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**MEETING REPORT**

*The Symposium celebrating the 40th anniversary of the formation of the Society for Medicines Research (SMR) was held December 11, 2006, in Westminster, U.K.*

# Society for Medicines Research: 40th Anniversary Symposium

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by Alan M. Palmer,  
F. Anne Stephenson and  
Robert J. Williams

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This meeting, held on December 11, 2006, in Westminster, UK, celebrated the 40th anniversary of the formation of the Society for Medicines Research (SMR). The origins of the Society can be traced back to a symposium organized by members of the Pharmacy Department of Chelsea College in London in 1965. The following year, the Society for Drug Research was formed. It was granted Charitable status in 1977 and changed its name to the Society for Medicines Research in 1994. This anniversary meeting aimed to showcase the best of medicines research and was organized in collaboration with the London Biotechnology Network and UK Trade and Investment (UKTI). It took place at the Department of Trade and Industry conference center in Westminster and attracted over 300 delegates. The meeting began with an overview of future strategies for medicines research and its funding in Europe.

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## Summary

The recent symposium of the Society for Medicines Research (SMR), held on December 11, 2006, in Westminster, UK, celebrated the 40th anniversary of the formation of the SMR. The meeting began with an overview of future strategies for medicines research and its funding in Europe. This session was followed by the 2006 SMR Award lecture, which was given by Dr. Napoleone Ferrara of Genentech, for the development of the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab for the treatment of cancer. The remainder of the meeting showcased the best of medicines research in the United Kingdom by highlighting a number of drug discovery success stories from several UK biotech companies, which covered the therapeutic areas of central nervous system, cancer and viral infection, along with regenerative medicine. © 2007 Prous Science. All rights reserved.

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This included a description of a new public-private partnership called the Innovative Medicines Initiative, which has been formed through a collaboration between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). This was followed by the 2006 SMR Award lecture, which was given by Dr. Napoleone Ferrara of Genentech for the development of the anti-vascular endothelial growth factor (VEGF) antibody *Avastin* (bevacizumab), a product now licensed for the treatment of cancer. The remainder of the meeting showcased the best of medicines research in the United Kingdom by highlighting a number of drug discov-

ery success stories from several UK biotech companies, which covered the therapeutic areas of central nervous system, cancer and viral infection, along with regenerative medicine.

## Medicines Research in Europe

The first speaker, Ian Ragan (Eli Lilly, UK), provided a perspective on the future of medicines research in Europe. Medicines research has a long history in Europe but current trends may leave the continent outside the world's top economic powers by 2030. Therefore, one of the major objectives

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Correspondence: [secretariat@smr.org.uk](mailto:secretariat@smr.org.uk)

**TABLE I. INITIATIVES SET UP TO TACKLE THE INNOVATION GAP IN MEDICINES RESEARCH**

European Union	Innovative Medicines Initiative (EU) Medicamentos Innovadores (Spain) Top Institute Pharma (Netherlands) ECRIN (France) Safety Biomakers (UK)
U.S.A.	FDA Critical Path Initiative (NIH) Safe and Innovative Medicines (PhRMA) Biomarker Initiative (PhRMA) Critical Path Institute (University of Arizona) Center for Biomedical Innovation (MIT)
Japan	Toxicogenomics Project (JPMA) Proteome Factory Consortium (JPMA) Large-scale Clinical Trial Network

of the European Union (EU) is to build the most competitive and dynamic knowledge-based economy in the world by 2010. A key element of this objective is the strengthening of Europe's science base. The biopharmaceutical environment is characterized by its focus on science and innovation and is therefore an important contributor to this goal. Furthermore, strengthening biomedical R&D will benefit patients and society by increasing the efficacy of drug discovery and development. Medicines research is facing a number of serious challenges, including: 1) a greater emphasis on real improvement over existing drugs; 2) increased emphasis on the safety of new medical entities (NMEs); and 3) a failure to improve the attrition of NMEs along the value chain. This, coupled with a downward pressure on prices, makes it difficult for the medicines research industry to deliver safe and effective new medicines.

Among several national and multinational initiatives addressing issues in drug R&D, the Innovative Medicines Initiative (IMI) is the most ambitious in its scope and size (Table I). The IMI is a public-private partnership which has been developed in collaboration between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). It proposes clear practical paths to accelerate the development of safe and more effective medicines by addressing bottle-

necks in the biomedical R&D process and making recommendations on how to address these. The specific recommendations presented in its Strategic Research Agenda are organized around four main topics: predictivity of safety evaluation, predictivity of efficacy evaluation, knowledge management and education and training to

develop the talent base needed for the EU biomedical environment of the future.

The vanguard of IMI is Innomed, which obtained 18 million Euro of funding from the European Commission in 2005. It represents a consortium of 16 Pharmaceutical companies, 14 Universities and 7 Small and Medium-sized Enterprises (SMEs) from across the EU. It is focused on identifying biomarkers for Alzheimer's disease and establishing new approaches to predict the side effect liability of potential new medicines.

### The SMR Award

Dr. Napoleone Ferrara from Genentech played a pivotal role in the discovery and development of *Avastin* (bevacizumab), the first U.S. FDA-approved therapy designed to inhibit angiogenesis.<sup>1</sup> Dr. Ferrara was the recipient of the 2006 SMR Award for his discovery and was presented with



The 2006 SMR Award lecture was given by Dr. Napoleone Ferrara of Genentech for the development of the anti-vascular endothelial growth factor (VEGF) antibody *Avastin* (bevacizumab) for the treatment of cancer. Dr. Ferrara was presented with the Award by SMR Chairman, Dr. Alan M. Palmer

his award, a fine, commemorative Welsh slate tablet, by the Chairman of the SMR, Alan Palmer (Pharmidex, UK), following which, Dr. Ferrara delivered the 2006 SMR Award Lecture.

In his lecture, Dr. Ferrara began by giving an historical introduction to the discoveries that led eventually to bevacizumab, a humanized monoclonal antibody directed against VEGF. This included an acknowledgment to Judah Folkman, who in 1971 was the first person to recognize that blocking angiogenesis may have beneficial effects in the treatment of cancer, "Antiangiogenesis may provide a form of cancer therapy worthy of serious exploration."<sup>2</sup> Then came descriptions of his own work that included the first purification and cloning of VEGF, one of the many factors that play a role in blood vessel formation; the identification of the four forms of VEGF, VEGF-A, -B, -C and -D; the VEGF receptors, VEGF-1 and VEGF-2, both tyrosine kinase receptors; the fact that the availability of VEGF is highly regulated with loss of a single allele or overproduction resulting in embryonic lethality and the observation that VEGF is expressed by many tumors. Finally, there was the seminal proof of principle experiment published in *Nature* in 1993, which demonstrated that inhibition of VEGF-induced angiogenesis with an anti-VEGF antibody suppressed tumor growth *in vivo* but had no effect on the tumor growth rate *in vitro*.<sup>3</sup> The humanized version of this antibody that recognizes all VEGF-A isoforms went into clinical trial in 1997 for combination treatment of metastatic colorectal cancer. The results clearly showed an increased median survival rate of 5 months for the bevacizumab-containing treatment arm. Adverse effects included arterial thrombotic events. Today, *Avastin* is licensed for use in combination with chemotherapy for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum and the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer.

Other trials (24 in total) are underway to assess the efficacy of bevacizumab therapy, including studies looking at earlier administration, other types of cancer and in combination with other anticancer agents. Further, Genentech have an active program to identify antibodies with improved properties relative to bevacizumab. Bevacizumab has a dissociation constant ( $K_D$ ) of 1 nM, and one way of improving efficacy may be to increase antibody affinity. However, Dr. Ferrara described a recent study where higher affinity antibodies were isolated, but interestingly, this resulted in no gain in efficacy but an increased toxicity. Particularly, an increased incidence of glomerulonephritis was reported. Parallels were drawn with the toxicity effects reported for VEGF receptor tyrosine kinase inhibitors currently in development.

The lecture was concluded with a progress report of additional uses for anti-VEGF therapies in diseases where VEGF dysfunction is implicated, e.g., diabetic retinopathy and age-related macular degeneration. Pegaptanib, a VEGF binding aptamer, and *Lucentis* (ranibizumab), a VEGF binding Fab dimer derived from bevacizumab have been approved for the treatment of age-related macular degeneration.

### Central nervous system disorders

Dr. Malcolm Sheardown (Paradigm Therapeutics, UK) introduced the CNS therapeutic area by describing the numbers of people affected worldwide. Thus, for example, the numbers of people who suffer from anxiety and depressive disorders is 500 and 360 million, respectively. The CNS market is large (USD 58 billion in the United States alone) and is increasing at an annual rate of about 20%. Despite this, most CNS disorders are poorly treated by currently available medicines. This emphasizes the need to discover safe and effective new medicines, which in turn relies upon identifying new molecular targets for CNS medicines.

The genomics revolution that began in the mid-1990s delivered a huge number of potential targets (>3000) from the "tractable target" classes. However, the vast majority of these have not yet been validated and lack sufficient data on function to allow them entry into the drug pipeline. They are, in a sense, "biological orphans." In order to make an assessment of the therapeutic utility of a novel target, data on *in vivo* mammalian function is essential.

Paradigm's approach is the thorough and systematic phenotyping of genetically modified mice. This has allowed them to identify a number of promising novel drug targets. One example is GPR92, a novel G-protein-coupled receptor (GPCR) that is expressed in small-diameter C fibers in the dorsal root ganglia and the trigeminal ganglion. GPR92 knockout mice have significantly reduced C fiber responses to noxious temperature and mechanical stimulation. By contrast, A $\beta$  fiber transmission showed no difference between knockout and wild-type animals. In the Chung chronic constriction injury model of neuropathic pain, there was an attenuation of responses to noxious stimuli in knockout animals and, unlike wild-type animals, they also failed to develop allodynia.

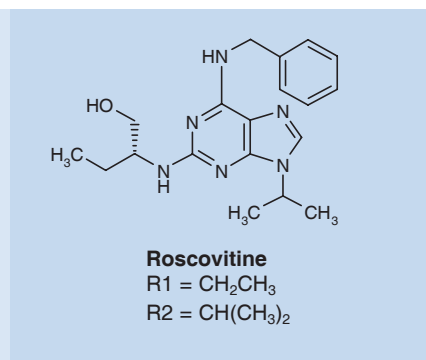
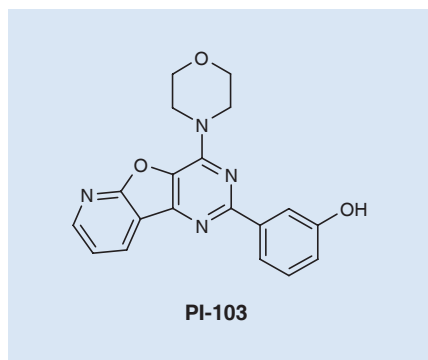
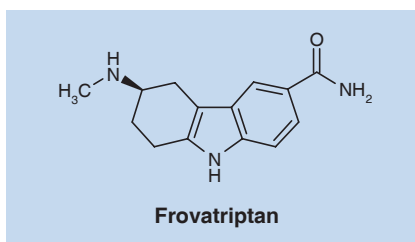
A role for GPR92 in bladder function was also observed. By inserting a catheter into the bladder dome, saline was infused at a constant rate. Bladder pressure was measured by a pressure transducer and micturition volume in a metabolic cage. After cystometry was complete, the bladders were removed and weighed. This showed that GPR92 may also have potential in the treatment of bladder disorders, particularly for overactive bladders. In summary, GPR92 is a target that has potential utility for the treatment of both neuropathic pain and overactive bladders.

Moving to the other end of the value chain, Dr. John Hutchinson (Vernalis, UK) described clinical studies with frovatriptan to support its use



in the prophylactic prevention of menstrual migraine. Frovatriptan is a 5-HT<sub>1B/D</sub> agonist. It was developed initially for acute use in the treatment of migraine. Of the seven triptans that are currently on the market, frovatriptan has the longest half-life (26 hours), as well as the lowest recurrence rate (17%). The flip-side of frovatriptan's long half-life is that the time taken to achieve maximal concentration is about 20 minutes longer than that of the other triptans. This delay in achieving therapeutic concentrations, means that frovatriptan tends not to be the first-line therapy for patients requiring rapid relief from excruciating migraine pain. It was recognized that this disadvantage could be overcome by using frovatriptan as a prophylactic for the prevention of menstrual migraine.

Menstrual migraine has a debilitating impact on the lives of many women. It is associated with falling estrogen levels prior to the onset of menstruation. There is often a family history and it is associated with an increased risk of stroke and white matter lesions in the cerebellum, which may lead to neurological problems in later life. A positive aspect, however, at least in terms of prophylactic treatment, is that between 60–80% of women can judge to within 1 day when a menstrual migraine will occur. Two clinical trials, MAM01 and MRM02, have been carried out. The results of MAM01 have been published; the MRM02 cohort of patients correspond to a subgroup that are difficult to treat since they are inadequate responders to triptan treatment once a migraine has occurred. The results from this second trial are as yet unpublished. For both, the primary indication was stopping the migraine and the



secondary indication was the characteristics of breakthrough headaches. The outcomes for both studies are consistent across the respective phase III programs. They showed significant benefit compared to placebo for both of these for two dosing regimens (i.e., 1 x 2.5 mg; 2 x 2.5 mg) with a very good patient compliance. Thus the potential short-coming of frovatriptan has been turned to advantage by altering its use. The efficacy and safety of frovatriptan in a novel indication, i.e., menstrual migraine, has thus now been confirmed and it has been submitted to the FDA for approval.

## Cancer

Dr. Michael Moore (Piramed, UK) delivered the first of three presentations describing the discovery of novel classes of anticancer compounds. He presented Piramed's progress in the discovery of a novel class of PI-3 kinase inhibitors and focused on the rationale for development of these compounds as anticancer and anti-inflammatory drugs. PI-3 kinases are a family of lipid kinases that catalyze the synthesis of phosphoinositol second messengers. PI-3 kinases are activated by cell surface receptor tyrosine kinases and GPCRs transmitting anti-apoptotic signals and regulating protein translation. PI-3 kinases exist in multiple isoforms and the p110  $\alpha$  isoform in particular has been shown to be mutated or overexpressed in a range of cancers. PTEN phosphatase is a tumor suppressor gene that negatively regulates the PI-3 kinase pathway and shows the highest rate of gene mutation in cancer after p53.

Dr. Moore went on to describe the discovery of a novel series of specific PI-3 kinase inhibitors based on the structure of PI-103. This compound inhibits the PI-3 kinase p110 $\alpha$  and  $\beta$  isoforms with IC<sub>50</sub>s of 2 and 3 nM, respectively. The lead optimization program was guided by the use of liganded crystal structures leading to the generation of a novel series of orally available molecules. Optimized compounds show high selectivity for PI-3 kinase, with <15% inhibition of a panel of 60 other kinases at a concentration of 3  $\mu$ M. In cellular systems these compounds inhibit phosphorylation of the downstream AKT and p70S6 kinases and exhibit antiproliferative activity in a range of tumor cell lines. *In vivo*, antitumor activity has been demonstrated in a range of xenograft models, including tumor regression with some cell lines. Dr. Moore went on to report the discovery of a series of p110 $\delta$  selective inhibitors. These compounds inhibit B- and T-lymphocyte, neutrophil and mast cell activation. Marked activity has been seen in a murine collagen type II-induced arthritis model and compounds from this series are being developed for the treatment of inflammatory diseases. The p110 $\delta$  isoform is also expressed in acute myeloid leukemia (AML) blasts and p110 $\delta$  inhibitors show marked inhibition of AML blast proliferation.

Dr. Bob Jackson (Cyclacel, UK) described the development of *Seliciclib* (roscovitine), an orally available cyclin dependent kinase (CDK) inhibitor. The CDK's are a family of 16 serine/threonine kinases

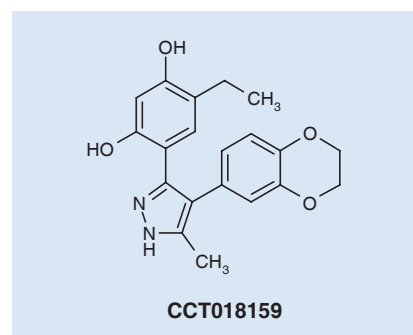
regulating cell cycle progression and transcription. CDK's are dysregulated in many cancers including non-small cell lung cancer (NSCLC), small cell lung cancer, melanoma, Ewing's sarcoma, nasopharyngeal cancer and a range of hematological malignancies. Roscovitine was originally identified as a CDK 1 and 2 inhibitor, which has subsequently been shown to inhibit CDK 7 and 9 with potencies in the 0.1–0.8  $\mu\text{M}$  range. Roscovitine induces apoptosis in a range of tumor cell lines *in vitro* with  $\text{IC}_{50}$  values in the 10–15  $\mu\text{M}$  range. The proapoptotic activity of roscovitine was shown to correlate with downregulation of the antiapoptotic protein mcl-1. *In vivo*, roscovitine shows single agent activity in xenograft models and synergistic activity with docetaxel.

Roscovitine has been administered to 70 patients in the phase I setting. Stable disease was recorded in 10 patients, including five patients with NSCLC. One partial response was recorded to a patient with hepatocellular carcinoma. A phase IIa study investigating roscovitine in combination with cisplatin and gemcitabine in NSCLC is ongoing. To date, 10 out of 12 patients on this study have been reported to have stable disease or shown a partial response. A randomized phase II study in NSCLC has been initiated with time to progression as the key endpoint. Roscovitine is also being investigated for potential utility in B-cell malignancies and nasopharyngeal carcinoma.

The final presentation in this session was delivered by Paul Workmann from the Cancer Research UK (CRUK) Centre for Cancer Therapeutics at the Institute for Cancer Research (ICR), Sutton, UK. Professor Workmann began by reinforcing a key message from this session—that optimal anticancer treatment will require combinatorial therapy hitting multiple targets, particularly to combat the problem of drug resistance. This may be achieved by using combinations of highly targeted, pathway-specific drugs or by hitting single, key

regulatory targets which themselves may not be mutated or overexpressed. An example of successful anticancer drug development using the latter strategy can be found in bortezomib, which inhibits the proteasome pathway. An emerging family of key regulatory proteins for anticancer drug discovery are cellular chaperones such as Heat Shock Protein 90 (HSP-90) Inhibitors. HSP-90 is an ATPase with an ATP binding site that regulates the proteasomal degradation of key oncogenic client proteins. Inhibition of HSP-90 has the potential to overcome 'addiction' to multiple oncogenes and prevent or overcome resistance. The remainder of Professor Workmann's presentation focussed on describing the discovery of a novel series of HSP-90 inhibitors highlighting the historical role of chemical biology and the use of structural biology and biomarkers in the ICR program.

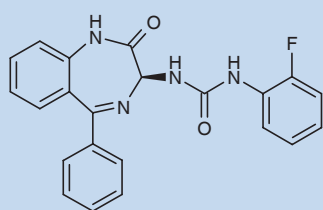
The first identified HSP-90 inhibitor, geldanamycin, was discovered by a chemical genomics screening approach in whole cells. A geldanamycin derivative, 17-AAG, is currently undergoing clinical evaluation. 17-AAG induces degradation of oncogenic client proteins in whole cells and shows potent antitumor activity *in vitro* and *in vivo* in preclinical models. In phase I clinical trials, prolonged stable disease has been observed in two melanoma patients. Biomarkers used as evidence of 'on-target' activity of 17-AAG have included decreased CDK4 levels and increased HSP-70 levels. Levels of mutated but not normal B-raf are found in tumor cells exposed to 17-AAG, which may be causally related to the activity seen in melanoma patients. The ICR drug discovery program was initiated in order to find a new class of HSP-90 inhibitors with improved 'drug-like' properties relative to AAG and 17-AAG. These included greater solubility, less susceptibility to cytochrome P450 3A4 (CYP3A4) and quinone oxidoreductase (NQO1) metabolism and multidrug resistance (MDR)-mediated cellular efflux and improved tolerability. Screening using a yeast-



based system yielded the diaryl pyrazole CCT018159. This compound was found to be ATP competitive, showed activity in whole cells and formed the basis for a lead optimization program undertaken with Vernalis. The chemistry program transitioned the pyrazole to an isoxazole-based template and was guided heavily by structural information derived from co-crystallization experiments. Both oral and intravenous candidates based on the VER50589 structure are currently in clinical trials.

### The discovery of potential new medicines for wound healing and viral infection

Professor Mark Ferguson is an academic at the University of Manchester and also the co-founder of Renovo, a biotech company dedicated to developing pharmaceutical products for the prevention and reduction of tissue scarring. His lecture began by the presentation of a convincing case for the need to develop such reagents and the underlying biology behind the use of *Juvista* (avotermin), human recombinant transforming growth factor  $\beta 3$  (TGF $\beta 3$ ), as an antiscarring agent. There are currently no approved therapies for the treatment of scarring. It is not just a cosmetic issue; postoperative scarring, burns and pathological disease also contribute to an estimation of 42 million cases per annum in the United States. Professor Ferguson's pivotal observation was that operations carried out on embryonic sheep tissue, i.e., E16, did not result in scarring in contrast to operations post-E16. Evidence has now been amassed to explain these findings in terms of the morphogenetic factor, TGF $\beta 3$ . For



The active [S(-)]-enantiomer of RSV604

example, TGF $\beta$ 3 in contrast to the TGF $\beta$ 1 and TGF $\beta$ 2 isoforms, is expressed at high levels in fetal tissues; TGF $\beta$ 3<sup>-/-</sup> mice do not heal post-wounding thus correlating the lack of TGF $\beta$ 3 with scar formation and, in animal models, treatment with recombinant TGF $\beta$ 3 reduced scarring. Interestingly, although TGF $\beta$ 1, TGF $\beta$ 2 and TGF $\beta$ 3 all mediate their effects via the TGF receptor, TGF $\beta$ 1 and TGF $\beta$ 2 do not have antiscarring activity. It is now known that TGF $\beta$ 3-TGF receptor interactions are distinct to TGF $\beta$ 1 and TGF $\beta$ 2 TGF receptor association resulting for TGF $\beta$ 3 in the activation of a different, i.e., rabGTPase, cdc42, downstream signaling pathway.

In terms of human studies, avotermin has an excellent safety profile having been administered to over 1,000 patients as a one-off dose with no side effects. This may be a result of it being a sticky molecule that binds with high affinity to collagen and fibronectin of the extracellular matrix resulting in retention at the site of injection. Five clinical trials are now ongoing to assess scar improvement in the adult population, actually young males, since they scar the most. TGF $\beta$ 3 is given as a one-off dose by intradermal injection at the site of the lesion either pre- or post-excision. The preliminary findings show that there is significant improvement with TGF $\beta$ 3 treatment versus placebo. Professor Ferguson ended by saying that antiscar activity is being assessed initially in

acute wounding in adults partly because of ethical considerations. In the long term, however, it is hoped that TGF $\beta$ 3 may be beneficial in the treatment of burns, particularly in children. To this end, in animal models of burns, intravenous delivery of TGF $\beta$ 3 is effective in reducing scarring.

The final talk of the day was delivered by Professor Ken Powell (Arrow Therapeutics, UK). He introduced human respiratory syncytial virus (RSV), which causes an illness that usually resembles a moderate to severe cold and is very contagious. RSV most often resolves on its own and does not cause major health concerns. However, the infection can become a problem when it is severe or leads to complications. Babies (especially those born prematurely), people with immune system problems, people with heart or lung problems, and older adults have an increased risk of developing complications from RSV infection. Arrow's RSV program began through a successful collaboration with Virogen Ltd, a company that spun-out from MRC Technology, the exclusive commercialization catalyst for the UK Medical Research Council (MRC). RSV604 has submicromolar anti-RSV activity against all clinical isolates tested of both A and B subtypes of the virus. The compound has a novel mechanism of action, a slow rate of *in vitro* resistance development, good ADME properties and a clean preclinical and clinical safety profile. In a three-dimensional human airway epithelial cell model RSV604 was able to pass from the basolateral to the apical site where it effectively inhibited virus replication. In preclinical studies RSV604 was well tolerated *in vivo* and exhibited an ideal pharmacokinetic and excellent safety profile allowing the initiation of successful phase I clinical trials. The compound is now partnered with Novartis and is in phase II trials in immunocompromised

adults. RSV604 represents the first in a new class of RSV inhibitors which has significant potential for the effective treatment of RSV disease.

## Conclusion

The meeting succeeded in showcasing a number of success stories in the discovery and development of new medicines. We should like to congratulate Dr. Ferrara, this year's SMR award winner. Previous winners of this award include imatinib (cancer), rosiglitazone (diabetes), olanzapine (schizophrenia), saquinavir (HIV infection), sumatriptan (migraine) and fluconazole (fungal infection). Finally, we should like to express our deep gratitude to Tony Jones and his team from the London Biotechnology Network along with Harriet Fear and her UKTI team for their generous help and support.

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Alan M. Palmer (Pharmidex, UK), F. Anne Stephenson (School of Pharmacy, UK) and Robert J. Williams (Cancer Research UK) are members of the Society for Medicines Research (SMR) Committee, which organizes conferences on behalf of the SMR. Details of forthcoming meetings can be obtained from the SMR Secretariat: 840 Melton Road, Thurmaston, Leicester, LE4 8BN, U.K. Tel: +44 (0)116 269 1048; Fax: +44 (0)116 264 0141; E-mail: [secretariat@smr.org.uk](mailto:secretariat@smr.org.uk); URL: <http://www.smr.org.uk>.