
MEETING REPORT

*Highlights of the Society for Medicines Research Symposium held
December 6, 2007, in London, U.K.*

Recent Disclosures of Clinical Drug Candidates

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The Society for Medicines Research meeting entitled *Recent Disclosures of Clinical Drug Candidates* provided an overview of some of the latest approaches being taken in a range of therapeutic areas such as oncology, immunology, central nervous system disease, gastroenterology and antiviral research.

The design of nonpeptide motilin agonists as gastric motility agents

Dr. Jon Seal (GlaxoSmithKline, Harlow, U.K.) gave the opening presentation describing the drug discovery program that led to the identification of a selective motilin agonist for the treatment of gastroparesis and functional dyspepsia.

The discovery of new therapies for the treatment of delayed gastric emptying represents an opportunity to offer improved symptomatic relief for patients with conditions such as gastroparesis (diabetic and idiopathic

Summary

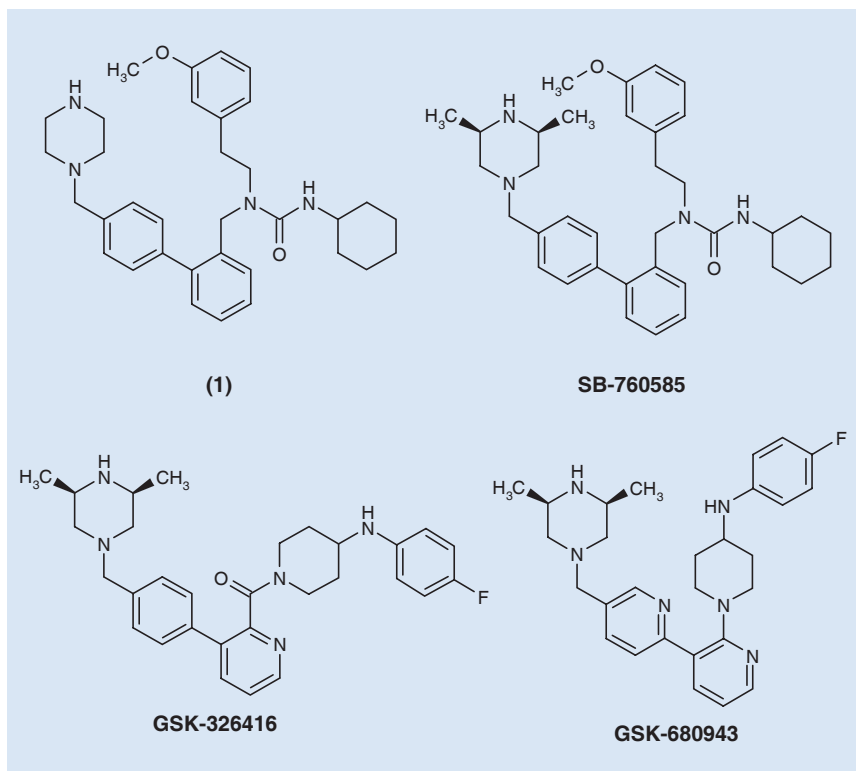
On December 6, 2007, the Society for Medicines Research held a one-day meeting entitled *Recent Disclosures of Clinical Drug Candidates*. The meeting brought together speakers from around the world representing both the pharmaceutical industry and academia. The meeting provided an overview of some of the latest approaches being taken in a range of therapeutic areas such as oncology, immunology, central nervous system disease, gastroenterology and antiviral research. © 2008 Prous Science, S.A.U. or its licensors. All rights reserved.

and functional dyspepsia without the unwanted side effects possessed by many previous and current therapies. In 1999, motilin, a 22-amino acid peptide hormone, was identified as the endogenous ligand of the orphan 7-TM, class A receptor GPR38 (now also known as the motilin receptor). Motilin is involved in regulating the coordinated activity of the gastrointestinal (GI) tract, particularly through inducing interdigestive (phase III) antral and duodenal contractions, but due to its peptidic nature, is not suitable as an oral prokinetic agent. **Erythromycin** is also an agonist of the motilin receptor and has demonstrated potent prokinetic activity in humans. Although often used off-label for the treatment of conditions associated with delayed gastric emptying in the clinic, erythromycin is unsuitable for long-term use due to its antibiotic activity.

The program at GlaxoSmithKline to identify orally active motilin agonists began from a high-throughput screening exercise which yielded a single attractive chemical starting point, the lipophilic (clogP 6.3) compound (**1**) with a human motilin (hMTLR) pEC₅₀ of 6.7 (*cf.* erythromycin A pEC₅₀ 6.2). Early optimization led to the urea **SB-760585**, with hMTLR pEC₅₀ of 7.3. SB-760585 also suffered from several potential ADMET liabilities including high lipophilicity, activity at hERG, moderately rapid clearance in microsomes and potent CYP3A4 inhibition.

In further iterations of optimization cycles attempts were made to improve and balance potency, lipophilicity and ADMET parameters.

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This was successful in identifying the pyridyl amide **GSK-326416**, which now possesses improved potency (hMTLR pEC₅₀ 7.7) and lipophilicity (clogP 4.1, logD 0.72) and no obvious ADMET liabilities *in vitro*. Further potency improvements were also achieved by introduction of a bipyridyl unit which yielded **GSK-680943** with an hMTLR pEC₅₀ of 9.1 and good ADMET parameters *in vitro*.

GSK-326416 was profiled further in *in vivo* pharmacokinetic experiments where it showed low to moderate oral bioavailability in rats and dogs, respectively (F% rat = 13%, dog = 58%). Both GSK-326416 and GSK-680943 showed effects in a rabbit gastric antrum *ex vivo* tissue assay with GSK-326416 demonstrating superior efficacy to GSK-680943 although the moderate efficacy of GSK-680943 was seen at much higher potency levels than GSK-326416. GSK-326416 also showed good efficacy in a human gastric fundus *ex vivo* tissue assay and in an *in vivo* rabbit fecal output model when dosed at 3 mg/kg i.v. GSK-326416 is now being further profiled as a gastroprokinetic agent.

Lacosamide, a novel anticonvulsant and analgesic with an innovative mode of action

Dr. Thomas Stöhr (UCB, Germany) presented UCB's **lacosamide** program aimed at the treatment of epilepsy and neuropathic pain.

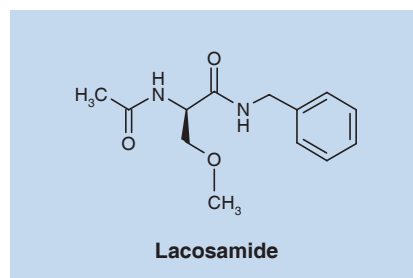
Lacosamide is a novel analgesic which is currently being evaluated in phase III clinical trials in painful diabetic neuropathy and as add-on therapy for partial seizures. In addition, it is being evaluated in phase II trials for osteoarthritic pain, fibromyalgia and migraine prophylaxis.

Lacosamide is a low-molecular-weight and highly soluble functionalized amino acid that was discovered from an academic program searching for D-Serine mimetics acting at the *N*-methyl-D-aspartate (NMDA) receptor utilizing *in vivo* screening; however, lacosamide was subsequently shown to have little or no effects on NMDA receptor function. Scientists at UCB rationalized that lacosamide overlaid structurally to some extent with phenytoin which is known to have

sodium channel modulatory activity. Subsequent detailed electrophysiological studies using the patch-clamp technique revealed that lacosamide shifted the voltage dependence of slow inactivation of voltage-gated sodium channels (VGSC) to more negative potentials thereby regulating the long-term availability of sodium channels. Unlike other analgesics and anticonvulsants targeting the sodium channel (e.g., lidocaine), lacosamide did not influence fast inactivation of VGSCs.

Further fishhook experiments with affinity ligands in rat brain homogenates and radioligand binding to recombinant proteins identified collapsin-response mediator protein 2 (CRMP-2) as another binding partner for lacosamide. Since CRMP-2 is involved in neuronal differentiation and axonal outgrowth, the effects of lacosamide on neurotrophin-induced axonal outgrowth were examined. Lacosamide specifically reduced excessive axon outgrowth induced by neurotrophic factors without effects on basal outgrowth further supporting an interaction of lacosamide with CRMP-2. Given the important role of neurotrophic factors in the pathophysiology of chronic pain, it is postulated that the interaction of lacosamide with CRMP-2 might potentially have disease-modifying effects.

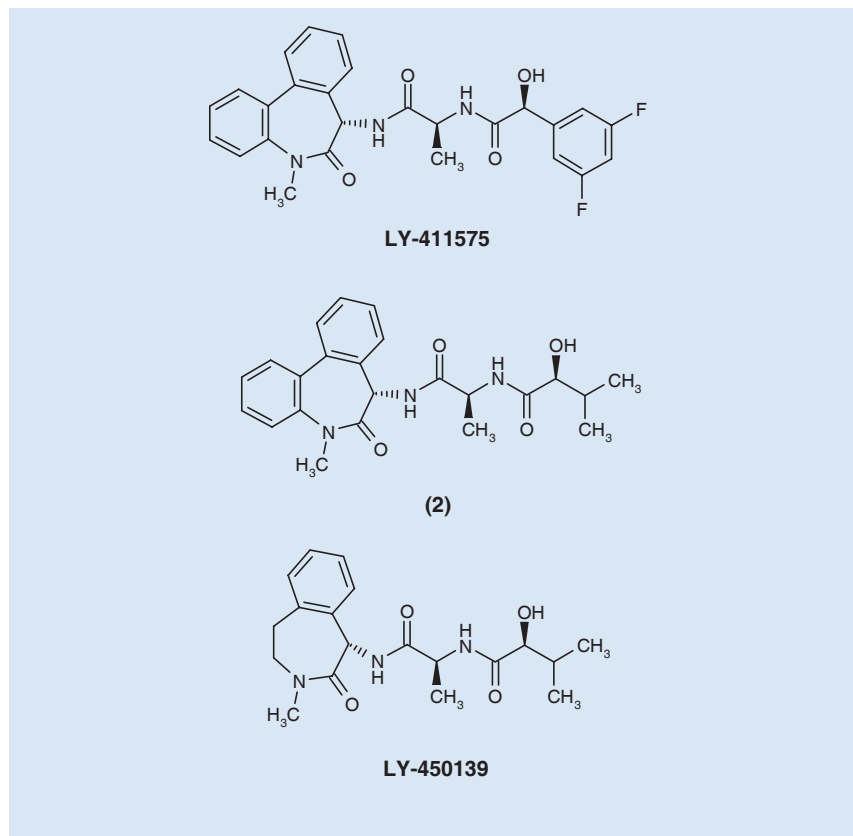
In animal models of chronic neuropathic and inflammatory pain, lacosamide showed a broad antinociceptive efficacy against allodynia and hyperalgesia as assessed by thermal and mechanical stimuli at doses of 3–30 mg/kg p.o. In contrast, lacosamide did not affect sensory thresholds in a model of acute pain. In the



streptozotocin model of diabetic neuropathic pain, in which lacosamide was directly compared to clinically used analgesics, lacosamide appeared to have the broadest efficacy indicating that lacosamide may have specific antihyperalgesic activity under conditions of chronic neuropathic, cancer and inflammatory pain. Lacosamide also showed anticonvulsant activity in various rodent models for partial and generalized seizures but was largely inactive against seizures induced by various chemoconvulsant agents such as picrotoxin or bicuculline. Lacosamide was also active in different models for status epilepticus and had disease-modifying effects in the kindling model.

Clinical results were also presented for lacosamide. In phase I, lacosamide was ~100% orally bioavailable, and ~15% protein bound with a t_{max} of 1–2 hours and a half-life of ~13 hours. Exposures in terms of C_{max} and AUC were dose proportional and ~95% of the drug is excreted in the urine. No interactions with food or a range of potentially coadministered drugs were seen though sodium channel-mediated dose-related increases in the PR interval (usually asymptomatic) were observed without any effect on QTc prolongation.

In efficacy studies, lacosamide is being developed as an oral adjunctive treatment for partial onset seizures. In a large, randomized, controlled trial, lacosamide (400 and 600 mg/day) reduced seizure frequency in subjects with uncontrolled partial-onset seizures when administered as adjunctive therapy. To date, the safety profile shows lacosamide has dose-related central nervous system and GI adverse events, a low rate of psychiatric events, and no weight gain or loss. In efficacy trials for neuropathic pain, lacosamide significantly reduced moderate to severe neuropathic pain due to diabetic polyneuropathy at 400 mg/day compared to placebo. Lacosamide at 400 mg/day also achieved clinically meaningful improvements in patients' quality of



sleep and daily routine activity levels. The most frequently occurring adverse events (lacosamide 200–600 mg/day vs. placebo) in double-blind trials were headache (9.3 vs. 9.6%), dizziness (16.3 vs. 5.2%) and nausea (10.3 vs. 6.2%).

Testing the Amyloid Hypothesis: Optimization and characterization of the functional γ -secretase inhibitor LY-450139

Dr. Jim Audia (Eli Lilly, U.S.A.) described a medicinal chemistry program aimed at developing selective γ -secretase inhibitors for the treatment of Alzheimer's disease.

Alzheimer's disease is now the fourth largest cause of death in the United States. Overproduction and/or reduced clearance of β -amyloid ($A\beta$) peptide play a critical role in the disease pathogenesis, according to the "Amyloid Hypothesis" of Alzheimer's disease. Among the modes of intervention suggested by this approach to Alzheimer's disease are inhibition of

β - and γ -secretases, the proteolytic enzymes implicated in the formation of $A\beta$ from its precursor molecule. Lilly has previously described dipeptide functional γ -secretase inhibitors capable of reducing $A\beta$ peptide levels in the brains of transgenic (PDAPP) mice and their subsequent optimization into highly potent dibenzocaproactam inhibitors suitable for chronic *in vivo* experimentation. Further optimization of this series has led to the identification and characterization (in transgenic and nontransgenic animal models) of inhibitors appropriate for challenging the Amyloid Hypothesis in a clinical setting.

Earlier lead optimization efforts had identified **LY-411575** as an 83 pM inhibitor in a HEK293 cell-based $A\beta$ assay. **LY-411575** was active *in vivo* in an $A\beta$ deposition assay but also demonstrated some "off-target" side effects via the "notch" pathway mechanism which are typically manifested as GI tract weight gain *in vivo*. Further optimization and testing identified analogue **(2)** as an 84 pM inhibitor in

a HEK293 cell-based A β assay. When tested *in vivo* at 0.3 mg/kg p.o., this compound demonstrated good efficacy in an A β deposition assay and some degree of separation from notch side effects at this dose. Given this first indication that notch side effects can be dissociated from efficacy, further lead optimization work was undertaken.

These efforts eventually yielded **LY-450139** as a potent oral *in vivo* inhibitor of A β plasma levels and brain deposition devoid of any significant notch-mediated toxicology. This compound was taken forward to human studies where it was well tolerated in both single and multiple ascending dose studies at doses of 60–140 mg/day and also demonstrated a reduction in the biomarker of plasma A β levels in healthy volunteers. Further clinical studies are now planned to test the efficacy in diseased patients.

NVP-AEB-071: Oral and specific inhibitor of T-cell activation for the prevention of graft rejection and the treatment of autoimmune diseases

Dr Juergen Wagner (Novartis, Switzerland) presented data on **NVP-AEB-071** (sotrastaurin), a selective and potent inhibitor of classical and novel protein kinase C (PKC) isoforms.

Multiple approaches have been pursued to control graft rejection, such

as ciclosporin, calcineurin inhibitors and rapamycin analogues. Only calcineurin inhibitors block T-cell activation but they suffer from severe side effects with only around 50% compliance and with around 80% of hospital readmissions due to the toxic side effects. The therapeutic effect is via interaction with PKC isoforms, which are centrally involved in the process of T-cell activation.

PKCs mediate signaling downstream of the T-cell receptor, with 10 isoforms currently identified. PKC inhibitors include staurosporine, a nonselective kinase inhibitor, and the maleimides that inhibit PKC β . In studying bisindolylmaleimide structures, researchers at Novartis noted that while the right-hand side of the structure (**3**) was not amenable to change, a series of analogues of the left-hand side could be generated that maintained activity. This led to the discovery of NVP-AEB-071.

NVP-AEB-071 specifically blocks early T-cell activation and has high selectivity for PKC over other kinases, with over 200 tested to date. Its main metabolizing enzyme is CYP3A4. In cynomolgus monkeys, once-a-day dosing is sufficient in graft rejection. In combination with a dose of ciclosporin ineffective in monotherapy, a remarkable prolongation of graft survival was observed. In humans, a single escalating dose study was carried out in healthy volunteers and the compound was well absorbed and tolerated with no severe adverse effects and few other adverse effects. Significant pharmacodynamic effects

were observed at doses as low as 50 ng in man.

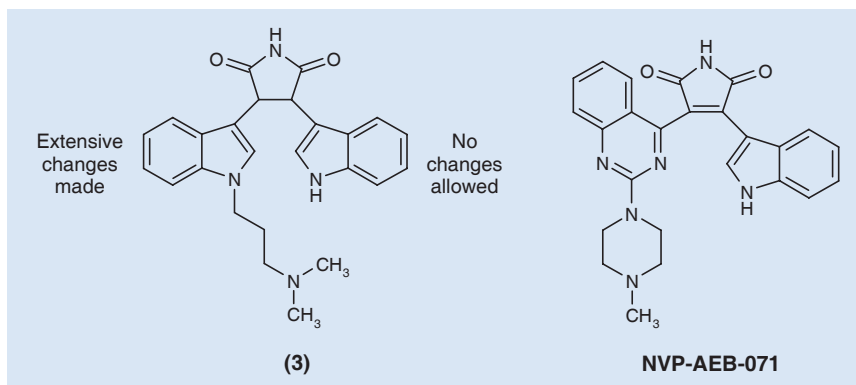
NVP-AEB-071 has also been studied in psoriasis patients, as this disease is strongly dependant on T-cell activation. A multiple dose study showed significant dose-dependent reduction in lesions at 2 weeks and the drug was well tolerated. Phase II trials are now under way on kidney transplant patients.

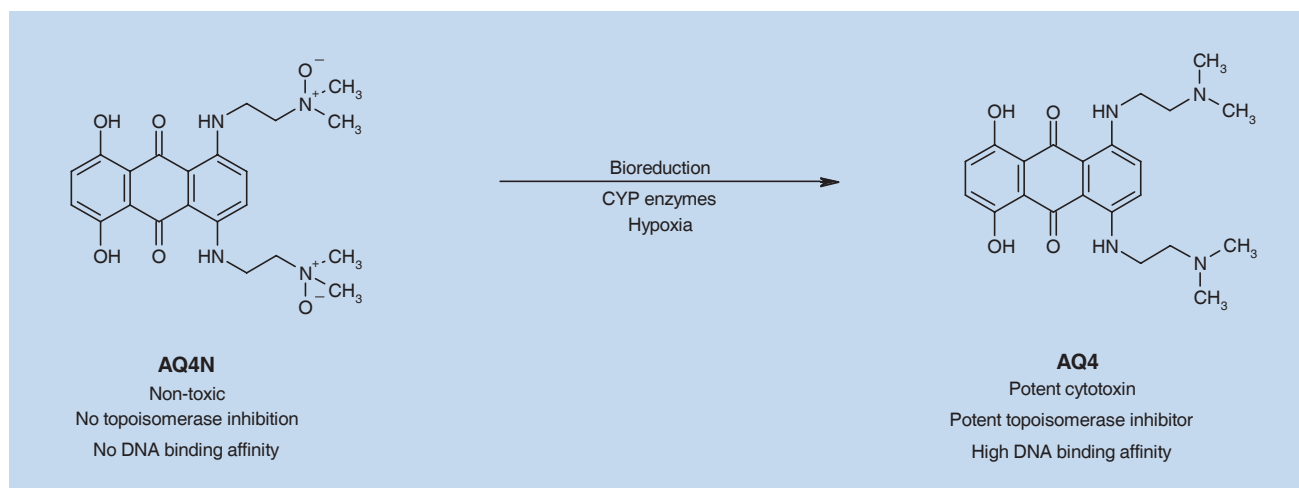
AQ4N (banoxantrone): A unique approach to tumor-selective therapy in phase I/II clinical trials

Prof. Laurence Patterson (The Institute of Cancer Therapeutics, University of Bradford, U.K.) described the extensive work carried out to date on the development of **AQ4N**, now also known as banoxantrone, which is a bioreductively activated antitumor agent currently in phase I/II clinical trials.

The natural product doxorubicin is a clinically utilized topoisomerase II inhibitor that, due to associated dose-limiting cardiotoxicity, led to the development of the synthetic agent mitoxantrone. However, both these compounds are classical cytotoxic agents that are not targeted to a tumor cell and, although clinically used, have the associated toxicities (e.g., immune suppression) associated with all cytotoxic agents. In order to target tumors, Patterson (and others) looked at the structure and physiology of a solid tumor and theorized that the formation of hypoxic regions, with cells that are distant from the blood supply or to which the oxygen supply is restricted, was a potential source of cancer-specific drug activation. On this basis, AQ4N was designed.

The anthraquinone AQ4 is a potent, highly toxic topoisomerase inhibitor that binds with high affinity to duplex DNA. Conversion of the side chain tertiary amine into its stable *N*-oxide leads to a nontoxic compound with no measurable DNA binding affinity and no activity as a topoisomerase inhibitor. Fluorescence micro-





scopy has clearly demonstrated the cytoplasmic accumulation of AQ4N in cells while the active metabolite binds strongly to DNA and as a consequence is localized in the nucleus. In the breast cancer cell line MDA-MB-231, AQ4N has an IC_{50} of around 20 μ M in normal oxygenated cells, whereas in hypoxic conditions, the IC_{50} increases around 1700-fold to 11 nM. Interestingly, AQ4N is activated in hypoxia by cytochrome P450 enzymes, which become reducing in the oxygen-free environment. The drug sensitizes tumors to clinically used agents such as gemcitabine, cisplatin, thiotepa and cyclophosphamide and has also been shown to be effective in combination with radiation.

AQ4N has moved into phase I clinical trials both as a single agent and in combination with radiation and cisplatin. Target tumors in phase I studies have been esophageal, glioblastoma, bladder cancer and general advanced malignancies and it is being developed as a single agent in phase II trials against acute lymphoblastic leukemia and non-Hodgkin's lymphoma. In the esophageal cancer phase I trial in combination with radiotherapy, AQ4N was shown to have a mean plasma half-life of 4.3 h, with AQ4 undetectable in plasma and the majority of drug excreted in urine unchanged. Neither the maximum tolerated dose nor dose-limiting toxicity was established in the study, with the highest dose of 497 mg/m².

In a second phase I proof of principle study in multiple advanced solid tumors, AQ4 production in the tumors was demonstrated in 30/32 tumors and correlated with the activation of glucose transporter 1 (GLUT-1), a marker of hypoxia that is also correlated with a poor prognosis. Activation in glioblastoma multiform was particularly interesting as AQ4N is able to cross the blood-brain barrier and a phase I study is now under way using AQ4N, temozolomide and radiation therapy.

There is still some way to go with the AQ4N, with an optimum dose still yet to be established and until phase II trials are completed, no indication yet as to therapeutic benefit. However, AQ4N, which is now licensed by the U.S. company Novacea, is one of the few new agents currently on trial that has come from an academic laboratory and has progressed into human trials and as such it should be celebrated.

The discovery of UK-453061: A next-generation NNRTI for the treatment of drug-resistant HIV

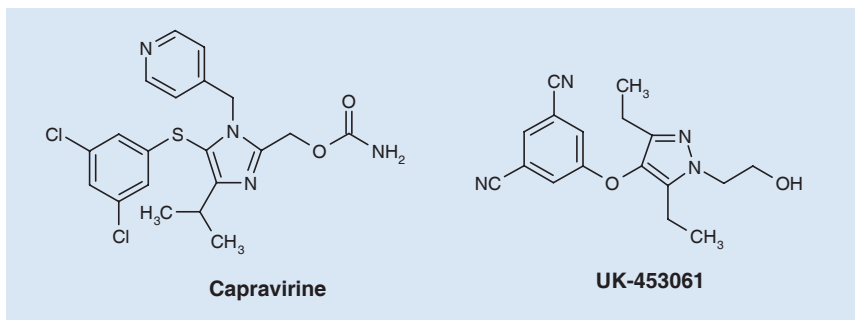
Dr Charlie Mowbray (Pfizer, U.K.) presented on the discovery of **UK-453061**.

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are established as key components of highly active antiretroviral therapy (HAART). In the clinic, drug combi-

nations containing NNRTIs with other antiretroviral agents can produce sustained reductions in viral load and slow the rate of disease progression. However, the currently approved NNRTIs suffer from side effects and drug-drug interactions and are susceptible to mutations in HIV reverse transcriptase (RT), in particular mutations such as K103N that can lead to resistance to the entire class. Thus, there is a need for a safe and well-tolerated NNRTI that retains activity against clinically significant drug-resistant viruses and can be conveniently combined with agents from other classes.

Publications describing the novel imidazole NNRTI **capravirine** showed for the first time that excellent antiviral activity versus wild-type virus could be maintained against viruses carrying clinically relevant mutations in RT. However, a Pfizer in-house analysis of published data and profiling suggested that capravirine had potential issues with dose size, dosing interval and drug-drug interactions which they sought to address in their own program.

Structure-based drug design led to a novel series of pyrazoles, yielding an early lead with moderate antiviral activity against viruses with both wild-type RT and the K103N mutant. Further optimization of this initial lead yielded a series of compounds with improved activity against wild-type and NNRTI-resistant strains of HIV



and excellent physicochemical, pharmacokinetic, pharmaceutical and pre-clinical drug safety properties.

Extensive profiling of one member of this series, UK-453061, revealed an excellent preclinical candidate. Of particular note were the physical properties of the compound, which reversed a trend for reported NNRTIs to possess increasing molecular weight and lipophilicity. These improved physicochemical parameters, leading to an improved pharmacokinetic profile, made UK-453061 a suitable candidate for clinical evaluation. Early clinical data showed the compound to have dose-proportional pharmacokinetics and to significantly reduce viral load.

Antipsychotic efficacy of a mGlu2/3 agonist prodrug from a phase II proof-of-concept schizophrenia study

Dr. Gerard Marek (Eli Lilly, U.S.A.) gave the final presentation of the meeting.

A frequent question is whether established models and pharmacological screens can detect novel psychotherapeutic drugs. Recently, agonists that act on metabotropic

glutamate 2/3 (mGlu2/3) receptors have been proposed to act as antipsychotic drugs based on their potential to suppress abnormal glutamate release involved in the pathophysiology of schizophrenia. A number of rigid glutamate analogues have been designed by researchers at Eli Lilly. These mGlu2/3 receptor agonists reverse the hyperactivity induced by psychomimetic drugs such as phencyclidine and amphetamine. The mGlu2/3 receptor agonist **LY-404039** is also active in another commonly used antipsychotic drug screen, the conditioned avoidance response.

In order to test the hypothesis that mGlu2/3 receptor agonists exert antipsychotic action, a methionine prodrug of LY-404039 (**LY-2140023**) was designed to overcome limited bioavailability of the parent molecule. Human pharmacokinetic data showed that this strategy improved bioavailability of the active substance from 3% to 49%. The prodrug LY-2140023 displayed no affinity for mGlu2/3 receptors.

A recent placebo-controlled phase II study of LY-2140023 in schizophrenic patients found that this mGlu2/3 receptor agonist prodrug was effective in reducing psychotic symp-

toms as reflected in the total PANSS (Positive and Negative Symptom Scale), negative PANSS and the positive PANSS scores. Improvements on PANSS total score were observed as early as week 1 and were maintained throughout the 4-week therapy phase of the study. The prodrug was well tolerated, did not induce extrapyramidal symptoms and was not associated with weight gain.

This phase II proof-of-concept study provides preliminary confirmatory evidence that a number of frequently used preclinical models can successfully predict antipsychotic efficacy for drugs that do not block dopamine D₂ receptors. This clinical study also focuses greater attention on psychotherapeutic mechanisms involving relatively subtle modulation of glutamate in the brain such as the presently described mGlu2/3 receptor agonists.

Conclusions

This was the second Recent Disclosures of Clinical Drug Candidates meeting organized by the Society for Medicines Research. The meeting proved to be a popular one with several different organizations represented. The range of topics gave an interesting perspective into the diversity of research, and into the research strategies adopted within the various organizations.

Dr. Richard Armer is Research Director at Lectus Therapeutics in Cambridge. Dr. Phillip Cowley is a Section Head in the Chemistry Department at Organon Laboratories, a part of Schering Plough Corporation, Newhouse, Scotland. Dr. Mark Searcey is Reader in Medicinal Chemistry in the School of Chemical Sciences and Pharmacy at the University of East Anglia. 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>.

