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ERA Long–Term Research Fellowship Project

G&K

Project's key info

Title of the project	INDIGO: Identifying new treatments for Nephrogenic Diabetes Insipidus using a Groundbreaking Organoid-based personalizable model system
Working Group involved in the project	Genes & Kidney Working Group (G&K)
Principal Investigator(s) of the project	Tom Nijenhuis (The Netherlands)
Duration	12 months
Fellowship Grant	34.495,00 €
Start of the fellowship	Within 6 months after notification of the grant award to the fellow.

Receiving Institute

Name of receiving institute	Department of Nephrology and Department of Medical BioSciences, Radboud University Medical Center, Nijmegen, The Netherlands
Supervisor's name	Tom Nijenhuis (The Netherlands)
Supervisor's e-mail address	Tom.Nijenhuis@Radboudumc.nl

Project's detailed description

Project description

Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus (NDI) is a genetic kidney disease causing the inability to concentrate urine due to an impaired renal tubular response to the antidiuretic hormone vasopressin (AVP), resulting in the excretion of excessive volumes of urine. It is clinically characterized by polyuria (10-15 litres daily), polydipsia and a resulting high risk of hypernatremic dehydration. Most cases are due to mutations in the vasopressin receptor gene (AVPR2; X-linked). Rare cases are due to variants in the aquaporin-2 gene (AQP2; autosomal recessive or dominant NDI).

Clinical and scientific unmet need

NDI can result in severe and potentially life-threatening complications, including failure to thrive, recurrent hypertonic dehydration potentially causing brain damage, developmental delays and intellectual disability, along with bladder dysfunction and hydronephrosis leading to urinary tract infections and chronic kidney injury. Currently, there is no effective causal treatment. Hence, it is imperative to identify effective drugs that could restore the disturbed AVPR2 and AQP2 function, which is identified as an unmet (research) need in the upcoming international expert consensus statement on diagnosis and management of NDI (Nat Rev Nephrol, *in press*).

Previous attempts using *in vitro* model systems to identify drugs to treat NDI have been

unsuccessful; models were flawed because of not being human-based, not adequately expressing AQP2 or AVPR2 (mutants), not showing reliably measurable vasopressin-sensitive functional water transport, and could certainly not be personalised.
We have now developed a human stem cell and organoid-based, AQP2- and AVPR2-expressing, vasopressin-responsive tubuloid swelling model capable of addressing this unmet need.

Project plan
We will apply our novel human organoid-derived tubuloid swelling model, which we have shown to be functional and vasopressin-sensitive, to mimic the patients' disturbed water handling and screen drugs to causally repair the defect, even in a personalized fashion. We have a putative set of chaperone drugs available to screen for their ability to translocate the mutated AVPR2 and AQP2 to their correct cellular location and to affect the functional swelling of tubuloids as a readout of rescued water transport. As a centre of expertise for NDI, we have access to the urine of outpatient NDI patients to develop patient-specific tubuloids and to confirm the methodology and therapeutic efficacy on NDI patient cells.

Goals of the project

This project utilises organoid technology to discover drugs capable of treating NDI. We aim to demonstrate that we can identify drugs that repair the defective water transport by screening them in our recently established vasopressin-responsive tubuloid swelling model. We will test a pre-determined set of chaperone drugs on their efficacy to rescue vasopressin-sensitive water transport in the presence of specific AVPR2 and AQP2 mutations theoretically amenable to rescue. If applicable, other drug libraries and other NDI mutations can be tested similarly.
To show the potential of future personalized drug screening, we will grow tubuloids from NDI patients' urine. Using these personalized tubuloids as *ex vivo* readout, we will confirm drug effects in cells from NDI patients, which comes closest to the *in vivo* situation in each specific NDI patient and is the crucial step towards personalized clinical translation.

Qualifications and/or expertise required to the fellow

The fellow should have:

- High level of motivation;
- Biomedical or medical background/degree;
- Affinity with translational research; laboratory experience is highly advantageous;
- Sufficiently proficient in the English language.