China Scholarship Council – University Maastricht

PhD Programme Application form

Basic information

- To be filled in by the prospective UM supervisors -

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 unit
- 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/

1b. Second Supervisor/copromoter:

- Title(s), initial(s), first name, surname: Dr., K., Kanin Wichapong
- Research group: Department of Biochemistry, 3D structure-function research unit
- Address for correspondence: Universiteitssingel 50, 6229ER Maastricht – the Netherlands
- Telephone: 0031-43-3884363
- E-mail: k.wichapong@maastrichtuniversity.nl

Website: https://www.3dstructure-function.nl/

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 (i.e. assistance in obtaining a visa, finding accommodation, etc.) of the visit 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 address:

- Telephone:
- E-mail: WeChat:
- 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:
- Telephone:
- E-mail:
- Website (if available):

3. Applicant's home university Master Thesis supervisor:

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

- Telephone:
- E-mail: WeChat:

4. Research field(s)

- Computer-Aided Molecular Design
- Structural Bioinformatics
- Drug Discovery and optimization
- Virtual Screening
- Molecular Dynamics (MD) Simulations
- Binding Free Energy calculations
- Protein-Protein Interactions
- Protein and Medical Biochemistry
- Sepsis and systemic inflammation

- SARS-CoV2 / COVID-19

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

Development and application of computer-based methods to facilitate drug discovery and drug design for the treatment of inflammatory responses.

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

Background:

The research group has been working on translation of 3D molecular models into novel therapeutic agents. By use of in silico methods (e.g. virtual screening (VS) and molecular docking), we can significantly accelerate drug discovery process. However, there are still some limitations of these methods; for example, VS often yields high false-positive rate and binding free energy (BFE) requires high computational cost and time. In this project, we aim to develop novel computational methods to overcome these limitations. Then, we will apply these new approaches to identify potent inhibitors for a number of clinically relevant targets. At the host research group, our main drug targets are proteins that play key roles in the cross-talk between Damage-Associated Molecular Patterns (DAMPs) and Neutrophil Extracellular Traps (NETs) pathway to induce (excessive) inflammatory responses and thrombosis.

We will use different computational methods to develop bioactive compounds against various targets, including enzymatic proteins, protein-protein interactions, and disordered proteins. We will use a new VS protocol to screen for novel druglike small-molecule inhibitors (and/or PROTACs) for the identified enzymatic protein. Additionally, we will apply molecular dynamics (MD) simulations to investigate protein-protein interactions (PPIs) and flexibility of both target and its ligands which can then be translated into a rational design of peptides to regulate PPIs. Moreover, we will use a newly developed BFE methods to predict binding affinities of candidate compounds which can then be utilized to prioritise and select compounds for experimental tests. Together with our local, national, and international collaborators, the selected compounds will be tested in different experiments (from in vitro assays to animal models).

Study objective:

The primary goal of this project is to develop new computational protocols (virtual screening and binding free energy calculations) for drug discovery and design.

Applications of these newly methods will lead us to the ultimate goal of this study, which is development of novel bioactive compounds (small-molecule inhibitors, PROTACs, and peptides) to regulate the immune- and immunothrombotic responses in the cross-talk between DAMPs and the NETs pathway.

Expected Results:

1. A new computational VS and BFE protocol to accelerate the drug discovery process. These newly developed methods should be fast and simple approaches which can be widely used among the drug modelling research communities.

2. Novel bioactive compounds that may be further developed into drugs for inflammatory diseases.

Requirements:

- The candidate should have strong background in biology, biochemistry, chemistry, and pharmaceutical chemistry
- Basic knowledge in computer programming is needed, and experience in artificial intelligence (AI), machine learning (ML), molecular modeling software, docking method, and other related in silico approaches is considered an advantage.
- Experience with programming languages in PERL, python, C++ is a plus.
- The candidate should be able to speak, write and communicate in English fluently, and also should be able to work independently as well as be a good team player to work in an international environment.

Group's performance: Publications: ; H-Index: ; number of citations .

In total, Dr. Nicolaes has 111 peer-reviewed publications Dr. Wichapong has 48 and. Both are co-inventor on several relevant patent applications in the field of atherosclerosis and inflammation.

Google Scholar:
- Dr Nicolaes: In total: h-index = 40, number of citations = 5553
since 2017: h-index = 26, number of citations = 2566
- Dr Wichapong: In total: h-index = 20, number of citations = 1161
since 2017: h-index = 15, number of citations = 959

Relevant Publications:

1. Hrdinova J, Fernández DI, Ercig B, Tullemans BME, Suylen DPL, Agten SM, Jurk K, Hackeng TM, Vanhoorelbeke K, Voorberg J, Reutelingsperger CPM, **Wichapong K**, Heemskerk JWM, **Nicolaes GAF**. Structure-Based Cyclic Glycoprotein Ibα-Derived Peptides Interfering with von Willebrand Factor-Binding, Affecting Platelet Aggregation under Shear, *Int J Mol Sci*. 2022 Feb 12; 23(4):2046.

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. Huckriede J, Anderberg SB, Morales A, de Vries F, Hultström M, Bergqvist A, Ortiz-Pérez JT, Sels JW, **Wichapong K**, Lipcsey M, van de Poll M, Larsson A, Luther T, Reutelingsperger C, de Frutos PG, Frithiof R, **Nicolaes GAF**. Evolution of NETosis markers and DAMPs have prognostic value in critically ill COVID-19 patients**,** *Sci Rep.* 2021; 11(1):15701.

5. **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.

6. Schumski A, Ortega-Gómez A, **Wichapong K**, Winter C, Lemnitzer P, Viola JR, Pinilla-Vera M, Folco E, Solis-Mezarino V, Völker-Albert M, Maas SL, Pan C, Perez Olivares L, Winter J, Hackeng T, Karlsson MCI, Zeller T, Imhof A, Baron RM, **Nicolaes GAF**, Libby P, Maegdefessel L, Kamp F, Benoit M, Döring Y, Soehnlein O. *Circulation*. 2021; 143(3):254-266**.**

7. 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.

8. **Wichapong K**, Alard JE, Ortega-Gomez A, Weber C, Hackeng TM, Soehnlein O, **Nicolaes GAF.**, Structure-Based Design of Peptidic Inhibitors of the Interaction between CC Chemokine Ligand 5 (CCL5) and Human Neutrophil Peptides 1 (HNP1), ***J. Med. Chem.,*** 2016; 59(9):4289-4301

9. Alard JE, Ortega-Gomez A, **Wichapong K**, Bongiovanni D, Horckmans M, Megens RT, Leoni G, Ferraro B, Rossaint J, Paulin N, Ng J, Ippel H, Suylen D, Hinkel R, Blanchet X, Gaillard F, D'Amico M, von Hundelshausen P, Zarbock A, Scheiermann C, Hackeng TM, Steffens S, Kupatt C, **Nicolaes GAF**, Weber C, Soehnlein O.,

Recruitment of classical monocytes can be inhibited by disturbing heteromers of neutrophil HNP1 and platelet CCL5., ***Sci. Transl. Med***., 2015; 7(317):317ra196.

10. Du J, Bleylevens IW, Bitorina AV, **Wichapong K, Nicolaes GA.** Optimization of compound ranking for structure-based virtual ligand screening using an established FRED-Surflex consensus approach, Chem Biol Drug Des. 2014; 83(1):37-51.

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

We are confident that our research group and the host institute are the place where PhD students will not only learn and train new scientific skills but they will also feel comfortable to adapt in new environments and cultures. Our research group has ample experience to supervise and support students to accomplish their study/research goals, helping them to pave their way for future career. For example, Dr. Jiangfeng Du, who had conducted his PhD dissertation at out lab from 2010-2014, is now an Associate Professor at Zhengzhou University. Dr Xiaosong Liu successfully defended her PhD dissertation in December 2021, and now she is working at the pharma-technology company (Insilico Medicine company) in Shanghai. Recently, Mrs Jiachang Tao, the third CSC PhD student, has been conducting her PhD dissertation at our lab since October 2021.

At the department of Biochemistry, 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 adapt in new cultures easily and they will enjoy both research & social activities in and outside the labs. Full 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 here at the host institute, providing excellent opportunities for students to broaden their knowledge in the fields of cardiovascular diseases.

Applicant's Curriculum Vitae (if available)

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8. Personal details

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

CSC-UM PhD programme start 1-9-2022

- 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: