BIOLOGICAL & MEDICINAL CHEMISTRY

BMCS Postgraduate Symposium XVII

Tuesday 9th January, 2024

The Medical Sciences Teaching Centre, Oxford University, Oxford

RSC INTEREST GROUP
BIOLOGICAL AND MEDICINAL CHEMISTRY SECTOR

#BMCSPostGrad24

Contents

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Programme

Tuesday 9th January

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9.40 Keynote lecture: Chemical Biology in Drug Discovery
David Hewings, Vertex, UK

10.10 Novel inhibitors of efflux pump NorA to target antimicrobial resistance
Janine Gray, Imperial College London, UK

10.30 Design and synthesis of novel allosteric modulators for the prostaglandin EP2 G protein-coupled receptor
Constance Dalton, University of Nottingham, UK

10.50 – 11.20 Refreshment break and exhibition

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11.20 Discovery of Hedgehog Acyltransferase Inhibitors to Target Hedgehog Signalling in Cancer
Efthymios S. Gavriil, Imperial College London, UK

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11.40 **FO01** Assessment of the Bioorthogonality of the Nitrile Imine 1,3-Dipole
***Mhairi Gibson**, University of Strathclyde, UK*
11.42 **FO02** Investigation of the central core of MEDS433: A Bioisosteric voyage into the Amide's Role
***Elena Martino**, University of Turin, Italy*
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***Daniel Webb**, University of Strathclyde, UK*
11.46 **FO04** Design, Synthesis and Pharmacological Testing of Novel Therapeutic Agents Designed to Enhance Insulin Secretion at the Trace Amine-associated Receptor 1
***Rhianna Lenham**, University of Nottingham, UK*
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***Elizabeth Bedwell**, University of Durham, UK*
11.50 **FO06** Discovery of PINK1 Activators as Treatments for Parkinson's Disease
***Arwa AlGhamdi**, University of Cardiff, UK*
11.52 **FO08** The Development of an on-DNA Micelle-Promoted Reductive Amination of DNA-Conjugated Amines to Access Previously Underexplored Peptidomimetics
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Programme

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***Sarah Phillips**, University of Cambridge, UK*
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***Ciyana James**, Queen's University Belfast, UK*
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***Michael Platt**, University of Oxford, UK*
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14.05 Synthesis of Novel Small Molecule Inhibitors for Snakebite Therapy
Nada Mosallam, University of Liverpool, UK

14.25 Identification Of Covalent Tools For Essential Leishmania Bromodomain LdBDF5
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14.45 – 15.05 Refreshment break and exhibition

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15.05 Structure-guided optimisation of N-hydroxythiazole-derived inhibitors of Factor Inhibiting Hypoxia-Inducible Factor-α
Thomas Corner, University of Oxford, UK

15.25 3-D Building Blocks: A Modular Synthetic Platform for Elaborating Fragments to 3-D Lead Compounds
Andres Gomez Angel, University of York, UK

15.45 Keynote lecture: Development of Selective, Brain Penetrant PI5P4Kg Inhibitors with Contrasting Binding Modes
Helen Boffey, University of Cambridge, UK

16.15 Closing remarks
John Skidmore, University of Cambridge, UK

16.25 Wine mixer & prizes

Programme

17.00 Meeting close

Chemical Biology in Drug Discovery

David Hewings

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David completed his MChem in Chemistry, MSc in Medicinal Chemistry for Cancer, and DPhil in Organic Chemistry (under the supervision of Prof. Stuart Conway) at the University of Oxford. He moved to the USA for postdoctoral research in Chemical Biology, first at Stanford University with Prof. Eric Kool, developing new techniques for the detection of nucleic acids, and then at Genentech. There, he worked on activity-based protein profiling (ABPP) of deubiquitinase enzymes. In 2018 he moved to Roche in Basel, Switzerland, as a Scientist in Medicinal Chemistry, and in 2020 returned to the UK, where he is currently a Principal Scientist at Vertex Pharmaceuticals. His work focuses on the application of Chemical Biology to drug discovery projects.

Chemical Biology, in its broadest sense, is the application of chemistry to improve our understanding of biology, but this gives little indication of what Chemical Biology can mean in practice in the context of drug discovery. I suggest that in a pharmaceutical setting, Chemical Biology encompasses both a set of challenges, such as assessing target engagement or developing hit finding strategies for previously-undruggable targets, and a set of techniques, such as chemical proteomics or induced proximity. New techniques, which contain chemistry at their core, are constantly expanding the range of challenges that Chemical Biology can help to tackle. I will present two case studies, one based on my postdoctoral research at Genentech, and another around the E3 ligase cereblon, which illustrate how chemical approaches can uncover new biology and how these new biological discoveries can in turn drive pharmaceutical innovation.

Novel inhibitors of efflux pump NorA to target antimicrobial resistance

J Gray[1], E Ledger[2], K Arvaniti[2], T Burden[1], T Lanyon-Hogg[3], J Riley[4], K Reed[4], I Gilbert[4], A Edwards[2], E Tate[1]

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The emergence of antimicrobial resistance (AMR) is a global health challenge expected to cause 10 million deaths per year by 2050, and the incidence of multidrug resistance has been accelerated by excessive prescription and misuse of existing antibiotics. This pressing problem is further exacerbated by a lack of financial incentives, and by regulatory barriers to novel antibiotic development. There is an urgent need for the development of novel antibiotics with a new mechanism of action to combat bacterial infections.

A key facet of AMR is driven by expression of efflux pumps which extrude drugs from the bacterium, preventing them from reaching their targets at a sufficient concentration to inhibit growth. This presentation details the identification of the first potent and druglike inhibitors of the Staphylococcus aureus NorA multidrug efflux pump in a novel high-throughput phenotypic screen. NorA was established as the cellular target through transposon mutagenesis and assays demonstrating inhibition of substrate efflux. Initial SAR exploration improved potency to low nanomolar concentrations in NorA EtBr efflux and synergistic antibiotic susceptibility assays. Pharmacokinetic studies in vitro and in vivo demonstrated that the novel lead series was suitable for testing in animal models. Subsequent in vivo experiments showed that the compounds were active in combination therapy with existing antibiotics in murine infection models.

Oral Speaker 10.30

Design and synthesis of novel allosteric modulators for the prostaglandin EP2 G protein-coupled receptor

C Dalton[1], C Laughton[1], N Holliday[2], S Mistry[1]

[1]School of Pharmacy, University of Nottingham, Nottingham, UK, [2]School of Life Sciences, University of Nottingham, Nottingham, UK

The prostagladin EP2 receptor (EP2) is a widely expressed G protein-coupled receptor activated endogenously by prostaglandin E2 (PGE2), which contributes to the development of chronic inflammation in cancer and has roles in diseases such as Parkinson's, endometriosis, arthritis and intercranial aneurysms etc. (Figure 1B).[1, 2] EP2 antagonism is considered a possible therapeutic approach to treat these diseases. Previously, numerous orthosteric antagonists (i.e. those that bind to the PGE2 binding site) have been synthesised.[1, 3] In 2020, "**Compound 1**" (Figure 1A) was reported as the first allosteric EP2 antagonist that demonstrates a reversible, agonist dependent mode of action.

As part of this communication we will report the synthetic route to "**Compound 1**" and our exploration of an expanded structure-activity-relationship dataset with modifications at the tetrahydrofuran moiety. Initial work identified two novel analogues of "**Compound 1**" displaying improved affinity for EP_2 compared to the literature compound whilst demonstrating an insurmountable mode of action indicitive of a negative allosteric modultor. Pharmacological characterisation was using conducted using both a NanoBRET competition binding study employing the G protein mimetic peptide TMR-Gαs19cha18 and a NanoBiT complementation assay with comparison against a known orthosteric antagonist. [3]

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2. X. Sun, L. Q., Prostaglandin EP2 receptor: Novel therapeutic target for human cancers (Review). *Int. J. Mol. Med.* **2018**, *42* (3), 1203-1214.
3. J. P. Farmer, S. N. Mistry, C. A. Laughton, N. D. Holliday, Development of fluorescent peptide G protein-coupled receptor activation biosensors for NanoBRET characterization of intracellular allosteric modulators. *FASEB J* **2022**, *36* (11), e22576.

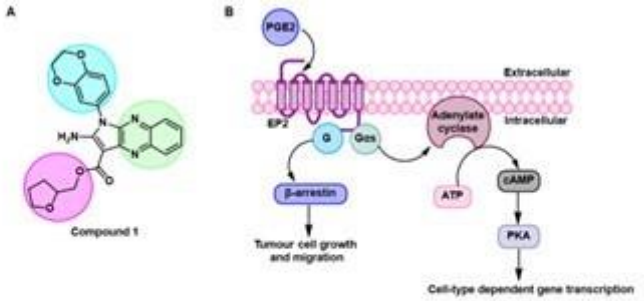


Figure 1. ***A.*** *Structure of "**Compound 1**" highlighting three regions of interest for structural modification; dioxane (blue- where most structural changes occurred in the literature), tetrahydrofuran (pink) and quinoxaline (green).* ***B.*** *PGE_2 binds and activates EP_2, $G_{\alpha s}$ -mediated induction of adenylate cyclase to increase cytoplasmic cAMP levels. Downstream events are then mediated through protein kinase A. EP_2 activation also induces ß-arrestin2 which is known to promote tumor cell growth and migration.*[1, 2]

Discovery of Hedgehog Acyltransferase Inhibitors to Target Hedgehog Signalling in Cancer

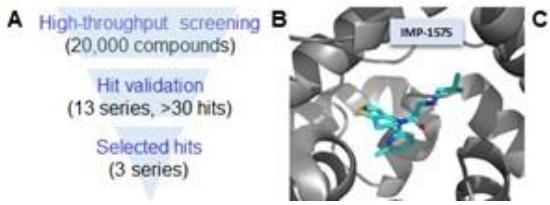
E Gavriil[1], Z Xiao[1], S Andrei[1], GL Senatla[1], A Chatwin[1], CE Coupland[2], P Kumar[2], L Carrique[2], S Afolaranmi[3], A Hayes[4]

[1]Department of Chemistry, Imperial College London, London, UK, [2]Division of Structural Biology, Wellcome Centre for Human Genetics, University of Oxford, Oxford, UK, [3]Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK, [4]Division of Cancer Therapeutics, Centre for Cancer Drug Discovery, The Institute of Cancer Research, London, UK, [5]Department of Pharmacology, University of Oxford, Oxford, UK, [6]National Heart and Lung Institute, Imperial College London, London, UK

The Hedgehog (HH) pathway is aberrantly activated in cancer and has an important role in cancer stem cell maintenance and in tumour-stroma crosstalk [1]. Hedgehog Acyltransferase (HHAT), a transmembrane protein at the endoplasmic reticulum, catalyses the palmitoylation of HH peptides (SHH, DHH, IHH), which is a critical step for their signalling activity [2]. HHAT has been identified as an interesting target in breast, lung, colon and pancreatic cancer [3-7]. Previously reported HHAT inhibitors are characterised by non-HH specific cytotoxicity [8] and high clearance [7]. We aim to discover potent, selective and *in vivo* active HHAT inhibitors, as a novel approach to target hedgehog signalling in cancer.

We have elucidated key structural details in the HHAT active site using photochemical probes [9] and Cryo-EM [10]. We have also developed a high-throughput biochemical assay, termed 'Acyl-cLIP' [11], and screened a library of 20,000 compounds against purified HHAT. Subsequent hit validation and selection provided three series for optimisation (Fig. 1A). Cryo-EM structure-based drug design (Fig. 1B) has guided hit optimisation, generating lead Compound A, a low nM HHAT inhibitor both in enzymatic and cellular assays. Compound A is also characterised by acceptable metabolic stability and excellent permeability (Fig. 1C). Furthermore, *in vivo* pharmacokinetic studies have shown that Compound A is orally bioavailable and achieves sufficient levels of free drug concentration (Fig. 1D). Therefore, Compound A is a suitable and unique chemical probe to validate the role of HHAT *in vivo* and target HH signalling in cancer models. Further optimisation of lead Compound A along with progression of additional hit series is ongoing.

References: [1] Cell Chem Biol 2017, 24, 252. [2] PLoS ONE 2015, 9, e89899. [3] Mol Cancer 2015, 14, 72. [4] Cancer Cell 2014, 25, 139. [5] Oncogene 2013, 32, 2335. [6] Cell Rep 2017, 21, 2813. [7] Oncogene 2015, 34, 263. [8] ACS Chem Biol 2016, 11, 3256. [9] Angew. Chem. Int. Ed. 2021, 60, 13542. [10] Mol Cell 2021, 81, 5025. [11] Chem Sci 2019, 10, 8995.



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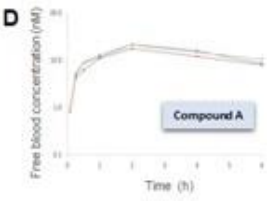
Cpd.	HHAT IC_{50} (μM)	CLint (μL/min/mg)
RUSKI-201	2.0	1822
IMP-1575	0.75	545
Compound A	0.024	36



Design and Synthesis of Metathesis-Stapled Peptides

Alison N. Hulme

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Stapled peptides, whereby cross-linking of two or more amino acid sidechains on an α-helical peptide is carried out via chemical synthesis, generally have a more compact structure, enhanced cell penetration, and are more resistant to proteolysis than their non-stapled counterparts.[1] Moreover, their metabolites are relatively safe, and recent studies suggest that stapled peptides offer an advantage over traditional drugs by averting the development of drug resistance. Hence stapled peptides have predictably sparked a growing interest from the scientific community since the early 2000s; with the first "all-hydrocarbon" metathesis-stapled peptides currently in late-stage clinical trials.

Stapled peptide sequences may be designed from natural peptide interaction sequences; by the excision of a helical fragment from a protein-protein interface (Figure 1a); through biological screening; and computationally.[1,2] Staples can be varied by sequence position, cross-linking chemistry, length of the tether and stereochemistry at the α-position (Figure 1b). Successful stapling is often indicated in the first instance by CD analysis, with a trend to higher peptide helicity upon stapling. We have shown that whilst α,α-disubstituted alanine derivatives are often used to promote helicity in metathesis-stapled peptides, their simpler (and more readily synthesized) mono-substituted counterparts can be equally as efficient.[2] Our recent work has focused on the development and application of add-on force fields for AMBER for the non-natural amino acids in stapled peptides.[3] These allow us to model stapled peptides with high efficiency and herald a new era in metathesis-stapled peptide design.

(a) (b)

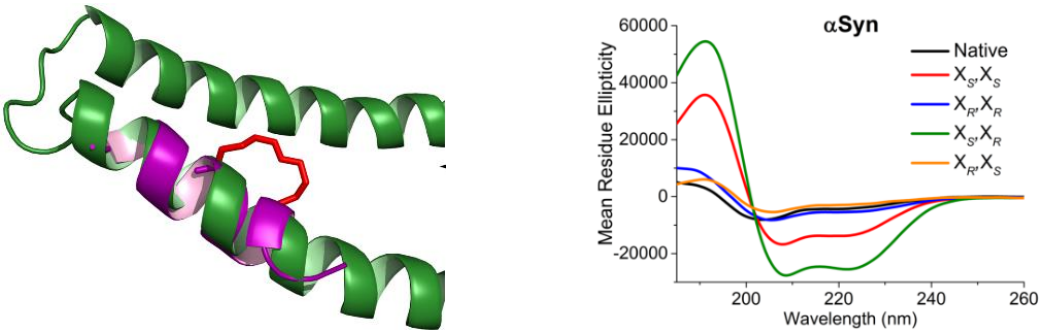

Figure 1. (a) Backbone alignment of an NMR refined solution structure of a metathesis-stapled α-helical segment (magenta) of α-Synuclein with the parent protein (green; PDB: 1XQ8). (b) Variation in helicity with α-position stereochemistry (X_S/X_R) in the metathesis-stapled peptide.[2]

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Oral Speaker 14.05

Synthesis of Novel Small Molecule Inhibitors for Snakebite Therapy

N Mosallam*[1], D Chong[1], R Gunasekar[1], N James[1], A Westhorpe[2], R Clare[2], S Hall[2], N Casewell[2], N Berry[1], P O'Neill[1]

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Snakebite envenoming is responsible for 81000-138000 deaths annually and 400000 cases of long-term morbidity, making snakebite the most lethal neglected tropical disease in the world. The only current treatment for snakebite is antivenom, which has various side effects; in addition to its administration in healthcare facilities only, which limits rapid treatment for rural communities. These factors highlight the need for novel snakebite treatments. An oral snakebite treatment would be ideal as a standalone therapy or to be given as a rapid pre-hospital treatment to neutralise the effects of snakebite envenoming. Although there are various toxins found in any specific snake venom, those encoded by the phospholipase A2 (PLA2), snake venom metalloproteinase (SVMP) are the most abundant ones across different snake species, which makes them attractive targets for snake venom treatment. This presentation will focus on SVMP small molecule inhibitors for snakebite treatment. Since SVMP shares structural similarities with human matrix metalloproteinase (MMP), we aim to repurpose existing MMP inhibitors for SVMP inhibition.

In our programme, we have successfully developed several scaffolds as SVMP inhibitors with optimum potency against five main snake venoms. Three series of SVMP inhibitors were developed. Thirty analogues were prepared in total with the majority of them displaying potent activity against SVMP and good *in vitro* drug metabolism and pharmacokinetic (DMPK) profiles. Molecular modelling has been used to define key binding interactions of homology and crystal structures of bound inhibitors enabling us to target molecules with selectivity against human MMP isoforms.

Five of the most potent derivatives with optimum DMPK profiles were tested for their *in vivo* pharmacokinetic properties and preliminary proof of concept *in vivo* experiments. Interestingly, three analogues displayed good oral bioavailability in mice, snake venom protection in a mouse model and modest half-lives which encouraged us to focus on these scaffolds for lead optimisation.

In conclusion, novel SVMP inhibitors have been developed with several analogues displaying good potency and pharmacokinetic properties. Further investigation is underway to improve molecule potency to develop a novel oral drug for SVMP inhibition to be used in combination with a PLA2 inhibitor as a new approach for snakebite therapy.

Oral Speaker 14.25

Identification Of Covalent Tools For Essential Leishmania Bromodomain LdBDF5

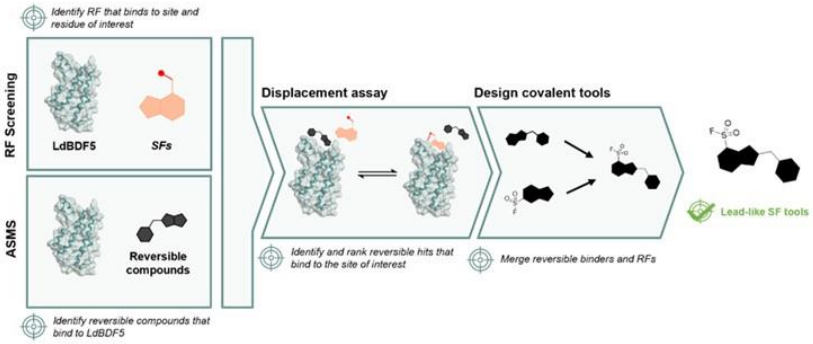
C Greenwood[1, 2], A Aatkar[1, 2], N Tomkinson[1], J Bush[2], E Grant[2]

[1]Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK, [2]Chemical Biology, GSK, Stevenage, UK

Parasitic infections cause a tremendous burden of disease in tropic and sub-tropic regions of the world. Visceral leishmaniasis(VL), the second largest parasitic killer in the world after malaria, is caused by *Leishmania donovani*, a human blood parasite transmitted by sandflies. Whilst treatments are available for VL, recent years have seen an emergence of parasite resistance to current therapies. Our work aims to identify novel inhibitors of essential Leishmania Donovani bromodomain factor 5 (LdBDF5). The essential nature of this protein results in a high resistance to mutations, key to prevent drug resistance. Identifying LdBDF5 inhibitors would therefore provide a novel method of treating VL.

Due to the key role bromodomains (BRDs) play in gene expression, LdBDF5 tools must be specific over human orthologs. To identify the most appropriate approach to target LdBDF5 with small molecules, crystal structures and protein sequences were examined. This study highlighted nucleophilic tyrosine residues unique to parasites that could be leveraged to gain selectivity over human BRDs. As such, it was believed that covalent inhibition *via* tyrosine targeting would be a valuable method to identify selective LdBDF5 inhibitors. A sulfonyl fluoride (SF) reactive fragment (RF) library was screened against human and parasite BRDs. Indeed, LdBDF5-selective SFs were identified, having modified the aforementioned tyrosine residues.

To rapidly identify chemical matter beyond a fragment space, libraries of drug-like reversible compounds were screened in an affinity selection-mass spectrometry (AS-MS) assay against LdBDF5 (Figure 1). The AS-MS assay identified a number of hits that bound reversibly to the protein, which were further assessed in a displacement assay to confirm site of binding (Figure 1). Finally, the most potent reversible binders and our hit SF fragments were merged to design two series of lead-like SFs. These demonstrated significant covalent modification and high binding efficiencies against LdBDF5. The results thus far have shown that a covalent strategy is suitable for selectively engaging parasite BRDs via the covalent modification of unique nucleophilic residues. Furthermore, an invaluable workflow was established, which through the rapid screening of covalent and reversible libraries and merging of the most potent hits, leads to the identification of potent lead-like SFs.



Structure-guided optimisation of *N*-hydroxythiazole-derived inhibitors of Factor Inhibiting Hypoxia-Inducible Factor-α

T Corner[1], R Teo[1], Y Wu[2], E Salah[1], Y Nakashima[3], G Fiorini[1], A Tumber[1], X Zhang[2], L Brewitz[1], CJ Schofield[1]

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The human 2-oxoglutarate (2OG)- and Fe(II)-dependent oxygenases factor inhibiting hypoxia-inducible factor-α (FIH) and HIF-α prolyl residue hydroxylases 1-3 (PHD1-3) regulate the response to hypoxia in humans via catalysing hydroxylation of the α-subunits of the hypoxia-inducible factors (HIFs). Small-molecule PHD inhibitors are used for anaemia treatment; by contrast, few selective inhibitors of FIH have been reported, despite their potential to regulate the hypoxic response, either alone or in combination with PHD inhibition.

We report molecular, biophysical, and cellular evidence that BNS, a reported *N*-hydroxythiazole-based PHD2 inhibitor, is, in fact, a broad spectrum 2OG oxygenase inhibitor, the inhibition potential of which can be tuned to achieve selective FIH inhibition. Structure-guided optimisation resulted in the discovery of *N*-hydroxythiazole derivatives that manifest efficient FIH inhibition (IC_{50} < 0.3 μM) and a substantially improved selectivity for FIH inhibition over PHD2 and other structurally-related 2OG oxygenases, including Jumonji-C domain-containing protein 5, aspartate/asparagine-β-hydroxylase and histone N^{ε}-lysine demethylase 4A.

The optimised *N*-hydroxythiazole-based FIH inhibitors modulate the expression of FIH-dependent HIF target genes and, consistent with reports that FIH regulates cellular metabolism, suppressed lipid accumulation in adipocyte cells. Crystallographic studies reveal that the *N*-hydroxythiazole derivatives compete with both 2OG and the HIF-α substrate for binding to the FIH active site. Given the modular structure and broad-spectrum 2OG oxygenase inhibitory activity of BNS, derivatisation of the *N*-hydroxythiazole scaffold has the potential to afford selective inhibitors for 2OG oxygenases other than FIH, which play important roles in fundamental pathophysioloigical process including epigenetic gene regulation, DNA/RNA damage repair and lipid metabolism.

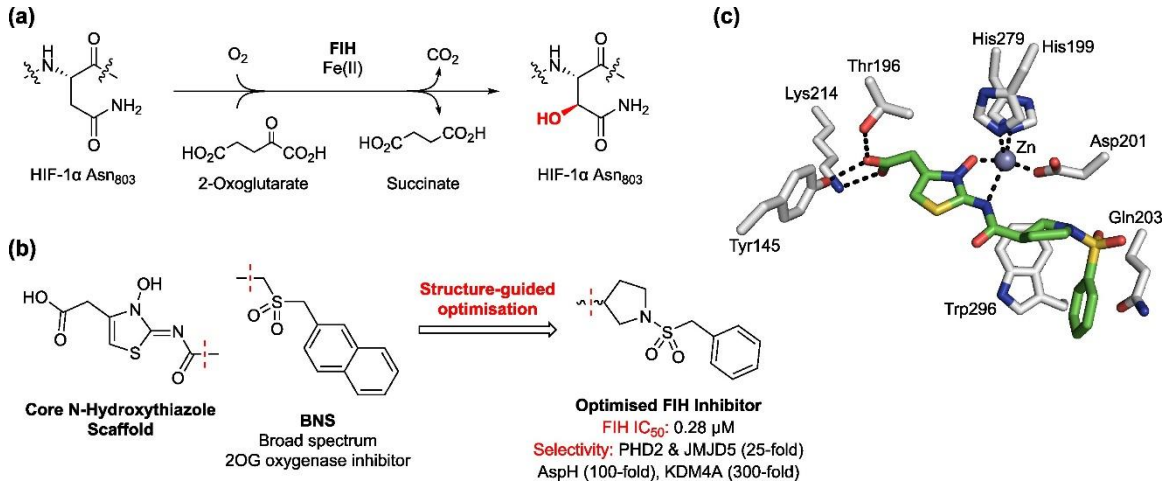


Figure 1. (A) FIH catalyses the C3 hydroxylation of Asn803 in HIF-1α. (B) Structure-guided optimisation afforded *N*-hydroxythiazole analogues that manifest efficient FIH inhibition and high levels of selectivity over structurally-related 2OG oxygenases. (C) Crystallographic studies reveal a 2OG- and substrate-competitive FIH binding mode.

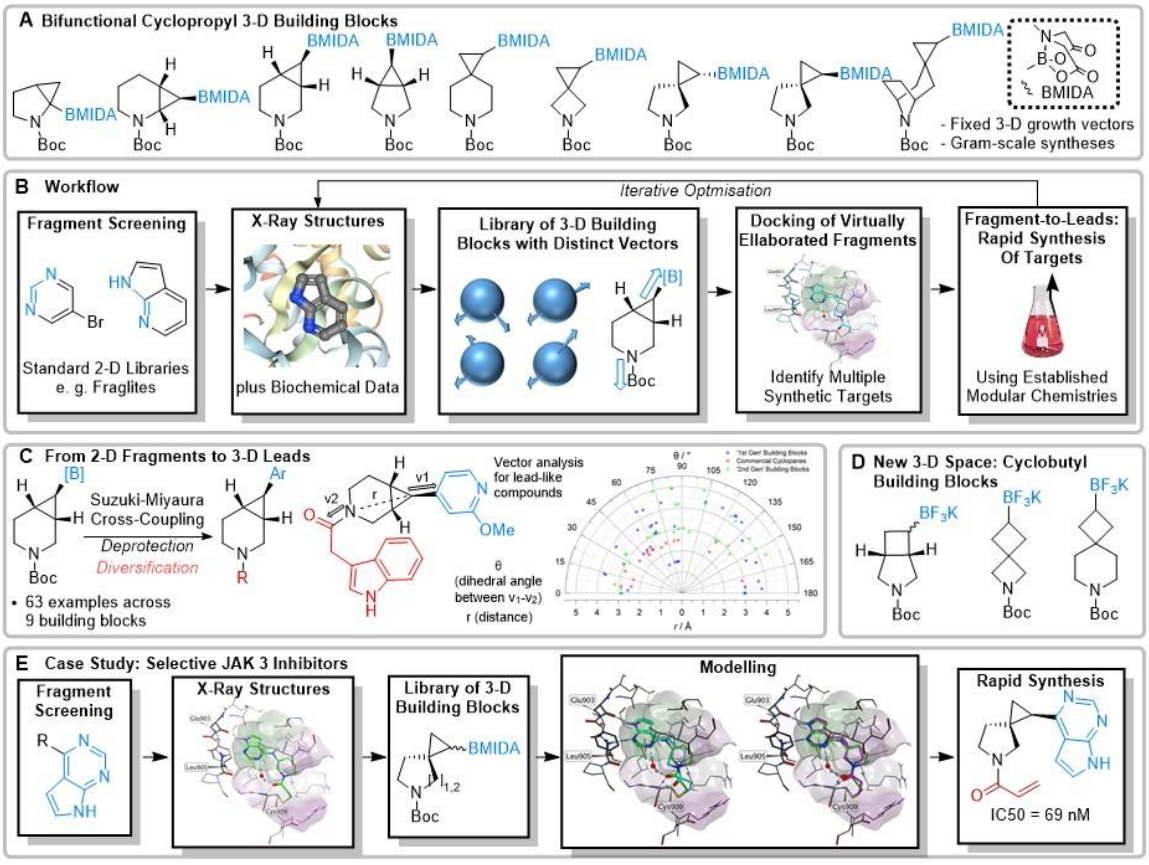
3-D Building Blocks: A Modular Synthetic Platform for Elaborating Fragments to 3-D Lead Compounds

Andres R Gomez-Angel[1], William T Butler[1], James R Donald[1], Hanna F Klein[1], Stephen Y Yao[1], Rebecca Appiani[1], James D Firth[1], Lucia Fusani[2], Simon C.C. Lucas[2], Peter O'Brien[1]

[1]Department of Chemistry, University of York, York,UK, [2]Hit Discovery, Discovery Sciences, Cambridge,UK

With the advent of Fragment Based Drug Discovery (FBDD) for the efficient sampling of chemical space, the overall rate of discovery of potential drug candidates starting from fragments has increased.[1] However, this increase has highlighted the need to further develop synthetic chemistry to support FBDD.[2] One of these needs is increasing the 3-D shape of potential drug candidates[3] and interest in 3-D shaped fragments has emerged.[4] Nonetheless, as current libraries possess many compounds with low 3-D shapes[5] and elaborating such compounds is challenging, we now present a new, modular approach for the conversion of 2-D fragments into 3-D lead-like compounds with potential for automation.

Our technology platform enables the rapid elaboration of 2-D fragments in three-dimensions. A series of bifunctional 3-D building blocks with defined elaboration vectors has been designed and synthesised (**A**, available from Key Organics). Making use of structural information acquired during standard FBDD campaigns, our technology platform allows for a computationally guided elaboration of fragments (**B**). Utilising the cyclopropyl MIDA boronate handle, elaboration with medicinally relevant aryl bromides via Suzuki-Miyaura cross-coupling can be achieved. Additionally, a variety of *N*-functionalisation reactions are demonstrated to give access to a series of lead-like compounds by the use of precedented pharmacophores (**C**)[6,7] – this provides access to a wide range of 3-D vector space. In order to expand this access a new series of cyclobutyl containing building blocks is also being investigated (**D**).Finally, the utility of our modular synthetic platform is further highlighted by the design and synthesis of selective JAK3 inhibitors utilising two of the designed 3-D building blocks (**E**). Full details will be presented.



Keynote Speaker 15.45

Development of Selective, Brain Penetrant Phosphatidylinositol 5-phosphate 4-kinase Gamma Inhibitors with Contrasting Binding Modes

Helen K. Boffey[a], Timothy P. C. Rooney[a], Henriette M. G. Willems[a], Simon Edwards[a], Greg G. Aldred, Christopher Green[a], Tina Howard[b], Derek Ogg[b], Tamara Romero[a], Duncan E. Scott[a], David Winpenny[a], James Duce[a], John Skidmore[a], Jonathan H. Clarke[a], and Stephen P. Andrews[a]

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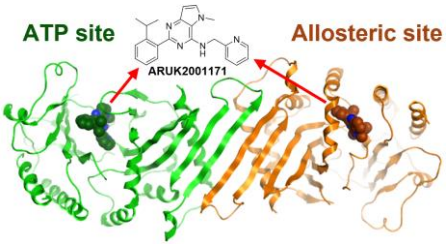
Phosphatidylinositol 5-phosphate 4-kinases (PI5P4Ks) are emerging as attractive therapeutic targets in diseases, such as cancer, immunological disorders, and neurodegeneration, owing to their central role in regulating cell signalling pathways that are either dysfunctional or can be modulated to promote cell survival. Different modes of binding may enhance inhibitor selectivity and reduce off-target effects in cells. By improving the physicochemical properties of the selective PI5P4Kγ inhibitor, NIH-12848[1], we have demonstrated that this chemotype engages PI5P4Kγ in intact cells and is selective over PI5P4Kα and PI5P4Kβ. Furthermore, the first X-ray structure of PI5P4Kγ bound to an inhibitor has been determined with this chemotype, confirming an allosteric binding mode (pdb: 7QIE). An exemplar from this chemical series (ARUK2001171) adopted two distinct modes of inhibition, including through binding to a putative lipid interaction site which is 18 Å from the ATP pocket[2].



In addition to this work, a virtual screening campaign using the PI5P4Kα isoform afforded tractable biochemical hit compounds for both PI5P4Kα[3] and PI5P4Kγ[4]. One series optimised towards PI5P4Kγ provided compounds with enhanced potency compared to ARUK2001171, isoform selectivity and favourable physicochemical properties. In contrast to ARUK2001171, an X-ray structure of a compound from this novel series (ARUK2001607) showed binding occurs exclusively in the ATP pocket of PI5P4Kγ. Significantly, these compounds demonstrate brain permeability in mice, and enabled the development of in vivo tool compounds for further evaluation of PI5P4Ks as a therapeutic target for neurodegenerative diseases.

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2. Boffey, H.K., Rooney, T. P. C., Willems, H. M. G., Edwards, S., Green, C., Howard, T., Ogg, D., Romero, T., Scott, D. E., Winpenny, D., Duce, J., Skidmore, J., Clarke, J. H., Andrews, S. P., Development of Selective Phosphatidylinositol 5-Phosphate 4-Kinase γ Inhibitors with a Non-ATP-competitive, Allosteric Binding Mode, *Journal of Medicinal Chemistry*, 2022, **65**, 3359-3370.

3. Willems, H. M. G., Edwards, S., Boffey, H.K., Chawner, S. J., Green, C., Romero, T., Winpenny, D., Duce, J., Skidmore, J., Clarke, J. H., Andrews, S. P., Identification of ARUK2002821 as an isoform-selective PI5P4Kα inhibitor, *RSC Medicinal Chemistry*, 2023, **14**, 934.

4. Rooney, T. P. C., Aldred, G. A., Boffey, H.K., Willems, H. M. G., Edwards, S., Chawner, S. J., Scott, D. E., Green, C., Winpenny, D., Skidmore, J., Clarke, J. H., Andrews, S. P., The Identification of Potent, Selective, and Brain Penetrant PI5P4Kγ Inhibitors as In Vivo-Ready Tool Molecules, *Journal of Medicinal Chemistry*, 2023, **66**, 804-821.

Poster Listing

No.	Title	Authors	Affiliations	Country
FO01 & P01	Assessment of the Bioorthogonality of the Nitrile Imine 1,3-Dipole	**M Gibson[1]**, C Jamieson[1], J Pettinger[2]	[1]Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK, [2]Chemical Biology, GlaxoSmithKline, Stevenage, UK	UK
FO02 & P02	Investigation of the central core of MEDS433: A Bioisosteric voyage into the Amide's Role	**E Martino[1]**, S Sainas[1], M Alberti[2], I Mannella[1], M Giorgis[1], P Circosta[3], D Boschi[1], ML Lolli[1]	1Department of Science and Drug Technology, University of Turin, Turin, Italy, 2Department of Science and Drug Technology, University of Oriental Piedmont, Novara, Italy, 3Molecular Biotechnology Center, University of Turin, Turin, Italy	Italy
FO03 & P03	Design, Synthesis, and In Vitro Characterisation of Activin Receptor-like Kinase 2 Degraders as a Novel Therapeutic Strategy Towards the Treatment of Diffuse Intrinsic Pontine Glioma	**Daniel Webb[1,2]**, William Esmieu[1], Katherine Jones[1], Ryan Tinson[1], Natsuko Macabuag[1], Ruzica Bago[1], Steve Clifton[1], Lampros Milanos[1], David Lindsay[2], William Kerr[2]	1Early Discovery, Charles River Laboratories, Saffron Walden, UK, 2Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK	UK
FO04 & P04	Design, Synthesis and Pharmacological Testing of Novel Therapeutic Agents Designed to Enhance Insulin Secretion at the Trace Amine-associated Receptor 1	**R Lenham**1,2, S Mistry1, C Laughton1, M Turner2	1School of Pharmacy, University of Nottingham, Nottingham, UK, 2School of Science and Technology, Nottingham Trent University, Nottingham, UK	UK
FO05 & P05	Vectorial Functionalisation of Pyrazolo[3,4-c]pyridines for Fragment-based Drug Discovery	**EV Bedwell**1, F Emery2, GC Clososki2, I Baxendale1, PG	[1]Department of Chemistry, Durham University, Durham, UK, [2]Faculdade de Ciencias Farmacéuticas, Universidade de São Paulo, Riberião Preto, SP, Brazil	

Poster Listing

FO06 & P06	Discovery of PINK1 Activators as Treatments for Parkinson's Disease	**A AlGhamdi**[1], O Lambourne[1], S Bell[2], L Wilhelm[3], E Yarbrough[4], G Holly[4], O Russell[2], I Ganley[3], M Goldbery[4], Y Mehellou	[1]School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, UK, [2]Wellcome Centre for Mitochondrial Research, Newcastle University, Tyne, UK, [3]MRC Protein Phosphorylation and Ubiquitylation Unit, University of Dundee, Dundee, UK, [4]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama, Birmingham, USA, [5]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama, Birmingham, USA, [6]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama, Birmingham, USA, [7]Wellcome Centre for Mitochondrial Research, Newcastle University, Tyne, UK, [8]MRC Protein Phosphorylation and Ubiquitylation Unit, University of Dundee, Dundee, UK, [9]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama, Birmingham , United States, [10]School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, UK	UK
FO08 & P08	The Development of an on-DNA Micelle-Promoted Reductive Amination of DNA-Conjugated Amines to Access Previously Underexplored Peptidomimetics	**M Anderson**, T Carton, M Waring	Department of Chemistry, Newcastle University, Newcastle upon Tyne, UK	UK
FO10 & P10	Development of Cleavable Linkers for Polymer-Drug Conjugates	**S Phillips1,** R Brewster2, R England2, M Park1, J Mandrup Kandemir1, D Spring1	1Yusuf Hamied Department of Chemistry, University of Cambridge, Cambridge, UK, 2AstraZeneca, Macclesfield, UK	UK
FO12 & P12	Targeting the cell-adhesion molecule PSGL-1 with a small molecule inhibitor	**C James1**, V Kanabar-Raivadera 2, CP Page2, L Martin1, GK Wagner1	1School of Pharmacy, Queen's University, Belfast, UK, 2School of Cancer and Pharmaceutical Sciences, King's College, London, UK	UK
FO16 & P16	The Development of 1,2,4-Triazine G-Protein Coupled Receptor 84 (GPR84) Antagonists	**Michael Malone1**, Graeme Milligan2, Andrew Jamieson1	1Chemistry, University of Glasgow, Glasgow,Scotland, 2Molecular Bioscience, University of Glasgow, Glasgow,Scotland	UK

Poster Listing

FO17 & P17	Discovery of Novel Small Molecules for the Treatment of Human Coronaviruses	**Elliott Smyth1,2**, Joao Pisco1, Nathalie Bouloc1, Jonathan Large1, Richard Foster2	1Chemical Biology, LifeArc, Stevenage,UK, 2School of Chemistry, University of Leeds, Leeds,UK	UK
FO18 & P18	Synthesis of Macrocyclic Ligands for the Bromodomain of CREBBP/p300	**Alistair Boyd1**, Mustafa Moroglu2, Stuart Conway3	1Organic Chemistry, University of Oxford, Oxford,UK, 2Medicinal Chemistry, GSK, Stevenage,UK, 3Chemistry, UCLA, Los Angeles, United States of America	UK
FO19 & P19	Bivalent chemical tools for investigating the tandem plant homeodomain finger-bromodomain cassette in TRIM24	**Michael Platt**, Stuart Conway	Department of Chemistry, University of Oxford, Oxford,UK	UK
FO20 & P20	Design, Synthesis, Biological Evaluation, and Molecular Modeling of Novel Benzofuran Derivatives as Targeted Cancer Chemotherapy	**A A. Osman 1,2,** E R. Mohamed 2, H A. Abdel-Aziz3, A M. El Kerdawy2,4, H Abdelrasheed Allam2	1Department of Pharmaceutical Chemistry, Faculty of Pharmacy, NewGiza University, Newgiza, Cairo 12256, Egypt, 2Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Cairo University, Cairo, P.O. Box 11562, Egypt, 3Applied Organic Chemistry Department, National Research Center, Dokki, Cairo 12622, Egypt, 4School of Pharmacy, College of Health and Science, University of Lincoln, Green Lane, Lincoln, Lincolnshire, UK	UK

Poster Abstracts

FO01 & P01 Assessment of the Bioorthogonality of the Nitrile Imine 1,3-Dipole

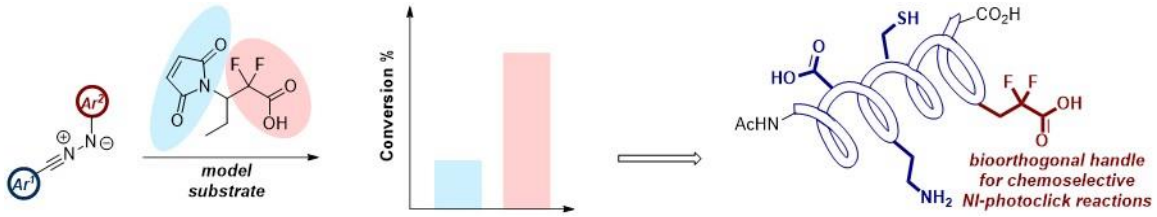
M Gibson[1], C Jamieson[1], J Pettinger[2]

[1]Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK, [2]Chemical Biology, GlaxoSmithKline, Stevenage, UK

The nitrile imine (NI) 1,3-dipole is a highly reactive and readily accessible synthetic intermediate generated via the photolysis of 2,5-disubstituted tetrazoles. Its ability to participate in 1,3-dipolar cycloadditions has enabled its application in a variety of synthetic methods. Of note, NIs have found application in medicinal chemistry, materials chemistry, and more recently, bioorthogonal chemistry. NI-mediated click reactions have recently found traction in bioorthogonal labelling techniques due to the light-activated, traceless nature of the system and the formation of stable, fluorescent adducts with biomolecules modified with an appropriate dipolarophile. While NIs are renowned for their proclivity towards cycloadditions, this species exhibits broad reactivity with a range of nucleophilic functionalities. Such functionalities are ubiquitous in biomolecules and therefore their promiscuous reactivity with the NI dipole may hinder its application as a true bioorthogonal labelling tool.

Previous work in our group has sought to explore the reactivity profile of the NI species through a series of competition experiments utilising a library of nucleophilic model substrates and dipolarophiles. Interestingly, the quantification of NI dipole reactivity with a range of carboxylic acid moieties revealed an enhancement in reactivity with decreasing pK_a of the acidic coupling partner. These findings have been expanded to assess the biorthogonality of the dipole through the competitive reaction of an electronically activated dipolarophile versus a highly acidic fluorinated carboxylic acid. A range of NI species were generated through photolysis of a 2,5-disubstituted tetrazole and their reactivity with a model substrate was quantified.

The selectivity observed demonstrated that NI reactivity can be tuned *via* modulation of the pK_a of an acidic coupling partner. The next phase of this work sought to exploit this observation by exemplifying the application of highly acidic carboxylic acid moieties as novel bioorthogonal handles for NI-mediated photoclick reactions. A suitable NI precursor has been identified which enhances chemoselectivity for the bioorthogonal handle, suppressing the reactivity of endogenous competing nucleophiles. Current work is ongoing to incorporate a selection of highly acidic bioorthogonal handles into model peptide sequences containing multiple nucleophilic amino acid residues, allowing the chemoselectivity of the NI with these novel bioorthogonal handles to be assessed.



Poster Abstracts

FO02 & P02 Investigation of the central core of MEDS433: A Bioisosteric voyage into the Amide's Role

E Martino[1], S Sainas[1], M Alberti[2], I Mannella[1], M Giorgis[1], P Circosta[3], D Boschi[1], ML Lolli[1]

[1]Department of Science and Drug Technology, University of Turin, Turin, Italy, [2]Department of Science and Drug Technology, University of Oriental Piedmont, Novara, Italy, [3]Molecular Biotechnology Center, University of Turin, Turin, Italy

Human Dihydroorotate Dehydrogenase (*h*DHODH) it's a key enzyme involved in the stereoselective oxidation of L-dihydroorotate (DHO) to orotate (ORO) in the *de novo* pyrimidine biosynthesis. Recent studies proved that inhibiting *h*DHODH constitutes a promising pharmacological strategy for treatment of hematological malignancies, such as acute myeloid leukemia (AML)[1,2], and viral pathologies [3,4].

In recent years, the MEDSynth research group has studies and designed a first generation of inhibitors based on hydroxypyrazolo[1,5-a]pyridine core scaffold, which acts as an unusual carboxylic acid bioisosters. The heterocycle is therefore linked to a biphenyl or diaryl ether via an amide linker [4].

Within the series, ***MEDS433*** emerged as the most promising compound, showing *in vitro* nanomolar activity against *h*DHODH and *in vivo* ability to achieve differentiation in AML cells. Currently, its development as a drug candidate is progressing through the pre-clinical phase for the treatment of AML. Despite its high potency, this lead compound suffers from poor solubility and optimization of its drug-like properties is necessary in order to perform further pre-clinical studies.

In this work, aiming to improve the solubility without losing in binding affinity, new analogues series was developed with the aim to study the role of the amide moiety through a bioisosterical approach. Theoretical design, synthesis and enzymatic assay are here presented and discussed.

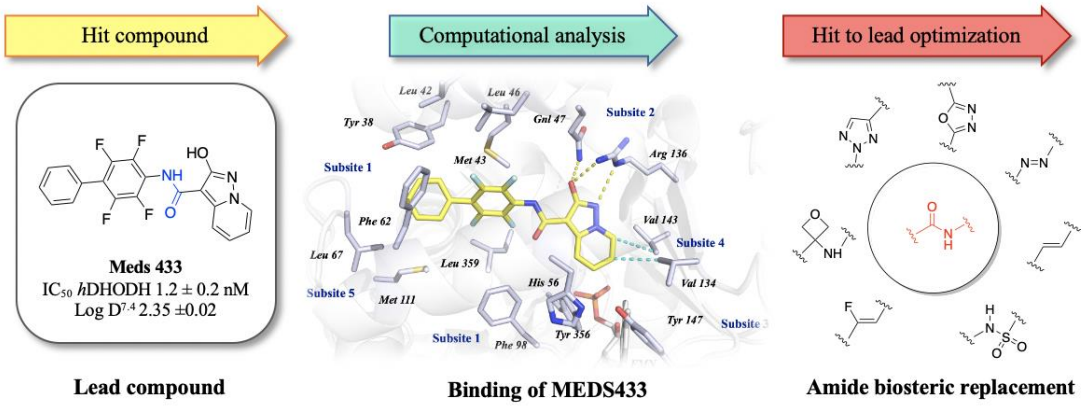


Figure 1: Hit to lead optimization of MEDS433 by bioisosteric approach.

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3. Dunn, M. C. C., Knight, D. A. & Waldman, W. J. *Antivir. Ther.* **2011,** *16*, 309–317.
4. Sainas, S. *et al.*, *J. Med. Chem.* **2018,** *61*, 6034–6055.

Poster Abstracts

FO03 & P03 Design, Synthesis, and *In Vitro* Characterisation of Activin Receptor-like Kinase 2 Degraders as a Novel Therapeutic Strategy Towards the Treatment of Diffuse Intrinsic Pontine Glioma.

Daniel Webb[1,2], William Esmieu[1], Katherine Jones[1], Ryan Tinson[1], Natsuko Macabuag[1], Ruzica Bago[1], Steve Clifton[1], Lampros Milanos[1], David Lindsay[2], William Kerr[2]

[1]Early Discovery, Charles River Laboratories, Saffron Walden, UK, [2]Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK

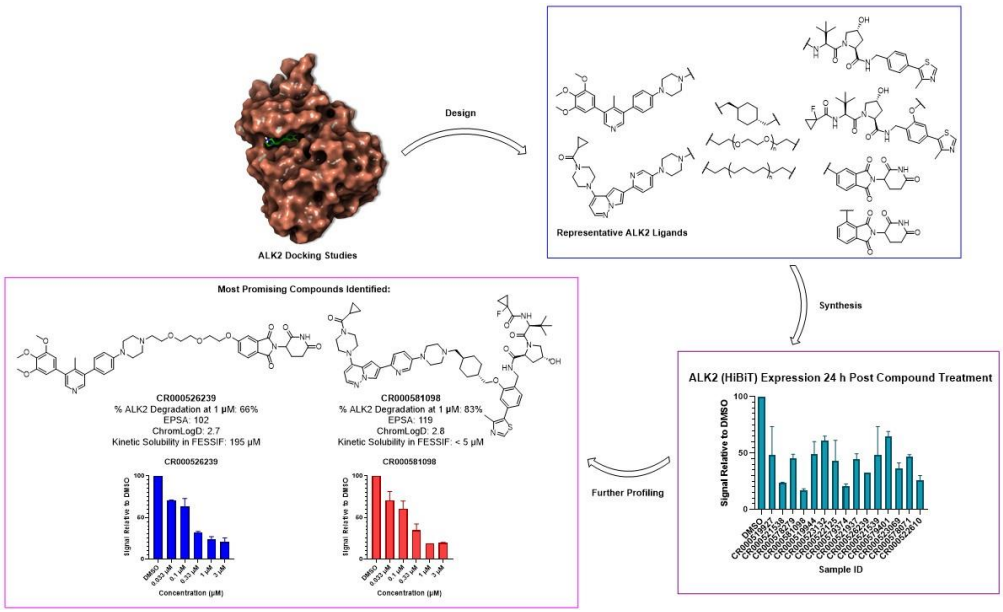
Diffuse Intrinsic Pontine Gliomas (DIPG) are grade IV tumours originating in the pons region of the brainstem. They account for 10–20% of all paediatric brain tumours and the median overall survival rate is 8–11 months after diagnosis.[1] Focal radiation therapy remains the only treatment option for DIPG patients and, to date, over 200 clinical trials using chemotherapeutic agents have failed to extend survival. Activin receptor-like kinase 2 (ALK2) has been identified as a potential target for therapeutic intervention in this disease, and several pre-clinical ALK2 inhibitors have been reported recently.[2,3] Herein, the design, synthesis, and biological evaluation of ALK2 proteolysis targeting chimeras (PROTACs) is explored as an alternative ALK2 targeting strategy.

The X-ray crystal structure of ALK2 bound to a small molecule inhibitor, LDN-212854, was used to dock ALK2 ligands across two distinct chemotypes, to identify suitable PROTAC-linker attachment points. A set of 15 ALK2 degraders was then designed, incorporating ligands for the E3 ligases, von Hippel-Lindau (VHL) and Cereblon (CRBN). Towards the synthesis of these targets, methods including high-throughput experimentation (HTE) were employed to optimise the efficiency of key chemical transformations. This initial set of compounds spanned a broad range of physicochemical property space, including a CLogD range of 1-6 and a TPSA range of 140-230. Western blot screening experiments were conducted to identify promising compounds that induced ALK2 degradation at a concentration of 1 µM, before profiling selected compounds further and demonstrating that our PROTACs induced ALK2 degradation in a dose-dependent manner. Chromatographic measures were used to experimentally measure the physicochemical properties of our degraders, EPSA and ChromLogD, and investigate how these values differed from the calculated properties, TPSA and CLogD. I*n vitro* ADME studies have been used to assess compound permeability, solubility, and metabolic stability, and to determine how these parameters are influenced by compound structure. Using the *in vitro* data obtained, a further iteration of compounds has been designed with the goal of improving potency and ADME properties. Synthesis and evaluation of these compounds is currently underway.

1. *J Korean Neurosurg Soc* **2018**, *61* (3), 343-351.

2. *Commun Biol* **2019**, *2*, 156.

3. *ACS Omega* **2021**, *6* (32), 20729-20734.



Poster Abstracts

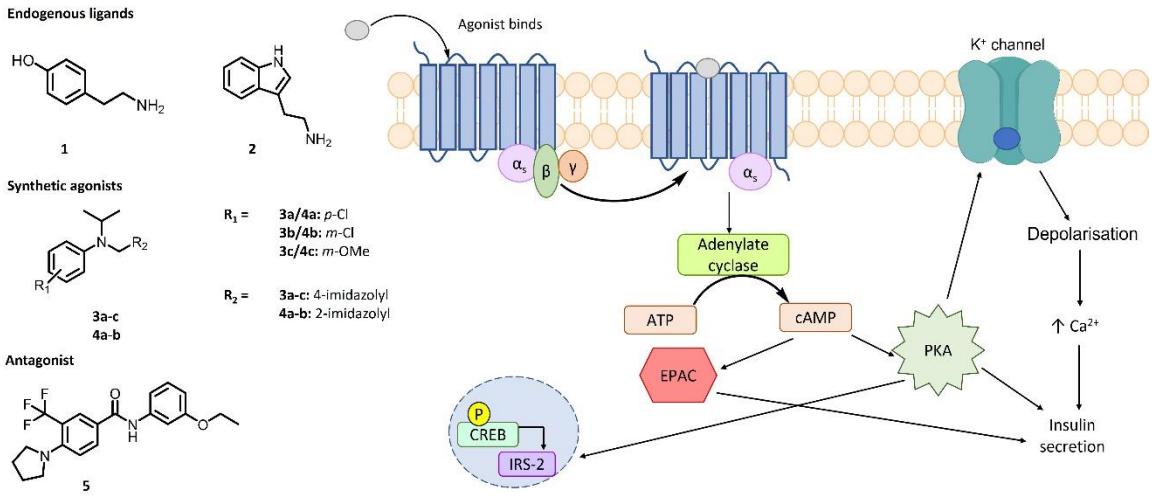
FO04 & P04 Design, Synthesis and Pharmacological Testing of Novel Therapeutic Agents Designed to Enhance Insulin Secretion at the Trace Amine-associated Receptor 1.

R Lenham[1,2], S Mistry[1], C Laughton[1], M Turner[2]

[1]School of Pharmacy, University of Nottingham, Nottingham, UK, [2]School of Science and Technology, Nottingham Trent University, Nottingham, UK

Insulin is widely considered the most important hormone involved in metabolic homeostasis with defects in its action or secretion causing diabetes mellitus, a condition afflicting over 400 million people worldwide. Although several oral hyperglycaemic agents have been developed to manage type 2 diabetes, their effectiveness often declines over time. Trace amine-associated receptor 1 (TAAR1) is a G protein-coupled receptor expressed throughout the body, including pancreatic β-cells. Pancreatic TAAR1 (below figure) can amplify insulin secretion via the activation of protein kinase A and EPAC signalling cascades, thus it is a potential therapeutic target for novel, oral hyperglycaemic drugs.

Five known TAAR1 agonists (**3a-c** and **4a-b**, *K*i= 4-138 nM) were resynthesized to validate the proposed pharmacology assays by determining their insulin secretion ability and capability to enhance cyclic AMP levels. Furthermore, as no crystal structure of TAAR1 has been determined, machine learning techniques were implemented for structure determination. Over 1000 potential models were generated and ranked based on their ability to dock the four known TAAR1 ligands (**1-3a** and **5**) with 2 models showing promising results. Novel analogues were designed, then docked into the homology models and their pharmacological properties evaluated *in vitro*. As part of this communication, we will describe the synthesis and pharmacological activity of the novel and repurposed literature compounds as well as the molecular docking studies.



Poster Abstracts

FO05 & P05 Vectorial Functionalisation of Pyrazolo[3,4-c]pyridines for Fragment-based Drug Discovery

EV Bedwell[1], F Emery[2], GC Clososki[2], I Baxendale[1], PG Steel[1]

[1]Department of Chemistry, Durham University, Durham, UK, [2]Faculdade de Ciencias Farmacéuticas, Universidade de São Paulo, Riberião Preto, SP, Brazil

Fragment-based drug discovery (FBDD) is now a well-established method of identifying novel drug candidates that is being applied to diverse targets from DNA to protein-protein interactions. Heterocycles have a privileged place in FBDD due to an ability to engage with the target protein through a wide variety of intermolecular interactions, coupled with the potential to optimise drug-like properties (lipophilicity, hydrogen bonding capacity, and polarity) through modification of substituents. However, the range of heterocycles in common usage remains limited which hinders development of new bioactive agents. Novel heterocyclic ring systems are therefore needed as valuable inputs to unlock elusive therapeutic targets.

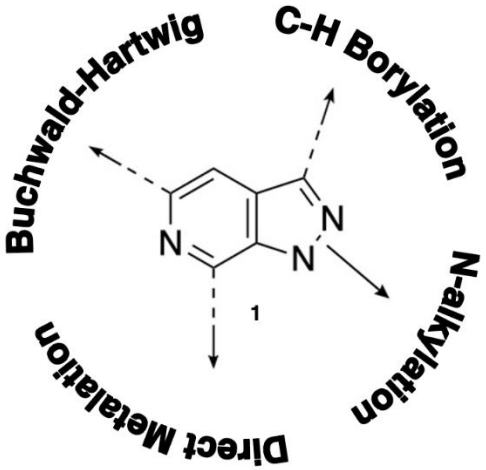
A challenge of working with novel heterocycles arises when introducing new substitution patterns requires complex *de novo* synthesis and strategies for late-stage functionalization are lacking. This limits the structural diversity that can be rapidly generated for testing in drug-discovery regimes and progress may stall while new synthetic routes are established.

To address these issues, we developed strategies for late-stage functionalisation of novel heterocyclic scaffolds to generate a diverse library of fragments. The pyrazolo[3,4-c]pyridine scaffold **1** was identified through a comprehensive enumeration of plausible yet unreported heteroaromatic rings in a virtual library designed to spark exploration of new chemical space.[1]

This poster presents synthetic routes to the pyrazolo[3,4-c]pyridine scaffold **1** optimised for large-scale batch or flow chemistries, and details regioselective methods to access the major growth-vectors. Specifically, using (1) metal-catalysed C-H borylation and Suzuki-Miyaura cross-coupling, (2) N-alkylation, (3) Buchwald-Hartwig amination, and (4) direct metalation chemistry with magnesium bases. These methods can be used individually or in sequence to generate an elaborated library of compounds based on the pyrazolo[3,4-c]pyridine scaffold **1**.

In addition to developing this synthetic methodology, this project aims to demonstrate the medicinal chemistry potential of the generated heterocycles. Computational docking and enzymatic assays with the sirtuin proteins of Leishmania parasites have been chosen to establish antileishmanial potential.

The future of this project will focus on synthesis and functionalization of other heterocycles of interest in the development of antileishmanial agents.



[1] WR. Pitt, DM. Parry, BG. Perry, CR. Groom, *J. Med. Chem.* **2009,** *52,* 2952–2963

Poster Abstracts

FO06 & P06 Discovery of PINK1 Activators as Treatments for Parkinson's Disease

A AlGhamdi[1], O Lambourne[1], S Bell[2], L Wilhelm[3], E Yarbrough[4], G Holly[4], O Russell[2], I Ganley[3], M Goldbery[4], Y Mehellou[1]

[1]School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, UK, [2]Wellcome Centre for Mitochondrial Research, Newcastle University, Tyne, UK, [3]MRC Protein Phosphorylation and Ubiquitylation Unit, University of Dundee, Dundee, UK, [4]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama, Birmingham, USA, [5]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama, Birmingham, USA, [6]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama, Birmingham, USA, [7]Wellcome Centre for Mitochondrial Research, Newcastle University, Tyne, UK, [8]MRC Protein Phosphorylation and Ubiquitylation Unit, University of Dundee, Dundee, UK, [9]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama, Birmingham , United States, [10]School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, UK

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease that affects almost 10 million people worldwide. Among the causes of PD are loss of function mutations in the serine/threonine protein kinase PINK1.**(1)** These mutations lead to impairment in mitophagy, a cellular process that removes damaged or depolarized mitochondria, which protects cells from oxidative stress and eventually neuronal cell death. The accumulation of damaged mitochondria can result in increased oxidative stress and inflammation, which are believed to contribute to the death of dopaminergic neurons in PD.**(2)** Upon mitochondrial depolarization, PINK1 gets stabilized on the outer mitochondrial membrane (OMM) and phosphorylates ubiquitin and the E3 Ubiquitin ligase, parkin, consequently triggering mitophagy. PINK1 activators have gained great attention as a potential therapeutic approach for PD by promoting neuroprotection through mitophagy. Several attempts have been made to develop small molecule PINK1 activators, including nucleobases, nucleosides, and their nucleotide prodrugs.**(3)** Encouraged by these efforts, the aim of this work is to design and synthesize small molecule activators of the PINK1 activators as a potential treatment of PD. We designed and synthesized a small series of PINK1 activators. These compounds were obtained in high purity (>95%) and with yields ranging from 10-35%. These compounds were found to be able to activate PINK1 in cells as judged by the phosphorylation if its physiological substrate parkin. Using *mito*-QC reporter assay in MEFs, PINK1 activation by nucleoside analogues resulted in triggering PINK1-dependent mitophagy, which was not observed in MEF PINK1 KO. Interestingly, the PINK1-dependent mitophagy caused by our nucleoside analogues was able to suppress the accumulation of phospho-ubiquitin caused by mitochondrial damaging agents such as niclosamide and CCCP, which is a hallmark of PD. In conclusion, we have discovered the first series of PINK1 activators that have the capability of suppressing the accumulation of phosphoubiquitin, which is toxic to neurons. Such compounds hold promise for future development as PD treatments.

Poster Abstracts

FO08 & P08 The Development of an on-DNA Micelle-Promoted Reductive Amination of DNA-Conjugated Amines to Access Previously Underexplored Peptidomimetics

M Anderson, T Carton, M Waring
Department of Chemistry, Newcastle University, Newcastle upon Tyne, UK

Hit generation is a crucial component of any drug discovery process. A plethora of methods exist, allowing for the screening of potential candidate molecules against a variety of targets, including high-throughput screening (HTS), fragment-based drug discovery (FBDD), and several *in silico* methods. DNA-encoded libraries (DELs) have emerged as a promising technology within the field of screening, due to their comparative benefits: large library sizes (>10^6 members) covering a diverse range of chemical space, time- and cost-effective synthesis and storage, and the relatively small amount of protein required for the screening.

Despite the numerous advantages of DELs, there remain limitations in the chemistries applicable to on-DNA synthesis as reactions occur in the presence of unprotected DNA, therefore, any reactions employed must be DNA-compatible. Specifically, reactions must be conducted in water and efficient at high dilutions while preserving the integrity of the DNA, i.e. cause no damage to the DNA tag. Ideally, transformations should be high-yielding for a broad substrate scope. One approach to facilitating reactions under aqueous conditions is through the application of micelle-forming surfactants, such as TPGS-750-M.

Reductive aminations play a crucial role in medicinal chemistry towards the synthesis of secondary and tertiary amines. In spite of this, reported on-DNA approaches are few and far between, typically utilising large excesses of amine to force the reaction. In fact, there are no published procedures applicable to a wide range of aldehydes, using amine-tagged DNA. **Herein is detailed the development of an on-DNA reductive amination, with amine on DNA, applicable to an incredibly diverse range of substrates (> 50), including aliphatic, aromatic, and heterocyclic aldehydes. The optimised micellar conditions yield high conversions (> 75%) to the desired amine for various on-DNA amines, both primary and secondary in nature.**

Peptoids are a class of peptidomimetics bearing resistance to proteolytic degradation and improved cell permeability, relative to many peptides, while maintaining the ability to mimic peptidic structures. Peptoids also boast an expansive side-chain diversity; hence, peptoid synthesis from a broad selection of aldehydes on DNA allows for the synthesis of a peptoidic DEL.

Poster Abstracts

FO10 & P10 Development of Cleavable Linkers for Polymer-Drug Conjugates

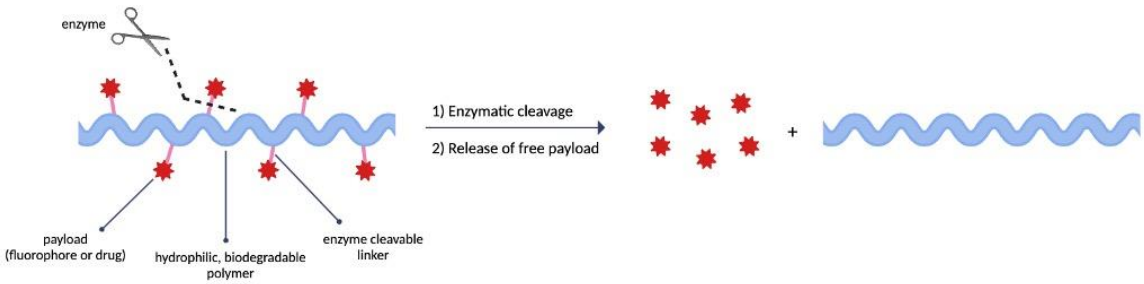
S Phillips[1], R Brewster[2], R England[2], M Park[1], J Mandrup Kandemir[1], D Spring[1]

[1]Yusuf Hamied Department of Chemistry, University of Cambridge, Cambridge, UK, [2]AstraZeneca, Macclesfield, UK

Polymer-drug conjugates (PDCs) are an important class of polymer therapeutic that consist of a polymer backbone conjugated to a small-molecule drug via a chemical linker. PDCs provide many benefits to the delivery of small molecular weight drugs for the treatment of cancer, such as increased circulation half life, high drug loading and increased hydrophilicity. Despite the benefits of PDCs as anti-cancer treatments, currently no polymer-small molecule drug conjugates have reached the drug market for oncology, due to off-target effects or reduced efficacy in comparison to the free drug.

For PDCs, the linker chemistry between the drug and the polymer is key to their efficacy: the linkers must enable efficient drug release from the polymer and the release may be selective within a particular disease environment, which reduces off-target toxicity. Enzyme cleavable linkers have exhibited effective and selective drug release in other cancer therapeutics, such as antibody-drug conjugates (ADCs); these linkers are susceptible to cleavage by enzymes that are upregulated in tumours. However, the linker chemistry for PDCs has typically focused on potentially sub-optimal and non-selective hydrolytic cleavage mechanisms. In addition, the use of enzyme cleavable linkers within PDCs has been limited to the peptidic cathepsin B cleavable linkers, which can be problematic due to their hydrophobicity and instability in rodent blood. Therefore, the toolbox of linkers used in PDCs needs to be expanded to include other types of cleavable linkers.

In this work, a series of enzyme cleavable linkers, with a fluorophore payload, were designed and synthesised to investigate their compatibility within PDCs. These enzyme cleavable linkers were conjugated to amino acid-based biodegradable polymers via amide couplings. The model PDCs were then incubated with their relevant enzymes and the fluorescence intensity was measured; they exhibited effective release of the fluorophore payload, with some PDCs showing selective release at lysosomal pH compared to the pH of blood plasma. The enzyme cleavable linkers that exhibited the most effective payload release were consequently conjugated to the anti-cancer drug doxorubicin and the biological activity of these PDCs will be tested.



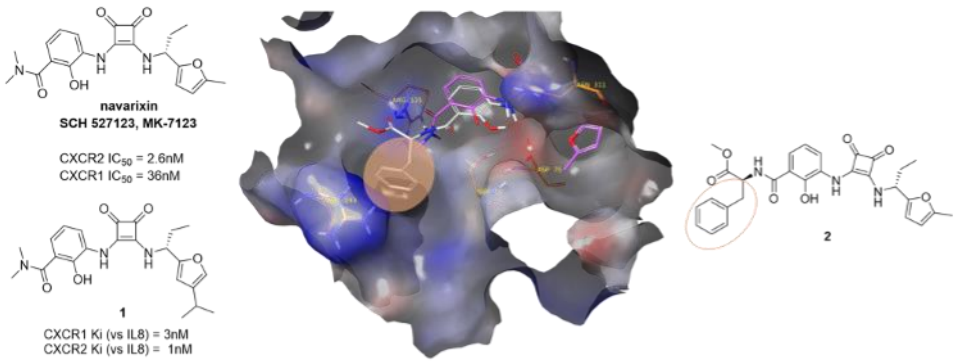
Poster Abstracts

P11 Exploration of Intracellular Binding Pockets of CXC Chemokine Receptors for Allosteric Modulation

R Francis[1], S Mistry[1], C Laughton[1], N Holliday[2]

[1]School of Pharmacy, University of Nottingham, Nottingham, UK, [2]School of Life Sciences, University of Nottingham, Nottingham, UK

Chronic inflammation is a major contributor to tumour growth. The CXC chemokine receptor (CXCR)/CXC ligand (CXCL) axis plays a vital role in the cancer microenvironment and is attributed to proliferation, angiogenesis, invasion, and metastasis. Drug discovery programmes have attempted to target CXCR1/2 using small molecule therapeutic agents (navarixin and danirixin), however toxic side effects resulted in phase II clinical trials being terminated. Mutation studies of CXCR2 have shown that the downstream signalling can be influenced by allosteric modulators binding to an intracellular site close to the G-protein binding region present in both CXCR1 and CXCR25. The most advanced class of compounds acting at this binding site are 3,4-diaminocyclo-3-ene-1,2-dione based antagonists (navarixin and **1**). Development of novel antagonists can be aided by in-silico techniques however one of the barriers to rational drug design for CXCR1 antagonists is the limited structural data available.
The aim of this work is to develop novel CXCR1 antagonists using a combination of in-silico and in-vitro methods. Molecular dynamic techniques and docking studies are being explored to construct and validate a homology model structure for the inactive, intracellular allosteric ligand bound state of CXCR1. Docking of known ligands for CXCR1 correlate with literature, validating the design and set a basis for further CXCR1 inhibitor design. Pocket and docking analysis have revealed a potential extension to the binding region between TM3 and 5. Extension of the previously described druggable binding pocket may play a key role in the design of a new class of CXCR1/2 antagonists. Ten 3,4-diaminocyclo-3-ene-1,2-dione based analogues were designed to probe this region and showed promising in-silico docking results. The series of analogues was subsequently synthesised and are under evaluation for activity at CXCR1. The in-vitro results obtained support the continued development of an accurate CXCR1 homology model along with structure-activity relationship studies for future drug design.



Poster Abstracts

FO12 & P12 Targeting the cell-adhesion molecule PSGL-1 with a small molecule inhibitor

C James[1], V Kanabar-Raivadera [2], CP Page[2], L Martin[1], GK Wagner[1]

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P-selectin glycoprotein ligand-1 (PSGL-1), a major selectin ligand expressed on leukocytes, plays a major part in tethering blood cells to endothelial selectins. It facilitates transmigration of leukocytes and platelets into inflamed tissue and drives chronic inflammatory processes [1]. PSGL-1 is upregulated on leukocytes from patients with chronic obstructive pulmonary disease (COPD) [2]. Pharmacological reduction of elevated PSGL-1 levels may therefore be a promising strategy for regulating PSGL-1-mediated cell adhesion in chronic inflammatory airway diseases.

We have previously shown that treatment of primary human peripheral blood mononuclear cells with the pro-inflammatory cytokine IL-1b leads to elevated PSGL-1 levels *in vitro* [3]. Herein, we report that these elevated PSGL-1 levels can be reduced to basal levels with a drug-like small molecule (Fig.1).

The molecular target(s) and mode of action of this inhibitor are currently unknown. To enable target identification studies, we have developed an optimised synthetic scheme for this inhibitor. The target molecule was obtained in 12% total yield over 6 synthetic steps.

To identify potential molecular targets involved in the inhibitor-mediated PSGL-1 downregulation, we used 5 computational target and activity prediction servers (RF QSAR, Swiss target prediction, SEA Search Server, SuperPRED and LigTMap) [4-8]. These algorithms compare the structure and binding profiles of a query inhibitor with that of the natural ligand. Ranking of potential targets from all servers identified common candidate targets, including several kinases.

This inhibitor is hypothesized to elicit a pro-drug effect, i.e., cleaved to the subsequent acid on entry into cell. The inhibitor and its acid analogue were tested against a panel of 140 kinases using a radioactive filter binding assay. As expected, the inhibitor was less active compared to the acid analogue against these enzymes. It reduced the residual activity of six kinases to less than 60%, and of one kinase to less than 30%.

Some preliminary docking studies were conducted on the hits obtained from the screening to identify potential strategies for further optimization. Docking results suggest that both the terminal carboxylate and the formylthienyl group may engage in critical interactions with the target enzyme. Evaluation of the inhibitor and analogues in cell models are currently underway and preliminary results will also be reported.

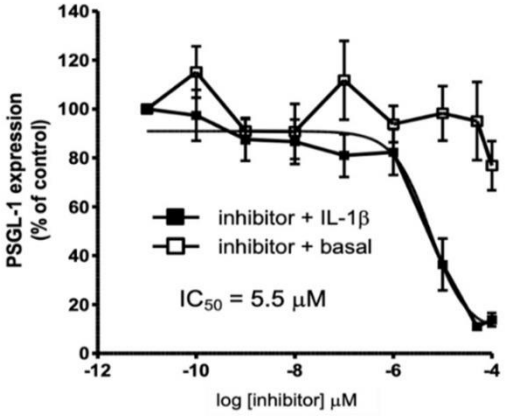


Fig. 1: Incubation with inhibitor leads to reduction of induced cell-surface PSGL-1 levels on hPBMCs treated with IL-1β. The inhibitor has no significant effect on constitutive cell surface PSGL-1 levels

Poster Abstracts

FO16 & P16 The Development of 1,2,4-Triazine G-Protein Coupled Receptor 84 (GPR84) Antagonists

Michael Malone[1], Graeme Milligan[2], Andrew Jamieson[1]

[1]Chemistry, University of Glasgow, Glasgow,Scotland, [2]Molecular Bioscience, University of Glasgow, Glasgow,Scotland

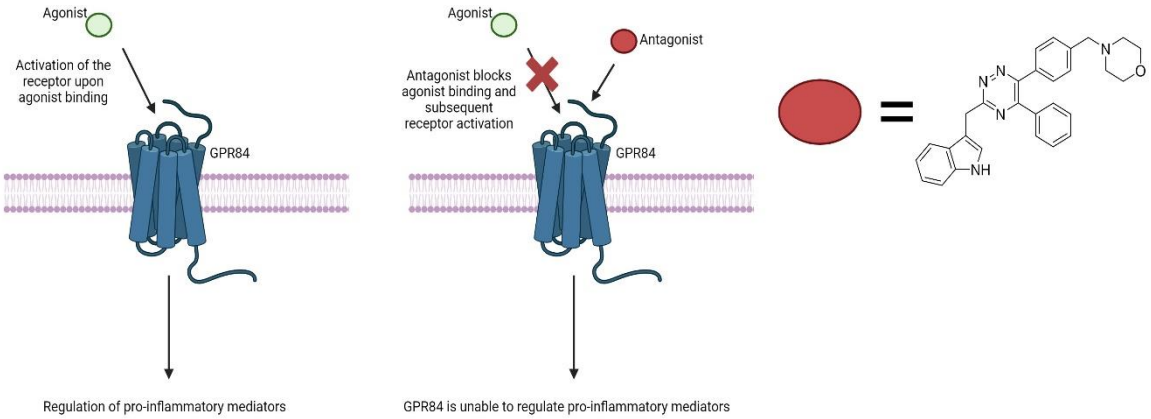
Over 800 G protein-coupled receptors (GPCRs) are encoded by the human genome with more than 30% of prescribed drugs in clinic targeting these proteins. Stimulation of GPCRs is a consequence of ligand binding, whereby the specific ligand-GPCR interaction elicits a range of cellular responses. Although extensively researched, a significant number of GPCRs require further pharmacological evaluation.

GPR84 is activated by medium-chain free fatty acids. However, due to the low potency of this class of ligand GPR84 remains categorised as an orphan receptor.[1] Due to the documented upregulation of GPR84 in various pro-inflammatory conditions, it is proposed that antagonising the receptor may be a potential therapeutic route for pro-inflammatory mediated diseases, such as ulcerative colitis.[2] Milligan, in collaboration with Jamieson, have reported the structure activity relationship (SAR) of a 1,2,4-triazine GPR84 antagonist series.[1, 2] However, the SAR was limited due to no current facile method known for the regioselective synthesis of unsymmetrical trisubstituted 1,2,4-triazines. Such a method is required for late-stage diversification and to further explore this sereies.[2]

This poster will outline some of the key findings surrounding the SAR of the 1,2,4-triazine GPR84 antagonist series. Additionally, the development of a regioselective synthesis of trisubstituted 1,2,4-triazines will be presented.[1, 2]

1 - Jenkins L, Marsango S, Mancini S, Al Mahmud Z, Morrison A, McElroy, Kirstie A. Bennett, Matt Barnes, Andrew B. Tobin, Irina G. Tikhonova, and Graeme Milligan, *ACS Pharmacol Transl Sci.* **2021**, 4(5):1598-1613.

2 - Amit Mahindra, Laura Jenkins, Sara Marsango, Mark Huggett, Margaret Huggett, Lindsay Robinson, Jonathan Gillespie, Muralikrishnan Rajamanickam, Angus Morrison, Stuart McElroy, Irina G. Tikhonova, Graeme Milligan, and Andrew G. Jamieson, *J. Med. Chem.* **2022**, 65(16): 11270-11290.



Poster Abstracts

FO17 & P17 Discovery of Novel Small Molecules for the Treatment of Human Coronaviruses

Elliott Smyth[1,2], Joao Pisco[1], Nathalie Bouloc[1], Jonathan Large[1], Richard Foster[2]

[1]Chemical Biology, LifeArc, Stevenage,UK, [2]School of Chemistry, University of Leeds, Leeds,UK

Three deadly coronavirus (CoV) infections have emerged in the last 20-years: SARS-CoV, MERS-CoV and the recent SARS-CoV-2 pandemic. SARS-CoV-2 is the latest coronavirus to infect humans, and the resulting pandemic created unprecedented challenges for healthcare systems around the world. Many of those infected with the virus experience mild symptoms or are asymptomatic, however some individuals encounter a more severe disease with long-lasting respiratory symptoms, and side-effects causing debilitating impairment and multiple organ damage. While vaccines are now widely available, patients need regular booster doses, so novel small molecule therapeutics may offer a complimentary method to addressing this disease.

One possible route to treat COVID-19, the disease caused by SARS-CoV-2, is to target the CoV-specific protein, non-structural protein 14 (NSP14). NSP14 is an essential CoV-specific protein responsible for maintaining replication fidelity, resistance to immune response and nucleoside analogue inhibitors, and increased virulence. SARS-CoV-2 NSP14 is well characterised structurally and biochemically but has not been subjected to significant inhibitor development. No marketed drug exists that targets NSP14, and there is evidence to suggest that inhibition could be a promising therapeutic strategy. The objective of this project is to synthesise and develop small molecules to selectively target NSP14, in order to create novel therapeutics for the treatment of past, present and future human coronaviruses.

A hit-to-lead medicinal chemistry campaign has been carried out for a non-nucleoside chemotype against NSP14, utilising a literature starting point with poor physicochemical properties. Biochemical assay and ADME data, as well as structural information, have been used to inform a design-make-test-analyse cycle. This cascade has ultimately led to the development of sub micromolar inhibitors of NSP14 with desirable physicochemical property profiles, which are positioned for further *in vitro* characterisation and lead development.

Poster Abstracts

FO18 & P18 Synthesis of Macrocyclic Ligands for the Bromodomain of CREBBP/p300

Alistair Boyd[1], Mustafa Moroglu[2], Stuart Conway[3]

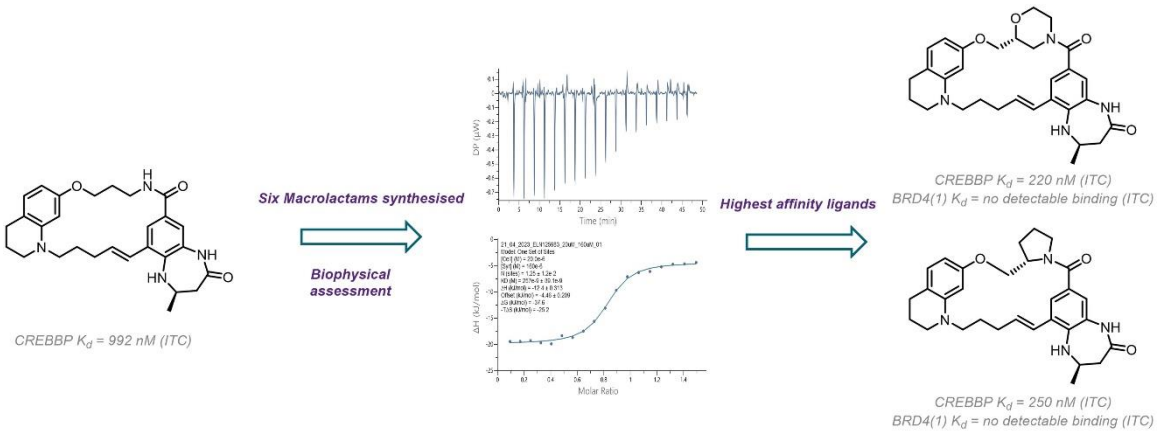
[1]Organic Chemistry, University of Oxford, Oxford,UK, [2]Medicinal Chemistry, GSK, Stevenage,UK, [3]Chemistry, UCLA, Los Angeles, United States of America

CREBBP/p300 are important proteins, comprised of ten distinct domains. One domain of particular interest within these paralogues' is the bromodomain which recognises the acetylated lysine tails of histones around which DNA is supercoiled.

Dysregulation of these proteins is implicated in several cancers including lymphatic and prostate, with therapies currently undergoing clinical trials that target these proteins.

In this work a novel approach has been undertaken to selectively target the bromodomains of CREBBP/p300, through the design and synthesis of macrocyclic ligands. These compounds are based upon an existing scaffold demonstrating an alternative conformation upon CREBBP when compared to that of the main off-target protein of BRD4(1).

This work builds upon previous macrolactam based ligands which bound the bromodomain of CREBBP with an affinity of around 1 µM. The work presented herein improves upon the previous design via synthesis of a small series of macrocyclic ligands, derived from a common intermediate. The resulting compounds' biophysical properties were assessed, and the data produced gave a range of binding affinities, with the two highest affinity compounds producing K_d values below 300 nM by ITC. Utilising the same assay, no binding was observed to BRD4(1) with all but one of the compounds. These data mean that four of the compounds have improve binding affinities compared to the macrocycle from which they were derived. With this data in-hand we hope to further assesses the selectivity and potency of these compounds. This work demonstrates the synthesis of the first series of high affinity macrocyclic ligands for the CREBBP/p300 bromodomain.



Poster Abstracts

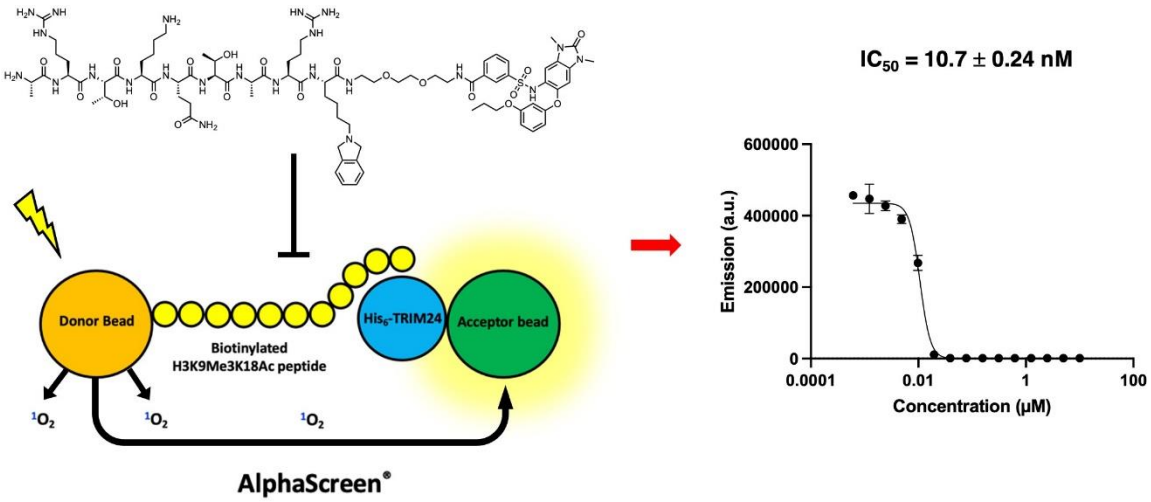
FO 19 & P19 Bivalent chemical tools for investigating the tandem plant homeodomain finger-bromodomain cassette in TRIM24

Michael Platt, Stuart Conway

Department of Chemistry, University of Oxford, Oxford,UK

Tripartite motif-containing protein 24 (TRIM24) is an epigenetic reader and E3 ligase protein involved in multiple biological processes including innate immunity and cell proliferation. Aberrant expression of TRIM24 has been observed in breast and prostate cancers, making the protein an attractive therapeutic target. Among its various functions, TRIM24 acts as an epigenetic reader of post translational modifications (PTMs) on histone tails. Its tandem plant homeodomain (PHD) finger-bromodomain (BRD) binds to histone 3 proteins carrying the K9 trimethylation (H3K9Me 3) or K18/K23 acetylation (H3K18/K23Ac) marks, respectively. In addition, studies have shown binding of a histone peptide *in cis* to the TRIM24 PHD and BRD, which raises the possibility of combinatorial readout.[1] However, the biological consequences of TRIM24 reading multiple PTMs on a single histone remain unknown; and there is, therefore, a need for development of chemical probes binding to *both* the PHD and BRD.

Currently, only two high affinity TRIM24 BRD ligands exist in the literature; while no TRIM24 PHD inhibitors have been reported.[2,3] BRD inhibition alone only partially displaces histones as it does not prevent binding to the PHD. Whereas bivalent chemical tools, which can simultaneously bind to both domains, could completely abolish histone binding to TRIM24. We have taken this approach and synthesised the first peptidomimetic bivalent compounds targeting the TRIM24 PHD and BRD. In AlphaScreen® competition assays, these compounds demonstrated low nanomolar IC50 values (10–30 nM) for the displacement of a dual-modified PHD-BRD binding histone peptide (H3K9Me 3 K18Ac); and an approximate 80-fold decrease in IC_{50} compared to the parent BRD ligand. Furthermore, these compounds showed superior inhibition over the current highest affinity TRIM24 BRD ligand, IACS-9571.[3] Future work with these compounds will enable elucidation of the biological consequences of chromatin association to TRIM24 and help us understand the biological functions of TRIM24 in more detail.



1 Tsai, W. W. *et al. Nat*. **2010**, 468 (7326), 927–932. [doi:10.1038/NATURE09542]

2 Bennett, J. *et al. J. Med. Chem*. **2015**, 59 (4), 1642–1647. [doi:10.1021/ACS.JMEDCHEM.5B00458]

3 Palmer, W. S. *et al. J. Med. Chem.* **2015**, 59 (4), 1440–1454. [doi:10.1021/ACS.JMEDCHEM.5B00405]

Poster Abstracts

FO20 & P20 Design, Synthesis, Biological Evaluation, and Molecular Modeling of Novel Benzofuran Derivatives as Targeted Cancer Chemotherapy

A A. Osman [1,2], E R. Mohamed [2], H A. Abdel-Aziz[3], A M. El Kerdawy[2,4], H Abdelrasheed Allam[2]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, NewGiza University, Newgiza, Cairo 12256, Egypt, [2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Cairo University, Cairo, P.O. Box 11562, Egypt, [3]Applied Organic Chemistry Department, National Research Center, Dokki, Cairo 12622, Egypt, [4]School of Pharmacy, College of Health and Science, University of Lincoln, Green Lane, Lincoln, Lincolnshire, UK

Cancer remains one of the major causes of morbidity and mortality worldwide, and for decades researchers have been trying to identify the origin of human cancer 1,2. Cancer is characterized by the dysregulation of several enzymes that play essential roles in cell division and differentiation such as protein kinases. For instance, epidermal growth factor receptor (EGFR) plays a substantial role in regulating tissue development and homeostasis 3. Thus, inappropriate activation of EGFR can lead to cancer initiation and progression 4. Benzofuran is a privileged scaffold that has been used to design several new anticancer agents which could inhibit the growth of multiple human cancer cell lines 5,6. Moreover, thiazol-2-yl-hydrazone moiety is a key fragment in several EGFR inhibitors 7,8. Thus, in the current work, a set of hybrid compounds containing both privileged fragments were designed and synthesized as novel EGFR inhibitors. Additionally, molecular docking simulations were performed for the designed compounds in the EGFR active site to confirm their binding capability to the EFGR kinase domain. All the newly synthesized compounds were capable of binding to the key amino acid Met768 in the hinge region of the kinase domain. Furthermore, SwissADME tool was used to predict the physicochemical and pharmacokinetic properties of the target compounds and to check their medicinal chemistry friendliness. Our future prospective is to evaluate the EGFR inhibitory activity as well as the cytotoxic activity of the designed compounds.

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Forthcoming Events in 2024

2024

3rd – 5th March	9th RSC-BMCS Fragment-based Drug Discovery Meeting Cambridge, UK
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25th April	35th Medicinal Chemistry in Eastern England Stevenage, UK
16th May	Hot Topics: Covalent Drug Discovery 2024 virtual
4th – 5th June	4th Synthesis in Drug Discovery and Development Virtual
9th – 11th September	3rd RSC / SCI New Therapeutics for Global Health Milton Keynes, UK
16th - 18th September	7th RSC-CICAG/RSC-BMCS Artificial Intelligence in Chemistry Cambridge, UK
10th – 13th October	9th GPCR's in Medicinal Chemistry Verona, Italy

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Initiatives and Announcements

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Each year, the BMCS offers a number of International Travel Prizes for use in the following year, up to a value of £2,000, to postgraduate students enrolled in research programmes (PhD or Masters) in UK institutions. The call for nominations will open on 1st March 2024.

The RSC BMCS Lectureship

Every two years, the BMCS seeks nominations of BMCS lectures to deliver lectures. These include an initial lecture as part of the RSC seriesof Thursday evening public lectures at Burlington House. The next call for nominations will be September 2024.

BMCS Lecturer for 2019/2020 was Dr David Witty formerly of Convergence.
BMCS Lecturers for 2020/2021 was Elisabetta Chiarparin of AstraZeneca and James Duffy of Medicines for Malaria Venture.
BMCS Lecturer for 2021/2022 was David Rees of Astex Pharmaceuticals.
BMCS Lecturer for 2022/2023 is James Crawford of Genetech.
BMCS Lecturer for 2023/2024 is Dafydd Owen of Pfizer

The RSC BMCS Researcher Mobility Fellowship

The BMCS is pleased to announce a new call for the Researcher Mobility Fellowships, to drive excellence in the UK-based science. These fellowships of up to £5,000 aim to support short-term placements (up to 3 months) between industry and academia in areas of interest to the BMCS, namely bioorganic chemistry, medicinal chemistry, chemical biology and agriscience. Applications should be jointly submitted by academic and industrial partners. Call for nominations open in January 2024.

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The BMCS is pleased to announce a new call for nominations for The Hall of Fame and associated medal, to recognize prominent chemists for outstanding, sustained, significant contributions to any area of interest to the BMCS, e.g. medicinal chemistry, agriscience, bioorganic chemistry, chemical biology. Call for nominations for the Hall of Fame 2024 close on 31st March 2024.

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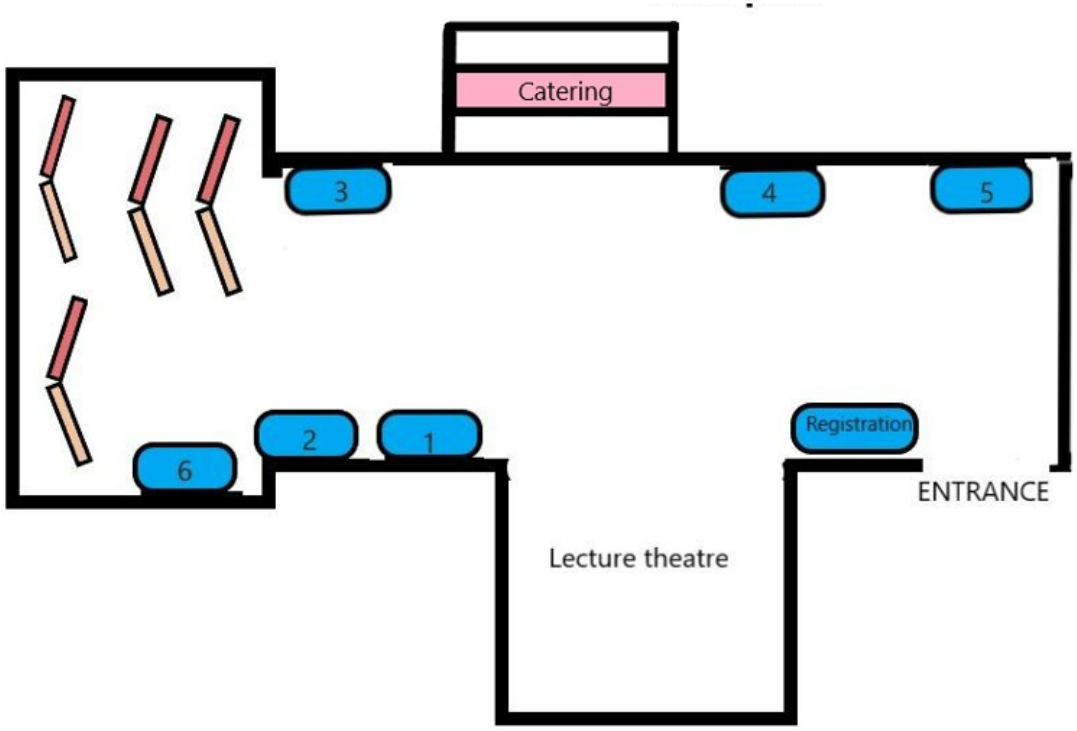

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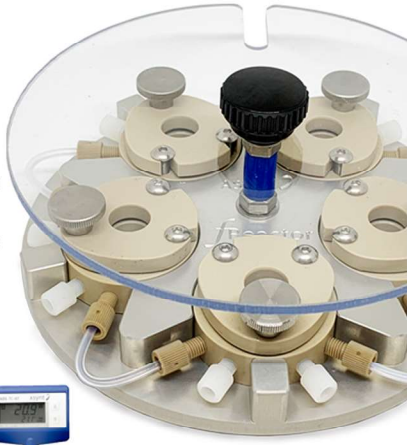

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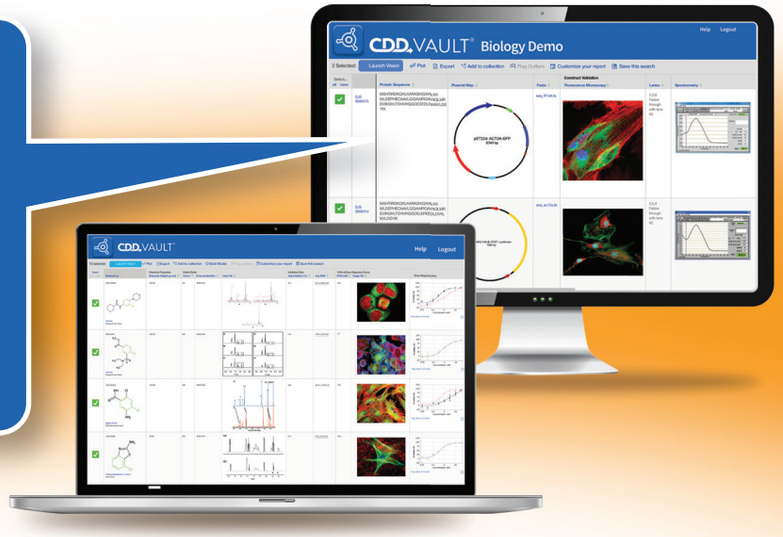

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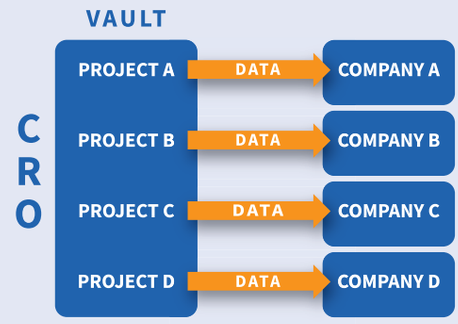
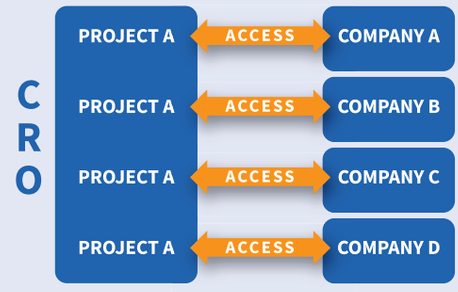


Basic Model

The CRO sets up one Vault with multiple Projects to hold data for each customer. Data can be exported and sent to the customer as needed.

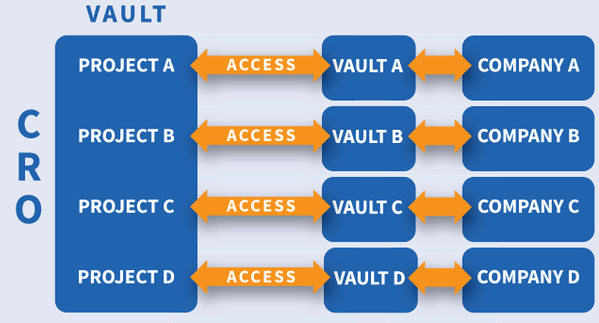
Best for: Low cost and maintenance



Collaborative Model

Customers are granted access to their Project within the CRO's Vault. This allows for real-time data visibility.

Best for: Quicker data access without needing to send emails



Individual Vault Model

An individual Vault is created for each customer. The CRO works and generates data within the customer's Vault.

Best for: The customer has a fully functional Vault and the CRO never needs to transfer data

Contact us to learn more! info@collaborativedrug.com

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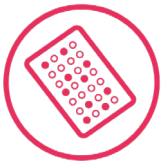
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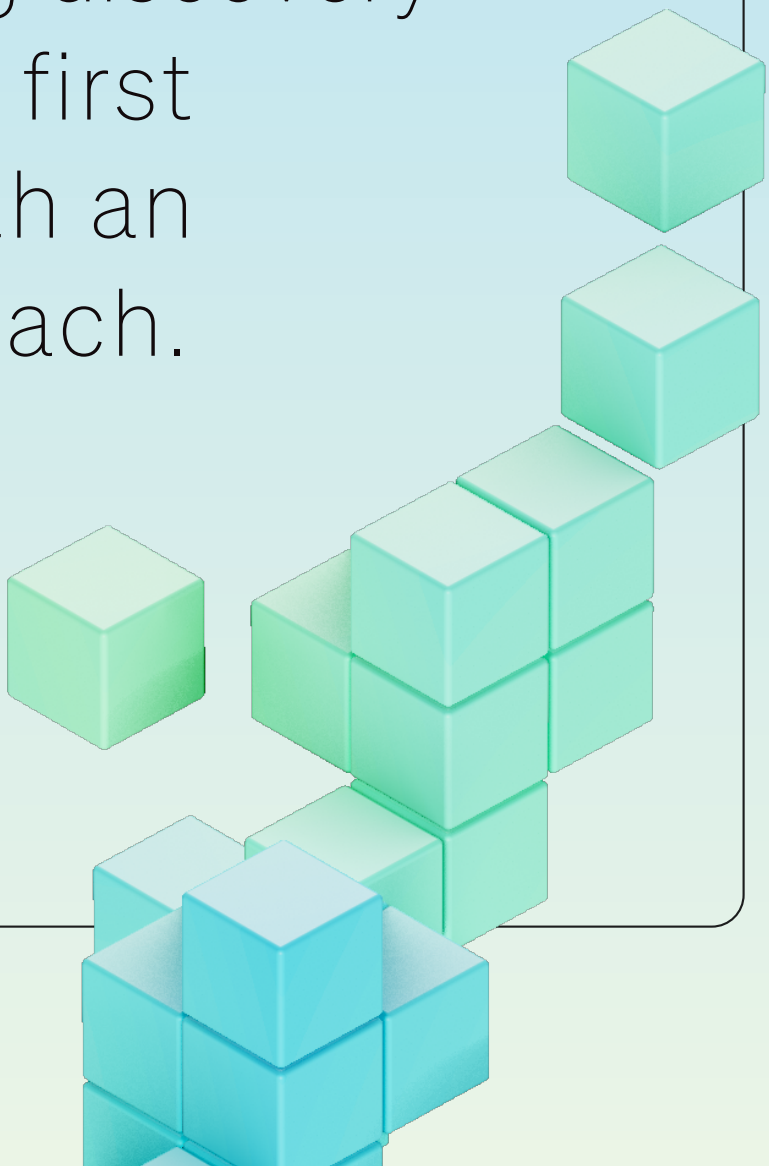

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Correct as of 03.01.2024