Solving the unsolved Rare Diseases

Public Symposium 2023

26 April 2023

Online & Prague, CZ

The Solve-RD project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779257.

Public Symposium

SOLVE-RD FINAL MEETING 2023

THE IMPACT OF SOLVE-RD ON RESEARCH & CARE OF RARE DISEASE PATIENTS

WEDNESDAY
26 APRIL 2023
08.30 AM – 12.30 PM

REGISTER NOW

TOWARDS THE FUTURE OF RARE DISEASE DIAGNOSTICS

08.30 AM – 10.15 AM | CHAIR: ANA RATH & GULCIN GUMUS

Keynote Lecture

TOWARDS A PERSONALISED SYSTEMS BIOMEDICAL APPROACH FOR THE DIAGNOSIS OF INHERITED METABOLIC DISEASES
Ines Thiele, University of Galway

Keynote Lecture

HYPERPERSONALIZED THERAPIES FOR THE LONG TAIL OF GENETIC DISEASE
Timothy Yu, Boston Childrens Hospital & Harvard Medical School

LOOKING FURTHER: PATIENT ORGANIZATIONS AND ADVANCING RD RESEARCH ON DIAGNOSIS
Gulcin Gumus, Eurordis

SOLVE-RD 2.0
Olaf Riess, University of Tübingen

IMPACT OF SOLVE-RD ON RESEARCH & CARE OF RARE DISEASE PATIENTS

10.45 AM – 12.30 PM | CHAIR: HAN BRUNNER & HOLM GRAESSNER

KEY SOLVE-RD ACHIEVEMENTS
Holm Graessner, University of Tübingen

GENOMIC REANALYSIS OF A PAN-EUROPEAN RARE DISEASE RESOURCE YIELDS >500 NEW DIAGNOSES
Alex Hoischen, Radboud UMC & Sergi Beltran, CNAG-CRG

ROUND TABLE: THE FUTURE OF RARE DISEASE DIAGNOSTICS IN EUROPE
Simona Bellagambi, Eurordis Board of Directors & Uniamo | Daria Julkowska, INSERM | Christina Kyriakopoulou, European Commission, DG Research & Innovation | Milan Macek, Charles University Prague | Olaf Riess, University of Tübingen | Lisenka Vissers, Radboud UMC | Timothy Yu, Boston Childrens Hospital & Harvard Medical School

www.solve-rd.eu

Public Symposium: The impact of Solve-RD on research & care of rare disease patients

Towards the future of Rare Disease Diagnostics

8:30 am – 10:15 am | Chair: Ana Rath & Gulcin Gumus

Keynote lecture

Towards a personalised systems biomedical approach for the diagnosis of inherited metabolic diseases

Ines Thiele, University of Galway

In this talk, I will present our recent advances in generating whole-body models of human metabolisms and demonstrate that they can predict known biomarkers of numerous inherited metabolic diseases. Furthermore, I will present how these models can provide further support for candidate genetic defects by predicting candidate biomarkers and comparing them with metabolomic data. Finally, I will show that these models can predict novel metabolite biomarkers that could aid in the diagnosis of an inherited metabolic disease.

Professor **Ines Thiele** is the principal investigator of the Molecular Systems Physiology group at the University of Galway, Ireland. Her research aims to improve the understanding of how diet influences human health. Therefore, she uses a computational modelling approach, termed constraint-based modelling, which has gained increasing importance in systems biology. Her group builds comprehensive models of human cells and human-associated microbes; then employs them together with experimental data to investigate how nutrition and genetic predisposition can affect one's health. In particular, she is interested in applying her computational modelling approach for better understanding of inherited and neurodegenerative diseases. Ines Thiele has been pioneering models and methods allowing large-scale computational modelling of the human gut microbiome and its metabolic effect on human metabolism.

Ines Thiele earned her PhD in bioinformatics from the University of California, San Diego, in 2009. Ines Thiele was an Assistant and Associate Professor at the University of Iceland (2009 - 2013), and Associate Professor at the University of Luxembourg (2013-2019).

In 2013, Ines Thiele received the ATTRACT fellowship from the Fonds National de la Recherche (Luxembourg). In 2015, she was elected as EMBO Young Investigator. In 2017, she was awarded the prestigious ERC starting grant. In 2020, Ines Thiele was named a highly cited researcher by Clarivate, and received the NUI Galway President's award in research excellence. She is an author of over 100 international scientific papers and reviewer for multiple journals and funding agencies.

Keynote lecture

Hyperpersonalized therapies for the long tail of genetic disease

Timothy Yu, Boston Childrens Hospital, Harvard Medical School

Dr. **Timothy Yu** is a neurogeneticist at Boston Children's Hospital and Harvard Medical School. He obtained his A.B. in biochemistry at Harvard College and his MD/PhD program at UCSF. After completing neurology residency at Massachusetts General Hospital and Brigham and Women's Hospital, he joined the faculty at Boston Children's Hospital, where he focuses on human genetics, neuroscience, and molecular medicine. He is a Staff Physician in the Division of Genetics and the Department of Neurology at BCH, Associate Professor at Harvard Medical School and an Associate Member of the Broad Institute. His research group works at the intersection of neurogenetics, neurobiology.

Looking further: Patient organizations and advancing RD research on diagnosis

Gulcin Gumus, Eurordis

This talk will be on the next steps for EURORDIS, as an umbrella patient organisation, to contribute to advancing diagnosis research and to support people living with ultra-rare and undiagnosed diseases at national and international levels.

Gulcin Gumus works at EURORDIS as Research and Policy Senior Manager. She is responsible for supporting the project management of the EU-funded pre-clinical research and research infrastructure projects as well as working on public affairs and advocacy topics relevant to rare disease research & policy. She is the coordinator of the EURORDIS Newborn Screening Working Group.

Gulcin did her Bachelor studies in Molecular Biology and Genetics. She holds a PhD in Fetal and Perinatal Medicine from the University of Barcelona where she worked on research projects by developing pre-clinical therapies for rare prenatal and childhood diseases.

Solve-RD 2.0

Olaf Riess, University of Tübingen

Olaf Riess will present an outlook as to how a Solve-RD 2.0 might look like. On one hand he will cover realistic follow-up and continuation options that focus on scientific and technological developments as well as on structural and institutional usage of Solve-RD achievements. On the other hand, he will present possible aspects of a Solve-RD 2.0 that might lie a bit further ahead, in the future.

Prof. **Olaf Riess**, MD, is full professor for Medical Genetics and Director of the Institute of Medical Genetics and Applied Genomics at the University of Tübingen. He is also founder and acting director of the Rare Disease Center Tübingen. He has more than 20 years of experience in clinical genetics and research of genetically caused disorders. He currently is and has been coordinator of numerous international, European and national funded consortia such as EUROSCA, MEFOPA, TECHGENE, RATstream, NeurOmics, and SOLVE-RD (together with Holm Graessner). He is also PI and spokesperson of one of four DFG funded NGS Competence Centers in Germany. Olaf serves in numerous advisory boards such as the German initiative for Rare

Diseases (NAMSE), the EFSN task force on spinocerebellar ataxias, the executive member of the Ataxia study group (ASG), as a board member of the International Rare Disease Research Consortium IRDiRC (Diagnostics Scientific Committee), the rare disease working group of the 1+MG project, and most recently to the Ministry of Health on the implementation of genome diagnostics into the health care system. For several years he was also a board member of the study section Neuroscience (Fachgutachter) of the German Research Foundation (DFG) and an associated Member of the Commission on genetic diagnostics (Gendiagnostik-Kommission) of the Ministry of Health (BfG). He is an active member of three European Reference Networks (ERNs). From 2016 to 2017 he served as President of the European Society of Human Genetics (ESHG). Since June 2021 he serves as President of the German Human Genetics Society. Published >480 papers.

Impact of Solve-RD on research and care of RD patients

10:45 am – 12:30 pm | Chair: Han Brunner & Holm Graessner

Key Solve-RD achievements

Holm Graessner, University of Tübingen

This talk will summarize and highlight the main Solve-RD achievements. It will in particular focus on the achievements that Solve-RD has reached with regard to the three key challenges that the project identified when starting. These challenges are: (i) Accessibility of unsolved RD cohorts with comprehensive genetic and phenotypic data; (ii) New and improved approaches for the discovery of novel molecular causes; and (iii) Translate discoveries to impacting clinical practice.

Holm Graessner has graduated in Biomedical Engineering, Electrical Engineering, German Language and Literature, Philosophy as well as Business Administration. He received his PhD “Summa cum laude” in 2004 and, then, he obtained his MBA degree in 2008.

He has been Managing Director of the Rare Disease Centre, since 2010, at the University and University Hospital Tübingen, Germany. He is Coordinator of the European Reference Network for Rare Neurological Diseases (ERN-RND). Together with Olaf Riess, he coordinates the H2020 Solve-RD project on “Solving the unsolved rare diseases”.

He has been co-leading one of the four working groups of the German Action Plan for Rare Diseases from 2010 until 2013. Since 2020, as a fellow of the European Academy of Neurology (EAN) he is a member of the management teams of the Neurogenetics Panel and the Rare Neurological Disease Coordinating Panel of the EAN.

Genomic Reanalysis of a Pan-European Rare Disease Resource Yields >500 New Diagnoses

Sergi Beltran, CNAG-CRG & Alexander Hoischen, Radboud UMC

We will present a key Solve-RD achievement: systematic cutting-edge research-driven re-analysis and ad-hoc expert review for about 10,000 undiagnosed individuals from more than 6,000 families resulted in overall diagnostic yield of 12.6%. Systematic reanalysis contributed to this by establishing a genetic diagnosis in 8.5% of the families. Discovered novel disease-causing variants comprise a broad range of genomic variants, including SNVs/InDels, non-canonical splice variants, mtDNA variants, copy number variations, structural variants, mobile element insertions and short tandem repeats.

Sergi Beltran holds a PhD in Biology and is the Head of the Bioinformatics Unit at the National Center of Genomic Analysis in Barcelona (CNAG-CRG) since 2012. Sergi's group is devoted to the development of sequencing data analysis and management tools and pipelines. The group collaborates with several national and international projects, mostly related to human health. Specifically on Rare Diseases, he leads the RD-Connect platform development (https://platform.rd-connect.eu), facilitating standardized data collation, sharing and analysis for undiagnosed diseases. Also on Rare Diseases, Sergi co-leads the ELIXIR Rare Disease Community and is a partner in H2020 Solve-RD (www.solve-rd.eu), H2020 EJP-RD (www.ejprarediseases.org), H2020 Genomed4ALL (https://genomed4all.eu/), IMI2 Screen4Care (https://screen4care.eu/) and Marató TV3 iGenCO. Sergi also participates in other projects including cancer or common diseases, such as H2020 B1MG, H2020 3TR, ISCIII-IMPACT and Ris3Cat VEIS, and collaborates with GA4GH, IRDiRC, MatchMaker Exchange and the 1+ Million Genomes Initiative. Sergi is an author in more than 80 peer-reviewed publications.

Alexander Hoischen's research group 'Genomic Technologies and Immuno-Genomics' has expertise in the identification of rare disease genes using latest genomics tools – since recently with a particular focus on immune-related disease genes. We have been the first identifying a disease causing dominant *de novo* mutation for a Mendelian disorder by exome sequencing followed by the identification of several disease genes for rare diseases. Following a six months' research stint in 2013 in the laboratories of my collaborators Prof. Eichler and Prof. Shendure (UW, Seattle; USA), I established the latest technology for accurate and large scale targeted re-sequencing (smMIPs) in Nijmegen. Recently we started to apply long-read sequencing and long-read mapping to unsolved rare disease cases.

After we applied latest genomic technologies successfully in the research of rare diseases, e.g. WES and MIPs; these were subsequently integrated into routine diagnostics. My research group now focuses on the genetic basis of immune diseases, with the most recent identification of a novel immunodeficiency that predisposes men to severe COVID-19.

In the last years we have shown that applications of novel and disruptive technologies allow new scientific insights and rapid translation into clinical and diagnostic practice at unprecedented speed. As part of my role in rare disease genomics I co-lead a work package in the EU-funded H2020 project SOLVE-RD (www.solve-rd.eu). I was also awarded the full PI status at the Radboudumc from 2019 onwards.

Round table: The Future of Rare Disease diagnostics in Europe

Simona Bellagambi, Eurordis Board of Directors and Uniamo | Han Brunner, Radboud UMC (moderator) | Daria Julkowska, INSERM | Christina Kyriakopoulou, European Commission, DG Research & Innovation | Milan Macek, Charles University Prague | Olaf Riess, University of Tübingen | Lisenka Vissers, Radboud UMC | Timothy Yu, Boston Childrens Hospital and Harvard Medical School

At this round table representatives from the rare disease community discuss what needs to change in rare disease diagnostics, the challenges and bottlenecks to take the next steps as well as concrete solutions on national, local, European and global level.

Simona Bellagambi is the representative of UNIAMO – the Italian Alliance for rare diseases –for the international relations. She was appointed Deputy General Secretary of EURORDIS-Rare Diseases Europe in November 2022 and has been part of the Board of Directors of EURORDIS since 2012.

She is the aunt of a twentyfive-year-old girl with Tuberous Sclerosis.

Simona served the Italian TSC Association from 1999 to 2009 as National Secretary and representative in the international network. She was also in charge of the designated help line service and contributed to the set-up of the Italian network of Centres of Reference for TSC. In addition, she has collaborated with UNIAMO, the Italian Federation for Rare Diseases, for which she became the representative in EURORDIS' Council of National Alliances in 2005. She has also, been the promoter and coordinator in Italy of international awareness events, such as Rare Disease Day and Decide sessions within the POLKA: Patients' Consensus on Preferred Policy Scenario for Rare Diseases project, as well as workshops on Centres of Expertise for the Rapsody project. In addition, Simona has spoken on RD issues in several national and international conferences.

Simona is a EURORDIS EUROPLAN advisor. She is a member of the Council of National Alliances. She is member of the NBS Working group and of the Community Engagement Task Force created by EURORDIS that support the interaction and the engagement with the different initiatives and networks currently existing in the field of diagnosis at the European and International levels

Han Brunner is Head of the Institute of Human Genetics at Nijmegen and Maastricht Medical Centers, where he pioneers genomic technologies in medical genetics. Han believes that rapid implementation of genomic technologies in Medicine is advantageous for patients, and families, and can make the care for people with rare diseases more effective.

His scientific work has shown that new mutations are the main cause of intellectual disability, which led to the acceptance of exome sequencing as a first-tier test in neurodevelopmental disorders. Recently, his group established the landscape of autosomal recessive diseases in European populations.

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 is the Scientific Coordinator of the European Joint Programme on Rare Diseases that brings together over 130 institutions representing different type of stakeholders (researchers, funders, clinicians & patients) from 35 countries from Europe and beyond, and is also responsible for the coordination of the IRDiRC Scientific Secretariat. 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 and Patients' Organizations. 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.

Dr **Christina Kyriakopoulou** is a senior policy officer in health research at the Directorate General for Research and Innovation at the European Commission. She holds a PhD in biochemistry, and she held postdoctoral positions in the areas of molecular biology and genome analysis. Christina joined the European Commission in 2003 and contributes to the European Union's research policies and the work programmes development for health research in the areas of genomics, rare diseases, innovative technologies of health data analyses, including in-silico tools and artificial intelligence for health.

Professor **Milan Macek Jr**. MD, DSc is the chairman of the largest academic medical / molecular genetics institution in the Czech Republic – Department of Biology and Medical Genetics of Charles University Prague-2nd School of Medicine and Motol University Hospital, and of the National Coordination Centre for Rare Diseases (www.nkcvo.cz; NKCVO) responsible for implementation of the ten year national strategy on rare diseases and resulting three national action plans. In addition, he is chairing the national Rare Disease Taskforce at the Ministry of Health. In this capacity his institute has been serving as a "clearing centre" for the dissemination of knowledge gathered within various international projects on rare disease-related research and diagnostics (e.g. EuroGentest.org, RD-Connect.eu, Solve-RD.eu, Norway Grants) to partners in Eastern Europe, Transcaucasia and the Middle East. In this capacity Prof. Macek is also the Czech National coordinator of Orpha.net. In his capacity as chairman of NKCVO he assured that since 2017 Czechia is ranking first within EU13 in terms of participation in European Reference Networks (ERN) for rare diseases.

Prof. Macek is also the past President of the European Society of Human Genetics (www.eshg,org; 2010-2011 ESHG), currently serves at the ESHG liaison for European National Human Genetics Societies (https://www.eshg.org/76.0.html). Under his leadership medical genetics was recognized as an official EU specialty in the Professional Qualifications Directive in 2011. He also closely collaborated with the Council of Europe on the ratification of the Additional protocol on genetic testing for health purposes to the Oviedo convention (2019). He had also been the past-board member of the European Cystic Fibrosis Society (ECFS.eu; 2007-2014) and is the current member of the European Cystic Fibrosis Registry board (https://www.ecfs.eu/ecfspr), whereby he published seminal papers on the disparities in cystic

fibrosis care between the “New” and “old” EU Member States. Moreover, he had also been the board member of the European Society of Human Reproduction and Embryology (www.eshre.eu; ESHRE) where he was responsible for three joint position statements of ESHG and ESHRE in the field of reproductive genetics as their senior author. Prof. Macek served at the European Commission Expert Group on Rare Diseases (formerly www.eucerd.eu) and is currently involved in the European Board of Member States for European Reference Networks for Rare Diseases (https://ec.europa.eu/health/ern_en), including the newly formed EU Advisory Board on ERN sustainability. He had also been member of the Diagnostic Committee of the International Rare Disease Consortium (www.irdirc.org). Prof. Macek is currently the president of the Czech Society of Medical Genetics and Genomics (www.slg.cz). Finally, he was the chief government advisor of the CZ EU Council presidency under which the EU Council recommendation on a field of action in rare diseases was been adopted in 2009.

Prof. Macek did his postdoctoral studies at the Department of Medical and Human Genetics at Humboldt University Berlin (1989-1992) followed by McKusick-Nathans Centre for Genetic Medicine, Johns Hopkins University in Baltimore (1992-1996). In 1992 he was also a fellow at Harvard School of Medicine in the field of non-invasive prenatal diagnosis of rare diseases.

His main research and clinical interests are in the field of molecular genomics of rare diseases, including their deep phenotyping, and in ways on how to bring genomics knowledge to the bedside via targeted therapies with orphan medicinal products. He has also been involved in health economics “cost of illness” studies in this regard. His citation index is over 11,000x with H –index of 34.

Prof. **Olaf Riess**, MD, is full professor for Medical Genetics and Director of the Institute of Medical Genetics and Applied Genomics at the University of Tübingen. He is also founder and acting director of the Rare Disease Center Tübingen. He has more than 20 years of experience in clinical genetics and research of genetically caused disorders. He currently is and has been coordinator of numerous international, European and national funded consortia such as EUROSCA, MEFOPA, TECHGENE, RATstream, NeurOmics, and SOLVE-RD (together with Holm Graessner). He is also PI and spokesperson of one of four DFG funded NGS Competence Centers in Germany. Olaf serves in numerous advisory boards such as the German initiative for Rare Diseases (NAMSE), the EFSN task force on spinocerebellar ataxias, the executive member of the Ataxia study group (ASG), as a board member of the International Rare Disease Research Consortium IRDiRC (Diagnostics Scientific Committee), the rare disease working group of the 1+MG project, and most recently to the Ministry of Health on the implementation of genome diagnostics into the health care system. For several years he was also a board member of the study section Neuroscience (Fachgutachter) of the German Research Foundation (DFG) and an associated Member of the Commission on genetic diagnostics (Gendiagnostik-Kommission) of the Ministry of Health (BfG). He is an active member of three European Reference Networks (ERNs). From 2016 to 2017 he served as President of the European Society of Human Genetics (ESHG). Since June 2021 he serves as President of the German Human Genetics Society. Published >480 papers.

Lisenka Vissers is appointed as professor of Translational Genomics at the department of Human Genetics at the Radboudumc in Nijmegen, The Netherlands. She performs her research to work at the crossroads of cutting edge science, genetic diagnostic testing, as well as tertiary level clinical care. Her work focusses on the elucidation of the genetic etiology of rare disease, and neurodevelopmental disorders in particular. To achieve this, she performs clinical utility studies with the latest technological innovations on longitudinal patient cohorts collected over more than 20 years. The lessons learned are subsequently translated to their use in every day clinical practice, allowing to benefit all patients with rare disease. Examples include the translation of genomic microarrays, exomes and genomes into routine genetic diagnostic care, which in parallel has also resulted in the elucidation of more than 85 novel disease-gene associations.

Dr. **Timothy Yu** is a neurogeneticist at Boston Children's Hospital and Harvard Medical School. He obtained his A.B. in biochemistry at Harvard College and his MD/PhD program at UCSF. After completing neurology residency at Massachusetts General Hospital and Brigham and Women's Hospital, he joined the faculty at Boston Children's Hospital, where he focuses on human genetics, neuroscience, and molecular medicine. He is a Staff Physician in the Division of Genetics and the Department of Neurology at BCH, Associate Professor at Harvard Medical School and an Associate Member of the Broad Institute. His research group works at the intersection of neurogenetics, neurobiology.

Stay tuned for live updates during the conference by following Solve-RD on Twitter at @solve_RD and please use our hashtag #solveRD if you tweet during the event!