SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Structural Biology Brussels

has the honor to invite you to the public defence of the PhD thesis of

Margot Van Nerom

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

Nucleation of polymorphs and pathological droplets formed through liquid-liquid phase separation in the context of neurodegenerative disease

Promotors:

Prof. dr. Dominique Maes
Prof. dr. Peter Tompa

The defence will take place on

Friday, August 30, 2024 at 4.00 p.m. in auditorium D.2.01

Members of the jury

Prof. dr. ir. Eveline Peeters (VUB, chair)
Prof. dr. Joris Messens (VUB, secretary)
Prof. dr. ir. Heidi Ottevaere (VUB)
Prof. dr. Peter Vekilov (University of Houston, USA)
Prof. dr. Ludo Van Den Bosch (KU Leuven)

Curriculum vitae

Margot Van Nerom obtained a Master's degree in Bioengineering Sciences: Cell and Gene Biotechnology: Molecular Biotechnology at the Vrije Universiteit Brussel. In 2020, she commenced a multidisciplinary PhD at the Structural Biology Brussels lab, supported by a strategic research program. Her research combines molecular biology with photonics and microfluidics.
Throughout her PhD, Margot has assisted in teaching a master's course and presented her research at international conferences, such as the prestigious European Molecular Biology Organization (EMBO) conference "RNA meets protein decay."

Abstract of the PhD research

Cellular organization has conventionally been viewed as microscopic organelles enclosed by lipid membranes. However, the discovery of membraneless organelles within cells has revolutionized cell biology. This type of cellular organization is preceded by the nucleation of droplets, formed through liquid-liquid phase separation (LLPS) and appears to play crucial roles in gene regulation, transport, stress regulation, and various other cellular functions. For example, stress granules, which are reversibly formed in eukaryotic cells in response to stress, serve to protect free RNA from entanglement through a complex network of RNA and RNA-binding proteins such as Ras GTPase-activating protein-binding protein 1 (G3BP1).

However, the primary genetic defect associated with familial amyotrophic lateral sclerosis is the expansion of a hexanucleotide repeat within the intronic region of the C9orf72 gene. This expanded repeat region gives rise to arginine-rich dipeptide repeats (RDPRs), which are highly toxic and exert their toxicity by dysregulating stress granules.

In this dissertation, we first study the connection between G3BP1 and RDPRs, revealing that RDPRs strongly bind to G3BP1, prompting G3BP1 to switch from a LLPS-inactive state to a LLPS-active state. Furthermore, it demonstrates that the primary driver for this switch-like behaviour of G3BP1 is the intrinsically disordered region 1 (IDR1). These new insights into the RDPR mechanism could pave the way for novel therapeutic targets in neurodegenerative diseases.

Secondly, this research introduces novel techniques to the LLPS field, such as photonic and microscopic detection in microfluidic platforms. Prior to their application in LLPS studies, a case study on the nucleation of crystal polymorphs within a microfluidic channel was performed, indicating that the mixing protocol used within a microfluidic channel impacts crystal nucleation. Finally, the newly designed microfluidic and photonic techniques were applied to LLPS studies, showcasing their potential and advantages in the LLPS field.