Fondation Maladies Rares. *Rare Dis Orphan Drugs J* 2022;1:xx
DOI: 10.20517/rdodj.2020.37

Rare Disease and Orphan Drugs Journal

Conference Report

Open Access

Foundation for Rare Diseases Annual Scientific Conference: Colloque Scientifique Annuel 2022

Fondation Maladies Rares

The scientific symposium was organized by the Foundation For Rare Diseases on 31 May 2022 in Paris. This event offers a day of exchange, debate, and meetings for all those involved in rare diseases, and it encourages the emergence of new research projects. The program is built around presentations of the Foundation's award-winning projects and the sharing of experiences. Thanks to all participants, the organizing team, and the supporting staff, the scientific symposium provided an enjoyable, lively atmosphere, the perfect prerequisite for productive discussions. In the following, we report on the scientific sessions and summarize their main scientific content, including topics of discussion.

How to cite this article: Fondation Maladies Rares. Foundation for Rare Diseases Annual Scientific Conference: Colloque Scientifique Annuel 2022. *Rare Dis Orphan Drugs J* 2022;1:14. http://dx.doi.org/10.20517/rdodj.2022.10

Received: 5 Jul 2022 **Accepted**: 6 Jul 2022 **Published**: 11 Jul 2022

Academic Editor: Daniel Scherman **Copy Editor**: Jia-Xin Zhang **Production Editor**: Jia-Xin Zhang

POSTER PRESENTATIONS

P1

MOOC: "diagnosing rare diseases: from the clinic to research and back"

Roseline Favresse[1,4], Laurence Faivre[2], Chrystelle Colas[3], Virginie Bros-Facer[4], Evan Gouy[5], Magda Granata[1]

[1]Fondation Maladies Rares, Paris, France.
[2]ERN Ithaca, Filière AnDDI-Rares, FHU Médecine Translationnelle et Anomalies du Développement TRANSLAD, CHU Dijon, UMR-Inserm 1231 GAD team, Dijon, France.
[3]ERN Genturis, Department of Genetics, Curie Institute, Paris, France.
[4]EURORDIS, Paris, France.
[5]Genetics Department, University Hospital of Lyon, Bron, France.

Correspondence to: Dr. Magda Granata, Fondation Maladies Rares, Paris, France. E-mail: magda.granata@fondation-maladiesrares.com

Launched in 2019, the European Joint Programme on Rare Diseases (EJP RD) brings over 130 institutions from 35 countries to create a comprehensive, sustainable rare disease ecosystem allowing a virtuous circle among research, care, and medical innovation.

Within the EJPRD, the French Foundation for Rare Diseases coordinates the development and

implementation of a streamlined academic online program on rare diseases research, organized as a series of five massive open online courses (MOOCs).
These five MOOCs cover the following topics:
1. Diagnosing rare diseases: from the clinic to research and back.
2. Innovative personalized therapies.
3. Translational research applied to rare diseases.
4. Clinical trial methodologies.

Rare diseases data: Ethics and regulatory challenges.

Each course is built with key opinion leaders and experts, including European Reference Networks representatives. MOOCs are freely accessed and hosted by the eLearning platform FutureLearn.

The first MOOC explores the diagnostic pathway of rare diseases from both clinical and research perspectives. The first two sessions took place in spring and autumn 2021, whereas the third one is currently ongoing. Thus far, more than 4000 participants from 140 countries have enrolled. These first sessions confirmed the need for training in diagnostic research for rare diseases in Europe and beyond. The extremely diverse audience of students, doctors, researchers, patients, patient representatives, etc., demonstrated the value of tailored training from novice to expert.

The four other MOOCs will be launched between 2022 and 2023 with the aim to reach a wider and wider public, thus boosting awareness of rare diseases.

P2

Innovative pedagogy: DEFIGAME and APOGEE, two new e-tools for the ERN ITHACA MOOC

Anne Hugon[1], Vincent Des Portes[2,3], Cora Cravero[4], Boris Chaumette[5], Sandrine Daugy[6], Solveig Heide[7], Caroline Immesoete[3], Denise Laporte[8], Isabelle Marchetti-Waternaux[9], Sylviane Peudenier[10], Marie-Pierre Reymond[11], Jonathan N. Berg[12], Jill Clayton-Smith[13], Maurizio Genuardi[14], Martin Krahn[15], Ute Moog[16], Edward Tobias[17], Peter Turnpenny[18], Johannes Zschocke[19], Dorica Dan[20], Sofia Douzgou Houge[21], Marianne Le Dref[22], Laurence Faivre[23,24], Rick Hennekam[25], Tjitske Kleefstra[26], A Manuta[27], Giovanni Mosiello[28], Alessandra Renieri[29], Samia Selatnia[22], Marco Tartaglia[30], Zeynep Tümer[31], Birute Tumiene[32], Dagmar Wieczorek[33], Lisenka Vissers[34], Klea Vyshka[22], Giuseppe Zampino[35], Alain Verloe[36,37]

[1]ITHACA, CR-AD Département de Génétique, APHP Paris Nord Université Robert DEBRE, Paris, France.
[2]Service de Neuropédiatrie, Hospices Civils de Lyon, Lyon, France.
[3]DéfiScience, Hospices Civils de Lyon, Lyon, France.
[4]Reference Centre for Rare Diseases with Psychiatric Manifestations, APHP.SU - Pitié-Salpêtrière hospital group, Paris, France.
[5]Reference Centre for Rare Diseases with Psychiatric Manifestations, Psychiatry-Neuroscience University hospital Sainte Anne, Paris, France.
[6]Association Génération 22, Paris, France.
[7]Reference Centre for Rare Intellectual Disabilities, APHP.SU - Pitié-Salpêtrière hospital group, Paris, France.
[8]Association Synrome d'Angelamn AFSA, Paris, France.
[9]Association Valentin APAC , Paris, France.
[10]Reference Centre for Rare Diseases, Rare Intellectual Disabilities and Multiple Disabilities, CHRU de Brest, Brest, France.
[11]DéfiScience, HCL Hospices Civils de Lyon, Lyon, France.
[12]Department of Clinical Genetics, Ninewells Hospital and Medical School, Dundee, UK.
[13]Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust, Manchester, UK.
[14]UOC Genetica Medica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
[15]Département de Génétique Médicale, APHM, Hôpital Timone Enfants, Marseilles, France.
[16]Clinical genetic department, Heidelberg University, Heidelberg, Allemagne.
[17]Academic Unit of Medical Genetics and Clinical Pathology, Laboratory Medicine Building, Queen Elizabeth University Hospital, University of Glasgow, Glasgow, UK.
[18]Clinical Genetics Department,, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK.

[19]Institute of Human Genetics, Medical University Innsbruck, Innsbruck, Autriche.
[20]Romanian National Alliance for Rare Diseases , Zalau, Roumanie.
[21]Avdeling for medisinskgenetikk, Haukeland universitetssjukehus, Haukeland, Norvège.
[22]ITHACA, Département de Génétique, APHP Paris Nord Université Robert DEBRE, Paris, France.
[23]Dept of Genetics and Centres of Reference for Development disorders and intellectual disabilities, CHU Dijon, Dijon, France.
[24]AnDDI Rare, CHU, Université de Bourgogne , Dijon, France.
[25]Department of Pediatrics, Academic Medical Centre, Amsterdam UMC, Amsterdam, Pays-Bas.
[26]Department of Human Genetics, Radboud University Medical Center, Nijmegen, Pays-Bas.
[27]Department of Urology, CHU, University of Rennes, Rennes, France.
[28]Departmentof Surgery, Urology and Neuro-Urology, Bambino Gesù Pediatric Hospital, Rome, Italy.
[29]Medical Genetics, AziendaOspedaliero-Universitaria Senese, Siena, Italy
[30]Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy.
[31]Department of Clinical Genetics, Copenhagen University Hospital, Rigshospitalet, Copenhaguen, Danemark.
[32]Clinical genetic department, Vilnius University Hospital Santaros Klinikos, Santariskiu, Vilnius, Lituanie.
[33]Human Genetics, Institute of Human Genetics and Anthropology, Heinrich Heine University, Düsseldorf, Allemagne.
[34]Department of Human Genetics, Radboudumc University, Nijmegen, Pays-Bas.
[35]Department of Woman and Child Health, Center for Rare Diseases and Birth Defects, Institute of Pediatrics, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.
[36]Département de Génétique, APHP Paris Nord Université Robert Debré, Paris, France.
[37]ITHACA, APHP Paris Nord Université Robert DEBRE, Paris, France.

Correspondence to: Anne Hugon, ITHACA, CR-AD Département de Génétique,APHP Paris Nord Université Robert DEBRE, Paris, France. E-mail: anne.hugon@aphp.fr

The ERN ITHACA RDB AP-HP, in Paris European Reference Network on Rare Congenital Malformations, Autism, and Intellectual Disabilities brings together experts from 70 University Hospitals in 22 European states. It covers more than 5000 rare genetic disorders. We want to offer free eLearning and eHealth tools in the European space as well as online learning and training opportunities to young specialists.

Défigame is a serious game created by FNMR "DéfiScience" dedicated to rare neurodevelopmental diseases (NDD). Its main objective is to encourage and develop screening and etiological diagnostic practices for NDD. The serious game is designed alongside the help of parents and specialists, and it allows medical practitioners to reinforce their knowledge in the diagnostic strategies and care of neurodevelopmental disorders in an interactive way, in order to implement clinical practice recommendations and coordinate activities of providing adequate healthcare and follow-up of patients [project co-financed, CEF EU2018-FR-IA-0184].

APOGeE (A Practical Online Genetics e-Education), an online interactive medical genetics textbook built with Moodle, written by various authors from the ITHACA network and other ERNs, will cover topics about biological genetics, formal genetics, a clinical and physiological approach to genetic diseases, precision medicine, and treatment of genetic diseases. By contributing to a structured postgraduate education program in the field of human genetics and rare diseases, the project aims to provide free and open-source interactive and asynchronous medical genetics learning materials for doctors and researchers from Europe and beyond, as well as from all socioeconomic backgrounds [project co-financed, CEF EU2020-FR-IA-0128].

P3

What is the impact of medical treatment on the daily lives of French patients with Wilson's disease?

Caroline Roatta

Association Bernard Pépin pour la maladie de Wilson, Service Neurologie Hôpital Lariboisière, 2 rue Ambroise Paré, Paris, France.

Correspondence to: Mrs. Caroline Roatta, ssociation Bernard Pépin pour la maladie de Wilson, Service Neurologie Hôpital Lariboisière, 2 rue Ambroise Paré, Paris, France. E-mail: wilson@abpmaladiewilson.fr

Wilson's disease is a rare disease characterized by an excessive accumulation of copper in the body, more particularly in the liver and the brain. A rare occurrence for a genetic disease, effective medical treatment is available if medication is instituted early and continued throughout life.

The Bernard Pépin Association for Wilson's Disease ABP Wilson is a French patient organization. In 2017, ABP Wilson carried out, in collaboration with the Rare Diseases Reference Center for Wilson's disease and other rare copper-related diseases CRMR Wilson, a study that confirmed the low level of compliance to the treatment of patients at the time, describing certain characteristics specific to this rare disease which increase this problem.

Faced with these conclusions, ABP Wilson proposed various reminder tools such as pill boxes and collaborated with the CRMR Wilson in the production of the film "The Wilson partner or taking lifelong treatment" in 2019.

In 2021, following the creation of its Scientific Council, the ABP Wilson carried out, in collaboration with the CRMR Wilson and with the institutional support of the Orphalan laboratory, a survey to better understand the impact of medication on the daily lives of patients.

The poster presents the main results of the survey and a discussion from the point of view of the patient organization as an invitation to co-construct projects involving public and private actors, from the world of medicine and the pharmaceutical industry, including researchers in humanities and social sciences, politics, and innovation, to improve the quality of life of patients and their families.

P4

Keutel syndrome: overview of half a century of research

Hervé Kempf

UMR 7365 CRS/UL Ingénierie Moléculaire et Physiopathologie Articulaire IMoPA, 9, Avenue de la Forêt de Haye, Vandœuvre-lès-Nancy, France.

Correspondence to: Hervé Kempf, UMR 7365 CRS/UL Ingénierie Moléculaire et Physiopathologie Articulaire IMoPA, 9, Avenue de la Forêt de Haye, Vandœuvre-lès-Nancy, France. E-mail: herve.kempf@inserm.fr

Keutel syndrome (KS) is a rare autosomal recessive genetic disorder first identified in consanguineous siblings back in 1971. Patients with KS, usually diagnosed during childhood, present major traits that include abnormal calcification of various tissues resulting in or associated with malformations of skeletal tissues, e.g., midface hypoplasia and brachytelephalangism; cardiovascular defects, e.g., congenital heart defect, peripheral pulmonary artery stenosis, and in some cases arterial calcification; and impairment of their respiratory function, e.g., dyspnea, wheezing, cough, and infections.

Nearly 30 years after it was first described, KS has been attributed to loss-of-function mutations in the gene encoding the matrix protein Gla or MGP. Only 42 cases have been reported in the literature, and eight different mutations in the Mgp gene have been identified in few families with variable penetrance and intrafamilial variability.

Studies on mice deficient in MGP $Mgp^{-/-}$, a faithful model of KS, have shown that pathologic mineral deposition, i.e., ectopic calcification, in cartilaginous and vascular tissues is the primary cause underlying

many of the abnormalities present in KS patients. However, the mechanisms explaining how MGP prevents abnormal calcification remain poorly understood.

This communication presents the current state of physio-pathological and molecular knowledge on this rare disease that is still poorly understood.

P5

Conveying recurrence risk for a somatic de novo pathogenic rare variant: what should the counseling be?

Ben Pode-Shakked[1,2], Tamy Shohat[1,2], Rachel Rock[1,2], Odelia Chorin[1,2], Meirav Segev[1,2], Annick Raas-Rothschild[1,2]

[1]Institute of Rare Diseases, Edmond and Lily Safra Children Hospital, Sheba Medical Center, Tel Hashomer, Israel.
[2]Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel.

Correspondence to: Prof. Annick Raas-Rothschild, Institute of Rare Diseases, Edmond and Lily Safra Children Hospital, Sheba Medical Center, Tel Hashomer, Israel. E-mail: annick.rothschild@sheba.health.gov.il

What should be the counseling for a de novo mutation recurrence? To highlight this, here we report on two families, and, to evaluate practices, we conducted a national anonymous online survey among medical geneticists in Israel. Of the 51 responders, 50% were licensed medical geneticists MD, 13% were medical genetics fellows, 33% were genetic counselors, and 4% were genetic counselors in training or other. Overall, 71% of responders reported 11 or more years of clinical experience, and 65% of responders worked mainly in prenatal or pediatric genetics. When asked what the recurrence risk at which they would convey to the parents of a child with a de novo pathogenic variant, 42% chose "1%", 9% chose "2%-3%", 8% replied "up to 5%", and 40% replied that the recurrence risk would depend on the genetic diagnosis. Notably, there was less consensus in a scenario in which trio-exome would reveal that the "de novo" variant was detected in a single read in one of the parents. As for their recommendation regarding future pregnancy of parents of a child with a *de novo* mutation, 74% of responders replied they would recommend testing for the variant via amniocentesis, 10% via chorionic villus sampling, and 16% replied their recommendation would depend on the genetic diagnosis.

We suggest that to evaluate the recurrence risk of a de novo mutation, genetic counseling should consider not only the specific genetic diagnosis and the variant but also the methodology through which the reported de novo variant had been detected and the parents studied.

P6

Exploring the existence of an answer to a medical need through personalized medicine: example in the context of acid ceramidase deficiency

Terence Beghyn

APTEEUS, Campus Pasteur Lille, 1 rue du Professeur Calmette, Lille, France.

Correspondence to: Dr. Terence Beghyn, APTEEUS, Campus Pasteur Lille, 1 rue du Professeur Calmette, Lille, France. E-mail: terence.beghyn@apteeus.fr

Contributing to therapeutic research in the context of rare diseases requires addressing both the urgent therapeutical need and the individual specificities of the disease. Setting up a relevant model is therefore critical to visualize, at the cellular level, the features that are closely related to the genetic defect and affected

by it.

To address these issues, APTEEUS has developed breakthrough methods which, when combined with APTEEUS' unique drug library of ≥ 2500 active principles of repurposable drugs, namely TEELibrary®, facilitate and accelerate "bench-to-bedside" translation.

Thus, using a mass-spectrometry LC-MS-coupled screening method in 384-well plate format, we assessed the effect of the compounds within the TEELibrary® on the ceramide accumulation in one patient's skin fibroblasts lacking the acid ceramidase enzyme ASAH1 activity.

From this personalized screen, two drug candidates were identified and further assessed on other patients' cells suffering from diseases within the spectrum of acid ceramidase deficiency. To date, the compassionate use of the identified compounds has been initiated by the medical team in four patients.

Together, our results show that personalized medicine can benefit the most people and allow for the development of new therapeutics.

To this end, and in order to provide data for medical follow-up, an LC-MS-based method to quantify circulating ceramides on dried blood spots, DBS, has been developed. This method provides a new tool to monitor the drug's efficacy in further clinical trials on larger panels of patients.

P7

Substrate reduction therapy in mucopolysaccharidoses targeting the glycosyltransferase β4GalT7, a key enzyme of glycosaminoglycan biosynthesis

Sandrine Gulberti[1], Nick Ramalanjaona[1], Anne Robert[1], Christel Valencia-Schmitt[2], Pascal Villa[2], Sylvie Fournel-Gigleux[1]

1UMR 7365 Université de Lorraine-CNRS, Ingénierie Moléculaire et Physiopathologie Articulaire IMoPA, Vandœuvre-Lès-Nancy, France.
2Plateforme de Chimie Biologie Intégrative de Strasbourg PCBIS, UAR 3286 CNRS-Université de Strasbourg, Illkirch, France.

Correspondence to: Sandrine Gulberti, UMR 7365 Université de Lorraine-CNRS, Ingénierie Moléculaire et Physiopathologie Articulaire IMoPA, Vandœuvre-Lès-Nancy, France. E-mail: sandrine.gulberti@univ-lorraine.fr

Mucopolysaccharidoses (MPSs) are a group of inherited lysosomal storage diseases caused by the deficiency of enzymes involved in the degradation of glycosaminoglycans (GAG). Their abnormal accumulation in tissues leads to progressive multiple organ dysfunction. MPSs share common features such as bone dysplasia, with neurologic symptoms in the most severe forms. Enzyme replacement therapy (ERT) has been proposed to treat MPS and consists in supplementing the deficient enzyme with a functional recombinant counterpart, with moderate efficiency due to low tissue distribution. Substrate reducing therapy (SRT), which consists in administrating small molecules able to inhibit GAG biosynthesis, arises as an alternative to MPS treatment.

In this project, we propose a new approach to SRT, developing small hydrophobic molecules that specifically inhibit β1,4-galactosyltransferase 7 (β4GalT7), a key enzyme involved in GAG initiation, to prevent GAG accumulation in tissues.
A primary in vitro high-throughput screening of the Prestwick Chemical Library has led to the selection of 15 compounds as potential inhibitors. Five compounds showing high inhibitor potency towards β4GalT7, have been selected for further in cellulo tests. We are first focusing on checking the capacity of the selected molecules to reduce GAG biosynthesis in cells. The search for chemical analogs of identified hits will be the

next step to provide new molecules, which will be further tested in ADME-toxicity assays.
We hope that this project will provide potent molecules that could help treat most types of MPS. Promoting the development of SRT, used alone or in combination with other therapeutics, could be proposed to treat severe forms of MPS and contribute to the improvement of the quality of life of patients.

P8

Therapeutic targeting of cathepsin C: from pathophysiology to treatment

Brice Korkmaz

INSERM U-1100, Research Center for Respiratory Diseases, Faculté de Médecine, Bâtiment 47C 10 Bld. Tonnellé, Tours, France.

Correspondence to: Brice Korkmaz, INSERM U-1100, Research Center for Respiratory Diseases, Faculté de Médecine, Bâtiment 47C 10 Bld. Tonnellé, Tours, France. E-mail: brice.korkmaz@inserm.fr

Cathepsin C attracts more and more attention from both scientists and clinicians because of its role in the activation of pro-inflammatory neutrophil serine proteases (NSPs); elastase, proteinase 3, and cathepsin G are implicated in certain chronic inflammatory/auto-immune disorders and cancer. Promising preclinical and clinical data suggest that pharmacological inhibition of NSPs might ameliorate these conditions.

Patients with Papillon-Lefèvre syndrome, an autosomal recessive condition with a prevalence of 1-4 per million, have a genetically determined deficiency in cathepsin C but, reassuringly, do not exhibit marked immunodeficiency despite the absence of neutrophil serine proteases in immune defense cells. Hence, the pharmacological control of cathepsin C activity in bone marrow precursor cells represents an attractive therapeutic strategy for NSP-mediated disorders. Recently, positive results have been announced from a phase 2 study with a cathepsin C inhibitor brensocatib®, currently in phase 3 clinical evaluation, in patients with non-cystic fibrosis bronchiectasis, a relatively rare condition in which potential respiratory pathogens frequently colonize the lungs, often leading to exacerbations. Due to overlapping phenotypes and similar underpinning molecular mechanisms for a number of diseases associated with inflammation, a positive effect in bronchiectasis patients could be translated directly to the potential treatment of other NSP-mediated inflammatory diseases. Lowering the constitutively produced NSPs by pharmacological inhibition of cathepsin C holds great promise for future therapies.

From the perspective of unmet medical needs, drug repurposing for rare diseases offers a great opportunity. Repositioning of cathepsin C inhibitors would be a particularly attractive approach for rare diseases for both scientific and commercial reasons.

P9

Needs of fathers and mothers of children with permanent neonatal hearing loss

Barbara Le Driant

CRP CPO UR 7273, Université de Picardie Jules Verne, chemin du Thil, Amiens, France.

Correspondence to: Dr. Barbara Le Driant, CRP CPO UR 7273, Université de Picardie Jules Verne, chemin du Thil, Amiens, France. E-mail: barbara.le-driant@u-picardie.fr

At birth, permanent neonatal hearing loss affects 1 child per 1000. Without early intervention, deafness could lead to severe developmental impairment. To avoid this, in France, since 2012, every newborn has received neonatal hearing screening. Despite the psychological distress generated by early screening, parents are not prepared for the diagnosis process following it. To our knowledge, no publicly available

study to date has focused on potential differences in fathers' and mothers' experience. Actually, no study has been conducted to investigate the needs of both parents with deaf children. The current research aims to fill this gap and propose good practice recommendations. For this purpose, we used the Family Needs Survey (Bailey et al., 1992) on 12 couples as a preliminary sample of hearing parents with a child affected by permanent neonatal hearing loss. The results show no statistical difference between fathers and mothers in categories of needs, but the classification of the ten most important needs points out both similarities and differences. For example, in the first and fourth places of the ranking, 100% of parents reported "information about services available for their child in the future" as their first need, whereas in fourth place, 92% of mothers reported the need for "information about child's behavior" while 75% of fathers reported the need for "information about child's development". We will continue this work on more participants and add the measurement of parental perceived stress using the Parental Stress Index and their experience of the diagnosis process they went through using interviews.

P10

Towards a better consideration of patient experience in complex regional pain syndrome

Colette Boris[1], Labarre Julien[1], Garnier Pierre-Henri[1,3], Nizard Julien[1,2]

[1]Service Douleur Soins Palliatifs Soins de Support, Ethique linique et Unité d'Investigation Clinique Douleur, Soins Palliatifs et Neurochirurgie, CHU de Nantes,Nantes, France.
[2]EA4391 Excitabilité Nerveuse et Thérapeutique, Créteil, France.
[3]Institut pour l'Etude des Relations Homme-Robots, Paris, France.

Correspondence to: Dr. Nizard Julien, Service Douleur Soins Palliatifs Soins de Support, Ethique linique et Unité d'Investigation Clinique Douleur, Soins Palliatifs et Neurochirurgie, CHU de Nantes. E-mail: julien.nizard@chu-nantes.fr

Body perception disorders (BDP) are common in CRPS, affecing 54%-84% of patients. Patients report hostile feelings, detachment, and distorted perceptions of their affected limb. Although there is growing evidence of likely involvement of BDP in the persistence of pain in CRPS, they are not routinely screened by clinicians. As patients are often reluctant to express these strange manifestations spontaneously, it seems preferable to help them to do so.

The Bath scale, specially developed to evaluate BDP in CRPS, includes six items exploring their different aspects. The seventh item leads to a particularly interesting situation: from the patient's description of what they are feeling, the clinician draws a picture of the affected limb and submits it to the patient for their approval.

The use of the scale during an initial consultation, followed by a separate doctor-patient interview, could allow evaluating the way the tool is received: Is there the feeling of important aspects raised that would not have been raised spontaneously? Does the patient feel embarrassed during the test? Does the test contribute to the feeling of being understood and mutual trust? Are there suggestions for a better adapted and more beneficial use?

Finally, this project aims to formalize the French version of the tool and formulate recommendations concerning its field of use and its mode of administration for a better consideration of patient feelings to favor personalized therapeutic choices, especially rehabilitation.

P11

Caregiver Configurations and Employment Situations for Caregivers of Children with Rare Diseases and Intellectual Disabilities CASEPRA

Aurore Pélissier[1], Anaïs Cheneau[1], Clémence Bussière[2], Marc Fourdrignier[3], Laure Wallut[1]

[1]Laboratoire d'Economie de Dijon, Univ. de Bourgogne Franche-Comté, Dijon, France.
[2]Equipe de Recherche sur l'Utilisation des Données Individuelles en lien avec la Théorie Economique, Univ. de Paris-Est Créteil Val de Marne, Créteil, France.
[3]Centre d'Etudes et de Recherches sur les Emplois et les Professionnalisations, Univ. de Reims Champagne-Ardenne, Reims, France.

Correspondence to: Aurore Pélissier, Laboratoire d'Economie de Dijon, Univ. de Bourgogne Franche-Comté. E-mail: aurore.pelissier@u-bourgogne.fr

The first national plan to help caregivers is an institutional recognition of their role. One of the priorities is the reconciliation of their personal and professional lives.

CASEPRA is a research project that seeks to identify and analyze the aid provided by parents of children with intellectual disabilities related to a rare disease, including those with a rare disability. Indeed, rare diseases and rare disabilities are often associated with the scarcity of expertise and available aid, with the combination of numerous solutions for compensating the disability, but also with uncertainty and a significant amount of time spent wandering in diagnosis. All of these elements are likely to influence the configurations of aid between informal aid and formal/professional aid and the employment situation of the parent-caregiver.

The poster presents this 30-month project by describing the stakes, the methodology exploratory qualitative phase, the quantitative investigation phase based on an online survey, the qualitative phase, and the first results of the exploratory qualitative phase. Ultimately, this project aims to identify the levers and obstacles to the recognition of the role of parents as informal caregivers and to the reconciliation of work and caregiving. By extension, the project could also shed light on other situations of assistance to fragile populations.

*CASEPRA-Pil project, winner of the "Human and Social Sciences and Rare Diseases" 2020 call for projects from the Fondation Maladies Rares.

**CASEPRA project, winner of the IReSP call for projects " Blanc session 11" 2020.

P12

Impact of cognitive and behavioral disorders in children with a rare neurodevelopmental disease on mothers' burden

Hennion Sophie, Vin Charlotte

Centre de Référence des Épilepsies Rares, des Malformations et Maladies Congénitales du Cervelet, service de neuropédiatrie, CHU de Lille, France.

Correspondence to: Dr. Hennion Sophie and Vin Charlotte, Centre de Référence des Épilepsies Rares, des Malformations et Maladies Congénitales du Cervelet, service de neuropédiatrie, CHU de Lille, France. E-mail: charlotte.vin@chu-lille.fr; Dr. Vin Charlotte, Centre de Référence des Épilepsies Rares, des Malformations et Maladies Congénitales du Cervelet, service de neuropédiatrie, CHU de Lille, France. E-mail: sophie.hennion@chru-lille.fr

Rare neurodevelopmental diseases are characterized by various cognitive and behavioral disorders which impair the daily life functioning of both patients' healthcare and their parents' psychological well-being and quality of life, depending on their severity. However, to date, the level of burden experienced by mothers of children with a rare neurodevelopmental disease, rare epilepsy, and cerebellum disorder is largely unknown. In this context, the aims of the present study were: (1) to quantify the mothers' burden

using standardized tools; and (2) to determine the cognitive and behavioral factors associated with these psychological consequences. In total, 85 children aged 1.25-17.5 years old with a rare neurodevelopmental disease were recruited for the current study. They underwent an exhaustive neuropsychological evaluation of global cognitive efficiency, attention, executive functions, social cognition, and the presence of behavioral or adaptive disorders in a routine care context. Moreover, their mothers completed the Zarit scale to assess caregiver burden. Mild to severe burden was reported by the majority of mothers in our sample. Mothers' burden was more prevalent when their child presented an intellectual disability, hyperactivity/inattention, executive deficits, oppositional or defiant behaviors, and adaptive disorders. No link was found with social cognitive abilities. Overall, mothers of children with a rare neurodevelopmental disease are likely to experience significant levels of burden. In forthcoming studies, we will examine the coping methods that are deployed to deal with it and extend our investigation to fathers of children with a rare neurodevelopmental disease.

SPEAKER PRESENTATIONS

S1

Infantile spinal muscular atrophy: from genetics to therapies

Suzie Lefebvre

T3S, INSERM UMR1124, Université Paris Cité, Faculté des Sciences Fondamentales et Biomédicales, Paris, France.

Infantile spinal muscular atrophy (SMA) is characterized by the death of motor neurons innervating skeletal muscles. Mutations or deletions of the survival motor neuron 1 (SMN1) gene cause SMA, leading to SMN protein deficiency. Indeed, the severity of the disease depends on the residual SMN protein levels synthesized from the copy gene SMN2. This ubiquitously expressed protein is part of a protein complex involved in different aspects of cellular homeostasis including RNA metabolism that are not yet fully understood. Three drugs for SMA treatment emerge from these studies: an antisense oligonucleotide nusinersen, AAV9-SMN gene therapy onasemnogene abeparvovec, and a small-molecule risdiplam. They treat the patient conditions remarkably better, although to variable degrees, suggesting that combining multiple treatments that individually increase different cellular processes rather than SMN dosage might also be necessary to improve therapies across the patient lifespan. It also highlights that early treatment gives the best patient outcomes. Here, the genotype-phenotype relationship will be presented as well as SMA biomarkers for helping to evaluate the efficacy of adjuvant therapies. Our screen identified another potential small molecule, flunarizine, that increases SMN localization in sub-nuclear domain Cajal bodies and improves the survival of spinal cord motor neurons and their neuromuscular synapses in an SMA mouse model. Research efforts to identify the mode of action are ongoing.

S2

100% resolution of the diagnostic impasse in neurodevelopmental diseases of genetic origin, near possibility or utopia?

Stéphane Bézieau[1,2]

[1]Nantes Université, CHU Nantes, service de génétique médicale, Nantes, France.
[2]Nantes Université, CHU Nantes1, CNRS, INSERM, l'institut du thorax, Nantes, France.

As we discover more about DTX resistance, it will become increasingly important to develop novel biomarkers for response to DTX, as well as patient monitoring strategies to stratify patients for treatment.

Circulating tumor cells: CTCs are nucleated tumor cells that are released into the peripheral blood from

High-throughput sequencing (HTS) has revolutionized the power of genetic testing for rare diseases. Many patients suffering from neurodevelopmental diseases of genetic origin have been able to break the diagnostic deadlock thanks to this evolution. Isolated or syndromic intellectual disability (ID), which affects 1-3% of the population, has seen a considerable increase in the rate of diagnosis, despite very significant genetic heterogeneity, with 1500 known genes and as many excellent candidates. Thanks to HTS, we have gone from 15% of diagnoses in ID at the beginning of the 2000s, with genome-wide techniques such as karyotype, ACPA, and comparative genomic hybridization or targeted techniques to study specifically, for example, the fragile X syndrome, to reach up to 60% of diagnoses thanks to genome sequencing. The reasons for this are technological but not solely. The high proportion of de novo mutations observed in ID has facilitated interpretation through the trio sequencing approach of both parents and child. However, although the heredity mechanisms exist in ID, the de novo hypothesis should not make us forget the other possibilities of transmission. The causes of ID of recessive origin are probably underestimated today. Despite the contribution of genome sequencing, 40% of genetic causes remain to be identified in ID patients after genome trios. New omics approaches such as RNA sequencing, long-read sequencing (LRS), and optical genome mapping (OGM) offer important perspectives to further improve the diagnostic rate in ID. Other aspects than the technological evolution are also to be considered to reach this goal.

S3

Molecular basis of BPAN disease

M Celle[1], Sandrine Aniorte[1], Marion Falabrègue[2], Francine Côté[2], Ludivine Walter[1], Bertrand Mollereau[1]

[1]Laboratoire de Biologie et de Modélisation de la Cellule, CNRS UMR5239, Ecole Normale Supérieure de Lyon, 46 allée d'Italie, Lyon, France.
[2]Institut Cochin, Equipe Fer et Immunité, INSERM U1016, CNRS UMR 8104 24, Rue du Fg St Jacques, Paris, France.

Beta-propeller protein associated with neurodegeneration (BPAN) is a rare neurodegenerative genetic disease characterized by iron brain accumulation. It is caused by mutations in the WDR45 gene, which is known to be involved in autophagy. In addition to autophagy perturbation of iron metabolism, ER stress response was also observed in some cellular and animal models of BPAN disease. However, the molecular mechanisms leading to neurodegeneration are still largely unknown in WDR45 mutants. To study the roles of WDR45, we established a Drosophila melanogaster BPAN disease model using RNAi and CRISPR-Cas9 strategies targeting dWDR45, the Drosophila WDR45 homolog. We demonstrated that flies harboring dWDR45 mutation mimic characteristics of the BPAN disease such as locomotors disorder, neuronal loss, and increased sensitivity to iron that are also associated with autophagy and ER stress response dysregulations. Therefore, we established a Drosophila preclinical BPAN disease model that will be a precious tool for investigating the molecular roles of WDR45 and further drug testing.

S4

The value of modeling diseases caused by mutations of ion channels to facilitate the emergence of new therapies

Phillipe Lory[1,2], Arnaud Monteil[1,2], Sophie Nicole[1,2]

[1]Institut de Génomique Fonctionnelle IGF, Univ Montpellier, CNRS, INSERM, Montpellier, France.
[2]LabEx 'Ion Channel Science and Therapeutics' ICST, Montpellier, France.

Ion channels are key players in cellular excitability. Their presence on neurons, muscle cells, and endocrine cells is essential for most physiological functions of neurotransmission, muscle contraction, and hormone secretion. Mutations in the genes coding for ion channels can lead to their dysfunction and be responsible for genetic diseases with a diversity of clinical manifestations, sometimes very severe

ones. These diseases are called "channelopathies". Our team studies the functional consequences of these mutations in order to decipher the molecular, cellular, and tissue mechanisms responsible for these channelopathies. Toward this goal, we develop cellular and animal models carrying representative mutations of these channelopathies. These preclinical models allow us to perform: (i) molecular analyses, e.g., electrophysiological patch-clamp defect; and (ii) phenotypic studies, e.g., search for ataxia, epilepsy, and muscle weakness, which indicate or validate a "loss-of-function" or "gain-of-function" aspect of these mutations. In addition, studying these "pathogenic" mechanisms allows us to deepen our knowledge of the physiological roles of these ion channels.

Modeling these channelopathies is also crucial to identifying new therapeutic strategies, because these rare diseases can only too rarely be treated by the current medication. In this context, our objective is to evaluate the interest in developing or repositioning ion channel modulators to improve the symptomatology of the channelopathies we study. In this presentation, our current studies of calcium Cav3.1 and sodium Nav1.4 and NALCN channel mutations, responsible for severe neurodevelopmental and neuromuscular diseases, are used to illustrate this strategy.

S5

Therapeutic of mitochondrial complex I deficiency: Screening and functional tests of candidate molecules

Naïg Gueguen[1,2], Valérie Desquiret-Dumas[1,2], Jennifer Alban[1,2], Justine Faure[1,2], Sacha Penard[1], Guy Lenaers[2], Pascal Reynier[1,2]

[1]CHU Angers, Biochemistry and Molecular Biology Unit, Angers, France.
[2]Univ Angers, Inserm U1083, CNRS UMR6015, MITOVASC, SFR ICAT, Angers, France.

Isolated deficiencies of mitochondrial complex I (CI), the first complex of the OXPHOS system, are the most frequent pediatric mitochondrial disorders. Despite an increasing interest in mitochondrial disease therapeutics, until now, no efficient curative treatment is available for these patients, mainly because of the heterogeneity of cellular response to candidate molecules among patients. We recently identified a common, strong metabolic blockade in the subset of patients with an impairment of the CI subunits assembly process. In these patients, the pyruvate entry in mitochondria was blocked through a ROS/AMPK-dependent pathway, and all the energy production relied on aerobic glycolysis, dramatically increasing cellular lactate production. In the present study, we thus aimed at adapting the so-called "substrate preference switch and metabolic flexibility strategy" to our CI-deficient fibroblast models by increasing succinate supply with two molecules: cell-permeable succinate and propionyl-l-carnitine. Our results demonstrate that succinate treatment in two CI-deficient fibroblast cell lines partially restored oxidative metabolism and decreased ROS production by the respiratory chain in one of the two patients. To further study the mechanism underlying these effects, it appears necessary to work on a unique cellular model to remove the cellular heterogeneity found in patients. We recently acquired a MCF7 cell line invalidated for the CI subunit NDUFS7 by CRISPR-Cas9 technology. We will perform fluxomic measurements to follow glucose oxidation in cells and transcriptomic analyses to decipher the signaling pathways involved in the succinate effect.

S6

Alteration of mitochondrial proteostasis and bioenergetics in Costello syndrome

Laetitia Dard[1,2,3], Christophe Hubert[1,2], Pauline Esteves[1,2], Wendy Blanchard[1,2,3], Ghina Bou-About[4], Lyla Baldasseroni[5], Elodie Dumon[1,2], Chloe Angelini[1,2,6], Véronique Guyonnet-Dupérat[1,2,7], Stéphane Claverol[2,8], Laura Fontenille[9], Karima Kissa[9], Pierre-Emmanuel Seguela[2,10,11], Jean-Benoît Thambo[2,10,11], Yann Herault[4], Nadège Bellance[1,2], Lévy Nicolas[5], Nivea Dias Amoedo[1,2,3], Frédérique Magdinier[5], Tania Sörg[4], Rodrigue

Rossignol[1,2,3], Didier Lacombe[1,2,6]

[1]INSERM U1211, Bordeaux, France.
[2]Bordeaux University, 146 rue Léo Saignat, Bordeaux, France.
[3]CELLOMET, Functional Genomics Center CGFB, 146 rue Léo Saignat, Bordeaux, France.
[4]Institut Clinique de la Souris - 1 rue Laurent Fries - 67404 Illkirch Cedex - Alsace, France.
[5]INSERM, UMR_1251, Marseille, France.
[6]Medical Genetics Department, Bordeaux University Hospital, Bordeaux, France.
[7]Vectorology facility of Bordeaux University, U1035, Bordeaux, France.
[8]Proteomics Facility, Functional Genomics Center CGFB, BP 68, 146 Rue Léo Saignat, Bordeaux, France.
[9]AZELEAD, 377 rue du Pr. Blayac, Montpellier.
[10]CHU Bordeaux, Haut-Lévèque Hospital, Cardiology department, Bordeaux, France.
[11]IHU LYRIC, Pessac, France.

Germline mutations that activate genes in the canonical RAS/MAPK signaling pathway are responsible for rare human developmental disorders known as RASopathies. Here, we analyzed the molecular determinants of Costello syndrome (CS) using a mouse model expressing HRASG12S, patient skin fibroblasts, hiPSC-derived human cardiomyocytes, a HRASG12V zebrafish model, and human fibroblasts expressing lentiviral constructs carrying HRASG12S or HRASG12A mutations. The findings reveal alteration of mitochondrial proteostasis and defective oxidative phosphorylation in the heart and skeletal muscle of Costello mice, which were also found in the cell models of the disease. The underpinning mechanisms involved the miR-221*-dependent inhibition of AMPKα2 expression and the concomitant alteration of LKB1 activation by mutant forms of HRAS, leading to alteration of mitochondrial turnover and bioenergetics. Pharmacological rescue of mitochondrial proteostasis via a patented drug restored organelle bioenergetics in HRASG12A/S cell models, reduced heart mass in CS mice, and reduced the occurrence of developmental defects in the CS zebrafish model.

S7

Development of a new antisense approach for all patients with cystic fibrosis

Christie Mitri[1], Nathalie Rousselet[1], Harriet Corvol[1,2], Olivier Tabary[1]

[1]Centre de Recherche Saint-Antoine CRSA, Inserm, Sorbonne Université, Paris, France.
[2]Pediatric Pulmonology Department, Trousseau Hospital, Sorbonne Université, Paris, France.

Cystic fibrosis (CF) is a complex rare disease because of its multiple mutations. It is caused by a dysfunctional CF transmembrane conductance regulator (CFTR) channel that mainly mediates chloride anion transport across the apical membrane epithelial cells. Current treatments are only specific to some mutations, leaving 15% of the patients with no suitable treatment. Hence, alternative strategies that are CFTR-independent are needed.

Anoctamine 1 (TMEM16A) is an alternative chloride channel that could compensate for CFTR deficiency. Interestingly, we showed that TMEM16A expression and activity are decreased in CF due to microRNA-9 overexpression. To this end, we developed an oligonucleotide antisense ASO TMEM16A that reestablishes its expression and activity.

Our aim is to study the effects of ASO TMEM16A on all the deregulated parameters in CF and show that it could potentially be effective for all patients regardless of their mutations.

The oligonucleotide potentiates TMEM16A activity and increases chloride efflux and mucociliary clearance in CF patient cells. ASO TMEM16A is detectable 30 days after subcutaneous injection in CF mice. It significantly increases their lifespan and improves symptoms such as gastrointestinal obstruction and fertility problems in CF male mice. Acute administration of 50 times the effective dose **showed no**

physiological changes. ASO TMEM16A is very specific, does not induce inflammation, and does not alter intracellular calcium mobilization or cell proliferation.

S8

Empowering parents of adolescents with rare diseases during the transfer from pediatric to adult services

Agnès Dumas[1,2,3], C Gabarro[1,2], E Le Roux[1,3], Corinne Alberti[1,2], I Cailbault[1], P Jacquin[3,4], Nizar Mahlaoui[5], H Mellerio[1,3,4]

[1]Université Paris Cité, ECEVE, UMR 1123, Inserm, Paris, France.
[2]Institut La Personne en Médecine, Université Paris Cité, Paris, France.
[3]GRMSA Groupe de recherche en médecine et santé de l'adolescent, Paris, France.
[4]Ad'venir, Transition unit, Adolescent medecine department, Robert Debré Hospital, Assistance Publique-Hôpitaux de Paris AP-HP, Paris, France.
[5]La Suite, Transition unit, Necker Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris AP-HP, Paris, France.

This study aimed at understanding the experience of transfer towards adult services of adolescents and young adults (AYAs) from the point of view of parents, in order to develop interventions addressing their needs.

In-depth interviews were conducted with 30 parents of AYAs with rare diseases before/during transfer. An inductive thematical analysis was made with the help of Nvivo.

A third of parents were concerned about their attendance in consultations in adult services. Parents who were more anxious about this issue reported that they felt powerless when interacting with doctors. They tended to be low- or middle-class mothers and/or had an experience of diagnosis wandering during which their voice was not heard. Overall, transfer was depicted positively, as a "normal" or "expected" step, or negatively, as a "challenge", "source of stress", or "hardship". Views about transfer were related to the severity of the disease and/or treatments and to parents' trust in the healthcare system and/or in the matureness of AYAs. Stressed parents reported conflicting values, as they were dismissed from the medical responsibility when the AYAs reached 18 years old but still felt morally responsible for their well-being for years after. Parents of AYAs with complex needs viewed the transfer as a hardship and reported a need for a transfer coordinator.

Some parents do not think of themselves as "caregivers" but only as "parents of sick children" and thus fail to know their rights as caregivers. Online video-based support can help to empower deprived parents.

S9

Achieving at school: the weight of subjective factors

Odile Rohmer, Marine Granjon, Maria Popa Roch

University of Strasbourg, Strasbourg, France.

Important laws and policies in favor of the social inclusion of people with disabilities have been adopted in the last decade in France, which speaks for the priority given to it at all social levels. Nevertheless, significant gaps persist between the political will to welcome students with disabilities in the mainstream system as any other children and the difficulties they regularly face during their school career. To shed light on this discrepancy, work in the humanities, and social sciences is a valuable contribution. In recent years, work in social psychology has highlighted the weight of beliefs and feelings that raise barriers to inclusive

education for all students. In this respect, research was undertaken to understand how teachers' beliefs and attitudes towards disability-related issues impact the implementation of the inclusion principle. The results suggest that negative perceptions impact how students self-conceptualize their capacity for academic achievement. From this perspective, we conducted several research programs that focus on the self-image built by students living with an illness or disability. In an experimental approach, we showed how the naïve beliefs of students with hemophilia echo those of their parents and teachers. We then showed the link between how students judge themselves and their success in school tasks. The results obtained in students with invisible impairments such as juvenile arthritis or dyslexia will be exposed.

S10

Psychosocial consequences of rare dermatological disorders

Pierre Ancet

Université de Bourgogne, Dijon, France.

Severe and rare dermatological disorders, such as giant congenital melanocytic nevi, are commonly experienced as traumatic sources of social stigmatization for both patients and their families. As such, it is important to address the social, communicational, and discursive dimensions of such disorders, which give rise to different types of discourse to which patients are exposed and which have an impact on the way they perceive and may seek to come to terms with their condition. The multiplicity of factors involved, communication, vulgarization, and social interaction processes, requires a multidisciplinary approach able to combine medical and social sciences.

Communication and information practices are consequently involved as they can be a way to answer patients' expectations in terms of social empathy, information needs, and personal fulfillment. We analyzed media devices, forums, social networks, press, etc., and self-presentation practices, aiming to identify multiple forms of expression and discourse around these conditions, as well as issues that can arise from these. We focused on the forms of self-presentation and dramatization in both online and face-to-face interactions. As social beings, individuals face pressure to perform a role in order to conform to the normative demands of society. These social activities are very important as they can provide access to different forms of recognition and self-esteem in private, professional, and public spheres.

This work contributes to producing a certain awareness and a critical approach to the construction of online self-identities among the young populations, generally more exposed to new forms of harassment and social contempt.

S11

The C3A suitcase: a set of short video tutos and handy tools for augmentative and alternative communication (AAC) with children affected by neurodevelopmental disorders

Esther Chalain[1], Oriane Graciano[1,3], Marielle Lachenal[6], Léa Zarka[7], Anne Hugon[2], Anna Maruani[1,3,5], David Germanaud[1,4,5]

[1]Centre de Référence Constitutif Déficiences Intellectuelles de Causes Rares, filière DéfiScience, Hôpital Robert-Debré, AP-HP, Paris, France.
[2]Centre de Référence Coordonnateur Anomalie du développement et DI - Ile-de-France, filière AnDDI-rares, ERN ITHACA, Hôpital Robert-Debré, AP-HP, Paris, France.
[3]Service de psychiatrie de l'enfant et de l'adolescence, DMU Innov-RDB, Hôpital Robert-Debré, AP-HP, Paris, France.
[4]Unité de génétique clinique, Département de génétique, DMU BioGeM, Hôpital Robert-Debré, AP-HP, Paris, France.
[5]Centre d'excellence InovAND, AP-HP, Paris, France.
[6]Isaac Francophone www.isaac-fr.org, France.

[7]Service communication, Hôpital Robert-Debré, AP-HP, Paris, France.

Difficulties in understanding, speaking, or interacting are common in people with neurodevelopmental disorders (NDD) across many of the diagnostic categories that are commonly encountered in rare developmental diseases, such as intellectual developmental disorders, autism spectrum disorders, developmental speech and language disorders, and their frequent combinations. They are often associated with difficulties in general comprehension or atypical sensory perceptions that make coming to the hospital a complicated, or even stressful, experience, especially for children. Augmentative and alternative communication (AAC), which consists in accompanying speech with gestures, pictograms, or images, could significantly and immediately improve communication with these children, all the more since some of them already use it, by transmitting soothing information about what is going to happen and by allowing them to express their needs and feelings. This project consisted of structuring simple AAC tools that fitted various typical hospital situations both at the reception and in consultations, making them immediately deployable by the staff to a wide range of children thanks to a series of mini-tutorials showing their interest and the basics of their use to the professionals. The result is a suitcase containing pictographic, laminated, or flexible communication panels for wall display; key rings with the essential pictograms; and a digital tablet containing the tools and six 5 min video tutorials including a demonstration of the basic gestural communication with the aid of the boards. The C3A suitcase, which is incentive, versatile, and scalable, could meet the legitimate needs of many centers where caregivers and staff are often helpless in facing the difficulties of these children and families.

S12

Challenges of moving from preclinical proof of concept to a drug candidate:identification of a new therapeutic option for idiopathic hypercalcemia

Daniela Rovito[1], Régis Lutzing[1], Céline Keime[1], Natacha Rochel[1], David Schilansky[2], Daniel Metzger[1], Magali Richard[2], Gilles Laverny[1]

[1]Institut de Génétique et de Biologie Moléculaire et Cellulaire IGBMC, Centre National de la Recherche Scientifique UMR7104, Institut National de la Santé et de la Recherche Médicale U1258, Université de Strasbourg, Illkirch, France.
[2]Home Biosciences, Paris, France.

The bioactive vitamin D 1α,25 dihydroxyvitamin D3 (1,25D) plays a key role in calcium homeostasis. It elicits its effect by binding to the vitamin D receptor (VDR), a member of the nuclear receptor superfamily. High endogenous 1,25D levels lead to hypercalcemia, a hallmark of several rare pediatric disorders, including infantile idiopathic hypercalcemia (IIH). Acute or chronic hypercalcemia has dramatic consequences on the patient's growth and/or quality of life. Current treatments do not target 1,25D/VDR signaling, are poorly efficient, and greatly impact the development of children.

A pluridisciplinary and translational study led by the team of Daniel Metzger and Gilles Laverny, in collaboration with Natacha Rochel, an expert on the VDR structure-function relationship, identified a vitamin D analog that acts as a VDR antagonist and normalizes 1,25D-induced hypercalcemia in mice, as well as 1,25D/VDR signaling in a fibroblastic cell line generated from a skin biopsy of an IIH patient. Thus, this compound could represent a potent and safe therapeutic option for patients with hypercalcemia secondary to high vitamin D levels.

The research consortium is now collaborating with clinical key opinion leaders and Home Biosciences - a biotechnology company operating along an asset-centric model - to progress towards the development of this drug candidate. This transition from preclinical proof of concept to clinical and pharmaceutical development is a critical step, requiring multiple competencies, strong expertise, and significant financialresources to efficiently progress towards an Investigational New Drug and Clinical Trial Application and derisk the program.