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**MEETING REPORTS**

*Highlights of the Society for Medicines Research Symposium held  
March 9, 2006, in London, U.K.*

# Cancer Treatments for the New Millennium

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**D**avid Thurston, Prof. of Anticancer Drug Design and Head of the Dept. of Pharmaceutical and Biological Chemistry, School of Pharmacy, University of London, U.K., opened the SMR Symposium held on March 9, 2006, with a presentation that overviewed the contribution of chemistry to the discovery and development of cancer therapies. The story began with the serendipitous discovery of the mustard family of agents in the 1940s, which led to the development of synthetic molecules still in use today. Chemical technologies have also been important in the development of anticancer agents from natural sources. For example, the so called "semi-synthetic" approach to modifying drug leads discovered in plant material has allowed workable quantities of novel agents to be obtained for commercial production, an example being paclitaxel. Chemical synthesis and screening of compounds has been a major paradigm in anticancer

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## Summary

The SMR Symposium *Cancer Treatments for the New Millennium* was held on March 9, 2006, at the National Heart and Lung Institute, Imperial College London. The conference program brought together an international line-up of speakers representing academia, biotech and large pharma to discuss the development status of a number of new innovative treatments for the treatment or prevention of cancer. Presentations also focused on how new technologies are being applied to the design of the next generation of cancer drugs and the fundamental biological challenges that must be addressed in attempting to discover effective new treatments. © 2006 Prous Science. All rights reserved.

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drug discovery and development. Approaches have evolved from primary screening against whole cancer cells to the popular approach today of screening against specific molecular targets. "Factory screening" of large numbers of compounds is, however, increasingly being replaced by more sophisticated drug discovery strategies. Structural biology techniques such as NMR and X-ray crystallography can reveal the molecular requirements for drug/target interactions greatly facilitating drug design. Computational *in silico* approaches are now emerging that allow for the virtual screening of many more compounds than can be screened physically. Once leads are identified, medicinal chemistry strategies are applied to design in characteristics compatible with favorable physiochemical and

metabolic properties. Chemical technologies have also been applied to the development of prodrugs and the linking of toxic payloads to antibody delivery systems.

The second speaker of the morning session was Dr. John Lyons, Director of Oncology at Astex Therapeutics, Cambridge, U.K. Dr. Lyons opened his presentation claiming that "small is beautiful" and described the Astex fragment chemistry-based approach to the identification of novel drug leads. The Astex approach is dependent on the use of NMR and X-ray crystallography together with drug fragment libraries to identify mM ligands that can be optimized for potency and drug-like properties. Dr. Lyons claimed that teams of three to four chemists could routinely move from

mM leads to compounds with low nanomolar potency in iterations of fewer than 100 analogues. As touched on by Prof. Thurston in his earlier talk, this approach avoids attrition in hit validation that occurs with high-throughput screening and does not necessitate investment in purchase and storage of large compound libraries. Initial leads possess molecular weights in the region of 120–250. Low nanomolar inhibitors of a range of kinase enzymes including p38, CDK2, kinase 4 and Akt, have been discovered using this strategy. **AT-7519** is a CDK1/CDK2 inhibitor in phase I clinical trials in the United States and United Kingdom.

Prof. David Jenkins, Director of Clinical Development, Global HPV Vaccines, GlaxoSmithKline (GSK), Belgium, provided a complete change of focus with the final presentation of the morning entitled *Vaccination against human papillomavirus infection: A new paradigm in cervical cancer control*. Prof. Jenkins described how understanding of the molecular biology of a disease can lead to the development of effective targeted treatments. Cervical cancer is a huge cause of cancer-related mortality in developing countries, causing more than 270,000 deaths per year globally. Cervical cancer is caused by human papillomavirus (HPV), a double-stranded DNA virus. Approximately 40 HPV types have been identified, with HPV-16 and -18 causing approximately 70% of cancer cases. The infection is spread by genital contact, and while many infections resolve spontaneously, in some people a persistent infection develops leading to intraepithelial neoplasia, which can progress to carcinoma. A prophylactic vaccine is needed, as currently those individuals at risk of developing cancer can only be detected and treated by mass screening programs (costing the U.K. £150 million/year and the U.S. \$3 billion/year). GSK has developed a prophylactic candidate HPV-16/18 vaccine. The vaccine, *Ceravix*, incorporates recombinant L1 capsid protein particles from HPV-16 and -18 together

with ASO4 adjuvant containing aluminum hydroxide and monophosphoryl lipid. The vaccine induces sustained antibody responses and T- and B-cell memory responses. Efficacy trials have shown complete protection against infection with HPV-16/18, and some cross protection against other strains has been noted. Elevated antibody levels have been seen so far out to 48 months post vaccination. More than 30,000 females have been enrolled into trials overall and a phase IV program is planned. Application for a marketing license has been filed in Europe, and filing in the United States is expected by the end of 2006.

The first presentation of the afternoon session was given by Prof. Herbie Newell, Director of Translational Research at Cancer Research UK and Prof. of Cancer Therapeutics at Northern Institute for Cancer Research, Newcastle, U.K. Prof. Newell described the rationale for focusing on DNA repair as a target mechanism for the identification of novel cancer drugs and gave an overview of progress made in the development of DNA repair inhibitors. DNA is constantly subject to damage, for example, environmental damage from ionizing radiation and replication errors during cell division. Consequently, living organisms have evolved mechanisms to repair DNA damage. If DNA is not repaired, apoptosis and cell death often follow. Indeed, the mechanism of action of many anti-cancer drugs is based on inducing DNA damage. The rationale for targeting DNA repair mechanisms in cancer drug discovery is based on the hypothesis that 1) DNA repair inhibitors may potentiate the activity of DNA damage-inducing chemotherapeutic agents; and 2) tumor cells may be inherently more sensitive to inhibition of DNA repair due to defects in these mechanisms in cancer cells. Prof. Newell went on to describe several classes of DNA repair inhibitors currently at various stages of development. Most advanced are *Patrin* (**lomeguatrib**; Fig. 1) and *Alkylade* (KRX-0402), irreversible inhibitors of

the enzyme O<sup>6</sup>-alkylguanine DNA-alkyltransferase in phase II and phase III development, respectively. Both agents have been shown to increase sensitivity to cytotoxic drugs. Prof. Newell spoke in most detail about inhibitors of poly(ADP-ribose)polymerase I (PARP), an enzyme that repairs strand breaks in DNA. The first prototypical inhibitor in this area, **PD-128763**, was found to induce hyperthermia and was not progressed as a drug candidate. The drug discovery team in Newcastle identified **UN-1085** as a potent PARP inhibitor ( $K_i = 10$  nM), and a subsequent structure-based design program undertaken in collaboration with Agouron led to the identification of a series of tricyclic PARP inhibitors. This program, using homology modeling from a chicken enzyme structure eventually yielded **AG-014699**, a tricyclic indole, as a candidate for clinical development. In xenograft models, AG-014699 potentiated the effects of **temozolomide**, topoisomerase I inhibitors and ionizing radiation and in some cases elicited complete cures. AG-104699 alone induced one complete response and three partial responses in 15 patients enrolled into a phase I melanoma trial, an impressive result for a phase I study.

An exciting recent finding has been that PARP inhibitors kill BRCA-deficient cells. CRUK is to conduct a phase II study examining the effects of **AG-014699** in patients harboring BRCA-deficient tumors. Prof. Newell finished his overview by describing progress in the identification of inhibitors of two key kinases, DNA-PK and ATM-kinase, enzymes that

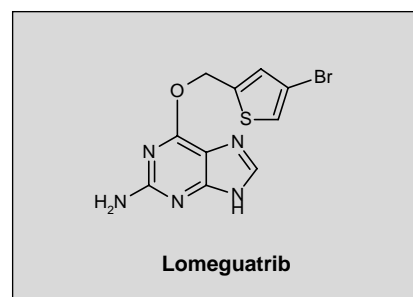


Fig. 1. DNA repair inhibitors.

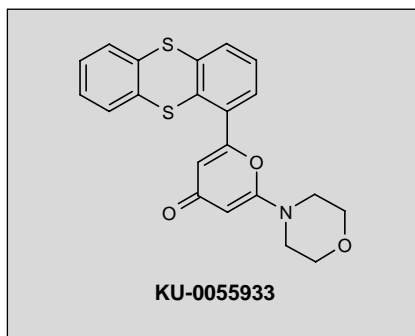


Fig. 2. ATM inhibitor.

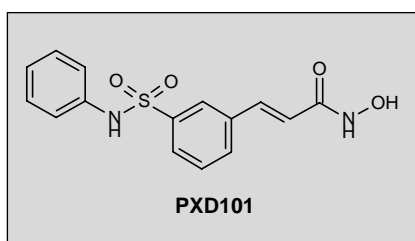


Fig. 3.

sense DNA damage and signal to repair proteins. DNA-PK binds to double strand breaks in DNA and the Newcastle University group has identified a prototype inhibitor, **UN-7441**, that sensitizes cells to the topoisomerase II inhibitors **doxorubicin** and **etoposide**. ATM kinase coordinates cellular responses to ionizing radiation-induced double strand breaks. An ATM inhibitor discovered by the UK biopharmaceutical company Kudos, **KU-0055933** ( $K_i = 0.013 \mu\text{M}$ ; Fig. 2), has been shown to sensitize cells to the effects of etoposide and **camptothecin**.

Nessa Carey, Head of Biology at the Danish/U.K.-based biopharmaceutical company Topotarget, discussed the discovery and development of the histone deacetylase (HDAC) inhibitor **PXD101** (Fig. 3). PXD101 is a hydroxamic acid and is a "pan inhibitor" of class I and class II HDAC enzymes. The compound is being developed in collaboration with U.S. company Curagen. PXD101 was identified in a screening program using HeLa cell extracts as an enzyme source and inhibits enzyme activity with an  $\text{IC}_{50}$  of 38 nM. Increased acetylation of histones 3 and 4 has

been used as a biomarker of PXD101 activity in *in vitro* and *in vivo* studies including clinical studies in humans. The compound inhibits the growth of a wide range tumor cell lines inducing differentiation, growth arrest or apoptosis. PXD101 inhibits tumor growth in a range of *in vivo* xenograft models and prolongs lifespan in leukemic mice. PXD101 inhibits the expression of the enzyme thymidylate synthase and sensitizes tumor cells to 5-FU both *in vitro* and *in vivo*. Synergistic activity has also been demonstrated with **dexamethasone**. No correlation with resistance to standard drugs has been observed, and experimentally it has proved very difficult to generate PXD101-resistant cells. PXD101 is currently in phase II trials in multiple myeloma in combination with dexamethasone and is also being investigated as a single agent. It is still totally unknown which specific HDAC enzymes are critical for mediating tumor cell growth and survival and indeed to what extent induction of acetylation of nonhistone proteins contributes to cellular responses to HDAC inhibition. In this context, it is interesting to note that individual hydroxamate compounds show differential activity in the NCI 60 cell line panel. The potential utility of HDAC inhibitors is also being explored in inflammatory diseases and neurodegeneration.

The second conference session finished with a presentation from Dr. Brian Huntley (Cambridge Institute for Medical Research, Cambridge, U.K.). Dr. Huntley focused on the biology of cancer, in particular the role of cancer stem cells in drug resistance and tumor growth. The cancer stem cell model proposes the existence of a specific subpopulation of cells capable of self-renewal. These cells can be quiescent, possess increased expression of drug efflux pumps and are not as "oncogene addicted" as more mature tumor cells. Cancer chemotherapy targets the "foot soldiers," that is, actively proliferating tumor cells, leaving quiescent stem cells intact and able to later mobilize and proliferate. Stem

cells have been proposed to be responsible for the re-emergence of disease in chronic myeloid leukemia patients following *Gleevec* (imatinib)-induced remissions. Following treatment with imatinib, small numbers of quiescent BCR-ABL-positive cells have been shown to remain harboring kinase mutations that confer drug resistance during subsequent accelerated and blast phases of the disease. Evidence to support the existence of stem cells has also been reported in acute myeloid leukemia (AML), breast cancer and CNS tumors. A further line of experimental studies has shown that viral transduction of granulocyte-monocyte progenitor cells with DNA encoding two fusion proteins, BCR-ABL and MOZ-TIP2, confers these cells with self-renewing properties and the ability to induce leukemias in mice. Dr. Huntley finished his presentation by describing an experimental paradigm for how stem cells may be targeted therapeutically. The antiapoptotic NF- $\kappa$ B pathway is activated in AML stem cells. These cells are ablated and subsequently unable to form colonies by exposure to **parthenolide**, a natural product NF- $\kappa$ B inhibitor. Little effect was seen on normal stem cells, demonstrating the potential for specificity using this approach.

The final session of the afternoon began with a presentation by Dr. Theresa M. Lavalley from EntreMed Inc. on the development of two microtubule disruptors that target angiogenesis. **2-Methoxyestradiol** (2ME2; Fig. 4) is a novel anticancer agent that was identified in the early 1990s. It is a molecule with an excellent safety profile and is orally available, having shown activity in a number of animal

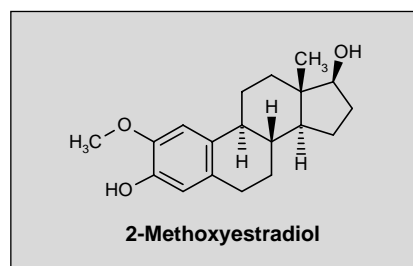
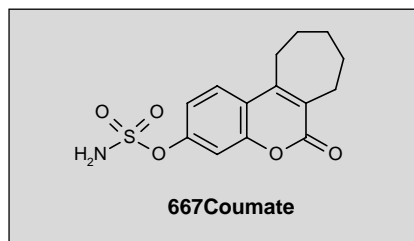


Fig. 4.

models. However, although 2ME2 has been shown to depolymerize microtubules at high concentrations *in vitro*, it is COMPARE negative with other antitubulin agents. Dr. Lavalley continued by describing the effects of 2ME2 on the transcription factor HIF-1 $\alpha$ . Tumors that contain elevated levels of HIF-1 $\alpha$  are aggressive and tend to be predictive of a poorer prognosis. 2ME2 has a profound downregulatory effect on HIF-1 $\alpha$ , which correlates with a decrease in vascular endothelial growth factor (VEGF) expression and contributes to the antiangiogenic effect of the drug. 2ME2 was shown to be very well tolerated in phase I clinical trials (no dose limiting toxicities observed) using a capsule formulation and has been reformulated as a nanocolloidal dispersion suitable for oral use in phase II combination studies. **ENMD-1198** (2-methoxyoestra-1,3,5(10),16-tetraene-3-carboxamide) is an analogue of 2ME2 with improved pharmacokinetic properties and possesses a different antiproliferative profile from the parent drug. ENMD-1198 is about to enter phase I clinical trials with serum VEGF and IL-6 being utilized as pharmacodynamic markers. Interestingly, preclinical safety studies have shown rats to be particularly sensitive to ENMD-1198 (maximum tolerated dose 60 mg/m<sup>2</sup> compared with 600 and 900 for dog and mouse, respectively).

An exciting day of talks aimed at outlining new targets and new drugs for cancer treatment was completed by Prof. Mike Reed, representing both academia (Imperial College and University of Bath) and industry (Sterix Ltd.). Prof. Reed's work has focused on steroid sulfatase inhibitors, developed in a productive collaboration with the symposium co-organizer Prof. Barry Potter and his colleagues. The development of aromatase inhibitors as antitumor agents, based on the ability of the molecules to inhibit the production of estrogen in hormone-dependent breast cancer, has been very successful, but may not be the whole story. Prof. Reed expanded on this by suggesting that, while aro-



**Fig. 5.**

matase inhibitors block the biosynthesis of estrogen, high levels of estrone sulfatase accumulate in breast tumor tissue, which correlates with a poor prognosis in postmenopausal breast cancer. **Androstenediol, dehydroepiandrosterone (DHEA)** and DHEA sulfate have all been shown to stimulate the proliferation of tumor cells via the estrogen receptor. Serum levels of DHEA-S indicate progressive disease in spite of low estradiol (E2) levels.

Prof. Reed and his colleagues identified a potent steroid sulfatase inhibitor in the form of **estrone-3-O-sulfamate**. This is a compound with low nanomolar activity against the enzyme and is orally active. This led to the identification of both steroidal and nonsteroidal "super" estrogens. The steroidal analogues focused on changes to estrone-3-O-sulfamate in the A and the D rings. Nonsteroidal analogues based upon a coumarin core were also developed and shown to have potent activity. **667Coumate** (STX-64; Fig. 5) is a tricyclic coumarin with activity *in vivo* similar to the parent estrone-3-O-sulfamate, but it is nonestrogenic. It had good activity in animal models, causing tumor regression, and has progressed into human trials. In a phase I trial against estrogen receptor-positive metastatic breast cancer, a cautious schedule of three cycles of 5 x 5 mg or 5 x 20 mg 667Coumate was administered orally. Levels of DHEA-S, DHEA, E1, E2, E1S, and androstenedione and testosterone were measured using GC/TANDEM mass spectrometry. Steroid sulfatase activity was also measured. An almost complete blockade was found at both doses, with an increase in the DHEA-S/DHEA ratio

and reduction in androstenediol levels. Although no effect on androstenedione was expected, decreases in this steroid were also seen, suggesting that the presence of the hormone may reflect DHEA-S conversion to DHEA in the cancer patient, rather than direct secretion by the adrenal cortex. In the phase I trial, 5/8 patients had stable disease for 2.5 to 7 months and only minor side effects were noted, one of which, the bad taste, was likely due to the DMSO formulation of the drug.

This meeting can be viewed as an on-demand webcast at [http://webcasts.prous.com/SMR\\_MAR\\_2006/](http://webcasts.prous.com/SMR_MAR_2006/).

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*The SMR Committee organizes conferences on behalf of the Society for Medicines Research four times a year. These one-day conferences are of a multidisciplinary nature, therapeutically focused and normally staged in or around London. Details about forthcoming meetings can be obtained from: SMR Secretariat, Triangle House, Broomhill Road, London SW18 4HX, U.K. Tel: +44 (0)20 8875-2431; Fax: +44 (0)20 8875-2424; E-mail: [secretariat@socmr.org](mailto:secretariat@socmr.org); URL: <http://www.socmr.org>.*