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: Dr. Eva Cuypers
- Research group: M4i, MSI in peri-operative diagnostics
- Address for correspondence: M4i, t.a.v. Eva Cuypers, Universiteitssingel 50, 6229 ER Maastricht, The Netherlands
- Telephone: +31 43 388 1501
- E-mail: e.cuypers@maastrichtuniversity.nl

1b. Second Supervisor/copromoter:

- Title(s), initial(s), first name, surname: , MD, PhD, Stefan Bouwense
- Research group: Maastricht University Medical Centre, HPB surgery
- Address for correspondence: P. Debyelaan 25, 6229 HX Maastricht

- Telephone: 043 3876543
- E-mail: stefan.bouwense@mumc.nl

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

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

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:
.5

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

1. Information on the applicant

- Initial(s), first name, surname: not known yet
- 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)
Peri-operative diagnostics of pancreatic cancer

5. Title of research plan for CSC-UM PhD Programme
Cyst or early pancreatic cancer? The molecular profile of single cells in fine needle aspirations as a fast and accurate detection method.

6. Short summary of research plan (max. 250 words) (A full plan has to be submitted later)
Pancreatic cancer has the worst cancer survival rates in the Western world and the Netherlands. Pancreatic cysts are often precursors of pancreatic cancer, however predicting which cyst will become cancer is difficult. As a result, sometimes cysts are misclassified as malignant and are removed by an unnecessary large pancreatic operation, having a major

impact on a patient's life, or a malignant degenerated cyst is often misclassified as benign and no longer can be treated.
Several attempts have been made to develop an accurate and rapid characterization of pancreatic cysts using conventional radiological imaging and methods using cytology, RNA and peptide analysis in fine needle aspirations (FNA)[1-3]. Nevertheless, due to low accuracy (cytology) or complex and time-consuming procedures (RNA/peptide analysis), there is no clinically accurate and useful method to characterize pancreatic cysts. At the moment, therefore, it is mainly decided on imaging to proceed with surgery, where it is often difficult to predict whether or not a malignancy is present.
Our research focuses on developing an applicable and accurate mass spectrometric imaging method, in which current knowledge and diagnostics is combined with extensive molecular information (lipids and metabolites), to better differentiate which pancreatic cysts are benign, malignant or may become malignant. Hereby, our in-house single cell mass spectrometric imaging technique is used to identify *in situ* the molecular profile of single cells in FNA, resulting in a fast and accurate clinical diagnosis.

Background: Pancreatic cysts neoplasms (PCNs) are diagnosed with increasing frequency, in up to 50% of patients, due to the widespread use of cross-sectional imaging of the abdomen for unrelated reasons [4].

The greatest challenge in the evaluation of PCNs is identifying the cysts with malignant potential or signs of malignancy. Mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), and solid pseudopapillary neoplasms (SPNs) are cysts that have to be considered as precancerous lesions which, following an adenoma-dysplasia-carcinoma sequence, potentially evolve into invasive pancreatic cancer [5].

Worldwide the surgical and gastroenterological society has become increasingly aware of the importance of adequately understanding the natural history of these lesions and identify characteristics and evaluative patterns of PCNs that help to risk-stratify surveillance and operative strategies. The burden of these PCNs with potential to become malignant is high i.e. when high-risk stigmata or worrisome features evolve/become present, the prevalence of malignancy (high-grade dysplasia and invasive carcinoma) reaches 60% for MD-IPMNs and 40% for BD-IPMNs in resected patients, knowing that pancreatic cancer has an overall 5 year survival rate of 11% [6]. In the case of the risk of evolution to, or presence of, pancreatic cancer in a PCN, pancreatic resection is necessary. Pancreatic surgery is regarded as surgery that has often a major impact on a patient's life with a substantial risk of complications and perioperative mortality rates up to 2-3% in even experienced pancreatic units [7]. At the moment, therefore, it is mainly decided on conventional imaging like CT or MRI and sometimes endoscopic fine needle aspiration (FNA), to proceed with surgery of the PCN(s). Still, despite extensive diagnostic work-up it remains difficult to predict whether or not a malignancy is present.

So, the malignant potential of PCNs is difficult to assess despite novel cross sectional imaging techniques and endoscopic biopsies. This clinical diagnostic problem may result in the overtreatment and harm of patients who have a non-malignant PCN and underwent surgery, or under-treatment of malignant evolved PCN that were treated conservatively [8].

There is an urgent clinical need to improve current diagnostic modalities to better assess PCNs and better predict the risk of malignancy and malignant transformation. Proper identification of PCNs has a major impact on the quality of life of patients, the need for surgery and health care costs [8].

1. Bertani, H., et al., *Needle-based confocal endomicroscopy in the discrimination of mucinous from non-mucinous pancreatic cystic lesions.* World J Gastrointest Endosc, 2021. **13**(11): p. 555-564.
2. Jabbar, K.S., et al., *Highly Accurate Identification of Cystic Precursor Lesions of Pancreatic Cancer Through Targeted Mass Spectrometry: A Phase IIc Diagnostic Study.* J Clin Oncol, 2018. **36**(4): p. 367-375.
3. Shirakami, Y., et al., *Micro-RNA Analysis of Pancreatic Cyst Fluid for Diagnosing Malignant Transformation of Intraductal Papillary Mucinous Neoplasm by Comparing Intraductal Papillary Mucinous Adenoma and Carcinoma.* J Clin Med, 2021. **10**(11).
4. Kromrey, M.L., et al., *Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study.* Gut, 2018. **67**(1): p. 138-145.
5. Fritz, S., T. Hackert, and M.W. Buchler, *Pancreatic intraductal papillary mucinous neoplasm--where is the challenge?* Dig Dis, 2015. **33**(1): p. 99-105.
6. Tanaka, M., et al., *Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas.* Pancreatology, 2017. **17**(5): p. 738-753.
7. Gleeson, E.M., et al., *Failure to Rescue After Pancreatoduodenectomy: A Transatlantic Analysis.* Ann Surg, 2021. **274**(3): p. 459-466.
8. Surci, N., et al., *The faith of non-surveilled pancreatic cysts: a bicentric retrospective study.* Eur J Surg Oncol, 2022. **48**(1): p. 89-94.

Study objective:

1. The development of a **new analytical method** to determine the molecular profile of single cells in fine needle aspirations of PCNs using mass spectrometry imaging

2. The development of a **recognition model** for PCNs into one of the 4 main classes: normal, low grade dysplasia (LGD), high grade dysplasia (HGD) or cancer

3. The development of a **prediction model** for the evolution and/or progression of PCNs into a malignancy based on molecular single cell profiles (biobank samples)

4. The **validation** of our analytical based recognition and prediction method on new prospective patient samples of PCNs

Expected Results: Pancreatic cancer is a deadly disease and early detection is considered the most effective way to improve survival.

PCNs in the general population are estimated to be present in 2–45% [19, 20]. The management of PCN comprise a clinically challenging entity as their biological behaviour ranges from benign to malignant disease. Consequently, correct management of PCN may prevent progression to pancreatic cancer while minimising the need for (high risk) invasive therapies like pancreatic surgery, lifelong screening and related costs and loss of quality of life. Unfortunately, with the present diagnostic approach to PCNs it is often difficult to differentiate between the various types of PCN and predict which lesions are at risk of becoming malignant or are already malignant.

Combining the current diagnostic approach with MSI may improve the differentiation of PCNs and improve the management of PCNs, so that a more patient specific risk assessment can be made of the PCN(s), improving the counselling of patients on PCNs for i.e. risk assessment, diagnostic approach and therapy.

Requirements: PhD should have basic knowledge in mass spectrometry and analytical chemistry, practical lab expertise including liquid handling (pipetting,…). He/She needs to be able to work with precious patient samples and know the basics of statistical tests.
Group's performance: Publications Eva Cuypers: 49 ; H-Index: 19 ; number of citations 998 (23/09/2022) .

- **Cuypers E**, Claes BSR, Biemans R, Lieuwes N, Glunde K, Dubois L, Heeren RMA
  On-the-fly' digital pathology of breast cancer based on a single single-cell mass spectrometry imaging database
  Anal Chem, 2022 Apr 26;94(16):6180-6190. doi: 10.1021/acs.analchem.1c05238.
  Impact factor (5 year):7.528; Q1 in category (7/87); times cited: 1
  Motivation: This paper is a direct results and good example of MSI translation into the clinical field. Results in this paper led to the filing of a patent.
- Goossens Pieter, Lu Chang, Cao Jianhua, Gijbels Marion, Karel Joël, Wijnands, Erwin Fazzi Gregorio, Hendriks Tim F R, Wouters Kristiaan, Smirnov Evgueni, van Zandvoort Marc, Balluff Benjamin, **Cuypers Eva**, Donners Marjo, Heeren Ron and Biessen Erik A. L
  Integrating Multiplex Immunofluorescent and Mass Spectrometry Imaging to Map Tissue Myeloid Heterogeneity in Its Metabolic and Cellular Context.
  Cell Metab. 2022 Aug 2;34(8):1214-1225.e6. doi: 10.1016/j.cmet.2022.06.012. PMID: 35858629
  Impact factor (5 year):35.104; Q1 in category (8/194); times cited: 0
  Luka Jeromel, Nina Ogrinc, Zdravko Siketić, Primož Vavpetič, Zdravko Rupnik, Klemen Bučar, Boštjan Jenčič, Mitja Kelemen, Matjaž Vencelj, Katarina Vogel-Mikuš, Janez Kovač, Ron M. A. Heeren, Bryn Flinders, **Eva Cuypers**, Žiga Barba, Primož Pelicon
  Molecular imaging of human hair with MeV-SIMS: a case study of cocaine detection and distribution in the hair of a cocaine user
  PLoS One 2022 Mar 25;17(3):e0263338. doi: 10.1371/journal.pone.0263338. PMID: 35333862; PMCID: PMC8956162.
  Impact factor (5 year):4.069; Q1 in category (28/134); times cited: 0
- Van Hese L, Vaysse PM, Siegel TP, Heeren R, Rex S, **Cuypers E**. Real-time drug detection using a diathermic knife combined to rapid evaporative ionisation mass spectrometry. Talanta. 2021 Jan 1;221:121391. doi: 10.1016/j.talanta.2020.121391. Epub 2020 Jul 21. PMID: 33076053.
  Impact factor (5 year):5.77; Q1 in category (11/87); times cited: 3
- De Boeck M, Dehaen W, Tytgat J, **Cuypers E**
  Microextractions in forensic toxicology: The potential role of ionic liquids
  TRAC-TRENDS IN ANALYTICAL CHEMISTRY, 2019 Feb, Vol 111, Page 73-84; DOI: 10.1016/j.trac.2018.11.036
  Impact factor (5 year):13.405; Q1 in category (1/87); times cited: 7
- Philippaert K, Pironet A, Mesuere M, Sones W, Vermeiren L, Kerselaers S, Pinto S, Segal A, Antoine N, Gysemans C, Laureys J, Lemaire K, Gilon P, **Cuypers E**, Tytgat J, Mathieu C, Schuit F, Rorsman P, Talavera K, Voets T, Vennekens R. Steviol glycosides enhance pancreatic beta-cell function and taste sensation by potentiation of TRPM5 channel activity. Nat Commun. 2017 Mar 31;8:14733. doi: 10.1038/ncomms14733. PMID: 28361903; PMCID: PMC5380970.
  Impact factor (5 year):17.763; Q1 in category (6/73); times cited: 92

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

This highly innovative **bio-analytical** project needs a PhD candidate that is eager to develop and learn new methods for diagnostic implementation. This includes repeatability and validation tests necessary for **clinical diagnostics**. Thanks to the collaboration with HPB surgery, patient samples are available. The focus of the project is developing, testing and implementation of the mass spectrometry imaging method

to translate towards a clinical setting. The PhD will be able to work with high-end mass spectrometry imaging equipment with spatial resolution capabilities to the single cell level. Moreover, statistical analysis such as PCA/LDA and recognition model building will be learned. Repeatability and validation tests and their principles will be taught. Since there is no direct contact with patients, there is no need for the PhD candidate to speak Dutch. However, an excellent knowledge of English is necessary. Therefore, we consider a CSC-PhD candidate, with chemistry/mass spectrometry background and practical lab experience to be the ideal candidate for this project. M4i's successful experience with previous CSC students make our motivation even stronger. It is important to note that one of the selection criteria will be that the student should be in his or her last year of their Master program. Students who already have received their master's degree are less eligible.
The outcome of this project is expected to make a major step forward in the **prevention, detection, treatment and prediction** of pancreatic cancer by developing a fast screening method on fine needle aspirations.

Applicant's Curriculum Vitae (if available)
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8. Personal details

Applicant
- Title(s), initial(s), first name, surname: not known yet

CSC-UM PhD programme start 1-9-2021

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