Bern Summer internship projects 2024

Project 1

Non-covalent inhibitors of acid ceramidase

For several rare Lysosomal Storage Disorders, the accumulation of toxic molecules called lysoglycosphingolipids is the primary cause of the destructive symptoms observed. Inhibition of the enzyme that generates these toxic molecules shows promise as an exciting new therapy. Existing inhibitors covalently react with the enzyme, increasing the risk of off-target toxicity. We have recently discovered a first-in-class non-covalent inhibitor and are in the process of optimising this hit and would welcome a new member to the team to help in this exciting endeavor. Synthesis and biological evaluation will take place at the Medicines Discovery Institute.

Director: Dr D. Heulyn Jones, Dr Helen Waller-Evans

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Project 2

Small molecule inhibition of HS3ST1

The HS3ST1 protein is increasingly an attractive target, both for the treatment of a rare Lysosomal Storage Disorder and for Alzheimer's disease. To our knowledge, only one small molecule inhibitor of HS3ST1 exists. We have recently synthesised this molecule and shown it is likely a promiscuous covalent inhibitor. The project will focus on removing this reactivity whilst retaining the 3D shape of the molecule to maximise the chance of discovering the first-in-class non-covalent inhibitor of HS3ST1. Computational design, synthesis and biological evaluation will take place at the Medicines Discovery Institute.

Project 3

Preparing for the next pandemic: Creating lead candidates that target against inflammation-induced cytokine storm

COVID-19 has overwhelmed some of the best healthcare system worldwide because many patients needed to be admitted to the intensive care unit. While coronavirus is the causative agent, the intense illness is caused by the abrasive immune responses - collectively known as "cytokine storm." Our immune system normally battles against infections, but in many COVID patients they go rogue flooding the body with cytokines. When bound to their receptors, the cytokines induce a high level of inflammation, hence the severe illness and even deaths. To prepare ourselves for the next pandemic, this project aims to adapt critical Chemical Biology techniques including organic/peptide synthesis and computational biology - to create novel hyper-stable peptide ligands as potential lead candidates for cytokine storms. The PI has co-published two peer-reviewed articles with the previous IQS Barcelona student.

Director: Dr Louis Luk

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Project 4

Future Cancer Vaccine: Designing a new Inhibition Mechanism targeting Oncogenic Transcription Factor.

Many transcription factors are oncogenic because their dysregulation results in aberrant gene expression and unregulated cell growth/migration. However, TFs were viewed as "undruggable" due to their intractable binding pockets. In collaboration with Bath University, we will adapt a high-throughput screening technology, called Transcriptional Block Survival (TBS), to create engineered binders - that can mediate the addition of chemical tags to TF for their proteolytic degradation. Binders with such a bioconjugation capacity can propagate the TF degradation events and effectively inhibit gene expression, hence superior candidates for mRNA vaccine design. The student will modify binders available in the laboratory for the intended TF bioconjugation reactions.

Director: Dr Louis Luk

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Project 5

Total synthesis of dibutyroxynonane, the sex pheromone of the orange wheat blossom midge

A synthetic route will be developed using a ring-closing metathesis as a key step in this synthesis. After a batch synthesis, the protocol will be adapted to continuous flow chemistry. Expansion towards an enantioselective synthesis would allow the efficient use of the pheromone in commercial traps.

Director: Prof. Thomas Wirth

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Project 6

Flow electrochemical functionalisation of phosphine oxides

The recent revival of electrochemistry in synthesis is expanding the chemist's toolbox for mediating chemical reactions. It provides a clear route for sustainable chemistry where the precision to initiate and terminate redox processes by switching on and off the electricity is superior to classical synthesis allowing easier access to reactive intermediates and target molecules. We will exploit this by investigating a versatile functionalisation of phospine oxides, which has been recently discovered in our laboratories. We will extend the substrate scope and related mechanistic experiments will be conducted. In addition, the reduction of organopnictogen oxides in general and utilisation of automated synthesis systems based on electrochemical flow-reactors will expand existing methodologies and address current challenges in sustainable chemistry.

Directors: Prof. Rebecca Melen, Prof. Thomas Wirth

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Project 7

Mechanisms of protein folding: Removal of dynamical bottlenecks via data-driven discovery of collective variables

Molecular simulations are extensively used in chemistry, to elucidate details of molecular processes that are particularly difficult to access experimentally. Specifically, molecular dynamics has developed into a universal tool across the discipline spectrum, from biology, to materials to energy conversion applications. Several bottlenecks must nonetheless be removed to increase scope and impact of existing techniques. Deep learning is currently providing novel strategies.
Understanding how proteins fold is paramount not only for fundamental research, but specifically as part of a broad strategy of drug design. The use of techniques of molecular dynamics has enjoyed a formidable boost from so called coarse-grain techniques, which are designed to accelerate efficiency and extend applicability. Such techniques require the choice of specific criteria to distinguish between several states in the system, including folded and manifold unfolded states. How to best define these states is often a result of intuition using empirical descriptors. This is technically called "exploration of configuration space" and descriptors that allow to distinguish states are called "collective variables", CV. Using neural networks, functions that take atomic coordinates as arguments and map them into CVs can be learned from data resulting from simulations obtained from generically designed CVs. This project intends to setup automatic protocols of unsupervised CV learning, which can be used across several flavours of molecular dynamics techniques, with emphasis on biological processes, due to their complexity and inherent inefficiency.
Explore novel, original approaches to molecular dynamics simulations, using concepts of nonlinear neural networks. Understand how machine learning/AI is changing the scope and impact of molecular sciences.
Design, code and document a simulation driver, that takes simulation data as input and learn coarse-grain variables, which are problem specific but universal in their machine learning representation.

Director: Dr Stefano Leoni

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Project 8

Advancing New Strategies for Structure Determination of Organic Materials from Powder X-ray Diffraction Data

The aim of the research project is to determine crystal structures of organic materials directly from powder X-ray diffraction data, exploiting state-of-the-art data-analysis methodology that is being developed in the research group of Professor Harris. The specific materials to be investigated in the project will focus primarily on materials of pharmaceutical and biological relevance. In some cases, the structure determination protocols will also involve the analysis of three-dimensional electron diffraction (3D-ED) data for the material of interest, as well as consideration of structural insights derived from solid-state NMR data. The student will undergo several training courses during the early stages of the internship, including training in laboratory safety and training in the use of general laboratory instruments. The student will then be trained in the specific research skills required to carry out the assigned research project, specifically training in: (i) techniques for preparing high-quality powder samples for the materials of interest, (ii) the use of powder X-ray diffraction instrumentation for recording high-quality powder X-ray diffraction data, and (iii) computational techniques for analysis of

powder X-ray diffraction data and 3D-ED data. In addition, the student will receive training in the recording, organization, appraisal and presentation of scientific data, as required in order to be well-prepared for regular scientific discussions on the progress of the project and planning the next steps in the research.

Director: Prof Kenneth Harris

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Project 9

Sub-Nanometre Frontier of Chemistry

As the global population grows and the demand for energy and goods rises, the environment faces unprecedented challenges. Unlocking the potential of catalysis can revolutionise sustainability, and our project is at the forefront of this transformative journey. Unlike traditional metal catalysts, our focus is on the catalytic properties of extremely small, supported transition metal clusters, paving the way for unparalleled advancements. We are investigating the catalytic properties of sub-nanometer particles through cutting-edge computer simulation techniques, targeting processes that promote clean energy and sustainability. Join us in shaping a greener and more efficient tomorrow through the power of innovation and catalysis. Together, we can positively impact the planet and responsibly meet the demands of a growing world.

Director: Dr Alberto Roldan

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Project 10

Small molecules therapeutics for rare diseases.

Drug discovery research in rare diseases are becoming increasingly important because governments in USA, UK among other are changing their policy to tackle these diseases. In my laboratory we already discover few molecules that show potential affects in rare muscular disease GNE and ADSSL1 myopathies. In these projects the students will be able to synthesise carbohydrate based molecules and analyse them via multi nuclear 1D and 2D NMR, Mass spectrometry and HPLC. Computational ADME can also be performed to assess the drug-like behaviour of these new scaffolds.

Director: Dr. Fabrizio Pertusati

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Project 11

Fluorinated analogues of miltefosine as antiparasitic drug

Miltefosine is the only drug approved for the treatment of leishmaniasis in tropical region of the world but not in many other due to some side effects. The present project aims to design and synthesis new fluorinated derivative of miltefosine that would maintain the antiparasitic activity but present less side effects on human due to reduced similarity with endogenous lipid molecules. Students will be able to synthesise these molecules and analyse them via multi nuclear 1D and 2D NMR, Mass spectrometry and HPLC. Computational ADME can also be performed to assess the drug-like behaviour of these new scaffolds.

Director: Dr. Fabrizio Pertusati

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Project 12
Novel supramolecular photoswitches for all-organic pyroelectric energy harvesting

Solar energy is one of the world's most promising sources of alternative energy and it is both low-cost, clean and widely available. Pyroelectric and ferroelectric materials, such as hybrid halide perovskite crystals, are a new class of solar harvesting material that have been developed into next generation solar cell technologies. However, there remain limitations with these materials including questions over their long-term stability and concerns over the high content of toxic elements including Pb. As such, the search for new, lower-toxicity materials continues. Analogous, all-organic crystalline photoswitches can provide an alternative that offer improvements in other key properties such as solubility and processability. Several small organic photoswitches are known that excite readily in the solution state, but not in the constrained environment of a neat single crystal matrix, e.g. spirooxazine, spiropyrans, azobenzenes. The encapsulation of these switchable molecules into supramolecular architectures provides a route to develop all-organic solid-state light harvesting media, as their crystal structure can be engineered to allow photoswitching to proceed without compromising the integrity of the crystalline environment. The student will use a combination of crystal engineering and co-crystallization techniques to create novel supramolecular photoswitches, and will gain experience in analyzing their chemical, structural and photophysical properties. This will include training on the state-of-the-art in-situ photocrystallography equipment currently being developed within our group at Cardiff University.

Director: Dr Lauren E. Hatcher

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Project 13

Title: Materials design for heterogeneous catalysis using computational simulation

Topic: Catalysis is vital for addressing the UN sustainability goals and supporting actions to achieve a more sustainable, circular economy - catalysis can both lower energy consumption for existing processes, and be harnessed to produce more green energy. Designing new heterogeneous (solid) catalysts is challenging, as there are many ways to combine the elements of the periodic table, and so computational simulation is vital to progressing research activities in this domain. The aim of this research project is to determine active catalytic species for synthesis of renewable energy vectors, such as hydrogen, and to improve these catalysts through targeted materials design (e.g., introduction of new elements to change the reactivity). The activities will use state-of-the-art density functional theory to model the catalyst and reagents/products, looking at both the thermodynamics and kinetics of reaction processes, under appropriate operating conditions. The student will undergo training in computational simulation and development complementary skills in Python programming, which is a flexible and transferable skill with value across multiple sectors. The student will have a dedicated workspace within the Translational Research Hub, Cardiff University, and will be supported by the PI, Dr Andrew Logsdail, and the broader research team, through a mixture of group and 1-to-1 meetings; the student will also benefit from interaction with experimental collaborators at the Cardiff Catalysis Institute. The outcome will be a student with strong awareness of how computational simulation can dictate catalytic knowledge, an ability to relate this with experimental work, and confidence to design new and improved catalysts.

Director: Dr Andy Logsdail

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Project 14

In search of novel antibiotics to tackle antimicrobial resistance

The continuing rise of antimicrobial resistance has led to the failure of antibiotics to treat common infections. It has been estimated that if no concerted effort to discover and develop new antibiotics will be made by all countries, by 2050 the number of deaths per year due to antibiotic-resistant infections will reach 10,000,000 with an associated cost to the global economy of $1 trillion. In this project we aim to investigate small molecules that hit novel targets crucial for bacterial survival as lipoteichoic acid biosynthesis or cell division for the discovery of novel classes of broad-spectrum antimicrobials.

Director: Michaela Serpi

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