Recent disclosures of clinical candidates: Highlights from the Society of Medicines Research Symposium


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Summary

This symposium featured an international lineup of speakers presenting on the discovery and clinical development of novel therapeutic agents. The presentations described a variety of mechanistic approaches including small molecules, monoclonal antibodies and a drug repurposing and covered therapeutics areas from oncology, anti-infectives and inflammation to anemia. The program also included the 2016 Society for Medicines Research Award Lecture given by Dr. Francis Cuss, Executive Vice President & CSO R&D, Bristol-Myers Squibb, on the discovery, development and delivery of Opdivo (nivolumab), which is a fully human anti-programmed cell death protein 1 (PD-1) antibody. The meeting was held at the National Heart and Lung Institute, Kensington, London, U.K. and was organized by the authors of this report.


2016 SMR Award Lecture: The Discovery, Development and Delivery of Opdivo

Dr. Francis Cuss, Executive Vice President & CSO R&D, accepted the 2016 Society for Medicines Research Award for Drug Discovery on behalf of the team of Bristol-Myers Squibb scientists who discovered, developed and delivered the novel immunotherapy Opdivo (nivolumab) a fully human anti-programmed cell death protein 1 (PD-1) antibody. Dr. Cuss discussed that immuno-oncology is widely recognized as a transformational opportunity that provides the potential for long-term survival for a meaningful proportion of patients with several types of cancer. He thanked the Society for Medicines Research for recognizing scientific innovation that can make a real difference in the lives of patients.

The scientific framework for tumor surveillance was first proposed by Nobel Laureate Macfarlane Burnet in the 1960s, but it was not until the 1990s when scientists identified the signaling molecules controlling activation of the immune system that Burnet’s vision could be realized. The identification of checkpoints in immune pathways together with advances in technologies for creating therapeutic human monoclonal antibodies made it possible to create the first checkpoint inhibitor—Yervoy—that would advance the field of immuno-oncology by demonstrating a long-term survival benefit in...
Dr. Bernard Barlaam from the IMED Oncology group at AstraZeneca Pharmaceuticals, Cambridge, U.K., described work that has led to the selection of a preclinical candidate for development of a novel oncology therapy. He started by describing the DNA damage repair (DDR) pathways that are critical for the cellular DNA damage response signaling events that are activated by DNA double strand breaks (DSBs). The two major DSB repair pathways are termed homologous recombination repair (HRR) and non-homologous end joining (NHEJ), with the former being very accurate but requiring undamaged sister chromatid DNA to template from. By contrast, NHEJ is not dependent on the presence of replicated DNA but tends to be less accurate. ATM plays a key role in the repair of DSBs: Upon detection of a DSB, ATM is activated and triggers cell cycle checkpoint and DNA repair. This presentation focused on development of inhibitors of ATM kinase in order to hypersensitize tumors to chemo- or radiotherapy which cause DSBs. ATM belongs to the PIKK (PI3K-like kinase) family of kinases, a small group of atypical protein kinases with homology to the lipid kinases, which includes ATM, ATR, mTOR and DNA-PK. The starting point for the work at AstraZeneca was a 15k cell-based assay that identified a novel quinoline carboxamide hit with selectivity over ATR. SAR-driven chem innovation that substituents at C6 could be used to improve physchem properties such as solubility by reducing logD. A potent analogue from this initial work < 1 nM biochemical IC50 and 46 nM cellular IC50 enabled in vivo target validation through antitumor efficacy when combined with the topoisomerase inhibitor irinotecan in an SW620 mouse model (1). Early dose-to-man (eD2M) and maximum absorbable dose (MAD) predictions based on in vitro measured and predicted parameters can be used as a guide to optimization (aspiration goal: eD2M of less than 50 mg and MAD of greater than 10 times eD2M). Further optimization was required to meet those expectations. This centered on increasing the overall permeability of the series by cyclization of the carboxamide at C3 to the C4 nitrogen substituent to yield cyclic ureas (‘fused scaffold’) and taking advantage of the increased potency seen with some basic side chains and their increased volume of distribution. Most of the C6 SAR from the carboxamide series could be directly transferred to this new series, including the benefit of a remote basic group. However, C4 SAR proved to be not so transferrable, presumably because of the more local effects of the cyclization in this region of the molecule. At C4, small cycloalkyls proved the most effective and ultimately AZD-0156 was selected which has a cellular IC50 of 0.58 nM, high solubility, low hERG liability and good permeability.
This exceptional potency is complemented by excellent selectivity within the PIKK family and against a panel of ca. 400 other kinases. The predicted human dose is < 10 µg and MAD is > 4000 µg. In preclinical in vivo mouse xenograft models, orally dosed AZD-0156 synergizes with olaparib (a poly[ADP-ribose] polymerase [PARP] inhibitor which promotes DSBs subsequent to single strand breaks) and irinotecan, producing tumor regressions. Phase I clinical trials combining olaparib and AZD-0156 are ongoing.

**Highly Potent and Selective DNA-PK Inhibitor M-3814 with Sustainable Antitumor Activity in Combination with Radiotherapy**

Dr. Thomas Fuchß, Associate Director, Merck Biopharma, Merck KGaA, Global R&D, Darmstadt, Germany, continued the oncology session with his presentation on a different approach to combination therapy by inhibiting the DNA-PK enzyme. DNA-PKcs (along with its regulatory subunits Ku70 and Ku80) is another crucial enzyme of the two major DNA repair mechanisms leading to NHEJ following DNA DSBs. When such DSBs are induced by radiotherapy or, for example, topoisomerase inhibitor chemotherapy, coadministration of DNA-PK inhibitors will abrogate the NHEJ mechanism and thus delay DNA repair of the DSBs and potentiate the antitumor effect. DNA-PKcs is a member of the serine/threonine kinase PIKK family of kinases. HTS screening was used to identify several chemical series and one singleton as starting points for lead optimization. The final clinical candidate molecule (M-3814 – structure not disclosed) arose from the singleton hit after modification of the core structure to increase stability, elimination of safety pharmacology relevant issues by careful attention to physicochemical properties and changes to the peripheral substituents to enhance cellular potency. M-3814 has an IC50 versus DNA-PK of 0.6 nM at 5 µM ATP and 18 nM at high ATP concentration of 1000 µM. This translated into good inhibition (60-110 nM) of 0.6 nM at 5 µM ATP and 18 nM at high ATP concentration. Moreover, the compound also showed excellent selectivity towards other members of the PIKK class and the wider human kinome. M-3814 potentiates the effect of radiation in a variety of cancer cell lines and xenograft models in a dose-dependent manner. In a 6-week duration experiment, M-3814 at 25 mg/kg in combination with radiation therapy of the FaDu squamous cell carcinoma of the head and neck (SCCHN) tumors in mouse, resulted at day 102 of observation in 100% survival of animals compared to only 10% survival for radiation only treated animals. Detection of DNA-PK autophosphorylation at Ser2056 is being used as a proximal PD biomarker for evidence of target engagement in both preclinical studies and the ongoing phase I clinical trials (which started in December 2014). The development plan includes use of M-3814 in radio- and chemotherapy and chemo–radio combination therapies.

**A Different Class of Oncology Therapeutic: Development of MOv18—a Novel IgE-based Therapeutic Targeting FRα**

Dr. David Edwards from the CR-UK Centre for Drug Development described the aim of the research into cancer with the goal to have 75% of patients surviving the disease for 10 or more years within 20 years. Next year sees the 25th anniversary of drug development at CR-UK, during which 130 projects have led to 100 agents entering clinical trials and 8 marketed drugs. Dr. Edwards described the development of a novel antibody therapy based on IgE rather than IgG. IgG antibodies bind to the tumor cell target with high affinity via the Fab domain, while IgGs bind to immune effector natural killer cells with only moderate affinity (10−7 M); also IgGs have relatively short tissue half-life (~2 days). Therefore IgG therapies need to be optimized by increasing tissue residence time and/or affinity towards the effector cells that drive the antibodies biological activity. In contrast to IgG, IgE antibodies bind to their effector cells (mast and eosinophil cells) with far higher affinity (10−2 M) and are far longer lived in tissues (~2 weeks) compared with IgG. This raises the possibility of developing an IgE agent that acts by a slightly different mechanism that could be used as a single agent or in combination with existing IgG antibody agents. Expression of folate receptor α (FRα) is upregulated in several cancers with very little expression in healthy tissues; the preferential expression of this target in tumor made it a good candidate target to evaluate IgE therapy as it ensured that healthy tissue toxicity could be kept to a minimum. FRα has been targeted by two IgGs in clinical trials including MOv18 IgG, although this agent is no longer in development. Therefore, MOv18 IgE (an IgE expressing the MOv18 IgG idiootype) was selected as a platform to test IgE as a therapy; the lack of potential healthy tissue activity and benchmark IgG clinical data being viewed as being highly desirable. One of the challenges faced by the project team was the lack of a suitable toxicology model as MOv18 IgE does not crossreact with nonhuman primate effector cells in a manner that is reflective of the human situation and a MOv18 IgE does not bind to rodent FRα. As a result, there was no toxicology model available, and an initial dose for studies was selected on the basis of the endogenous IgE levels; the rationale for the starting dose was unique as it was based on an evaluation of the agent for the effector cell rather than for the tumor cell target as is the case for other IgG therapies. Despite these hurdles the trial for MOv18 IgE is currently recruiting patients.

**Discovery of the Clinical Candidate JNJ-53718678, a Potent and Orally Bioavailable Fusion Inhibitor of RSV**

Dr. Sandrine Vendeville, from the Janssen Infectious Disease Unit, described the discovery and development of an oral agent against respiratory syncytial virus (RSV).
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RSV represents a disease burden to three distinct patient groups: young children, in whom it is responsible for 6.7% of all deaths between 1 month and 1 year; certain high-risk adults, including those with respiratory disease; and the elderly. The RSV fusion protein (RSV-F) is essential for the initiation of the replication cycle of the virus. Fusion inhibitors exert their antiviral effect by stabilizing the pre-fusion form of the protein, thereby locking a trimer of proteins together. Despite development of HTS hits, it had proved challenging to identify an oral compound, but interest was reignited with the development of BMS-433771. A medicinal chemistry campaign, starting with diverse azaheterocyclic series, resulted in the clinical candidate JNJ-63718678, an orally bioavailable picomolar RSV-F inhibitor.

The crystal structure of JNJ-53718678 complexed to RSV-F shows one molecular of compound bound to the protein trimer, occupying two of the three binding pocket lobes. A challenge for the project team was the subsequent development for a pediatric setting as a primary indication, while most therapies are first developed and approved in adults before being trialed in children. JNJ-53718678 has been evaluated in a phase II challenge study in healthy volunteers and the results support further evaluation in a pediatric setting.

Recent Disclosure of a Development Candidate to Treat Severe Acute Pancreatitis

Dr. John Liddle (GSK Discovery Partners in Academia, Stevenage, UK) highlighted the GlaxoSmithKline (GSK) Discovery Partnerships with Academia (DPAc) model for sharing the risk and reward of academic collaborations to deliver quality medicines. The kynurenine monooxygenase (KMO) project, run between GSK and the University of Edinburgh (Mr. Damian Mole, MRC Senior Clinical Fellow and Consultant Surgeon) was presented to exemplify this approach. Severe acute pancreatitis (SAP) is the leading gastrointestinal cause of hospital admissions, usually triggered by gallstones or excessive alcohol intake; in 1 in 4 patients, AP will progress to multiple organ failure, for which there is no specific therapy. A GSK-sponsored experimental medicine study with the University of Edinburgh showed a strong association between the 3-hydroxykynurenine (3HK) metabolite and disease severity. 3HK is formed exclusively by the action of KMO and KMO knockout mice show protection against organ damage following experimental pancreatitis. Targeting an i.v. therapy, a hit ID strategy based on the structural knowledge of kynurenine substrate was initiated.

This led to the identification of the benzoxazole series of inhibitors that enabled rapid SAR evaluation. The 5 and 6 positions were found to be the best handles for potency and DMPK parameters, with an aryl chloro interaction being important for KMO potency.

After further rounds of optimization considering cellular potency, free concentrations, on/off rates and i.v. clearance, GSK-065 was identified as having the best overall profile. GSK-065 was found to be efficacious in an animal model of SAP and is currently being evaluated further as a preclinical candidate.

Out with the Old Proposed Indication, Bring in the New Clinical Compound for the Potential Treatment of Sickle Cell Disease

Dr. Nick Clarke (Pfizer Rare Diseases Unit, London, U.K.) presented the approach taken at Pfizer to look for reposi-tioning opportunities for legacy Pfizer clinical assets. PF-04447943 is a phosphodiesterase PDE9 inhibitor (2, 3) that was identified and optimized as a treatment for aspects of Alzheimer’s disease (AD).

The compound has excellent PDE9 potency, good selectivity and good CNS exposure and showed significant efficacy in a variety of cognition rodent models. It was progressed into six clinical studies including single ascending dose, multiple ascending dose and food effect studies. No safety issues were reported and following cerebrospinal fluid (CSF) collection and analysis, target engagement in
Disclosures

M. Hann, W. Alderton, R. Davenport and P. Williams are in paid employment of their respective organizations. All authors are SMR Committee members for which no remuneration is paid.


References


