

— 2026 — SCIENTIFIC SYMPOSIUM



**PiTT
HOPKINS**
RESEARCH
FOUNDATION

**ACCELERATING RESEARCH.
INSPIRING HOPE.
TRANSFORMING LIVES.**



JULY 10 - 11, 2026

RESEARCHER &
SCIENTIFIC SYMPOSIUM



VIRTUAL EVENT
EASTERN TIME (ET)



PITTHOPKINS.ORG



PHRF Mission Statement

The mission of the Pitt Hopkins Research Foundation (PHRF) is to support research dedicated to finding a treatment, and an eventual cure of Pitt Hopkins syndrome and other similar disorders. The PHRF is also dedicated to supporting the Pitt Hopkins community with resource recommendations, parental support and the latest medical information.

The Board of Directors of the Pitt Hopkins Research Foundation is comprised of individuals dedicated to advancing research and supporting families of children and adults with Pitt Hopkins Syndrome. The Board is actively engaged in fundraising efforts towards research, in providing parental support to families worldwide, and in offering communication and media representation for the Foundation.

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Friday, July 10th, 2026

Virtual conference via Zoom. All times are in Eastern Time (ET)

- 11:00 – 11:05 a.m. **Welcome**
Audrey Davidow Lapidus
President, Pitt Hopkins Research Foundation
- 11:05 – 11:25 a.m. **Microbiota Transplant Therapy for Pitt Hopkins**
James Adams, PhD – Autism Research Program, Arizona State University
Khemlal Nirmalkar, PhD – Biodesign Center for Health Through Microbiomes, Arizona State University
- 11:30 – 11:50 a.m. **Clinical Trial Update: RVL-001 for Pitt Hopkins**
Richard Novak, PhD
Co-founder and CEO, Unravel Biosciences
- 11:55 – 12:15 p.m. **Tcf4 in gut development; investigating underlying causes of gastro-intestinal problems in Pitt Hopkins syndrome**
Simone Mesman, PhD
Molecular Neuroscience lab, Swammerdam Institute of Life Sciences, Faculty of Science, University of Amsterdam
- 12:20 – 12:40 p.m. **Defining the Functions of Neurodevelopmental Disease-Associated Transcription Factor TCF4 in Activity-Dependent Gene Expression in Neurons**
Tõnis Timmusk, PhD
Department of Chemistry and Biotechnology
Tallinn University of Technology, Estonia
- 12:45 – 1:05 p.m. **Harnessing CRISPR Activation (CRISPRa) to Upregulate TCF4 Expression in Neural Cells from Pitt-Hopkins Syndrome Patients**
Gad Vatine, PhD
Physiology and Cell Biology Department and Regenerative Medicine and Stem Cell (RMSC) Research Center
Ben-Gurion University of the Negev
- 1:05 – 1:35 p.m. *Lunch Break*



- 1:35 – 1:55 p.m. **Exploring the Cell Biology and Cell Therapy Potential of PTHS**
Victor Li, PhD
Co-founder and CEO, Stemcellerant
- 2:00 – 2:20 p.m. **Beyond the Diagnosis: Natural History and Practical Management of Pitt Hopkins Syndrome**
Jessica Duis, MD, MS
Vice President, Clinical Development, Neurology at Epicrispr Biotechnologies
- 2:25 – 2:45 p.m. **Grann Pharmaceuticals & Pitt Hopkins Research Foundation: mRNA Lipid Nanoparticles for the Treatment of Pitt Hopkins Syndrome**
Thomas Temple
Founder and CEO, Grann Pharmaceuticals
- 2:50 – 3:10 p.m. **Mahzi Presentation**
Christina Theodore-Oklot, PhD — VP Clinical Outcomes Research, Mahzi Pharmaceuticals
Emily Radomile – Vice President, Program Management and Clinical Operations, Mahzi Therapeutics
Tom Brennan, PhD – Senior Vice President of Nonclinical Development, Mahzi Therapeutics
- 3:15 – 3:35 p.m. **De-repressing microRNA sites as a tunable strategy to restore TCF4 in Pitt-Hopkins syndrome**
Marwan Ghanem
Lippi Lab at Scripps Research
- 3:40 – 4:00 p.m. **Activating TCF4 expression with synthetic duplex RNAs**
David Corey, PhD
Rusty Kelley Professor of Medical Sciences
Department of Pharmacology and Biochemistry
UT Southwestern Medical Center
- 4:05 – 4:25 p.m. **Progress on AAV9-U7-snRNA-Mediated Promoter Modulation Gene Therapy for Pitt-Hopkins Syndrome**
Afrooz Rashnonejad, MSc, PhD
Assistant Professor & Principal Investigator,
Center for Gene Therapy
Abigail Wexner Research Institute at Nationwide Children's Hospital
- 4:25 – 4:30 p.m. *Closing Remarks*



Saturday, July 11th, 2026

Virtual conference via Zoom. All times are in Eastern Time (ET)

- 11:00 – 11:05 a.m. **Welcome**
Audrey Davidow Lapidus
President, Pitt Hopkins Research Foundation
- 11:05 – 11:25 a.m. **Modulation of IGF-1 Signaling for the Treatment of Pitt Hopkins Syndrome**
Rachel Groth, PhD
Head of External Innovation and Patient Advocacy,
Neuren Pharmaceuticals
- 11:30 – 11:50 a.m. **Activating TCF4 expression with synthetic duplex RNAs**
David Corey, PhD
Rusty Kelley Professor of Medical Sciences
Department of Pharmacology and Biochemistry
UT Southwestern Medical Center
- 11:55 – 12:15 p.m. **Microbiota Transplant Therapy for Pitt Hopkins**
James Adams, PhD – Autism Research Program, Arizona State University
Khemlal Nirmalkar, PhD – Biodesign Center for Health Through Microbiomes, Arizona State University
- 12:20 – 12:40 p.m. **Mahzi Presentation**
Christina Theodore-Oklota, PhD — VP Clinical Outcomes Research, Mahzi Pharmaceuticals
Emily Radomile – Vice President, Program Management and Clinical Operations, Mahzi Therapeutics
Tom Brennan, PhD – Senior Vice President of Nonclinical Development, Mahzi Therapeutics
- 12:45 – 1:05 p.m. **Exploring the Cell Biology and Cell Therapy Potential of PTHS**
Victor Li, PhD
Co-founder and CEO, Stemcellerant
- 1:05 – 1:35 p.m. *Lunch Break*



- 1:35 – 1:55 p.m. **Clinical Trial Update: RVL-001 for Pitt Hopkins**
Richard Novak, PhD
Co-founder and CEO, Unravel Biosciences
- 2:00 – 2:20 p.m. **Grann Pharmaceuticals & Pitt Hopkins Research Foundation:
mRNA Lipid Nanoparticles for the Treatment of Pitt Hopkins
Syndrome**
Thomas Temple
Founder and CEO, Grann Pharmaceuticals
- 2:25 – 2:45 p.m. **De-repressing microRNA sites as a tunable strategy to
restore TCF4 in Pitt-Hopkins syndrome**
Marwan Ghanem
Lippi Lab at Scripps Research
- 2:50 – 3:00 p.m. **Bi[o]hub: A Patient-Driven Partnership between
COMBINEDBrain and the Pitt Hopkins Research Foundation**
Julia Dominguez
Clinical/Translational Research Coordinator, COMBINEDBrain
- 3:05 – 3:25 p.m. **From Diagnosis to Daily Life: What Actually Helps in Pitt
Hopkins Syndrome**
Jessica Duis, MD, MS
Vice President, Clinical Development, Neurology at Epicrispr
Biotechnologies
- 3:25 – 3:30 p.m. *Closing Remarks*



Abstracts & Participant Biosketches



James Adams, PhD

James Adams is a Professor at Arizona State University in the Biodesign Center for Health Through Microbiomes. He has published over 180 papers, including over 70 on autism. He was the principal investigator on two clinical trials of microbiota transplant for autism.



Khemlal Nirmalkar, PhD

Khemlal Nirmalkar, Ph.D., is a Research Scientist in Dr. Rosa Krajmalnik-Brown's lab at the Biodesign Center for Health Through Microbiomes at Arizona State University. Working closely with Dr. Rosa Krajmalnik-Brown and Dr. James Adams, he studies the gut microbiome and mycobiome in autism, and Pitt-Hopkins syndrome. His research focuses on understanding microbial ecology and the roles of microbial genes and metabolites, particularly in response to Microbiota Transplant Therapy (MTT).

Title: *Microbiota Transplant Therapy for Pitt Hopkins*

Abstract: Most children and adults with PTHS have chronic constipation and related gastrointestinal symptoms that typically begin in childhood and can last for decades. These GI symptoms are associated with abnormal bacteria and yeast in their gut. We will summarize the results of the first clinical trial of Microbiota Transplant Therapy (MTT) for children with PTHS, and present preliminary results from the second clinical trial for children and adults with PTHS.



Richard Novak, PhD

Richard Novak is the founding CEO of Unravel Biosciences, Inc., which he spun out from the Wyss Institute at Harvard University to develop therapeutics for orphan diseases using a novel AI drug prediction and in vivo screening platform. Prior to Unravel Bio, he was a Lead Engineer at the Wyss Institute at Harvard University where he managed the Microengineering Team and led development of human Organ Chips, Organism-on-Chip screening platforms, and analytical and diagnostic instrumentation for accelerating therapeutics discovery and precision diagnostics. Richard received his PhD in Bioengineering from UC Berkeley/UC San Francisco where he developed microfluidic single cell analytical and diagnostic platforms for forensic, therapeutic, and

basic research applications. He is the founder of Future Scientist, a nonprofit that works with resource-poor communities to design sustainable solutions through their prototyping and

development hub in Panama. Richard also is a founder of Rhinostics Inc., a medical consumables company that has developed an automatable sample collection platform that accelerates and expands access to respiratory, blood, and genomic laboratory testing through integration with existing lab automation instruments. He is a Termeer Fellow and former DARPA Riser.

Title: *Clinical Trial Update: RVL-001 for Pitt Hopkins*

Abstract: Unravel Biosciences has initiated a proof-of-concept study to evaluate the safety and efficacy of RVL-001 (vorinostat oral suspension), an orally administered, once daily novel treatment for Pitt Hopkins syndrome (PTHS). The study, located in Medellin, Colombia, will dose 5 PTHS patients and consists of a placebo and two doses for each participant, with the order randomly assigned. Four patients have already been dosed with RVL-001. Vorinostat was identified as a potential therapeutic for PTHS through BioNAV™, Unravel Biosciences' proprietary drug discovery platform, ranking highly in predictive scoring across many of the 20 patients analyzed using their transcriptomes as well as analysis of transcriptomes from iPSC and other PTHS models. In a pre-clinical TCF4-deficient mouse model of PTHS by the Pitt Hopkins Research Foundation, vorinostat demonstrated improvements in both central nervous system (CNS) and systemic abnormalities. The proof-of-concept study is testing the hypothesis that vorinostat, identified by Unravel's BioNAV™ platform as a potential therapeutic for PTHS, is safe and potentially effective in the treatment of this condition.



Simone Mesman, PhD

Dr. Simone Mesman completed her PhD in Molecular Neuroscience at the University of Amsterdam (2016), where her research focused on the development of midbrain dopamine neurons — from early progenitor differentiation through to dopaminergic subtype specification. This work led to a growing interest in the transcription factor Tcf4, resulting in two publications on its role in brain development and midbrain dopaminergic neuron specification.

Following a period teaching Biology at the University of Amsterdam, Dr. Mesman joined the Molecular Neuroscience lab as Assistant Professor in 2018. Her current research centres on the role of Tcf4 in brain development, with a particular focus on oligodendrogenesis

and neuronal specification in the medulla oblongata. Next to this she recently started a research-line on Tcf4 in gut development. She collaborates with clinical and academic partners on Pitt-Hopkins syndrome and myelination, bringing a multidisciplinary perspective to understanding Tcf4 function across multiple aspects of brain development.

Title: *Tcf4 in gut development; investigating underlying causes of gastro-intestinal problems in Pitt Hopkins syndrome*

Abstract: Gastrointestinal (GI) complications are among the most prevalent and debilitating comorbidities in Pitt-Hopkins syndrome (PTHS), affecting up to 80% of patients in the form of severe bloating and chronic constipation. These symptoms profoundly impact the quality of life of both patients and their caregivers. Despite this high prevalence, the underlying aetiology of GI dysfunction in PTHS remains poorly understood, and current clinical management does not differ from that applied to the general population. A deeper mechanistic understanding of GI involvement in PTHS could therefore reveal patient-specific therapeutic targets, inform preventive strategies, and ultimately improve quality of life for those affected.

Here, we demonstrate that TCF4 is broadly expressed throughout the developing murine gut and the adult human gut, with expression localised specifically to endothelial cells of the gut lining and neuroendocrine cells within the gut epithelium. Transcriptomic analysis of the developing murine gut revealed significant dysregulation of genes associated with gut maturation and functioning upon partial or complete loss of Tcf4, indicating an important role

for this transcription factor in normal gut development. Histological examination of gut tissue from PTHS patients revealed disrupted epithelial architecture, including distorted crypt morphology. Furthermore, colonic tissue displayed granuloma formation — organised aggregates of activated macrophages and multinucleated giant cells — indicative of a heightened local immune response.

Taken together, our findings demonstrate that loss of TCF4 has a significant impact on gut development and point to dysregulated immune activation as a potential contributor to GI pathology in PTHS patients. These results provide a first mechanistic framework for understanding GI complications in PTHS and highlight novel avenues for targeted therapeutic intervention.

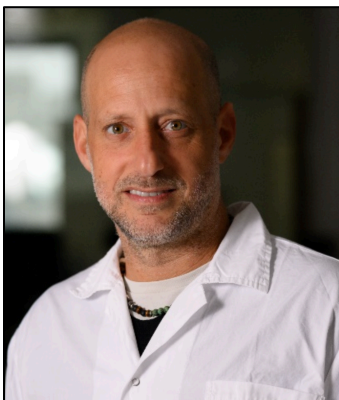


Tõnis Timmusk, PhD

Tõnis Timmusk (TT) is a molecular neurobiologist with more than 30-years research interests in gene regulation and signaling in the nervous system. After obtaining PhD in medical sciences from Karolinska Institutet, Sweden in 1994 he continued his scientific career in Karolinska Institutet and Uppsala University in Sweden and in University of Helsinki in Finland. Since 2002 he is full professor of molecular biology at Tallinn University of Technology, Estonia. TT has published more than 100 publications, including in *Nature*, *Science*, *Nature Genetics*, *Neuron*, *Journal of Neuroscience*, *eLife* and others. His published work has contributed to the understanding of the function, signaling and gene regulation of neurotrophic factors of nerve growth factor (NGF) and glial-cell derived neurotrophic factor (GDNF) family ligands and their receptors and to activity-dependent transcriptional mechanisms that underlie nervous system function in health and disease. TT has also published studies of several nervous system diseases, including Parkinson and Huntington diseases, schizophrenia and cognitive disorders. His lab is also studying the function and mechanism of action of the bHLH transcription factor TCF4, the gene of which is mutated in Pitt-Hopkins syndrome (PTHS) and associated with schizophrenia. TT has been the principal investigator of many projects, including the highly prestigious Wellcome Trust International Senior Research Fellowship, and the inventor of several international patent and patent application families. He is the scientific co-founder of two biotech companies.

Title: *Defining the Functions of Neurodevelopmental Disease-Associated Transcription Factor TCF4 in Activity-Dependent Gene Expression in Neurons*

Abstract: Transcription Factor 4 (TCF4) is a basic helix-loop-helix transcription factor that regulates neuronal differentiation and signaling. TCF4 has been implicated in schizophrenia and other neuropsychiatric disorders, and its mutations cause Pitt-Hopkins syndrome, a neurodevelopmental disorder characterized by intellectual disability. TCF4 functions through dimerization with other factors, and its transcriptional activity is regulated by neuronal activity through cAMP signaling. However, the broader role of TCF4 in activity-dependent transcriptional regulatory network in neurons remains unknown. Here, we mapped genome-wide TCF4 binding in rat primary cortical neurons showing TCF4 enrichment primarily at distal regulatory regions containing three predominant E-box TCF4-binding motifs. Using in vitro E-box DNA pulldown, we identified RUNX1T1, YBX1, NONO, and SFPQ and further validated them as TCF4 interactors and co-regulators of its transcriptional activity. RNA sequencing analysis of Tcf4 knockdown in primary neurons showed widespread alterations in activity-dependent gene expression, affecting pathways related to synaptic signaling, transcriptional regulation, and mitochondrial respiratory function. The latter was corroborated by reduced mitochondrial density in neurites after depolarization. Collectively, these findings provide insights into TCF4 role in transcriptional regulation, with implications for neuronal homeostasis and neurodevelopmental disorders.



Gad Vatine, PhD

Prof. Vatine received his PhD in 2011 from Tel Aviv University where, he studied the mechanisms underlying the circadian clock using zebrafish as a model. He then did a short postdoc at Bar-Ilan University where he established a zebrafish model for the rare psychomotor disability disorder MCT8-deficiency. Next, he joined the laboratory of Dr. Clive Svendsen at the Regenerative Medicine Institute (RMI) at Cedars-Sinai where he pioneered the concept of disease modeling at blood-brain barrier (BBB) using patient-specific induced pluripotent stem cells (iPSCs). In 2017, he became an independent PI at The Physiology and Cell Biology Department and the Regenerative Medicine and Stem Cell Research Center at Ben-Gurion University of the Negev. The Vatine lab generates personalized bioengineered platforms, such as Organs-on-Chips, to study mechanisms underlying various rare neurological disorders, and to test potential treatments. He is also the director of the BGU-iPS-core facility.

Title: *Harnessing CRISPR Activation (CRISPRa) to Upregulate TCF4 Expression in Neural Cells from Pitt-Hopkins Syndrome Patients*



Victor Li, PhD

Victor Li is a fundamental cell biologist, and CEO and cofounder of StemCellerant, a company focused on accelerating personalized medicine through new technology. Victor was trained at Harvard Medical School and Stanford University, and is a member of the American Society of Cell Biology, International Society of Stem Cell Research, AAAS, and other organizations.

Title: *Exploring the Cell Biology and Cell Therapy Potential of PTHS*

Abstract: The cellular mechanisms behind Pitt-Hopkins Syndrome (PTHS) and its complex pathogenesis are not fully understood. We aim to model the cell biology of PTHS through patient-specific induced pluripotent stem cell (iPSC)-derived neurons and glia. Using advanced stem cell differentiation to generate these distinct lineages in vitro, we wish to dissect the cellular deficits driving pathogenic outcomes. Characterizing these human-derived cellular phenotypes establishes a platform to bridge biology and medicine. Ultimately, by clarifying these precise cell-biological phenotypes, we wish to guide the design of targeted therapeutics and regenerative cell therapies for PTHS.



Jessica Duis, MD, MS

Dr. Jessica Duis is Vice President, Clinical Development, Neurology at Epicrispr Biotechnologies. She is passionate about the development of transformative treatments for individuals with rare disorders. She has over 15 years of experience in the clinical development of gene therapy, small molecules (in particular antisense oligonucleotides), and peptides, with a focus on innovative clinical trial design and sensitive novel endpoints, including digital health technology for which she has been involved in the process for qualification in the EU and USA. She led many projects to develop rare-disease clinical outcome assessments, including clinical global impression scales and digital

health technologies.

She practices in the fields of Pediatric Genetics, Neurogenetics, and Special Care Medicine, serving pediatric and adult patients with complex needs, and is affiliated with the HCA health system. She did her medical training at Johns Hopkins in Baltimore, MD, including a postdoctoral research fellowship with the Department of Psychiatry focusing on psychiatric disease associated with toxic fetal environment, imprinting disorders (in particular chromosome 15 disorders), and Mendelian Disorders of the Epigenetic Machinery, including bench and translational work and additional medical training. Her Masters and postdoctoral work included novel delivery mechanisms for precision therapies.

Dr. Duis has one of the deepest clinical experience bases in Pitt Hopkins syndrome (PTHS) of any physician nationally and internationally. She has evaluated and followed a large cohort of individuals with PTHS across the lifespan, characterizing natural history — including age at first parental concern, age at diagnosis, and the developmental, behavioral, and medical domains most affected — and translating those findings directly into bedside management. Her PTHS-focused work spans the full range of complex, symptom-cycling issues that define the condition: differentiating seizures from breath-holding spells and stereotypies, guiding EEG work-up and rescue medication planning, and building layered management strategies for gastrointestinal dysfunction, sleep disruption, breathing abnormalities, and behavior change. She is known for translating natural history data and case experience into concrete, actionable guidance for both clinicians and caregivers.

More broadly, she has founded and developed translational Centers of Excellence spanning medical care, translational research, outcome measure design, and clinical trials for PTHS and other rare neurogenetic conditions, and has developed and directed end-to-end clinical development of precision therapies for neurogenetic, neurodegenerative, metabolic, and neuromuscular conditions. Her clinical and regulatory experience spans 15 years and includes design of adaptive Phase 1/2/3 trials, Phase 1-4 clinical development, and alignment on surrogate endpoints for accelerated approval and global clinical-regulatory strategy. Her true passion is improving day-to-day quality of life for individuals with PTHS and other rare conditions who have unmet needs — she is a fierce patient advocate who works tirelessly to ensure truly transformative, precision treatments become a reality for the patients who need them.

Friday Title: *Beyond the Diagnosis: Natural History and Practical Management of Pitt Hopkins Syndrome*

Friday Abstract: This session offers physicians a working framework for recognizing and managing Pitt Hopkins syndrome (PTHS), a TCF4-related neurodevelopmental disorder. Dr. Duis will open with an overview of the patient population — average age of first parental concern versus age of diagnosis, the most common presenting symptoms across developmental domains, and how these have shifted with improved diagnostic access. The remainder of the talk moves into clinician-level decision-making drawn from real patient cases: distinguishing seizures from breath-holding spells and stereotypies when EEG capture is difficult, medication selection (including why levetiracetam is often poorly tolerated and alternatives to consider), and the layered management of GI dysfunction, sleep disruption, and behavioral change — conditions that frequently cycle into and mask one another. Attendees will leave with a practical, stepwise approach to working up ambiguous paroxysmal events and sequencing behavioral versus pharmacologic interventions in medically complex PTHS patients.

Saturday Title: *From Diagnosis to Daily Life: What Actually Helps in Pitt Hopkins Syndrome*

Saturday Abstract: This session will serve as a practical guide for parents and caregivers navigating the day-to-day realities of Pitt Hopkins syndrome. Drawing on real case examples and caregiver-reported experiences, this talk covers what to watch for and do around communication (AAC strategies that actually get used at home and school), sleep

disturbances, GI issues and constipation management, behavior changes and their underlying causes, breathing abnormalities and breath-holding, and when to push for seizure evaluation. The goal, as always, is concrete, take-home guidance — what to try, what to ask your medical team, and when to advocate harder — to help every family move from managing symptoms to improving quality of life.



Thomas Temple

Inspired by the resilience and legacy of my grandmother, Grannan, who lost her battle with neuroblastoma cancer in 2018, I founded Grann Pharmaceuticals with a mission to improve the quality of human life. Our work focuses on the development of mRNA lipid nanoparticle-based treatments, aiming to reverse medical conditions caused by genetic abnormalities and mutations. Driven by cutting-edge nanotechnology, our goal is to create innovative solutions for diseases, ensuring that our advancements have a profound and positive impact on the lives of patients worldwide.

Title: *Grann Pharmaceuticals & Pitt Hopkins Research Foundation: mRNA Lipid Nanoparticles for the Treatment of Pitt Hopkins Syndrome*

Abstract: Grann will present pre-clinical animal data regarding the use of PIT-1, Grann's proprietary mRNA lipid nanoparticle encoding TCF4. Additionally, Grann will walk the community through our background, our prior in-human experience with our mRNA lipid nanoparticles, and the plan moving forward with PIT-1, including how we plan to initiate in-human testing of PIT-1 by the fall of this year. We look forward to meeting the wider community and answering any questions they may have.



Christina Theodore-Oklota, PhD

Dr. Christina Theodore-Oklota is the Vice President of Clinical Outcomes Research at Mahzi Therapeutics, where she focuses on conducting research to support clinical endpoint selection and development in rare neurodevelopmental disorders. Dr. Theodore-Oklota has extensive experience across multiple therapeutic areas of drug development, implementing clinical outcome assessments to evaluate the effectiveness of new treatments through patient reports and neuropsychological evaluations. She is a clinical psychologist specializing in pediatrics, having earned her degree at Suffolk University in Boston. Before joining the pharmaceutical industry, she was a research fellow at The Warren Alpert Medical School of Brown University and the Stanford School of Medicine,

where she worked on the clinical treatment and assessment of psychological and cognitive outcomes of pediatric oncology, HIV, and pain patients.

In her work in drug development, Dr. Theodore-Oklota has specialized in developing novel assessments in rare diseases that accurately and efficiently characterize treatment experience using innovative methods and brief, targeted symptom assessments. Externally, she has been a contributor and panelist at multiple endpoint workshops and was invited to speak by the Institute of Medicine on how to better define, implement, and assess patient-centered endpoints in pediatric clinical trials. She has also published multiple papers and presentations on the qualitative and psychometric validation of symptom instruments and health-related quality of life assessments.



Emily Radomile

Emily Radomile is Vice President, Program Management and Clinical Operations at Mahzi Therapeutics. She has 23+ years' experience in drug development, with a focus on rare genetic diseases. Her expertise includes early-stage candidate development, and she has been responsible for designing pre-IND and IND-enabling plans, mapping critical-path timelines, developing natural history study protocols, managing regulatory meeting preparation, and driving first-in-human clinical protocol development. She has led operations across multiple therapeutic programs and has broad experience across rare disease development, including Pitt Hopkins syndrome, WWOX-DEE, X-linked hypophosphatemia (XLH), liposomal acid lipase deficiency (LALD), mucopolysaccharidosis type IIIB (MPS IIIB), Niemann-Pick type C, glycogen storage disease, among others. Her professional background also includes teaching and advanced training in leadership and organizational change. She served as a Lecturer for "Project Management in Clinical Research" at Boston College's William F. Connell School of Nursing and holds certificates in "Change Management" from the Prosci Institute and "Leading Complex Projects" from the UC Berkeley Haas School of Business Executive Education program. Ms. Radomile holds a BA in psychology from Boston University and a BSN from UMASS Boston.



Tom Brennan PhD

Dr. Tom Brennan is Senior Vice President of Nonclinical Development at Mahzi Therapeutics, where he leads IND-enabling strategy and nonclinical development for AAV9 gene therapies and antisense oligonucleotide (ASO) programs targeting severe pediatric neurodevelopmental disorders, including TCF4-, WWOX-, CHD2-, and SCN2A-associated syndromes. He brings over 25 years of experience in translational neuroscience, with deep expertise in disease modeling, biodistribution and transgene expression analysis, and pharmacodynamic evaluation across gene, antibody, and engineered cell therapy platforms.

Prior to joining Mahzi, Dr. Brennan co-founded Walking Fish Therapeutics and served as Vice President of Preclinical Development, where he advanced AAV-engineered B cell therapies for Fabry disease and established in vivo platforms for B cell-mediated therapeutic protein delivery. Earlier, he spent more than a decade at FivePrime Therapeutics as Vice President of Pharmacology, leading preclinical efforts supporting five IND submissions and contributing to the development of an FDA-approved therapy for gastric cancer, with a focus on immuno-oncology and target validation.

He began his industry career at Deltagen, where he co-led the generation and neurobehavioral phenotyping of over 1,500 knockout mouse models, now archived at The Jackson Laboratory. Dr. Brennan completed postdoctoral fellowships in neuroscience at Genentech and the University of California, San Francisco, and earned his PhD in Biomedical Science from the University of Texas Health Science Center at Houston.



Marwan Ghanem PhD

Marwan Ghanem is a PhD candidate in the Lippi Lab at Scripps Research, where he develops RNA-based strategies to correct haploinsufficiency in neurodevelopmental disorders. His current work focuses on Pitt-Hopkins syndrome, combining high-resolution mapping of microRNA–target interactions with programmable de-repression to restore TCF4 expression from the intact allele with the broader aim of extending this dosage-restoration platform to other haploinsufficient targets. He received his B.S in Neuroscience and Biology from Oberlin College in 2022.

Title: *De-repressing microRNA sites as a tunable strategy to restore TCF4 in Pitt-Hopkins syndrome*

Abstract: Pitt-Hopkins syndrome is a severe neurodevelopmental disorder caused by haploinsufficiency of the transcription factor TCF4, making restoration of TCF4 protein levels a central therapeutic goal. Conventional approaches such as gene replacement, gene editing, or splice-switching antisense oligonucleotides (ASOs) are constrained by delivery capacity, toxicity, off-target effects, or the availability of suitable target sequences. To overcome these limitations, we are developing a de-repression strategy, which relieves the healthy TCF4 allele from microRNA (miRNA)-mediated repression by disrupting miRNA–target interactions (MTIs) in the 3'UTR, enabling tunable restoration of TCF4 levels.

We used human iPSC-derived and mouse excitatory neurons to map high-confidence, brain-enriched MTIs on the TCF4 3'UTR. We determined MTIs that are conserved between mouse and human, supporting cross-species modeling and clinical translatability. We show that complete miRNA loss of function leads to increases in TCF4 mRNA and protein levels, indicating high miRNA-mediated regulation. As proof of concept that the miRNA response elements (MREs) in the 3'UTR repress TCF4 levels, we performed endogenous 3'UTR replacement and observed increased TCF4 expression.

To pinpoint the MREs whose blockade restores TCF4 levels, we engineered an iPSC line in which endogenous TCF4 is tagged with a fluorescent reporter, providing a quantitative, scalable readout of TCF4 protein. Using this reporter, we will run a medium-throughput dCasRx (RNA-guided CRISPR) screen to nominate the most effective de-repression sites. Collectively, this establishes MTI de-repression as a scalable, tunable therapeutic strategy for TCF4.



David Corey, PhD

David Corey received his BA degree in chemistry in 1985 from Harvard and his PhD in chemistry from UC Berkeley in 1990 in the laboratory of Dr. Peter Schultz. He did postdoctoral work at UC San Francisco until 1992, when he started his independent career at UT Southwestern Medical Center in Dallas, rising to Full Professor in 2003. Dr. Corey has authored over 200 scientific papers, is an editor of *Nucleic Acids Research*, Founder of Iris Medicine, founding Scientific Advisory Board member of the Ono Pharma Foundation, and former President of the Oligonucleotide Therapeutics Society.

Title: *Activating TCF4 expression with synthetic duplex RNAs*

Abstract: Pitt-Hopkins syndrome (PTHS) is a haploinsufficient, neurodegenerative disease caused by the deficient expression of transcription factor 4 (TCF4). Compounds that activate TCF4 gene expression and increase levels of functional TCF4 protein might benefit

most PTHS patients. Double-stranded RNAs (dsRNAs) are synthetic oligonucleotide compounds that can activate gene expression by targeting promoter sequences. Here, we use public sequencing data to define promising promoter regions to identify potential target sites. We discover several gene-activating dsRNAs and obtain data supporting the conclusion that their impact is due to sequence-specific target engagement at the TCF4 promoter. ChIP-qPCR reveals gene activation is accompanied by an increase in the recruitment of RNA Pol II to the TCF4 promoter. Our results suggest that dsRNAs targeting the TCF4 may be an approach to increasing TCF4 expression, providing a potential starting point for therapeutic discovery.



Afrooz Rashnonejad, MSc, PhD

Afrooz Rashnonejad, MSc, PhD, is an Assistant Professor of Pediatrics at The Ohio State University College of Medicine and a Principal Investigator at the Jerry R. Mendell Center for Gene Therapy at Nationwide Children's Hospital (NCH). Her research focuses on developing adeno-associated virus (AAV)-based gene therapies for neurological and neuromuscular diseases. As part of her doctoral work, she developed a prenatal gene therapy approach for Spinal Muscular Atrophy (SMA) under the mentorship of Dr. Guangping Gao (Director of the Center for Gene Therapy, UMass Medical School) and Dr. Ferda Ozkinay (Ege University).

She later completed her postdoctoral training in Dr. Scott Harper's lab at NCH, where she developed RNA-targeting therapies, including AAV-U7snRNA and AAV.CRISPR-Cas13, and miRNA-mediated gene therapies for FSHD. Her lab investigates therapies for neurological and neuromuscular diseases such as Pitt-Hopkins syndrome, CMT1B neuropathy, Nemaline Myopathy, and RYR-1-related myopathy. She is also advancing in-utero therapies for severe congenital neuromuscular diseases. Dr. Rashnonejad has chaired ASGCT's New Investigator Committee and serves on the Musculoskeletal Cell and Gene Therapy Committee, and also the Prenatal Cell and Gene Therapy Committee. She was honored to receive the ASGCT Excellence in Research Award in two consecutive years, 2019 and 2020. Dr. Rashnonejad also serves on the scientific advisory boards of several patient foundations.

Title: *Progress on AAV9-U7-snRNA-Mediated Promoter Modulation Gene Therapy for Pitt-Hopkins Syndrome*

Abstract: Pitt-Hopkins syndrome (PTHS) is a haploinsufficiency neurodevelopmental disorder caused by loss-of-function mutations or deletions in the Transcription Factor 4 (TCF4) gene. The estimated prevalence of PTHS is 1 in 41,000 individuals, marked by intellectual disability, significant delays in motor development, absence of functional speech, and breathing difficulties. TCF4 is expressed especially in the nervous system and regulates gene expression by interacting with other proteins to either promote or inhibit transcription. Due to its large size and multiple known protein isoforms, TCF4 poses a challenge for traditional gene replacement approaches. However, since patients still have one functional copy of the gene, enhancing TCF4 expression presents a promising alternative. Here, for the first time, we modified U7 small nuclear RNAs (U7-snRNAs) to modulate TCF4 promoter activity and enhance its expression, proposing a novel gene therapy approach for PTHS.

We designed 3 U7 small RNA cassettes targeting different regions of the TCF4 promoter that we predicted could modulate the promoter activity. We assessed the efficiency of U7 cassettes through transient transfection in HEK293 cells to evaluate their ability to enhance TCF4 expression. Next, we generated AAV9 viral particles and validated their effectiveness in an in vitro model with human PTHS patient cell lines, employing RT-PCR and immunofluorescent imaging to measure TCF4 expression. Functional assays were used to determine the effect of the treatment on cellular health as well. In addition, we used mouse embryonic fibroblasts (MEFs) from a mouse model that expresses the green fluorescent protein under the human TCF4 promoter as an additional model system to further validate our approach. We also

evaluated the efficiency of AAV9.U7-TCF4 in enhancing TCF4 expression in a transgenic mouse model that carries the human TCF4 promoter with GFP downstream of TCF4 gene.

In vitro studies in HEK293 cells and PTHS patient-derived astrocytes demonstrated elevated TCF4 expression following transient transfection with the U7 cassette, as confirmed by qRT-PCR and immunofluorescence staining at 72 hours post-transfection. The enhanced expression of TCF4 improved the survival of co-cultured mouse motor neurons interacting with patient-derived induced astrocytes, providing functional evidence of the treatment's efficacy. Moreover, using mouse embryonic fibroblasts expressing GFP under the control of the human TCF4 promoter, we showed upregulation of GFP expression 72 hrs after treatment with AAV9.U7-TCF4. Interestingly, stereomicroscopic imaging of brain tissues revealed increased GFP fluorescence in the injected animals compared with the uninjected controls after 6 months post-injection, confirming TCF4 protein expression. The qRT-PCR analysis of the intracerebroventricular injection of 4.4×10^{10} vgc of AAV9.U7-TCF4 into transgenic mice showed a 1.4-fold increase in TCF4 transcript levels at 1 and 6 months post-injection.

We developed a novel U7-siRNA-based technology that enables modulation of TCF4 promoter activity. Altogether, our in vitro results in HEK293 cells, PTHS patient-induced astrocyte cell lines, and mouse embryonic fibroblasts expressing GFP under the human TCF4 promoter, along with in vivo studies in a transgenic mouse model, demonstrate the effectiveness of this approach. Our novel therapeutic strategy holds great promise and may offer advantages over current gene replacement approaches, as it leverages the endogenous gene to produce all naturally occurring TCF4 isoforms, rather than overexpressing a single transcript. This novel technology enables the upregulation of gene expression and has the potential to become a promising new approach for treating haploinsufficiencies more broadly.



Rachel Groth, PhD

Rachel Groth, PhD, is the Head of External Innovation and Patient Advocacy at Neuren Pharmaceuticals. She is a seasoned drug hunter who collaborates closely with leading investigators at Academic Medical Centers and patient advocacy groups to advance the development of treatments for neurodevelopmental disorders. She believes strongly that forging deep collaborations with patients and caregivers, scientists, and clinicians across the research ecosystem is necessary to make meaningful medicines.

Rachel serves on the Scientific Advisory Boards of Global Genes, the International FOXP1 Foundation, and the GIGYF1 Foundation. She has worked in biopharma for the last 15 years in roles of increasing responsibility. Before moving to industry, Rachel was a

postdoctoral fellow at Stanford University in the Department of Molecular and Cellular Physiology. Rachel earned a Ph.D. in Neuroscience from the University of Minnesota and a B.A. in Biology and Neuroscience from Macalester College.

Title: *Modulation of IGF-1 Signaling for the Treatment of Pitt Hopkins Syndrome*

Abstract: Pitt Hopkins syndrome (PTHS) is a rare monogenetic neurodevelopmental disorder with no approved treatments. PTHS is caused by insufficient levels of TCF4, a transcription factor that regulates expression of key proteins involved in communication between neurons at synapses. Given that insulin-like growth factor 1 (IGF-1) regulates synaptic transmission, we hypothesize that increasing IGF-1 in the brain may be a potential treatment mechanism to evaluate for PTHS. We conducted a 13-week open-label clinical trial of the investigative drug NNZ-2591, a metabolite of IGF-1 that promotes IGF-1 signaling, administered as a twice daily oral liquid to children and adolescents 3-17 years of age with PTHS. NNZ-2591 was well-tolerated and caregivers and clinicians reported clinically meaningful improvements across core symptoms, including communication, social interaction, cognition, and motor skills.

Julia Dominguez

Clinical/Translational Research Coordinator, COMBINEDBrain

Title: *Bi[o]hub: A Patient-Driven Partnership between COMBINEDBrain and the Pitt Hopkins Research Foundation*

Abstract: This short presentation will delve into the COMBI[o]mics study, which builds on our collaborative efforts to pair biological samples with symptom data across rare neurodevelopmental disorders (like Pitt Hopkins!). The overarching goals are to accelerate biomarker discovery and the development of outcome measures -- both goals will improve readiness for future clinical research.