Joint Transnational Call 2020
Kick-off meeting – funded projects

April 14th 2021
13h-18h CET

Content :

AGENDA

13h00 – 13h15 **Introduction to EJP RD**
Daria Julkowska, Inserm, EJP RD Coordinator
10 min presentation + 5 min discussion

13h15 – 13h30 **Introduction on the JTC2020 and presentation of the monitoring of JTC2020 projects**
Florence Guillot, ANR, JTC2020 call secretariat
CSO-MOH, WP9 leader
10 min presentation + 5 min discussion

13h30 – 13h45 **Presentation of the ethics monitoring of JTC2020 projects**
Annalisa Landi, FGB, WP4 leader
10 min presentation + 5 min discussion

13h45 – 14h00 **Presentation of EJP RD Trainings**
Birute Tumiene, VUHSK, Pilar 3 Leader
10 min presentation + 5 min discussion

14h00 – 14h40 **Presentation of JTC 2020 funded projects**
5min per project + 10 min general discussion

- WilsonMed
- ARMED
- DBAGenCure
- FANEDIT
- ProDGNE
- EpiThe4FSHD

14h40 - 15h10 ***30 min BREAK***

15h10 – 15h25 **Presentation EJP RD Virtual Platform and FAIRification service**
Speakers to be confirmed
10 min presentation + 5 min discussion

15h25 – 16h05 **Presentation of JTC 2020 funded projects**
5min per project + 10 min general discussion

- SILENCELQTS
- TC NER
- CHARLIE
- GET-READY
- TreatRP
- AAK-INSIGHT

16h05 – 16h20 **Presentation of the EJP RD Clinical study support office**
Marta del Alamo, ECRIN, WP20
10 min presentation + 5 min discussion

16h20 – 16h50 ***30 min BREAK***

16h50 – 17h30 **Presentation of JTC 2020 funded projects**
5min per project + 10 min general discussion

- MECPer-3D
- TREAT-SGS
- CureMILS
- TREATKCNQ
- TREAT-ARCA
- SCN1A-up!

17h30 – 17h45 **Presentation of EJP RD Translational Research services**
Anton Ussi, EATRIS, WP19
10 min presentation + 5 min discussion

17h45 – 18h00 Closure of the meeting

ABSTRACTS

EJP RD Trainings

Birute Tumiene, VUHSK, Pilar 3 Leader

Through its comprehensive education and training programme, Pillar 3 "Capacity building and empowerment" is raising the level of knowledge and know-how and enhance research and innovation capabilities within the RD research and care community. A wide range of topics includes but is not limited to various aspects of data management, registries, biobanks, ontologies, data FAIRification, genetic standards, genomics, undiagnosed diseases, orphan drug development, health technology assessment, pharmacovigilance, European Medicines Agency, disease models and more. Education and training activities are targeted at researchers in various career stages from students to PhDs, postdocs and experienced researchers and involve education and training interests along the whole R&I pipeline, from basic and pre-clinical to clinical and translational research. Some of these courses are also addressed at patient representatives enabling a joined training of patients and researchers whilst others are specifically dedicated to patient representatives to provide them with the knowledge, skills and tools to become equal partners in rare disease research. Pillar 3 training programme includes face-to-face courses ranging from short 1 or 2-day workshops to 3 or 5 days residential training, comprehensive online academic RD research courses (with a phased development of specific modules which will be added progressively on the e-learning platform), training workshops and mobility fellowships of 1 to 6 months duration. All training courses are provided free of charge and fellowships for coverage of travel and accommodation expenses are available for participants from usually underrepresented countries and patient representatives. Several training courses are changing location each year to ensure wide participation across Europe.

EJP RD Vitual Platform and FAIRification service

Speakers to be confirmed

The EJP RD Virtual Platform aims to open a single door to discover and access data and tools useful for rare disease research. The Virtual Platform operates as a federated ecosystem coupled with robust standards and compliant to FAIR principles infused procedures to aid data discovery, linkage and sharing.

- Resources: catalogues of rare disease patient registries, biobanks, animal models, cell lines libraries, services and documentation to foster translational and clinical research.
- Tools: Genomic, multi-omics repositories and analysis platforms, signaling pathway curation and system biology modelling.
- FAIRification & data standards mean to harmonize and standardize RD relevant data at record level.

The development of the Virtual Platform must be fit for purpose and based on user needs. The EJP RD partners in this pillar would welcome collaborations with JTC2020 funded consortia for the co-design of the Virtual Platform.

In particular, EJPRD Pillar 2 colleagues will present the facilities for identifying resources and services they provide, encompassing biobanks and biosamples, cell lines and iPSC, phenomics, genomics and multi-omics data deposition and analysis, pathways and networks construction and curation, as well as guidance producing FAIR data results. Furthermore, plans allowing to make JTC2020 funded projects' data discoverable in the future through the EJP RD Virtual Platform to foster collaborations for future research will be discussed.

EJP RD Clinical study support office

Marta del Alamo, ECRIN, WP20

ECRIN and EJP RD as a facilitators of multinational clinical research for Rare Diseases (RD) in Europe

Investigator-initiated trials are conducted mainly as single-centre or multiple-centre setting in one country. This fact might bias studies' outcomes or limit trial initiation within one country. This last constraint is especially remarkable in the case of rare diseases (RD), considering the limited number of patients per country. The main hurdle for academic investigators is due to the fragmented health and legal systems within Europe.

ECRIN and EJP RD Clinical Studies Helpdesk can help to circumvent the challenges associated to RD clinical research by supporting European Reference Networks (ERN) and RD investigators in design, planning and performing clinical studies:

1. The EJP RD Clinical Studies Helpdesk provides support to plan multinational clinical trials for Rare Diseases. This service facilitates:
   - Access to RD experts
   - Access to methodologists, experts on the development of innovative statistical design
   - Operational planning of the trial: site selection, cost estimation, country selection, regulatory requirements

2. Providing support to perform multinational clinical trials (operational coordination), as part of ECRIN services.

EJP RD Translational Research services

Anton Ussi, EATRIS, WP19

Led by Fondazione Telethon and EATRIS, EJPRD WP19 provides cost-free support and services to translational research projects, to make the journey to the patient smoother and faster. The services include:

- Mentoring and advice from industry, regulatory, commercial experts;
- Support in defining follow-on funding strategy for successful projects;
- Troubleshooting and access to specialised facilities and resources for translational research.

These services are available for projects in most areas, including cell & gene therapy, small molecules, drug repurposing, biologics, biomarker development and diagnostics. You will hear about the services and how to make contact with the team.

JTC2020 funded projects

WilsonMed: Multimolecular targeting of copper overload in Wilson disease

Partners	Country
Schmidt, Hartmut (Coordinator) Westfälische Wilhelms Universität	Germany
Kroemer, Guido Inserm-U1138	France
Polishchuk, Roman TIGEM	Italy
Socha, Piotr IPCZD	Poland
Zischka, Hans HMGU/TUM	Germany
Collaborators	**Country**
Przybyłkowski, Adam Medical University of Warsaw	Poland
Litwin, Tomasz Institute of Psychiatry and Neurology in Warsaw	Poland
Patient Advocacy Organisation	**Country**
Association Bernard Pépin pour la maladie de Wilson	France
Associazione Nazionale Malattia di Wilson O.N.L.U.S.	Italy
Morbus Wilson e.V.	Germany
Polish Association of Wilson Disease Patients	Poland

Wilson disease (WD) results from a defect of copper (Cu) transporter ATP7B leading to high oxidative stress due to Cu accumulation, mostly in the liver. Currently, therapy is based on anti-Cu compounds identified decades ago. However, a portion of WD patients do not respond, show non-compliance, and miss adequate therapy in case of high emergency, including liver transplantation. WilsonMed is a unique partnership that unites leading experts of basic/translational research, clinicians, and PAOs to (i) provide novel treatment options, (ii) launch proof-of principle studies in preclinical models, (iii) assess predictive biomarkers for monitoring of therapy, and (iv) disseminate novel concepts first-hand to PAOs. The partners of WilsonMed are stemming from distinctive fields having long-lasting expertise of state-of-the-art research, including (i) novel chemically-tailored Cu chelators having improved efficacy, (ii) screening of anti-Cu moieties, including repurposed drugs (iii) compound-induced enhancement of tissue-specific autophagy, (iv) gene-editing/silencing methodology, and (v) establishment of novel WD models. Having achieved important milestones in their individual fields, the partners combine activities by sharing advanced cellular platforms, animal models, and multi-molecular concepts for the short-term implementation of innovative treatment strategies. The expertise of the WilsonMed partners and PAOs will be synergistically combined to contribute to a significant enhancement in the management and therapy of patients having WD.

ARMED : Antioxidant treatment as a novel therapeutic option for microvillus inclusion disease

Partners	Country
van IJzendoorn, Sven (Coordinator) ACADEMISCH ZIEKENHUIS GRONINGEN	The Netherlands
Arango, Diego Institut de Recerca a Biomedica de LLEIDA (IRBLleida)	Spain
Cerf-Bensussan, Nadine Imagine Institut des Maladies Genetiques Necker Enfants Malades	France
Bakowsky, Udo Philipps-Universität Marburg	Germany
Collaborators	**Country**

Michaux, Grégoire Univ Rennes, CNRS, IGDR	France

Microvillus inclusion disease (MVID) is a very rare and severe genetic bowel disorder that affects infants and young children. Degeneration of their small intestine causes the patients' inability to absorb nutrients from the diet and makes them life-long dependent on intravenous feeding. Unfortunately, most patients also die from the severe complications that accompany long-term intravenous feeding. Recently, we have identified a cellular defect in MVID that is accountable for the degeneration of the small intestine and, importantly, could be treated with the antioxidant N-acetylcysteine (NAC) in a mouse model of MVID. NAC is an inexpensive, safe, EMA/FDA-approved drug primarily indicated for the treatment of paracetamol intoxication. Although repurposing of NAC for the treatment of MVID seems fitting, a clinical study in MVID patients is not trivial. NAC is contraindicated for children under the age of 2 and therefore may not represent the best choice for the treatment of MVID in infants. In the proposed study, we aim to identify other antioxidant drugs that can be used in children of all ages by using human cell lines, organoids and animal models of MVID. Moreover, we intend to evaluate the drug formulation, dose and route of administration that are most efficient and suitable in MVID patients. The results obtained from this study will pave the way for a first-in-human clinical trial with the long-awaited prospect of improving nutrient absorption and decrease the need for intravenous feeding, ultimately increasing life expectancy and quality of life for MVID patients.

DBAGenCure : Lentiviral-mediated gene therapy for Diamond Blackfan Anemia: Preclinical Safety and Efficacy Studies

Partners	Country
Bueren, Juan (Coordinator) Instituto Investigación Sanitaria Fundación Jiménez Díaz	Spain
LAFONTAINE, DENIS L.J FONDS DE LA RECHERCHE SCIENTIFIQUE	Belgium
Beléndez, Cristina Hospital General Universitario Gregorio Marañon (HGUGM)	Spain
LEBLANC, Thierry	France

Hôpital Robert-Debré	
Niemeyer, Charlotte University Medical Center Freiburg	Germany
SCHMIDT, MANFRED GeneWerk GmbH	Germany
Collaborators	**Country**
Da Costa, Lydie AP-HP Robert Debré, University of Paris	France
Patient Advocacy Organisation	**Country**
Asociación Afectados Blackfan Diamond España	Spain
Association Francophone de la Maladie de Blackfan-Diamond (AFMBD)	France
Diamond-Blackfan-Anämie Selbsthilfe E.V.	Germany

Diamond-Blackfan Anemia (DBA) is an inherited bone marrow failure (IBMF) syndrome mainly characterized by red cell aplasia, congenital anomalies and increased risk of cancer. The annual incidence of DBA is 5 per million life births. So far, mutations in 20 DBA genes have been identified, although mutations in RPS19 are the most frequent (25%). Hematopoietic stem cell transplantation (HSCT) from familiar or fully matched (10/10) unrelated donors is indicated in transfusion-dependent patients, but many patients lack a suitable donor, and the output of HSCTs from alternative donors is still poor. Based on the encouraging results obtained by members of this Consortium in an ongoing gene therapy trial in another IBMF syndrome (Fanconi anemia, FA), now we aim at developing the preclinical studies required for a subsequent gene therapy trial in DBA patients with mutations in RPS19. We have already developed two lentiviral vectors capable of reverting the phenotype of DBA hematopoietic progenitor cells in vitro. In this proposal, in vitro and also in vivo experimental studies will be conducted to demonstrate the efficacy of a gene therapy approach to correct both the ribosomal biogenesis and erythropoietic defects characteristics of DBA. In parallel, bio-distribution, toxicity and proviral insertion site studies will be performed according to EMA guidelines. Studies conducted will allow us to apply for an Orphan Drug Designation both at EMA and FDA, aiming at developing a gene therapy trial in RPS19-DBA patients to prevent and/or rescue the BMF characteristic of the disease.

FANEDIT : Gene editing as a novel therapeutic strategy in Fanconi anemia

Partners	Country
Río, Paula (Coordinator) Instituto Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD, UAM)	Spain
Corn, Jacob ETH Zurich	Switzerland
Cathomen, Toni Universitätsklinikum Freiburg (UKLFR)	Germany
Mussolino, Claudio Universitätsklinikum Freiburg (UKLFR)	Germany
Soulier, Jean Hôpital Saint-Louis et Université de Paris	France
Sevilla, Julián Fundación para la Investigación Biomédica del Hospital Infantil Universitario Niño Jesús	Spain
Collaborators	**Country**
Verhoeyen, Els CIRI, INSERM, EVIR, ENS de Lyon	France
Patient Advocacy Organisation	**Country**
Fundación Anemia de Fanconi	Spain

Fanconi anemia is a DNA repair syndrome characterized by congenital abnormalities, cancer predisposition and early onset of bone marrow failure in the patients. Allogenic hematopoietic stem cell (HSC) transplantation is currently the only curative treatment for the bone marrow failure in Fanconi anemia (FA). However, only 25% of the patients have a suitable donor (human leukocyte antigen (HLA)-identical donor) and severe side effects are associated to this treatment, specially increased incidence of squamous cell carcinoma. Recent studies from FANEDIT

members have shown the feasibility to correct hematopoietic stem cells from FA-A patients using lentiviral vectors. Strikingly, corrected cells engrafted in the patients in the absence of any conditioning and showed a marked proliferative advantage. Although lentiviral vector therapy has demonstrated to be safe in different clinical trials, the possibility to precisely correct the mutation in the patient would be the ideal therapeutic strategy. Thanks to the advance in gene editing strategies in this new project we aim to go one step further in the development of safer and more precise gene therapy strategies that allow the correction of the different mutations described in the 22 different genes involved in the disease. For this purpose, novel gene editing strategies and delivery systems will be tested in FA HSCs. Importantly, safety studies using different platforms will be conducted to identify the best-suited programmable nucleases for further clinical development.

ProDGNE : Novel therapeutic approaches to target GNE Myopathy

Partners	Country
Videira, Paula (Coordinator) Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa	Portugal
Lochmüller, Hanns Children's Hospital of Eastern Ontario Research Institute	Canada
Caboni, Pierluigi Università degli Studi di Cagliari	Italy
Horstkorte, Rüdiger Martin-Luther-University Halle-Wittenberg	Germany
Collaborators	**Country**
Fabrizio Pertusati Cardiff University	United Kingdom
Patient Advocacy Organisation	**Country**
Associazione Gli Equilibristi – HIBM	Italy

GNE myopathy (GNEM) is a rare severely debilitating muscle disease which affects 1 to 9:1,000,000 people among all ethnicities, with elevated carrier rates in populations

of Eastern Europe and Asian heritage, including Jewish, Persian, East Indian, Arab and Japanese. GNEM is characterized by hypo-sialylation of muscle glycoproteins, atrophy and weakness of skeletal muscles, causing severe impairment of function and quality of life. It is caused by mutations in the GNE gene which encodes biosynthesis of the sialic acid enzyme. There are no approved therapies and research efforts on sialylation-increasing therapies such as Neu5Ac and ManNAc are challenged by drug absorption and the absence of biomarkers in clinical development which are the main focus of our project. ProDGNE aims to overcome these obstacles through a joint collaboration among European and Canadian experts in clinical GNEM and basic research in sialic acid, organic synthesis, and -OMICS. Our developed prodrug when processed within cells becomes an active therapy, highly increasing sialic acid in GNEM patient cells and demonstrating a higher stability when compared to clinically tested drugs.
The ProDGNE consortium will develop proof of principle studies fostering early stage development for innovative therapeutic strategies tested in vitro in patient derived cells and in vivo in GNE animal models that mimic the pathological mechanism in patients. Moreover, post-translational modifications will be explored and the newly identified biomarkers, will be utilized to monitor efficacy.

EpiThe4FSHD : Safety and efficacy of a possible epigenetic therapy for FSHD muscular dystrophy

Partners	Country
Gabellini, Davide (Coordinator) IRCCS Ospedale San Raffaele	Italy
Al-awar, Rima Ontario Institute for Cancer Research	Canada
Schotta, Gunnar Ludwig-Maximilians-Universität München	Germany
Eraslan, Serpil Koc University Hospital	Turkey
Siciliano, Gabriele Azienda Ospedaliera Universitaria Pisana (AOUP)	Italy
Collaborators	**Country**

MacLaren, Ann Triphase Accelerator	USA
Manca, Laura University of Pisa	Italy
Vozzi, Giovanni University of Pisa	Italy
Patient Advocacy Organisation	**Country**
Unione Italiana Lotta alla Distrofia Muscolare	Italy

Facioscapulohumeral muscular dystrophy (FSHD) is the most prevalent muscle disease that afflicts both children and adults regardless of their gender. FSHD is caused by aberrant gain of expression of the double homeobox 4 (DUX4) gene causing toxic effects in muscle cells. Despite the consensus on the pivotal role of DUX4 and several clinical trials, there is currently no cure or an effective therapeutic approach for FSHD patients. In our studies, we identified a novel regulator of DUX4 expression. Targeting this factor allows to block DUX4 expression and rescues the pathogenic behavior of muscle cells from FSHD patients. The treatment is safe to healthy muscle cells. Based on our results, we will use cellular and animal models of the disease to investigate a novel pharmacological approach that could represent a promising therapeutic option for FSHD patients.

SILENCELQTS : SGK1 inhibition as a novel therapeutic approach in Long QT syndrome

Partners	Country
Wilde, Arthur (Coordinator) Amsterdam University Medical Center, location Academic Medical Center	The Netherlands
Crotti, Lia Istituto Auxologico Italiano, IRCCS	Italy
Odening, Katja University of Bern (UNERN)	Switzerland

Gepstein, Lior Technion – Israel Institute of Technology	Israel
Collaborators	**Country**
Vidal, Marc LQT Therapeutics, Inc.	Canada
Patient Advocacy Organisation	**Country**
Stichting Hart4Onderzoek	Netherlands

Congenital long-QT syndrome (LQTS) is a rare inherited disorder (prevalence close to 1:2500) associated with life-threatening arrhythmias and sudden cardiac death (SCD) in relatively young and otherwise healthy individuals. LQTS has a heterogeneous genetic basis, with various LQTS subtypes caused by mutations in distinct genes related to cardiac ion channel function. Current symptom-directed therapies aimed at reducing arrhythmia triggering events, including lifestyle changes, beta blockade, and left cardiac sympathetic denervation, only partly prevent arrhythmic events, and SCD still occurs in a substantial number of LQTS patients.
Within SILENCE-LQTS, we will investigate a novel, mechanism-targeted therapy, comprising pharmacological inhibition of the serum and glucocorticoid regulated kinase-1 (SGK1). In contrast to current symptom-directed therapies, this novel approach is designed to correct the pro-arrhythmic alterations in sodium homeostasis caused (in)directly by the underlying genetic defect. Efficacy of a SGK1 inhibitor, developed by our industry partner, will be systematically tested in vivo and on the cardiomyocyte and whole heart level in well-established unique transgenic rabbit and mouse models of different LQTS subtypes. Furthermore, its efficacy will be tested in human iPS-derived cardiomyocytes (hiPSC-CMs) obtained from LQTS patients and in 2D/3D engineered hiPSC-CM tissues. These pre-clinical studies will establish the anti-arrhythmic potential of SGK1 inhibition, paving the way for future clinical application aimed at preventing SCD in LQTS.

TC NER : Transcription stress Counteracted by Nutritional interventions of Exceptional importance for rare DNA Repair diseases

Partners	Country
Hoeijmakers, Jan (Coordinator) University of Cologne	Germany

Laugel, Vincent Strasbourg University Hospital	France
Mastroberardino, Pier G. Istituto Firc di Oncologia Molecolare	Italy
Vermeij, Wilbert Princess Máxima Center	The Netherlands
Altunoglu, Umut Koc School of Medicine	Turkey
Collaborators	**Country**
Vermeulen, Vim Eramsus MC	The Netherlands
Patient Advocacy Organisation	**Country**
Stg. Amy and Friends	Netherlands

Rare genome instability syndromes such as Cockayne syndrome (CS) and trichothiodystrophy (TTD) display segmental but dramatic accelerated aging reflecting multi-morbidity in many organs and tissues. The most severe clinical hallmark is neurodegeneration, often limiting life expectancy to childhood and strongly affecting QoL. Unfortunately, presently no cure exists. We have recently found that reducing daily nutrition is of tremendous benefit for DNA repair-deficient progeroid mouse mutants, which very closely mimic the human repair disorders. All features of accelerated aging were unequivocally delayed, and lifespan was extended by 200%, simply by reducing food intake. Most impressive was the effect on neurodegeneration: instead of slowing down or halting signs of severe neurodysfunction, tremors and imbalance even disappeared, revealing significant improvement (Vermeij et al., Nature 2016).
Clinical observations from one TTD (XPD) patient has recently provided additional and consistent data: when parents chose to partially reduce caloric intake in their child, motor and cognition improvement has been observed including reduced tremors, improved balance and walking.
Within this consortium we aim to mechanistically understand the interplay between nutrition, metabolism, transcription stress and neuronal functioning and explore effects in other rare genome instability syndromes (e.g. ataxia telangiectasia, Fanconi anemia). These aspects will be studied at multiple levels (e.g. cells, organoids, mouse models, cells from patients) to provide improved evidence-based advice.

CHARLIE : CHAnging Rare disorders of LysInE metabolism

Partners	Country
van Karnebeek, Clara (Coordinator) Stichting Katholieke Universiteit	The Netherlands
Dimitrov, Bianca University of Heidelberg	Germany
Fillat, Cristina Centro de Investigación Biomédica en Red , M.P (CIBER)	Spain
Leavitt, Blair University of British Columbia	Canada
Coene, Karlien Stichting Katholieke Universiteit	The Netherlands
Hrabé Angelis, Martin Helmholtz Zentrum München	Germany
Ia Marca, Giancarlo University of Florence	Italy
Linster, Carole University of Luxembourg	Luxembourg
Patient Advocacy Organisation	**Country**
Familias GA1	Spain
Selbsthilfegruppe Glutarazidurie ev.	Germany
Vereniging Volwassenen, Kinderen en Stofwisselingsziekten	Netherlands

Rare inborn errors of lysine metabolism such as pyridoxine-dependent epilepsy (PDE) and glutaric aciduria type 1 (GA1) cause debilitating, often progressive neurologic symptoms. Although early detection via better diagnostics and newborn screening

enables initiation of a medical diet, this therapy is often not effective resulting varying outcomes and considerable disease burden. Our international CHARLIE project synergizes the expertise of GA1 and PDE patient representatives, basic and clinical scientists, to collaboratively identify biomarkers, new disease mechanism, and importantly develop and test new therapies. One strategy inhibits the upstream enzyme, with the potential to reduce build-up of damaging metabolites thereby preventing brain damage. We will first apply this genetic therapy in PDE and GA1 model systems, such as neuronal stem cells and mouse models. Furthermore, we will investigate gene therapy to rescue the deficient GA1 enzyme and reduction of highly reactive toxic molecules in PDE. To evaluate and compare the efficacy of these different treatment approaches, we will perform behavioral, biochemical, morphological, enzymatic, untargeted metabolomics analyses. With our patient advocacy organizations, we will prioritize the most promising treatment strategy/-ies as well as enhance trial readiness. To inform the families, professionals, and stakeholders, we will organize regular meetings. Together we will pursue knowledge translation from bench to bedside, e.g. clinical trials and drug access, towards improved outcomes for PDE and GA1 patients and families.

GET-READY: Genetic therapy for EYS- and USH2A-associated retinal disease

Partners	Country
COLLIN, Rob (Coordinator) STICHTING KATHOLIEKE UNIVERSITEIT NIJMEGEN	The Netherlands
GYORGY, Bence INSTITUT FUR MOLEKULARE UND KLINISCHE OPHTHALMOLOGIE BASEL	Switzerland
STIEGER, Knut JUSTUS-LIEBIG-UNIVERSITY GIESSEN	Germany
TRAPANI, Ivana FONDAZIONE TELETHON	Italy
KALATZIS, Vasiliki INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)	France
REMAUT, Katrien UNIVERSITEIT GENT	Belgium

SIKSNYS, Virginijus Vilnius University	Lithuania
Patient Advocacy Organisation	**Country**
Stichting Oogfonds Nederland	Netherlands
Retina Suisse	Switzerland
Pro Retina Deutschland e.V.	Germany
Retina Italia Onlus	Italy
Retina France	France
Retina Pigmentosa	Belgium

The retina is a tissue that lines the back of the eye, and is responsible for receiving, modulating and transmitting the incoming light signal to the brain for image interpretation. A disruption in any of these steps can result in visual impairment. An important cause of vision loss is mutations in one of many genes important for retinal structure and function. Such mutations cause the retina to degenerate over time and give rise to a group of rare diseases collectively named inherited retinal diseases (IRDs). Although there is no definitive cure, there has been much progress made over the last ten years in terms of genetic therapies. In particular, gene augmentation therapy, which consists of introducing a healthy copy of the mutated gene into the patient's retina, has proven the most promising and has even been approved for the treatment of IRD due to mutations in one gene. This approach however is not applicable to genes exceeding the size of the currently used gene vehicles, including two of the most frequently mutated genes, EYS and USH2A. The aim of our proposal is to address these current limitations. We will develop alternative therapeutic approaches, and in parallel optimise novel larger vehicles that can ensure a proper delivery of EYS and USH2A coding sequences to the retina. If successful, our project will result in the treatment of a non-negligible patient population, and consequently improve the life-quality of these patients as well as reduce the socio-economic burden due to progressive vision loss.

TreatRP : Translating cGMP analogues into a treatment for retinitis pigmentosa

Partners	Country
Marigo, Valeria (Coordinator) University of Modena and Reggio Emilia	Italy

Schipper, Nicolaas RISE Research Institutes of Sweden	Sweden
Paquet-Durand, Francois Mireca Medicines GmbH	Germany
Urtti, Arto UEF-University of Eastern Finland	Finland
von der Leyen, Heiko Medizinische Hochschule Hannover	Germany
Agca, Cavit SU Sabanci University	Turkey
Murro, Vittoria AOUC Azienda Ospedaliero - Universitaria Carreggi	Italy
Collaborators	**Country**
Per Ekström Lund University	Sweden
John Groten PamGene International B.V.	The Netherlands
Patient Advocacy Organisation	**Country**
PRO RETINA Deutschland e. V.	Germany
Retina Italia odv	Italy

Retinitis pigmentosa (RP) is characterised by loss of those cells in the eye that respond to light. These cells are called photoreceptors. Most forms of RP are today untreatable, and while individually they are rare, together they constitute a major cause of vision loss and blindness in the working age population. Because RP can be caused by mutations in more than 90 different genes, it is important to target common processes so that patients with different mutations may benefit from the same treatment. The goal of this proposal is, in fact, the development of a drug and treatment protocol for different forms of RP.
The partners in this consortium previously found that high levels of the signalling molecule cyclic guanosine-3'-5'-mono-phosphate (cGMP) in photoreceptors cause

cell death and consequently blindness. In previous collaborations they developed a new compound and delivery system, LP-CN03, which delayed the degenerative process and preserved photoreceptors in three animal models of RP.
Now, TreatRP proposes to further advance the pre-clinical development of this promising approach, so that it will be ready for a clinical trial at the end of the project. To this end TreatRP aims at the pharmaceutical development of LP-CN03 to obtain a compound that meets all the requirements for the use in the clinic. This includes the study of the targets in photoreceptors of the new drug, as well as its possible toxicity, and finally the design of the first-in-man clinical trial protocol to enable an efficient and rapid translation of the new treatment to RP patients.

AAK-INSIGHT : Aniridia – Novel therapeutic tools to treat or prevent progressive cornea opacification

Partners	Country
Lagali, Neil (Coordinator) Linkoeping University	Sweden
ZHOU, Huiqing Radboud University	The Netherlands
Ashery-Padan, Ruth Tel Aviv University	Israel
LATTA, Lorenz Saarland University	Germany
BREMOND GIGNAC, Dominique University Hospital Necker Enfants Malades, APHP	France
GÜVEN, Sinan Izmir Biomedicine and Genome Center	Turkey
Collaborators	**Country**
COLLINSON Martin Institute of Medical Sciences	United Kingdom
CISTERNINO Salvatore	France

INSERM, Faculty of Pharmacy Université de Paris 4	

The objective of our project is to develop a therapeutic strategy for patients suffering from progressive loss of the cornea's transparency leading to blindness. Aniridia is a rare, inherited disease caused by mutations in the PAX6 gene, which fails to properly produce a protein essential for normal eye development and function. Today, there is no effective treatment for this blinding disease, resulting in severe vision loss and developmental problems from infancy and throughout life. We have recently identified three drugs that are already approved for treatment of unrelated disorders and our data strongly suggest that repurposing these therapeutic molecules could be effective in preventing or treating existing blindness by restoring corneal transparency. AAK-INSIGHT combines EU partners with complementary expertise, advanced tools and relevant disease models to validate selected drugs along with gene therapy to reverse the phenotype of this rare disease. We will test these therapeutic candidates in diverse cellular models we have developed or isolated from patients and also in purpose-designed mouse models. Our efforts focus on identifying of the mechanism by which these molecules act on PAX6 in corneal cells. The present opportunity to bring together European experts allows for the first time the study of potential therapeutic tools in the same cellular and animal models, aiming eventually to treat aniridia patients by drug repurposing. Our aim is to progress on the translation of novel therapeutics for use in future clinical trials.

MECPer-3D : Personalized MECP2 gene therapy using CRISPR/Cas9 technology coupled to AAV-mediated delivery in 3D cell culture and KI mice.

Partners	Country
Meloni, Ilaria (Coordinator) University of Siena	Italy
Chillon, Miguel Fundacio Vall d'Hebron Institute de Recerca (VHIR)	Spain
Ladewig, Julia Central Institute of Mental Health (ZI)	Germany
Herault, Yann Centre Européen de Recherche en Biologie et en Médecine	France

Chiariello, Mario Core Research Laboratory (CRL)	Italy
Patient Advocacy Organisation	**Country**
ASSOCIAZIONE ITALIANA RETT- AIRETT	Italy

Rett syndrome is one of the most common causes of intellectual disability in girls, resulting in severe cognitive and physical disabilities. The classic form is caused by mutations in the transcriptional regulator MECP2. Effective therapies are not available and gene editing based on CRISPR/Cas9 combined with Homology Directed Repair appears an appealing option for the development of new therapies. We already engineered a gene editing toolkit and demonstrated its ability to efficiently correct the most common MECP2 mutation, c.473C>T - p.T158M, in patient cells. Based on these results, in this project we will further validate constructs for this mutation and validate toolkits for other MECP2 mutation hotspots. To characterize the potential of our approach in a relevant context and define its efficiency in a human 3D model, we will employ cerebral organoids differentiated from patient-derived induced pluripotent stem cells. Thanks to the ability of some AAV serotypes to cross the Blood Brain Barrier (BBB) following intravenous injection, we will test our system in KI mice to validate efficacy and safety in vivo. Moreover, since available AAV serotypes have an imperfect brain tropism, with significant distribution to other organs, new serotypes will be developed and validated for their ability to cross the BBB in the mouse and their efficacy and specificity in human cells. These experiments will allow us demonstrating the full potential of gene editing as a therapeutic option for Rett and for other neurodevelopmental disorders currently lacking an effective treatment.

TREAT-SGS : Development and preclinical testing in human cell models and transgenic mice of a novel treatment for Schinzel-Giedion Syndrome

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Schinzel-Giedion Syndrome (SGS) is a rare disease usually leading to death in the first decade of life. SGS is caused by increased stability of the SETBP1 protein and there is no treatment. While the disease is multi-system, a major burden on affected children and their families are the intractable seizures that occur frequently in any given day.
In collaboration with the SGS Foundation we have developed stem cell models derived from four children and their healthy parents, and we have made four mouse models of SGS. We have re-purposed an internationally approved drug currently used to treat multiple sclerosis that can reverse molecular signatures of SGS.
The purpose of this proposal is to perform preclinical proof-of-principle studies to assess this drug and investigate its mechanism of intervention to create a viable treatment for SGS. These studies include: 1) protein and lipid turnover in single cells from mouse and human before and after drug treatment; 2) changes in synaptic vesicle release to understand if this is rescued by drug treatment, which is especially relevant for seizure control; 3) drug effects on mouse brain structure and behaviour, as well as bioavailability of the drug in mouse SGS models; 4) the effects of the drug in developing human brain cells, tracking how single cells differentiate; and 5) machine learning approaches using all data across all research objectives to aid in determining the validity of the drug as a future treatment for SGS children.

CureMILS: A reprogramming-based strategy for drug repositioning in patients with mitochondrial DNA-associated Leigh syndrome

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Mitochondrial DNA (mtDNA)-associated Leigh syndrome (MILS) is an untreatable brain disease affecting 1/100,000 newborns. MILS is typically caused by mtDNA mutations in the ATP-generating subunit MT-ATP6. Drug discovery is particularly challenging for MILS. The limited access to patient neural tissue and the impossibility to engineer mtDNA hinder the development of the cellular and animal models needed for treatment discovery.
Our consortium will employ neural cells generated from MILS patients via cellular reprogramming to carry out large-scale screenings using repurposable drugs, thereby allowing the identification of therapeutic strategies.
Our proof-of-concept study demonstrated that this approach is feasible and relevant. After screening 150 FDA-approved compounds, we identified phosphodiesterase 5 inhibitors (PDE5i) as a potential therapy for MILS. Compassionate use of PDE5i is now proving to be beneficial in a MILS patient. We propose to extend this approach using the largest available library of repurposable compounds (8,000). We will validate hit compounds by combining mitochondrial profiling with multi-omics analysis using reprogramming-derived neural models (neural progenitors, neurons, and brain organoids) from different MILS patients.
Our consortium will identify drugs suited for repositioning as interventions in MILS, laying the foundation for a multi-national clinical trial and a concrete path towards a cure for MILS. Moreover, we will establish a paradigmatic working pipeline for reprogramming-driven drug discovery of rare neurological disorders.

TREATKCNQ : Targeted treatment for KCNQ related encephalopathies: retigabine analogues, repurposed drugs and allele specific knock down

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The KCNQ-encephalopathies (KCNQ-E) are a group of severe epilepsies with onset in the first months of life, characterized by treatment resistant seizures and developmental delay. They are caused by mutations in genes encoding a type of potassium channels, that normally act as "brakes" regulating brain excitability. Both a severe lack and excess of channel function can result in the development of KCNQ-E. Seizures in children with KCNQ-E often respond poorly to anti-epileptic drugs, and more importantly, therapies for the developmental problems are currently unavailable. With the aim to develop improved therapies for KCNQ-E, we will establish a consortium of researchers with expertise in KCNQ-related pathology and drug development, and access to a set of disease-relevant assays and disease models, such as fluorescence-based assays of potassium flux in cells, rodent and human neuronal cultures expressing KCNQ mutations, and mice modeling the characteristics of KCNQ-E. We will design and test safer and more potent analogues of retigabine, a drug that acts on KCNQ-channels but was recently withdrawn from the market due to side effects, and perform high-througput drug screening to identify novel openers and blockers of KCNQ channels. In parallel, we will study the treatment potential of RNA interference, a biological process that can be exploited to reduce the expression of a disease-causing gene copy. Using this approach, we expect to provide pre-clinical evidence for different types of targeted treatments that have the potential to improve the developmental outcome of KCNQ-E.

TREAT-ARCA : Designing a toolbox of paradigmatic treatments for a targeted molecular medicine approach to autosomal-recessive ataxias

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Autosomal-recessive cerebellar ataxia (ARCA) is a heterogeneous group of rare neurodegenerative genetic diseases that share the common hallmark of progressive damage to parts of the nervous system that coordinate movement, such as the cerebellum. Despite its devastating consequences in daily life on mobility and communication and reduced life span, no disease-modifying treatment is available for these disabling disorders. TREAT-ARCA aims at designing and testing a new complementary treatment strategies, including both repurposed and newly identified molecules, as well as gene therapies in two exemplary multisystemic flagship ARCAS: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) and COQ8A-ataxia (ARCA2). In addition, TREAT-ARCA aims at identifying and validating biomarkers that will enable to follow treatment. This will directly complement our consortium's prior clinical trial-readiness work on these ARCAs (see

PREPARE consortium; www.prepare-ataxia.com), thus now attaining all prerequisites required for directly facilitating clinical treatment trials in these two ARCAs.

SCN1A-up! : Therapeutic strategies for Dravet syndrome: upregulation of endogenous SCN1A and modulation of remodeling.

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Dravet syndrome (DS) is a rare, devastating encephalopathy of early childhood characterized by drug-resistant epileptic seizures, cognitive deficits and ataxia. DS is initially caused by loss-of-function mutations in SCN1A encoding the main Na+ channel of GABAergic neurons that lead to widespread disinhibition in mouse models recapitulating DS. Later pathologic remodelling can modify other signalling pathways. Available treatments are only partially effective against seizures.
The overall objective of SCN1A-up! is to develop more effective treatments for DS with a bottom up approach, targeting SCN1A loss of function, the primary cause of the disease, and pathologic remodeling that can develop at later stages, therapeutic concepts that could be applied also to other diseases. An effective disease-preventing or -modifying treatment for DS will most likely need a polytherapy with different approaches and drugs. To fulfil this challenging task, we will develop two complementary strategies:
1) Increase expression levels of the wild type SCN1A allele (patients are heterozygous) by developing CRISP-ON virally delivered techniques (classic gene therapy does not allow delivery of the large SCN1A gene) and screen for small molecule drugs, strategy for which we have already obtained a proof of concept;
2) Identify new signaling pathways to be targeted with drugs, which may be implicated in pathologic remodeling.
All approaches will be tested and validated extensively in vitro and in vivo in animal and human models, and we will test synergistic effects and model polytherapy.