

## Therapy Analysis

Welcome to the monthly newsletter for *Pharmaprojects*, the Update Analysis. This issue features a Therapy Analysis article on antibiotic resistance and we also review the 5th Rodman & Renshaw Global Healthcare Conference, the 10th Annual C21 Bioventures and the 44th ASCO. All the usual *Pharmaprojects* highlights follow, including details of three new drug development strategies, and some examples of the free news stories published on our website in our News Digest section. This month's Search Tip shows you how to search *Pharmaprojects* for NCEs.

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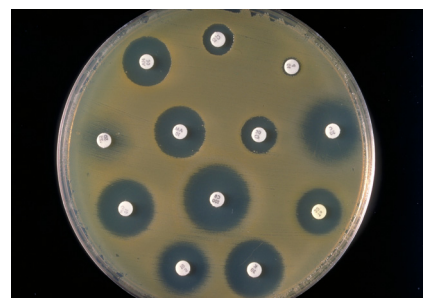
### Antibiotic-resistance: fighting the superbugs

#### A clinical marvel

**In 1928 in a basement laboratory of St Mary's Hospital, London, microbiologist Alexander Fleming noticed a halo of inhibition of growth around a culture of *Staphylococcus aureus* bacteria that had been contaminated by a blue-green mould. The mould, *Penicillium notatum*, appeared to be releasing a substance that was inhibiting the bacterial growth and causing lysis of bacterial cells. Naming the active substance penicillin, Fleming reasoned that it could have therapeutic potential if produced in large quantities. What followed was one of the greatest medical advances of all time – the discovery of antibiotics.**

The clinical significance of Fleming's discovery was not immediately realised, and it was not until 1939 that Howard Florey and his colleagues at Oxford University demonstrated the ability of penicillin to kill infectious bacteria in mice. Subsequent isolation and mass production of the antibiotic led to its availability on the beaches of Normandy in the 1944 D-Day landings, saving many lives.

Penicillin belongs to a group of antibiotics called  $\beta$ -lactams. These antibiotics are so-named due to the  $\beta$ -lactam ring in their structure, and were originally found to be active against Gram positive bacteria. They are bactericidal, and act by inhibiting the synthesis of peptidoglycan, a key polymer in the structure of bacterial cell walls. The  $\beta$ -lactam nucleus of the penicillin molecule acetylates a key serine residue, preventing the final cross-linking of the peptidoglycan layer, thus disrupting cell wall synthesis. In the years after the discovery of penicillin, availability of antibiotics allowed effective treatment for many previously untreatable diseases, such as meningitis, syphilis and gonorrhoea, and revolutionized the treatment of bacterial infections.



An agar plate testing for antibiotic resistance

#### A new threat

Despite early promise, the success of antibiotics in the treatment of bacterial infections was to be short-lived. Since the development of the first antibiotics, resistant strains of bacteria, in particular *Staphylococcus aureus*, have become an increasing obstacle to the successful use of antibiotics. When penicillin was first introduced in 1943, resistant *S. aureus* infections were almost unheard of. However, in 1947, a resistant strain was identified. By 1950, around 40% of nosocomial *S. aureus* infections were penicillin-resistant, and this figure rose to around 80% by 1960. Penicillin resistance in *S. aureus* is mediated by  $\beta$ -lactamase. This enzyme, produced by the bacterium, hydrolyses the  $\beta$ -lactam ring of the penicillin structure, rendering it inactive. In the face of increased penicillin resistance, methicillin, a narrow spectrum  $\beta$ -lactam antibiotic became the first-line choice in the treatment of *S. aureus* infections. Like penicillin, methicillin acts by disrupting bacterial cell wall synthesis. The presence of an ortho-dimethoxyphenyl group attached to the penicillin nucleus made methicillin relatively resistant to cleavage by  $\beta$ -lactamase through steric hindrance and therefore effective against penicillin-resistant bacteria.

However, in 1961 a strain of *S. aureus* resistant to meticillin was identified in the UK. This strain, which has since become known as meticillin-resistant *Staphylococcus aureus* (MRSA) acquired the ability to be resistant to treatment with all  $\beta$ -lactam antibiotics, including meticillin, oxacillin, nafcillin and dicloxacillin. MRSA is present on the skin and nasal passages of 1 in 3 people, without becoming pathogenic. However, if MRSA enters the body, it is able to cause infection. MRSA infections commonly occur in the hospital setting, often in immunocompromised patients, or those with open surgical wounds, ulcers or intravenous catheters. The symptoms depend on the type of infection, but can include boils, abscesses, styes and carbuncles, as well as skin infections such as cellulitis and impetigo. More serious MRSA infections include septicaemia, septic shock, infective endocarditis and pneumonia.

Incidence of MRSA is increasing. A 2007 report by the US Centers for Disease Control and Prevention (CDC) estimated that the number of MRSA cases nationwide had more than doubled from 127,000 in 1999 to 278,000 in 2005, with over 17,000 attributable deaths. Similarly, the UK Office for National Statistics reported 1,629 MRSA-related deaths in England and Wales, compared to just 51 in 1993. The emergence of MRSA has meant that the glycopeptide antibiotic vancomycin became the drug of choice for treating MRSA. However, strains of MRSA which are resistant to vancomycin have recently emerged. While not as prevalent as MRSA, VRSA may pose a problem for the future of antibiotic therapy.

In 1986, another common antibiotic-resistant bacterium was identified (vancomycin-resistant enterococcus (VRE)). Enterococci are bacteria commonly found in the faeces of humans, and are commonly responsible for urinary tract and wound infections. Until recently, enterococcus infections were readily treatable with antibiotics.

*Clostridium difficile* is a Gram positive bacillus. First described in 1935, it is so-named due to the difficulty in culturing the bacteria on culture medium. A commensal bacterium of the gut, *C. diff.* does not usually present a disease risk. However, use of broad-spectrum antibiotics can lead to a disruption of the gut flora, giving rise to conditions such as antibiotic-

associated diarrhoea, caused by overgrowth of *C. diff.* The bacterium is also resistant to most antibiotics, and forms heat-resistant spores which are able to tolerate extreme temperatures. Therefore, *C. diff.* has become a problem in the hospital environment, and even commonly-used hospital disinfectants can fail to kill the bacterium.

Merely 60 years after the commercial availability of antibiotics, antibiotic-resistant bacteria represent a significant chink in our protection against infection.

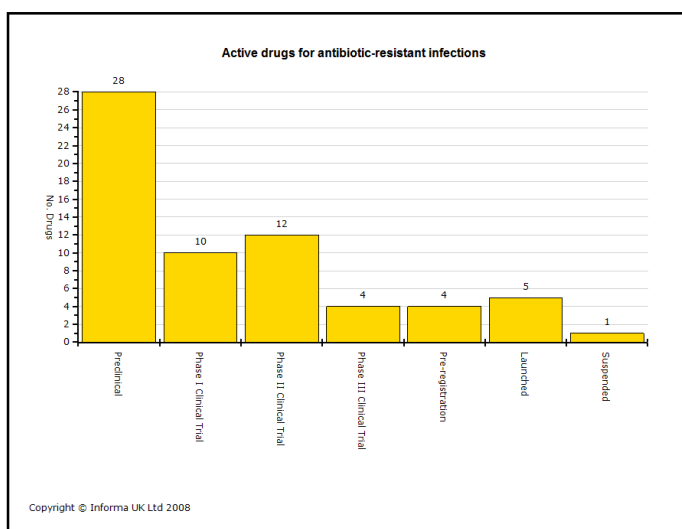
### How do they do it?

Since the introduction of antibiotics, bacteria have developed numerous mechanisms of resistance to antibiotics. In clinical environments such as hospitals, intensive use of antibiotics means there is high potential for bacteria to acquire antibiotic resistance. Under such circumstances, multi-resistant strains of bacteria are relatively common, and give rise to common resistant nosocomial infections such as MRSA, *C. diff.*, and VRE. Several common resistance mechanisms have been identified. Many antibiotics work by inhibiting a key bacterial protein. Bacteria may mutate, deleting the target protein, thereby rendering the antibiotic ineffective. Alternatively, mutation of the target protein may inhibit binding of the antibiotic, preventing its action. Trimethoprim resistance occurs by such a mechanism, and is mediated by alterations in the target enzyme, dihydrofolate reductase (DHFR). Similarly, a mutation in the topoisomerase enzyme, DNA gyrase, is responsible for resistance to quinolone antibiotics such as ciprofloxacin. Target modification also plays a part in antibiotic resistance. In addition to  $\beta$ -lactamases, MRSA commonly produces an additional penicillin binding protein, PBP2. This binding protein is not susceptible to inhibition by penicillin.

Another mechanism of resistance is evolution of efflux pumps. In certain cases, efflux pumps actively expel the antibiotic from the bacterial cell, conferring resistance. This is common in tetracycline-resistant Gram negative bacteria, whereby a p-glycoprotein-mediated efflux pump is employed to remove the antibiotic from the bacterium. Another important resistance mechanism involves acetylation of the antibiotic, causing inactivation. This is seen in chloramphenicol resistance.

### Treatments for resistant infections

In recent years, there has been active development of antimicrobial drugs to treat antibiotic-resistant infections. Currently there are 5 drugs launched for antibiotic resistant infection, with many more in the late stages of development (Graph 1). In particular, 1999 saw the launch of Sanofi-Aventis' Synercid, an injectable drug consisting of two synergistic streptogramin antibiotics, dalfopristin and quinupristin. Dalfopristin inhibits bacterial ribosomes, preventing the early phase of protein synthesis, while quinupristin targets the late phase of protein synthesis by inhibiting translocation. A Phase III trial in 443 patients with skin and skin structure infections caused by *S. aureus*, including MRSA, showed a cure and improvement rate of 71.2%, and an eradication rate of 66% for *S. aureus*. Synercid is launched in several countries worldwide, and for both MRSA and vancomycin-resistant *E. faecium*. It was previously made available on an emergency use programme for the treatment of Gram positive bacterial infections.



**Graph 1: World status of antibiotic-resistant drugs in active development**

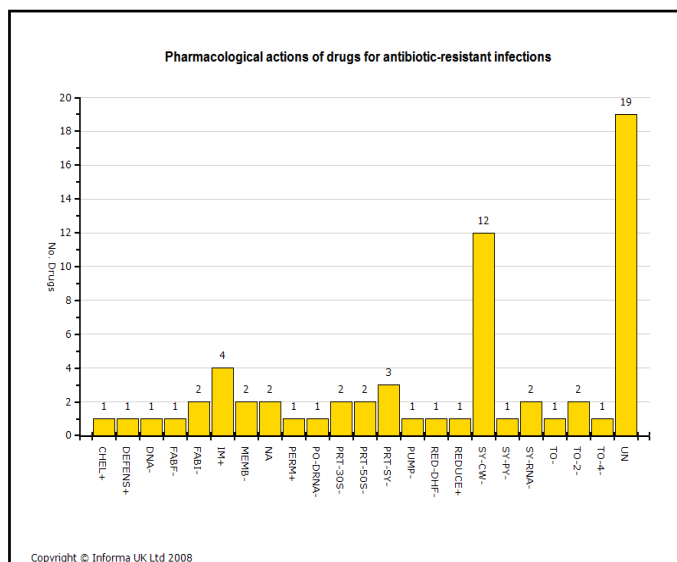
In 2002, Wyeth launched Tygacil (tigecycline) for the treatment of nosocomial antibiotic-resistant infections, such as MRSA. A derivative of tetracycline, tigecycline represents the first clinically-available drug in a new class of antibiotics known as glycylcyclines. While structurally similar to tetracycline, a substitution at the D-9 position gives tigecycline a broader spectrum of action. It is bacteriostatic, and acts by inhibiting the bacterial 30S ribosomal subunit. In Phase III trials, tigecycline demonstrated non-inferiority to vancomycin, with an MIC for MRSA of 0.12µg/ml, compared to 1.0µg/ml for vancomycin. Tigecycline is launched in several markets, including Australia, Germany, the UK and the US, and is awaiting registration in Canada, India, South Africa, Switzerland and Venezuela.

Another novel development in antibiotic therapy is Pfizer's Zyvox (linezolid), a first-in-class oxazolidinone antibiotic. Linezolid is the only currently available agent in this class. Oxazolidinones inhibit the initiation of bacterial protein synthesis by preventing interaction between the 30S and 50S ribosomal subunits. In a Phase III trial in patients with MRSA infection, treatment with linezolid decreased hospital admission time over a 2 week period compared to vancomycin. Linezolid is currently launched in Japan for the treatment of MRSA and VRE infections, and is launched in several other markets for the treatment of VRE, as well as nosocomial and community-acquired pneumonia.

In addition, the San Franscan outfit Theravance has developed telavancin (TD-6424), a lipidated glycopeptide antibiotic, for the treatment of Gram positive infections. It has a broad spectrum of action, inhibiting the transglycosylation step of peptidoglycan synthesis, thereby disrupting the formation of bacterial cell walls. In December 2006, Theravance filed a US NDA based on the Phase III ATLAS I and II trials, for the treatment of complicated skin and skin structure infections (cSSSIs), including infections involving MRSA. An EU filing for cSSSIs has also been made. In these Phase III trials, telavancin treatment achieved clinical cure in 78% of patients, compared with 70% for vancomycin. In 1867 cSSSI patients, including 719 MRSA patients, 10mg/kg once-daily for 7-14 days produced clinical cure and microbiological eradication rates of 90.6 and 89.9%.

**Is prevention better than cure?**

Another possible breakthrough in the fight against antibiotic resistance is the development of prophylactic vaccines. Originally developed as an immunogen to develop a hyperimmune globulin passive vaccine, Acambis' ACAM-CDIFF vaccine has shown early promise in the prevention of *C. diff*-associated diseases (CDAD). In a US Phase I trial in 50 healthy young adults, a single injection of ACAM-CDIFF vaccine produced 10-fold higher levels of anti-toxin-A and -B IgG compared with patients who had previously recovered from a *C. diff* infection. In another Phase I trial in elderly patients, seroconversion rates were 100% and 75% for *C. diff* toxin-A and -B, respectively. Side-effects were mild, with no serious adverse events reported.



Code	Pharmacology Description
CHEL+	Chelating agent
DEFENS+	Defensin agonist
DNA-	DNA antagonist
FABF-	Fab F inhibitor
FABI-	FAB I inhibitor
IM+	Immunostimulant
MEMB-	Membrane integrity antagonist
NA	Not applicable
PERM+	Membrane permeability inhibito
PO-DRNA-	DNA directed RNA polymerase inhibitor
PRT-30S-	Protein 30S ribosomal subunit inhibitor
PRT-50S-	Protein 50S ribosomal subunit inhibitor
PUMP-	General pump inhibitor
RED-DHF-	Dihydrofolate reductase inhibitor
REDUCE+	Reducing agent
SY-CW-	Cell wall synthesis inhibitor
SY-PY-	Pyruvate synthase inhibitor
SY-RNA-	tRNA synthetase inhibitor
TO-	Topoisomerase inhibitor
TO-2-	DNA topoisomerase ATP hydrolysing inhibitor
TO-4-	DNA topoisomerase IV inhibitor
UN	Unidentified pharmacological activity

**Graph 2: There are various pharmacological strategies in development for the treatment of antibiotic-resistant infections**

## New beginnings

In response to the challenge of antibiotic resistance, pharmaceutical companies continue to develop novel antimicrobials which may lead to a new generation of drugs for the treatment of such infections. While many 'traditional' antibiotics act by disrupting cell wall synthesis, today pharmaceutical companies are employing various novel mechanisms of action in order to combat these resistant bacteria (Graph 2) by targeting the very protein the bacteria are mutating. Indeed, several early stage compounds are currently in development for antibiotic-resistant infections (Graph 1). S Korean pharmaceutical company Dong-A Pharma is developing DA-7218, the lead in a series of orally-available oxazolidinone drugs for the treatment of Gram positive infections. It is currently in a US multiple ascending-dose Phase I study in patients with Gram positive infections, including MRSA, to assess safety, tolerability and pharmacokinetics. Previous studies have shown potential for daily dosing with DA-7218. Dependent on further development, approval is expected in 2013.

Several preclinical compounds are also showing early promise. Merck & Co's platencin, a natural product and dual inhibitor of FabH and FabF, has shown potent activity in preclinical studies, with no toxicity observed. Platencin does not show cross-reactivity to antibiotic-resistant strains such as MRSA and VRE. Also in preclinical development is Replidyne's diaryldiamine anti-infective, REP-3123, indicated for the treatment of antibiotic-resistant *C. diff* infections. A hamster model has previously shown REP-3123 to be superior to vancomycin. It also inhibited moxifloxacin- and clindamycin-resistant strains of *C. diff*. Replidyne expects to file an IND in the second half of 2008.

Phynova is developing PYN-6. Currently in preclinical studies, PYN-6 has shown activity against MRSA and vancomycin- and teicoplanin-resistant bacteria. Phase I trials are planned for 2008, with Phynova seeking to out-license PYN-6 after completion of Phase II development.

## Future perspective

From the early beginnings of 80 years ago, antibiotics have become the mainstay of treatment for bacterial infections. In recent years, antibiotic-resistant bacteria have become a significant obstacle to the future treatment of bacterial infections, and an ongoing challenge for healthcare services worldwide. However, with the continued development of new therapies, there is hope that antibiotics can overcome the threat posed by such bacteria, and continue to be effective in the future.

*Jonathan Stephens*

*Image courtesy of the Centers for Disease Control and Prevention*

### Search Strategies

In Drug Profile Search:

([Any Indication] = Infection, MRSA  
OR [Any Indication] = Infection, vancomycin-resistant  
OR [Any Indication] = Infection, clostridium difficile  
OR [Any Indication] = Infection, clostridium difficile

prophylaxis)  
And [Active, Ceased, Fully Launched] = Active

Graph 1:  
Graph By: World Status

Graph 2:  
Graph by: Primary Pharmacology Code

# Did you know the US FDA's drug approval rate declined by 13% in 2007?

(You would if you read RAJ Pharma)

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## Conference Report

### 10th Anniversary C21 BioVentures Napa, California, 20th – 22nd May 2008

This year C21 BioVentures returned to the site of its inaugural meeting in Napa, California, to celebrate its tenth birthday. Amidst the rolling hills and vineyards of the San Franciscan wine country, the meeting once again provided an ideal opportunity for emerging life science companies, larger pharmaceutical companies and venture capitalists from the Bay Area and beyond to raise capital, partner and network.

Over 450 attendees from 315 companies were welcomed for two days of leadership sessions and company presentations by Robert Lee Kilpatrick, a partner of the meeting's hosts Technology Vision Group and Matt Gardner, CEO of co-hosts BayBio. Kelly Slone, Director of the Medical Industry Group, extended the welcome and provided some context for the deal-making and financing that was to follow with the fact that 30% of all venture capital investment is in the life sciences business.



One of the first of 66 private companies to present this year was Falco Biotherapeutics. Formed through the recent merger of Farallone Therapeutics and Lactrys Biopharmaceuticals, this transatlantic start-up company has offices in both the Netherlands and California. CEO Dr Michel Bergh gave an insight into Falco's work on a series of novel small protein therapeutics called 'engineered loop-containing affinity molecules' or EICams. Based on human proteins, EICams contain binding regions similar to monoclonal antibodies and have the potential to bind and neutralize bacterial toxins and inflammatory cytokines. The company plans to utilise genetically-modified *Lactobacillus*, administered orally to present cell surface-bound EICams locally and at high concentrations in the GI tract. Initially targeting two indications with this approach, *Clostridium difficile*-associated diarrhoea and inflammatory bowel disease, Falco intends to partner for co-development and co-commercialization following Phase I/IIa trials.

In the area of osteoporosis Aursos announced worldwide partnering opportunities for its lead compound, black bear parathyroid hormone (BB-PTH (1-34)). New to Pharmaprojects, Aursos is a young biotech company based in Michigan which aims to benefit from the evolutionary advantages that allow black bears to hibernate for up to 6 months without loss of bone density. BB-PTH (1-34) is currently in in vivo testing and slated for an IND filing in 2010.

The afternoon continued with further company presentations, private tabletop meetings and informative panel sessions. Wednesday's proceedings came to a conclusion with delegates visiting the Jacuzzi Family Vineyards for dinner. There was a relaxed and friendly atmosphere as attendees mingled around the elegant Grand Piazza, indulged in wine and olive oil tast-

ing and took in the stunning views of the Sonoma Valley.

Day two saw Verva Pharmaceuticals showcase its diabetes and obesity-focused pipeline. Since its formation in late 2007, Verva has chosen to keep a relatively low profile and took advantage of C21 BioVentures as the perfect place to introduce itself to the broader market. It announced that it is seeking partners worldwide for all its compounds. This includes VVP-808, a reprofiled glaucoma therapeutic with an alternative mechanism of action in the treatment of Type II diabetes. Having shown promise in murine models of diabetes, Verva plans to take VVP-808 into a six month Phase IIa trial later this year. Also in the pipeline and with a recently filed IND is a fat formation inhibitor under development for obesity.

Following lunch, Californian company Asphelia provided a snapshot of its pipeline, which is based largely on in-licensing products for the treatment of inflammatory bowel diseases. ASP-1002, obtained through a sublicense from Ovamed, is a drinkable preparation of eggs of the porcine whipworm, *Trichuris suis*. Asphelia believes that the eggs trigger an immune response rebalancing the immune system and positively impacting inflammatory diseases. Asphelia disclosed plans for a Phase IIa trial for Crohn's disease in Australia within the next couple of months. ASP-2002, licensed from Mitsubishi Pharma, is an oral integrin antagonist that has already been evaluated in Phase I trials. The company has been granted an IND and intends to initiate a Phase II ascending-dose trial in patients with ulcerative colitis before the end of the year. Also presented was ASP-1001, a topical formulation of an iodinated contrast medium, for the treatment of allergic rhinitis. Asphelia's main goals for C21 were to secure investment partnerships and regional development and marketing agreements.

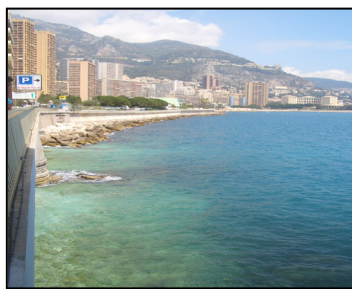
Closing drinks on Thursday afternoon afforded attendees the chance to conduct some last minute networking and socializing as well as reflecting on two highly stimulating and successful days of partnering and deal making. With over 40% growth on last year and 932 tabletop meetings scheduled between participants, there can be no question that C21 BioVentures celebrated its tenth birthday in fine style.

*Paddy Newton*

### 5th Rodman & Renshaw Global Healthcare Conference May 19-20th 2008 - Monte Carlo

The Annual European Rodman & Renshaw Healthcare conference once again took place in the idyllic surroundings of Monte Carlo, against a backdrop of the Monaco Grand Prix preparations and the drama of the Cannes film festival nearby. In a city swarming with the rich and powerful where for many the primary mode of transport is emblazoned with the leaping horse of the Ferrari logo, the conference could hardly fail to impress. It kicked off in style with a cocktail event on an ocean-view veranda, where the mood was set for an event filled with discussions about the climate of the industry and a significant amount of deal-making. The main entertainment event held the next evening played host to a spectacular and energetic set by Mary J Blige, followed by a late-night fireworks display to ensure the conference truly made its mark in Monaco.

During the meeting there were presentations by a wide variety of companies, opening up discussions with investors and big pharma firms for licensing deals, collaborations and, of course, investments. Sepal Pharma, a drug discovery company developing plant stress hormones sourced from Jasmine, was amongst those presenting. Its jasmonate derivatives have been found to have unexpected anticancer properties, due to their ability to bind a mitochondrial target in tumour cells. Laboratory findings demonstrated their potential to destroy cancer cells while leaving normal cells unscathed, thereby possibly avoiding hepatic cellular damage associated with major anticancer drugs such as paclitaxel. The exciting preclinical results for these potential first-in-class drugs will have to wait to be verified in human trials, which are expected in 2010.



**The idyllic Monte Carlo bay provided the backdrop to this year's conference**

Another small pharmaceutical company entering a major therapeutic field was Rib-X Pharmaceuticals. This private company is researching novel antibiotics aimed at overcoming multidrug resistance. So far Rib-X has successfully generated 2 Phase II clinical programmes, one for a broad-spectrum quinolone and the other for an extended spectrum oxazolidinone, with impressive cure rates against difficult pathogens such as MRSA, and a pipeline of further compounds waiting in the wings.

A larger company, BioLineRx, openly discussed the company policy for constantly reprioritising the pipeline according to each candidate's likelihood of success, and not being afraid to dump projects, and do so frequently, irrespective of the stage reached, if they fail to meet expectations. The therapeutic focus is also kept intentionally wide, as its sole aim is to develop the strongest possible pipeline of potential drugs. Demonstrating the variety within its pipeline, data was presented for two very different leading candidates. The first, BL-1020, is a Phase II GABA-enhanced antipsychotic NCE, which has demonstrated good safety, passage across the blood-brain barrier and significant improvements in schizophrenia symptoms. It also improved cognition in preclinical studies. The second candidate is BL-1940, a liquid myocardial implant that turns into a gel in situ, providing a temporary scaffold following a heart attack to prevent remodelling of cardiac tissue.

Medgenics gave an interesting presentation of its unique therapeutic approach. This consists of treating chronic diseases using its 'bio-pump' platform technology, consisting of an epidermal sample transformed by an adenoviral vector to introduce a gene for a therapeutic protein into the patients' own cells. This can be implanted back into the patient to allow 4-6 months of constant protein release. The company presented Phase I trial results for EPODURE in anaemia patients, demonstrating safety and protein delivery. A hepatitis-C therapy, Infradure, releasing interferon- $\alpha$ , is also in development.

Another company with an unusual therapeutic approach is Neotropix, a small private company that identifies oncolytic animal viruses, rather than human viruses, therefore avoiding inherent safety risks and using natural targeting, bypassing the need for genetic engineering. Neotropix is focused on

niche disease areas with no or few therapies available as yet. The lead candidate, NTX-010, is in Phase I/II trials in carcinoma, small cell and neuroendocrine cancers. It has produced some solid efficacy data so far with >50% of patients treated showing a clinical response. A path to potential-SPA registration trials for NTX-010 is already mapped out. Neotropix also reported on its earlier-stage preclinical candidates, NTX-400 and NTX-100.

Overall a wide variety of companies appeared at the conference, highlighting some of the remarkable and innovative developments in the pharmaceutical industry today. The sociable, friendly atmosphere and brisk pace of presentations meant a huge amount and variety of information was shared, with many contacts and potential agreements made. Time will tell how many of these come to fruition, but based on the happy faces at the end of the conference, we can expect great things from the industry in the future.

*Alix Biancardi*

#### **44<sup>th</sup> ASCO Annual Meeting- Chicago, IL, 30th May- 3rd June**

Chicago's vast McCormick Place once again played host to the American Society of Clinical Oncology Annual meeting. With over 35,000 attendees, this year's poster, symposia and education sessions were set to be better than ever.

It is estimated that in 2008, approximately 1,437,180 new cancer cases will be diagnosed in the US, and cancer will claim the lives of an estimated 565,650 people. Cancer death rates have been decreasing steadily over the last 15 years, in part due to better diagnosis, superior understanding of the subject and of course, better treatment strategies. The ASCO foundation aids both oncologists and patients by supporting the development of accurate, physician-approved cancer information.



**Chicago played host to this year's ASCO Annual meeting**

Once again the 'blockbusters' dominated the meeting with a multitude of results from various comparator trials in a wide range of cancers; however, it was the presentation of clinical results from lesser known, and potentially just as exciting drug treatments, that turned heads.

RAD-001 was on everybody's lips and results from a late-breaking Phase III trial even made it onto the front cover of the ASCO '08 Daily News. In Saturday's Genitourinary Cancer Oral Abstract session, researchers found it to be a safe and effective treatment for patients with metastatic renal cell carcinoma whose disease had progressed on VEGFr therapies. In the 410-patient trial, a median progression-free survival of 4 months was observed on RAD-001 compared to only 1.9 months on placebo. According to Dr. Motzer, of Sloan-Kettering Cancer Center, "This is the first Phase III trial that establishes clinical benefits and provides safety information for this new agent."

Targeted cancer therapies, such as Exelixis' XL-765, a selective dual oral inhibitor of Class I PI3K isoforms and mTOR, were the topic of many clinical science symposia. XL-765 has shown potent *in vivo* inhibition of the PI3K pathway signaling leading to tumour growth inhibition or shrinkage in a dose-dependent manner in multiple human xenograft tumor models exhibiting dysregulated PI3K pathway signaling. Activation of the PI3K pathway is a frequent event in human tumours, promoting cell proliferation, survival and resistance to chemotherapy and radiotherapy. mTOR is also often activated in human tumours and plays a central role in tumour cell proliferation. It can be activated via upregulation of PI3K, or via PI3K-independent mechanisms. In the reported Phase I dose escalation trial, XL-675 administered to patients with advanced solid malignancies orally twice a day for cycles of 28 days up to 120 mg resulted in no dose-limiting toxicities. One non-small cell lung cancer patient had stable disease after 6 cycles and another patient with testicular carcinoma that had progressed under multiple chemotherapy regimes demonstrated a clinically-significant reduction in alfa-foetoprotein from 11,000 to 7,000 U/L and radiological stable disease after 1 cycle.

Sunday saw a plethora of talks and poster sessions take place, including a molecular therapeutic oral abstract session. Results from a dose-escalation Phase I trial of Curis' hedgehog (Hh) pathway antagonist were among the abstracts presented. Aberrant Hh signaling pathway activation has been implicated in a variety of cancers via both Hh ligand-independent and -dependent overexpression. GDC-0449 is a first-in-human, first-in-class, potent systemic inhibitor of Hh signal transduction. It was shown that in 19 patients with refractory solid tumours non-respondent to prior therapy, GDC-0449 150-540mg/kg was safe and showed objective re-

sponses and clinical benefit. Two patients each with basal cell and adenocystic carcinoma had stable disease. There was 1 partial response in a basal cell carcinoma patient. It had a favorable pharmacokinetic profile with a  $t_{1/2}$  of >7 days with no dose-limiting toxicities found.

In the same session, results from two Phase I trials for MK-0646, a humanized IgG1 MAb that binds to IGF1R, were presented. IGF1R is a tyrosine kinase receptor that mediates both mitogenic and antiapoptotic pathways and has been found to be expressed in a variety of tumours. IGF1R activation also mediates resistance to a broad range of cytotoxic and targeted agents. In trial P001 in 53 patients with advanced solid tumours, MK-0646 1.25-20mg/kg iv every week was shown to be safe and tolerable with three patients having stable disease for over 3 months. It had a  $t_{1/2}$ , Cl and AUC of 95hr, 0.007ml/min/mg and 39.4mg/ml/hr, respectively. The 2<sup>nd</sup> trial reported was P002 in 36 patients. It also showed that MK-0646 was well tolerated at loading doses up to 20mg/kg and maintenance doses up to 15mg/kg.

Once again, ASCO's annual meeting was a veritable success, fulfilling the foundation's mission of providing and stimulating education and enthusiasm in the field of cancer research. We eagerly look forward to next year's annual meeting certain that it will be even bigger and better than this year.

*Sophie Green*

*The 45th ASCO Annual Meeting will be held in Orange County Convention Center Orlando, Florida, May 29 - June 2, 2009*

## New Targets

### amine oxidase (flavin containing) domain 2

This nuclear protein, also known as AOF2, is a component of several histone deacetylase complexes. It is also a histone demethylase activity (it demethylates the 'Lys-4' of histone H3) and this is believed to be responsible for an ability to silence genes. Research suggests that inhibition of AOF2 can reactivate genes normally suppressed during cancer.

Progen is developing compounds that inhibit AOF2 as anticancers, they are part of Progen's epigenetics programme.

AOF2 belongs to the **Enzyme** Target Family Group and its EC number is **1.4.3.4**. Its Entrez Gene ID is **23028**.

### keratin 6A

More commonly known as KRT6A this type II cytokeratin is the most abundant isoform of keratin 6. It is present in the epithelial lining of oral mucosa, oesophagus, hair follicles, palm and sole epidermis, epithelial cells of the nail bed and the filiform papillae of the tongue. Mutations in KRT6A are known to lead to pachyonychia congenital type 1.

TD-101 is a short interfering RNA (siRNA) specific for the N171K point mutation in the keratin 6A gene, under development by TransDerm for the treatment of pachyonychia congenita.

Its Entrez Gene ID is **3853**.

## glutamate receptor, metabotropic 7

Glutamate receptor, metabotropic 7 (GRM7) belongs to the Group III family of metabotropic glutamate receptors which are known to be linked to inhibition of the cyclic AMP cascade. It is expressed in many areas of the brain and may act presynaptically to regulate neurotransmission in the hippocampus and play a role in learning and memory.

Addex is developing GRM7 negative allosteric modulators (NAM) for the treatment of depression and post-traumatic stress syndrome.

MGLUR7 belongs to the **Receptor>GPCR>Metabotropic glutamate** Target Family Groups. Its Entrez Gene ID is **2917**.

Glutamate 7 receptor antagonists are coded in *Pharmaprojects* as **EAA-G-7-**.

## New Drug Development Strategy

The following drug development strategy is new to the July edition of *Pharmaprojects*.

### CD317 antagonist

Xencor is developing CD317 antagonists as a treatment for multiple myeloma.

CD317 antagonists are coded in *Pharmaprojects* as **CD-317-**.

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**TrialTrove**

Real-Time Clinical  
Trials Intelligence

## Companies New to *Pharmaprojects*

**Aduro Biotech** is developing early-stage cancer therapies.

**ApopLogic Pharmaceuticals** is a biotechnology company focused on the development of compounds for the treatment of cancer.

**Aursos** is a biotechnology company engaged in the development of products for the treatment of osteoporosis.

Brisbane-based **Avantogen** is developing drugs in the areas of oncology and vaccines.

**Balboa Biosciences** is developing therapeutics for disorders affecting the CNS and for the treatment of acute and chronic pain.

**BSP Pharma** is engaged in the development of products based on natural ingredients, particularly those found in the fruit of the shea tree.

**Chakra Biotech** develops drugs for CNS disorders.

**CellCeutix** is a biopharmaceutical company engaged in the development of treatments for cancer and inflammatory diseases.

**Critical Biologics** is investigating the use of recombinant human gelsolin for use in critical care complications associated with low plasma gelsolin levels.

**EnzymeRx** is a biotech outfit focused on the development of treatments for refractory gout.

**Ergonex Pharma** is focused on the development and commercialization of well tolerated and effective products for unmet indications.

**Falco Biotherapeutics** is focused on the development of therapeutics using its proprietary EICam technology.

**Genelux** is a privately-held biomedical company focused on the development of diagnostic and therapeutic solutions for cancer and inflammatory diseases for which no effective treatment exists.

Swiss company **GenKyoTex** is working on drugs that block oxygen radical-producing enzymes.

**GlycaNova** is a Norwegian biopharmaceutical company developing compounds derived from medical mushrooms, particularly polysaccharides which stimulate the immune system.

**Grifols** is a group of companies which develops, manufactures and markets plasma derivatives, IV therapy, enteral nutrition, diagnostic systems and medical materials.

**iQur** is focused on the detection, monitoring and treatment of viral liver disease.

**Mentor** supplies surgical aesthetic products and cosmetic dermatological products to plastic surgeons worldwide. It is moving into therapeutics.

**Meldex** is a pharmaceutical company based around its platform technologies in polymer and film systems.

**Migco** Pharmaceuticals develops treatments for diseases of the nervous system.

**Minster Pharmaceuticals** is a drug development company specializing in compounds for the treatment of neurological and psychiatric conditions.

**Navitas Pharma** is a late-stage pharmaceutical company engaged in the development of products for the treatment of cardiovascular and metabolic disorders.

**Nexigen** is a start-up company developing its own pipeline of therapeutic peptides.

**Opal Therapeutics** is developing novel HIV and hepatitis-C vaccines.

**Orcrist Bio** develops and commercializes therapeutics for areas in which a clear market opportunity exists, including stem cell mobilization technologies.

**PharmaNeuroBoost** is focused on the development of CNS therapies, primarily combinations of its proprietary drug pi-pamperone

**PDC Biotech** in-licenses early-stage compounds for the treatment of preterm labour and primary dysmenorrhoea.

**Pulmo BioTech** is developing a range of molecular imaging agents based on nuclear medicine for the imaging on the circulatory system of the lungs.

**Replikun Biotech** is focused on the development of vaccines for cancer and infectious diseases, as well as developing a delivery system for gene therapy.

**Revotar Biopharmaceuticals** develops anti-inflammatories for a range of indications.

**RhinoCyte** is developing neural progenitor cells for diagnostic and therapeutic purposes.

**Saneron** is a biotechnology R&D company, focused on developing neurological and cardiac cell therapies, utilising stem cell and other cell types.

**Sepal Pharma** is developing a portfolio of novel jasmonate-derived anticancers.

**Silamed** is engaged in the development of anticancers using its silicon medicinal chemistry platform to improve the activity of new and existing compounds.

**TCA Cellular Therapy** is an R&D company developing stem cell therapies for neurological diseases such as spinal cord injuries, Parkinson's disease and amyotrophic lateral sclerosis.

**Tiltan Pharma** is an Israeli company developing antiangiogenic cocktails for use in cancer therapies.

**Theravida** is focused on the development of combination products for the treatment of urological and CNS disorders.

**TransDerm** develops nucleic acid-based therapies to inhibit target gene expression in skin, including RNAi agents.

**ViraBiotech** is developing a biological prophylactic universal ant-influenza treatment.

**ViroLogik** deals with the development, testing and marketing of new medications and forms of treatment for viral infections, using patented procedures to influence the interaction of cellular and viral factors.

**ViroStatics** is a biotechnology company focusing on the development of immunotherapeutics for the treatment of HIV/AIDS and viral infections.

**Znomics** is developing new pharmaceutical products for the treatment of human diseases, using its zebra-fish based drug discovery platform.

## Mergers, Acquisitions, Name Changes and Joint-Ventures

**Newron** has acquired **Hunter-Fleming**.

**Sepracor** has acquired **Oryx Pharmaceuticals**.

Pharmaceutical giant **Hoffmann-La Roche** has acquired **Piramed**.

**Sirtris**, a company investigating drugs that activate sirtuins, a newly-discovered class of enzymes involved in aging, has been acquired by **GlaxoSmithKline**.

**BioProgress** will henceforth be called **Meldex**.

## Pharmaprojects News Digest

The following are taken from our selection of news stories listed on the *Pharmaprojects* website. Go to [www.pharmaprojects.com](http://www.pharmaprojects.com) for more of the same, and to subscribe to our free RSS feed.

### Genzyme files plerixafor in the EU and the US

Genzyme has filed for approval of its chemokine inhibitor plerixafor (Mozobil) in both the EU and US markets. Plerixafor is a small molecule which binds to the chemokine 4 receptor and is intended to enhance stem cell mobilization for collection and subsequent re-implantation of haematopoietic stem cells in patients undergoing this procedure as a result of lymphoma and multiple myeloma.

Currently, these disorders are treated with high-dose chemotherapy which has the effect of destroying bone marrow, where haematopoietic stem cells are primarily found. To counter this, patients receive an autologous transplant of stem cells following chemotherapy to replenish the cell populations and maintain healthy blood composition. In order to be collected, stem cells must be mobilized into the blood, a lengthy process which some patients are not able to complete, meaning a transplant is not possible.

Genzyme conducted two Phase III trials, each in around 300 patients with lymphoma or myeloma, which both showed a significant increase in the number of patients that achieved the target threshold for stem cell collection as well as the number undergoing a successful transplantation. Plerixafor is already available in Europe and the US under compassionate use programmes and formal launch is expected in 2009.

### GlaxoSmithKline makes cancer cell genomic data available to all cancer researchers

GlaxoSmithKline (GSK) has released genomic profiling data for over 300 cancer cell lines via the US National Cancer Institute's cancer Bioinformatics Grid (caBIG) initiative, a network of infrastructure and tools that enables the collection, analysis, and sharing of data and knowledge along the entire research pathway from laboratory bench to patient bedside.

Dr. Richard Wooster, Director of Translational Medicine Oncology, R&D, GSK, said, "We hope this data will further drive the identification of predictive biomarkers and lead to shorter, more directed clinical trials allowing us to bring drugs more quickly to patients who need them".

The data comes from cell lines derived from a wide variety of tumours, including breast, prostate, lung and ovarian cancers. It is hoped that this will reduce the cost and time usually involved in identifying and cataloguing individual cell lines, particularly for smaller or non-commercial organizations.

Interested researchers can download this free data through caArray at <https://cabig.nci.nih.gov/tools/caArray>.

## Exhibition Calendar

Our team of experienced Account Managers will be demonstrating and promoting the full capabilities of *Pharmaprojects* and other services from Informa Healthcare at a host of international conferences throughout the year. If you would like to brush up on your searching techniques, discuss your subscription requirements or hear about planned product enhancements, then please visit our stand at one of the venues listed below. To schedule an appointment with your dedicated account manager, please e-mail:

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Dates	Conference	Details
August 4-7	<b>Drug Discovery and Innovative Therapeutics World Congress</b>	World Trade Center Boston and The Seaport Hotel, Boston MA  For information: <a href="http://www.drugdisc.com/">http://www.drugdisc.com/</a>

## Further Information

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## Search Tip of the Month - Search Pharmaprojects for NCEs.

The powerful search facilities available on *Pharmaprojects* can be used for a variety of research purposes. This month's search describes how to specifically for NCEs and eliminate any drugs that are line extensions, new formulations or biologicals from your results.

Pharmaprojects V5.2 (Web)

Quick Search

New Open Save Save-As Delete

Print Copy Export Help

type here GO

New Chemical Entity - W/C 22 Jun 2008 [284]

Find:

Logic  
YES

Search

Standard Search

- Company Pipeline
- Therapy Pipeline
- Alert Service
- New Products
- New Chemical Entity

Main Details  
Company/Status Data  
Activity Data  
Target Data  
Pharmacokinetics  
Chemical Data

- Origin of Material Code
- Origin of Material Description
- CAS Number
- Rotatable Bonds
- Hydrogen Bond Acceptors
- Hydrogen Bond Donors
- AlogP
- Molecular Weight
- Chemical Name Includes
- Chemical Structure
- New Chemical Entity

Patent Data  
Country Data  
Ratings  
Major Events  
Alert Service  
Latest Change

Add  
Delete  
Clear  
Replace  
(...)  
(.X.)  
Search  
Results  
Profile  
Graph

In standard search, simply click on the New Chemical Entity button

You can also search for non-NCEs by changing the logic in the dropdown box to 'No'

Hits	And/Or	(...)	Group	Expression	Value
24168			New Chemical Entity	=	YES

View  
Web

Visit the *Pharmaprojects* Web site for Search Tips of the Month which have featured in previous issues of the Update Analysis.