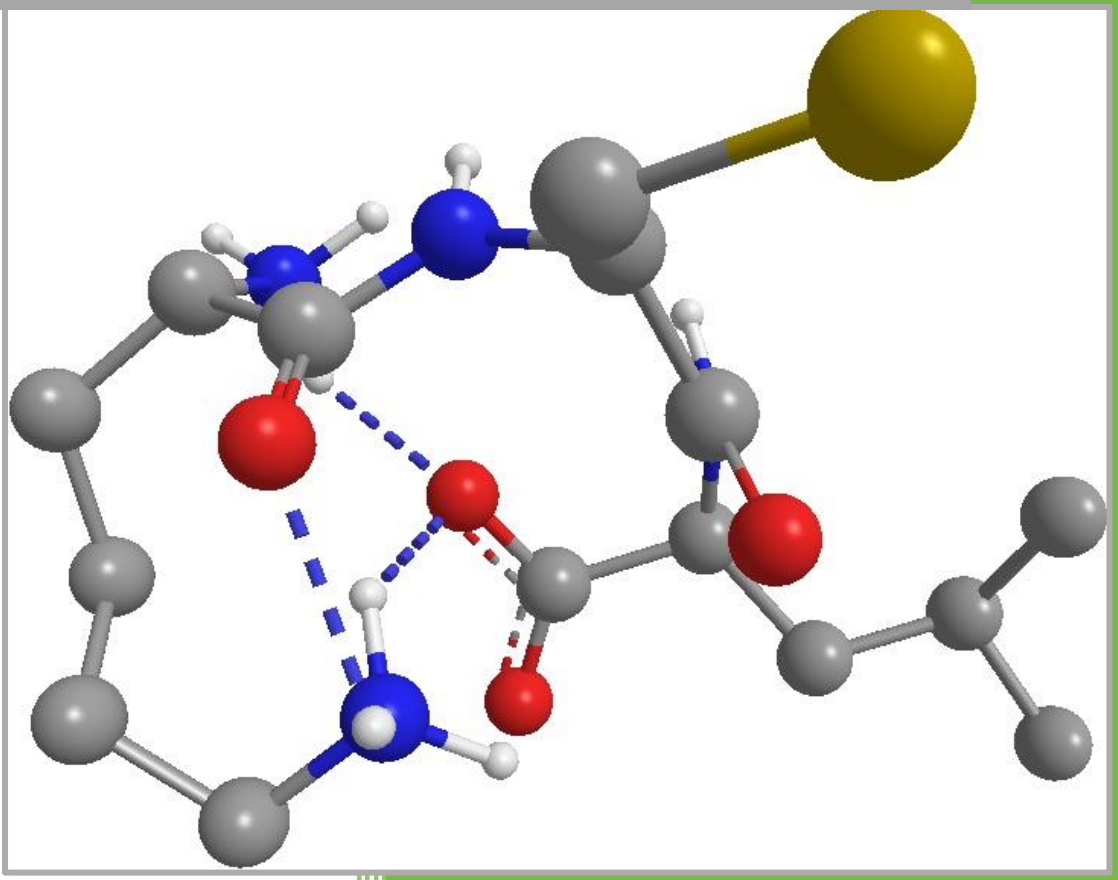
KING'S College LONDON

2021-2022

Centre for Doctoral Training in Chemistry for a Healthy & Sustainable Society



Department of Chemistry

King's College London

Chemistry for a Healthy & Sustainable Society

We are delighted to announce the formation of the centre for doctoral training in Chemistry for a Healthy and Sustainable Society at King's College London. This ambitious programme beginning in 2021 will produce graduates who have expertise in Chemistry but whose experience transcends traditional boundaries and to become conversant in the languages of Biology and/or Physics. This is in line with the strengths of KCL Chemistry where we carry out state of the art research at the interfaces of chemistry and the life sciences and physical sciences. We believe that major global challenges such as **climate change**, **sustainable energy production**, **antimicrobial resistance** and **emerging pathogens** can only be solved by harnessing interdisciplinary research and state of the art techniques such as **synthetic biology, synthetic chemistry, single molecule techniques** and **molecular modelling**. This CDT aims to train outstanding chemists who are comfortable in multidisciplinary settings, can work in diverse teams to solve complex problems and will be agile enough to apply their knowledge to future scientific challenges.

To apply:

1. Read the projects detailed below. We recommend that you contact supervisors informally before you apply and have a first and second choice in mind. We will ask you to confirm your choice should you receive and offer.

2. Send your CV and a research statement as a single pdf to PGR-chemistry@kcl.ac.uk
   Your research statement must detail:
   a) Describe your previous research experience (final year projects, summer placements, year in industry etc).
   b) Why you want to do a PhD and why you chose this programme

3. Fill out an application on the Kings online application system here. **Please note that your references must be submitted within 7 days of the application deadline.**

The current application deadline can be found on FindaPhD.com

For information on eligibility and English language requirements see our website

The start date for successful candidates will be October 2022

We look forward to welcoming you to King's Chemistry!

KCL Chemistry Department: Research Environment and Facilities

We are proud to have been ranked as the top Chemistry Department in London by the Guardian league table for the last two years and 3rd in London in the Complete University Guide 2021.

King's College London has a unique multidisciplinary and collaborative environment. The growing Department of Chemistry at King's excels in interdisciplinary research where chemistry is a central science tying together physics and biology. The department is based in Britannia House, which was refurbished in 2018 with new labs and facilities for chemistry (including 400 MHz NMR, analytical and Prep HPLC, LCMS, LC-HRMS, GCMS, peptide synthesiser), biochemistry/microbiology and biophysics including an ongoing capital investment of £4 million. We have access to further excellent facilities in the Mass Spectrometry Centre (Franklin Wilkins Building, Denmark Hill), the Nikon Imaging Centre (Guys Campus) and our Cryo-EM facility. The KCL Centre for Biomolecular Spectroscopy covers high field NMR (including a 500 MHz Bruker instrument including a triple resonance (^{1}H/^{13}C/^{15}N) cryoprobe and 700 MHz Bruker instrument equipped with a quadruple resonance (^{1}H/^{13}C/^{15}N/^{31}P) cryoprobe), Biacore, ITC and native mass spectrometry. The NMR facility has recently been expanded to accommodate an 800 MHz instrument. KCL has fully equipped X-ray crystallisation services with extensive access to the Diamond synchrotron source via the block allocation system.

KCL Chemistry department is outward looking and has strong links to the Randall Division of Cell and Molecular Biophysics, Department of Imaging Chemistry, Physics and the Institute of Pharmaceutical Sciences within KCL and other London Chemistry Departments. King's excellence in Chemistry enhances its strength in Biomedical Sciences and we are members of King's Health Partnership and The Francis Crick Institute which can enable translation of scientific development toward clinical applications. We are members of other doctoral training centres (BBSRC LiDo and BiPAS). Equality is central to the ethos of KCL Chemistry, with a dynamic and fulfilling research culture for all, and an emphasis championing diversity and inclusion in science.

The Programme

The PhD programme is 4 years, including thesis writing. While the majority of your time on the programme will be spent carrying out state of the art research it is also important that you gain transferable skills, have the opportunity to fill gaps in your knowledge through taught modules and

have access to mentorship and feedback on your progress. To this end we have created a PhD doctoral training programme to complement and support this interdisciplinary research.

1. Transferable skills

While research in your chosen area will be your primary focus over the course of your 4 year PhD we believe that it is also important to develop transferable skills to both complement and enhance your research skills which will improve employability in your chosen industry. We require all students to take at least 10 days of transferable sk ills training each year.
KCL offers extensive PGR training courses from communicating your science to a lay audience, leadership skills, data management, presentation and writing skills.

Attendance of internal departmental seminars is mandatory. Additionally, all students are expected to attend external national and international conferences to present their work. Funds for travel are available.

2. Taught Modules to support your PhD research

All students can access of our taught modules in the Chemistry department and through our links with biochemistry, imaging and physics can also access modules in other departments which will complement their PhD studies and help to fill gaps in their knowledge.

Chemistry Frontiers, *Advanced Topics in Chemistry 1 & 2*, *Chemistry of Disease and Therapy* and *Catalysis*, *Protein Structure and Function* and *Advanced Biophysical Techniques* offer a range of topics that will help to support your research on the projects outlined below.
A full list of modules on our chemistry programme is available here.

3. Teaching and Outreach Opportunities

At KCL chemistry we are committed to delivering outstanding teaching to our undergraduates. We are lucky to have an engaged and diverse student body. Our department also has dedicated teaching staff who are engaged in education research and exemplify best practice. We offer all PhD students the opportunity to participate in teaching including lab demonstration and delivering small group teaching as well as supervision of undergraduates during their final projects. For all these teaching levels, training is provided as well as peer observation of teaching so you can improve your skills.

Beyond our internal teaching we have an active outreach programme, from staging public lectures to schools to bringing school groups to our labs and providing work experience opportunities for

students. There are opportunities for PhD students to be involved in these activities and with the widening participation unit at KCL.

4. Supervision and Mentoring

King's Chemistry is committed to ensuring all our PhD students receive excellent supervision and any additional support required during their studies. All projects have two supervisors and we anticipate that you will spend approximately equal time in both supervisors' labs. You will receive health and safety training from our excellent technical team and an induction course provided by the CDS as well as induction in Britannia House.

All PhD students will have a thesis committee which consists of both supervisors and a third academic staff member. The thesis committee and student meet within 3 months of the PhD starting and then between 9 and 12months. This second meeting involves a viva and allows the student to upgrade from MPhil to PhD. Meetings occur annually thereafter or as required. This process is intended to ensure students and supervisors understand their responsibilities and that students have ample opportunity for internal and external feedback and support. Additionally, the postgraduate tutor (Dr.Graeme Hogarth) meets all new PhD students and is available to offer support as needed and our PGR administrator (Cairn Macfarland) is available for day to day administrative support. The departments seeks feedback and input from our post graduate community through our **PGR Student Staff Liaison Committee.**

Additionally, peer support is offered through ***PostDoc ChemComm*** our community of active PhD and Post doctoral researchers who have created an internal seminar series delivered by and for early career researchers. This includes research presentations by PGR and postdoctoral researchers as well as careers events.

Important contacts:

If you require support with the application process, please contact the Chemistry Postgraduate Administrator Cairn Macfarland PGR-chemistry@kcl.ac.uk

For informal enquires about the programme contact Dr. Sarah Barry sarah.barry@kcl.ac.uk

For informal enquiries about specific projects please contact academic supervisors directly.

PhD Research Projects

Below is a list of the projects, followed by detailed descriptions, available to start in October 2021. The projects are all interdisciplinary and span techniques from organic synthesis to computational chemistry and take in themes from AMR to protein folding. Each project has a supervisory team of at least two chemistry academics. You can find more information on each research group on our website

Mapping the Folding and Assembly Landscapes of Amyloidogenic Peptides

Supervisory Team: Antoni Borysik, **Martin Ulmschneider**

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The aggregation of unstructured amyloidogenic peptides is implicated in a number a diseases including Alzheimer's and Creutzfeldt-Jakob disease. In isolation, amyloidogenic peptides are characterised by the absence of a defined 3-dimensional conformation, but adoption of structurally ordered assemblies is associated with pathogenesis, in a process that is poorly understood. Ordered peptide assemblies have been shown to interact with biological membranes promoting pore formation, membrane penetration and cell death. Understanding the molecular mechanisms orchestrating the disorder-to-order transition and self-assembly of amyloidogenic peptides provides an opportunity for the design of new therapeutics to prevent disease. The characterisation of these early disease forming events represents a significant challenge, however, due to the unstructured nature of the peptide monomers, which thwarts exploration via established structural techniques. It is not known, for example, if the transition to order requires a transient template within each peptide monomer or if structure emerges as a consequence of self-assembly or lipid binding.

This project will entail the development of new methods to characterise the folding and assembly landscape of amyloidogenic peptides. The ability to pinpoint amino acids that are critical for peptide aggregation and the characterisation of transient structure within the unfolded ensembles will provide a new blueprint to understand peptide misfolding disorders. The method will sit at the interface between biophysics and computational biology with the student developing and applying *in silico* methods to define the unstructured peptide ensemble and identify amino acids critical for peptide assembly.[1-2] The computational methods will be corroborated by state-of-the-art experimental techniques developed by the Borysik group that can quantify the degree of disorder in biomolecules with amino acids resolution.[3-4] The project will be complimented by a range of biochemical and membrane assays aimed to unearth the foremost molecular events in peptide misfolding disorders.

References

[1] C. H. Chen et al*. J. Amer. Chem. Soc.* 2019, **141,** 12, 4839-4848.
[2] J. P. Ulmschneider & M. B. Ulmschneider. *Accounts of Chemical Research* 2018*,* **51 (5)***,* 1106-1116
[3] R. E. Salmas and A. J. Borysik *Commun Bio* 2021, **4**, *199*
[4] R. E. Salmas and A. J. Borysik *Anal Chem* 2021, **93**, 7323

Single-Protein Approaches to Mechano-Enzymology

Supervisory Team: Ismael Díez-Pérez, Sarah Barry

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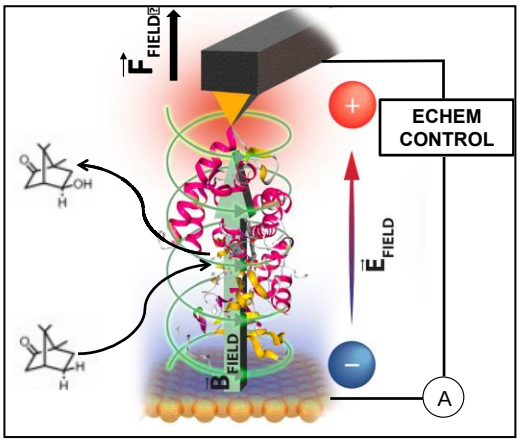

Enzymatic catalysis is a prominent example of the rich, yet complex, dynamism inherent in any biomolecular process, and illustrative of how an atomic, but static, crystallographic picture of protein machinery is insufficient to provide a complete mechanistic description. Among the countless enzymes' families, **redox-active enzymes catalyse the most demanding reactions in biology with tremendous potential in bio-manufacturing**[1]. Today, most information on protein function comes from rational mutagenesis based on crystal structure. While this *static picture* has been pivotal to identify key residues/chemical interactions in the enzyme active site that are directly involved in the catalytic process, studies have shown that even fully silencing such interactions still results in some cases in a 1000-fold catalytic activity versus same reaction in bulk[2]. This illustrates the lack of understanding of the **physical forces that underpin enzymatic catalysis**[3] and confers to enzymes their astonishing synthetic efficacy. This biological enigma has been long elusive due to the limited number of experimental approaches able to directly address directional forces in an enzyme molecular machinery while dynamically monitoring its activity.

This project will focus on the cytochrome P450 family of redox enzymes. P450s enable most drug metabolism in cells and are of interest as biocatalysts due to their ability to activate inert C-H bonds and catalyse selective oxidation reactions *e.g.* hydroxylation[1]. P450s contain many flexible regions and undergo conformational change during catalysis. However, the effect of these changes on catalysis are poorly understood. To investigate, we will exploit cutting-edge biophysical approaches to trap individual enzymes in a nanoscale junction (see image) as a unique way to interrogate force stimuli (including mechanical forces) along crystallographic directions of the protein backbone. Precise electrical measurements of the single protein junctions[4] will allow detection of single enzyme turnover and generate insight into the relationship between protein dynamics/conformational change and catalytic function.

Such fascinating and strongly interdisciplinary proposal combining chemistry, molecular biology, enzymology, and biophysics makes sense only when two supervisory teams covering the very different disciplines of the project join forces; the Díez-Pérez group is leader in the emerging field of BioMolecular Electronics and internationally recognized for its pioneering nanobiotech approach in single-protein electrical detection. The Barry group has extensive experience in discovery and characterisation of novel enzymes with emphasis in cytochrome P450s[5]. The student will have the opportunity to work in an emerging field with important applications to biotechnology.

References: [1] M. Girhard *et al*. in *Cytochrome P450* 451–520 (Springer International Publishing, 2015). [2] Carter, P. & Wells, J. *Nature* **332,** 564–568 (1988).[3] Arieh Warshel *et al. Chem. Rev.* **106,** 3210-3235 (2006).[4] A.C.Aragones *et al Nature* **531**, 88–91 (2016) & M. P. Ruiz *et al. J. Am. Chem. Soc.* 2017, **139**, *43*, 15337-15346.[5] Alkhalaf, L. M et al *J. Am. Chem. Soc.* 2019, **141**, *216.*

Development of Organelle-Specific Membrane Reporters

Supervisory Team: Prof. Ulrike Eggert, Dr. Andre Cobb

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Group Site:
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www.kcl.ac.uk/research/cobb

Membrane structures, including the plasma membrane, the Golgi, the endoplasmic reticulum (ER), the nuclear envelope and different vesicles are critically important for nearly all cellular processes. Membranes compartmentalise different cellular functions and provide essential structural components. They are vital as signalling platforms and enable transport and uptake of cargoes. Mammalian cells express many thousand distinct lipid species with a diversity and complexity approaching that of proteins, yet overall our knowledge of the biological roles of lipids lags far behind that of proteins.

It has long been postulated that the physicochemical characteristics of lipids define many membrane properties like membrane tension, fluidity, phase separation and mechanical stability. Small molecules have been valuable tools to sense and report on changes in these physicochemical properties, but are only now being used to study membranes in cells rather than in model systems. **The goal of this interdisciplinary PhD is to synthesise and use small molecules that localise to different organelles inside the cell and report locally on the physical properties of membranes, filling a critical gap in our knowledge**.

It has been challenging to study lipids because they cannot be manipulated as easily as proteins. The Eggert group has developed a method to change lipid levels in cells by removing enzymes that make lipids and we have shown that specific lipids are required to maintain the structures and functions of the plasma membrane and internal organelles. We will build on these data to study how membrane properties changes when lipids and membranes are perturbed. We will start by using imaging tools like Flipper-TR, a fluorophore that can sense changes in membrane tension, or Laurdan, a sensor of membrane fluidity. Working with the Cobb group, the student will synthesise derivatives of these probes with tags that will localise them to specific organelles. The student will then use advanced cell culture and imaging techniques to investigate how the physicochemical properties of membranes change, and affect cellular functions, when lipids are perturbed.

The student will be trained in a broad range of emerging techniques including organic synthesis, biophysics, advanced microscopy and cell biology.

References

[1] P. Parijat et al. *ACS Chem. Biol.* 2021, **16,** 1, 225-235.
[2] J. G. Carlton et al. *Nat Rev Mol Cell Biol*. 2020, **21**, 3, 151-166.
[3] G. E. Atilla-Gokcumen et al. *Cell*. 2014, **156**, 3, 428-39.

Discovery of New Post-Translational Modifications using Photoredox Catalysis

Supervisory team: Dr. Manuel Müller, Dr. Andre Cobb,

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Post-translational modifications (PTMs) control the structure and function of many proteins. Given their importance in biology, there is a continuing need to develop novel tools to systematically catalogue the distrubution of PTMs. This demand is especially pronounced for PTMs that occur on the polypeptide backbone – a dramatically understudied class of PTMs.[1] This project aims to develop a chemistry-driven approach to discover new instances of protein backbone modifications. To do so, the PhD student will develop a photoredox reaction to selectively functionalise backbone-modified peptides. Based on this reaction, they will then devise a technology to enrich backbone-modified proteins from biological samples. Finally, the student will test the function of candidate backbone modifications by leveraging protein semi-synthesis (well-established in our group)[2], biochemical, biophysical[3] and/or genetic tools. If successful, this project will provide unprecedented insights into where, when and how protein backbone modifications contribute to biological regulation.

Candidates will receive training in cutting-edge chemical syntheses and chemical biology techniques. They will be embedded in the research groups of Andre Cobb (synthesis)[4] and Manuel Müller (chemical biology) in the department of chemistry, King's College London.

References

[1] M. M. Müller, *Biochemistry*, 2018, **57**, 177-185.
[2] S. Margiola, K. Gerecht and M. M. Müller, *Chem. Sci.,* 2021, **12**, 8563-8570.
[3] T. Zhang, K. Hansen, A. Politis and M. M. Müller, *Biochemistry*, 2020, **59**, 3683-3695.
[4] R. Fanelli, D. Berta, T. Földes, E. Rosta, R. A. Atkinson, H.-J. Hofmann, K. Shankland and A. J. A. Cobb, *J. Am. Chem. Soc.*, 2020, **142**, 1382-1393.