Unravelling the molecular mechanisms of Parkinson's disease and related synucleinopathies

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Protein misfolding and aggregation are common events in a wide variety of neurodegenerative disorders, such as Alzheimer's or Parkinson's disease (PD). Aging is the major known risk factor for the development of neurodegenerative diseases, but mutations in several genes are associated with familial forms. In PD, aggregation of alpha-synuclein (ASYN) in Lewy bodies and the loss of dopaminergic neurons from the substantia nigra, are typical pathological hallmarks. Our limited understanding of the molecular mechanisms underlying protein aggregation and neurodegeneration has complicated the development of novel therapeutic approaches. In our studies, we exploit different model organisms and employ diverse molecular approaches to unravel the molecular basis of neurodegenerative disorders. We are using novel cellular models where central aspects associated with ASYN dysfunction are recapitulated and we are now using powerful imaging approaches to investigate how different types of protein-protein interactions influence conformational changes in ASYN and how those relate to the initial oligomerization events associated with its toxicity. Altogether, our approaches will contribute for the development of novel strategies for therapeutic intervention in protein misfolding disorders.

Small molecules to interrogate and intervene in cellular redox

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Small molecules are widely used to sense and quantify species involved in redox biology. They can also deliver a reactive species to a specific site and so perturb the redox status. But which should you use and why? How can chemical reactivity and physicochemistry inform your choice? The lecture will explore the chemical design, advantages and limitations of strategies to localise small molecules to specific sites, focussing on mitochondrial delivery using triphenylphosphonium (TPP) cations (Figure 1). It will draw examples from our own work e.g. MitoCDNB [1] and MitoPerSulf [2]. It will distinguish between colocalization and delivery, and explain the design of control compounds. It will also highlight chemoselectivity in modifications and detection (e.g. octyl itaconate [3]), and the use of TPP as an MS tag for quantification (e.g. of endogenous thioester-based acylating agents [4]).

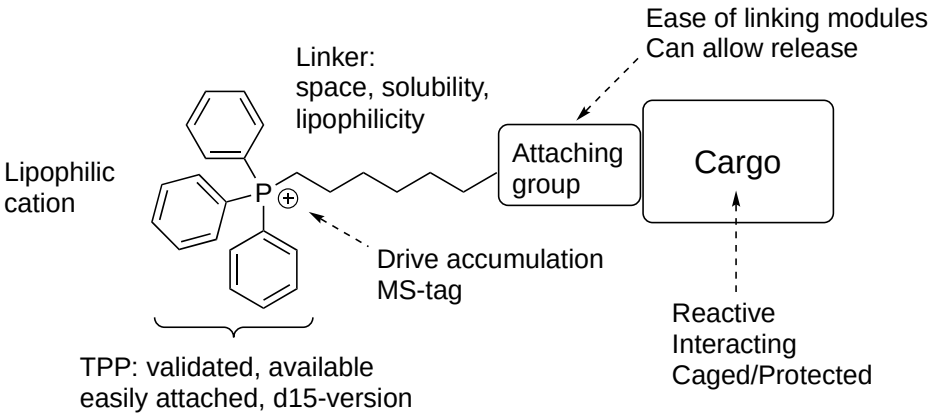

Figure 1. Generalised structure of a probe, sensor or drug targeted to the mitochondrial matrix by TPP

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Tackling health challenges with chemical tools: incursions into drug design and drug toxicity

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The focus of our research group lies on two major research areas: the design, synthesis and evaluation of new anticancer and antibacterial drugs, and the elucidation of mechanisms of toxicity associated with xenobiotic agents of therapeutic or environmental relevance. Recent examples from both approaches will be selected for presentation and discussion.
The combined use of *in silico* tools, chemical synthesis and proof-of-concept biochemical and biological testing will be presented to describe the targeting of epigenetic pathways with relevance to cancer initiation and progression, and of glycolysis enzymes overexpressed in cancer cells. Our advances in exploring the potential of small organic molecules in cancer immunotherapy and in tackling novel targets against methicillin-resistant *Staphyloccocus aureus* (MRSA) will also be discussed.
The use of mass spectrometry-based Omics approaches to elucidate systemic effects of drugs on major biochemical pathways will be addressed in the context of the proposed repurposing of the asthma drug montelukast.

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Synthesis of indolobenzoazepinone scaffolds as active epigenetic modulators: challenges and opportunities

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Paullones constitute an important class of compounds featuring a broad range of biological activities and notably antitumor action [1]. These molecules share a common indolobenzoazepinone scaffold, with variations in the substitution pattern. Due to the increasing importance of these compounds in medicinal chemistry, an efficient synthetic strategy for the preparation of this scaffold would be of high interest. Along these lines, we have recently reported the use of a Pd-driven cascade process that allows the regioselective preparation of benzofuran-, indole- and 1H-isochromen-1-imine-type derivatives through a heterocyclization-oxidative Heck cascade transformation [2]. The application of the intramolecular variant of this approach has also been applied to the preparation of differently substituted paullones featuring an exocyclic olefin at the C7 position of the benzazepinone ring. We propose the application of a one-pot protocol to efficiently prepare this scaffold from simple reactants, following a Sonogashira-heterocyclization-Heck coupling cascade process to obtain indolobenzoazepinones in a straightforward fashion.

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