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Clarivate Analytics

Meeting Report

Recent Clinical Disclosures and SMR Award. Highlights from The Society for Medicines Research Symposium

London, UK – December 5, 2019

P. Brown[1], S. Butterworth[2], M.M. Hann[3], P. Jeffrey[4], R. Porter[5], M.E. Swarbrick[6] and S.E. Ward[7]

[1]Pam Brown Consulting Ltd, Stevenage, UK; [2]University of Manchester, Manchester, UK; [3]GlaxoSmithKline, Stevenage, UK; [4]Bicycle Therapeutics, Cambridge, UK; [5]RodPorterConsultancy, Ashwell, UK; [6]Cancer Research UK Therapeutic Discovery Laboratories, Cambridge, UK; [7]Cardiff University, Cardiff, UK

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Summary

On December 5, 2019, The Society for Medicines Research (SMR) held a 1-day meeting in London on Recent Clinical Disclosures. The symposium featured an international lineup of speakers presenting on the discovery and development of novel therapeutic agents covering a variety of mechanistic approaches in therapeutic areas including oncology, anti-infectives and inflammation. The program also featured the 2019 Society for Medicines Research Award Lecture, given by Dr. Andrew Chan of Genentech, on the discovery and development of ocrelizumab, a humanized anti-CD20 monoclonal antibody for the treatment of multiple sclerosis. The meeting was held at Friends House, London, UK.

Key words: Ocrelizumab – UCB-6876 – UCB-9260 – SPR-206 – BOS-172722 – Bicycle toxin conjugates – AZD1390 – Nemiralisib

Correspondence: The Society for Medicines Research, Q House, Troon Way Business Centre, Humberstone Lane, Thurmaston, Leicester, LE4 9HA, UK. E-mail: secretariat@smr.org.uk.

2019 SMR Award Lecture: Targeting B Cells: Journeys of Anti-CD20 Therapeutic Antibodies – Discovery and Development of Ocrelizumab

Dr. Andrew Chan (Genentech, USA) was the 2019 recipient of the SMR Award for Drug Discovery for **Ocrelizumab** (Genentech). Dr. Chan opened his lecture with a brief overview of the pathogenic roles of B cells in cancers and autoimmune disorders and a summary of the cumulative experiences to date in the clinic with anti-CD20 therapeutic monoclonal antibodies (MAbs). The originating studies of a predecessor MAb, rituximab, which had been efficacious in a range of autoimmune disorders including multiple sclerosis (MS), stimulated interest in B-cell depletion as a therapeutic strategy, as well as off-label use of rituximab in MS. Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20 on B cells, designed to have reduced immunogenicity than nonhumanized rituximab. Initial studies with ocrelizumab in lupus and rheumatoid arthritis were stopped following an analysis of the opportunistic infection rate which was specifically

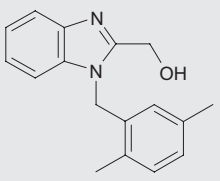
elevated in Asian populations. A follow-up trial in MS was reported in 2010 which was then followed by three parallel phase III trials which led to the approval of ocrelizumab initially for primary progressive MS (PPMS) and subsequently relapsing–remitting multiple sclerosis (RMS). The study in PPMS, where there were no other approved therapies, demonstrated a 24% reduction in the risk of the Confirmed Disability Progression (CDP) using the standard scales of Expanded Disability Status (EDDS) compared to placebo. Improvements were seen in PPMS patients treated with ocrelizumab in timed 25-foot walk, whole brain volume and T2 lesion brain volume, and these improvements were sustained beyond the end of the study to the current date. For RMS, 2-year treatment showed reduction in inflammatory lesions in the brain and reduced annual relapse rate compared to the standard of care at the time, beta-interferon. This benefit was also sustained beyond the end of the study through the 4-year follow-up. The understanding gained from these studies and the subsequent phase IV follow-up safety and efficacy studies in both broader populations and to assess any potential cancer risk, is now directing the next generation of immunomodulators for further B-cell therapeutic opportunities.

Tackling Protein–Protein Interactions Through Stabilization of Desired Conformations of Target Proteins. The Discovery of Small-molecule Inhibitors of TNF

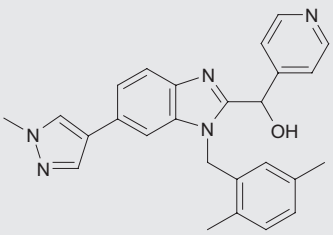
To date, interfering with the tumor necrosis factor (TNF)/TNF receptor (TNFR) pathway using a small molecule to disrupt this protein–protein interaction (PPI) has not proved a viable approach toward an anti-inflammatory drug at this important biology node. In contrast, anti-TNF antibodies have proved to be some of the most successful drugs in the last two decades. Despite this, the challenge of trying to find effective small-molecule inhibitors at this PPI continues and Jim O'Connell (UCB, UK) described an exciting new possible approach that he and colleagues at UCB have been pursuing.

Beginning over 10 years ago, UCB adopted a fragment-based approach to look for weak binders to TNFR1 using SPR (Biacore) and an MSD competition assay, which they then hoped to optimize by crystallizing with receptor aided by their collaborators at DeCode/Beryllium. In the SPR assay they used the ligand, TNF, to check that compounds would be selective for TNFR1 in the knowledge that TNF could be a target in its own right. Unexpectedly, a series of benzimidazoles, exemplified by **UCB-6876** were shown by SPR to bind specifically to TNF and did not bind to TNFR1. Rather than inhibiting the TNF:TNFR1 interaction, however, they were found to be stabilizers in the MSD competition assay. SPR confirmed the stabilization of the TNF:TNFR1 complex and then mass spectrometry was used to show that these molecules stabilize the TNF trimer itself, protecting the trimer from dissociating to monomer induced by DMSO. Moreover, this technique also showed that the compound was able to stop the interchange of mouse and human TNF monomers, a process normally leading to mixed mouse:human trimers. It seemed, therefore, that stabilization of TNF resulted in the subsequent stabilization of the TNF:TNFR1 complex. It was interesting that only a single compound bound per trimer, but this MOA did not provide an obvious route to a drug to block TNF signaling. They were excited to discover, however, that UCB-6876 inhibited in an L929 TNF-α cytotoxicity assay. X-ray crystallography finally showed how UCB-6876 bound to a novel asymmetrical crystal form of the TNF trimer. The compound is bound in a cryptic binding pocket which is absent in the apo structure. With insights from the structure in hand, medicinal chemists rapidly optimized compounds with improved affinity and DMPK properties leading to **UCB-9260** (K_D of 13 nM) which was active in both mouse and human biochemical assays and showed oral activity in a mouse CAIA model of rheumatoid arthritis. Molecular modeling studies using molecular dynamics suggested that TNF stabilized by the UCB compounds may be a metastable form produced during the formation of the symmetrical trimer from monomers and dimers. Further crystallographic studies have shown that this asymmetric trimer is only able to bind two receptor molecules, in contrast to symmetrical TNF which supports the binding of three receptor molecules leading to the potential of TNF/TNFR1 to aggregate into complexes and to raft formation. It is the formation of these rafts that likely propagates the inflammatory signal and explains how blocking raft formation by stabilizing a nonproductive form of the complex acts in an anti-inflammatory.

UCB, in collaboration with Sanofi, have optimized the compounds further and are continuing to evaluate compounds



UCB-6876



UCB-9260

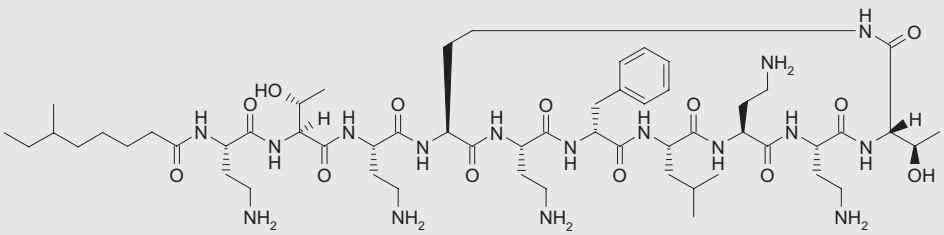
in preclinical models in order to produce a molecule suitable for clinical trials. The prospect of an effective small-molecule drug working in this highly validated biology space is intriguing from many perspectives, not least the opportunity for CNS-penetrating anti-TNF drugs which is not currently exploitable with antibodies.

This work is recently published in *Nature Communications* (1).

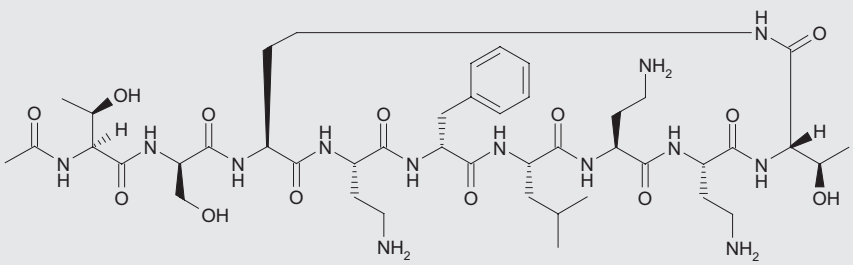
Next-Generation Polymyxin Analogue SPR-206 for Multidrug-resistant Gram-Negative Infections

Dr. Troy Lister from Spero Therapeutics, USA, described work leading to the identification of **SPR-206**. There remains a great unmet need for treatment of problematic Gram-negative bacterial infections. As an example, in the United States, over 50% of infections caused by *Acinetobacter baumannii* are resistant to carbapenems, while the resistance rate in *Pseudomonas* species is over 20%. One series of compounds that can address this issue is the polymyxin antibiotics, **polymyxin B** (PMB) and polymyxin E (colistin), which are finding increased use in the clinic despite serious safety concerns, in particular kidney toxicity (nephrotoxicity) which severely limits dosing.

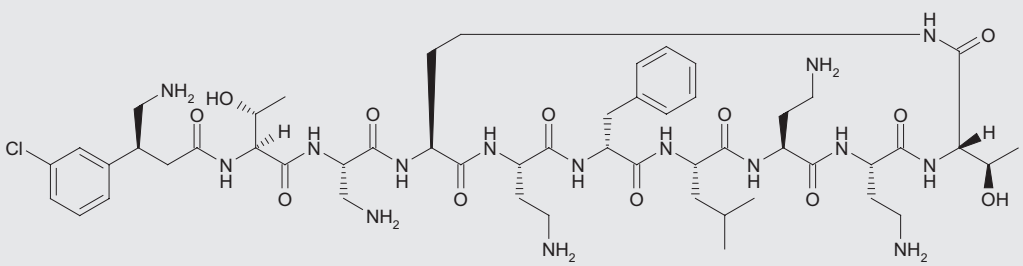
Polymyxins consist of a cyclic heptapeptide core with a tripeptide tail capped at the N-terminus with a lipid chain. An earlier modified polymyxin, **SPR-741**, lacking the N-terminal chain and with a modified linear peptide, which lacks intrinsic activity but potentiates the action of other antibiotics, shows reduced toxicity and has been successfully taken into the clinic by Spero Therapeutics. Initial discovery work leading to SPR-206 was carried out at Cantab Anti-infectives and revolved around the development of modified polymyxin analogues which retained antibacterial activity while showing reduced in vitro toxicity. This involved replacing the diamino butyric acid (Dab) residue adjacent to the core with diamino propionate (Dap), and



Polymyxin B



SPR-741



SPR-206

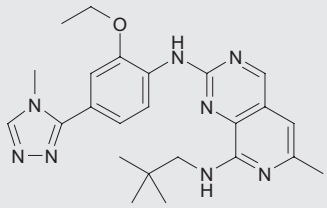
replacing both the N-terminal lipid chain and first Dab residue with an amine-containing group of specific regio-and stereochemistry. Using a mouse model of renal toxicity, the team was able to demonstrate that in vivo toxicity was related to both in vitro cytotoxicity against the kidney proximal tubule cell-line HK-2 and to in vivo kidney exposure. This led to a focus on optimizing antimicrobial activity, while reducing in vitro cytotoxicity and keeping in vivo kidney accumulation to a minimum (2), resulting in the β-branched amino propionate SPR-206 which showed over 10-fold lower cytotoxicity with similar kidney exposure to PMB. Following encouraging mouse toxicity, the compound was progressed to the cynomolgus monkey, since the dog is not a suitable model for polymyxins. In a non-GLP study in the monkey, SPR-206 at 60 mg/kg/day gave no increase in blood urea nitrogen (BUN) and a 1.5× increase in serum creatinine, whereas polymyxin at 12 mg/kg/day resulted in a 2× increase in BUN, 3× increase in serum creatinine, and more marked renal histopathology results. In vitro, SPR-206 showed very encouraging activity against a wide range of recent clinical isolates with a lower MIC_{90} compared to colistin against species of all four key pathogens, *Acinetobacter*, *Escherichia coli*, *Klebsiella* and *Pseudomonas aeruginosa*. Encouragingly, SPR-206 demonstrated improved activity against a range of clinical isolates of polymyxin-resistant *A. baumannii*. In in vivo infection models in the mouse, SPR-206 behaved similarly to PMB in the thigh, and with significantly improved activity in the lung. A 14-day GLP repeat dose toxicology study in the monkey showed near identical safety profiles for SPR-206 and SPR-741 at equivalent exposure, and a NOAEL for SPR-206 of 30 mg/kg indicating a greater than 6-fold safety margin over free exposure required for efficacy.

SPR-206 is currently undergoing a single-center single-ascending-dose/multiple-ascending dose phase I clinical study with a planned 108 subjects in Australia.

MPS1 Kinase Inhibitors Targeting Breast Cancer

Prof. Spiros Linardopoulos from the Institute of Cancer Research (ICR), UK, discussed his team's work on the discovery and in vivo efficacy of MPS1 inhibitors as a novel approach to target basal-like breast cancer. Basal-like breast cancer has received considerable attention in recent years, however, despite this effort conventional chemotherapy primarily with taxane remains the main therapeutic option. A significant issue in identifying new, effective therapeutics may be related to the high degree of heterogeneity and aneuploidy characteristic of basal-like breast cancer. From this the ICR team targeted MPS1 (also known as TTK), one of the main spindle assembly checkpoint kinases, based on the concept that cancer cells may be targeted by the introduction of a detrimental level of aneuploidy. MPS1 (monopolar spindle kinase-1) is a serine/threonine tyrosine kinase and is involved in regulation of the SAC (spindle assembly checkpoint), a protein complex that ensures the correct chromosome alignment during mitosis. siRNA kinome screening across multiple breast cancer cell lines supported the identification of MPS1 as an exciting target.

Prof. Linardopoulos went on to briefly describe, starting from two screening hits and a scaffold hop, the identification of **BOS-172722** (3), a potent and selective MPS1 inhibitor (IC_{50} 12 nM at 1 mM ATP). BOS-172722 had no hERG or P450 liabilities and good pharmacokinetics (PK).



BOS-172722

In multiple breast cancer cell lines, robust synergy of BOS-172722 with paclitaxel was seen maximizing mitotic defects, increasing aneuploidy and consequent cell death. In vivo synergy was also seen in patient-derived xenograft and systemic metastatic models using clinically relevant doses of paclitaxel (15 mg/kg i.v.) typically dosed weekly and well tolerated daily doses (e.g., 40 mg/kg p.o. q.d.) of BOS-172722.

Bicycle Toxin Conjugates: The Magic Bullet Delivered by Bicycle

Dr. Gavin Bennett (Bicycle Therapeutics Ltd, UK) outlined the recent clinical progress of the novel Bicycle toxin conjugate (BTC) **BT-1718**.

Bicycles® are bicyclic peptides constrained via a chemical scaffold, which confer structural stability, leading to high affinity and selectivity usually associated with traditional antibodies. The proprietary on-phage binding assay informs on compound selection driven off highly specific hit to lead chemistry and enabling optimal drug candidate design with a large binding footprint targeting specific PPIs. Bicycles can be designed to carry payloads to a specific target and their relatively small size (1.5-3 kDa) allows rapid tissue penetration and extravasation and coupled with renal elimination bystander effects at the liver and gut are minimized.

BT-1718 is the first BTC to enter clinical evaluation and consists of an MT1–MMP (membrane type 1–matrix metalloproteinase) binding peptide linked to the maytansinoid toxin DM1 via a hindered cleavable disulphide linker. MT1–MMP is a cell surface matrix metalloprotease with an established

role in cell invasion and metastasis and is overexpressed in many tumor types including lung, breast, bladder and fibrosarcoma. Rapid and target-specific localization of a ^{68}Ga-conjugated MT1–MMP-binding Bicycle to an MT1–MMP-expressing tumor was observed in vivo. This contrasted with the nontargeting comparator peptide and antibody demonstrating zero and minimal tumor penetration, respectively. Evaluation of BT-1718 across a range of solid tumor xenograft models showed profound efficacy, providing complete tumor regression over the dose range of 3 to 10 mg/kg in murine models following intravenous administration. Preclinically, the rapid and extensive tissue penetration provided efficacy even in very large, heterogeneous patient-derived xenograft models with tumor volumes > 1000 mm^3 as compared with the more standardized models of 200 mm^3.

BT-1718 is currently being evaluated in a phase I clinical trial in collaboration with Cancer Research UK. To date, BT-1718 has been dosed to over 30 patients from an unselected population of a variety of tumor types. The dose-escalation phase began with a twice-weekly dosing regimen of 0.6 to 9.6 mg/m^2 and then moved to a once-a-week dosing regimen from 9.6 mg/m^2 up to the current level of 32 mg/m^2. The clinical PK of BT-1718 are in line with the preclinical data, with a moderate plasma clearance rate (CL_p) of 33.6 ± 24.5 L/h, steady-state volume of distribution (V_{ss}) of 12.5 ± 7.3 L (similar to extracellular fluid) and a resultant plasma terminal half-life ($t_{½}$) of 0.2 to 0.5 h. Preliminary clinical tumor biopsy data confirms localization and retention of DM1 toxin in the tumor beyond the short $t_{½}$ in plasma.

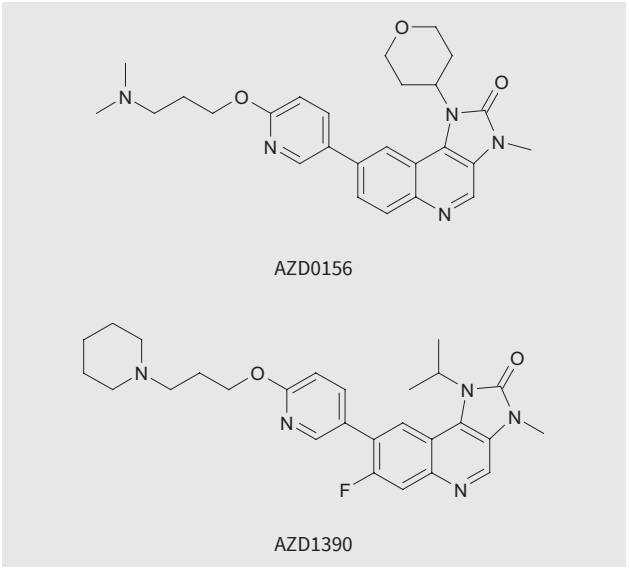
Dr. Bennett also discussed the progress with other compounds from the BTC stable. Additional BTCs have been developed to target EphA2 (**BT-5528**) and Nectin-4 (**BT-8009**). Both compounds demonstrated profound efficacy across a range of xenograft models and offer a differentiated approach compared to standard antibody–drug conjugates (ADCs). BT-5528 is efficacious without signs of bleeding, coagulopathy or abnormal liver function which led to the discontinuation of ADC approaches targeting EphA2 and is currently under early clinical evaluation. BT-8009 is currently in IND-enabling studies. Concluding his talk, Dr. Bennett highlighted the unique opportunity and potential for the BTC platform for effective and efficacious solid tumor targeting with an improved safety profile.

Discovery of the Clinical Candidate AZD1390: A High-quality, Potent and Selective Inhibitor of ATM Kinase with the Ability to Cross the Blood–Brain Barrier

Dr. Kurt Pike (AstraZeneca, UK) provided a brief introduction to human DNA damage response (DDR) pathways and the potential sensitivity of tumors to inhibition of these pathways due to i) frequent loss of one or more DDR pathway, ii) increased replication stress and iii) high intrinsic rates of DNA damage. For example, signaling through ATM (ataxia telangiectasia mutated kinase) is essential to both homologous and nonhomologous repair pathways and ATM inhibition is known to sensitize tumors to DNA damage in in vitro and in vivo models. This was followed by a summary of the work at AstraZeneca that led to the discovery of their first clinical ATM inhibitor—**AZD0156**. During the optimization of an initial amidoquinoline hit, the AZD0156 team was able to improve potency and PK properties while also achieving high selectivity, particularly over closely related DDR-associated kinases DNA-PK and ATR, which are also members of the atypical phosphatidylinositol 3-kinase-related kinase (PIKK) family (4, 5).

Dr. Pike then highlighted that despite good overall properties, AZD0156 demonstrates poor brain penetration, which limits its potential utility in treatment of primary CNS cancers such as glioblastoma, or CNS metastasis of cancers of peripheral origin. AstraZeneca therefore sought to develop a brain-penetrant ATM inhibitor that they were confident could achieve therapeutic concentrations in the brain. The primary aim was a molecule with in vitro efflux ratio < 2 in an MDCK brain model expressing both Pgp and BRCP efflux pumps. Data was presented showing the importance of the dual expression, as the proteins can act synergistically to increase efflux of compounds that would not be clearly identified by the separate MDCK models. In addition, compounds were tested at lower concentrations than may typically be used to ensure there was no effect of saturation at supraphysiological concentrations. Secondly, in vivo unbound brain:plasma ratio $K_{p,uu}$ in mouse was calculated using a time course to allow assessment of AUC and equilibration rates, with a target of $K_{p,uu}$ greater than 0.3. Under these experimental conditions, AZD0156 has measured efflux ratio of 23 in the MDCK brain and $K_{p,uu}$ < 0.03, consistent with its poor CNS exposure.

Optimization of compound properties in these assays resulted from three key areas of SAR around the AZD0156 core. Modification of the tetrahydropyran ring in AZD0156 to an iso-propyl substituent reduced molecular weight and polar surface area, resulting in an analogue with retained activity but efflux ratio of 3. Substitution of the ortho positions of the bi-aryl ring with fluorine also improved permeability, which may be explained by more subtle conformational effects. Finally, modification of the dimethylamino side chain to reduce pKa significantly improved permeability but at the expense of activity against ATM. Cyclization to the more lipophilic piperidine resulted in a smaller but significant improvement in permeability without negatively impacting on activity, and when combined with the changes above resulted in the clinical candidate **AZD1390**. This molecule demonstrates similar potency and selectivity to AZD0156 with low efflux in the MDCK brain model. The $K_{p,uu}$ in mouse remains below 0.3 (0.1), however, more detailed investigations in rodent (both in vitro and in vivo) demonstrated that AZD1390 is a substrate for rodent



efflux transporters but not human efflux transporters and that this was responsible for the limited brain exposure in rodent. To further increase confidence that human brain exposure would not be impaired, AstraZeneca utilized its strategic collaboration with the Karolinska Institutet to generate [^{11}C]AZD1390 and perform PET studies in cynomolgus macaques which demonstrated the $K_{p,uu}$ to be 0.33 in this species. These results supported the clinical development of AZD1390 and the human brain exposure of the compound was further demonstrated by PET studies on healthy volunteers. AZD1390 is currently undergoing early clinical assessment, in combination with radiotherapy, in patients with intracranial malignancies.

The Translation of Inhaled Drug Lead Optimization Strategies into Clinical Pharmacokinetics and Pharmacodynamics Using Two Distinct PI3Kδ Inhibitors

Dr. Malcolm Begg (GlaxoSmithKline, UK) presented preclinical and clinical data on two structurally distinct potent and selective PI3Kδ inhibitors with subtly different profiles in studies aimed at understanding the relationship between compound properties and human profile.

Phosphoinositol 3-kinase (PI3K) signaling is a key pathway in the regulation of the immune response and is the continued focus of significant research efforts (6). PI3Kδ is highly enriched in leukocytes making it an attractive target for the treatment of inflammatory conditions such as asthma, chronic obstructive pulmonary disease and autoimmune diseases. Inhaled drug delivery has several advantages in the treatment of lung disorders including quick onset of action and beneficial safety profile due to low systemic exposure. Lung retention can be achieved by optimizing molecules to be highly soluble and to bind to lung tissue, or to be relatively insoluble and retained by slow dissolution. **GSK2292767** and **GSK2269557** (nemiralisib) are structurally distinct PI3Kδ inhibitors (7) and have similar potency, selectivity and permeability profiles but differ in their solubility: GSK-2292767 is relatively insoluble (4 μg/mL in simulated lung fluid [SIF]), whereas nemiralisib has high solubility (333 μg/mL for the HCl salt in SIF). The two molecules underwent similar first-time-in-human (FTIH) studies to determine the consequence of different drug solubility on the human PK and pharmacodynamic (PD) profile of inhaled PI3Kδ inhibitors.

Two independent FTIH studies in healthy volunteers who smoke were conducted. Each was a single-center, double-blind, placebo-controlled trial in two parts: part A an escalating single-dose crossover design and part B a 14-day repeat dose parallel group design. The primary endpoint was safety and tolerability, with a secondary endpoint of plasma PK. In addition, exploratory assessments included sputum PIP_3 levels as a PD marker and day 14 bronchoalveolar lavage PK (8, 9). Both molecules were well tolerated with no significant adverse events reported. Plasma PK started to reveal the different human profiles, with nemiralisib demonstrating a plasma t_{max} of approximately 5 min compared to approximately 45 min for the less soluble GSK2292767 following a 500-μg dose using GSK's Ellipta device. Both drugs reduced PIP_3 in sputum at 3 h post dose, but only nemiralisib did so at 24 h after a single inhaled dose. Both molecules showed a linear PK/PD relationship. Although bronchoalveolar lavage showed lung retention at 24 h for both drugs, analysis of intracellular material from individual cells by LiveCell MS suggested an absence of GSK2292767 at the 24-h timepoint, consistent with the lack of PD response.

In conclusion, these studies offered a unique opportunity to compare two similar molecules with differing solubilities in matching clinical studies. Lung retention was achieved for both compounds, but a maintained PD response was only observed with the high solubility molecule.

Disclosures

P. Brown is a consultant to Spero Therapeutics, Inc. M.E. Swarbrick is an employee of Cancer Research Technology Ltd., a wholly owned subsidiary of Cancer Research UK, who are collaborating with Bicycle Therapeutics Ltd. on the clinical trial of BT-1718 as mentioned in Dr. G. Bennett's talk. S.E. Ward's salary is paid by Cardiff University. He and his group received funding from the Welsh Government, Medical Research Council, Wellcome Trust. The other authors are in paid employment of their respective organizations. P. Brown, S. Butterworth, M.M. Hann, P. Jeffrey, R. Porter and M.E. Swarbrick are SMR Committee members, for which no remuneration is paid.

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