The peritoneal microenvironment in the pathogenesis of peritoneal carcinomatosis

Jesse Demuytere

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GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

Supervisors

Prof. Dr. Wim Ceelen
Dept. of human structure and repair (GE38)
Ghent university, Belgium

Prof. Dr. Geert Berx
Dept. of Biomedical Molecular Biology (WE14)
Ghent University, Belgium

Prof. Dr. Anne Hoorens
Dept. of Diagnostic Sciences (GE32)
Ghent University, Belgium

Members of the examination Committee

Prof. Dr. Thierry Bové (chair)
Dept. of human structure and repair (GE38)
Ghent university, Belgium

Prof. Dr. Wouter Willaert (secretary)
Dept. of human structure and repair (GE38)
Ghent university, Belgium

Prof. Dr. Olivier de Wever
Dept. of human structure and repair (GE38)
Ghent university, Belgium

Prof. Dr. Steven Goossens
Dept. of Diagnostic Sciences (GE32)
Ghent University, Belgium

Prof. Dr. Karen Geboes
Dept. of Internal Medicine and Pediatrics (GE35)
Ghent University, Belgium

Prof. Dr. Sabine Tejpar
Dept. of Oncology
KU Leuven, Belgium

Prof. Dr. Kjersti Flatmark
Department of Tumor Biology
University of Oslo, Norway

CRIG
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CONTACT

Department of Human Structure and Repair (GE38)
Experimental surgery lab
Jesse.demuytere@ugent.be
T +32 9332 4198
www.ugent.be

molecular cellular oncology lab
SURGX
EXPERIMENTAL SURGERY LAB

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Summary

Cancer consists of more than only cancer cells, and can be likened to an ecosystem of cancer and noncancerous cells leading to disease.

Peritoneal metastasis (PM) occurs when cancer spreads to the peritoneum, the membrane lining our abdomen. Patients faced with PM face a grim prognosis, despite current therapies including cytoreductive surgery and intraperitoneal chemotherapy (CRS+HIPEC). Recently, a **paradigm shift** has occurred in the field of cancer science. Whereas cancer science was previously focused on cancer cell behavior, the concept of the tumor microenvironment (TME), consisting of cancer cells interacting with non-cancerous immune and stromal cells has taken center stage. The TME might be important in the development of PM as well, yet little is known about the composition and functions of the TME. A unique component of the PM TME consists of mesothelial cells, which form the mesothelial membrane. These cells were seen as a passive barrier to PM, yet recent research points towards complex mechanisms and interactions taking place within mesothelial cells, in response to cancer. The Scottish surgeon Stephen Paget described the "**seed and soil**" theory at the end of the nineteenth century, hypothesizing that the is rather driven by interaction with the metastatic location, "the soil".

In this dissertation, I investigated the **functions** of the peritoneal "soil", or TME, and how it interacts with the "seed" in the pathogenesis of PM of ovarian and colorectal cancer (CRC). I demonstrated that stromal cells in the CRC PM TME, cancer-associated fibroblasts, originate from mesothelial cells. By demonstrating the existence of an intermediate state of cells displaying both mesothelial and cancer-associated fibroblast characteristics, we prove the existence of a transition process by which mesothelial cells gain mesenchymal characteristics. Second, we investigated the **effects and benefits** of HIPEC in a clinical trial in ovarian cancer PM, and further defined the potential effects of hyperthermia on a pharmacokinetic and transcriptomic level. Additionally, we demonstrate that cisplatin HIPEC preferentially accumulated in the stroma of ovarian cancer PM, outlining a potential role for the TME in **modulating treatment** responses. Finally, we detail the **TME of CRC PM** on a previously unknown resolution using single-cell RNA sequencing, showing epithelial cell diversity, coupled with heterogeneity in fibroblast and macrophage populations, and uncover location-specific and subtype-specific cell populations in the TME.

Publications

ORCID-ID: 0000-0003-0096-2798

Journal Articles (A1)

- **Demuytere, J.** *et al.* Effects of hyperthermia on cisplatin tissue penetration and gene expression in peritoneal metastases: results from a randomized trial in ovarian cancer. *British Journal of Surgery* 111, znae078 (2024).
- **Demuytere, J.** *et al.* Preclinical Activity of Two Paclitaxel Nanoparticle Formulations After Intraperitoneal Administration in Ovarian Cancer Murine Xenografts. *IJN* **19**, 429–440 (2024).
- **Demuytere, J.**, Ceelen, W., Van Dorpe, J. & Hoorens, A. The role of the peritoneal microenvironment in the pathogenesis of colorectal peritoneal carcinomatosis. *Experimental and Molecular Pathology* 104442 (2020) doi:10.1016/j.yexmp.2020.104442.
- Ceelen, W., **Demuytere, J.** & de Hingh, I. Hyperthermic Intraperitoneal Chemotherapy: A Critical Review. *Cancers* **13**, 3114 (2021).
- Chia, D. K. A., **Demuytere, J.**, Ernst, S., Salavati, H. & Ceelen, W. Effects of Hyperthermia and Hyperthermic Intraperitoneal Chemoperfusion on the Peritoneal and Tumor Immune Contexture. *Cancers* **15**, 4314 (2023).
- Arjona-Sanchez, A. *et al.* External multicentre validation of pseudomyxoma peritonei PSOGI-Ki67 classification. *Eur J Surg Oncol* **49**, 1481–1488 (2023).

Book Chapters

- **Demuytere, J.**, Ernst, S., van Ovost, J., Cosyns, S. & Ceelen, W. Chapter Four - The tumor immune microenvironment in peritoneal carcinomatosis. in International Review of Cell and Molecular Biology (eds. Aranda, F., Berraondo, P. & Galluzzi, L.) vol. 371 63–95 (Academic Press, 2022).

Presentations

ESSO 43, Antwerp, BE
Oncopoint 2023, Ghent, BE
ISSPP2022, Huntington Beach, CA
SSO 2022, Dallas, TX
ESSO 2020, virtual
BWGE 2019, Brussels, BE