SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Structural Biology Brussels

has the honor to invite you to the public defence of the PhD thesis of

Magdalena Kolata

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

The role of chaperone-usher adhesins in colorectal cancer associated *E. coli*

Promotor:
Prof. dr. Han Remaut (VUB)

The defence will take place on **Thursday, July 4, 2024 at 4.00 p.m. in I.2.01**

The defence can also be followed through a live stream:
https://tinyurl.com/es2fztd2

Members of the jury

Prof. dr. ir. Damya Laoui (VUB, chair)
Prof. dr. Joris Messens (VUB, secretary)
Prof. dr. Luc Leyns (VUB)
Prof. dr. Colinda Scheele (KULeuven)
Prof. dr. Christophe Beloin (Institut Pasteur, France)

Curriculum vitae

Magdalena Kolata studied Molecular Biotechnology and Technical Biochemistry at the Lodz University of Technology in Poland. She conducted her master's thesis project at Lille 1 University – Science and Technology in France. In 2016, she commenced her PhD under the supervision of Professor Dr. Han Remaut at the VIB-VUB Center for Structural Biology. During her doctoral studies, she supervised a master's thesis student, three bachelor's students, and organised practical courses for master's students. Her scientific achievements include winning a flash talk prize at an international workshop, contributing a book chapter, and having a first-author publication currently under revision.

Abstract of the PhD research

Colorectal cancer (CRC) ranks as the third leading cause of cancer-related deaths worldwide, and recent years show an increased incidence in early onset CRC. Emerging research highlights the intricate role of intestinal bacteria in CRC development and progression. Attention goes out to pathogenic *E. coli* strains, which contain the polyketide synthase (*pks*) island and produce colibactin, a genotoxin inducing double-strand DNA breaks and resulting repair-induced mutations. CRC patients exhibit an elevated presence of *pks*+ and adherent-invasive *E. coli* (AIEC), and an increased incidence of *pks*-associated mutagenesis profiles.

This work investigates the occurrence and importance of adhesins in CRC-associated *E. coli*, since previous work has shown that *pks*-mutagenesis requires a close and direct contact of bacteria and host cell. For most pathogenic *E. coli* specific adherence via chaperone-usher pili (CUP) forms an important component of host colonisation. CUPs show a high genetic diversity, with different *E. coli* strains possessing at least 50 distinct CUP gene clusters, expected to target distinct glycan or protein receptors. To elucidate the molecular determinants of CRC-associated *E. coli*, we isolated and characterized *E. coli* strains from patients with colorectal cancer. Genome analysis revealed that previously described putative AIEC biomarkers are specific to the B2 phylogroup rather than the AIEC pathotype. The CU pilus systems of CRC-associated *E. coli* isolates showed an occurrence correlated with the A/B2 phylotype with no apparent enrichment for specific pilus types. The presence of other virulence factors varied among the strains suggesting heterogeneity in CRC-associated *E. coli*.

In a second part of this work, I worked on the development of a novel phage display methodology to derive a large-scale annotation of the *E. coli* piliome, comprising 80 different CUP adhesins. This approach enables parallelized characterization of the diverse array of CUP adhesins, paving the way for a comprehensive understanding of their biological roles in the infectious disease processes.

Based on prior knowledge of their receptor binding profiles, we investigated the importance of *E. coli* type 1 pilus adhesin FimH and F9 pilus adhesin FmlH in a transgenic mouse model that develops microbe-induced colorectal cancer. We demonstrated the critical role of these adhesins in CRC progression via colibactin-mediated cytotoxicity and showed that the use of a pharmacological FimH inhibitor hinders bacterial adhesion and attenuates CRC progression. Taken together, our findings demonstrate the potential of anti-adhesive strategies as effective tools against pathogenic *E. coli* by targeting the CUP adhesins to suppress the progression of CRC, especially in high-risk patients. Further investigation is required to unveil the genetic factors linked to AIEC and CRC-associated strains.