SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Structural Biology Brussels

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

Hung Huy NGUYEN

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

Validation of *in silico* design and covalent modification of intrinsically disordered proteins

Promotors:

Prof. dr. Peter Tompa

Dr. ir. Kris Pauwels

The defense will take place on

Thursday, July 9th, 2020 at 16:00 h

and will be held for a limited audience. The defense can be followed through live stream:
Join live event

Members of the jury:

Prof. dr. ir. Wim De Malsche (VUB, chairman)
Prof. dr. Dominique Maes (VUB, secretary)
Prof. dr. Peter Tompa (VUB, promotor)
Dr. ir. Kris Pauwels (VUB, co-promotor)
Em. Prof. dr. Daniel Charlier
Prof. dr. Ann Massie
Prof. dr. André Matagne (Université de Liège)
Prof. dr. Annalisa Pastore (King's College London)

Curriculum vitae

Hung Huy Nguyen graduated as an Engineer of Biotechnology from the Hanoi University of Technology (Vietnam) in 2010. Immediately after obtaining a Master of Science in Molecular Biology with the grade of Great Distinction at the Vrije Universiteit Brussel in 2013, he started his PhD study that focused on engineering the human calpain-calpastatin system. So far, his PhD research led to 4 first author publications in international peer-reviewed journals and 2 book chapters. His work was also presented at several (inter)national conferences and academic meetings.

Abstract of the PhD research

Human m-calpain is an intracellular cysteine protease that irreversibly modulates the activity of many proteins. Its activity is tightly controlled by calcium and by an endogenous intrinsically disordered protein (IDP) inhibitor called calpastatin. The role of calpain activity in cancer, neurodegeneration and inflammation makes it an appealing protein for structural/functional studies and drug development.

An in-depth biophysical characterization of calpain has been hampered by complicated, multistep and labour-intensive purification protocols, resulting in samples of compromised purity. Hence, we developed a new affinity-based method that captures calpain efficiently from a complex biological mixture with only a single chromatographic step and in a considerably reduced time.

IDPs are unique with their remarkable conformational flexibility and structural plasticity, which is their functional state. The peculiar behaviour of IDPs renders them a challenging yet relevant model for protein design. Still, designing novel IDPs has so far been completely neglected. For the first time we have demonstrated the successful *de novo in silico* design of an IDP that fulfils its specific function, yet doesn't have any sequence similarity to any existing natural counterpart.

IDPs, being ubiquitously involved in biological and pathological processes, are also potential therapeutic targets. Yet, members of this "disorderome" have not yet been successfully targeted by drugs, primarily because traditional design principles are hampered by their highly dynamic, heterogeneous structural state. In an attempt to tackle this problem, here we describe a possible generic method for the targeting of IDPs via covalent modification. Although there are contradictions between the structural and functional properties of modified IDPs due to the natural complexity of the test system, this is actually a reasonable starting point for drug-development efforts.