LDRTCNews

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Letter from the Director

Drug Development as a Business Decision Impacts Patients with Rare Disorders

Last week, I got the news that a trial that might offer the only hope for an otherwise deadly disorder in infants will not be pursued. Within the complex and evolving landscape of healthcare, drug development represents a critical intersection of science, business, and ethics. Bringing new drugs to market is a process often driven by potential profitability. This business-centric approach significantly influences the development of treatments for rare disorders where the patient population is small and the return on investment is often uncertain. Patients with rare disorders and their clinicians often find themselves at a complex and frustrating crossroads. The high cost of drugs and the pharmaceutical industry's hesitancy to pursue drug development for less profitable conditions significantly impact the quality of life and treatment options for these patients.

Pharmaceutical companies, like all businesses, aim to maximize profits. Drugs for common conditions such as diabetes, hypertension, and cholesterol management have a guaranteed market, ensuring steady revenue streams. In contrast, treatments for rare disorders – known as orphan drugs – serve a small number of patients, making them less commercially attractive despite their often higher pricing. Developing a new drug is a costly and risky endeavor. The process from discovery through clinical trials to market approval can take over a decade and cost upwards of over $2 billion. This high investment in terms of time and finance naturally steers pharmaceutical companies towards drugs that promise high returns, typically those targeting common diseases with large patient populations.

Clinicians are often caught in the ethical dilemma of wanting to provide the best possible care but are constrained by the realities of the healthcare system. They witness the disparities in treatment access and are forced to navigate these inequities on a daily basis, which can be distressing and demoralizing.

The decision by pharmaceutical companies not to pursue drug development for certain rare disorders due to low return on investment leaves patients feeling neglected and marginalized. In addition, the high cost of already existing drugs and the selective nature of drug development based on profitability disenfranchise patients with rare disorders, leaving them and their clinicians in a precarious position. Patients face financial burdens, limited treatment options, and the emotional toll of feeling forgotten by the system. Addressing these issues requires a concerted effort from governments, pharmaceutical companies, healthcare providers, and patient advocacy groups to ensure that profitability does not overshadow the fundamental right to health and equitable treatment access.

The orphan drug legislation, offering incentives like tax credits, grants for clinical research, market exclusivity, and regulatory fee waivers, may aim to offset the lower profitability of orphan drugs and encourage their development. While this has led to an increase in orphan drug approvals, the question of accessibility and affordability remains critical. Orphan drugs, once developed, are often exorbitantly priced, reflecting the high cost of their development and the need to recoup investments from a smaller patient base. This pricing model can make these drugs inaccessible to many patients, especially in countries without robust healthcare funding or insurance coverage for rare diseases. Given that none of the rare disorders pose a real public health concern, in developed countries such as the US and UK, the clinicians are utilized as gatekeepers of medical economics and are sometimes expected to put the financial burden of patient care in front of what is the best interest of the patient. I am mostly reminded by the cost of the drugs that I prescribe by the "Managed Care" companies that actually manage the care of my patients without knowledge or expertise in that specific rare disorder.

Patient advocacy groups play a crucial role in highlighting the needs of those with rare disorders. Collaborations between these groups, pharmaceutical companies, and government bodies can lead to more effective strategies for drug development and funding. Such partnerships can also ensure that the voices and needs of patients are heard in the drug development process. The development of Kalydeco, in collaboration with 65 Roses, is a prime example of how patient advocacy groups can play a crucial role in drug development. This partnership not only led to a groundbreaking treatment for CF but also set a precedent for how pharmaceutical companies and patient organizations can work together to accelerate medical advancements. 65 Roses, a patient advocacy group named for the way some children mispronounce "Cystic Fibrosis," played a pivotal role in the development of Kalydeco. This collaboration highlighted several key aspects: 65 Roses provided invaluable insights into the patient experience of living with CF. This perspective was crucial in shaping the research and development process. In addition, patient advocacy groups, including 65 Roses, have long been instrumental in raising funds for CF research. Their contributions were vital in supporting the early stages of Kalydeco's development. The success of Kalydeco underscores the importance of patient-centric approaches in developing treatments for complex genetic diseases.

Drug development, inherently a business decision, has profound implications for patients with rare disorders. While profitability drives the pharmaceutical industry, the need for treatments in rare diseases presents both a challenge and an opportunity for a more inclusive approach that will engage both the patients and clinicians who are not only experts in the field but also have mutual devotion and responsibility for these patients. Balancing business objectives with ethical responsibilities requires innovative strategies, collaborations, and a commitment to ensuring that all patients, regardless of the prevalence of their condition, have access to effective treatments. The future of drug development for rare disorders lies in finding synergies between commercial success and the overarching goal of improving patient health and quality of life.

Ozlem Goker-Alpan, MD

Contents

LDRTCNews is produced by the Lysosomal & Rare Disorders Research & Treatment Center.

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2023: A Year in Review Highlights from the LDRTC Clinical Trials and Research Unit

Lauren Noll

LDRTC ENROLLED OVER TWENTY PATIENTS ACROSS BOTH DISEASE GROUPS WHOSE DATA CONTRIBUTED TO FDA APPROVALS.

The Clinical Trials Research Department at Lysosomal and Rare Disorders Research and Treatment Center, Inc. runs multiple registries, sponsor-initiated treatment studies and nontreatment studies as well as investigator-initiated studies. Over the course of the past year our department has grown due to increasing numbers of studies and increasing numbers of patients enrolled. We expanded our team of three full-time coordinators to a team of six with a manager, four full-time coordinators and one full-time assistant.

Throughout 2023, we successfully maintained and updated data for over two hundred Gaucher, Fabry, and Pompe patients across various registries.

Approximately fifty patients throughout the year have been receiving regular treatment they wouldn't have been able to receive commercially spread across numerous studies. We opened seven new studies, which consisted of one observational, two prescreening, one oral treatment, one infusion, and two gene therapy. Of those seven new studies, our site enrolled the first patient in four of them.

Our team attended various patient conferences across the country, including the Fabry Patient Conference in Greensboro, NC, Niemann-Pick in Orlando, FL, Gaucher Patient Conference in NJ, Sanfillipo in Hershey Park, PA, MPS in MD, and Tay-Sachs in Reston, VA. These patient conferences allow us to showcase our facility and what we can offer patients, as well as learning

Clinical Research

THE HIGHLIGHT OF OUR YEAR WAS SEEING TWO TREATMENTS GET APPROVED BY THE FDA FOR COMMERCIAL USE.

Seven new studies - one observational, two prescreening, one oral treatment, one infusion and two gene therapy.

PATIENT ADVOCACY MEETINGS LDRTC ATTENDED IN 2023
National Fabry Disease Foundation (NFDF)- Family Education Conference in Greensboro | NC
Gaucher Community Alliance (GCA) - Patient & Family Conference in Cherry Hill | NJ
National MPS Society - 37th Annual Family Conference in Bethesda | MD
National Niemann-Pick Disease Foundation (NNPDF) - Family Support & Medical Conference in Orlando | FL
National Tay-Sachs & Allied Diseases Association (NTSAD) - 45th Annual Family Conference in Reston | VA
Team Sanfilippo Foundation (TSF) at Hershey Park | PA

about new treatments and/or issues currently facing those who live with these rare genetic diseases.

The highlight of our year was seeing two treatments get approved by the FDA for commercial use. The first approval came in May 2023 for the treatment of Fabry disease. The Elfabrio (pegunigalsidase alfa) studies started in our office back in 2013 as Phase 1 studies, which were first in human. This medication is an enzyme replacement therapy (ERT), which is administered every two weeks. Since the initiation in 2013, we have run multiple Elfabrio studies, which include Phase 2, Phase 3, and expanded access with no gaps over the past ten years.

The second approval came in October 2023 for Pompe disease. Pombiliti (cipaglucosidase alfa-atga) and Opfolda (miglustat) are a combination therapy which consists of an ERT infusion and an oral chaperone every two weeks.

These combination therapy studies started in 2016 and have been running with patients enrolled since the start. We enrolled over twenty patients across both disease groups whose data contributed to these FDA approvals. The personal sense of pride that is felt knowing that our hard work directly contributed to new medications being approved by the FDA to treat these rare genetic diseases is hard to describe. We thank all of our patients who have been with us for years enrolled in these studies. It is because of you that we get to be a part of these major events that provide options for treatment for patients whom are affected by these diseases.

As we move through 2024, we plan to attend many patient conferences to continue our outreach to help positively impact the rare disease community. We are excited for the currently running studies, old and new, as well as the upcoming studies not yet open. Although we do not expect any FDA approvals for studies in which we have participated in this next year, we are seeing an increase in gene therapy studies coming down the pipeline. Gene therapy offers a level of excitement all of its own, given the potential impact this type of treatment will have for our patients. We look forward to continuing to be able to contribute to the advancement of new therapies for Lysosomal disorders through clinical trials research.

Revolutionizing Kidney Health in Patients with Fabry Disease: Unraveling Novel Urine Biomarkers for Early Detection of Nephropathy

Andrew Friedman and Margarita Ivanova, PhD

Nephropathy, the deterioration of kidney function, significantly contributes to morbidity and mortality in individuals with FD. Standard laboratory tests used to assess kidney function may lack sensitivity, potentially delaying diagnosis and treatment. Furthermore, currently, available biomarkers for FD diagnosis are not associated with kidney function status, underscoring the need for accurate detection of kidney involvement to develop effective therapies and prevent late, irreversible complications in FD patients. Timely diagnosis and monitoring of kidney function in FD patients are crucial for effective management and the prevention of severe renal complications.

Traditional laboratory tests used to assess kidney function, such as serum creatinine and estimated glomerular filtration rate (eGFR), are not sensitive enough to detect early renal involvement in FD. At an early stage, clinical laboratory signs of kidney involvement, such as a decline in renal function, may be absent. However, the accumulation of Gb3 and Lyso-Gb3 can lead to inflammation and progressive podocyte loss in the kidneys. Podocyte loss is an irreversible event that impairs the glomerular filtration barrier, resulting in decreased kidney function. Inflammatory factors arising from kidney injury can serve as potential diagnostic and therapeutic biomarkers, offering valuable insights beyond current laboratory tests.

There is a growing interest in the exploration of urinary biomarkers as valuable tools for both the diagnosis and monitoring of nephropathy in FD. Urinary biomarkers hold promise as non-invasive tools in providing insights into the FD-related kidney disease. These biomarkers may include specific proteins, cellular elements, or metabolites that are excreted in urine and can be quantified to assess renal health. They offer several advantages, including non-invasive sample collection, potential early detection of renal involvement, and the ability to track disease progression over time. Gb3, the precursor molecule of Lyso-Gb3, accumulates in various tissues and organs of FD patients. While Lyso-Gb3 is a breakdown product of Gb3, the measurement of Gb3 itself can provide insights into the extent of glycolipid accumulation. In Fabry nephropathy, the kidneys are one of the primary sites of Gb3 accumulation. Quantifying urinary Gb3 levels can help assess renal involvement and guide the management of kidney-related complications. Gb3 measurements in urine can complement the assessment of Lyso-Gb3 levels, offering a more comprehensive view of glycolipid storage in the body.

While the primary pathological hallmark of FD is sphingolipid deposition, recent research has shown downstream events play a major role in disease progression and severity, that immune-based biomarkers in urine can provide valuable insights to further the understanding of the disease process. FD involves chronic inflammation, and the accumulation of Gb3 and its derivatives can trigger an inflammatory response in affected tissues, contributing to organ damage, including renal and cardiovascular complications. Excessively stored glycosphingolipids in cells can activate immune cells, leading to the release of pro-inflammatory cytokines. These cytokines play a role in initiating and sustaining the inflammatory response.

Examples of Immune-Based Urinary Biomarkers

Cytokines: Pro-inflammatory cytokines and tumor necrosis factor-alpha (TNF-α) may be elevated in the urine of FD patients, indicating ongoing inflammation.

Chemokines: Chemokines like monocyte chemoattractant protein-1 (MCP-1) are involved in attracting immune cells to sites of inflammation. Elevated urinary levels of MCP-1 can signify immune cell recruitment in response to glycosphingolipid accumulation.

Cellular Markers: The presence of immune cells, such as macrophages, in urinary sediment or the detection of specific immune cell-derived proteins can also serve as biomarkers of immune system activation.

Monitoring immune-based biomarkers in urine can provide valuable information for disease management in FD. These biomarkers may help assess the severity of inflammation and guide treatment decisions, including the timing and effectiveness of therapies such as enzyme replacement therapy (ERT). Tracking changes in immune-based biomarkers over time can aid in understanding disease progression and tailoring therapeutic approaches.

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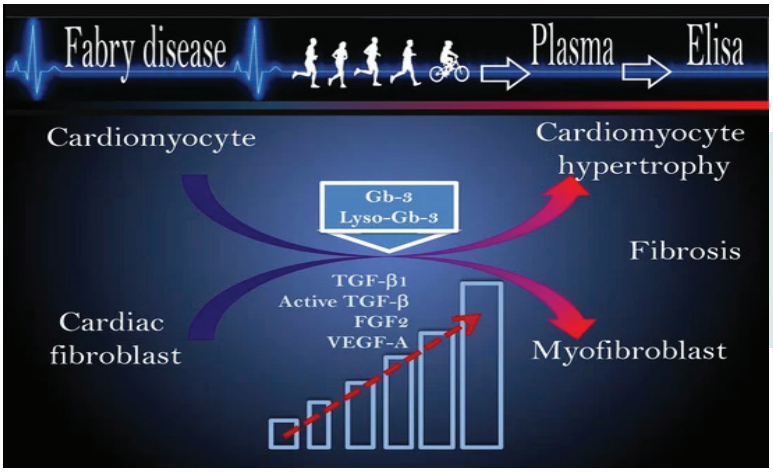
TGF-β1 and VEGF-A as Key Molecules for Advancing Cardiac Diagnostics in Fabry Disease



Discovering biomarkers like circulated TGF-β1 and VEGF-A brings us closer to better understanding and treating Fabry disease-associated cardiomyopathy.

Margarita Ivanova, PhD

Fabry disease (FD) is a Lysosomal disorder that occurs due to α-galactosidase A deficiency, causing the accumulation of globotriaosylceramide (Gb3) and its metabolite globotriaosylsphingosine (Lyso-Gb3). While FD occurs in a spectrum of manifestations, the most common symptoms of FD include cardiovascular complications and hypertrophic cardiomyopathy (HCM). Cardiovascular complications contribute substantially to morbidity in FD and are the leading cause of premature death in male and female patients.

Clinical diagnostic tools such as echocardiogram and cardiac MRI are used to evaluate cardiac involvement, but due to variations in hypertrophic cardiomyopathy and myocardial fibrosis patterns in patients with FD, it is essential to identify biomarkers that can predict early cardiac outcomes.

In our center, we studied whether levels of circulated bloodstream growth factors, such as TGF-β1 and VEGF-A, could be used to diagnose and monitor cardiac damage progression in patients with Fabry disease. This research has the potential to improve the accuracy and efficiency of diagnosing and treating Fabry disease-associated cardiomyopathy, ultimately leading to improved outcomes for patients.

We found that the elevated TGF-β1 correlates with HCM and myocardial fibrosis in male and female FD patients, indicating its potential biomarker for diagnosis of an early stage of cardiac fibrosis, even before hypertrophy is detected. Moreover, the elevation of TGF-β1 and active-TGF-β1 associated with Lyso-Gb3 elevation provides evidence of a chronic inflammatory state and the activation of fibrosis in FD patients [1].

Angiogenesis biomarker VEGF-A correlates with plasma Lyso-Gb3 and is associated with hypertrophic cardiomyopathy in FD patients. Thus, serum TGF-β1 and VEGF are predictive biomarkers for adverse cardiovascular events in FD.

Gender differences in the secretion of TGF-β1, VEGF, and FGF2 can explain patterns of cardiac involvement in male vs. female FD patients, with fibrosis occurring early in the course in females.

Facts about VEGF and TGF-β

The transforming growth factor-β (TGFβ) isoforms are upregulated and activated in myocardial diseases and have an important role in cardiac repair and remodeling, regulating the phenotype and function of cardiomyocytes, fibroblasts, immune cells, and vascular cells [2]. The vascular endothelial growth factor (VEGF), a homodimeric vasoactive glycoprotein, is the key mediator of angiogenesis. Angiogenesis, the formation of new blood vessels, is responsible for a wide variety of physio/pathological processes, including cardiovascular diseases (CVD). Cardiomyocytes (CM), the main cell type present in the heart, are the source and target of VEGF-A [3].

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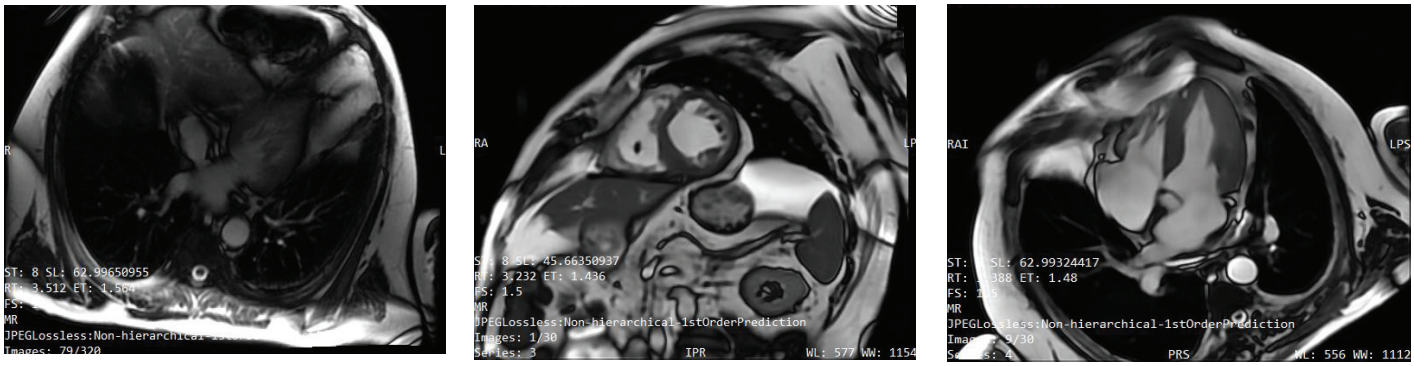
Biomarkers for Detection and Monitoring of Cardiac Damage in Fabry Disease

These biomarkers provide the objective tools to diagnose, assess disease severity, monitor progression, and guide therapeutic interventions.



Cardiac MRI | Imaging techniques help assess cardiac involvement and structural abnormalities such as LVH, left ventricular wall thickening, and myocardial fibrosis

Ozlem Goker-Alpan, MD

Fabry disease (FD) is a Lysosomal disorder resulting from a deficiency in α-galactosidase A, leading to the accumulation of globotriaosylceramide (Gb3) and its metabolite globotriaosylsphingosine (Lyso-Gb3).

While FD manifests in various ways, its most common symptoms include cardiovascular complications and hypertrophic cardiomyopathy (HCM). These cardiovascular issues significantly contribute to morbidity and, unfortunately, serve as the primary cause of premature death in both male and female FD patients.

Timely diagnosis and effective management of Fabry disease cardiomyopathy are critical for improving patient outcomes. Clinical biomarkers play a pivotal role in this regard, offering valuable insights into the cardiac status of affected individuals. These biomarkers provide the objective tools to diagnose, assess disease severity, monitor progression, and guide therapeutic interventions.

Biomarkers play a crucial role in the diagnosis and monitoring cardiomyopathy in Fabry disease. Early detection of the disease, assessment of cardiac involvement, and tracking disease progression are essential for effective management and improving patient outcomes.

There are clinical tools, such as echocardiograms and cardiac MRI scans, that are employed to assess cardiac involvement. However, the variations in hypertrophic

cardiomyopathy and myocardial fibrosis patterns among FD patients highlight the need for biomarkers that can predict early cardiac outcomes.

We have recently undertaken a study to explore the potential of immune markers, particularly TGF-β1, known as the master regulator of fibrosis, and VEGF-A, a key mediator of angiogenesis, in evaluating cardiac manifestations in Fabry disease (FD).

Our current research at the Lysosomal Disease Treatment and Research Center (LDRTC) has uncovered that heightened levels of TGF-β1 are associated with the initial stages of cardiomyopathy (HCM) as well as myocardial fibrosis in FD patients across genders.

This suggests that TGF-β1 could serve as an early biomarker for cardiac fibrosis, detectable even before the onset of hypertrophic changes. Additionally, the concurrent elevation of TGF-β1 and its active form alongside increased Lyso-Gb3 levels points to a sustained inflammatory response and the initiation of fibrosis in FD patients.

This inflammatory state is further characterized by the dysregulation of inflammatory cytokines, which contribute to the pathogenesis and progression of cardiac involvement in FD, marking a potential therapeutic target for early intervention [1].

Clinical Laboratory Biomarkers for Monitoring Patients with Fabry Disease Cardiomyopathy

Troponins (cTnI and cTnT)

- Cardiac troponins I (cTnI) and T (cTnT) are sensitive markers of myocardial injury. Elevated levels may indicate myocardial damage in Fabry cardiomyopathy.
- These biomarkers are valuable for monitoring cardiac events and responses to treatment.

Natriuretic Peptides (BNP and NT-proBNP)

- Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) reflect cardiac stress and are elevated in heart failure.
- Serial measurements can track disease progression and therapeutic efficacy.

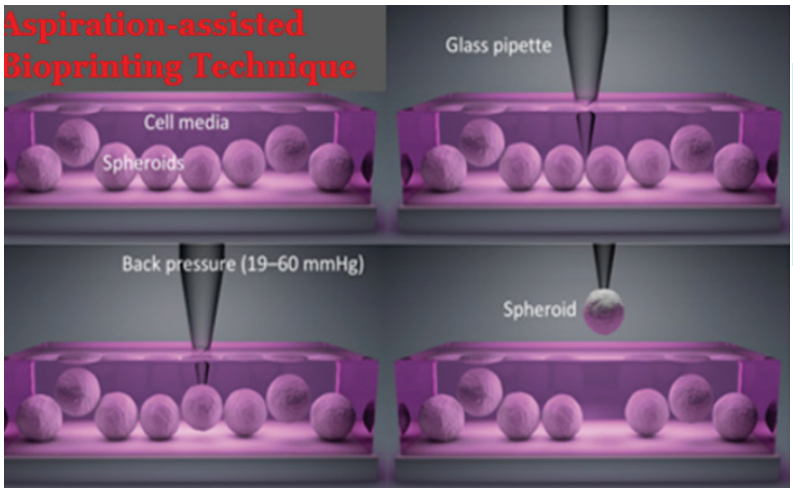
Electrocardiography (ECG) and Holter Monitoring

- Regular ECG and Holter monitoring assist in identifying arrhythmias and conduction abnormalities.
- Monitoring QT intervals is essential due to the risk of life-threatening arrhythmias.

Ejection Fraction (EF) and Strain Imaging

- Echocardiographic assessment of EF and strain imaging help quantify cardiac function and detect changes over time.

The First 3D Bioprinted *In-Vitro* Bone Model for Gaucher Disease



- 3D bone model has the potential to uncover the bone pathophysiology involved in GD
- A 3D model of bones can be used to evaluate the efficacy of different drugs

Figure: Aspiration-assisted Bioprinting Technique is a novel method for precise positioning of tissue spheroids in both scaffold-free and scaffold-based manners. Spheroids can be picked and lifted into the air by aspiration forces and then printed at remarkable placement precision.

- The first 3D bioprinted bone GD model, which is composed of osteoblast and osteoclast cells.
- Bioprinting of spheroids enabled the formation of constructs with native-like cell density and phenotypic relevance to skeletal abnormalities associated with GD.
- Our findings demonstrate that the in-vitro 3D bone model for GD can be used as a disease platform to study physiologically and phenotypically relevant symptoms for GD, enabling the development of novel therapeutics.

Margarita Ivanova, PhD

Gaucher disease (GD) is the most prevalent Lysosomal disorder caused by mutations in the GBA1 gene. This leads to a deficiency of the Lysosomal enzyme glucocerebrosidase and, as a result, the accumulation of glycosphingolipids in cells.

GD primarily affects monocyte lineage cells, including macrophages, which play essential roles in the immune system and are involved in osteoclast differentiation and osteoclast–osteoblast communication during bone development and remodeling. 80% to 95% of patients with GD, including asymptomatic ones, present with varying forms of bone involvement, such as structural changes, severe bone pain, and osteoporosis.Alteration of bone remodeling in GD causes various structural bone pathologies such as Erlenmeyer flask deformity, bone modeling abnormality, osteonecrosis, lytic lesions, and early osteoporosis. However, our understanding of the cellular aspects involved in abnormal bone remodeling is still incomplete.

The translational research group from our center collaborated with Dr. Ozbolat from Penn State University to develop the first 3D human model of GD using aspiration-assisted freeform bioprinting. This technology provides a platform device for decoding the cellular basis of developmental bone abnormalities in GD.

The techniques include the formation of spheroids from co-cultured human bone marrow-derived mesenchymal stem cells and peripheral blood mononuclear cells derived from GD patients, followed by differentiation into osteoblast and osteoclast lineages.

Co-differentiated spheroids were then 3D bioprinted into rectangular tissue patches that mimic bone tissue.

The results revealed positive alkaline phosphatase (ALP) and tartrate-resistant ALP activities, with multi-nucleated cells demonstrating the model's efficacy, corroborating with gene expression studies. There were no significant changes in differentiation to osteogenic cells but pronounced morphological deformities in spheroid formation, more evident in the 'severe' cohort.

Overall, the presented GD model has the potential to be adapted to personalized medicine not only for understanding the GD pathophysiology but also for personalized drug screening and development.

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Deciphering Sanfilippo Syndrome: Insights and Prospects for Promising Adjunct Therapies

Study aims

This study aims to establish baseline trends for each biomarker and track changes over time.

After collecting and analyzing this initial data, a follow-up treatment study will be initiated, administering Ambroxol to enrolled patients.

- The monitored biomarkers include serum heparan sulfate, urinary glycosaminoglycans (GAGs), and serum neurofilament light chain (NfL), which is a promising biomarker for tracking neurological symptom progression.

Arooj Agha

Mucopolysaccharidosis (MPS) Type III, also known as Sanfilippo syndrome, is a rare autosomal recessive genetic disorder. It is characterized by the body's inability to effectively break down a specific type of carbohydrate called heparan sulfate. This disorder is part of a larger group of Lysosomal disorders. Lysosomes are membrane-bound organelles containing enzymes responsible for breaking down complex molecules, including carbohydrates like heparan sulfate. Sanfilippo syndrome has several subtypes, most are associated with a deficiency in a specific lysosomal enzyme, and one type (Type C) is a tranferase deficiency, but all lead to the accumulation of substrate within lysosomes. In some cases, patients may have residual enzyme activity, but it is insufficient to prevent symptoms of the disorder.

The most severe subtype, Type A (MPS IIIA), is caused by a deficiency in the enzyme sulfamidase or heparan N-sulfatase. Patients with Type A experience rapid symptom progression, including developmental delays, progressive intellectual disabilities, hyperactivity, speech impairment, and coarse facial features. Type B (MPS IIIB) is characterized by a deficiency in the enzyme α-N-acetylglucosaminidase, and patients exhibit similar symptoms to Type A, such as intellectual disability, developmental delays, and speech problems. Type C (MPS IIIC) involves a deficiency in the enzyme heparan acetyl CoA: α-glucosaminide N-acetyltransferase, and symptoms progress more slowly compared to Types A and B. Patients may experience developmental delays and behavioral issues like hyperactivity. The rarest subtype, Type D, results from insufficient N-acetylglucosamine 6-sulfatase production and activity, progressing faster than Type C but similar to Types A and B. Since MPS III is a neurodegenerative disease, neuropathic manifestations are expected in each subtype.

The "Natural History Study of Patients with Sanfilippo Disease(s) (MPS3)" aims to collect unique biomarker data for all types of the disease over a 6-month period, with at least three specimen collection time points. The monitored biomarkers include serum heparan sulfate, urinary glycosaminoglycans (GAGs), and serum neurofilament light chain (NfL), which is a promising biomarker for tracking neurological symptom progression. This study aims to establish baseline trends for each biomarker and track changes over time. After collecting and analyzing this initial data, a follow-up treatment study will be initiated, administering Ambroxol to enrolled patients. The same biomarkers will be collected during the treatment phase for consistency and to monitor biomarker trends and changes.

References | NCT05705674

Decoding Bone Pathology in Pediatric Gaucher Disease Through Exploration of Immune Biomarkers and Growth Factors

Study aims

Evaluate secreted biomarkers and growth factors in pediatric patients with GD, with emphasis on bone involvement.

- Primary study objectives | Assessment of blood-based biomarkers (bone-related and inflammatory biomarkers) and the severity of bone involvement in pediatric GD patients.
- Secondary study objectives | Analyze the association between growth factors and Gb1, Lyso-Gb1, chitotriosidase CCL18 activation, and clinical parameters in pediatric patients with GD.

Heather Goodwin

Gaucher disease (GD) is a rare, inherited metabolic disorder that affects approximately 1 in every 20,000 live births. Individuals with GD lack the enzyme necessary for metabolizing glucosylceramide, a glycosphingolipid, resulting in its accumulation in various tissues, including the spleen, liver, and bone marrow.

Bone disease associated with GD results from a complex set of accumulated events. These include abnormal bone development presenting as a vertebral remodeling defect and abnormalities in the growth process of long bones.

A hallmark of GD on radiological imaging is the Erlenmeyer flask deformity (1, 2). Bone destruction can occur due to osteonecrosis, and cystic/lytic lesions may be observed with or without avascular necrosis. Reduced bone mineral density can lead to pathologic fractures, which can start in teenage years and result in early osteoporosis in both female and male patients with GD.

Pain is one of GD's prime and debilitating symptoms, often associated with other structural skeletal involvement (3).

Normal bone and skeletal growth is influenced by both environmental and genetic factors. During childhood, rapid bone growth occurs as bone tissue is added to the epiphyseal plate, which lengthens the bones. Bones are thickened as bone tissue is added to the surface, increasing the diameter. The process of bone remodeling and repair continues after birth and into adulthood. The underlying mechanisms of regulation and complications of bone development in pediatric GD patients, however, are not yet fully understood. Abnormalities of skeletal growth and bone turnover could be a result of abnormal regulation by growth factors. Given that chronic inflammation leads to alterations in the function and differentiation of osteoclasts and osteoblasts, which participate in bone growth and remodeling, and that a cascade of immune-mediated inflammatory reactions is set off by substrate deposition in GD, we hypothesize that these inflammatory events interfere with the normal process of bone growth, mineralization, and remodeling in pediatric GD patients.

To study this, we are recruiting ten GD patients aged five to twenty-one years with and without bone involvement

Inclusion Criteria for the Study

Subject eligibility is determined according to the following criteria prior to entry into the study:

- The parent or legal guardian and the participant who is eligible to provide assent are able and willing to provide informed consent and assent when applicable.
- The participant is 5-21 years of age at the initial visit.
- The participant has a confirmed diagnosis of GD Type 1 or Type 3 (biochemically and/or genetically).
- In the investigator's opinion, the subject is capable of understanding and complying with protocol requirements.

to participate for a period of twelve months. Plasma samples from healthy children in the same age range will be used as controls. Skeletal involvement will be assessed using DEXA scans, X-rays, and patient-reported outcome surveys; biochemical data will be obtained from blood and urine samples. Combined, this data will allow us to evaluate the relationship of GD-mediated inflammation and growth factor dysregulation with bone involvement seen in pediatric GD patients.

Further, we aim to identify blood-based biomarkers correlated with bone involvement in GD patients to assess the correlation between levels of cytokines and other inflammatory markers with the severity of bone involvement, and to analyze the association of growth factors and Lyso-Gb1 (a biomarker of GD) with markers of macrophage activation and clinical parameters in pediatric GD patients.

This clinical study (ClinicalTrials.gov ID: NCT 06116071) commenced in December 2023 and will be actively enrolling patients until early 2025.

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Case Report

Gaucher Disease and Immune Thrombocytopenic Purpura (ITP)

Gaucher disease (GD) is an inherited disorder that results from the deficiency of an enzyme responsible for breaking down a fatty substance within the organelles of cells, called lysosomes. Low levels of an enzyme (glucocerebrosidase) allow lipid-laden cells, called Gaucher cells, to build up in tissues like the spleen, liver, and bone marrow, resulting in inflammation, immune dysfunction, and progressive organ involvement.

There are three clinical types of GD. Type 1 is the most common type in the US and does not affect the brain primarily. The symptoms are broad and can include spleen and liver enlargement, thrombocytopenia, bone pain, fatigue, swollen stomach, easy bruising, tiredness, easily broken bones, and nosebleeds. Type 2 affects infants and predominantly involves neurological function with progressive brainstem involvement. Type 3 has more severe systemic involvement than Type 1 and has a spectrum of neurological problems.

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A 17-year-old female with Neuropathic Gaucher disease Type 3 (nGD3) presented with a tennis ball-sized ecchymosis to the left lower leg without trauma. She had a second smaller bruise on the same extremity. She also complained of recent daily nose bleeds in the morning that would often last for forty minutes. She had heavy menses, which had not changed from baseline. Her recent medical history includes hospital admission for pneumonia secondary to COVID-19 in August 2023 and abdominal pain secondary to a ruptured ovarian cyst in September 2023. She tested positive for parvovirus in November 2023. She is currently receiving enzyme replacement therapy (ERT) infusions every other week and an investigational oral SRT daily for her Gaucher disease.

On examination, the patient looked pale and tired. No petechiae or purpura were noted. Spleen and liver were enlarged. The spleen was palpable approximately 3-5 cm below the costal margin, and the liver edge was palpable. Neurologically, the patient was at baseline.

Labs was ordered, including CBC w/diff and coagulation panel. From this sample, labs reviewed platelets to be 17k (ref.140-400K), Hgb 9.0 (ref. 11.7-15.5g/dL), and Hct: 28.9 (ref. 35.0- 45%). aPTT/PT were WNL and elevated D-dimer of 0.56 (ref. <0.5mcg/mL). Previous platelet level on June 9, 2023, was 139K, and 243K on January 1, 2022, both with normal Hgb and Hct. A confirmatory repeated CBC showed platelets: 22K, Hgb: 9.2, and WBC: 4.2 (ref. 4.5-13 thousand/uL). Patient was recommended to be evaluated by Children's Hospital. There, a CT of the abdomen was done, showing an increase in spleen size of 17.4 cm from 15 cm in August 2023.

On November 17, 2023, there was a workup for thrombocytopenia/pancytopenia, including antiplatelet antibodies, viral titers, CMP 20, reticulocyte count, and haptoglobin. On this specimen, the platelet count was 18K, Hgb was 8.0, MCV 25.7 (ref. 34-46) WBC was 4.2 (ref. 4.5-13.0 thousand/uL). Smear showed nucleated RBC with microcytosis, poikilocytosis, ovalocytes, and hypochromasia. Total iron 13 (ref: 27-164 mcg/dL), TIBC normal. Antiplatelet antibodies (qualitative was positive for IgG and IgM). Patient was referred to pediatric hematology for evaluation and treatment. The patient was diagnosed with Immune Thrombocytopenia (ITP).

For treatment, she received a high dose of IVIG. After the 1st dose of IVIG, follow-up labs showed a platelet count of 87K, WBC count of 5.1, and Hgb of 9.5gm/dl. Reticulocyte count of 4.0 (0.5-1.5). Patient responded well with IVIG.

What is ITP?

Immune Thrombocytopenia (ITP) is a type of platelet disorder. In ITP, the blood does not clot as it should due to low platelet count, which can lead to easy bruising and bleeding (5). ITP can be classified as acute, persistent, or chronic. In acute ITP, it often lasts less than three months (6). It mainly occurs in children between ages of two to six, and it is a more common type of ITP. In persistent ITP, the disease lasts for three to twelve months and has not undergone spontaneous correction or remission on its own. Lastly, chronic ITP lasts twelve months or more and mostly affects adults. Chronic ITP affects women three times more often than it affects men (6).

ITP is caused by the dysfunction of the immune system. Typically, the immune system helps the body fight off infections and diseases. In people with ITP, the immune system produces antiplatelet antibodies that attach themselves to the surface of blood platelets as if the platelets were "foreign" or invading bacteria or viruses (6). As the affected platelets circulate in the bloodstream, they are recognized as abnormal by the spleen and removed from the blood. The more platelets are removed by the spleen, the level of platelets in the blood drops (6).

In most cases, the cause of ITP is unknown, however, but it may be preceded by an infection that can trigger the immune system to start destroying the body's own platelets (5). Other possible causes include antibiotics, antiviral medicines, or medicines to treat inflammation (5). Vaccines, such as the measles-mumps-rubella (MMR), which rarely can raise the risk of ITP, especially in children (5). In addition, it is rarely reported with COVID-19 vaccines (6).

ITP in children often resolves spontaneously within three months. A minority of affected children go on to have chronic ITP. Management of non-life ITP includes activity restrictions that would carry a risk of bleeding from traumatic injury. Children with platelet count <30K/microL should avoid contact sports. Avoid taking antiplatelet and anticoagulant medication, other nonsteroidal anti-inflammatory drugs (NSAIDs), and anticoagulants should be avoided if the patient's platelet is <20K/microL. All patients should have ongoing monitoring for development of bleeding symptoms and regular measurements of platelet count, the frequency of which depends on the degree of thrombocytopenia. Controlling of menes is for postmenarcheal female patients. Hormonal therapy may be warranted to control severe menorrhagia, and antifibrinolytics may also be considered. Controlling nosebleeds is another way to manage ITP. This includes keeping the nasal mucosa moist (humidifier or saline nose spray) and discouraging nose picking. Antifibrinolytics may be considered if bleeding is severe.

If life-threatening hemorrhage occurs (e.g., intracranial hemorrhage, major trauma, gastrointestinal bleeding with hemodynamic instability, pulmonary hemorrhage with cardiopulmonary compromise), immediate intervention is required. It is recommended for combination of all of the following therapies.

1. Platelet infusions: A bolus dose of 10 to 30mL/kg, followed by continuous infusion. Patients with ITP generally require larger-than-normal doses of platelets in transfusion due to rapid destruction.
2. Methylprednisolone: 30 mg/kg per day up to 1g IV for three to four days
3. IVIG: given 1g/kg per day for one to three days
4. Thrombopoietin receptor agonist (TPO-RA): e.g., Romiplostim SQ

Incidence of ITP in GD

The rate of incidence of ITP in GD is not fully recorded. In fact, an international survey showed that only 20% of hematologists included GD1 in the differential diagnosis of a patient with anemia, thrombocytopenia, hepatomegaly, splenomegaly, and bone pain (1). This is interesting considering that at the time of diagnosis of Gaucher, patients present with several hematological signs and symptoms, including splenomegaly (86%), anemia (64%), thrombocytopenia (56%), bleeding history, and monoclonal gammopathy of undetermined significance (2). This is why physical exams and patient interviews can help providers with the differential to include GD. Important clues to diagnose thrombocytopenia can be obtained during systematic physical examination. First, general physical examination by inspection, palpation, and auscultation can inform one on the general health of the patient, e.g., the presence of comorbidities. Second, examination of the skeletal system can shed light on potential causes of thrombocytopenia. For instance, if a patient has splenomegaly, GD should be included in the differential (4).

ITP Unrelated to GD

In the cases of ITP occurring unrelated to GD, the annual incidence of ITP in the US was 6.1 per 100,000 persons, higher among females versus males (6.7 vs. 5.5), and highest among children aged 0-4 years (8.1) and adults aged ≥65 years (13.7) (3).

Conclusion

Although the patient's lyso-GL1 level was elevated, it was trending down at the time of ITP diagnosis. It is hard to differentiate whether ITP was caused by immune dysfunction alone or if it was correlated to GD. In conclusion, more research needs to be done in order to fully understand the connection between ITP and Gaucher disease.

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Comprehensive CME Series on Lysosomal Disorders

The 2023 Lysosomal Diseases CME Series presents three lectures addressing Lysosomal disorders in a systems approach. Ozlem Goker-Alpan hosted experts to discuss different disorders through an organ.

Dr. Walla Al-Hertani opens the series by discussing building and maintaining a multidisciplinary team for Lysosomal disorders. Dr. Al-Hertani outlines challenges in the current care models for Lysosomal disorders and how precision medicine fits in.

The following lecture overviews managing cardiomyopathies in Lysosomal disorders.

John Jefferies, MD, describes the cardiologist's role in the team approach to care and lists best practices to manage and treat cardiomyopathies in Lysosomal disorders.

Dr. Goker-Alpan closes the last webinar of the CME Series covering the pulmonary manifestations of Lysosomal diseases with John Bach, MD. He speaks about assessing, monitoring, and managing respiratory involvement in Lysosomal disorders and explains how to prevent respiratory failure and avoid resorting to tracheostomies.

Highlights of CME Series 2023

Modules

- Building and Maintaining a Multidisciplinary Team for Lysosomal Disorders
- Managing Cardiomyopathies in Lysosomal Disorders
- Respiratory Involvement in Lysosomal Disorders

Predicting Nephropathy Progression in Fabry Disease

Ozlem Goker-Alpan, MD

At LDRTC, the ongoing research is focused on identifying additional immune-based biomarkers and understanding their roles in FD. In addition, we are investigating the relationships between immune activation, glycosphingolipid accumulation, and clinical outcomes.

In this pilot study, urinary biomarkers related to inflammation and renal injury while compared to standard laboratory measures of kidney function, are evaluated. The study will involve fifty subjects aged eighteen to eighty, divided into four cohorts:

- Treated FD patients without clinical evidence of nephropathy.
- Treated FD patients with clinical evidence of nephropathy.
- Untreated FD patients (Naïve).
- Non-FD age-matched controls without clinical evidence of nephropathy (healthy controls).

The study will span twenty-four months, during which potential nephropathy-related biomarkers will be measured in FD patients and compared to those in healthy controls. Patients will be monitored for twelve months, with urine collection at 6-month intervals. The study commenced in September 2023 and is actively enrolling patients until early 2025.

In summary, immune-based biomarkers in urine offer a promising avenue for understanding the inflammatory aspects of Fabry disease. By quantifying these biomarkers, researchers and clinicians can gain insight into the immune response, inflammation severity, and potentially tailored treatment strategies to address both the metabolic and immune components of this complex genetic disorder.

References | NCT06065605

Empowering Families: LDRTC's Inaugural Gaucher Educational Meeting for Affected Families and Children

During the meeting, we launched "Our Journey with Gaucher Disease," a book published by LDRTC with stories written by patients and their families impacted by Gaucher disease.

LDRTC hosted its first Gaucher Disease Patient and Family Education Meeting on May 5, 2023, in Middleburg, VA.

The guest speaker, Ravi Kamath, MD, PhD, educated the audience about the evaluation and management of the skeletal manifestations of Gaucher disease in children and young adults.

Ozlem Goker-Alpan, MD, Founder and CMO of the Lysosomal & Rare Disorders Research & Treatment Center, closed the event by thanking the attendees and reinforcing LDRTC's dedication to the rare community. "We are committed to advancing the understanding and treatment of this disease and are delighted to offer this educational meeting."

"LDRTC is proud to provide this opportunity for patients and their families to learn more about Gaucher disease, a rare and debilitating genetic disorder," said the Founder and CMO of the Lysosomal & Rare Disorders Research & Treatment Center.

Ozlem Goker-Alpan, MD

GRID Symposium 2023 Highlights

From Asymptomatic to Severe, the Variability in Lysosomal Disorders: Integrating the Basics with Current Clinical Practices

The 2023 Genetic, Rare & Immune Disorders Symposium (GRIDS) took place from November 19th to 20th in Middleburg, Virginia.

LDRTC celebrated its 9th GRIDS by hosting over two hundred attendees and researchers, in person and virtually, from Brazil, Canada, Colombia, Egypt, Germany, India, Ireland, Israel, Italy, Japan, Mexico, Morocco, Nepal, Pakistan, Portugal, Russia, Spain, Turkey, the United States and the United Kingdom.

The keynote speaker, Dr. Konrad Sandhoff, opened the summit, sharing his journey as a chemist into the world of sphingolipids and sphingolipidoses. He also addressed the mechanisms and impact of secondary ganglioside and lipid deposition in Lysosomal disorders.

During the first day of the symposium, experts discussed basic mechanisms in Lysosomal disorders - phenotypic diversity and cell biology, biomarkers and other genetic approaches in LDs, current clinical challenges in Lysosomal disorders - newborn screening and LDs in the neonatal period, and the application of novel technologies in LDs - role of AI in Lysosomal disorders.

On the second day of the event, experts presented the next-generation therapies in LDs, including developing therapies for diseases caused by the deficiencies of Lysosomal sialidases, delivering CRISPR to the brain, and small molecule therapies for primary and secondary sphingolipidosis. The summit continues with lectures on current therapeutic challenges in Lysosomal disorders and who is the candidate for gene therapy, Intrathecal vs. Trojan Horse approach in treating neuropathic LDs, the timing of initiation of ERT, and disease outcomes for patients with MPS.

After the presentations, a group of LD experts went to LDRTC to participate in the GRIDS Clinic. After reviewing patient records and visiting with them, they advised patients with debilitating disorders. If you would like to watch the CME lectures from 2023 GRIDS, please visit https://www.gridssymposium.org/

AGENDA

BASIC MECHANISMS IN LYSOSOMAL DISORDERS: PHENOTYPIC DIVERSITY AND CELL BIOLOGY

- Activator Proteins as Determinants/Influencers of the Spectrum of LDs Phenotypes
- Cell Death Pathways and Danger Associated Molecular Patterns as Determinants of Phenotypes: A Comparison of Gaucher and Fabry Diseases
- Mechanisms and Impact of Secondary Ganglioside and Lipid Deposition in Lysosomal Disorders

BIOMARKERS AND OTHER GENETIC APPROACHES IN LDs

- Novel Diagnostic Techniques in Lysosomal Disorders Using Glycomic Profiling with Mass Spectrometry
- RNAs as Biomarkers in Lysosomal Disorders (LDs)
- Misfolding of Acid Sphingomyelinase, Associated with Niemann-Pick A/B, as a Risk Factor for the Development of Parkinson Disease

CURRENT CLINICAL CHALLENGES IN LYSOSOMAL DISORDERS: NEWBORN SCREENING AND LDs IN THE NEONATAL PERIOD

- Newborn Screening in Lysosomal Disorders from RUSP to Reality
- Use of Biochemical and Genetic Methods in Newborn Screening Programs
- Diversity and Equity in Newborn Screening Programs for Family Engagement and Access to Expert Care
- Current Guidelines for the Management of Asymptomatic Infants with Pompe Disease Diagnosed in Neonatal Period

THE APPLICATION OF NOVEL TECHNOLOGIES IN LDs: ROLE OF AI IN LYSOSOMAL DISORDERS BIG DATA TO ARTIFICIAL INTELLIGENCE AND CHALLENGES

- The Experience from the Spanish Registries for Predicting the Complications in Gaucher Disease
- Development of an Advanced Machine Learning Algorithm for Early Diagnosis of Gaucher Disease
- A New Approach to Identifying Patients with Fabry Disease Using a Machine Learning Algorithm

NEXT-GENERATION THERAPIES IN LDs

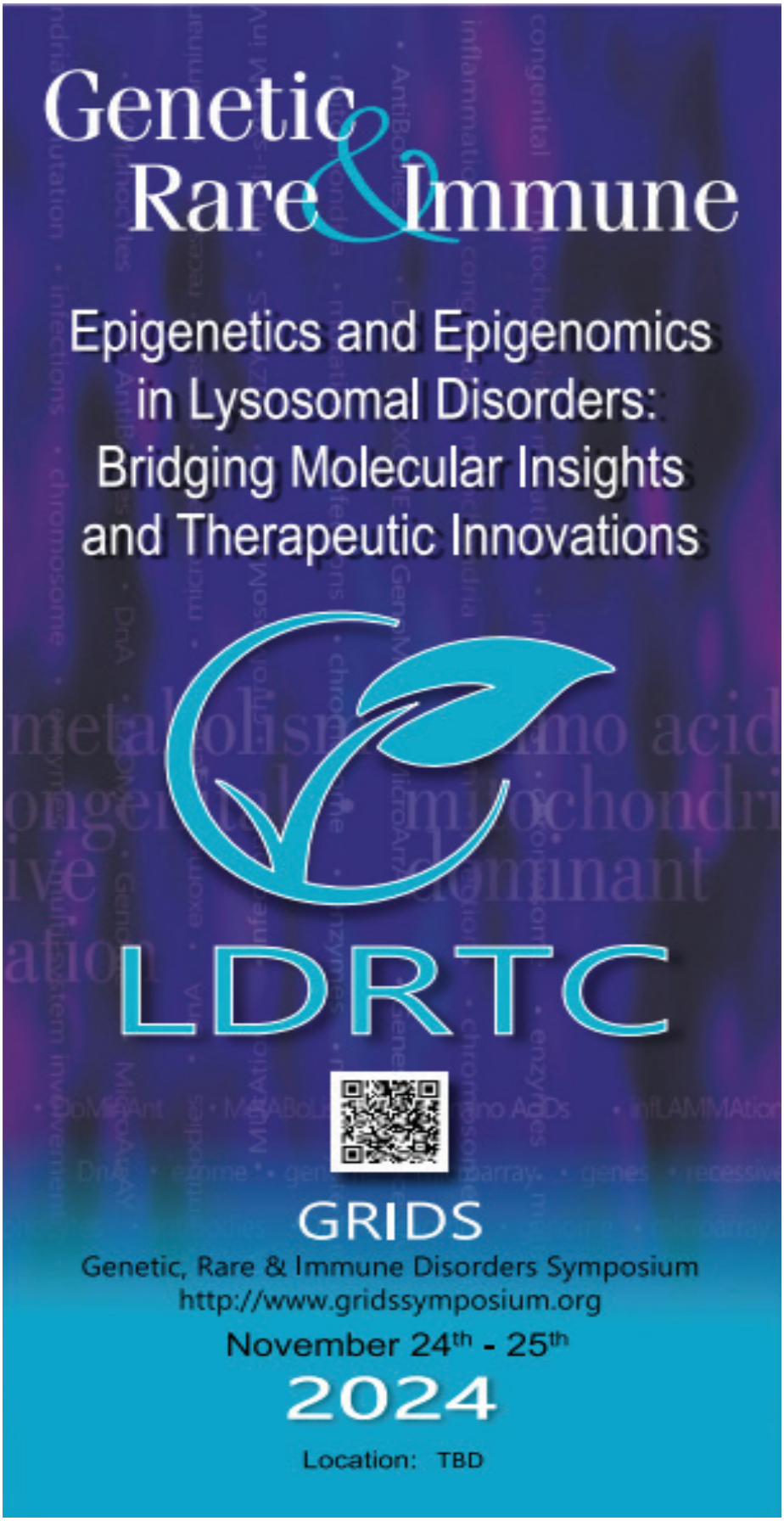
- Developing Therapies for Diseases Caused by the Deficiencies of Lysosomal Sialidases (Sialidosis, Galactosialidosis) and N-Acetyltransferases (Mucopolysaccharidosis IIIC)
- Delivering CRISPR to the Brain - A New Treatment Strategy for Mucopolysaccharidoses
- Small Molecule Therapies for Primary and Secondary Sphingolipidosis

CURRENT CHALLENGES IN LYSOSOMAL DISORDERS

- Who is the Candidate for Gene Therapy: Disease Severity and Phenotypes as Determinants of Therapeutic Efficacy
- Intrathecal Vs. Trojan Horse Approach in Treat Neuronopathis LDs
- The Timing of Initiation of ERT and Disease Outcomes for Patients with MPS
- Egyptian GD3 Patients: A Unique Cohort Typical and Atypical Presentations

GRID Symposium

Genetic & Rare Immune DISORDERS SYMPOSIUM (GRIDS)



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