China Scholarship Council – University Maastricht

PhD Programme Application form 2024

Basic information
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1. Information on prospective UM supervisors and Promotor

1a. First Supervisor/promoter:

- Title(s), initial(s), first name, surname: Assoc Prof, G.A.F., Gerry Nicolaes
- Research group: Department of Biochemistry, 3D structure-function research
- Address for correspondence: Universiteitssingel 50, 6229ER Maastricht, the Netherlands
- Telephone: 0031-43-3881688
- E-mail: g.nicolaes@maastrichtuniversity.nl

Website: https://www.3dstructure-function.nl/
https://www.carimmaastricht.nl/research/facilities/structural-bioinformatics

1b. Second Supervisor/copromoter:

- Title(s), initial(s), first name, surname: Dr., K., Kanin Wichapong
- Research group: Department of Biochemistry, 3D structure-function research
- Address for correspondence: Universiteitssingel 50, 6229ER Maastricht, the Netherlands
- Telephone: 0031-43-3881688
- E-mail: k.wichapong@maastrichtuniversity.nl

Website: https://www.3dstructure-function.nl/
https://www.carimmaastricht.nl/research/facilities/structural-bioinformatics

1c. Promotor (if applicable): Assoc Prof, Gerry A.F. Nicolaes

2. Information on UM Faculty/ Department/ Institute/ School contact person:

When the application is granted by both the CSC and UM, the contact person is responsible for the practical arrangements of the integration of the PhD candidate:

- Initial(s), first name, surname: Assoc Prof, G.A.F., Gerry Nicolaes
- Research group: Department of Biochemistry
- Address for correspondence: Universiteitssingel 50, 6229ER Maastricht – the Netherlands
- Telephone: 0031-43-3881688
- E-mail: g.nicolaes@maastrichtuniversity.nl

- To be filled in by the applicant if already known –

1. Information on the applicant

- Initial(s), first name, surname:
- Male/female:
- Current work/study address:

- E-mail:
- Private address:

2. Details of applicant's home university

Note! A separate letter of recommendation by the supervisor or faculty dean of the home university is required.

- Name of home university:
- Address:
- E-mail:
- Website (if available):

3. Applicant's home university Master Thesis supervisor:

- Title(s), initial(s), first name, surname:
- Address for correspondence:
- E-mail:

4. Research field(s)

- Computer-Aided Molecular Design
- Structural Bioinformatics
- Drug Discovery and Development
- Protein-Protein Interactions
- Protein and Medical Biochemistry
- Protein Expression and Purification
- Sepsis and Systemic Inflammation
- Immunothrombosis
- SARS-CoV2 / COVID-19

5. Title of research plan for CSC-UM PhD Programme

Investigation of Protein Arginine Deiminase (PAD4) and Neutrophil Elastase (NE) interactions: Translation of molecular mechanism into novel therapeutic options to treat immunothrombotic disease

6. Short summary of research plan (max. 250 words) (A full plan must be submitted later)

Background:

The research group has been working on translation of protein-protein/ligand interactions into novel diagnostic and therapeutic agents by integration of computational and experimental methods. The main targets being investigated at the host research group are proteins that play key roles in the cross-talk between Damage-Associated Molecular Patterns (DAMPs) and Neutrophil Extracellular Traps (NETs) pathways that can induce (excessive) inflammatory responses and thrombosis. During NET formation (process called NETosis), several substances and proteins, such as histones, cell-free DNA (cfDNA), neutrophil elastase (NE), and protein arginine deiminase 4 (PAD4), are released into extracellular space. PAD4 is a promiscuous enzyme and several studies have revealed that PAD4 can citrullinate (a conversion of arginine into citrulline residue) various proteins including itself, after which the functions of the citrullinated proteins can be altered. However, a productive interaction between NE and PAD4, which are both released during NETosis, has never been investigated.
In this project, the PhD candidate will investigate the interactions between PAD4 and NE by means of biophysical, biochemical, chemical and computational approaches, such as direct binding measurement (e.g. BiaCore), Western blot, mass spectrometry, protein modelling, molecular docking, and molecular dynamics (MD) simulations. The derived results will not only provide molecular details of the interactions between PAD4 and NE but they will also lead to the development of novel therapeutic agents (i.e. small compounds, peptides, and engineered proteins) to target NET-mediated diseases (e.g. cardiovascular disease, (systemic) inflammatory disease, sepsis and COVID-19.)

Study objective:
- To investigate interactions between PAD4 and NE
- To develop novel therapeutic agents to target the toxic components of NETs

Expected Results:
- We expect to unravel the molecular mechanisms and interactions between PAD4 and NE both of which are released into the extracellular spaces during NETosis.
- We expect to translate the derived results (PAD4-NE interactions and 3D models) into novel diagnostic and therapeutic agents.

Requirements:
- The candidate should have a strong background in biology, biochemistry, chemistry, and pharmaceutical chemistry.
- The candidate should have experience and skills in related experiments, such as protein expression and purification, Western blot, and mass spectrometry.
- Having experience and skills in biophysical methods (e.g., Biacore and ITC measurements) is a plus.
- Basic knowledge in computer programming and experience in artificial intelligence (AI), machine learning (ML), molecular modeling software, docking methods, and other related in silico approaches are considered advantages.

- The candidate should be able to speak, write, and communicate fluently in English (at a B2/C1 level). Additionally, they should be able to work independently as well as be a good team player in an international environment.

Group's performance: Publications: ; H-Index: ; number of citations, but also statements of recognition of the team or the team members.

In total, Dr. Nicolaes has 116 and Dr. Wichapong has 55 peer-reviewed publications, respectively. Both are co-inventor on several relevant patent applications in the field of atherosclerosis and inflammation.

Google Scholar:
- Dr Nicolaes: In total: h-index = 43, number of citations = 6267
since 2018: h-index = 30, number of citations = 3017
- Dr Wichapong: In total: h-index = 22, number of citations = 1546
since 2018: h-index = 16, number of citations = 1292

Relevant Publications (5 Major Publications related to the proposal):

1. Huckriede J, Beurskens DMH, Wildhagen KCCA, Reutelingsperger CPM **Wichapong K**, **Nicolaes GAF**. Design and characterization of novel activated protein C (APC) variants for the proteolysis of cytotoxic extracellular histone H3, *J Thromb Haemost.* 2023; Accepted

2. Liu X, **Wichapong K**, Lamers S, Reutelingsperger CPM, **Nicolaes GAF.** Autocitrullination of PAD4 does not alter its enzymatic activity: In vitro and in silico studies*, Int J Biochem Cell Biol.* 2021;134:105938.

3. Liu X, Arfman T, **Wichapong K**, Reutelingsperger CPM, Voorberg J, **Nicolaes GAF.** PAD4 takes charge during neutrophil activation: Impact of PAD4 mediated NET formation on immune-mediated disease, *J Thromb Haemost.* 2021; 19(7):1607-1617.

4. **Wichapong K**, Silvestre-Roig C, Braster Q, Schumski A, Soehnlein O, **Nicolaes GAF.** Structure-based peptide design targeting intrinsically disordered proteins: Novel histone H4 and H2A peptidic inhibitors. *Comput Struct Biotechnol J*. 2021; 19:934-948.

5. Silvestre-Roig C, Braster Q, **Wichapong K**, Lee EY, Teulon JM, Berrebeh N, Winter J, Adrover JM, Santos GS, Froese A, Lemnitzer P, Ortega-Gómez A, Chevre R, Marschner J, Schumski A, Winter C, Perez-Olivares L, Pan C, Paulin N, Schoufour T, Hartwig H, González-Ramos S, Kamp F, Megens RTA, Mowen KA, Gunzer M, Maegdefessel L, Hackeng T, Lutgens E, Daemen M, von Blume J, Anders HJ, Nikolaev VO, Pellequer JL, Weber C, Hidalgo A, **Nicolaes GAF**, Wong GCL, Soehnlein O., et al., Externalized histone H4 orchestrates chronic inflammation by inducing lytic cell death. *Nature*. 2019; 569(7755):236-240.

7. Motivation for CSC-UM PhD application (max. 250 words)
Two separate letters are required, one from the student and one from the promotion team.

Our research group and host institute are the place where PhD students will not only learn new scientific skills but they will also feel comfortable adapting to new environments and learn about other cultures. Our group has ample experience to supervise and support students to accomplish their study/research goals, helping them to pave their way for their future career. For example, Dr. Jiangfeng Du, who conducted his PhD dissertation at our lab from 2010-2014, is now an Associate Professor at Zhengzhou University (China). Dr Xiaosong Liu successfully defended her PhD dissertation in December 2021, and now is working as a postdoctoral researcher at the Pasteur Institute in Paris (France). Since

October 2021, Mrs Jiachang Tao, a third CSC PhD student, has been conducting her PhD research at our lab.

At the Biochemistry department of CARIM, especially at our group, we continuously have PhD and internship students from around the world. Working in an international environment will help students to understand and adapt to new cultures easily and they will enjoy both research & social activities in and outside the labs. State-of-the-art facilities (e.g. high-performance computers and other machines & equipment needed to perform related experiments) are available at the host institute; thus, students can promptly start their project. Moreover, several research topics (i.e. drug discovery/development, peptide synthesis, clinical thrombosis and Haemostasis, and *in vivo* imaging) are conducted at the host institute, providing excellent opportunities for students to broaden their knowledge in the fields of cardiovascular diseases and drug discovery.

Applicant's Curriculum Vitae

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8. Personal details

Applicant
- Title(s), initial(s), first name, surname:

CSC-UM PhD programme start 1-9-2024

- Surname:
- Nationality: Chinese
- Date of Birth:
- Country and place of birth:

9. Master's degree (if applicable)

Note! Add a copy of your Master's degree to your application

University:
Faculty/discipline:
City and country:
Date:
Grade average:
Title Master's thesis (if applicable):
Thesis grade: