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

Conjugation and encapsulation of photoactive metal complexes for medicinal applications

Durham University, Department of Chemistry

Supervisory Team

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Project overview/context

Photocatalytic metal species have been shown to be exciting compounds for a range of biologically relevant applications. These species have been demonstrated to have anti-cancer and anti-bacterial properties as well as being able to carry out protein tagging and acting as luminescent probes. Despite all these medicinally relevant applications, being able to deliver these metal species selectively into cells or bacteria is still a pressing challenge. This leads to these types of compounds having many detrimental off target effects. This project will utilise fluorinated metal ligands to conjugate these species onto encapsulation and targeting vectors to tackle this challenge.

Research Project

Photocatalysis has seen a renaissance over the past decade, with research groups such as the MacMillan (USA) and the Booker-Milburn (UK) groups driving new green synthetic methodology development.[1] Recently, attention has turned to medicinally relevant applications of photocatalysis.[2] Many researchers have shown the value of photoredox and metallophotoredox reactions in cellular environments with applications such as protein tagging, anticancer therapies and anti-bacterial development. Despite the variety of medicinal applications reported, the ability to get photocatalysts into aqueous and cellular environments remains a challenge and being able to target specific cells has been difficult to achieve. This has limited the use of these catalytic systems to mainly cell surface applications. To address the aforementioned challenges this project looks to develop new iridium catalysts which are conjugated onto a encapsulation or targeting vector.[3] This project will use a tagging approach through a perfluoroaromatic ligand to conjugate the active photocatalyst onto any desired peptide, peptoid or polymer which incorporates a nucleophilic residue. This will build upon previous work reported at Durham.[4] This approach has a major advantage over the current state-of-the-art, as it offers a highly flexible way to attach chemical entities onto peptide/peptoid/polymer backbones compared to the rigid and time-consuming process of synthesising bespoke ligands.

We will develop a general conjugation stratergy for the attachment of photoactive metal complexes to bioavailable backbones. Using these optimised reaction conditions we will generate a library of conjugated peptides, peptoids and polymers which will be further elaborated to generate encapsulated macromolecular structures.

We will optimise a range of ‘backbones’ to which photocatalysts are appended. The versatility of the perfluoroaromatic ligation strategy allows us to work with peptides, peptoids and synthetic polymers bearing pendant nucleophilic groups such as hydroxyl, amine, phenol or thiol groups. Peptide backbones will improve the aqueous solubility of otherwise hydrophobic complexes, and allow for the inclusion of cell-penetrating or organelle targeting sequences. Peptoid backbones can offer similar advantages, with the additional feature of improved stability towards hydrolysis or enzymatic degradation. Attachment of complexes to synthetic polymer scaffolds can offer further improvements in hydrolytic stability, along with the inclusion of secondary functionality such as stimulus-response and the ability to self-assemble into nanostructures such as micelles. A range of pendant

targeting groups will be attached to different backbones within the library, enabling the production of targeted delivery platforms for prodrugs to bacteria, or cancer cell lines.

Compounds within the library will be screened to determine their antimicrobial properties. We will focus our studies initially on *P. aeruginosa,* an opportunistic pathogen which causes respiratory and wound infections. Treatment is in many cases complicated by the ability of the bacteria to form extended biofilms. Here, we will combine known biofilm dispruting peptides or peptoids with iridium prodrugs to create dual-function systems. Cell penetration and localisation will be probed through the application of high resolution microscopy techniques.[5]

We will also expand our studies to explore the anti-cancer properties of compounds in the library. Here, we will match targeting ligands to specific cell lines (e.g. EGFR targeting peptides, galactose-HepG2). Macromolecular systems are particularly well suited to the delivery of iridium prodrugs in these cases, because of the enhanced permeation and retention effect in addition to the convenient inclusion of specific targeting ligands.

References

[1] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322-5363.
[2] J. B. Geri, J. V. Oakley, T. Reyes-Robles, T. Wang, S. J. McCarver, C. H. White, F. P. Rodriguez-Rivera, D. L. Parker, E. C. Hett, O. O. Fadeyi, R. C. Oslund, D. W. C. MacMillan, *Science* **2020**, *367*, 1091.
[3] C. S. Mahon, Z. Tong, N. H. Voelcker and M. Müllner, *Biomacromolecules*, **2021**, 22, 441-453.
[4] a) W. D. G. Brittain, S. L. Cobb, *Org Biomol Chem* **2019**, *17*, 2110-2115. b) D. Gimenez, C. A. Mooney, A. Dose, G. Sandford, C. R. Coxon, S. L. Cobb, *Org Biomol Chem* **2017**, *15*, 4086-4095.
[5] X. Jin, J.-E. Lee, C. Schaefer, X. Luo, A. J. M. Wollman, A. L. Payne-Dwyer, T. Tian, X. Zhang, X. Chen, Y. Li, T. C. B. McLeish, M. C. Leake, F. Bai, *Sci Adv,* **2021**, *7*, 43.

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: Home · Application Portal (microsoftcrmportals.com)

Please select the course 'PhD in Molecular Sciences for Medicine (EPSRC CDT)', which is registered in the Chemistry Department and indicate the reference

Training & Skills

This project involves working at the chemistry-biology interface and will give the student broad training across chemical synthesis, polymer chemistry, biology and microscopy. Specific training will be given in the following areas:

- Small molecule chemical synthesis, including ligand synthesis and metal complex generation
- Small molecule characterisation including NMR spectroscopy, mass spectrometry, HPLC and UV-Vis spectrophotometry
- Synthetic polymer chemistry including a range of polymerisation approaches and post polymerisation modifications
- Macromolecular characterisation techniques including size-exclusion chromatography, static and dynamic light scattering
- Biochemical assays for bacteria and cancer cells
- Optical microscopy techniques including confocal, super-resolution and single-molecule fluorescence microscopy; and computational image analysis.

MoSMed22_12 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, academic transcripts, the contact details of two referees and proof of English language proficiency if relevant.

Within the MoSMed CDT we are committed to building a diverse community based on excellence and commitment. To that end in our recruitment of Doctoral Researchers we welcome applications from outstanding candidates of all backgrounds regardless of ethnicity, disability, gender identity, sexual orientation and will consider all applications equally based on merit.

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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