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Clarivate Analytics

Meeting Report

Recent trends and technologies towards medicines of the future. A joint meeting of the SMR and the RSC BMCS

London, UK – December 8, 2017

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Contents

Summary

On December 8, 2017, the Society for Medicines Research (SMR) and the Biological and Medicinal Chemistry Sector of the Royal Society of Chemistry (RSC BMCS) jointly hosted a 1-day meeting in London on "Recent trends and technologies in medicinal chemistry towards medicines of the future." This well-attended meeting was a combination of medicinal chemistry, chemistry-based drug discovery-enabling technologies and chemical biology from academic, industry and not-for-profit groups. The meeting was primarily focused on talks from U.K. groups to reflect the breadth of work taking place across the U.K. to advance our understanding and prosecution of targets, technologies, and lead series to underpin medicines research.

Key words: Membrane protein drug discovery – Protein misfolding – Antibody–drug conjugates – Phenotypic activity-driven target identification – Cyclotrimerization chemistry – Macrocycles – Protein–protein interactions

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Finding New Targets

Mass spectrometry and its role in membrane protein drug discovery

Prof. Dame Carol Robinson (Oxford University) began by giving a short overview of the history of using mass spectrometry in determining the interactions between soluble protein subunits in her research group. She then described the process of studying membrane proteins and in particular, highlighted how utilizing micelles provides a protective bubble that ensures the solubility of membrane protein complexes; in the gas phase the detergent is then shaken off without affecting the integrity of the protein structure. This is achieved, in part by the application of nanoelectrospray and in part through control of conditions that allows the complex to remain intact in the gas phase of a mass spectrometer. Thus the subunit stoichiometry and ligand-binding properties of membrane complexes could be determined directly.

This method was applied to examine the structure of a membrane-embedded protein pump, the ATP-binding cassette transporter P-glycoprotein (P-gp) when bound to small molecules. Using the technology described, the group were able to measure rates of lipid-binding and calculate K_D values. They were able to conclude that negatively charged molecules bound more favorably to the P-gp than zwitterions. P-gp efflux pumps show multidrug resistance to, for example, chemotherapies; these findings which illustrated how binding of small molecules to such efflux proteins affects changes to additional binding affinities and conformations, are immensely useful and applicable to small-molecule drug discovery.

Prof. Robinson also highlighted the role and importance of lipids in stabilizing membrane proteins and stated that they should be considered when examining the membrane proteins themselves. The group developed a mass

spectrometry platform that enabled the simultaneous determination of the presence of interfacial lipids and the stoichiometry of the membrane proteins. The role of such lipids in transient and stable interactions with a range of membrane proteins, including G protein-coupled receptors (GPCRs), could then be rationalized and understood (1-3).

Drug discovery approaches for protein misfolding and aggregation diseases

Dr. Peter Astles (Eli Lilly) began by defining the term *amyloidosis* as a group of diseases in which misfolded aggregated proteins build up in tissue. While amyloidosis was originally thought to be one substance it is now known that there are many different types of amyloidosis that are caused by the aggregation of many different types of protein. These can be either genetic in origin or acquired.

The progression from misfolding to aggregation was highlighted ultimately ending in disease arising from either loss of normal function or gain of toxicity. The initial protein aggregation is thought to be slow and reversible, i.e., the initial onset of disease is slow, with the growth phase occurring at a faster rate (4).

Drug discovery efforts can be summarized as i) modulating protein levels; ii) targeting post-translation modifications, e.g., kinase inhibitors; iii) kinetic stabilization of nontoxic oligomers; and iv) inhibitors of aggregation, for example with protein–protein interaction (PPI) inhibitors.

An example of a molecule stabilizing nontoxic oligomers is tafamidis (Fig. 1). This molecule binds between the interface of two protein dimers and in doing so kinetically stabilizes the resultant tetramer. This reduces further amyloidogenicity; the compound has low toxicity and good oral bioavailability and is currently in clinical development (5).

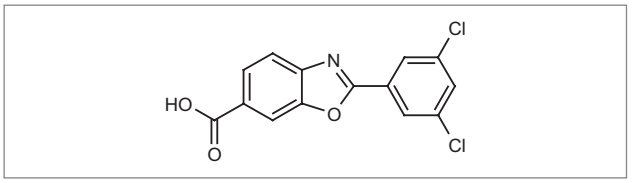

Figure 1. Structure of tafamidis, a candidate for the prevention of amyloidosis.

The pathology of Alzheimer's disease was outlined. This was shown to involve the formation of amyloid plaques and neurofibrillary tangles (NFT), which lead to neurodegeneration and inflammation, and neuronal toxicity respectively was depicted. This led to the connection between tau and AD wherein tau and β-amyloid deposits have been found to be hallmarks of Alzheimer's disease. The correlation between tau pathology and cognitive decline and neurodegeneration in Alzheimer's disease was graphically depicted (6). While in normal pathology tau binds and stabilizes axonal microtubules, in Alzheimer's disease this process is disrupted, the tau proteins aggregate, and thus microtubules become defective leading to a diseased neuron (Fig. 2).

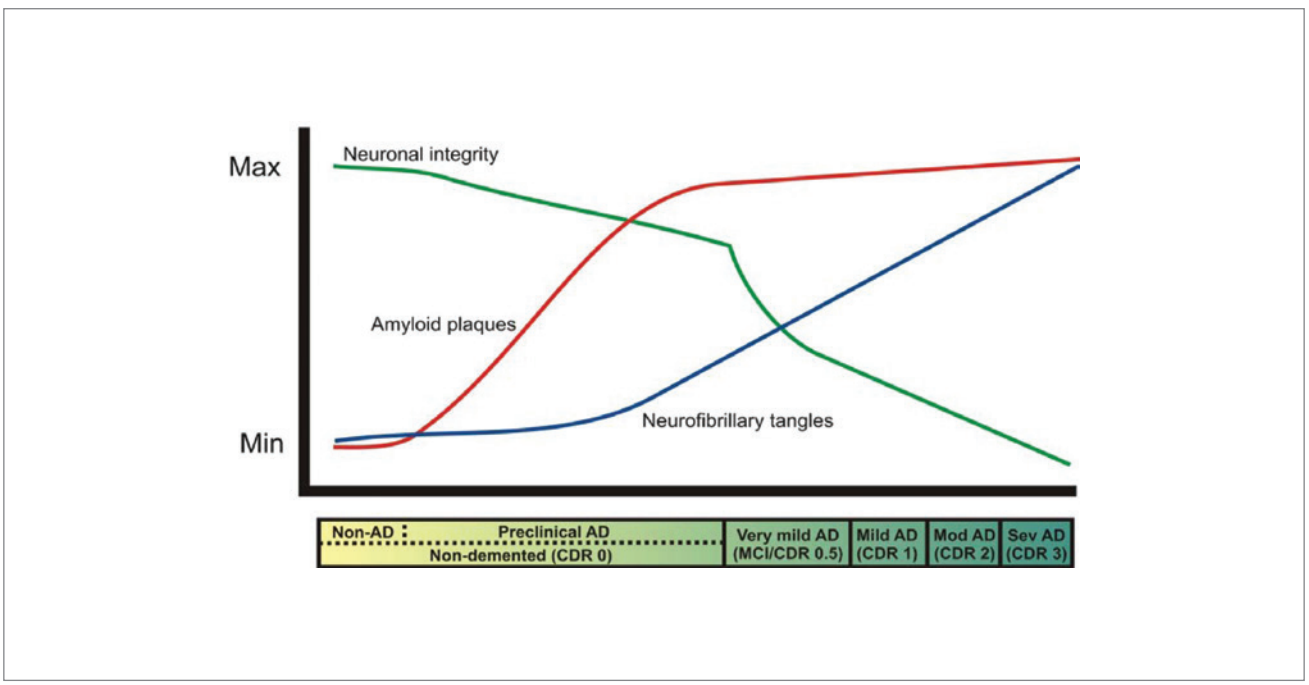

Figure 2. Relationship between neuronal integrity and amyloid plaque build-up.

There were shown to be advances in determining the structure of tau fibrils by cryo-electron microscopy (cryo-EM); through the use of this technology key segments for aggregation have been identified. This includes the VQIVYK segment, the structure of which has been determined by X-ray crystallography. Another segment, D-TLKIVW, has been found to inhibit the elongation of tau fibrils (7). The peptide thus caps the end of a tau fibril and prevents further accumulation—it does not interact with monomeric tau. The functional effect of the inhibitor was shown in a HEK-293T cell assay whereby D-TLKIVW was shown to reduce seeded tau aggregation in a dose-dependent manner (8).

Developing Leads at the Interface of Biology and Chemistry

ADCs at LifeArc: design, analysis & application

This talk, by Elizabeth Love (LifeArc), began with an explanation of LifeArc, which is the rebranded MRC Technology. They have in-house expertise on antibody engineering, small-molecule drug discovery and diagnostics development. They aim to bridge the gap between basic research and early drug discovery and work with industry, charities and universities.

The talk focused on antibody–drug conjugates (ADCs) and contained two case studies. An outline of the structure of an ADC was given followed by an explanation of their mode of action (MoA). This is summarized in Figure 3.

ADCs bind to the tumor-specific antigens and become internalized. The drug payload is then released through cleavage of the linker and the drug is free to bind to its molecular target leading to apoptosis of the cancer cell.

An overview was given of conjugate analysis wherein the average drug-to-antibody ratio (DAR) is determined and how that impacts on the efficacy of the drug and the pharmacokinetic/pharmacodynamic characteristics of the ADC. A short summary of ADC linkers and types of payloads was highlighted.

The first case study centered on anaplastic lymphoma kinase (ALK)-targeting ADCs for neuroblastoma. This project is run in collaboration with the Mount Sinai School of Medicine (New York). ALK is a transmembrane receptor tyrosine kinase; the mutation or overexpression of this receptor is thought to drive oncogenesis and correlates with poor prognosis in patients with neuroblastoma, a rare childhood cancer (9).

Antibodies were generated using hybridoma technology and 1,152 clones were screened by ELISA and flow cytometry for binding to human and mouse ALK. To screen antibodies for use in an effective ADC strategy, several methods were employed. One of these is intracellular localization which was determined using flow cytometry. In this case, the total fluorescence signal of a tag-bound antibody was measured both inside and outside of a cell; the cells were then washed/quenched and the fluorescence signal inside

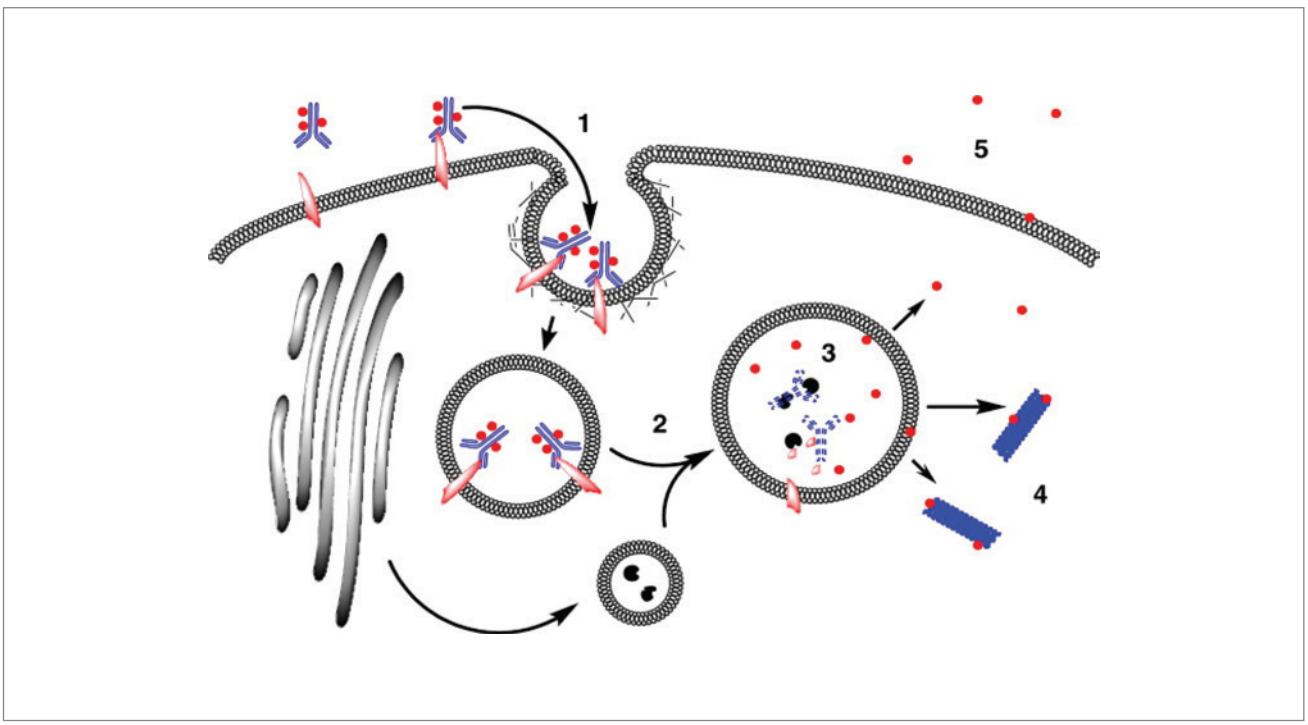

Figure 3. Antibody–drug conjugates' mode of action.

the cell measured. This allowed the measurement of the quantity of antibody that could be, or had been, internalized into the cell. Eventually the team was able to conclude that ALK-ADCs are able to induce cell death in a manner reflective of their binding capabilities. The next steps for the project are to determine whether these results translate in vivo.

The second case study centered on the question of whether a selective antibody could direct a nonselective small molecule. This was carried out in the context of matrix metalloproteinases (MMPs), which degrade structural components of the extracellular matrix. The team studied MMP-9 and screened for an antibody selective against this metalloproteinase (10). They created an ADC wherein the small molecule and the antibody maintained activity when conjugated and sought to use the antibody binding kinetics to drive the ADC selectivity. The selectivity of these conjugates was explored using biochemical assays and early observations are that selectivity between the MMPs can indeed be achieved. The group is currently trying to determine the K_D of small molecules using further technologies such as SPR.

The talk was concluded by summarizing that ADCs could provide new opportunities for small molecule selectivity.

Proteins, lipids and drug discovery: from malaria to the common cold

Prof. Ed Tate (Imperial College London) gave a talk expanding on his group's interest in understanding protein lipidation as a post-translational modification. Profiling of protein lipidation using chemical proteomic technologies (11) involves tagging with small reporters which do not disrupt metabolism and function, but can be chemoselectively labeled to open up quantitative whole proteome studies. For example, a terminal alkyne-containing myristoyl derivative (YnMyr) can be incorporated into a biological system and, following lysis and extraction, ligated with a multifunctional azide label via click chemistry to study the role of *N*-myristoyltransferase (NMT). This approach has been used to validate NMT as an antimalarial drug target (12).

Through a broad public–private partnership involving academic institutions, pharmaceutical companies, research councils and nongovernment organizations, high-throughput screening has been used to identify several series of NMT inhibitors with differing selectivity profiles across parasitic species and human orthologues (13). A synergy screening approach was then taken to identify replacement fragments which could be appended to the indazole hit to generate a lead indazole inhibitor, and further optimization led to the identification of an imidazolopyridine lead series (14) with picomolar activity against parasite NMTs.

Prof. Tate moved on to discuss human rhinovirus (HRV, common cold virus) as a common cause of exacerbation in chronic obstructive pulmonary disease and asthma, leading to secondary and bacterial infections. A safe, effective anti-cold drug could have significant benefit for the most severely affected patients, but no antiviral or vaccine is available due to the vast range of variants, and more than 20 years of attempts to target the virus itself has failed to yield an effective drug. Chemical proteomics using YnMyr has demonstrated that the HRV capsid is myristoylated in infected cells, and this is potently inhibited by NMT inhibitors. Using undisclosed picomolar human NMT inhibitors IMP-1088 and IMP-1031, NMT inhibition has been shown to be nontoxic to cells over the period of HRV infection, to prevent cell death following HRV infection in HeLa cells and to block formation of infectious virus. Further studies have shown NMT inhibitors to be broad-spectrum antipicornaviral agents.

For the final section of his talk, Prof. Tate returned to chemical proteomics, briefly discussing the dual tagging of Sonic hedgehog protein in living cancer cells to probe its function, and approaches to probing dynamic acylation across living systems more generally.

Enabling Hit Finding

Phenotypic activity-driven target identification

Prof. Paul Wyatt (University of Dundee) spoke about three of the Drug Discovery Unit's programs to illustrate phenotypic activity-driven target identification and representing one of the unit's remits of research into infectious diseases of low- and middle-income countries. He first described the identification of DDD-853651/GSK-3186899 (Fig. 4), a preclinical candidate for the treatment of visceral leishmaniasis with a novel mechanism of action, arising from a Wellcome-funded collaboration with GlaxoSmithKline focused on the kinetoplastids. The pyrazolopyrimidine series which delivered '899 was initially identified through its activity against the *Leishmania donovani* strain, and SILAC (stable isotope labeling in cell culture) technology was used to identify CRK12, CRK6, CYC9, CRK3, CYC6 and STE11 as specific binders to this series of compounds. Resistant *L. donovani* cell lines were then generated by growing clonal parasites in the presence of two separate pyrazolopyrimidine analogues, and whole-genome sequencing identified a single nucleotide polymorphism (SNP) at position 1715 of the gene encoding CRK12 in all 6 independently generated

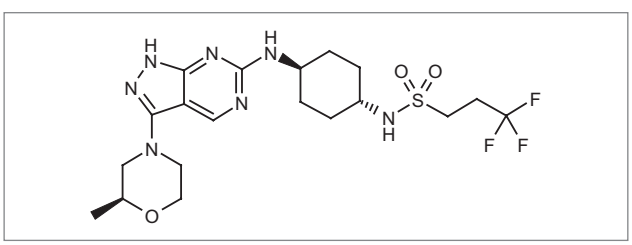

Figure 4. Structure of DDD-853651/GSK-3186899, a candidate for the treatment of visceral leishmaniasis.

cell lines. Reconstitution of combinations of mutations and amplifications found in the resistant cell lines, and co-overexpression studies were used to confirm that the principal target of the series is the CYC9-activated form of CRK12. Further evidence of this entirely novel mechanism of action was obtained using the kinobead technology from Cellzome to study *Leishmania* lysates which had been incubated with varying concentrations of pyrazolopyrimidine. In summary, DDD-853651/GSK-3186899 is a drug-like compound with efficacy in a visceral leishmaniasis mouse model which is being advanced towards human clinical trials.

The second area covered was an antimalarial collaboration with the Medicines for Malaria Venture (MMV) (15), where the clinical candidate DDD-107498 (Fig. 5) was identified from a hit series of quinolines. DDD-107498 has long predicted human half-life, potent antimalarial activity against all life-cycle stages of the *Plasmodium* parasite and an acceptable safety margin, with the potential for a single dose cure. In addition, it prevents mouse-to-mouse transmission and is highly efficacious in mouse chemoprotection models. Part of the MMV development portfolio, DDD-107498 has been licensed to Merck KGaA for clinical development. Once again, the MoA of this phenotypically identified compound series was determined by sequence analysis of DNA from resistant mutants. Inhibition of translation elongation factor 2 (eEF2) was further confirmed by molecular and cellular biology studies. eEF2 has a key role in protein synthesis, inhibition of which could be demonstrated in wild-type malaria parasites.

The third part of Prof. Wyatt's talk referred to a multicenter (National Institute of Allergy and Infectious diseases, Foundation for the National Institutes of Health, Universities of Dundee, Cape Town and Cambridge, supported by the Bill and Melinda Gates Foundation) collaboration on tuberculosis drug discovery, aimed at generating validated hit series. An integrated biology and medicinal chemistry approach to hit triage from phenotypic screening is being used to identify optimal starting chemical space and novel MoA. For example, compounds with a cell wall synthesis MoA are often associated with high lipophilicity, and correspondingly such compounds can be promiscuous. Inhibition of the cytochrome bc1 complex cytochrome b subunit (Qcrb) is a known antituberculosis mechanism of concern due to the promiscuity of the bc1 complex (16). The TBK6 series, exemplified by DDD-00079282 (Fig. 6), is considered a high-quality starting point due to its good drug-like properties, reasonable in vitro potency and modest efficacy in an in vivo screening model. It has an unknown MoA, although cell wall targets and likely Qcrb have been ruled out. Hit-to-lead chemistry was initiated to address the MoA, improve potency and to remove the Ames liability associated with the potential aminoindazole metabolites. Target identification using resistant mutants found large genomic duplication encompassing the *GuaB2*/*IMPDH* gene. The identity of IMPDH, a key enzyme in the synthesis of guanine, as a molecular target was further confirmed through pulldown experiments (Cellzome). Although the biological profile of the TBK6 series was broadly promising, compounds were found to be poorly active in a more stringent mouse efficacy model and levels of guanine, which can rescue inhibited growth in vitro, were found to be high in patient lung samples. As a result, the pursuit of the TBK6 series and IMPDH as a target have been halted.

In summary, phenotypic screening is being used at the Drug Discovery Unit as a means to identify preclinical candidates and high-value validated molecular drug targets for the treatment of neglected diseases.

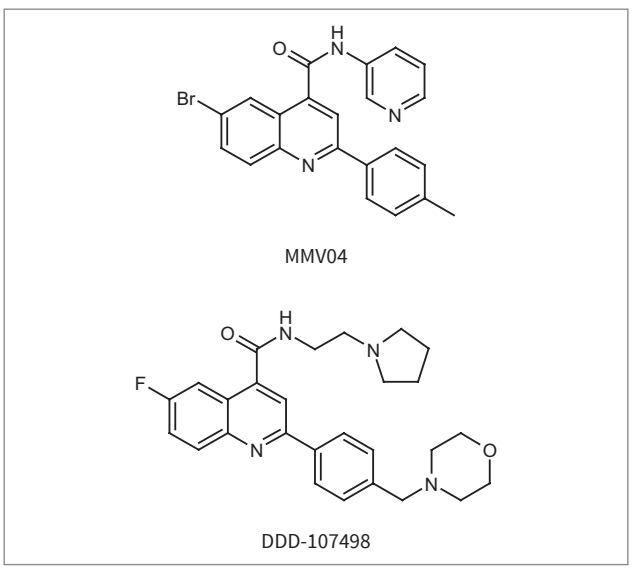

Figure 5. An example structure of the MMV04 quinoline series and structure of DDD-107498, an antimalarial candidate.

Antibody-enabled small-molecule drug discovery

Dr. Alastair D.G. Lawson (UCB) gave a talk in which knowledge from interactions of function-modifying antibodies with target proteins is being used to inform small-molecule drug discovery.

Many pharma companies today have a balance of both antibody and small molecule projects in their research portfolio, and the remarkable rise of therapeutic antibodies over the last 30 years has shown the potential for taking on PPIs in medicine.

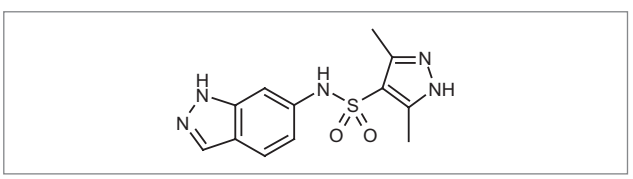

Figure 6. Structure of DDD-00079282, an example of the TBK6 series of antituberculosis compounds.

Aside from development entities in their own right, antibodies also provide insight into the optimal mechanism by which PPIs can be modulated and thereby provide useful information to guide small-molecule design and screening. The approach is particularly relevant to the problem of tackling PPIs at allosteric sites, with antibodies guiding drug discovery especially in the following areas:

- Providing clinical, or at least in vivo, validation of the target, and in so doing reducing biological risk around the target.
- Providing chaperone function in structural studies, such as X-ray crystallography and cryo-EM (17).
- Stabilizing biologically relevant, but possibly rarely sampled, conformations of target proteins. A good example is the recently described structure of the β_2-adrenoceptor in the active conformation, achieved through stabilization of this functional state using a camelid-derived VHH (18).
- Providing wet lab definition of conformations of target proteins predicted by molecular dynamics simulations. Recent work within UCB has allowed a linking of X-ray crystallography and function-modifying antibodies with molecular dynamics simulations for IgE, for example (19).

PPIs are an important, if challenging class of targets. It has become clear that in developing effective inhibitors of PPIs, ligands need to be not only capable of efficiently filling the biological space in the binding pocket but also intrinsically rigid enough to inhibit the PPI function maximally (20).

Finally, Dr. Lawson highlighted the vast potential of fragment screening to sample new areas of chemical space that are significantly less accessible using existing compound collections. The UCB fragment library consists of some 20,000 fragments based on clinically validated chemical space (21). Libraries such as this one have been applied to antibody-stabilized screening of targets (22).

Making Leads into Chemistry-driven Candidates

Macrocycles in 3D: a journey towards intracellular activity

Dr. Elisabetta Chiarparin (IMEDBiotech Unit, AstraZeneca) started by recognizing the growing importance that macrocycles are having as viable lead matter for drug discovery programs, leading to some 70 macrocyclic molecules of both natural and synthetic origin currently in clinical development.

Macrocycles can be attractive starting points as they often have very high levels of potency and selectivity against most pharmaceutical target classes and can offer excellent developability properties. On the other hand, they can occupy nonclassical regions of chemical space and are often difficult to synthesize. This lecture focused on the development of methods to model macrocyclic conformation to aid medicinal chemistry design and thereby improve efficiency within macrocyclic drug discovery programs.

The first example highlighted (23) was a macrocyclic version of an MTH1 lead structure, which featured a short pegylated macrocyclic ring of very similar lipophilicity with much enhanced potency at the target (Fig. 7).

The acyclic lead compound is significantly more flexible and can access multiple unproductive and nonbioactive conformations with incumbent energy penalties and consequently lower affinity. The AstraZeneca group started by looking at free ligand conformations using nuclear magnetic resonance (NMR) methods; chemical shifts of key ligand residues differed greatly between bioactive and nonbioactive conformations which were then rationalized using ligand docking into the protein active site. In this way, specific 1H chemical shifts of the free ligand were identified as being bioactive conformational signatures and were targeted in subsequent analogue designs. These NMR signatures are very straightforward to measure and along with

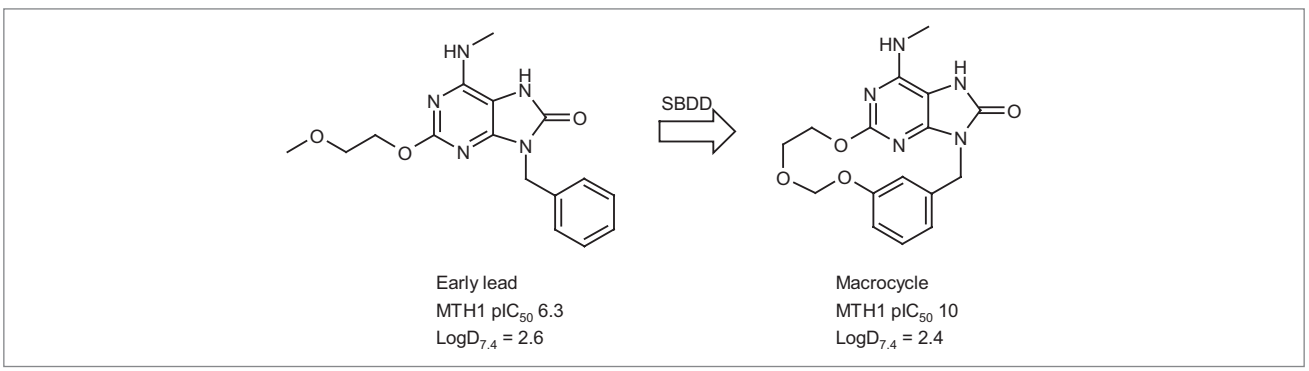

Figure 7. The evolution of an MTH1 hit using structure-based design.

ligand potency can rationalize 3D structure–activity relationships (SAR).

A second example (24) concerned PPIs with the BCL6 (B-cell lymphoma 6) target protein (Fig. 8). PPIs have traditionally been a challenging target class, and difficult to obtain very potent ligands.

In this case, optimization of an initial weak fragment hit led to a nanomolar potency macrocyclic inhibitor. Once again an evaluation of the free ligand bioactive conformational determinants using a combination of NMR chemical shift analysis and potency values allowed for rapid improvements in ligand potency. An important step in this process was to assess the fraction of conformers available to any prospective ligand design that could adopt a bioactive-like conformation and thereby enjoy a potency advantage. Optimizing macrocyclic ligand designs to match the bioactive X-ray-bound conformations led to optimal ligand k_{on} rates, and further increase in potency was largely driven by slow k_{off} values from the target protein.

A second PPI example concerned inhibitors of Mcl-1 (25). In this example, a micromolar hit was developed into a more polar, nanomolar lead (Fig. 9).

Rational linker SAR could be obtained by measuring the free ligand conformations: N-Me amide analogue is fully preorganized into the bioactive conformation and it shows 10-fold higher affinity and on rate kinetic, than the nonmethylated N-H analogue, which was instead locked in a nonbioactive conformation. Similar analysis of free ligand signatures and potency were used to focus synthetic efforts of proximal substitutions in the macrocyclic ring. A second chemical series was also developed against the Mcl-1 target, which has led to an exquisitely potent clinical candidate—AZD-5591—for treatment of hematological cancers. In this case, the lead structure contained a biaryl unit which showed atropisomerism. Metadynamics and experimental NMR and SFC data on the free ligand were used to optimize the biaryl linkage for the bioactive preferred atropisomer.

The talk concluded with a summary of the integrated platform that underpins this work.

AstraZeneca have invested in an efficient NMR platform, combined with computational modeling and X-ray crystallography to rapidly inform and enhance the design hypotheses of the medicinal chemist (Fig. 10).

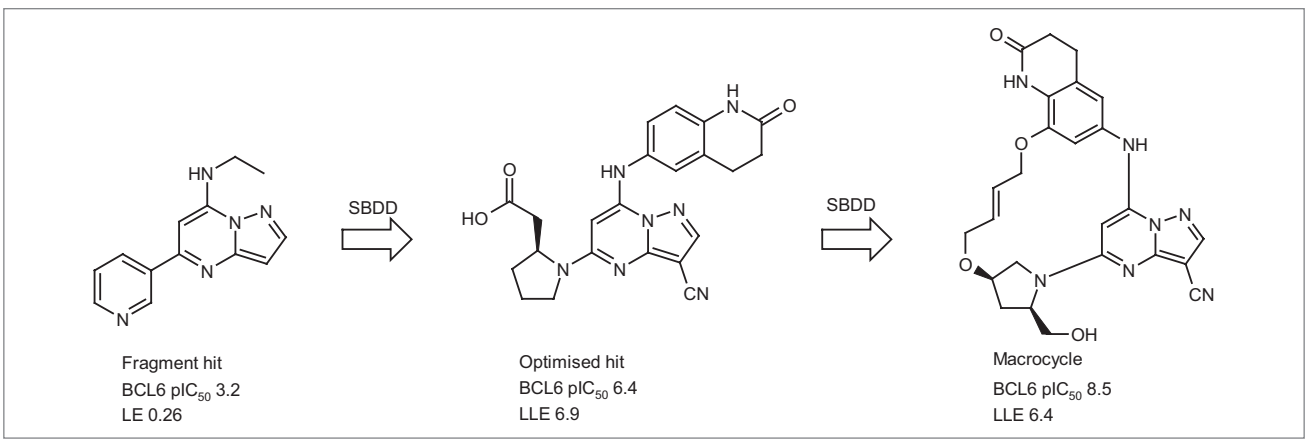

Figure 8. The evolution of a BCL6 hit using structure-based design.

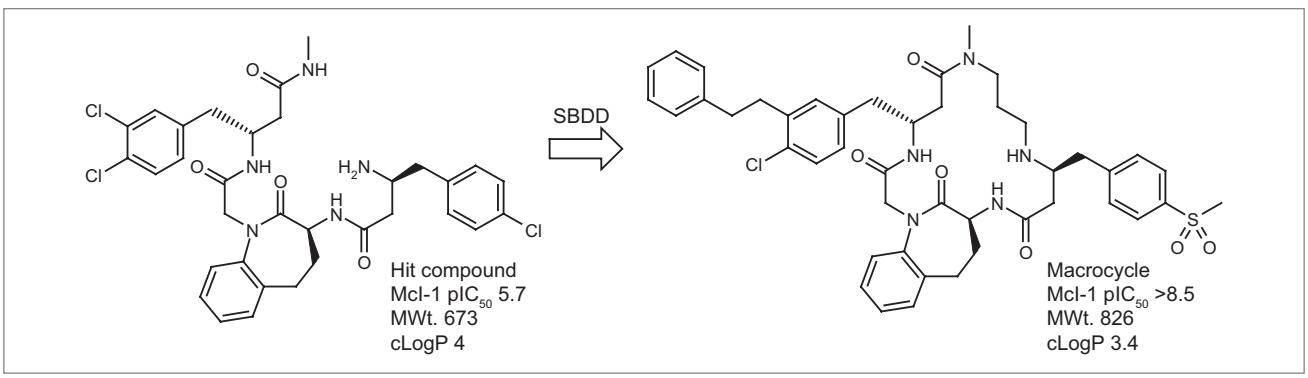

Figure 9. The evolution of a Mcl-1 hit using structure-based design.

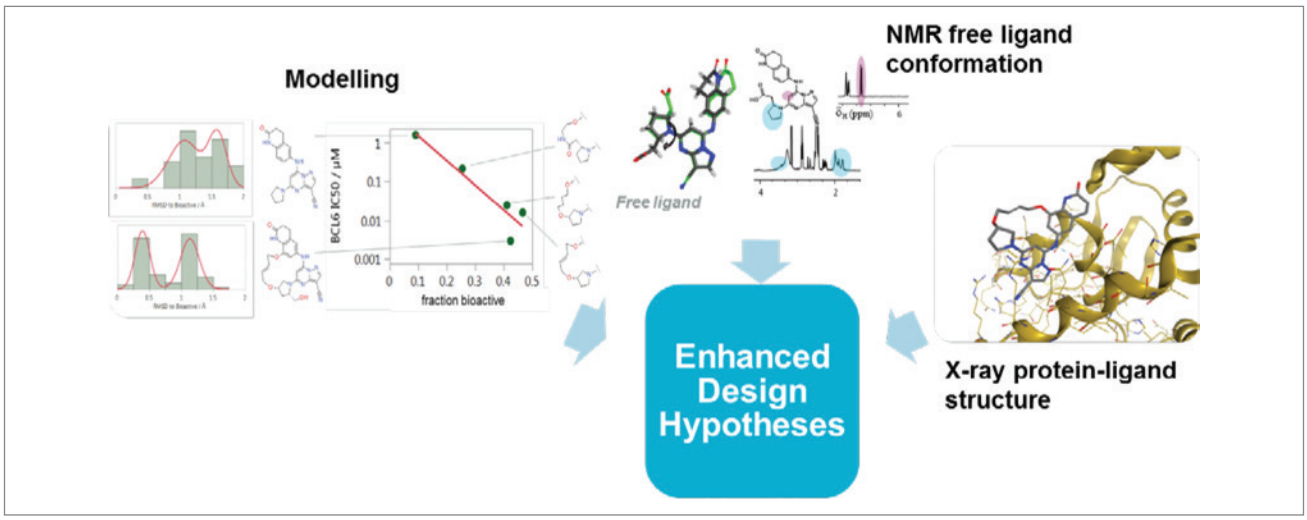

Figure 10. The AstraZeneca platform to enhance compound design.

A song of 6p—genuine diversity in short order: development of facile 2+2+2 cyclotrimerization chemistry and applications in drug discovery

Dr. Simon Peace (GlaxoSmithKline) spoke about the GlaxoSmithKline PI3Kδ (phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit δ isoform) program. This is a promising target for asthma, chronic obstructive pulmonary disease and autoimmune diseases, but selectivity over the other PI3K isoforms (α, β and γ) is critical for safe target engagement.

In earlier work, a potent indazole series had been identified (26) with subsequent efforts directed at lower clearance versions of this series (Fig. 11) (27).

The initial lead was deconstructed and a range of alternative hinge binders were investigated. One early hit from these efforts was a 2,3-dihydrobenzofuran. A synthetic strategy was developed to make these core structures, with a disubstituted dihydrobenzofuran being a key intermediate (Fig. 12).

To access this intermediate, a cyclotrimerization reaction was developed from a literature method starting from an alkyne and suitable diyne which was reportedly selective for the meta-arrangement of the two substituents in the product (Fig. 13) (28).

Development of the method in collaboration with the University of Strathclyde allowed for efficient regioselective control to favor the desired meta-isomer. Functional group tolerance was good, and both protic and aprotic solvents could be used in the trimerization reaction. Importantly, no excess of the valuable monoyne was needed. Attempts to make the 6-membered tetrahydropyran analogue were unsuccessful. A noted limitation to the chemistry was the need for an entropically favorable linker and anything in excess of a 3-atom linker was not successful.

The dihydrobenzofuran series showed an excellent potency and a selectivity profile against the PI3K isoforms that was comparable to that of the lead molecules. Most notably, the series also demonstrated good oral pharmacokinetics with improved clearance compared to the starting leads. The chemistry was sufficiently flexible that the team was able to sample chemical space rapidly. This allowed a comprehensive evaluation of substituent positions around the dihydrobenzofuran ring system to assess the influence of analogues on selectivity,

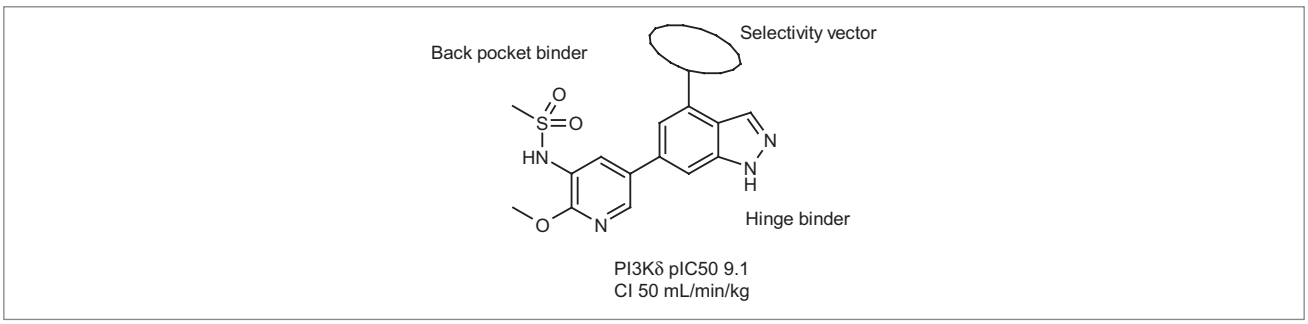

Figure 11. An earlier indazole-based series of potent PI3Kδ inhibitors.

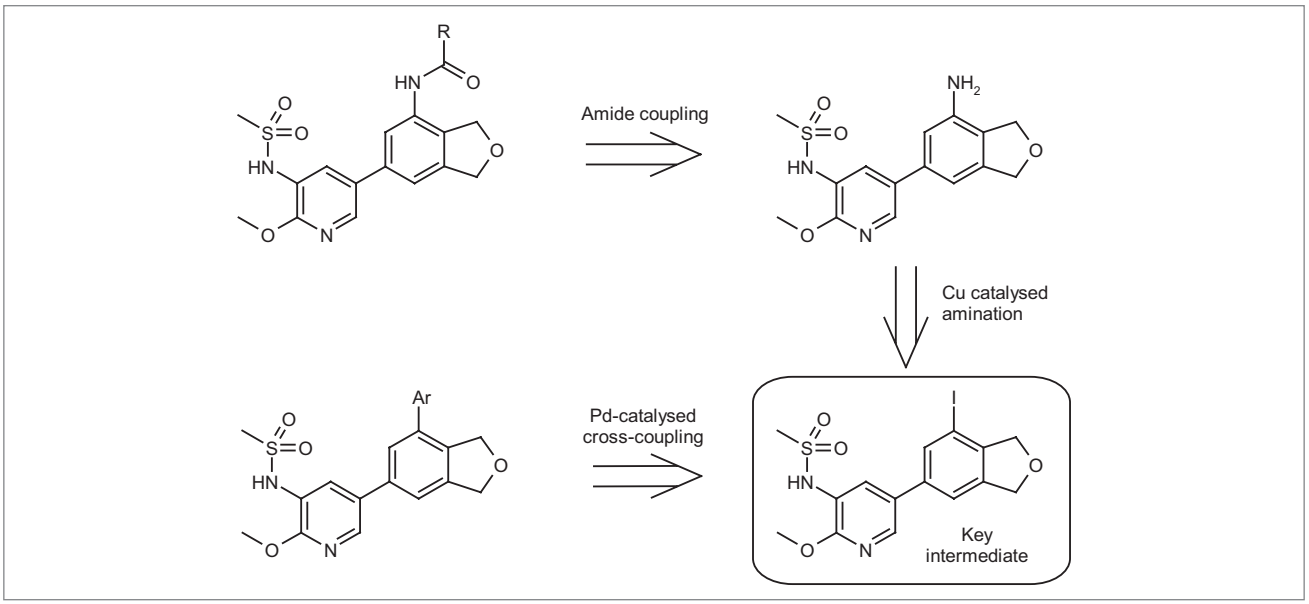

Figure 12. Synthetic strategy for building dihydrobenzofuran-based targets.

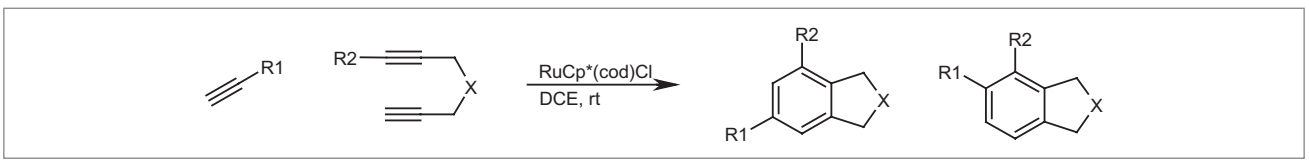

Figure 13. A cyclotrimerization strategy to construct the dihydrobenzofuran core.

accessing specific residues within the active site and clearance. Ultimately the chemistry did allow the team to test a range of hypotheses to drive the optimization of the series.

Disclosures

D.C. Pryde, N.M. Ahmad and M.E. Swarbrick are in paid employment of their respective organizations. D.C Pryde is an SMR Committee member and N.M. Ahmad and M.E. Swarbrick are RSC BMCS committee members, for which no remuneration is paid.

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