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TheRaCil Project: Advancing Therapies for Pediatric Renal Ciliopathies - Coordination by Institut *Imagine*, Funded by Horizon Europe

Institut *Imagine*, a university hospital research center (Inserm, AP-HP, Université Paris Cité), also labeled Carnot Institute, will coordinate a project funded through Horizon Europe, the European Union's framework program for research and innovation for the period 2021-2027. Led by Sophie Saunier who is heading the Laboratory of Inherited Kidney disease at Institut *Imagine*, the project "Therapies for Renal Ciliopathies" (TheRaCil) has been selected in the call "Development of new effective therapies for rare diseases". This project brings together 16 partners (main interacting participants at 15 institutions in 6 countries) and 3 European consortia with the ambition to develop appropriate and targeted treatments for pediatric renal ciliopathies. TheRaCil will benefit from a European Commission funding of 7,425,446 euros and a co-funding of 540,520 euros from UK Research and Innovation (UKRI).

Development of effective new therapies for rare diseases: the case of renal ciliopathies

Renal ciliopathies are rare genetic diseases caused by dysfunction of the primary cilium, impacting tissue development and balance. Pediatric renal ciliopathies, including nephronophthisis (NPH) and autosomal recessive polycystic kidney disease (ARPKD), contribute to 15% of childhood chronic kidney disease (CKD) and often progress to end-stage kidney disease (ESKD), which poses significant challenges for patients, families, and healthcare systems. TheRaCil aims to address the urgent need for effective treatments for these conditions. TheRaCil project is a multidisciplinary consortium including clinicians, geneticists, biotechnology companies, and experts in complementary research fields such as cilia biology, bioinformatics, data science, and artificial intelligence (AI) along with patient advocacy groups. By leveraging the expertise of this consortia, TheRaCil aims to develop prognostic tools and therapies that can benefit most patients affected by renal ciliopathies.

A unique, interdisciplinary network to bring treatment to patients

The consortium's primary objective is to develop targeted therapies for pediatric renal ciliopathies, by proposing safe and effective solutions. One of the key strategies employed by TheRaCil is the integration of major European ciliopathy databases, which will provide access to a vast amount of clinical, biochemical, and genetic information from a diverse range of renal ciliopathy patients worldwide. This comprehensive dataset will enable researchers to better understand the disease mechanisms, identify potential therapeutic targets, and stratify patients based on specific characteristics.

A project focused on therapeutic innovation and clinical readiness

TheRaCil will utilize AI-based tools to analyze the collected data and identify dysregulated disease-associated pathways. This approach will facilitate the development of small molecules that target these pathways, as well as the exploration of antisense oligonucleotide (ASO) technology to rescue the expression of key proteins associated with renal ciliopathies. By employing a multi-parameter pipeline based on patient-derived materials and robust preclinical models, the project aims to identify and validate novel therapeutic options.

"TheRaCil aims to pave the way for the translation of preclinical findings into clinical trials. By establishing a large cohort of pediatric renal ciliopathy patients and utilizing AI-based tools, the project aims to identify eligible patients for specific treatments, thereby advancing the concept of precision medicine. The involvement of patient associations and the definition of relevant endpoints for future clinical trials will further enhance the readiness of these therapies for clinical implementation" Explains Sophie Saunier, coordinator of the project.

► About Institut *Imagine*

Located on the campus of the Necker-Enfants malades hospital, Institut *Imagine* is a world leader in research, care and teaching on genetic diseases. Its unique architecture, designed by Jean Nouvel and Bernard Valéro, brings together 1,000 researchers, physicians, teacher-researchers, engineers and health care personnel in a single location to work with patients, with the ambition of accelerating research and diagnosis and therapeutic innovation to change the lives of families affected by genetic diseases. The Institut *Imagine* has been certified “Institut hospitalo universitaire” (IHU), in 2011 and 2019 and a “Institut Carnot”, in 2020. It is supported by six founding members, including AP-HP, Inserm and Université Paris Cité, as well as by private partners and patrons. Every day in France, 64 babies are born with a genetic disease. Nearly 8,000 genetic diseases affect more than 3 million people, of which nearly one in two is undiagnosed and more than 8 in 10 have no dedicated treatment. Faced with this public health emergency, the challenge is twofold: to diagnose and to cure. www.institutimagine.org

► About Assistance Publique - Hôpitaux de Paris / Greater Paris University Hospitals:

The leading hospital and university centre (CHU) in Europe, Greater Paris University Hospitals and its 38 hospitals are organised into six hospital-university groups (AP-HP. Centre - Université Paris Cité ; AP-HP. Sorbonne Université ; AP-HP. Nord - Université Paris Cité ; AP-HP. Université Paris Saclay ; AP-HP. Hôpitaux Universitaires Henri Mondor et AP-HP. Hôpitaux Universitaires Paris Seine-Saint-Denis) and are centered around five universities in the Île-de-France region. Closely linked to large research bodies, Greater Paris University Hospitals include four international hospital-university institutes (Institut du Cerveau, ICAN, IMAGINE, FOrEoSIGHT) and the largest French health data repository (EDS). As a major stakeholder in applied research and health innovation, Greater Paris University Hospitals hold a portfolio of 650 active patents, and each year its clinicians sign off nearly 10000 scientific publications and over 4,000 research projects are under development, all promoters combined. In 2020, Greater Paris University Hospitals were awarded the Institut Carnot label, which is recognition of the quality of partner research: Carnot@AP-HP offers industrial stakeholders applied and clinical research solutions in the health sector. In 2015, Greater Paris University Hospitals also founded the Greater Paris University Hospitals Foundation to support the biomedical and health research performed in all its hospitals. <http://www.aphp.fr>

► About Université Paris Cité

Université Paris Cité is a multidisciplinary research-intensive university in the heart of the capital, which has reached the highest international level thanks to its research, the diversity of its training courses, its support for innovation, and its active participation in the construction of the European research and training area. Université Paris Cité is made up of three faculties (Health, Sciences and Societies, and Humanities), a component institution, the Institut de Physique du Globe de Paris, and a partner research organization, the Institut Pasteur. Université Paris Cité has 63,000 students, 7,500 teacher-researchers and researchers, 2,700 administrative and technical staff, 21 doctoral schools and 119 research units. www.u-paris.fr

► About Inserm

OrphanDev (INSERM) is an INSERM department, F-CRIN certified, and a French national network of expertise specialized on rare diseases. This network will participate in the preparation of ODD applications to the EMA/FDA, the assistance and/or scientific advice to clinical protocols as well as the recruitment of patients in clinical trials by proposing strategies according to the limitations and objectives of these trials interacting with the EMA, the EU national health authorities and HTA agencies (regarding preclinical and clinical drug development in rare diseases).

► About Ruprecht-Karls-Universität Heidelberg

The Faculty of Biosciences at Heidelberg University is one of the most lively and interactive life science faculties in Europe. Research conducted within the Faculty covers a broad range of disciplines, from molecular biosciences to biodiversity, including biotechnology and pharmaceuticals, and considers questions on all experimental and computer-assisted levels of structural and systems biology. The breadth and quality of the research conducted within the life sciences community in Heidelberg is illustrated by the number of special research areas and training networks which are supported by third-party funding.

► About Uniklinik Köln (University Hospital of Cologne)

As a modern maximum care hospital with around 1,500 beds, the University Hospital of Cologne is dedicated to science-oriented, innovative medicine and undertakes important societal responsibilities in research, education, and patient care. Annually, the University Hospital of Cologne treats over 491,000 patients, of which more than 62,500 are admitted as inpatients. With approximately 12,000 employees from over 100 nations, the University Hospital of Cologne ranks among the largest employers in Cologne and is one of the leading university hospitals in Germany.

► About Universitair Medisch Centrum Utrecht

Care, research and education are the three mainstays of UMC Utrecht. These mainstays are inextricably intertwined in our ongoing efforts to improve people's health. Leading scientific research, groundbreaking innovation and collaboration with patients and other interested parties form the basis of our first-rate healthcare. UMC Utrecht is quick and eager to put improvements into practice. High-quality education guarantees the influx of new talent required to maintain and strengthen our position at the forefront of healthcare. The UMC Utrecht employs 952 scientific research staff and there are 213 professors. The academic hospital employs 1,690 PhD students and in 2022, 223 PhD students obtained their PhD degrees. In 2022, there were 3,020 scientific publications, 85% of which were Open Access.

UMC Utrecht has a center of expertise for hereditary and congenital kidney and urinary tract disorders. Patients with cystic kidneys, early kidney failure or disturbed kidney lineage (renal hypoplasia/dysplasia/agenesis) can come here for diagnostics, treatment, hereditary counselling and scientific research.

► About University of Münster

With approximately 44,500 students, the University of Münster is one of the largest universities in Germany. The University draws students, scholars and researchers from around the world – and not only because of its broad range of degree programmes and multifaceted research profile, but also the atmosphere and quality of life in Münster. As a research-oriented university, the University of Münster oversees pioneering research in the fields of the humanities, social sciences, natural sciences, life sciences, business and economics, and law. Some 580 professors and 4,850 academic staff members teach and conduct research in 15 faculties. Two clusters of excellence, 19 collaborative research centres (SFBs), several research training groups and independent junior research groups, numerous interdisciplinary research centres and research projects provide the foundation for inter- and transdisciplinary collaborations and excellent individual research at the disciplinary level. Researchers in Münster maintain professional contacts all over the world. Through official partnerships and cooperation agreements, the University of Münster has cultivated ties with more than 550 universities and scientific institutes worldwide.

► About Københavns Universitet (University of Copenhagen)

The University of Copenhagen was founded in 1479 and today has 37,000 students and 10,000 employees – of whom more than 5,000 are researchers – and revenues of DKK 9.4 billion. With its 5,000 researchers and 37,500 students, the University boasts an international research and study environment and is highly ranked on the leading ranking lists of the world's best universities. The University offers researchers and students the

opportunity to develop their talent and launches ambitious interdisciplinary initiatives to support its strong academic communities. Through research-based teaching – and by involving them in research – students are equipped to address society's challenges and needs. The University of Copenhagen is working towards becoming one of the world's greenest campus areas, leaving as little environmental and climate footprint as possible. The University facilitates cross-organisation collaboration, liaises with the business community and helps students find relevant programmes and projects in the field of sustainability. The University also focuses on gender equality and sees diversity as a strength.

► About Medetia SAS

Focusing on paediatric ciliopathies, the French preclinical biotech #Medetia develops innovative therapies for genetic diseases affecting kidney, retina, bone or cartilage. Medetia is poised to enter into clinic in 2025 with a well-tolerated small molecule to treat a rare retinal degenerative disease (LCA10). Thanks to its close relationship with two major research institutes in France, Inserm and Imagine, Medetia fosters its expertise in selecting other preclinical programs and transforming them into proprietary pipelines. In June 2023, Medetia also announced a strategic partnership with the international pharmaceutical group Ipsen to build some of these other pioneering drugs.

► About Stichting Radboud Universitair Medisch Centrum

Radboud university medical center is an institute for patient care, research and education & training, located in Nijmegen, the Netherlands. Our mission is to have a significant impact on health and healthcare. We aim to be a frontrunner in the development of innovative, sustainable and affordable healthcare. By offering excellent quality, participatory and personalised healthcare, operational excellence and sustainable networks. Our more than 10,000 employees and over 3,000 students do their utmost every day to make a positive contribution to the future of health, healthcare and medical sciences.

► About Universitätsklinikum Heidelberg

The Universitätsklinikum Heidelberg in Germany is a major university medical center. The institution offers a thriving research environment in the field of genetics, where cutting-edge discoveries and innovative therapies are actively pursued. Multidisciplinary teams of genetics researchers collaborate tirelessly to advance our understanding of genetic diseases and pave the way for new therapeutic approaches. With a commitment to excellence in research, education and healthcare, they are at the forefront of genetic medicine, offering hope and solutions to patients worldwide.

► About Medizinische Genetik Mainz

Medizinische Genetik Mainz offers genetic counselling and a wide range of diagnostic services to patients and colleagues from all clinical disciplines, clinics and other medical institutions and specialty centers. We aim to turn the increasingly complex set of data into applicable results to support clinicians in finding the most appropriate therapeutic approach and clinical management of patients. Our team brings decades of experience in the interpretation and interrogation of datasets. Medizinische Genetik Mainz nicely demonstrates the complementary power and added value of close interrelationships between the clinic, diagnostics and research. Our laboratory was among the first that implemented massively parallel sequencing techniques on a broader diagnostic scale and transferred these into the clinic. Innovative diagnostics allows early and targeted prevention and the use of tailored therapies finally improving the efficacy and quality of clinical treatment. Our mission is to foster genetics in routine clinical care and to provide cost-efficient, high-quality services with short turn-around times.

► About Ospedale San Raffaele SRL

IRCCS Ospedale San Raffaele is a university and research hospital established in 1971, capable of offering specialised care for the most complex medical conditions. In 1972, the hospital was officially recognised as a research hospital (Istituto di Ricovero e Cura a Carattere Scientifico, IRCCS), and in 2012 it became part of Gruppo San Donato. With over 60 clinical units and 100 research laboratories, IRCCS Ospedale San Raffaele combines both clinical and scientific activities through a translational approach whereby discoveries made in the laboratory inform clinical practice and research is driven by clinical needs.

► About Hybridize Therapeutics

Hybridize Therapeutics is a biotech spin-off from the Department of Nephrology at the Leiden University Medical Center (LUMC) that was founded in 2019. Hybridize develops RNA-based therapies for untreated kidney diseases. Their first breakthrough project targeted BK virus, a latent kidney-resident virus that is activated upon immunosuppression in kidney transplant and hematopoietic stem cell transplant patients that leads to devastating clinical complications.

► About Newcastle University

Newcastle University is a founding member of the Russell Group of Research-intensive universities, and a Global Top 110 university (QS World University Rankings 2024), Newcastle University is dedicated to excellence, creativity and innovation, pioneering solutions that can change our world. Newcastle University has a stellar track record in rare disease research. We have benefited from decades of collaboration between the University and Newcastle Upon Tyne Hospitals NHS Foundation Trust. We have united almost 100 experts from across these organisations to form Newcastle Centre for Rare Disease where the planned research will be undertaken together with the Translational and Clinical Research Institute.

► About Ciliopathy Alliance

The Ciliopathy Alliance (CA) was formed in 2010 by patient groups, patients, clinicians and scientists with a mission to improve the lives of children and adults affected by ciliopathies. The CA is a UK-registered charity with international membership. In 2012, the CA organized the first CILIA conference, which is now held biennially and is the largest cilia conference worldwide. Ciliopathy patients and patient groups are invited to attend the conference and participate in a dedicated patient involvement/engagement event. The CA will establish a PELSI (patient, ethico-legal and societal issues) Advisory Board with patients, family members and groups representing the renal ciliopathies, as well as contributing to other work packages as required.



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UNIVERSITÄT HEIDELBERG
ZUKUNFT SEIT 1386



Radboudumc
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Inserm

HEIDELBERG
UNIVERSITY
HOSPITAL

Contact Details :

Sophie Saunier

Project Coordinator

Institut Imagine

sophie.saunier@inserm.fr

Nouara Lhocine

Project Manager

Institut Imagine

nouara.lhocine@institutimagine.org

Anne Lenoir

Communication officer

Institut Imagine

anne.lenoir@institutimagine.org