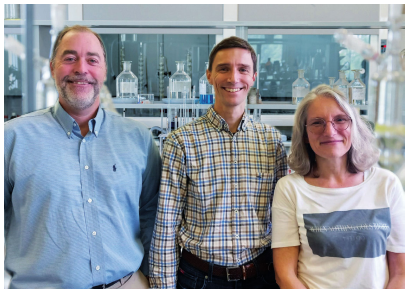
Thanks to patient organisations and European incentives for research into pathophysiology and therapy, over the last decade rare diseases have received growing attention. In the set of rare diseases, mitochondrial diseases are one of the largest and most frequently occurring subgroups. The Mitochondrial Investigations Laboratory on the Ghent University Hospital campus aims to unravel pathophysiological mechanisms of these disorders and has engaged in a new route of therapeutic opportunities.

Mitochondrial diseases are challenging to identify as they can affect almost any organ, in any combination and symptom onset can appear at any age. Currently, for most of these disorders no curative treatment is available. Receiving a final diagnosis after a long odyssey is for most patients a relief even if no curative options can be offered. The Mitochondrial Investigations Laboratory was founded in 1995, by prof. dr. Rudy Van Coster. “He set up this laboratory after achieving his PhD at Columbia University, New York, on the topic of OXPHOS and PDH deficiency,” says prof. dr. Arnaud Vanlander, the current head of the laboratory. “Rudy Van Coster profiled the lab as the national reference centre for biochemical evaluations of mitochondrial functioning and subsequently expanded its fame via many international collaborations. Initially the laboratory focussed on diagnosing mitochondrial diseases in patients and discovering new mitochondrial diseases. Today, the lab strengthens its diagnostic performance by implementing new techniques. It also enlarged its activities by further exploration of pathophysiological mechanisms and by searching for appropriate targeted therapies.”



Arnaud Vanlander (middle) with his team members Joél Smet (l.) and Boel De Paepe (r.)

Added value

With the advent of genetic tools becoming largely available, diagnosing rare diseases has become more straightforward. “Genetic results however are not always easy to interpret and sometimes ask for confirmation. Here, biochemical analyses add value.” The Mitochondrial Investigations Laboratory can explore pathogenicity of genetic variants, by assessing enzyme activities, evaluate oxygen consumption, cell viability and perform targeted microscopic analyses as well as proteomics analysis.

Zebrafish model

A subgroup of mitochondrial diseases encompasses the group of mitochondrial amino-acyl tRNA synthetases deficiencies (aARS2). “The diagnosis is often easily made by genetic analyses. However, much about the pathophysiology of these diseases remains to be discovered. Even within one family the clinical presentation can vary substantially between individuals. To find what causes this variability, a zebrafish model of aARS2 deficiency was set up in order to try to unravel the biochemical background of the disease, using multi-omics tools, and evaluate why some organs are more prone to aARS2 deficiency than others. Moreover, the aARS2-deficiencies are possibly an actionable group for treatment strategies. Aside of the research on pathophysiological mechanisms, the zebrafish model is used to explore treatment options to be extrapolable in men.”

To improve management of mitochondrial disorders, the lab aims to open a new research pipeline, exploring the possibilities that neuronal induced pluripotent stem cells can offer in diagnostics and pathophysiology research in mitochondrial diseases. As the central nervous system involvement constitutes an important disease burden in mitochondrial diseases, modelling the disease in neuronal cells will potentially offer better insights on its dysfunction and how this can be reversed.

Collaborations

Finally, the Mitochondrial Investigations Laboratory has many running collaborations with other research units in Belgium and abroad, asking to explore the role of mitochondrial dysfunction in particular diseases. Also, evaluation of potential toxicity of pharmaceutical compounds on mitochondria, i.e. mitotoxicity, yielded several frequently referenced papers.

In the field of mitochondrial medicines still much has to be discovered. The Mitochondrial Investigations Laboratory has engaged to contribute to this quest, utilizing the latest research technologies.

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