GHENT UNIVERSITY

RARE-MED: PRECISION MEDICINE IN RARE DISEASES: FROM FUNCTIONAL GENOMICS AND DISEASE MODELLING TO GENE THERAPY

RARE-MED is a multidisciplinary consortium for basic and translational research on precision medicine for rare diseases, to address missing heritability using systems genetics and functional genomics, to facilitate disease modelling using CRISPR/Cas9-mediated genome editing of aquatic model organisms (zebrafish, Xenopus) and of cellular systems, to introduce new gene therapies based on antisense oligonucleotide- or CRISPR/Cas9-based genome editing. RARE-MED will bring UGent in a unique strategic position as an international reference center for rare diseases.

Leading scientists:

Faculty of Medicine and Health Sciences - Center for Medical Genetics: Prof. Elfride De Baere, prof. Paul Coucke, prof. Kathleen Claes, prof. Björn Menten, prof. Bruce Poppe

Faculty of Medicine and Health Sciences – Department of Ophthalmology: prof. Bart Leroy

Faculty of Medicine and Health Sciences – Department of Pediatrics: prof. Martine Cools

Faculty of Sciences – Department of Plant Biotechnology and Bioinformatics: prof. Kathleen Marchal

Faculty of Sciences – Department of Biomedical Molecular Biology: prof. Geert Berx

Faculty of Pharmaceutical Sciences – Laboratory for General Biochemistry and Physical Pharmacy: prof. Stefaan De Smedt, prof. Katrien Remaut

 # new professorships: 3

Project description

The search for DNA variants responsible for Mendelian diseases has been a tremendous success in human genetics over the past 30 years. Disease-causing genes have been identified for almost 5.000 Mendelian disorders, and this number will only increase as whole genome sequencing (WGS) is more generally applied. However, our ability to interpret the functional and clinical significance of individual variants has not kept pace with the ease with which we find them. In addition, an increasing number of studies revealed the importance of non-coding variants, representing an unexplored yet emerging field in genomics of Mendelian disease. Closing the 'interpretive' gap between the large-scale identification and interpretation of DNA variants relevant for Mendelian disorders provides unprecedented opportunities for precision medicine, in which treatment is based on the individual's unique genetic profile.

Precision medicine is particularly of interest for inherited rare diseases, as each of them is caused by mutations in a different gene or molecular pathway. Over 7,000 rare diseases have been identified worldwide, together affecting up to 8% of the population. For many inherited rare diseases, the underlying genes are yet to be identified or have an unknown function. This proposal aims to establish and strengthen a multidisciplinary consortium for basic and translational research on precision medicine for rare diseases. Enlargement of the consortium with the proposed ZAP profiles is a prerequisite to keep pace with recent scientific developments and to confirm the leading position of Ghent University (UGent) within the outlined scientific fields. We will focus on different niches of inherited rare diseases for which extensive expertise is available at UGent and that affect in aggregate a large number of individuals: blindness, connective tissue disorders, hereditary cancer syndromes, intellectual disability and disorders of sex development. The molecular pathogenesis of these disorders was intensively

studied for over 10 years at UGent, resulting in a catalogue of DNA variants and a large biobank of genetic material of patients awaiting further studies and personalized treatment. Specifically, we strive to combine the expertise of a least three UGent faculties to the following research fields, all of which are required in view of precision medicine:

1. Missing heritability. Although the advent of whole exome (WES), whole genome (WGS) and transcriptome (RNA-seq) sequencing led to the development of a plethora of bioinformatics tools, there is a need for innovative systems genetics and functional genomics approaches for data integration, to interpret candidate disease-causing mutations including those located in the non-coding portion of the genome, and to better understand pathways implicated in disease. Data generated by computational approaches should be assessed by further disease modelling (see 2).
2. Disease modelling. We aim to fully exploit the advantages of efficient and flexible genome editing approaches using RNA-guided nucleases (CRISPR/Cas9) to generate models of disease, not only by gene knockout but also by the introduction of specific point mutations in any gene of interest. Two model organisms will be used in this multidisciplinary project: zebrafish and *Xenopus*. Both are vertebrate model organisms that are easy and cheap to maintain and that are amenable to straightforward and efficient methods for functional genomics. In order to tackle the functional assessment of non-coding variants, which is even more challenging, we propose a platform based on cellular systems, including patient-derived induced pluripotent stem cells (iPSCs), enabling us not only to model disease, but also to test rescue strategies with therapeutic implications (see 3).
3. Gene therapy. In those families with a clear-cut disease-causing mutation (see 1), opportunities such as gene therapy will be explored. Apart from gene augmentation, alternative and innovative therapeutic strategies that can overcome the possible limitations of currently used approaches will be investigated. Examples are antisense oligonucleotide (AON)-based modulation of RNA splicing and CRISPR/Cas9-based genome editing. The preclinical efficacy of these approaches will be assessed in the most suitable animal model or cell culture system, such as patient-derived iPSCs (see 2).

In summary, this multidisciplinary RARE-MED proposal will create new opportunities for research on precision medicine of rare disorders, based on the existing excellence of three UGent faculties. Importantly, the rare disease niches studied here are exemplary for other inherited rare diseases with a tremendous genetic heterogeneity, increasing the scientific and societal impact of this project.

Proposed impact

The impact of rare diseases on the quality of life of affected individuals and the accompanying economic burden have not received enough public attention, which can partially be explained by the fact that these diseases are individually rare. With a few exceptions, rare disease patient organisations have not developed large fundraising activities. We believe that there is an unmet need for patients with rare diseases, their families and involved patient organisations to develop new initiatives to increase rare disease research. The current proposal will help raise societal awareness of the need to identify and understand the underlying disease mechanisms as a step towards the development of novel effective therapies. The consortium will not only provide new insights that will impact the quality of life of patients with rare disorders, but also forge long-lasting ties between young researchers, patients, patients' caretakers, patient organisations and policy makers, with lasting societal impact.

Finally, this interdisciplinary and sustainable RARE-MED consortium will enforce basic and translational research at UGent, with a direct impact on diagnosis, prevention, prenatal options and treatment of rare diseases. Importantly, this approach is broadly applicable not only for rare but also for more common, multifactorial disorders. Taken together, RARE-MED will bring UGent in a unique strategic position as an international reference center for rare diseases.