EPSRC Centre for Doctoral Training (CDT) in Molecular Sciences for Medicine (MoSMed)

Polymer-based biosensing platforms for bacterial proteins

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Project overview/context

Modern healthcare has enabled vast improvements in human life expectancy and quality of life, but a significant barrier to further improvements in treatments of many diseases is the lack of rapid diagnostic tests to enable their timely identification. The development of sensors to rapidly detect bacteria and other pathogens would enable earlier diagnosis, and more appropriate treatment, for a range of infectious diseases, as well as presenting opportunities to detect these pathogens in the environment and prevent their transmission. Within this interdisciplinary project, we will develop polymer based biosensing platforms to detect bacterial proteins, using sensitive, label-free detection strategies.

Research Project

Many pathogens produce carbohydrate binding proteins (lectins) which interact with carbohydrates displayed on surfaces to enable them to enter or adhere to cells. These recognition processes are key to the pathogenicity of many viruses and bacteria, and could be harnessed to provide diagnostic information to identify or monitor the progression of disease, in addition to presenting scope for the development of new therapeutics. In this project, we will design and synthesis polymers that resemble the mammalian cellular surface, and exploit natural recognition mechanisms to detect disease-associated proteins. These materials will be explored as the basis for new diagnostic devices, using sensitive, label-free detection strategies.

Recently, we have developed a polymeric receptor for the carbohydrate recognition domain of the cholera toxin – the protein responsible for the acute diarrhoea associated with cholera – with nanomolar K_d.[1] This synthetic glycopolymer can prevent entry of the native toxin into human intestinal cells (IC50 5.7 nM). The glycopolymer was subsequently used to construct a porous silicon-based optical biosensor for the carbohydrate recognition domain of the *E. coli* heat labile toxin (LTB), the causative agent of travellers' diarrhoea.[2] This platform could be regenerated by application of a thermal stimulus, presenting a pathway to the development of regenerable biosensing devices.

We will develop new glycopolymer-based sensors for disease-associated lectins, using thermal wave transport analysis (TWTA)[3] and the heat transfer method (HTM).[4] These strategies have been used in the Peeters group to develop selective biosensors for bacteria including *E. coli* and *S. aureus* in comlex biological matrices. 'Cellulomimetic' polymer scaffolds, incorporating units resembling mammalian phospholipids, and carbohydrate motifs, will be prepared via controlled radical polymerisation routes. Interactions between polymers and lectins will be assessed using biophysical analysis techniques (e.g. *via* isothermal titration calorimetry, surface plasmon resonance), before high-affinity receptors

are attached to electrode surfaces. Optical detection and thermal analysis will be used to translate polymer-lectin recognition to biosensors enabling specific, sensitive detection of bacterial lectins. To discriminate similar bacterial lectins, glycopolymers will be combined into sensor arrays, with multivariate analysis used to identify analytes through pattern-based approaches.[5]

References

1. C. S. Mahon, G. C. Wildsmith, D. Haksar, E. de Poel, J. M. Beekman, R. J. Pieters, M. E. Webb and W. B. Turnbull, *Faraday Discuss.*, 2019, **219**, 112-117.
2. E. E. Antunez, C. S. Mahon, Z. Tong, N. H. Voelcker and M. Müllner, *Biomacromolecules*, 2020, 10.1021/acs.biomac.0c01318.
3. S. Redeker, K. Eersels, O. Akkermans, J. Royakkers, S. Dyson, K. Nurekeyeva, B. Ferrando, P. Cornelis, M. Peeters, P. Wagner, H. Diliën, B. v. Grinsven and T. J. Cleij, *ACS Infect. Dis*, 2017, **3**, 388-397.
4. B. v. Grinsven, K. Eersels, O. Akkermans, S. Ellermann, A. Kordek, M. Peeters, O. Deschaume, C. Bartic, H. Diliën, E. S. Redeker, P. Wagner and T. J. Cleij, *ACS Sens.*, 2016, **9**, 1140-1147.
5. L. Mitchell, E. J. New and C. S. Mahon, *ACS Appl. Polym. Mater.*, 2021, **3**, DOI: 0.1021/acsapm.1020c01003.

Training & Skills

Working at the interface of the chemical and biological sciences, the student will develop an interdisciplinary skillset. Training will be provided in the following areas:

- Synthetic polymer chemistry, including controlled radical polymerisation techniques and post-polymerisation modifications.
- Macromolecular characterisation techniques including size-exclusion chromatography, static and dynamic light scattering
- Protein expression and purification
- Biophysical analysis techniques including isothermal titration calorimetry and surface plasmon resonance
- Surface chemistry
- Multivariate statistical analysis
- Biosensing detection strategies including advanced thermal techniques and optical detection

Further Information

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How to Apply

To apply for this project please visit the Durham University application portal to be found at: https://www.dur.ac.uk/study/pg/apply/

Please select the course code F1A201 for a PhD in Molecular Sciences for Medicine and indicate the reference MoSMed21_10 in the 'Field of Study' section of the application form. Please note that there is no need to submit a Research Proposal with your application however we do require a Covering Letter, CV, an academic transcript, the contact details of two referees and proof of English language proficiency if appropriate.

Should you have any queries regarding the application process at Durham University please contact the Durham MoSMed CDT Manager, Emma Worden at: emma.worden@durham.ac.uk

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