PACS2 RESEARCH FOUNDATION

MEDICAL UNIVERSITY OF WARSAW

CENTRUM DOSKONAŁOŚCI CHORÓB RZADKICH I NIEZDIAGNOZOWANYCH

WARSZAWSKI UNIWERSYTET MEDYCZNY

# UNLOCKING HOPE FOR THE ULTRA-RARE

on therapeutic options for ultra-rare diseases, interdisciplinary partnership and the active involvement of patients in this process

## CONFERENCE PROGRAMME

**Dear & Honorary Members of the Community of Parents and Carers for Patients with Ultrarare Disorders,**

CENTRUM DOSKONAŁOŚCI CHORÓB RZADKICH I NIEZDIAGNOZOWANYCH

WARSZAWSKI UNIWERSYTET MEDYCZNY

**Dear Ladies and Gentlemen,**

It has been my great pleasure to welcome you in the name of Center of Excellence for Rare and Unknown Disorders of Medical University of Warsaw to this first of its kind and unique conference 'Unlocking hope for the Ultra-rare'.

While rare disorders have so far gathered public attention, those 'rarer than rare patients' are in many instances still anonymous. Needless to say, we all have enormous work to do in order for the things to change. Public recognition is one thing, as at the same time we need to remember that our first and foremost goal is to find and improve care for patients with ultrarare conditions.

**Our community consists of parents, patients, scientists, clinicians and policy regulators from all over the world. That in itself provides hope for a multitude of approaches at the scientific, clinical and policymaking levels.** What has always struck me most in the world of rare/ultrarare disorders compared to the common conditions is this multidimensionality of looking into innovative cure driven by the persistence of individual members of rare and ultrarare communities.

Last and most important thing. When two years ago the parents of a young girl with a PACS2 disorder came up to me and said their lifetime goal was to find cure for their child's condition, I thought: 'Well, this is precious and I will do my best but… I have other patients, duties, organizational matters etc.'

Now, two years later and thanks to them, I am a different man and there's hardly a day that I don't think about PACS2 while gradually recognizing more and more the importance of caring for other patients with ultrarare disorders.

**Let's all change then!**

In the name of the organizers,

*Krzysztof Szczałuba, MD PhD*
*Director of Excellence Center for Rare and Unknown Disorders*
*Medical University of Warsaw, Poland*

**Welcome!**

In February 2022, our world was turned upside down when our twin daughter, Lena, was diagnosed with an ultra-rare neurological disorder, PACS2 syndrome. With no available treatment, no scientific publications on the disease, we were faced with a devastating reality. But instead of giving up, we chose to create hope - for Lena and all children affected by PACS2 syndrome.

At that time, we couldn't have imagined that by September 2024, more than 60 researchers and clinicians from around the world would be working alongside us to advance treatments for this disease. Nor could we have dreamed that these leading experts would gather here in Warsaw to discuss - together with broader rare disease community - the vital role of **interdisciplinary collaboration to cure rare diseases**.

And today, it is happening.

Thank you for being here with us. Imagine what more we can achieve for rare diseases when we work together.

We also extend our deepest gratitude to **the Excellence Center for Rare and Unkonown Disorders at the Medical University of Warsaw**, which has supported us from the very beginning and shaped this event with us.

.

*Malgorzata (Gosia) & Piotr Kosla*
*Parents of Lena - affected by PACS2 syndrome - and her twin sister, Zuzanna*
*Founders of PACS2 Research Fundation*
*www.pacs2research.org*

**ON THE FOLLOWING PAGES...**

- the conference program
- profiles of the speakers
- abstracts of posters submitted for the poster session

# UNLOCKING HOPE FOR THE ULTRA-RARE PROGRAMME

## Themes:

| | | |
|---|---|---|
| IDEA SHARING | PRE-CLINICAL RESEARCH | CLINICAL OBSERVATIONS |
| DRUG REPURPOSING | ADVANCED THERAPIES | PLATFORMS / INITIATIVES |

## DAY 1: September 4th - part 1/3

| | | | | |
|---|---|---|---|---|
| 09:00 | 09:30 | Welcome Session | Malgorzata & Piotr Kosla Krzysztof Szczaluba, PhD | PACS2 Research Foundation (PL) Excellence Center for Rare and Unknown Disorders, Medical University of Warsaw (PL) |
| 09:30 | 10:00 | The model to cure ultra-rare: Patient-led collaborative research networks | Malgorzata & Piotr Kosla | PACS2 Research Foundation (PL) |
| 10:00 | 10:25 | PACS2 Cure Odyssey: The Promise of Drug Repurposing | Ethan Perlstein, PhD | Perlara PBC (US) |
| 10:25 | 10:50 | Leveraging drug repurposing screens for rare disease using cell painting and AI | Andre Van Marle, PhD | Charles River Laboratories (NL) |
| 10:50 | 11:10 | Coffee Break | | |
| 11:10 | 11:35 | PACS2 syndrome modeling in the nematode Caenorhabditis elegans for drug repurposing screening | Krzysztof Drabikowski, PhD | Institute of Biochemistry and Biophysics of the Polish Academy of Sciences (PL) |
| 11:35 | 12:00 | A primer on the PACS proteins and their roles in PACS1 and PACS2 syndromes | Prof. Gary Thomas | University of Pittsburgh (US) |
| 12:00 | 12:25 | PACS2 patients: what is wrong with their metabolism - looking for metabolic alterations in PACS2 syndrome using patients' fibroblasts | Prof. Mariusz Wieckowski | The Nencki Institute of Experimental Biology, Polish Academy of Sciences (PL) |

# UNLOCKING HOPE FOR THE ULTRA-RARE PROGRAMME

## Themes:

| | | |
|---|---|---|
| IDEA SHARING | PRE-CLINICAL RESEARCH | CLINICAL OBSERVATIONS |
| DRUG REPURPOSING | ADVANCED THERAPIES | PLATFORMS / INITIATIVES |

## DAY 1: September 4th - part 2/3

| | | | | |
|---|---|---|---|---|
| 12:25 | 12:50 | Pathogenic mechanisms associated with PACS Syndromes: uncovering novel therapy avenues | Alicia Guemez-Gamboa, PhD | Northwestern University (US) |
| 12:50 | 14:00 | Lunch break | | |
| 14:00 | 14:25 | Pacs2(E209K) mouse model advanced phenotyping | Kacper Łukasiewicz, PhD | Medical University of Bialystok (PL) |
| 14:25 | 14:50 | Proteomics-Driven Insights into PACS2 Research Models | Dominik Cysewski, PhD | Medical University of Bialystok (PL) |
| 14:50 | 15:15 | Protein Degradation Malfunctions in Rare Diseases: A Case Study of Unidentified Neurological Disorder. LumiRare Initiative. | Wojciech Pokrzywa, PhD | International Institute of Molecular and Cell Biology (PL) |
| 15:15 | 15:30 | Coffee Break | | |
| 15:30 | 15:55 | RNA editing approaches to treat PACS2 syndrome | Ambra Speciale, MSc | University of Oxford (UK) |
| 15:55 | 16:20 | Advancing rare disease research: The JAX Center for Precision Genetics | Prof. Steve Murray (online) | The Jackson Laboratory (US) |

# UNLOCKING HOPE FOR THE ULTRA-RARE PROGRAMME

## Themes:

| | | |
|---|---|---|
| IDEA SHARING | PRE-CLINICAL RESEARCH | CLINICAL OBSERVATIONS |
| DRUG REPURPOSING | ADVANCED THERAPIES | PLATFORMS / INITIATIVES |

## DAY 1: September 4th - part 3/3

| | | | | |
|---|---|---|---|---|
| 16:20 | 16:45 | Antisense Oligonucleotide Treatment Targeting PACS2: The Relentless Pursuit of a Targeted Therapy | Sarah Glass, PhD (online) | n-Lorem Foundation (US) |
| 16:45 | 17:00 | Wrap-up of the day | Malgorzata Kosla | PACS2 Research Foundation (PL) |

## DAY 2: September 5th - part 1/2

| | | | | |
|---|---|---|---|---|
| 09:00 | 09:25 | 1000 Cures: A Y Combinator for Rare | Ethan Perlstein, PhD | Perlara PBC (US) |
| 09:25 | 09:50 | Individualised Nucleic Acid Therapies for Rare Diseases | Prof. Carlo Rinaldi | University of Oxford (UK) |
| 09:50 | 10:15 | ERDERA - The European Rare Diseases Research Alliance and how patients could be involved in the partnership | Daria Julkowska, PhD | EJP RD (EU) |
| 10:15 | 10:40 | Czech Center for Phenogenomics: Advancing Gene Function Studies and Preclinical Therapy Development | Jan Procházka, PhD | Czech Center for Phenogenomics (CZ) |

# UNLOCKING HOPE FOR THE ULTRA-RARE PROGRAMME

## Themes:

IDEA SHARING | PRE-CLINICAL RESEARCH | CLINICAL OBSERVATIONS

DRUG REPURPOSING | ADVANCED THERAPIES | PLATFORMS / INITIATIVES

## DAY 2: September 5th - part 2/2

| | | | | |
|---|---|---|---|---|
| 10:40 | 12:00 | Coffee Break connected with Posters Presentations | | |
| 12:00 | 12:25 | Patient's registry & Natural History Study for dispersed patient community; how European Reference Networks can support it | Maciej K. Janik, MD, PhD | Medical University of Warsaw (PL) / ERN RARE-LIVER (EU) |
| 12:25 | 12:55 | The role of a Natural History Study and development of Clinical Outcome Assessments in the path to therapy | Heather Olson, MD, PhD (online) | Boston Children's Hospital (US) |
| 12:55 | 13:35 | Lunch break | | |
| 13:35 | 14:50 | Panel Discussion:<br>How to embrace collaboration and bring patients to the research table | Krzysztof Szczaluba, PhD<br>Ethan Perlstein, PhD<br>Tomasz Grybek<br><br>Prof. Carlo Rinaldi<br>Daria Julkowska, PhD | Medical University of Warsaw (PL)<br>Perlara PBC (US)<br>Borys the Hero Foundation / Eurordis<br>Oxford University (UK)<br>EJP RD (EU) |
| 14:50 | 15:00 | Closing Remarks | Malgorzata & Piotr Kosla | PACS2 Research Foundation (PL) |

# UNLOCKING HOPE FOR THE ULTRA-RARE

## SPEAKERS

**Krzysztof Szczałuba, MD, PhD | Medical University of Warsaw**

Dr. Krzysztof Szczaluba, a clinical geneticist, is the Director of Excellence Center for Rare and Undiagnosed Diseases at Medical University of Warsaw (MUW).

Dr. Szczaluba scientific interests centers around the genetics of rare disorders, with a particular focus on neurodevelopmental conditions. His work began with the provision of the first clinical and genetic data on ARX gene mutations in Partington syndrome. He has also conducted studies on extrapyramidal symptoms in primary dystonia and examined the effects of deep brain stimulation in type 1 dystonia.

His focus on central nervous system (CNS) disorders continued with research into the genotype-phenotype correlations of posterior fossa syndromes and malformations, particularly in Joubert syndrome and other ciliopathies, including pontine tegmental cap dysplasia. He later became one of the first researchers to describe disorders related to calcineurin, FARSA, MACF1, and SETD5.

Currently, as part of a Neurogenetic/Neuroscientific workforce, his research is concentrated on the neurobehavioral, epileptic, and ophthalmological characteristics of larger patient groups with Joubert syndrome, other ciliopathies, and syndromes such as PACS2, Coffin-Siris, Rett, and Kabuki. In certain instances of these and other rare conditions, he has been working on experimental treatments.

As the leader of the Center of Excellence for Rare and Unknown Disorders at MUW, he has recognized the importance of collaborative efforts and a multidisciplinary approach in both clinical and scientific settings.

**Małgorzata (Gosia) Kośla | PACS2 Research Foundation**

Gosia holds a degree in Quantitative Methods & Finance from the Warsaw School of Economics (WSE) and a dual Master's in International Management from WSE and NOVA Business School in Lisbon. She is an accomplished manager with extensive experience in leading teams of 20+ people in pharmaceutical sector (GSK).

Gosia is also a dedicated mother to Lena, who has PACS2 syndrome, and her twin sister, Zuzanna. In her role as President of the PACS2 Research Foundation, she oversees administrative tasks, crafts the foundation's storytelling strategy, enhances its media visibility and plan fundrasing activities. She serves as a representative in the European Patient Advocacy Group within the European Reference Network EpiCARE. In October 2024, Gosia will begin multidisciplinary studies in biotechnology and psychology at University of Warsaw.

**Piotr Kośla | PACS2 Research Foundation**

Piotr holds a degree in Finance from the Warsaw School of Economics and a dual Master's in International Management from the Warsaw School of Economics and the National University of Singapore. He brings extensive experience from the biotech and medical devices sectors (Biogen, Abbott), with a strong track record across multiple geographies and cultures.

As a father to Lena and Zuzanna, Piotr is deeply involved in the PACS2 Research Foundation, where he excels in networking, managing cash flow, and building international relationships, all while running daily job as Chief Operating Officer in Polish #1 e-commerce for diabetics. Additionally, Piotr serves on the Community Advisory Board at Simons Searchlight.

# UNLOCKING HOPE FOR THE ULTRA-RARE

## SPEAKERS

**Ethan Perlstein, PhD | Perlara PBC**
Ethan is the founder and CEO of Perlara PBC, the first biotech Public Benefit Corporation, and cofounder and CEO of Maggie's Pearl, a clinical-stage joint venture of Perlara and a rare disease family that is currently sponsoring a Phase 3 drug repurposing study at Mayo Clinic. Ethan actively works with dozens of relentless families driving toward cures with focus on congenital disorders of glycosylation, mitochondrial diseases and neurodevelopmental & neurodegenerative diseases.
Ethan holds PhD from Harvard University (Department of Molecular and Cell Biology) where he worked in the laboratory of Professor Stuart Schreiber. He completed an independent postdoctoral fellowship at the Lewis-Sigler Institute at Princeton University.

**Andre van Marle, PhD | Charles River Laboratories**
Trained as a molecular neurobiologist., André van Marle received his PhD at the Free University of Amsterdam on regulation of axonal mRNAs In 1997. Upon working on ligand-gated ion-channels at the MRC in Cambridge, he completed several post-doctoral studies focused on nuclear hormone and G-protein coupled receptors. In 2005, he accepted a position with Galapagos to oversee the adenoviral libraries forming the basis of Galapagos' functional genomic platform to feed their target discovery pipeline. Eventually, his performance led to an Associate Director function and lead a team to evaluate innovative technologies to identify and validate novel drug targets. He successfully implemented CRISPR gene editing and screening to discriminate scaffold and activity gene functions, knocking down endogenous proteins using antibodies and cell painting. In 2021, Andre joined Charles River as a senior group leader where he is involved in client projects with a focus around fibrosis and rare diseases.

**Krzysztof Drabikowski, PhD | Institute of Biochemistry and Biophysics of the Polish Academy of Sciences**
Dr. Drabikowski studies the molecular mechanisms of the cellular stress response at the whole organism level in a model of Caenorhabditis elegans. He is also developing methodologies for drug development at the level of the entire organism in C. elegans. Dr Drabikowski graduated from the Faculty of Biology, University of Warsaw. He did his doctoral thesis at the Friedrich Miescher Institute for Biomedical Research in Basel, Switzerland and defended his PhD thesis in biochemistry at the Biozentrum Universität Basel. Dr Drabikowski did his postdoctoral training at the Friedrich Miescher Institute for Biomedical Research in Basel and at The Scripps Reseach Institute in La Jolla, USA. He continued his research as an Assistant Professor (Wissenschaftlishe Assitent) at the Department of Biology of the Albert Ludvig Universität in Freiburg, Germany. Since 2012, he has been working at the IBB PAS.

**Prof. Gary Thomas, PhD | University of Pittsburgh School of Medicine**
Professor in Microbiology and Molecular Genetics. Dr. Thomas' team discovered PACS1 and its orthologue PACS2 and leads a multi-PI team at the University of Pittsburgh that is determining—from the atom to the whole organism—how the recurrent de novo missense mutations in PACS1 and PACS2 cause neurodevelopmental disorders and how to interfere with these pathways to reduce disease. He has a broad background in cell biology and enzyme biochemistry, with specific training and expertise in cell biology, infectious disease, and neurobiology. His team was the first to demonstrate the role of furin as a proprotein convertase and to generate potent and selective furin inhibitors currently used to investigate SARS-CoV-2. His studies on furin led to the discoveries of PACS1 and PACS2 and their roles in membrane traffic, metabolism, and disease. He earned a PhD in 1984 from the Biozentrum (Basel) and then was a Damon Runyon-Walter Winchell postdoctoral fellow at the University of Oregon. In 1987, he became a founding member of the Vollum Institute (OHSU, Portland). In 2012, he was recruited to the University of Pittsburgh.

# UNLOCKING HOPE FOR THE ULTRA-RARE

## SPEAKERS

**Prof. Mariusz R. Więckowski | NThe Nencki Institute of Experimental Biology, Polish Academy of Sciences**

The head of the Laboratory of Mitochondrial Biology and Metabolism at the Nencki Institute of Experimental Biology PAS. Prof. Mariusz R. Wieckowski is leading expert in mitochondrial field, mitochondrial bioenergetics, oxidative stress and close interactions between endoplasmic reticulum and mitochondria in the context of several pathological situations. His recent research is focused on different aspects of intracellular oxidative stress and pharmacological toxicity to mitochondria (e.g., in the context of rare and metabolic disorders). Recently, within the frame of three Horizon 2020 projects he is working on the role of mitochondria and oxidative stress in nonalcoholic fatty liver disease and in obesity development and progression.

**Alicia Guemez-Gamboa, PhD | Northwestern University**

Dr. Alicia Guemez-Gamboa earned her PhD in Biomedical Sciences from the Universidad Nacional Autonoma de Mexico. She then completed postdoctoral training at the University of California, San Diego and at The Rockefeller University. Dr. Guemez-Gamboa is currently an Assistant Professor at the Department of Neuroscience at the Feinberg School of Medicine in Northwestern University. Her laboratory is focused on investigating the pathogenesis of neurodevelopmental disorders by coupling human genetics, next generation sequencing, and disease modeling using animal and stem cells. Particularly, the Guemez-Gamboa group uses induced pluripotent stem cells to generate neural progenitors, neurons, and forebrain - organoids predisposed to neurological disorders. Characterization of these models helps elucidating the mechanisms of disease of a variety of brain connectivity defects and laying the groundwork for the development of new therapeutic approaches and personalized medicine.

**Kacper Łukasiewicz, PhD | Medical University of Białystok**

Dr. Kacper Łukasiewicz is a neuroscientist affiliated with the Center for Experimental Medicine and the Laboratory of Psychiatry Clinic at the Medical University of Bialystok. He holds an MSc in Molecular Biology from the University of Warsaw and earned his PhD in Neuroscience from the Nencki Institute of Experimental Biology, Polish Academy of Sciences. Dr. Łukasiewicz completed his postdoctoral research in the Zuo Laboratory at the University of California, Santa Cruz, where he investigated mouse models of autism spectrum disorders and explored the therapeutic potential of psychedelics. His primary research interests lie in the use of animal models to study neurological and psychiatric disorders.

Since 2022, Dr. Łukasiewicz has been leading a research project on the Angelman syndrome population in Poland. In 2024, he was awarded the prestigious Visegrad Fellowship, which supports his work on advanced phenotyping of PACS2 mice at the Czech Center for Phenogenomics.

**Dominik Cysewski, PhD | Medical University of Białystok**

Dominik Cysewski received his MSc in Medical Biotechnology from the University of Warsaw and his PhD in Molecular Biology from the Institute of Biochemistry and Biophysics of the Polish Academy of Sciences. He is an expert in protein research with over ten years of experience, confirmed by many scientific articles and collaborations. Dominik is an Assistant Professor leading a group of proteomics research at Medical University of Bialystok (MUB). In his work, he applied various modern technologies, both experimental and computational. His primary research tool is liquid chromatography coupled with high-resolution mass spectrometry. He participates in projects that aim to address socially relevant issues, which brought him to work closer to the clinic. Such as the Fragile X Syndrome research, which he focused on in his doctoral thesis, or the current research project on Angelman Syndrome in the Polish population.

# UNLOCKING HOPE FOR THE ULTRA-RARE

## SPEAKERS

**Natalia Szulc, MSc | International Institute of Molecular and Cell Biology in Warsaw, LumiRare**

Natalia Szulc is a 4th-year PhD student in Dr. Wojciech Pokrzywa's laboratory, focusing on the evolutionary adaptation of proteins to avoid premature degradation and the molecular basis of disease mechanisms, especially those rare in the malfunction of the ubiquitin-proteasome system. She holds two M.Sc. degrees from the University of Warsaw: in computational engineering (2021) and molecular biotechnology (2018) and has authored over 10 scientific publications. Natalia Szulc heads the PRELUDIUM research grant and is a recipient of the Fulbright Junior Research Award for a research stay at Harvard University. She also won the 2021 prize for the best master's thesis in bioinformatics in Poland. One of the founders of LumiRare.

**Wojciech Pokrzywa, PhD, DSc | International Institute of Molecular and Cell Biology in Warsaw, LumiRare**

Dr. Wojciech Pokrzywa is head of the Protein Metabolism Laboratory at the International Institute of Molecular and Cell Biology in Warsaw, one of Poland's top research institutes. Since 2017, he has been leading his research group (pokrzywalab.com), focusing on the mechanisms of protein metabolism by studying the regulation of translation, the ubiquitin-proteasome system, chaperone networks and muscle exophers. His team uses a combination of biochemical, microscopy, molecular genetics and bioinformatics techniques, supported by assays on mammalian cells and the nematode C. elegans. He completed his PhD at the Catholic University of Louvain in Belgium, studying the ubiquitin-proteasome system in yeast. He then joined the laboratory of Prof. Thorsten Hoppe at the University of Cologne, Germany, where he completed a postdoctoral fellowship studying proteostasis during development and ageing in C. elegans. Dr. Pokrzywa is the author of more than 35 scientific publications, including articles on rare diseases, and has received numerous national and international research grants from organizations such as EMBO, the German Research Foundation, the National Science Centre and the Foundation for Polish Science.

**Ambra Speciale, DPhil student | University of Oxford**

Ambra Speciale is a medical biotechnologist (MSc) and a final-year DPhil student in Paediatrics at the University of Oxford, working in the Rinaldi lab. Her research focuses on understanding RNA editing functions in neurological diseases and exploring RNA editing as a potential therapeutic strategy for rare and ultra-rare disorders, such as PACS2 syndrome. Since joining Oxford in 2019, Ambra has been dedicated to uncovering new therapeutic targets to improve treatment options for patients. She is also passionate about science outreach and actively engages in initiatives to promote scientific understanding and communication.

**Prof. Carlo Rinaldi | University of Oxford**

Carlo Rinaldi completed his medical education and residency in adult neurology in 2010 both with distinction at the University of Federico II, Naples, Italy. In 2009 he joined the Neurogenetics Branch at the National Institute of Health (Bethesda, MD, USA) under the supervision of prof. Fischbeck, to work on the mechanisms of pathogenesis of spinal and bulbar muscular atrophy (SBMA or Kennedy's disease) and other genetic diseases of the motor unit and where he also obtained a PhD in Neuroscience with the thesis entitled: 'From Disease Gene Identification to Therapeutic Targets in Neuromuscular Diseases'. In 2015 he joined the lab of Prof. Matthew Wood at the University of Oxford as a Clinical Research Fellow and in December 2016 was awarded a Wellcome Trust Career Development Fellowship, followed by a UKRI MRC Senior Clinical Fellowship in 2023 to establish his independent research lab (https://www.rinaldi-lab.com/). He is an Honorary Consultant Neurologist at the John Radcliffe Hospital in Oxford and at the National Hospital for Neurology and Neurosurgery in London and Principal Investigator in the recently established Oxford-Muscular Dystrophy UK Centre for Translational Neuromuscular Science Centre.

# UNLOCKING HOPE FOR THE ULTRA-RARE

## SPEAKERS

**Sarah Glass, PhD | n-Lorem Foundation**
Dr. Sarah Glass is the Chief Operating Officer of n-Lorem Foundation. Sarah received her PhD in Molecular Genetics at Ohio State University where she trained in rare inherited cancer syndromes. She has over 20 years of experience in clinical development and research across academia, pharmaceutical companies, and CROs. Sarah brings significant strengths and experience as an accomplished research geneticist, rare disease drug developer, and clinical trialist. She is acclaimed for forging key strategic partnerships across rare disease sectors and has driven efficiencies to decrease patient/caregiver burden in clinical research. Most notably, Sarah combines the professional expertise and training with the perspective of a parent. This allows Sarah to not only personally understand the challenges faced by our patients and their families, but also to translate this understanding into n-Lorem's paradigm shifting platform solution for the ultra-rare community.

**Daria Julkowska, PhD | European Joint Programme for Rare Diseases (EJP RD)**
Daria Julkowska has a PhD in molecular biology and pursued her scientific vocation by the post-doctoral experience in cellular biology, at Institut Pasteur, Paris and extensive training in communication and European Union counselling. She also holds MSc in Management of Research from the University of Paris Dauphine. She coordinated the European Joint Programme on Rare Diseases and is currently the scientific coordinator of ERDERA rare diseases partnership that brings together over 180 institutions representing different type of stakeholders (researchers, funders, clinicians, industry & patients) from 36 countries from Europe and beyond. She is involved in the rare diseases field since 2010. She developed and put into action a set of collaborations facilitating research, including the partnerships with European Research Infrastructures, Patients' Organizations and industry. She has an extensive knowledge and understanding of European funding schemes and programmes and serves as the chair of the Expert Group on support for the strategic coordinating process for European partnerships of the European Commission. In 2020 she received EURORDIS Black Pearls Award for the European Rare Diseases Leadership. This year (2024) she obtained the title of "Wybitny Polak" in France, a competition promoted by the Polish Promotional Emblem Foundation, the main goals of which are to create a positive image of Poles, show their achievements and distinguish and promote people who have achieved success in the country and abroad.

**Jan Procházka, PhD | Czech Center for Phenogenomics (CCP), Institute of Molecular Genetics of the Czech Academy of Sciences**
Dr. Jan Procházka is a distinguished developmental and cell biologist with a focus on the mechanisms underlying human rare diseases, use of transgenic models to elucidate complex genetic disorders and gene therapy development. With a PhD from Charles University and postdoctoral training at the University of California, San Francisco, Dr. Procházka has built a career in understanding the cellular and molecular mechanisms driving organ development and pathology. Currently serving as Deputy Director at the Czech Center for Phenogenomics, Dr. Procházka has been instrumental in advancing reverse genetics and phenotype characterization efforts, contributing to the functional annotation of nearly 500 genes with many associated with human pathologies. His leadership at CCP has solidified the center as a hub for the study of gene function, the generation of precise genetic models, and the full preclinical pipeline necessary for the development of novel therapies.

# UNLOCKING HOPE FOR THE ULTRA-RARE

## SPEAKERS

**Maciej K. Janik, MD, PhD | Medical University of Warsaw, ERN RARE-LIVER**
Maciej K. Janik, MD, PhD is a hepatologist at the Department of Hepatology, Transplantology and Internal Medicine of the Medical University of Warsaw. His passion is research focusing on autoimmune liver diseases and quality of life. He is involved in and holds leadership positions in a Quality of Life Working Group of the European Reference Network RARE-LIVER. He is involved in several international research projects that assess the impact of chronic diseases on patients' well-being, genetic factors in autoimmune liver disease, and novel biomarkers in these entities.

**Heather Olson, MD, PhD | Boston Children's Hospital**
Dr. Olson an assistant professor in the Department of Neurology, Division of Epilepsy and Clinical Neurophysiology at Boston Children's Hospital. She is a child neurologist with expertise in Epilepsy, Clinical Neurophysiology, Neurogenetics, and Fetal/Neonatal Neurology and she directs the CDKL5 Center of Excellence at Boston Children's Hospital. She completed a career development award from NINDS titled "Diagnosis and genotype-phenotype correlations in early life epilepsy and CDKL5 Deficiency Disorder". She is site-PI for the collaborative International CDKL5 Clinical Research Network (ICCRN) study, funded by NINDS. She has been site-PI for several industry-sponsored clinical trials in genetic Developmental and Epileptic Encephalopathies, and she has funding for a pilot study of ketogenic diet for prevention of epileptic spasms in infantile-onset genetic epilepsies. Dr. Olson has published on genotype-phenotype correlations in epilepsy genetics and the medical impacts of genetic diagnosis. Dr. Olson led a collaborative effort to first describe the recurrent genetic variant in PACS2 and its clinical presentation, and she provided a patient-derived cell line to support Gary Thomas' work investigating functional impacts. Dr. Olson in collaboration with Dr. Szczaluba are preparing an application to NINDS for a Natural History Study for PACS2-related disorders.

**Tomasz Grybek | Borys the Hero Foundation, EURORDIS**
Tomasz Grybek is a CEO of the Foundation of Borys the Hero, he is a member of the Board of Directors of EURORDIS – Rare Diseases Europe. Member representing patients' organizations nominated by the European Commission to the Paediatric Committee of the European Medicines Agency (EMA PDCO) and Member of the Coordinating Group of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA).
Patient Advocate involved as an e-PAG Member of ERN-ITHACA and Patient Board Member of MetabERN. Cooperates closely with the Rare Disease Centre of Medical University in Gdansk.
He is a father of a child living with rare neurological disease called metachromatic leukodystrophy.

**Prof. Steve Murray | The Jackson Laboratory**
Dr. Steve Murray is a Professor at the Jackson Laboratory (JAX) with more than 20 years of experience developing and studying mouse models of disease, including structural birth defects and other rare diseases. As Senior Director of Genetic Resource Science at JAX, his program focuses on the large-scale generation of mouse genetic resources for the greater scientific community, including the Knockout Mouse Phenotyping Program, which aims to interrogate gene function through the systematic deletion of every gene in the genome. His research focus includes the development and application of new technologies and methods to model rare disease mutations in mice. He is one of Principal Investigators of the JAX Center for Precision Genetics, which aims to build new models for rare disease with the goal of advancing therapeutic development for these conditions.

**Title: Angelman syndrome in Poland: current diagnosis and therapy status. Future directions for the community.**

*Suleja Agata, Milska-Musa Katarzyna, Przysło Łukasz, Bednarczyk Marzena, Kostecki Marcin, Matryba Paweł, Rozensztrauch Anna, Dwornik Michał, Opacki Marcin, Śmigiel Robert, Polish Association of Families with Angelman Syndrome [Stowarzyszenie Rodzin z Zespołem Angelmana], Cysewski Dominik, Łukasiewicz Kacper*

**Abstract:** Angelman syndrome (AS) is a rare disorder caused by imprinting errors and the loss of function of the maternal UBE3A gene copy. It is a severe neurodevelopmental condition that impairs multiple systems, making coordinated care by multiple specialists crucial. As of 2022, there was no reliable data on Polish patients with AS, in contrast to other countries. Our goal was to change this situation through caregivers-researchers collaboration. Initially as an informal group 'Angelman Syndrome Project' subsequently as 'Association of Families with Angelman Syndrome' caregivers participated in the research process, setting direction of the ongoing research.

We conducted an online survey covering aspects such as the age of diagnosis, type of genetic background, and access to specialist care. The analysis included 70 patients with a median age of 60 months and was recently published (Suleja et al., 2024; Orphanet J Rare Dis). The distribution of genetic backgrounds in Polish patients matches the published worldwide data, and the most advanced genetic testing methods are widely available. However, access to specialist care remains limited, and there is a significant delay between the onset of symptoms and diagnosis. Current ongoing comprehensive questionnaire study extends the most important aspects of the AS diagnosis and therapy in Poland.
Additionally the research part was supported by caregivers activities, such as online discussions about the challenges of caring for rare diseases and gatherings of families affected by these conditions.

---

**Title: Cure HSPB8**

*Kordala Anna, Cure HSPB8*

**Abstract:** HSPB8 Myopathy is an ultra-rare, adult-onset muscle disease first described in 2015 by Ghaoui and colleagues. Currently, there is no treatment available for this debilitating condition, with management focusing primarily on maintaining the patient's quality of life. Although only a few dozen cases have been identified so far, we believe this number significantly underrepresents the true prevalence of the disease.
We are proud to introduce Cure HSPB8, a research-focused, patient-driven advocacy group dedicated exclusively to HSPB8 Myopathy. Our vision is a future where HSPB8 Myopathy is conquered, treatments are accessible, and the community stands united. Our mission includes facilitating translational research, identifying the true number of affected individuals and families, and providing comprehensive, evidence-based information to patients, clinicians, and researchers through our website, curehspb8.org.

To achieve these goals, we have launched a Global Patient Registry in partnership with Sanford CoRDS, aiming to gain invaluable insights into the natural history of the disease. Our research efforts are focused on developing treatments through drug repurposing strategies and original drug development. To identify more HSPB8 Myopathy patients, we are actively raising awareness among physicians and academics.

We invite conference attendees to visit our poster and engage with us:

- **Clinicians**: Learn about HSPB8 Myopathy symptoms and the importance of referring patients for genetic testing.
- **Academics**: Explore available research resources and how we can support your work on HSPB8 Myopathy.
- **Patients and advocacy groups**: Share experiences and discuss the best ways to support our communities.
- **Data specialists**: Collaborate with us to uncover the true number of HSPB8 patients.
-

Together, we can end HSPB8 Myopathy.

**Title: The drug discovery journey for a patient with Dup15q Syndrome**

*Blanca Torroba, Berke Gurkan, Monika Hiller, Olena Fedorenko, Larissa Butler, Ethan Perlstein, Dario Magnani, Ludovico Buti, Michael Templin, Lauren Black, David Fischer, Roxana S Redis*

**Abstract:** Maternal 15q duplication (Dup15q) syndrome is a developmental disorder caused by the presence of at least one extra maternally derived copy of the Prader-Willi/Angelman critical region (PWACR). This region is approximately 5 Mb long and within chromosome region 15q11.2-q13.3. Maternal Dup15q syndrome is characterized by hypotonia and motor delays, variable intellectual disability, autism spectrum disorder and epilepsy. Although 40 genes are located in the PWACR, evidence supports the overexpression of the ubiquitin-protein E3A ligase (UBE3A) gene as the predominant molecular cause of the phenotypes observed in Dup15q syndrome. Therefore, the lowering of UBE3A expression by antisense oligonucleotides (ASOs) might be able to reduce the severity of the symptoms.

The goal of this project was to develop an ASO-based therapy for a single Dup15q patient. Non-allele specific ASOs targeting UBE3A transcripts were screened in control human fibroblasts using transfection. ASOs with 50% to 96% UBE3A knockdown efficiencies were selected for potency determination in fibroblasts, followed by immunotoxicity studies in human peripheral blood mononuclear cells (PBMCs) to minimize the risk of potential inflammatory related adverse events upon administration in the patient.
ASOs were further selected based on UBE3A mRNA knockdown efficacy and potency in Dup15q iPSC-derived cortical neurons. Ongoing studies are focused on characterizing the functional phenotypes of control and Dup15q patient neurons using Microelectrode Arrays (MEAs), followed by phenotype rescue for lead selection.

---

**Title: Leveraging drug repurposing screens for rare disease using cell painting and AI**

*Jeroen Esselink, Gurvan Mahe, Peter Racz, Matt Campbell, Ethan Perlstein, Kristin Kantautas, Dominik Cysewski, Kacper Łukasiewicz, Piotr Kośla and André van Marle*

**Abstract:** Drug repurposing is one of the few opportunities to address the unmet need for treatment of ultra rare diseases caused by genetic mutations. The identification of potential drug repurposing candidates relies on screening repurposing compound collections in relevant assays that capture the molecular mechanisms underlying the disease. However, when a disease is so rare that little is known about the function of the mutated protein, relevant assays are sparse and may require deployment of unbiased screening approaches. In this respect, Cell Painting might be part of the solution. This image-based technique allows morphological cell profiling by using multiplexed fluorescent dyes in high throughput.

Here, we apply cell painting and machine learning to examine over 3000 cellular morphological features in PACS2 E209K and unaffected "healthy" primary fibroblasts. We successfully identified approximately 100 cellular features that allow discrimination between these cell types. After subsequent optimization and full automation of this assay, it was fit for high throughput screening and allowed for investigation of ~6000 repurposing compounds for their ability to push PACS2 E209K cells towards a cellular morphology resembling that of "healthy" cells. Approximately 60 hits were identified that could be grouped in several modes of actions. Finetuning of our Machine learning models and further examination of the performance of the hits in compound concentration curves, allowed us to select a handful promising candidates for further validation in other advanced in vitro and in vivo models.

**Title: New treatments for children with achondroplasia**

*Maria Jedrzejczyk, Adam Kubicki-Fraczek, Michal Ordaka, Magdalena Bujalska-Zadrozny*

**Abstract:** Achondroplasia, the most common form of dwarfism, is caused by a pathogenic variant in the FGFR3 gene, disrupting endochondral ossification. Traditional management has been primarily symptomatic, addressing complications such as foramen magnum stenosis and sleep-disordered breathing. Recent advancements have introduced precision therapies targeting the molecular pathogenesis of achondroplasia.

Vosoritide, a C-type natriuretic peptide analogue, has been approved to enhance linear growth in children with achondroplasia. Clinical trials have demonstrated significant increases in growth velocity and improved body proportionality, counteracting the inhibitory effects of the FGFR3 mutation. Infigratinib, an orally administered FGFR1–3 inhibitor, has shown promise in early trials, demonstrating increased growth rates and improved skeletal development.

Navepegritide, a long-acting CNP analogue, is under investigation for its potential to provide consistent growth stimulation with weekly dosing, showing favorable tolerance and efficacy in preliminary data. RBM-007, an RNA aptamer targeting FGF2, and SAR-442501, a monoclonal antibody against FGFR3, are in early clinical development, each aiming to normalize chondrocyte proliferation and endochondral ossification.

These novel therapies represent a paradigm shift in achondroplasia management, offering potential for improved growth outcomes and reduced disease burden. Ongoing studies are essential to fully evaluate long-term safety, efficacy, and the impact on overall quality of life for individuals with achondroplasia.

---

**Title: Proteomic analysis of soft tissues from mice with PACS2 gene mutation**

*Tomasz Kowalczyk, Arkadiusz Żbikowski, Kacper Łukasiewicz, Michał Ciborowski, Dominik Cysewski*

**Abstract:** Phosphofurin acidic cluster sorting protein 2 (PACS2) is a multifunctional protein critical for maintaining cellular homeostasis. Together with PACS1, PACS2 plays a crucial role in the transport of proteins between cellular membranes, thereby contributing to the regulation of essential processes such as apoptosis, mitochondria-endoplasmic reticulum interactions, and, consequently, Ca2+ flux, lipid biosynthesis, and autophagy. The significance of the PACS2 gene becomes particularly evident when considering the biological effects of mutations in this gene. Missense mutations, such as E209K and E211K (glutamic acid-to-lysine substitutions), have been associated with PACS2 syndrome, an ultra-rare disease. To understand the molecular alterations occurring in soft tissues, proteomic analyses were performed using tissues from a Pacs2+/E209K mouse model (10-12 weeks old). Tryptically digested proteins were separated using a nano-LC system coupled with Orbitrap Fusion MS, and data collection was performed via Data Independent Analysis (DIA). We quantified over 7,000 proteins, depending on tissue type. Tissues from mice carrying the PACS2 gene mutation exhibited a greater propensity for potential fibrosis in the liver. The spleen also showed similar tendencies toward fibrosis; however, at this stage of mouse development, these findings are not definitive. Additionally, liver tissue displayed abnormalities in lipid metabolism and potential lipid accumulation, as well as disruptions in Na+ ion transport. In contrast, the kidneys, unlike the liver, showed a higher potential for localized inflammation in mice with the PACS2 gene mutation. The kidneys also exhibited potential abnormalities in intracellular transport and ion metabolism, particularly involving Ca2+, as well as possible changes in the structure of the cellular cytoskeleton. Notably, the PACS2 mouse heart did not exhibit any significant molecular changes compared to controls at this stage of development.

www.PACS2research.org
www.misjaLEK.pl