapies are available to treat type 1 Gaucher disease (GD1) but these expensive treatments are generally not prescribed in the less aggressive forms of GD1. Little is known about these untreated patients and their evolution. An improved understanding of this subpopulation should simplify the identification of patients at risk of complications and permit follow-up recommendations specific to this phenotype. Here, we report the first step of the GANT study, whose primary objective is to describe the clinical, biological and radiological features of French untreated patients. Untreated GD1 patients identified in the French Gaucher Disease Registry (FGDR) were included and exhaustive data were collected for 42 untreated patients. The patients were 24 females and 18 males with a median age at diagnosis of 42 years [0.1 - 84]. Eight had a N370S homozygous mutation, 18 had a N370S heterozygous mutation, and 7 of them a L444P mutation. Median time of follow-up before inclusion was 12.2 years [1-41.2]. Six were previously treated for 1.6 years, but hadn't received any treatment for 4.9 years before their inclusion. Six (14%) were splenectomized. Splenomegaly was present in 21 patients (58.3%). From diagnosis to inclusion, mean platelet counts (139 500 /mm^3[38 000/mm3- 456 000/mm3]) and hemoglobin (13.2 g/dl [10.1 g/dl- 15.3g/dl]) remained stable. At the last evaluation, an increased number of patients complained of bone pain, but none had any bone crisis. In this study, we describe the largest cohort of untreated GD1 patients and their evolution from diagnosis to inclusion. The set of data collected, and the set-up of the prospective study, will improve our understanding of the spontaneous evolution of this subpopulation and help optimize recommendations for its follow-up and care.

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Intracerebral gene therapy in children with metachromatic leukodystrophy: Results of a phase I/II trial

Caroline Sevin[a,b], Thomas Roujeau[c], Nathalie Cartier[b], Thomas Baugnon[d], Catherine Adamsbaum[e], Monique Piraud[f], Sabata Martino[g], Philippe Mouiller[h], Célia Couzinié[i], Céline Bellesme[a], Clémence Castaignède Lalande[a], Carine Cormary[a,b], Mark M. Souweidane[j], Marie-Anne Colle[k], Oumeya Adjali[i], Dolan Sondhi[l], Ronald G. Crystal[l], Patrick Aubourg[a,b], Michel Zerah[m], *[a]Neuropediatrics Unit, Bicêtre Hospital, Le Kremlin-Bicetre, France, [b]Inserm U1169, Le Kremlin-Bicetre, France, [c]Paediatric Neurosurgery Department, Gui de Chauliac Hospital, Montpellier, France, [d]Department of Anesthesiology and Critical Care, Hôpital Necker Enfants Malades, Paris, France, [e]Departments of Pediatric Imaging, Bicêtre Hospital, Le Kremlin-Bicetre, France, [f]Service de Biochimie et Biologie Moléculaire Grand Est, Centre de Biologie et de Pathologie Est, Hospices Civils de Lyon, Bron, France, [g]Department of Chemistry, Biology and Biotechnologies, University of Perugia, Perugia, Italy, [h]Atlantic Gene Therapies, INSERM UMR 1089, Université de Nantes, CHU de Nantes, IRS2 Nantes Biotech, Nantes, France, [i]INSERM UMR 1089, Institut de Recherche Thérapeutique IRT UN, Nantes, France, [j]Department of Neurosurgery, Weill Cornell Medical College, New York, New York, NY, United States, [k]INRA UMR U703, Animal Pathophysiology and Biotherapy for Muscle and Nervous system Diseases, UMR 703 PAnTher INRA/ONIRIS, ONIRIS, CS 40706, F-44307, Nantes, France, [l]Department of Genetic Medicine, Weill Cornell Medical College, New York, NY, United States, [m]Paediatric Neurosurgery Department, Université Paris Descartes and Assistance Publique-Hôpitaux de Paris, Hôpital Universitaire Necker, Paris, France*

No treatment is available for symptomatic early-onset forms of metachromatic leukodystrophy (late infantile-LI; early juvenile-EJ MLD), a devastating lysosomal disease caused by defect in arylsulfatase A (ARSA) gene. We describe herein the results of a phase I-II clinical trial, using intracerebral administration of an adeno-associated viral vector serotype rh.10 coding for human ARSA enzyme (AAVrh.10-hARSA), over a 2-years follow-up. Four MLD children (aged between 9 months and 5 years ½, 3 LI and 1 EJ) received 1012 or 4x1012 vector genome of AAVrh.10-hARSA, at a pre-symptomatic (N = 2) or early-symptomatic (N = 2) stage of their disease, administered at 12 location sites in the white matter of the centrum semiovale. Patients received corticosteroids from D-1 to D + 10. All patients were alive at the last timepoint. Two patients were withdrawn from the study at M + 12 (parents' decision). 36 AEs and 8 SAEs were reported. One SAE was attributed to the neurosurgical procedure (intracranial suffusion, that resolved spontaneously). One SAE (seizures at M + 8) was declared treatment-related by the sponsor. Vital parameters and standard biology were unremarkable. AAVrh.10-hARSA was detected in urine up to D + 2 and in blood up to M + 3. Anti-AAV neutralizing factors raised up to M + 12, then tended to stabilize or decrease. There was no evidence for cellular immune response against ARSA transgene. Hyper-T2 signals around the injection sites were detected from M + 3 onwards and remained stable thereafter, independently on the vector dose and without clinical impact. ARSA activity in CSF, undetectable before treatment, increased significantly after injection, reaching 20%-70% of control values at the last assessment, with a dose dependent effect, attesting for vector functionality. Despite long-lasting restauration of ARSA activity, symptomatic patients continued to deteriorate and presymptomatic patients developed MLD disease, that was not significantly different from the natural history of the disease. Reasons for this insufficient efficacy will be discussed.

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Abnormal GM2 accumulation alters the function of the autophagic pathway in early-onset Tay-Sachs disease mouse model

Volkan Seyrantepe, Nurselin Ates, Melike Can, Tugce Sengul, Secil Akyildiz Demir, *Izmir Institute of Technology, Izmir, Turkey*

Tay-Sachs disease (TSD) is an inborn error of metabolism, a prototypical lysosomal disease of the nervous system. In humans, the fatal infantile acute form is the most common, and with no current treatment, prevention and palliative care the only options. TSD mice did not mimic human infantile TSD, and although mice showed some early pathology and storage of GM2 ganglioside, clinical disease would take many months to develop. The extremely mild disease in the TSD mice was likely due to a biochemical bypass, a neuraminidase. We recently demostrated that at least one of the principal murine neuraminidase, Neu3, responsible for the biochemical bypass in the catabolism of the GM2 ganglioside. The Hexa-/-Neu3-/- mice were healthy at birth, but died at 5 months of age. The Hexa-/-Neu3-/- mice exhibited progressive neurodegeneration with neuronal loss, Purkinje cell depletion, and astrogliosis. Thus, the Hexa-/-Neu3-/- mice mimic the neuropathological and clinical abnormalities of the classical early-onset Tay-Sachs patients. Autophagic flux (the rate at which autophagic vacuoles are processed by lysosomes) is reduced in most lysosomal diseases. To confirm that Hexa-/-Neu3-/- mice have dysfunctional autophagy we measured the protein levels of LC3I, LC3II, p62, Beclin and Lamp-2 by Western blotting. Although p62 and Beclin1 were only slightly elevated in cortex and cerebellum of 5 months old Hexa-/-Neu3-/- mice, the ratio of LC3II/LC3I remained unchanged relative to age-matched wild-type mice and single knockouts. In contrast, immunohistochemical analysis of fibroblast and brain sections displayed increased numbers of LC3(+) organelles suggesting that both autophagosomes and autolysosomes persist in

these conditions. Taken together, these findings suggest that GM2 accumulation leads to both an induction of autophagy and an impairment of autophagic flux. Further studies are needed to explore the effects of modulators of autophagy on Tay-Sachs phenotype in cell culture and in mice.

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A consensus conference for cognitive endpoints for clinical trials and natural history studies in MPS diseases

Elsa G. Shapiro[a], Jennifer L. Greenberg[a], Mark Dant[b], Christine Lavery[c], Johanna van der Lee[d], Darren Janzen[e], Kathleen Delaney[f], Brian Bigger[g], *[a]Shapiro Neuropsychology Consulting LLC, Portland, OR, United States, [b]National MPS Society, Durham, NC, United States, [c]UK Society for Mucopolysaccharide Diseases, Amersham, United Kingdom, [d]Academic Medical Center, Amsterdam, Netherlands, [e]Oregon Health & Science University, Portland, OR, United States, [f]BioMarin Pharmaceutical Inc, Novato, CA, United States, [g]University of Manchester, Manchester, United Kingdom.*

FDA and UK MPS society workshops provided impetus for the US and UK MPS societies to organize a Consensus Conference, funded by 18 pharmaceutical companies. Previous workshops emphasized the need for common data elements and agreement on best practices across clinical trials using cognition and adaptive behavior as endpoints. For this Consensus Conference, a steering committee selected an expert 15-member panel and a facilitator. The conference attendees included 80 expert clinicians and physicians, representing 18 countries as well as 40 representatives from industry. A literature review (tests and best practices) was conducted prior to the proceedings. The expert panel, using a modified Delphi process, was open to observation. Workshops on cognitive and related endpoints were run in parallel to the consensus proceedings. The expert panel members made 12 recommendations with more than 90% agreement. The cognitive tests were the Bayley Scales of Infant Development for under age 3 and the Wechsler scales for over age 3; for impaired patients unable to do the Wechsler Scales, the Kaufman Assessment Battery for Children and the Differential Abilities Scales. The Vineland Adaptive Behavior Scales were suggested for all ages and impairments. General recommendations included best-practice guidelines on: multi-site protocols in international trials, standards for translations, assessor qualifications and training, transitioning between tests, and reporting metrics. Natural history data recommendations included use of already gathered material and the endorsement for a repository to share data. Two papers were published and two more are planned. A survey of the participants and supporters is being conducted and analyzed for this presentation. The consensus conference results will need periodic updating because of revised tests and practices. This consensus process can be a model for other neurodegenerative diseases with the goal of ensuring comparability among natural history studies and clinical trials.

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Priapism in a Fabry disease mouse model is associated with upregulated penile nNOS and eNOS expression

Jin-Song Shen[a], Xing-Li Meng[a], Arning Erland[a], Taniqua Day[a], Siamak Jabbarzadeh-Tabrizi[a], Robin Ziegler[b], Teodoro Bottiglieri[a], Seng Cheng[b], Raphael Schiffmann[a], *[a]Baylor Research Institute, Dallas, TX, United States, [b]Sanofi, Framingham, MA, United States*

Fabry disease is a glycosphingolipidosis caused by deficient activity of α-galactosidase A; it is one of a few diseases that are associated with priapism, an abnormal prolonged erection of the penis. The goal of this study was to investigate the pathogenesis of Fabry disease-associated priapism in a mouse model of the disease. We found that Fabry mice develop late-onset priapism [12% (25/214) vs. 0.5% (1/212) in wild-type]. Neuronal nitric oxide synthase (nNOS), which was predominantly present as the 120-kDa N-terminus-truncated form, was significantly upregulated in the penis of 18-month-old Fabry mice compared to wild type controls (~5-fold). Endothelial NOS (eNOS) was also upregulated (~2-fold). NO level in penile tissues of Fabry mice was significantly higher than in wild type controls at 18 months. Gene transfer-mediated enzyme replacement therapy reversed abnormal nNOS expression in the Fabry mouse penis. Penile nNOS level was restored by antiandrogen treatment, suggesting that hyperactive androgen receptor signaling in Fabry mice may contribute to nNOS upregulation. The phosphodiesterase-5A expression level and the adenosine content in the penis, which are known to play roles in the development of priapism in other etiologies, were unchanged in Fabry mice. In conclusion, these data suggested that increased nNOS (and probably eNOS) content and the resulting elevated NO production and high arterial blood flow in the penis may be the underlying mechanism of priapism in Fabry mice. Furthermore, in combination with previous findings, this study suggested that regulation of NOS expression is susceptible to α-galactosidase A deficiency, and this may represent a general pathogenic mechanism of Fabry vasculopathy.

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α-Galactosidase A activity modulates DNA methylation of androgen receptor promoter in Fabry disease endothelial cells

Jin-Song Shen, Kunitoshi Shigeyasu, Yoshinaga Okugawa, Taniqua Day, Raphael Schiffmann, Ajay Goel, *Baylor Research Institute, Dallas, TX, United States*

Fabry disease is caused by deficient activity of α-galactosidase A (α-gal A) and subsequent accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3). Previous studies showed that a number of genes are abnormally expressed in Fabry patients and a mouse model of the disease. The aberrant gene expression may play important roles in the pathogenesis of Fabry disease; however, the molecular basis by which α-gal A deficiency causes the altered gene expression remains to be elucidated. In present study, we tested whether α-gal A deficiency can affect DNA methylation, which is one of the most important epigenetic mechanisms for gene regulation. We examined the effect of α-gal A activity on the methylation status of two specific CpG regions in androgen receptor (AR) gene, whose expression is upregulated in Fabry disease. α-Gal A activity in a Fabry patient-derived endothelial cell line was manipulated by stable gene-transduction or short-term treatment with exogenous enzyme or α-gal A-specific inhibitor. Methylation level of each CpG site was quantitatively analyzed by bisulfite pyrosequencing. We found that decreased α-gal A activity and increased Gb3 accumulation in Fabry disease endothelial cells are associated with decreased methylation level of one of the CpG regions in AR promoter. This CpG region is located within the core promoter of AR gene and its methylation has been shown to be associated with AR gene silencing; thus, hypomethylation of this region might contribute to upregulated AR in Fabry disease. Methylation level of LINE-1, a marker for global methylation, was not affected by α-gal A deficiency. In conclusion, this study provides evidence that α-gal A