PARTNERSHIPS: FUTURE MODELS FOR DRUG DISCOVERY

HIGHLIGHTS FROM THE SOCIETY FOR MEDICINES RESEARCH SYMPOSIUM HELD ON JUNE 20TH 2013 AT THE LILLY RESEARCH LABORATORIES, MANOR HOUSE CONFERENCE CENTRE, ERL WOOD MANOR, WINDLESHAM, SURREY, UK

G.J. Macdonald¹, M. Brunavs², P.V. Fish³ and S.E. Ward⁴

¹Janssen Pharmaceutical Companies of Johnson and Johnson, 2340 Beerse, Belgium; ²Lilly Research Centre, Ltd., Erl Wood Manor, Sunninghill Road, Windlesham, Surrey GU20 6PH, U.K.; ³UCL School of Pharmacy, 29/39 Brunswick Square, London WC1N 1AX, U.K.; ⁴University of Sussex, Brighton BN1 9QJ, U.K.

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SUMMARY
With the intention of bringing together leading academic researchers, industry scientists, business development experts and scientific policy makers, the Society for Medicines Research (SMR) hosted a highly engaging and thought-provoking meeting entitled “Partnerships: Future Models for Drug Discovery” at the Lilly Research Centre in Windlesham, Surrey. With the challenges to discover and develop innovative and differentiated new medicines having never been greater and with many questions arising around the viability of current pharmaceutical business models, this meeting offered the opportunity to explore potential new ways to bring innovation and productivity to the drug discovery sector. Through a series of presentations from leading figures from across the public and private sector, the conference aimed to explore novel business models for research and development and to discuss on the changing dynamics around the interactions between traditional models for academia, industry and funders.

Key words: Innovative new medicines – Drug discovery – Dynamics and interactions – Traditional models

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In the morning session, entitled “Future models for drug discovery. Which road to take?”, Dr. Dale Edgar (Lilly Research Laboratories) provided the introductory presentation “Strategy and governance of research partnerships – a personal perspective”. In this personal testimony, Dr. Edgar shared his own vision on the critical need to identify improved models of sustainability for the pharmaceutical industry and on the many challenges and opportunities that these may present. He highlighted the now familiar story of the current biopharma environment of declining R&D efficiency, despite the considerable technical advances in drug discovery and development over recent years. His fundamental belief was that government and academic researchers conduct basic research to advance the scientific knowledge and understanding of disease, while the pharmaceutical companies conduct basic research, then translate that research into the discovery and development of new medicines. This was demonstrated by figures showing that 12% of new molecular entities approved during 1990-2007 were discovered through public sector research, with many prominent examples from within the oncology field. Examples of some of these successful drugs include Eli Lilly’s dihydrofolate reductase/thymidylate synthase inhibitor Alimta® (pemetrexed) from Princeton University, Bristol-Myers Squibb’s mitotic inhibitor Taxot® (paclitaxel) from Florida State University, Merck’s histone deacetylase (HDAC) inhibitor Zolinza®...
(vorinostat) from Columbia University, and Merck/Schering-Plough’s DNA alkylating agent Temodar® (temozolomide) from Aston University in the U.K.

Drawing on the current high levels of public (e.g., NIH USD 30 billion) and private (pharma USD 49.4 billion & biotech USD 18 billion) funding, he raised the issue around the need to find clearer synergy between research institutes, and argued that companies should engage in more effective precompetitive partnerships. These partnerships, such as TransCelerate, the NIH National Center for Advancing Translational Sciences and the Innovative Medicines Initiative (IMI), are already in place and are aspiring to reduce the devastating level of attrition in late-stage clinical trials. Finally, Dr. Edgar emphasized the elements that make a successful partnership, and in particular highlighted that transparency and trust were essential components.

In the second presentation, Dr. Jackie Hunter (Ol Pharma Partners) discussed “What is open innovation and why it matters for drug discovery”. In line with the theme of other speakers, Dr. Hunter emphasized the changing world of pharmaceutical research, highlighting the increasing focus on personalized medicine and the proportion of big pharma clinical portfolios that are now comprised of in-licensed projects, in some cases around 50%. She described the traditional pharma R&D model as “closed innovation”, prosecuted within corporate research centers, and contrasted this with other industries, such as Proctor & Gamble and Royal Philips Electronics, that have been quicker to realize the value of more open models of research. Additionally, although most pharma companies have external partnerships and engage in precompetitive consortia, few are truly using the concept of open innovation. Early positive indications were highlighted –Lilly’s PD2, GSK’s Scinovo, GSK Tres Cantos Open Lab’s, UCB biologicals plant, Sage Bionetworks, Merck-Serono Open Innovation Portal—, although none of these have yet matured to the point of delivering a major impact. The need and potential for sharing information across centers was highlighted, in addition to the growing numbers of websites which seek to harness the power of social media and crowdsourcing to answer challenging problems in R&D. A striking example was given for the need to be receptive to ideas from outside our traditional boundaries by Jack Andraka, a young school scientist who conceived a new method for early-stage cancer detection and who, at first, struggled to attract serious research attention. Dr. Hunter ended on an optimistic note, highlighting the increasing number of precompetitive consortia through the diverse IMI workstreams and EU-AIMS, which aim to foster innovation across institutional boundaries.

Concluding at the morning session, Dr. David Fox from the Royal Society of Chemistry (RSC) gave a forward looking presentation, entitled “Bridging the translational gap”, which outlined both the challenges and opportunities faced by medicines research. He proposed that the changing shape of the pharmaceutical industry requires new, effective partnerships to be established in the medicines R&D sector and suggested that the U.K. was well-placed to respond to this challenge. The strengths he outlined included: 1) a track record of investment and innovation in drug discovery; 2) a talent pool of world-class scientists with a track record of successful drug discovery and access to high-quality training; 3) collaboration in an environment that encourages free and constructive exchange of knowledge; 4) networks of well-developed relationships across industry/academia/NHS, capitalizing on geographical proximity of research centers; and 5) effective lines of communication between scientists and funders to shape funding policy.

The four principal challenges were identified as attrition, duplication & redundancy, fragmented model and skills. Each challenge was then repositioned as an opportunity where the development of effective partnerships would lead to a clear benefit for all. For example, as large pharmaceutical companies are dependent on in-licensing for ~50% of their late-stage clinical portfolios, it was proposed that by investing in the professionalization of drug discovery in academia, along with providing a line-of-site to patients, not only would attrition be reduced, but also a more integrated model of drug discovery across the sectors would be created.

The RSC has been working alongside a group of learned societies as part of the Drug Discovery Pathways Group (DDPG) to put forward a series of proposals on how best to bridge the translation gap between fundamental research and clinical research in order to maximize benefit to patients. The gap could be effectively bridged by the dual application of drug discovery expertise combined with experimental medicine. The drug discovery expertise would be underpinned by the application of the core model of selecting the “right target” (or pathway), identifying the “right compound” (or other modality) and applying the “right study” to inform decisions which have relevance to the clinical situation.

One proposal being advanced by the RSC is that these core competencies could be established within regional Therapeutic Centers of Excellence (TCE) based around clusters where there is a preexisting co-location of Department of Health investment, Medical Research Council investment and disease expertise. There are a number of examples of such centers of excellence already established which may be viewed as a spectrum of academia-centric through to industry-centric models. Furthermore, a commitment to sustainability through long-term, portfolio-based funding and investment in training would be needed for the long-term success of such TCEs from all partners.

Particular emphasis was placed on the need to provide a more “permeable” environment that encourages and values increased movement of highly skilled researchers across disciplines and sector boundaries in order to drive forward medicines research, as well as support continuous career development. In this permeable environment, an industrial chemist could capitalize on opportunities to transition between academia, biotech and contract research organizations (i.e., cross-sector) while also building skills in, for example, clinical research, toxicology and systems biology (i.e., cross-discipline).

The afternoon session focused on the theme of “How to undertake successful drug discovery in academic laboratories and research institutes”, and started with a presentation from Dr. Richard Angell (Translational Research Office [TRO], University College London), entitled “Pharma-biotech-university: Drug Discovery – a personal perspective”. In a varied career, Dr. Angell has worked in pharma, in biotech, and now in academia. As such, he was able to present a unique view of the strengths and weaknesses inherent in the operations of these three groups and make it plain why it is in the interests of all of them to work together in future drug discovery efforts. He
highlighted that of the large number of pharmaceutical companies which existed in the early 1990s, just four “big pharma” companies remain in the U.K. today, with mergers and site closures accounting for much of the reduction. Resulting redundancies and the thirst for talent among smaller start-up companies and institutions means that large numbers of experienced drug discoverers are now working outside of traditional “big pharma”.

As drug discovery has progressed over the last two decades, many new methodologies have come to the forefront. Which are best is hard to tell. To offset the financial risk in trying to find out, and to take advantage of the vast talent pool now existing beyond its confines, “big pharma” needs to reach out to the smaller companies and universities. As an example of the kind of work large pharmaceutical companies do well, Dr. Angell reviewed the discovery and development of lapatinib, an orally active dual tyrosine kinase inhibitor for breast cancer and other solid tumors. Lapatinib, like many drugs, was proposed as a candidate only after aspects such as enzyme activity, cellular potency, pharmacokinetics, the maximization of in vivo efficacy and the reduction of in vivo toxicity had been optimized. Here, “big pharma” scores the expertise of its staff, operating within a data- and finance-rich environment and making it ideally suited to carry out the multi-parameter optimization needed for late-stage lead projects in highly competitive areas. However, these companies can often be too data-rich and miss what is truly important. Often they are averse to risk, preferring to tackle targets within their comfort zone and knowledge base.

By contrast, biotech organizations are more willing to take on riskier and more novel targets, and often focus more, out of necessity, on the most relevant data. Smaller teams can heighten scientist ownership and morale/reward, promoting faster discovery. These aspects were all in play during the discovery of RSV-604, a novel inhibitor of respiratory syncytial virus, by Arrow Therapeutics. Arrow screened a relatively modest-sized collection (20K compounds) and found just one hit. Structure–activity relationship (SAR) development and lead optimization delivered A-60444 (RSV-604), a significantly more potent inhibitor in Arrow’s plague assay than the poorly efficacious and teratogenic standard-of-care ribavirin. A clinical trial was undertaken which showed promising results, but Arrow lacked the resources to make the testing statistically significant. Here, partnering became essential to drive the drug forward to the patient. Novartis joined the project in 2005 and provided the necessary capital, before Arrow Therapeutics was eventually acquired by AstraZeneca in 2007 for a cost of USD 150 million.

Universities offer a non-linear approach to drug discovery, with many groups, each with their own expertise and across different institutions, coming together to construct successful funding proposals. Dr. Angell drew attention to the collaborations of the TRO with external groups as diverse as Cancer Research UK, GlaxoSmithKline, Sigma-Aldrich and the Universities of Sussex and Cambridge. Academia scores by being able to investigate the most cutting-edge science and more speculative areas in a highly collaborative environment, lowering the risk barrier for the entry of industrial groups from both biotech and pharma. Diverse responsibilities among senior academics and the hierarchical nature of universities can stand in the way, but partnership with industry provides the focus, the data management and the financial benefit to overcome these drawbacks. Dr. Angell concluded that no one methodology worked in isolation, and that an appropriate balance between them all is the only way forward in an environment where payers are demanding higher quality at lower prices.

In the second presentation of the session, Dr. Robert Williams (Cancer Research UK) talked on “Collaborative approaches to the discovery and development of new anticancer drugs”, and began by reviewing the burden cancer causes for sufferers, carers and drug discoverers. He highlighted the low return on investment endured by drug companies in terms of new products launched, rising R&D costs, preclinical and clinical attrition rates, patent expirations and the like, all making the amount of venture capital available for “discovery end” biotech efforts ever smaller. Cancer Research UK and its commercialization arm, Cancer Research Technology (CRT), are therefore attractive partners for pharma and biotech. In 2011/12, Cancer Research UK spent £332 million on research, entirely from public donation, supporting 4,000 scientists and research centers, and running CRT.

CRT’s business strategy has been to progress leads into the optimization phase and then out-license them to potential industrial partners, once the risk of the early-phase discovery has been removed. It has been very successful in this strategy, having worked with 30 groups in preclinical and clinical development and been involved in three partnered marketed drugs. CRT has also been involved in the creation of more than 24 start-up companies. In December 2009, it entered into a three-year, multi-project alliance with AstraZeneca to identify drugs targeting cancer cell metabolism, and has recently extended the deal for a further two years to 2015. CRT has also been involved in academic consortia models, where groups of collaborating hand-picked world-class scientists are being brought together to solve specific issues. One such group is Senectus Therapeutics, Ltd., a virtual drug discovery company looking to deconvolute senescence signaling. AstraZeneca has bought into this concept too, signing a deal with Senectus in March 2011.

Future consortia model efforts are proposed to tackle additional topics, such as cancer stem cells, epigenetics and early diagnosis. A recent investment of £50 million from the European Investment Fund (EIF) has allowed CRT to alter its business model. Now CRT is looking to take its products through to the end of phase I clinical trials before looking for collaborators, de-risking pharma investment still further. Cancer Research UK’s status as a charity also allows it, in collaboration with CRT, to continue the development of leads shelved by industrial organizations and potentially resurrect them at no risk to pharma. Eight deals along these lines have so far been signed by Cancer Research UK, and Dr. Williams highlighted the small-molecule monocarboxylate transporter 1 (MCT 1) inhibitor AZD-3965 as an example. All these efforts are taking place alongside Cancer Research UK’s core work to understand and provide proof of mechanism within a wide variety of cancers, again providing the knowledge industrialists need to collaborate with confidence.

Concluding the session, Dr. Paul Brennan (Structural Genomics Consortium, SGC) in his talk entitled “Pre-competitive chemical probes for target discovery”, presented a different approach to target validation and risk reduction. The objective of the SGC is to promote drug discovery by substantially increasing the number of medically relevant protein structures, as well as related reagents and
protocols, available in the public domain. In this way, resources to aid with target validation are created such that everyone can access them, stimulating new projects and providing further de-risking. The idea has won a lot of support from industry, with eight major pharma companies listed by Dr. Brennan as financial contributors.

The SGC aims to create chemical probes which are selective for individual protein families. They eschewed a finer level of selectivity, i.e., for individual proteins themselves, as impractical given the resources available to them. Nonetheless, the aim within protein families is to generate probes with high cellular potency and selectivity over other branches of the phylogenetic tree. To facilitate this, SGC develops assays using purified proteins, identifies hits through the screening of focused sets, virtual screening, fragment-based approaches and high-throughput screening (HTS), conducts SAR development and carries out secondary testing to establish cellular activity and selectivity in much the same way as any industrial team. However, the SGC coordinates many resources in different locations to carry out this work. The close geographical proximity of the Diamond Synchrotron at the Harwell Science and Innovation Campus facilitates protein work and structural biology. Collaboration with pharma provides access to compound collections and to probe optimization, and screening takes place at both Oxford and Cambridge universities.

As an example of its work, Dr. Brennan highlighted the SGC’s involvement with epigenetics. Epigenetic mechanisms of gene regulation have a profound role in normal development and disease processes. An integral part of this mechanism occurs through lysine acetylation of histone tails, which are recognized by bromodomains. SGC discovered that BET bromodomains can be inhibited by relatively simple compounds containing a 3,5-dimethylisoxazole motif. In an effort to take advantage of this finding, SGC approached Pfizer and screened 75 compounds selected from their collection containing this substructure, and found actives selective for CREB-binding protein (CREBBP), which they followed up with additional synthesis. CREBBP is a general transcriptional co-activator involved in many biological processes, such as maintenance of genomic stability, by affecting DNA replication and DNA repair, as well as cell growth, transformation and development. Ultimately, the SGC uncovered SGC-CBP30, a selective inhibitor of CREBBP, and EP300 (another transcriptional co-activator), samples of which are available to all.

In the final session, entitled “Bringing innovation to the pharmaceutical and biotechnology sector”, Dr. Jason Witherington (EpiNova DPU, GSK) opened with his presentation “Drugging the epigenome: Innovative collaboration is the key”. He began by posing the question “can the R&D productivity gap be filled by early biological understanding through industry-academic collaborations?” He proposed employing a discovery-rich approach to explore novel biology as a “high risk but high return” strategy, thereby increasing critical information earlier in the drug discovery process and so shifting attrition to the cheaper phase. Dr. Witherington then described the discovery and molecular characterization of potent small-molecule inhibitors that disrupt the function of the BET family of bromodomains. Using the BET program as an example, he also described the preclinical advances that were realized through external collaborations.

Epigenetic mechanisms of gene regulation have a profound role in normal development and disease processes. An integral part of this mechanism occurs through lysine acetylation of histone tails, which are recognized by bromodomains. The discovery and thorough characterization of highly selective inhibitors of BET bromodomains, such as I-BET762 and I-BET151, have proved to be valuable chemical probes in exploring the role these proteins play in disease. Access to chemoproteomics through the EpiNova-Cellzome alliance was identified as a method to inform clinical strategy through a deeper understanding of BET interacting proteins. Traditionally, the pharma industry has been reliant on recombinant screening panels expressing single protein targets. However, bromodomains occur in isolation and in complex with other domains and these different protein complexes modify function. A triple purification strategy was adopted where the system of interest was investigated with a BET inhibitor (I-BET), an acylated H4 histone tail and an antibody against BRD2/3/4, and then an MS-proteomic analysis identified the BET interacting proteins. Hence, proteomics was proposed as a valuable complementary approach to platforms of single target screening.

The presentation concluded with several examples of preclinical highlights emerging from EpiNova-academic collaborations which have produced data in model systems supporting the role of BET inhibitors in the treatment of diseases such as inflammation, cancer (multiple myeloma, MLL-fusion leukemia) and diabetes. For example, in collaboration with Diane Mathis and Christophe Benoist at Harvard Medical School, it was demonstrated that I-BET mediated long-term protective effects in a mouse model of diabetes. I-BET
irreversibly blocks type 1 diabetes in NOD mice, reflecting a combined effect of fostering antiinflammatory monocytes/macrophages and provoking islet beta cell proliferation.

Looking beyond the BET family of bromodomains, chemical probes for BAZ2, GSK-2801 (non-BET bromodomain), and a selective jumonji H3K27 demethylase inhibitor, GSK-J1, have been discovered in collaboration with the SGC. These chemical probes are now freely available to explore the roles of these proteins in disease models. Hence, epigenetic proteins are now proving to be tractable targets available to explore the roles of these proteins in disease models. Hence, epigenetic proteins are now proving to be tractable targets for small-molecule modulation and their role in disease can be explored to identify new drug targets for the treatment of diseases important to human health.

In the final presentation of the day, Prof. Shaun Stauffer (Vanderbilt University), discussed a novel model being implemented in the Vanderbilt Center for Neuroscience Drug Discovery to pursue collaborative academic/industry research programs for novel CNS targets, in his talk entitled “CNS Drug Discovery in Academia: The Mission, The Model and Recent Successes”. In his introduction, Prof. Stauffer highlighted a number of compelling reasons for pursuing more drug discovery in academia, which included: 1) that many of our new targets are much more complex and require a much greater understanding of complex pharmacology; 2) the ability to invest time in basic science, without many of the timeline and business pressures; 3) the higher flexibility inherent in academic environments; 4) the availability of grant funding to support more exploratory drug discovery; and 5) the recent downturn in pharma has provided academia with a rich source of seasoned drug discovery scientists. He described the origins of the Vanderbilt Center for Neuroscience Drug Discovery, which was initiated in 2003 by Prof. Jeff Conn (ex. Merck) and has grown steadily over the last 10 years, recruiting leading industry scientists from large pharmaceutical companies, including Pfizer, Lilly and Bristol-Myers Squibb. Today, the center has over 100 scientists, a budget of USD 100 million and expertise and capabilities in HTS, in vitro pharmacology, in vivo behavioral pharmacology, medicinal chemistry and drug metabolism and pharmacokinetics (DMPK), allowing drug discovery programs to be prosecuted from screening through to the selection of clinical candidates. The available capabilities and the strategies being followed in each of these departments was outlined, with an emphasis on the efficiencies that had been realized in working together in a closely integrated organization. In addition to their internal capabilities, the scientific team has access to a wider network of expertise within the large research infrastructure offered by Vanderbilt University, including access to a PET imaging center.

Prof. Stauffer also provided an overview of the current project portfolio of the center, highlighting the many industry partners, such as Johnson & Johnson, AstraZeneca and Bristol-Myers Squibb, that were collaborating on targets for schizophrenia, Alzheimer’s disease, Parkinson’s disease and depression. He discussed on some of the funding and research models, together with some of the achievements that had been realized to date, including patents, publications and new contracts originating from the basic research activities. Moving to a more scientific focus, a comprehensive overview was given on the discovery collaboration and licensing agreement with Johnson & Johnson, around the identification of metabotropic glutamate receptor mGlu5 positive allosteric modulators for the treatment of schizophrenia and other CNS disorders. This was a collaboration initiated in 2008 and running initially for three years, which involved a joint research team comprising medicinal chemistry, pharmacology and DMPK from both Vanderbilt University and Johnson & Johnson, working together to progress the research project. Many of the initial project challenges were outlined, including the moderate potency and poor drugability of known mGlu5 modulators and how these issues had framed the focus and objectives of the project. The high complementarity of the collaboration partners, the opportunities for both teams to realize “win-win” interactions and the highly integrated nature of the project team were highlighted as critical success factors. This ultimately led to the delivery of a preclinical development candidate in a timeline that was highly competitive with other internal projects. In concluding this overview, Prof. Stauffer discussed the critical impact that both the pharma and academic partner had brought to the project and some of the lessons that had been learned over the course of the collaboration. The latter included the need to achieve highly effective communication, to set up efficient systems for data exchange and the alignment of project resources.

DISCLOSURES

Mike Brunavs is an employee of Eli Lilly and Company; Paul Fish is Professor of Medicinal Chemistry at the UCL School of Pharmacy; Gregor J. Macdonald is a Senior Director and Head of Neuroscience Medicinal Chemistry at Janssen, Belgium; Simon E. Ward is Professor of Medicinal Chemistry and Director of the Translational Drug Discovery Group at the University of Sussex, UK and Executive VP at BioCrea, Dresden, Germany.
The SMR Committee organizes conferences on behalf of the Society for Medicines Research four times a year. These one-day conferences are multidisciplinary in nature and focus on various aspects of medicines research. Details of forthcoming meetings can be found at http://www.smr.org.uk or by e-mail to secretariat@smr.org.uk.