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Research Opportunities at the School of Chemistry

There are two different schemes across Chemistry, Engineering and Maths:

1. 6 Dalian University of Technology/University of Leicester PhD scholarships funded by CSC (CSC provides stipend and UoL provides international fee waiver)
2. 7 DUT-UoL Collaborative PhD Studentships
   (DLI provides 20,000 RMB and University of Leicester provides international fee waiver. Only available to DLI students)

We are not considering applications for the two funding sources separately. Shortlisting for interview will be carried out purely on the basis of quality and aptitude for the PhD project for which you have applied. Only at the point of interview and appointment of successful candidates will we begin to consider funding source. If you get through to the interview, you will be asked about your funding preference (only to be considered for CSC, only to be considered for DUT, preference for CSC but also consider DUT, preference for DUT but also CSC, or no preference) and then we will allocate projects at that stage.

A formal application to the University of Leicester is essential (this can be carried out here https://le.ac.uk/study/research-degrees/funded-opportunities/cse-dut-partnership) and the **deadline for applications is: 5th January 2025**. Please choose two research projects and make it clear on your application form which is your first and which is your second choice research project. We will be holding **online interviews from 6th to 13th February 2025**, so please check your email account regularly to find out if you have been selected for an interview. You should receive an email inviting you to interview by Friday 24th January 2025.

With your application, please provide:

- CV
- Degree certificates and transcripts of study already completed and if possible transcripts to date of study currently being undertaken
- Personal statement
- Evidence of English language if available
- In the references section, please enter the contact details of two academic referees in the boxes provided or upload reference letters if already obtained
- In the funding section, please state **DUT 2025 scholarship**
- In the research proposal section, please provide the names of the **project supervisors and the project titles** you want to be considered for. You can select up to 2 projects. List both in order of preference. (a research proposal is not required)

We have a number of different research projects available in organic chemistry, inorganic chemistry and physical chemistry. Please take a look through the 12 different research projects which are available in the School of Chemistry.

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Organic Chemistry

1. Antibody Drug Conjugates for the Simultaneous Delivery of Small Molecule and Inorganic Drugs to Cancer Cells

Prof. Steve Bull – sdb45@leicester.ac.uk

Project Title	**Antibody Drug Conjugates for the Simultaneous Delivery of Small Molecule and Inorganic Drugs to Cancer Cells**	
Project Highlights:	1.	Synthetic Chemistry
	2.	Antibody Drug Conjugates
	3.	Bioinorganic Drugs

Project Overview (Maximum 350 words)

The startling statistic that 1 in 2 people will develop some form of cancer during their lifetime means there is an urgent need to develop new cancer therapeutics, however, many cancer drugs adversely affect healthy cells, causing serious side effects that prevent them from being used in the clinic.

The Bull group are developing ways to address this '*friendly fire*' cancer drug toxicity problem through use of antibody-drug conjugates (ADC) to selectively deliver anti-cancer drugs to cancer cell. In this approach, a small-molecule drug is covalently attached to an antibody that is specific for binding antigens that are overexpressed on the surface of a cancer cell. The resultant ADC then binds specifically to the outside of the cancer cell, resulting in selective internalisation that triggers drug release within the cancer cell to selectively kill a tumour.

Cancer relapse in patients is a major problem, with fatal tumour recurrence often occurring due to the presence of persistent cancer stem cells (CSCs) that are a sub-population of cancer cells that are resistant to many chemotherapy/radiotherapy treatments. The Suntharalingam group are developing metal-complexes as drugs to target these CSCs, thus potentially preventing tumour reoccurrence in patients, however many bioinorganic drugs are also toxic towards healthy cells which can prevent their use in the clinic.

This project will develop new versatile linker constructs that can be used to attach bioinorganic drugs to cancer recognition antibodies to produce bioinorganic ADCs as potential anti-cancer therapeutics. The linker used to attach the drug payload to the antibody will contain a peroxynitrite responsive unit that will only be cleaved in cancer cells that are known to produce elevated levels of peroxynitrite. Ultimately, we wish to design an ADC that can simultaneously deliver both a small molecule anti-cancer drug and a bioinorganic drug as a double therapeutic dose that can kill both cancer cells and CSCs, since this will maximise the chances of developing effective non-relapsable cancer treatments (**Figure 1**).

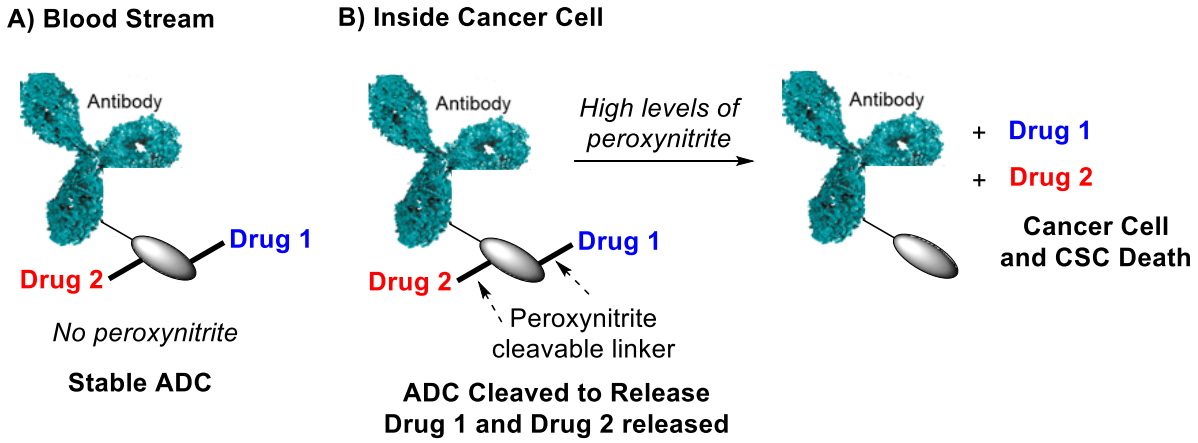

Figure 1: A) *ADC containing an antibody and two drug molecules that is specific for binding to a cancer cell. The antibody fragment of the ADC will bind to the cancer cell and be internalised.* **B)** *High levels of peroxynitrite that are only present in the cancer cell will then cleave the ADC linker to simultaneously release drug 1 and drug 2 that will then combine to kill the cancer cell/CSC.*

This highly multidisciplinary project will involve chemical synthesis and characterisation, photophysical and biophysical methods, antibody conjugation, mono- and 3D-layer cell culture, and other sophisticated biological/medical techniques. Consequently, this studentship will provide many of the skills required to pursue a career in the life sciences or drug discovery in academia and/or the pharmaceutical industry.

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2. *Phosphorylation Inducing Pharmaceuticals to Modulate Hub Proteins*

Dr. Richard Doveston – r.g.doveston@leicester.ac.uk

Project Title	**Phosphorylation Inducing Pharmaceuticals to Modulate Hub Proteins**	
Project Highlights:	1.	New pharmaceutical tools
	2.	Developing novel synthetic organic chemistry routes
	3.	Interdisciplinary chemical biology approach

Project Overview (Maximum 350 words)

A major challenge in pharmaceutical research and development is to develop new drugs that overcome issues associated with resistance and negative side effects. Engineering 'smart' molecules to control our body's natural regulatory responses via 'induced proximity' is a promising alternative strategy to the traditional protein inhibition approach. This potential has been exemplified through the development of bifunctional ProTaC molecules for targeted protein degradation [1]. **Aim:** In this project we will expand the toolkit of proximity inducing molecules by developing phosphorylation-inducing chimeras (PhICs) that promote phosphorylation of specific target proteins [2]. Phosphorylation is a critical regulatory mechanism in our bodies, and harnessing this for therapeutic use has enormous potential. However, this approach has not yet been fully explored.

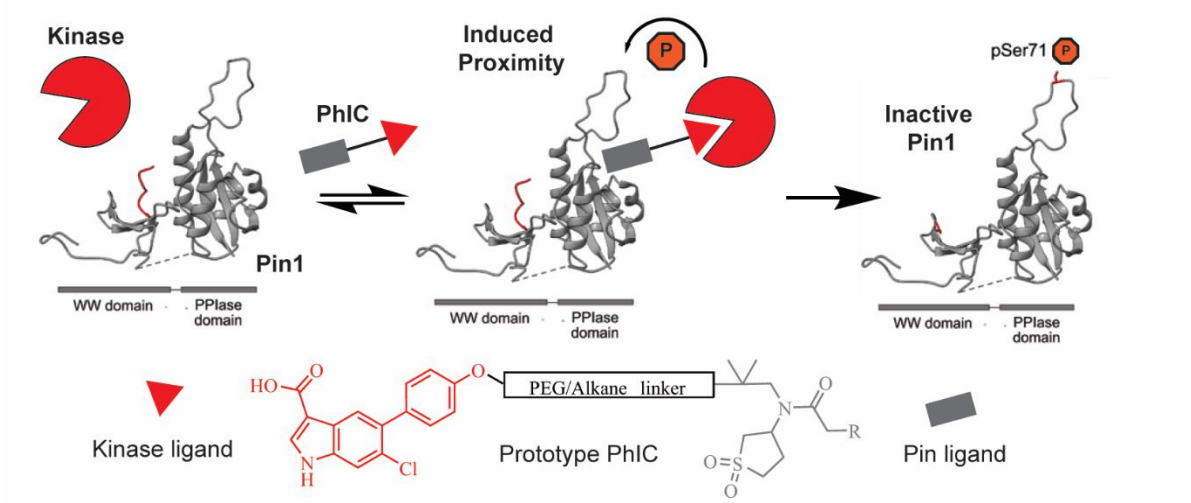

Figure 1. Pin1 inactivation via PhIC induced phosphorylation of Serine 71. Bottom: Prototype Pin PhIC combining an allosteric AMP kinase ligand (red) and the sulfopin Pin1 ligand (grey), joined by a chemical linker.

Specifically, we will develop PhICs that target an important communication hub protein called Pin1. Pin1 is a prolyl isomerase protein that is heavily implicated in many cancer types and inhibiting its activity has been shown to be an effective therapeutic strategy. Pin1 activity is inhibited through its phosphorylation by kinases such as PKA and DAPK1, and we have recently demonstrated how these events differentially regulate Pin1 function [3]. Selectively inducing Pin1 proximity with these kinases will allow us to tune Pin1 activity toward optimal therapeutic efficacy, and expand understanding of the multiple roles Pin1 plays in the cell. This approach could also be expanded to other hub proteins such as 14-3-3 which our group has extensively studied [4].

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This will be an interdisciplinary project combining drug design, organic synthesis, biophysical evaluation, structural biology, and cell-based experiments. It will provide excellent training in the field of chemical biology and, because of the novelty of the project, we envisage it will lead to multiple high-impact publications.

References:

[1] *Optimization of class I histone deacetylase PROTACs reveals that HDAC1/2 degradation is critical to induce apoptosis and cell arrest in cancer cells.* Joshua P. Smalley, India M. Baker, Wiktoria A. Pytel, Li-Ying Lin, Karen J. Bowman, John W.R. Schwabe, Shaun M. Cowley, James T. Hodgkinson, *J. Med. Chem.* **2022**, 5642-5659.

[2] *Phosphorylation-Inducing Chimeric Small Molecules.* Sachini U. Siriwardena, Dhanushka N. P. Munkanatta Godage, Veronika M. Shoba, Sophia Lai, Mengchao Shi, Peng Wu, Santosh K. Chaudhary, Stuart L. Schreiber, and Amit Choudhary, *J. Am. Chem. Soc*. **2020**, 14052–14057.

[3] *Dissecting the functional behaviour of the differentially phosphorylated prolyl isomerase, Pin1.* Danielle F. Kay, Adem Ozleyen, Cristina Matas De Las Heras, Richard G. Doveston, Aneika C. Leney, *Protein Science* **2024**, e5138.

[4] *Characterizing the protein–protein interaction between MDM2 and 14-3-3σ; proof of concept for small molecule stabilization.* Jake A. Ward, Frederick W. Muskett, Richard G. Doveston et al., *J. Biol. Chem.* **2024**, 105651.

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3. A new chemical release strategy for drug delivery and medical diagnostics

Dr. Richard Hopkinson – richard.hopkinson@leicester.ac.uk

Project Title	**A new chemical release strategy for drug delivery and medical diagnostics**	
Project Highlights:	1.	Synthesise novel drugs and chemical probes attached to cephalosporins, which will be released by β-lactamase enzymes.
	2.	Validate β-lactamase-mediated release of the drugs and chemical probes using NMR and fluorescence spectroscopy.
	3.	Use confocal fluorescence imaging and cytotoxicity assays to identify release in cell cultures.

Project Overview (Maximum 350 words)

Getting medicines and diagnostics selectively to where they are needed in the body is very challenging. This is because diseased cells are very similar to healthy cells, which means that the molecules cannot distinguish between the two. To address this issue, we need new methods to deliver medicines and diagnostics to the sites of disease. Work in this project will therefore focus on developing a novel and exciting delivery strategy.

Our strategy involves attaching medicines and diagnostics to cephalosporin protecting groups (CPGs). These CPG-containing delivery agents (CPG-DAs) will be substrates of β-lactamase enzymes, which will remove the CPG and release the medicine or diagnostic. β-Lactamases are not found in humans but can be synthesised and attached to antibodies that target diseased cells. Prior treatment with the β-lactamase-antibody conjugate can then enable targeted delivery of the medicine/diagnostic to the diseased cell after CPG-DA treatment. Bacteria that naturally have β-lactamases will also be targeted by CPG-DAs, which means that drug-resistant bacterial infections can be diagnosed and treated.

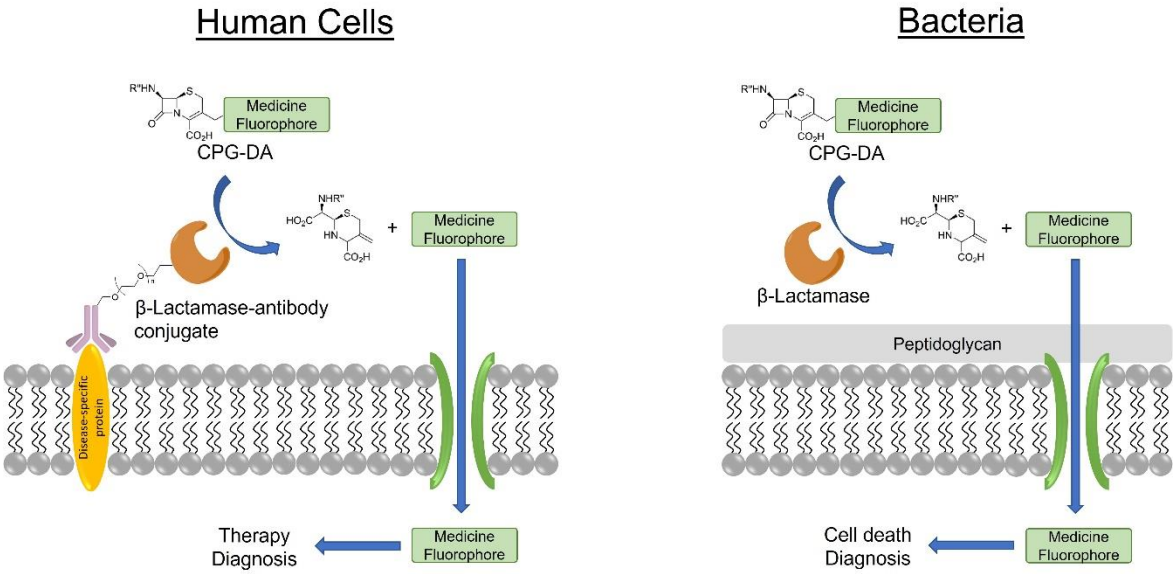

Figure 1. *CPG-DAs are sensitive to β-lactamases. In diseased human cells, β-lactamase-antibody conjugates can be used to release medicines and diagnostics from CPG-DAs (left). CPG-DAs will also release medicines and diagnostics in drug-resistant bacteria (right).*

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Work in this project will initially involve synthesis of a library of CPG-DAs. These molecules will contain a CPG and either a medicine (antibacterial medicines as well as anti-cancer and other medicines targeting human cells) or a fluorescent molecule that can be detected in diseased cells (diagnostics). After synthesis and characterisation, the CPG-DAs will be incubated with β-lactamases prepared in house and the mixtures will be monitored by NMR and fluorescence to confirm medicine/fluorophore release. Work will then move to cellular studies, where the CPG-DAs will be tested for the toxicity in diseased human cells (pre-treated with a β-lactamase-antibody conjugate) and bacteria, and for their ability to induce fluorescence using confocal imaging.

Collectively, the project will discover and validate a novel chemical release strategy and will ultimately produce new medicines and diagnostics for human diseases.

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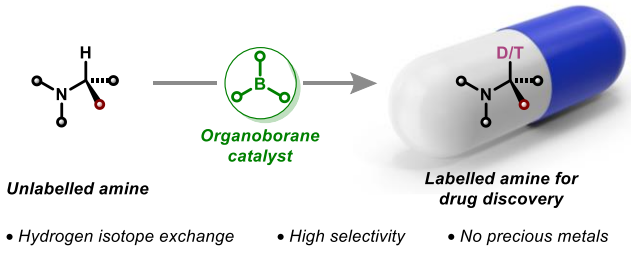
4. Organoborane Catalysed Hydrogen Isotope Exchange in Amines

Dr. Alex Pulis – a.pulis@leicester.ac.uk

Project Title	**Organoborane Catalysed Hydrogen Isotope Exchange in Amines**	
Project Highlights:	1.	Discovers efficient synthetic methodology with direct industrial chemistry applications (e.g. drug discovery)
	2.	Utilises unexplored reactivity of boron-based catalysts.
	3.	Boarders on the traditional realms of organic and inorganic synthesis and therefore provides a unique training opportunity suitable for careers in industry (e.g. pharmaceutical, agrochemical, etc) and academia.

Project Overview (Maximum 350 words)

The synthesis of deuterium- and tritium-labelled organic compounds is crucial throughout academic and industrial research. They are utilised in reaction mechanism investigation, neutron scattering, and in the drug discovery process from target identification to clinical trials. For example: (1) Receptor binding studies rely on the use of tritium-labelled molecules; (2) deuterium-labelled MS standards aid identification of metabolites from animal and human studies; (3) deuterium-labels serve as simple bioisosteres for ^{1}H and can alter ADME properties, and; (4) regulatory authorities often require radiolabelled (i.e. tritium) in vivo metabolism studies. Approved deuterium-labelled drugs are increasing in prevalence, and deuterium-derivatives offer the opportunity for new chemical entities, but no clear regulatory framework has yet been established. Therefore, synthetic methods that allow for precise control of regio-, chemo- and stereoselectivity will be of strategic importance and a late-stage incorporation approach via direct exchange (ie the direct replacement of H for D or tritium in a complex molecule) avoids the need for costly and time consuming *de novo* synthesis.



The project will build on the Pulis' group expertise in main group catalysis,[1-3] and will utilise the unusual and unique ability of organoboranes to activate α-amino C(sp^3)–H bonds in the development of a new approach to late-stage deuterium- and tritium-labelling of amine-containing pharmaceutical compounds. The new methodology will be regioselective and deliver high levels of isotope incorporation that is suitable for a variety of different industrial and academic research applications.

We have exciting preliminary results from which to launch this project. We will first identify and optimise suitable deuterium-donors, including readily accessible deuterated amines and deuterium gas as a surrogate for tritium gas. Substrate scope will be investigated on model molecules that feature functional groups and moieties important to drug discovery, including heterocycles. The methodology will be applied to the late-stage-deuteration of approved amine containing drug molecules, such as gefitinib (anticancer), fluopromazine (antipsychotic), donepezil (Alzheimer's treatment), fluoxetine (antidepressant), cetirizine (antihistamine), and loperamide (antidiarrheal) to show case the power of the methodology to end users. In addition, late stage tritiation will be carried out with established industrial partners.

[1] Alvarez-Montoya, Gillions, Winfrey, Hawker, Singh, Ortu, Fu, Li, Pulis, *ACS Catalysis* **2024**, *14*, 4856.
[2] Basak, Alvarez-Montoya, Winfrey, Melen, Morrill, Pulis, *ACS Catal*. **2020**, *10*, 4835.
[4] Basak, Winfrey, Kustiana, Melen, Morrill, Pulis, *Chem. Soc. Rev.* **2021**, *50*, 3720.

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5. Direct α-Functionalisation of Amines with Fluoroalkyl Groups

Dr. Alison Stuart – alison.stuart@leicester.ac.uk

Project Title	**Direct α-Functionalisation of Amines with Fluoroalkyl Groups**	
Project Highlights:	1.	Provide a new synthetic strategy for the late-stage functionalisation of amines with fluoroalkyl (CF_3 and CF_2H) groups to form structurally-diverse, α-fluoroalkyl amines.
	2.	Perform mechanistic studies by multinuclear NMR spectroscopy and DFT calculations to understand and control the reaction.
	3.	Provide excellent training for a research career in either academia or industry (e.g. in medicinal chemistry, agrochemistry, process chemistry, as well as in fine and speciality chemicals).

Project Overview (Maximum 350 words)

Introduction. The incorporation of fluorine is used to improve the physicochemical properties of drug candidate molecules. For example, the 2,2,2-trifluoroethylamine group (NCH_2CF_3) is used as a bioisostere for amides because it enhances hydrolytic stability whilst retaining size, polarity, nitrogen basicity and hydrogen bond donor ability (Figure 1A). The 2,2-difluoroethyl group (CH_2CHF_2) is another important fluorinated group which is used as a lipophilic hydrogen bond donor and is a stable bioisostere for alcohol, ether, thiol, amine and amide pharmacophores (Figure 1B). However, the introduction of both of these fluorinated groups remains a significant challenge since they are normally synthesised using either harsh reagents or metal-catalysed processes that limit functional group tolerance. We propose a new approach to address these problems using hypervalent iodine reagents to facilitate a completely different disconnection (Figure 1D), compared to traditional methods (Figure 1C), and this new strategy will enable the repurposing of readily available amines for selective fluoroalkylation.

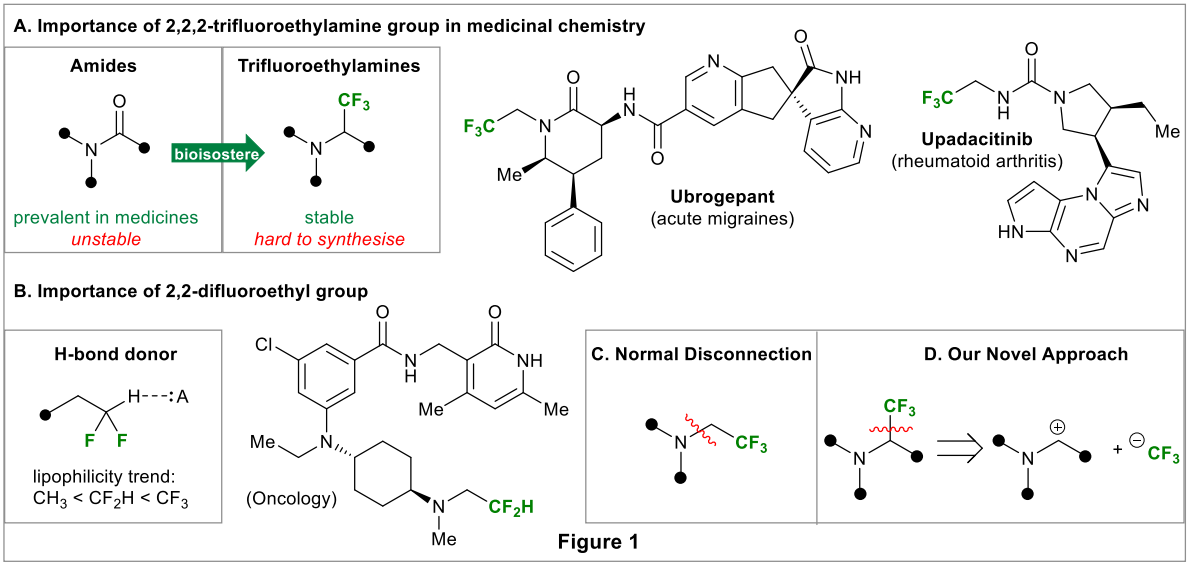

Figure 1

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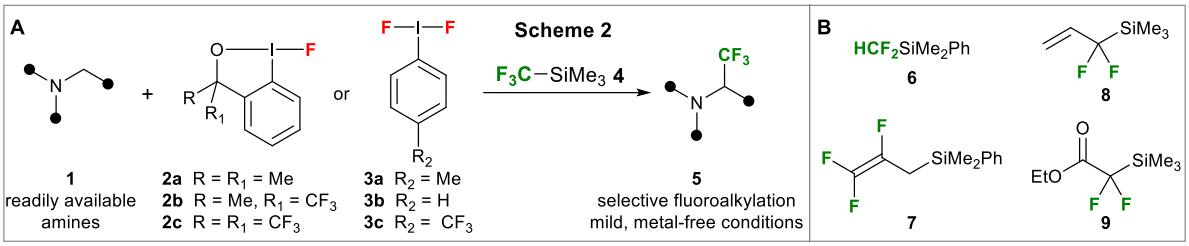
Research Aim. This research project will develop new synthetic methodology for directly converting a diverse range of amines under mild reaction conditions to α-fluoroalkylated products relevant to medicinal chemistry (Scheme 2A). We have exciting preliminary results that demonstrate the direct trifluoromethylation of tribenzylamine. Mechanistic studies will be performed with a series of hypervalent iodine fluorides to investigate the structure-activity relationship between the hypervalent iodine reagent and the basicity of the amine. A major advantage of this new approach is that a variety of fluoroalkyl groups will be introduced into the amine simply by changing the silyl reagent (Scheme 2B). The ultimate goal will be to showcase the late-stage fluoroalkylation of amines in drugs such as Varenicline (smoking cessation), Seroquel (antipsychotic), Fentanyl (analgesic), Lexapro (anti-depressant) and Nefazodone (anti-depressant).



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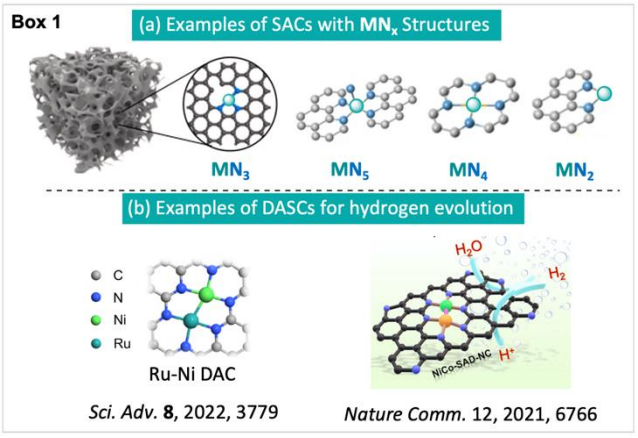
Inorganic Chemistry

6. Diatomic Catalysts (DACs) Driving Fine Chemical Synthesis: Electrochemical Methodologies for the Future

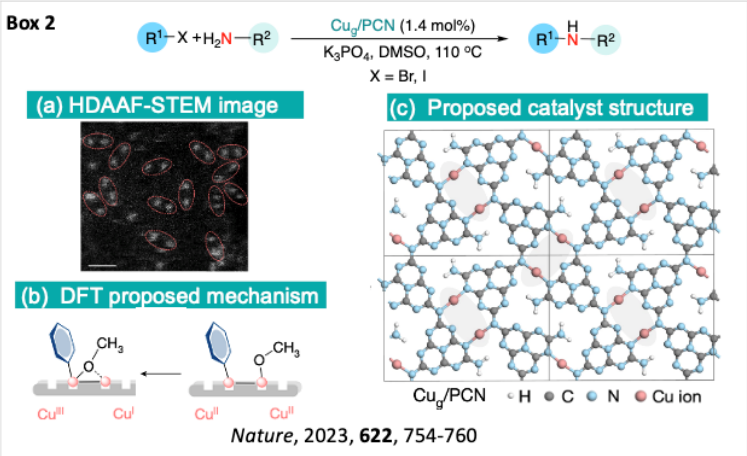
Dr. Qun Cao – pc52@leicester.ac.uk

Project Title	**Diatomic Catalysts (DACs) Driving Fine Chemical Synthesis: Electrochemical Methodologies for the Future**	
Project Highlights:	1.	Explore new synthetic strategy for *N*-doped carbon supported diatomic catalysts using via pore confinement strategy[5] with Metal Organic Frameworks (MOFs) or covalent organic frameworks (COFs) as precursor and pyrolysis of bimetal polymers.[3a,6]
	2.	Develop entirely new electrochemical methods for C-C and C-N bond cross-coupling reaction as proof-of-concept demonstrations, application to pharmaceutical synthesise (training e.g., GC, GC-MS, NMR, XRD).
	3.	Characterisation of diatomic catalysts and mechanistic studies using advanced characterisation techniques (**Box 4**, e.g., STEM, SEM, XPS, operando XAS, and synchrotron-based Mössbauer spectroscopy - supported by EPSRC collaboration grant obtained by Dr. Qun Cao with Prof. Jianguo Wang and Prof. Yanqiang Huang at Zhejiang University of Technology (ZJUT) and Dalian Institute of Chemical Physics (DICP).

Project Overview (Maximum 350 words)



In recent years, a new class of heterogeneous catalysts, namely single-atom catalysts (SACs), are emerging as a new frontier in catalysis science. With the active metal centre of the catalyst exists as isolated single atoms, SACs can serve as a bridge between homogeneous and heterogeneous catalysts with the possibility of integrating the merits of both types of catalysts such as high activity, selectivity, stability and reusability.[1] Heteteroatom (e.g., N, O, P and S) doped carbon-based materials are the most frequently used support materials for SACs. and can be used to coordinate to transition metals (M) to form uniform MN_x centre (x = 2-6, controlled by precursors, metal loadings and pyrolysis temperature) (**Box 1**).[2] These well-defined MN_x structures provide SACs with promising properties that can mimic homogeneous catalysts (e.g., metal complexes of bipy, terpy and phen) for fine chemical organic synthesis.[2]



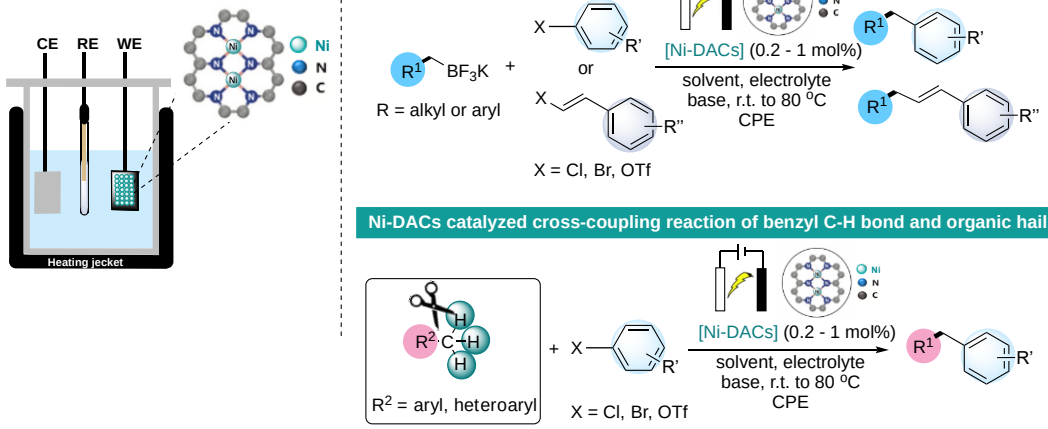
More recently, advancedments highlight that the incorporation of adjacent single-atom sites, termed diatomic catalysts (DACs), can enable synergistic effects and lead excellent catalytic activity in the field of energy-related transformations for small molecular activation (e.g., hydrogen evolution, oxygen evolution, CO_2 reduction).[3]

In the context of fine chemical synthesis, DACs as catalysts has been underexplored, warranting further investigation to unlock their potential in this domain. Indeed, only recently Cu-DACs was reported to show exceptional performance for C-N cross-coupling reactions (**Box 2**),[4] underscores the timeliness and significance of the proposed research endeavour.

In this project, we will investigate the new synthetic approach for manufacturing diatomic catalysts and exploit their inherent properties to revolutionise fine chemical synthesis by creating completely new electrocatalytic heterogeneous carbon-carbon bond cross-coupling strategies as proof-of-concept examples. This project is highly interdisciplinary and at the intersection of cutting-edge organic synthesis, electrochemistry, and state-of-the-art heterogeneous catalysis. Success in the area will bring both economic and environmental benefits and enable the manufacture of fine chemicals, for the first time, via electrocatalytic heterogeneous C-C couplings using DACs. The understanding of catalytic mechanisms will enable the design of new DACs systems for other organic synthesis systems, electrochemical H_2O_2 synthesis, reverse hydrogen storage.

Box 3

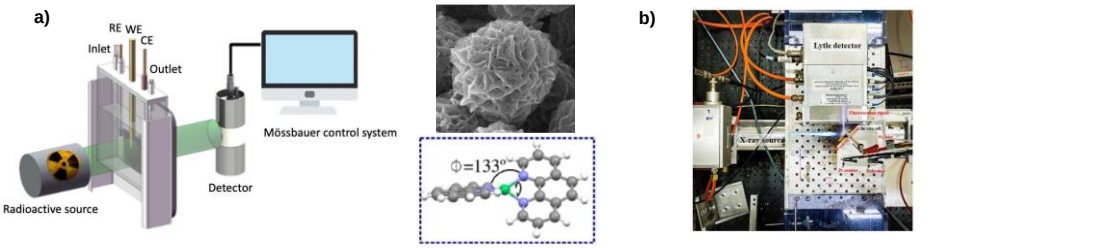
Ni-DACs catalyzed cross-coupling reaction of alkyl trifluoroborate and organic hailides



Ni-DACs catalyzed cross-coupling reaction of benzyl C-H bond and organic hailides

Box 4

***In situ* operando Mössbauer and XAF analysis for electrocatalysis with SACs by Prof. Huang (collaborator at DICP)**



J. Am. Chem. Soc. 2022, 144, 47, 21741–21750

Huang and co-workers, *Nat Energy*, 2018, 3, 140–147

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(1) A. Wang, et.al., *Nature Reviews Chemistry*, 2018, **2**, 65–81. **(2)** Z. Song, et.al., *Adv Energy Mater*, 2020, **10**, 2001561. **(3)** a) S. Zhang et. al., *Nat. Commun.*, 2023, **14**, 3634; b) A. Kumar et.al., *Nat. Commun.*, 2021, **12**, 6766; c) J. Jiao et.al., *Nat. Chem.*, 2019, **11**, 222–228; d) Y. Panet.al., *Matter*, 2020, **2**, 78–110. **(4)** X. Hai et.al., *Nature*, 2023, **622**, 754–760. **(5)** Y.-X. Zhang et. al., *J. Am. Chem. Soc.*, 2023, **145**, 4819–4827. **(6)** L. Han et.al., *Sci. Adv.*, 2022, **8**, eabm3779.

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7. Titanocene Catalysts for Improved Electrochemical Kinetics of Li-S Batteries

Dr. Sandy Kilpatrick – sandy.kilpatrick@leicester.ac.uk

Project Title	**Titanocene catalysts for improved electrochemical kinetics of Li–S batteries**	
Project Highlights:	1.	Synthesis of titanocene catalysts and application as redox mediators in electrolyte solutions.
	2.	Li–S battery development and electrochemistry.
	3.	Advanced characterisation before/after battery cycling and under *in situ* conditions, e.g. by SEM, EXAFS, SSNMR, XRD analysis.

Project Overview (Maximum 350 words)

Lithium–sulfur batteries (LiSBs) are considered as a game-changing technology to meet the demand for safe and high-performance energy storage systems for the next generation. LiSBs work on the principles of electrochemical redox reactions ($S + 2Li \rightarrow Li_2S$) and possess an incredibly high energy density (2600 Wh kg^{-1}), theoretical capacity (1675 mAh g^{-1}), lower cost, and low environmental impact. However, commercialisation of LiSBs is hindered by major scientific hurdles such as the dissolution of higher-order polysulfides into the electrolyte, and sluggish electrochemical kinetics of the battery chemistry.

A recent computational study revealed that metallocenes based on titanium – titanocenes ($TiCp_2$) – show high promise as functional additives to suppress the shuttle effect and enhance the electrochemical performance of LiSBs. However, these theoretical predictions have yet to be experimentally realised.

This PhD project strongly aligns with the 'Smart Chemical Engineering' theme, combining organometallic synthesis, battery assembly, and advanced characterisation techniques. Titanocenes will be applied for the first time as novel electrolyte additives, spanning across 3 objectives (Fig. 1):

(I) Titanocene complexes will be synthesised using air-free techniques (Schlenk-line and glovebox) and fully characterised (e.g. NMR spectroscopic and X-ray diffraction analysis), in Dr Kilpatrick's laboratory within the *Sustainable Synthesis and Catalysis* group in the School of Chemistry.

(II) Electrochemical properties and battery performance will be tested at the *Centre for Sustainable Materials Processing,* employing ultra-high sulfur content cathodes and the novel synthesised titanocene complexes as a redox mediators in the electrolyte.

(III) Materials will be characterised using scanning electron microscopy (SEM) before/after battery cycling and under operational conditions using X-ray absorption near-edge structure (EXAFS), solid state NMR (SSNMR), and *in situ* XRD at national facilities.

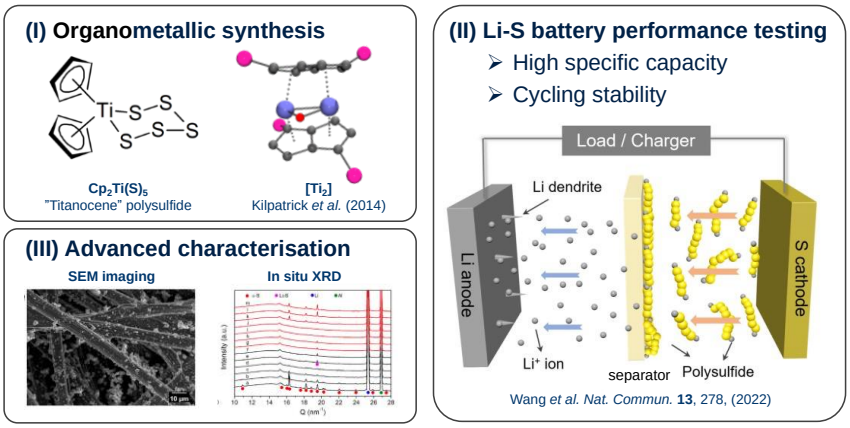
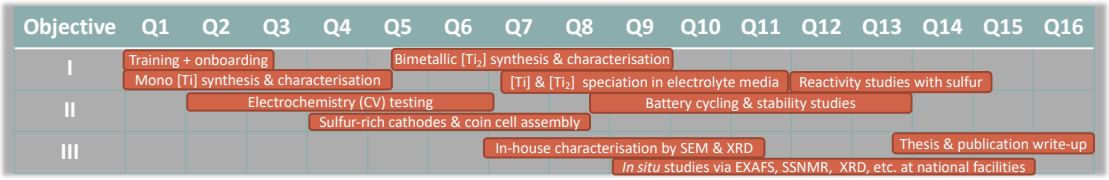


Figure 1 Outline of the scientific objectives and technical skills to be gained from the project.

Training will be provided at the beginning of the project to help the student start these investigations, and strong support and mentorship will be provided by the supervisory team throughout the 4-year project (Scheme 1).



Scheme 1 Timeline and objectives.

Building on Kilpatrick *et al.*'s report of a di-titanium "double-sandwich" which shows reactivity with sulfur relevant to LiSBs, this PhD project will harness the potential of titanocene catalysts for 'Smart Chemical Engineering', in applications as redox mediators for the first time.

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8. Lanthanide-based anti-breast cancer stem cell agents

Dr. Fabrizio Ortu – Fabrizio.ortu@leicester.ac.uk

Project Title	**Lanthanide-based anti-breast cancer stem cell agents**	
Project Highlights:	1.	Application of lanthanide metals in chemical biology
	2.	First application of lanthanide metals as anti-cancer agents
	3.	Strong training within world-leading groups in inorganic chemistry and chemical biology

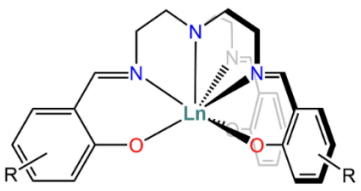
Project Overview (Maximum 350 words)

Background

The chemistry of lanthanide metals has attracted significant attention over the last 50 years, owing to the numerous applications based on their remarkable physicochemical properties.[1] Of particular interest are the applications as contrast agents for medical imaging, laser technology and molecular magnetism. Nonetheless, their biological activity is not developed and lags behind that of transition metals. In recent years there has been a lot attention towards the development new metallo-pharmaceuticals for targeting Cancer Stem Cells (CSC).[2,3] These are a particular population of tumour cells that have the ability to self-renew, differentiate, and form metastatic tumours. Crucially, CSCs are responsible for recurrence of breast cancer, which is the most common cancer for women across the globe.[3]

The Project

Applications of lanthanides in chemical biology are hugely limited by their complex coordination chemistry, especially in aqueous media. Additionally, lanthanide metals have never been tested for their toxicity against CSCs, which provides a great opportunity for breaking open this research field. The aim of this project will be to synthesise a new family of Ln metals complexes supported by Schiff-base tripodal ligands known as 'Tresal',[4] based on a tris(2-aminoethyl)amine scaffold, and characterise in detail their physicochemical properties *e.g.* X-ray studies, NMR spectroscopy, mass spectrometry, magnetism (SQUID, EPR), and photoluminescence. We will develop a rigorous structure/function relationship for these new compounds, exploiting that highly tuneability of the ligand scaffold which enables numerous possibilities in terms of lipophilicity and steric hindrance around the metal centre. These compounds will then be tested for their toxicity against breast CSCs and will provide the very first examples of this application for any Ln metal.



Ln = La-Yb
R = halide, alkyl

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2. J. Northcote-Smith, K. Suntharalingam, *Curr. Opin. Chem. Bio.*, **2023**, *72*, 102237.
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9. Smart Manganese Catalysts for Privileged Bioactive Molecules

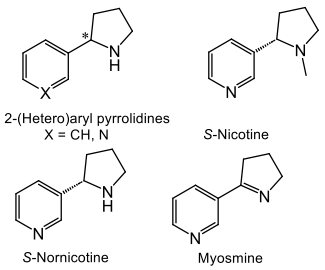
Dr. Greg Solan – gas8@leicester.ac.uk

Project Title	**Smart Manganese Catalysts for Privileged Bioactive Molecules**	
Project Highlights:	1.	To exploit the earth abundance, cost effectiveness and health benefits of manganese in catalyst design
	2.	To employ inventive strategies to produce chiral manganese catalysts
	3.	To apply these catalysts to the synthesis of chiral 2-(hetero)aryl pyrrolidines: species ubiquitous in alkaloid natural products, bioactive molecules and pharmaceuticals.

Project Overview (Maximum 350 words)

Introduction

Optically active 2-(hetero)aryl pyrrolidines represent prominent structural motifs that feature extensively in bioactive molecules, alkaloid natural products and pharmaceuticals. Of particular note, *S*-nicotine extracted from tobacco, is one of the most important bioactive natural products with an approximate current usage that exceeds one thousand tons per year. As a consequence of the medicinal potential of nicotine and related alkaloids (*e.g.*, treating Parkinson's disease, dementia and depression), considerable effort has been spent in the development of effective routes to chiral precursors that can be utilised to synthesise them. With respect to *S*-nornicotine, several strategies have been reported for its asymmetric synthesis. However, these methods are often complicated by the need for multiple steps and/or the reliance on expensive catalysts and starting materials. By contrast, a more attractive and direct approach involves the asymmetric hydrogenation (AH) of 2-(3-pyridyl)pyrroline (myosmine), with hydrogen gas (or other hydrogen sources), owing to the availability of the precursor and the inherent process economy. Nonetheless, to date this particular transformation has proved problematic to achieve since the precious metal catalysts employed (typically iridium-based) have a tendency to undergo deactivation on account of the coordination ability of the pyridine moiety in the substrate.



In this programme, we turn our attention to using catalysts based on the first-row transition metal, manganese, since it is not only earth abundant but is also advantageous from an economic and health standpoint. Moreover, recent research by our group and others has shown that precisely designed chelating ligands can activate Mn(I) complexes towards AH reactions with catalytic turnover frequencies that can rival or even outstrip that of the precious metal catalysts, while allowing appreciable functional group tolerance (including to *pyridyl groups*). Hence, this project will build on our rich experience in this area by designing chiral manganese catalysts that can facilitate not only the direct conversion of myosmine to *S*-nornicotine, but also the AH of various substituted (hetero)aryl cyclic *N*-alkyl imines.

Project outline

This PhD project will be focused on:

i) the synthesis of a family of well-defined chiral manganese catalysts [1st/2nd year], and

ii) the application of these chiral manganese catalysts to the asymmetric hydrogenation of a range (hetero)aryl-appended cyclic *N*-alkyl imines [2nd/3rd year].

To explore the impact of the chiral chelating ligand on the effectiveness of the manganese catalyst to impart enantiocontrol, we aim to synthesise a range of chiral chelating ligand frames differing in their steric and electronic profile. Following coordination to manganese, these complexes will be assessed

initially for the AH of myosmine to *S*-nornicotine. The degree of enantioinduction and conversion will then be used to inform the subsequent ligand design. A full suite of routine spectroscopic techniques will be used to characterise the manganese catalysts as well as the chiral amine products including chiral HPLC.

In short, this cross-disciplinary programme (inorganic-organic-pharmaceutical) will see the development of a new family of inexpensive and 'smart' chiral manganese catalysts that can mediate the formation of chiral α-(hetero)aryl pyrrolidines. There will be opportunities to cultivate industrial partners that will be actively pursued.

Key references: *Mn-Catalysed (De-)Hydrogenation*	[1] Solan *et al*., Manganese(I)- catalyzed asymmetric (transfer) hydrogenation of ketones: An insight into the effect of chiral *PNN* and *NN* ligands*. J. Catal.* 2023, **418**, 40. [2] Solan *et al*., Organometallic Mn(I) Complexes in Asymmetric Catalytic (Transfer) Hydrogenation and Related Transformations, *ChemCatChem* 2024, **16**, e202301567. [3] Solan *et al*., Asymmetric Transfer Hydrogenation of Ketones Improved by *PNN*–Manganese Complexes, *J. Org. Chem.* 2024, **89**(17), 12318. [4] Solan *et al*., Dehydrogenation of primary alcohols to carboxylic acids in water catalyzed by PN_HN-manganese(I) carbonyl complexes. *J. Catal.* 2024, **436**, 115601. [5] Solan *et al*., Robust and efficient transfer hydrogenation of carbonyl compounds catalyzed by *NN*-Mn(I) complexes. *Dalton Trans.* 2023, **52**, 10574.

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Physical Chemistry

10. Understanding how nature uses heme iron: learning new chemical tricks from old proteins

Dr. Phil Ash – philip.ash@leicester.ac.uk

Project Title	**Understanding how nature uses heme iron: learning new chemical tricks from old proteins**	
Project Highlights:	1.	Ultrafast spectroscopy
	2.	Protein chemistry
	3.	Use of international facilities

Project Overview (Maximum 350 words)

Redox properties of metal-containing proteins are critically important to many (bio)catalytic processes. One third of all known proteins contain a redox-active metal, and almost one quarter of all protein structures that have been reported contain a transition metal. Metal-containing proteins capable of extracting energy from H_2 gas, capturing CO_2 from the atmosphere, or performing complex oxygenation reactions, rely upon the ability to stabilise and control a range of unusual metal oxidation states in an aqueous environment. This crucial chemistry occurs at extremely fast rates, and relies on specific movements of the protein structure (protein dynamics) that cannot be studied using conventional structural methods. Understanding how these fast dynamics combine with fundamental transition metal chemistry is a major challenge. Addressing this challenge will enable the production of more efficient catalysts for 'green' energy, better drug molecules, and a more complete understanding of the natural world.

This project aims to investigate the catalytic mechanisms and structural dynamics of iron-containing heme proteins that are vital for life on Earth. State-of-the-art X-ray and laser spectroscopic and structural studies will be combined with computational analysis to reveal critical but elusive transient intermediates. This goal will be achieved by studying protein reactions in real time on ultrafast timescales. The outcomes of this project will provide a step change in our understanding of the mechanism of heme proteins, and will reveal key structural details that explain how biology is able to use the same heme iron complex to carry out a wide range of diverse chemistry.

The successful PhD student will gain a broad range of interdisciplinary skills in laser spectroscopy, electrochemistry, chemical biology, structural biology, and biophysics whilst addressing critical questions about how nature achieves efficient chemical control.

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11. Engineered Nanoparticle-Polymer Interfaces: Sustainable Catalysts for Environmental Remediation and Clean Energy

Prof. Andrew Ellis – andrew.ellis@leicester.ac.uk

Project Title	**Engineered Nanoparticle-Polymer Interfaces: Sustainable Catalysts for Environmental Remediation and Clean Energy**	
Project Highlights:	1.	Novel surface engineering technique for controlling nanoparticle-polymer interfaces for advanced materials and catalysis applications
	2.	Cutting-edge research combining materials science, nanotechnology, and catalysis, with potential for high-impact publications
	3.	Interdisciplinary training in advanced materials characterization and catalysis, preparing students for leading roles in academia or industry

Project Overview (Maximum 350 words)

Surface processing of polymeric materials with nanoparticles has emerged as a powerful approach to enhance material properties, offering unprecedented control over surface characteristics at the nanoscale. This technique holds immense potential across diverse fields, including catalysis, electronics, energy conversion, and environmental remediation. By modifying surfaces with nanoparticles, researchers can impart novel functionalities such as improved catalytic activity, enhanced optical properties, and superior chemical resistance, while maintaining the bulk properties of the underlying material. At Leicester, we have made significant progress in addressing a fundamental challenge in this field: the uniform dispersion of nanoparticles on plastic surfaces. This breakthrough opens up new possibilities for modifying plastic surfaces with a wide range of functional nanoparticles.

Building on this foundation, this PhD project aims to expand the applicability of our technique and explore its potential in heterogeneous catalysis. The research has two primary objectives:

1. Extend the technique to a diverse range of nanoparticle-polymer systems. This will involve systematically investigating various nanoparticle types (including metal oxides, noble metals, and composite nanostructures) in combination with different polymer substrates (such as polyethylene, polypropylene, and engineering plastics). The goal is to optimize the dispersion process, application methods, and embedding parameters for each material combination, establishing a comprehensive framework for surface modification across different systems.
2. Explore the use of nanoparticle-modified plastic surfaces as recyclable and reusable substrates for heterogeneous catalysis. This novel approach combines the catalytic properties of nanoparticles with the practical benefits of plastic substrates, potentially revolutionizing fields such as environmental remediation, fine chemical synthesis, and energy conversion. The research will investigate the catalytic activity, selectivity, and stability of various nanoparticle-plastic systems under different reaction conditions, with a particular focus on their reusability and long-term performance.

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The project will employ advanced characterization techniques such as XPS, STEM, and AFM to understand nanoparticle-substrate interactions and their evolution during catalytic processes. Catalytic performance will be evaluated through model reactions, studying the influence of factors such as nanoparticle size, morphology, and surface density on catalytic efficiency.

This interdisciplinary research offers an excellent opportunity to contribute to cutting-edge developments in materials science, nanotechnology, and catalysis. The outcomes are expected to expand the fundamental understanding of nanoparticle-polymer interactions and lead to the development of novel, efficient, and sustainable catalytic systems, with potential for high-impact publications and patent applications.

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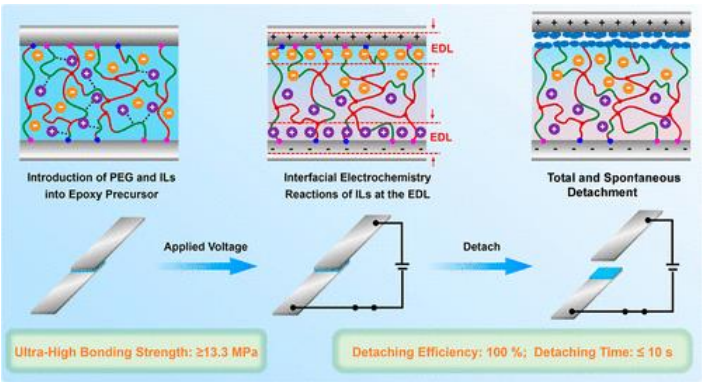
12. Electrochemical debonding of adhesives using novel deep eutectic solvents

Dr. Jake Yang – my216@leicester.ac.uk

Project Title	**Electrochemical debonding of adhesives using novel deep eutectic solvents**	
Project Highlights:	1.	Investigate the mechanism of adhesive failure at electrochemical interfaces
	2.	Formulation of deep eutectic solvents as additives for 'switchable' adhesive
	3.	Design adhesives with recycling applications in photovoltaics, EV batteries and aerospace

Project Overview (Maximum 350 words)

Adhesives with ultra-high bonding strength (>10MPa) have an estimated market value of £7.0 billion in 2020. In this proposed work the author aims to use electrochemistry as an external 'stimulant' to rapidly and selectively debond off-the-shelf adhesives which are otherwise designed to cure irreversibly.(1) The vision is to develop a new category of *'deep eutectic solvent*' infused adhesives which can detach from metal substrates at demand and when desired. This proposal is multidisciplinary, including methods of investigation including electroanalysis, the study of adhesive strength, polymer chemistry, and imaging of solid electrolyte interface. The vision is to understand the fundamental science behind electrochemical-induced adhesion failures from a bottom-up approach, providing key insight crucial to *design to recycle* complex components used in aerospace, automotive and electronics industries. Moreover, adhesives are widely used as composite binders in composite magnets and wind turbine blade fillers etc. However, because adhesive polymer chemistries are traditionally designed to bond irreversibly it renders a challenge to reuse, repair and recycling of end-of-life gadgets. The recyclability of technologically critical metals from end-of-life components play a critical role in achieving sustainability goals and a circular economy.



In 2022, Wei *et al.* have shown that electrochemistry can be used to detach epoxy-based, ionic-liquid-modified adhesives from aluminium subtracts (fig).(2) In their work, the epoxy-based adhesive was mixed with 10% [BMIM]BF_4 by weight to achieve 13MPa adhesion strength. By applying ca. 90V DC voltage across the two stainless steel substrates for tens of seconds, the electrolysis of the BMIM cation and BF_4^- anion produces H_2 and F_2 gases at the cathode and anode, respectively. Ionic liquids are, however, toxic and expensive which precludes the wider application of use at industrial scale.

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The key scientific questions this project aims to address are: 1) can deep eutectic solvents, which are environmentally friendly alternatives to ionic liquid and are cheaply available, be used to achieve adhesion failure? 2) if so, what is the mechanism of adhesive failure and can we use this technology to design *debondable adhesives* to use to recycle, for example, end-of-life composite supermagnets (wind turbines) and lithium-ion batteries (electric vehicles).

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2. M. Wu, S. Chen, Y. Mei, L. Liu, Y. Wei, Interfacial electrochemistry-induced detachable adhesives with ultra-high bonding strength and detaching efficiency. *ACS Applied Materials & Interfaces* **14**, 41456-41467 (2022).