China Scholarship Council – University Maastricht PhD Programme

Application form

Basic information
----

1. Information on prospective UM supervisors and Promotor

1a. First Supervisor/promoter:

- Title(s), initial(S), first name, surname: Dr. Berta Cillero-Pastor
- Research group: Spatial omics group for regenerative medicine, cBITE department-MERLN, Faculty Health Medicine & Life Sciences

- Address for correspondence: PO Box 616, 6200 MD Maastricht
- Telephone: M +31 (0) 616208450
- E-mail: b.cilleropastor@maastrichtuniversity.nl

- Title(s), initial(S), first name, surname: Dr. Chris Arts
- Research group: Dept. Orthopedics, Faculty Health Medicine & Life Sciences

- Address for correspondence: PO Box 616, 6200 MD Maastricht
- Telephone:
- E-mail: j.arts@mumc.nl

1b. Second Supervisor/copromoter:

- Title(s), initial(S), first name, surname:
- Research group:

- Address for correspondence:
- Telephone:
- E-mail:

- Title(s), initial(S), first name, surname:
- Research group:

- Address for correspondence:
- Telephone:
- E-mail:

1c. Promotor (if applicable): **– see above**

- Title(s), initial(S), first name, surname:
- Research group:

- Address for correspondence:
- Telephone:
- E-mail:

2. Information on University Maastricht Faculty / Department/ Institute/ School contact person:
When the application is granted by both CSC and UU 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: Dr. Berta Cillero-Pastor

- Research group: Spatial omics group for regenerative medicine, cBITE department-MERLN, Faculty Health Medicine & Life Sciences

- Address for correspondence: PO Box 616, 6200 MD Maastricht
- Telephone: M +31 (0)616208450
- E-mail: b.cilleropastor@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 of faculty dean of the home university is required.

- Name of home university:

- Address:

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

3. Applicant's home university supervisor of his Master Thesis:

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

- Address for correspondence:

- Telephone:
- E-mail: WeChat:

4. Research field(s)

重大新药创制 / Major New Drugs Discovery

新材料技术 / Advanced Materials Technology

人类健康与疾病的生物学基础 / Biological Foundations of Human Health and Diseases

重大传染病防治 / Prevention and Treatment of Major Infectious Diseases

材料设计与制备的新原理与新方法 / New Principles and Methodologies for Materials Design and Fabrication

Mass spectrometry

Extracellular vesicles

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

Cell-bacteria interactions through extracellular vesicles: molecular messages for successful biomaterial implant design

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

Background:

Increasing antimicrobial resistance is a global issue due to the extensive use of non-specific antibiotics with devastating consequences. Orthopaedic devices are the most common surgical devices associated with implant-related infections and Staphylococcus aureus (S. aureus) is the most common pathogen in bone infections and implant rejection (1). New biomaterials with antimicrobial properties are being developed to improve osteointegration and avoid biofilm formation. The majority of these materials are chemically modified and functionalized to reduce bacteria growth without taking into account the host response. In this line, many of the studies on new biomaterial characterization don't investigate bacteria signaling pathways and how host cells specifically respond to these changes.

Extracellular vesicles (EVs) are biological membranous particles released by the majority of cells, with sizes ranging from nm to μm. There exist different EV subpopulations, which include exosomes, microvesicles or apoptotic bodies, and each of them vary on their biogenesis mechanism, composition, size or function (2). EVs enable communication between cells and tissues by allowing the exchange of different biomolecules—referred as cargo—such as proteins, lipids or nucleic acids. EVs may function as communication channels between bacteria and host cells (3).

Study objective:

This study aims to determine whether extracellular vesicles play a crucial role in quorum sensing and modulate the anti-inflammatory host response upon exposure to newly synthetized antimicrobial biomaterials employed for bone regeneration.

In this project, we will develop *in vitro* models to study cell-bacteria communication through extracellular vesicles. Importantly, these models will be developed in bioreactors, capable of mimicking in vivo scenarios under very well controlled conditions. EVs will be isolated from bacterial cultures, osteoblasts and macrophages, using filtration, SEC and ultracentrifugation and characterized by electron microscopy and classical molecular biology techniques. In addition, mass spectrometry-based proteomics and imaging methods will be developed to characterize the EV cargo upon different cell/bacteria/implant combinations. In particular, SILAC, iTRAQ and fluorescence methods will be developed to track the cell or bacterial origin for accurate proteomics at single cell resolution. Data independent acquisition will be employed in a TIMS-TOF system for improved sensitivity and protein coverage. ELISA and gene expression for interleukin (IL)-8, monocyte and chemoattractant protein (MCP)-1will be performed to assess the degree of proinflammatory reaction.

Expected Results:

We hypothesize that the EVs cargo obtained from bacteria and cell cultures will be modified based on the biomaterial surface properties. Newly antimicrobial biomaterials will reduce the bacteria signaling cascades promoting cell proliferation and biofilm formation. As such,

macrophages stimulated with bacterial EVs cultured in newly antimicrobial synthetized implant surface will induce a lower proinflammatory response. Overall, we expect a reduction of proinflammatory molecular profiles of macrophages and osteoblasts and an improvement on tissue regeneration capacity.

Requirements: cell culture experience, microbiology, chemistry/analytical chemistry background preferably in mass spectrometry

Group's performance: Publications: 104; H-Index: 26; number of citations: 2735.

7. Motivation for CSC-UM PhD application (max. 250 words)

We have extensive experience on the characterization of biomaterials and the development of imaging and mass spectrometry methods in the field of cartilage and bone. Our group is running an international NWA research program to combat AMR (https://nwa-dartbac.eu). An expert on EVs purification and analysis is part of our DARTBAC team.

We are currently supervising one CSC student with excellent results and received 1 CSC PhD student this year. These students are able to integrate well with the groups, the research and training expectations. Most importantly, they are able to mature and become new potential young leaders in the scientific and industrial biomedical community.

Applicant's Curriculum Vitae (if available)
----

8. Personal details

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

CSC-UM PhD programme start 1-9-2023

- 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 (201 or 985 if available):
Faculty/discipline:
City and country:
Date:
Grade average:
Title Master's thesis (if applicable)
Grade for thesis:

References:

1- Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-18. doi: 10.1179/2047773215Y.0000000030. Epub 2015 Sep 7. PMID: 26343252; PMCID: PMC4768623.

2- Doyle LM, Wang MZ. Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. Cells. 2019 Jul 15;8(7):727. doi: 10.3390/cells8070727. PMID: 31311206; PMCID: PMC6678302.

3- Peng Y, Yin S, Wang M. Extracellular vesicles of bacteria as potential targets for immune interventions. Hum Vaccin Immunother. 2021 Mar 4;17(3):897-903. doi: 10.1080/21645515.2020.1799667. Epub 2020 Sep 1. PMID: 32873124; PMCID: PMC7993133.

5 major publications, with citation scores after 2016

1- Barre, F. P. Y., Flinders, B., Garcia, J. P., Jansen, I., Huizing, L. R. S., Porta, T., Creemers, L. B., Heeren, R. M. A., & Cillero-Pastor, B. (2016). Derivatization Strategies for the Detection of Triamcinolone Acetonide in Cartilage by Using Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging. Analytical Chemistry, 88(24), 12051-12059. https://doi.org/10.1021/acs.analchem.6b02491. Citations: 67

2- Barre, F. P. Y., Paine, M. R. L., Flinders, B., Trevitt, A. J., Kelly, P. D., Ait-Belkacem, R., Garcia, J. P., Creemers, L. B., Stauber, J., Vreeken, R. J., Cillero-Pastor, B., Ellis, S. R., & Heeren, R. M. A. (2019). Enhanced Sensitivity Using MALDI Imaging Coupled with Laser Postionization (MALDI-2) for Pharmaceutical Research. Analytical Chemistry, 91(16), 10840-10848. https://doi.org/10.1021/acs.analchem.9b02495Enhanced Sensitivity Using MALDI Imaging Coupled with Laser Postionization (MALDI-2) for Pharmaceutical Research. Citations: 65

3- van Vugt, T. A. G., Arts, J. J., & Geurts, J. A. P. (2019). Antibiotic-Loaded Polymethylmethacrylate Beads and Spacers in Treatment of Orthopedic Infections and the Role of Biofilm Formation. Frontiers in microbiology, 10, [1626]. https://doi.org/10.3389/fmicb.2019.01626. Citation: 58

4- Schumacher, A., Vranken, T., Malhotra, A., Arts, J. J. C., & Habibovic, P. (2018). In vitro antimicrobial susceptibility testing methods: agar dilution to 3D tissue-engineered models. European Journal of Clinical Microbiology & Infectious Diseases, 37(2), 187-208. https://doi.org/10.1007/s10096-017-3089-2. Citations 45.

5-Othman, Z., Pastor, B. C., van Rijt, S., & Habibovic, P. (2018). Understanding interactions between biomaterials and biological systems using proteomics. Biomaterials, 167, 191-204. https://doi.org/10.1016/j.biomaterials.2018.03.020. Citation: 65