INTERNATIONAL LSD RESEARCH NETWORK

News Letter No.1 May 20, 2022

- GREETING-

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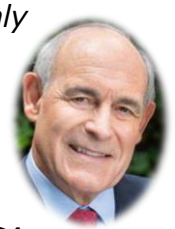
Director, Southern Tohoku Institute of Neuroscience /Prof.(EM)Tokyo Jikei University, Tokyo, Japan

How are you all? In order to establish an international network for lysosomal disease research, we are pleased to present the newsletter of the International LSD Network and to announce the publication of this article. We planned this project with the hope that LSD researchers around the world can easily exchange new information and promote research exchange on LSD. Futhermore, the world saw the tragedy ***in Ukraine****. We need to unite for further peace. The International LSD Network will also contribute to research for peace by uniting the people of the world. Simultaneously, we organize International LSD web conference (see https://www.ildweb.jp/). Your support is highly appreciated.*

-MESSAGE FROM US-



Robert R. Desnick, M.D.PhD
Dean for Genetics and Genomic Medicine and
Emeritus Professor Mount Sinai School of Medicine, New York, USA

The Lysosomal Disease Center at the Ichan School of Medicine at Mount Sinai in New York City brings greetings to all the LSD-ologists worldwide. It is spring-time above the equator and as the cherry blossoms bloom so too we emerge with an international electronic letter to share the recent news and advances in our field. The early updates of unpublished and published basic, translational, and clinical findings are important to share and acknowledge the responsible scientists and clinicians.

. Also news about our colleagues young and older. Please share the newsletters with your young colleagues so that they appreciate that the field is constantly advancing with new insights and findings using the latest technologies. We are on the cusp of moving from effective treatments to cures, as studies of gene therapies are underway to fix or augment the genetic defects in these diseases. Gene therapy or other new methods are needed to treat the neurological LSDs and other neurological disorders. AI May lead to faster diagnoses and pregnancy genetic heterozgote detection should reduce the birth of affected bab with these tragic debilitating diseases. Techniques such sas prenatal genetic testing will allow selection of normal embryos at the eight cell stage for in vitro fertilization. Prenatal screening is already in place in many countries. We should be seeking the expansion of prevention as well as effective treatments of these diseases wherever possible. This Newsletter initiated by Professor Yoshikazu Eto should gain distribution to our colleagues worldwide. Your support is needed to share the latest LSD science and news. We look forward to the blossoming of the field, your greetings and LSD news in this quarterly electronic newsletter. Wishing you all great science and clinical achievements.

MESSAGE FROM SOUTH

Han-Wook Yoo, M.D., Ph.D. Emeritus Professor Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Many congratulations on a good start by Professor Eto's initiative to network LSD persons around the glove. It is increasingly important to communicate very closely between stakeholders (physicians, researchers, bio-pharms, even patient advocacy group) regarding rare disease, particularly LSDs in order to share creative ideas, figure out patients' unmet needs, and to apply rapidly advancing technologies for the best care of LSD patients. We need to encourage many newcomers in this field to join together.

MESSAGE FROM LATIN AMERICA

Prof. Roberto Giugliani, Dept. Genetics UFRGS, Med. Genet. Serv. HCPA, DASA and Casa dos Raros, Porto Alegre, Brazil

Latin America welcomes and supports this initiative, which will contribute to bringing together LSD specialists from all regions. International collaboration is extremely important to further develop initiatives to improve the understanding, screening, diagnosis and treatment in lysosomal diseases. We hope that this newsletter will reach a diverse community, including health professionals, scientists, patient advocates, members of the pharma and healthcare industry, and governmental authorities. We look forward to receiving this quarterly newsletter with content relevant to the LSD field!

KEY PERSONS IN LYSOSOMAL STORAGE DISEASES

The idea of the lysosome as the 'recycling plant' of the cell established. Prof de Duve was awarded the Nobel Prize for his discoveries in 1974.

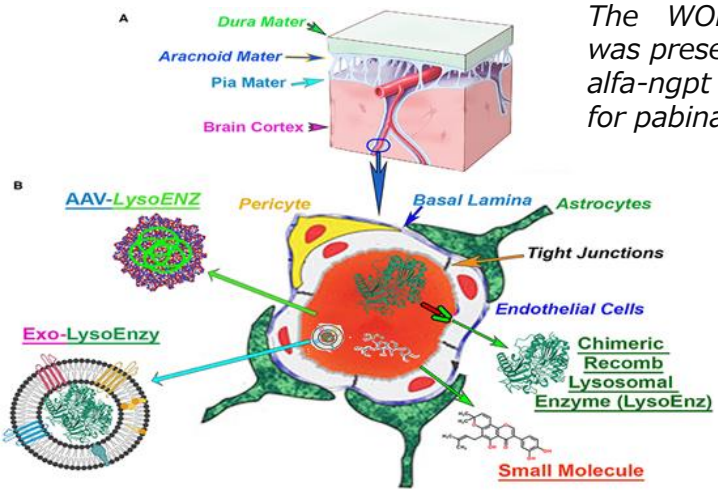
In 1965 , Henri G. Hers, Belgian biochemist established the concept of lysosomal storage diseases, based on his Pompe disease research.

Dr. Roscoe Brady, NIH identified enzyme deficiencies in Gaucher, Fabry and Niemann-Pick type A/B diseases and also first established Enzyme replacement therapy in Gaucher and Fabry diseases, In 1960s-1980s.

Novel CNS Treatment for LSD

More than 80% of LSD patients present an involvement of the central nerve system (CNS) with a broad spectrum of severity.Patients exhibit seizure, ataxia, developmental delay, gait disturbances etc. Now, there are several trials to treat the CNS: 1) Intraventricular ERT for MPS II (Crinigen, Japan) 2) Transferrin receptor antibody binding enzyme (JCR, Denali) 3) AAV8/9 (MPS I, II, III, IV) /Lentivirus gene therapy (MLD, MPS I, II) (US, EU) 4) Small molecules in Gangliosidosis etc (Sanofi).

Two procedures for the CNS ERTs were approved in Japanese government, 2021.



Mariola J. Edelmann1 and Gustavo H. B. Maegawa CNS-Targeting Therapies for Lysosomal Storage Diseases: Current Advances and Challenges Front. Mol. Biosci., 12 November 2020*

The WORLDSymposium 2022 New Treatment Award was presented to Sanofi Genzyme for avalglucosidase alfa-ngpt (Nexviazyme®) and to JCR Pharmaceuticals for pabinafusp alfa (IZCARGO®)

JCR now 7 pipelines for LSD

1. *MPS II (Hunter) approved in Japan*
2. *MPS I (Hurler) – Phase I, II*
3. *MPS IIIA –Preclinical*
4. *MPS VII (Sly)- Preclinical*
5. *MPS IIIb- Preclinical*
6. *Pompe disease-Preclinical*
7. *Gm2-gangliosidosis-Preclinical*

Nobel CNS treatment for MPS II

Prof. Paul Harmatz MD *General Pediatric Gastroenterology, UCSF Benioff Children's Hospital Oakland , CA*

Prof. Paul Harmatz presented his lecture in 17th Internaional LSD Web Conference (https://www.ildweb.jp) , April 23, 2022.

Two major treatment procedures for the CNS of MPS II patients:

1. *Intrathecal/Intraventricular ERT using Hunterase by Prof. Okuyama T. & Prof. Jin DK (Seo JH, Okuyama T et al. Mol Ther Methods Clin. Dev. 2021)*
2. *Transferrin antibody binding ERT(Pabinafusp alfa, Izucargo) : intravenous ERT can treat CNS, since the enzyme can cross BBB . (Okuyama T. et al. Mol. Ther. 2021; Giugliani R. et al. Int. Mol. Sci. 2021).*

Two procedures for the CNS treatment of MPS II were approved by Japan PMDA,, 2021, 2022.

MPS Type I : Clinical Trial Started

A phase I/II clinical study of intravenous administration of JR-171, a blood-brain barrier crossing enzyme, in mucopolysaccharidosis type I started in Japan and Brazil : Takashi Hamazaki, M.D., Ph.D. (Osaka City University Graduate School of Medicine, Japan) presented at World Symposium , 2022

Fetal ERT for LSD- First Successful in Utero a Fetus with Infantile Pompe Disease –UCSF

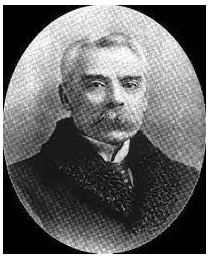
Tippi MacKenzie, Professor of Surgery at the University of California, San Francisco and the Director of the Eli and Edythe Broad Institute for Regeneration Medicine succeeded in fetal ERT for Pompe disease, 2021. She caried out first in utero enzyme replacement therapy of infantile Pome disease. Six doses of in utero ERT improved clinical pictures, normal development, normal plasma CK, and avoidance of glycogen storage after 6months follow up. In UCSF, phase 1 trial is open for patients enrollment (MPS1,2,4a,6,7), infantile Pome, neuropathic Gaucher, Wolman disease. Contact : paul.Harmatz@ucsf.edu

1. *Schwab ME, MacKenzie TC. Prenatal Gene Therapy, Clin Obstet Gynecol. 2021 Dec 1;64(4):876-885.*
2. *Quoc-Hung Nguyen et all Tolerance induction and microglial engraftment after fetal therapy without conditioning in mice with Mucopolysaccharidosis type VII. ci Transl Med 2020 Feb 26;12(532)*

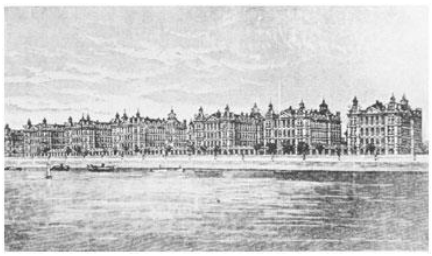
Current Progress of Gene Therapy for LSD

First Gene therapy and most expensive drug for LSD, Libmeldy (MLD) approved in Dec 2021, EMA) :The one-off treatment has a list price of ***£2.8 million*** *offered on the NHS after the health service negotiated a confidential discount, 2022.*
Now, several successful gene therapy treatments for LSD are now publishing:

1. *MPS I gene therapy using lentivirus vector: B.Gentner et al. N Engl J Med 2021; 385:1929-1940*
2. *Treatment of skeletal and non-skeletal alterations of mucopolysaccharidosis type IVA by AAV-mediated gene therapy, Bertolin J et al. Nature communication, 2021, 12;5343.*
3. *Lentivirus-mediated gene therapy for Fabry disease. A. Kahn et al. Nature Communication, 12: 1178-1177, 2021.*



Prof. W. Anderson, Baron K. Takagi



St. Thomas Hospital, London

Japan and Fabry disease

In 1989, Professor Anderson in the UK reported also Fabry's disease at the same time as Dr. Fabry in Dortmund, Germany. Anderson came to Japan to teach in Japanese naval medical training school, 1874-1879 for 5 years. He taught Baron Takagi (Founder of Jikei Medical School, 1881) sent him to St. Thomas Hospital, 1874. Takagi proposed Dietary theory of Beriberi and carried out large scale of world first clinical trials using navy ships, 1884 . This research was the catalyst for the discovery of vitamin B1.

WINE MAKING AND GENETICS

Professors Linda and Ed McCabe

We moved to the Pacific Northwest in the beautiful Columbia River Gorge in 2017 to be closer to our adult children, and to pursue editing our two journals, Molecular Genetics and Metabolism (MGM) and MGM Reports, writing, and making wine. We will briefly discuss the similarities between wine making and genetics. Medicine is an art and a science, and so is wine making. There is a long history for both with science more recently providing an understanding of older processes. We often discuss the historical links of what we do today when we are making our wine. For example, we use wooden basket presses for our cherries and grapes: a small ratchet operated one for our cherry-honey dessert wines and a larger hydraulic one for our grape wines. These basket presses have evolved from devices that originated in the Second Century AD/CE.

Genetics had an explosion of information with the growth of molecular genetics, including the Human Genome Initiative in the 1980s, followed by the Human Genome Project, and the sequencing of our genomes and those of many other species. Genome sequencing has revealed vital information about grape varieties. For example, Primitivo and Zinfandel grapes, once thought distinct varietals, are now known to have identical DNA sequences. American wine making moved from the large-scale manufacture of inexpensive sweet wines to fine varietal grape wines by smaller vintners beginning in the 1970s. We made our first wines in 5-gallon carboys as graduate students in 1970. Then we became busy with raising children, and managing our careers and our ranch, and did not return to making wine until 2013, then 1-gallon at a time. (We now use the 1-gallon fermenters for our overnight yeast starter cultures for our 50- to 500-liter fermentations.) In 2017, we began to increase our production as we accumulated experience and equipment for a larger commercial operation. In 2022, our goal is to make 150 cases or 1,350 liters of wine. We will always be a small operation with our eventual annual goal of 500 cases or 4,500 liters, which will require about 12,000-pounds of grapes and 200-pounds of cherries.

If you want to learn more about Double Strand Wine, including the origin of our name (you might be surprised), then please visit http://www.doublestrand.wine. Enjoy!

Autumn at Garnier Vineyards, Mosier, Oregon. Vines go to the Columbia River, with Coyote Syncline, Washington, beyond. The vineyard is beautiful and their grapes are outstanding, and they are less than 3 miles from Double Strand Wine.

-LSD related Meeting Schedule- 2022～2023-

May 16-19, 2022 American Society of Cell and Gene Therapy, Washington DC
May 29-31, 2022 Fabry Disease UpDate Meeting, Wurzburg, Germany
Aug. 30-Sept. 2, SSIEM symposium, Freiburg, Germany
Oct. 11-14, 2022, European Society of Cell and Gene therapy, Edinburgh , UK
Feb. 22-25, 2023, World Symposium, Orlando, Florida, USA

MESSAGE FROM CHICAGO ; *Prof. Gregory Grabowski*

New Insight of Gaucher Disease

The past four decades have ushered in expansive understandings of the basic mechanisms of and treatments for LSDs. Indeed, the role of lysosomes in cellular metabolism has evolved from a digestive "garbage can" to a critical sensor and control center for modulating cellular growth, development, metabolism, and immune responses. Gaucher disease (GD) has highlighted the disturbances of these control mechanisms and their corrections with enzyme therapy (ET), the first and most successful ET. These successes in reversing much of the visceral disease in GD type 1 spurred the developments of such therapies in many other LSDs directed at their disease initiating events, i.e., insufficient enzyme/protein for normal cellular function. These successes in GD type 1 also brought focus to principles for LSD therapies: 1) supplying sufficient therapy to alleviate target cell stresses, 2) to intervene early before onset of irreversible damage to cells, i.e., early and sufficient treatment led to better outcomes, and 3) the existence of sequestered sites that diminish effectiveness of ET, e.g., the CNS, and highlight the need for additional adjunctive therapies to decrease toxic substrates and/or to target other metabolic disruptions of GD, including systemic and CNS inflammation. The increased clinical experience with the great variation in all the GD phenotypes has underscored the need to identify other genes that influence and modify the expression of GD even among siblings; GD, and also other LSDs, can no longer be characterized as "single gene traits." Understanding these modifier genes will provide additional targets for adjunctive therapies and potentially insights into the root mechanisms of the increased risks of developing Parkinson disease and Lewy Body Dementia in heterozygote carriers of altered GBA1, the gene causal to GD. These are areas of current intensive multidisciplinary research groups in academia, private foundations and the commercial centers provide a basis enhanced life-time outcomes for those with GBA1-related diseases as well as other LSDs.

Gaucher disease: Basic and translational science needs for more complete therapy and management. G. A. Grabowski, A. H. M. Antommaria, E. H. Kolodny and P. K. Mistry. Mol Genet Metab 2021 Vol. 132 (2):59-75.

Venglustat and Neurological Gaucher disease, type 3

Prof. Raffi Schiffmann,(LDN Project PI) presented positive results at World symposium 2022, "Venglustat combined with imiglucerase positively affects neurological features and brain connectivity in adults with Gaucher disease type 3. *The 12-month double-blind phase 2 trial evaluated the efficacy and safety of Venglustat in combination with imiglucerase in 11 patients aged 18 years and older with GD3. All patients included in the trial had received enzyme replacement therapy for at least 3 years and had achieved non-neurological therapeutic goals. The primary end points were safety, tolerability, and changes in GL-1 and glucosylsphingosine (lyso-GL-1) concentrations in cerebrospinal fluid and plasma. Secondary end points included neurological and systemic disease measures.*

AcknOwledgements: We would like to thank Prof. Robert Desnick (New York), Prof. Paul Harmatz (Oakland, CA), Profs Linda and Edward McCabe (Oregon) and Prof. Gregory Grabowski (Chicago) for their assistance in editing this newsletter. Thank you for kind messages from Prof. Han-Wook Yoo (Seoul) and Prof. Roberto Giugliani (Porto Alegre).

PEACE AND HELP TO UKRAINE

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