



Update Analysis

July 2007, Volume 28, Issue 3

Therapy Analysis

Welcome to the monthly newsletter for *Pharmaprojects*, the Update Analysis. This issue features a Therapy Analysis article on drug addiction, including alcohol, nicotine and narcotic addiction. We also review the 4th Rodman & Renshaw Global Healthcare conference, Digestive Disease Week 2007, and the 9th Annual C21 Bioventures. All the usual *Pharmaprojects* highlights follow, including details of 7 new targets, and a selection of news stories from our website included in our new News Digest section. This month's Search Tip shows you how to use the Alert Service function on *Pharmaprojects*.

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Drug addiction: kicking the habit

Drug addiction is the compulsive dependence on a substance, either legal or illegal, characterized by compulsive drug consumption with associated loss of control in limiting intake, craving and surfacing of an emotional state in the absence of the drug. This compulsion may be psychological, physical or both, and can progress from one to the other, but in many cases the consequences for the addict and those around them can be dire. These include the obvious detrimental effects on the user's health, but also their finances - drugs can be costly and a user can easily lose their job if addiction spirals out of control. Relationships can also suffer, and society often pays a heavy price in terms of the costs associated with treating those afflicted, and also the judicial costs of trying and then incarcerating illegal drug users or those who turn to crime to fund their habit.

One in three people on the planet currently smokes cigarettes, and by 2020 the number of smokers worldwide is expected to increase to 1.7 billion, with the majority of this growth to occur in the developing world. In the US, it has been estimated that up to 4% of the general population is alcohol-dependent, and in the UK there is currently much focus on the culture of 'binge-drinking'. The numbers of regular users of other drugs, including 'hard drugs' such as heroin, cocaine and methamphetamine, also continues to rise at an alarming rate both in the developed and developing world.



The dangers and addictive properties of cocaine were only observed at the turn of the 20th century — it was introduced into clinical use as a local anaesthetic in 1884.

The reason for this worldwide pandemic? Use of psychotropic drugs is certainly not a modern phenomenon. Evidence for the use of mind-altering substances, both medicinally or for religious practices or pleasure can be traced back to the earliest human civilizations. Today, alcohol use is a significant part of many Western cultures, and the use of other drugs is widely accepted in many areas. However, it was during the 20th century that drug use began to be viewed as a serious threat to our society - a modern 'plague'. This has been brought about, in part, by abundant supplies becoming available through the use of modern agricultural and chemical synthetic techniques, and the creation of worldwide illicit distribution networks.

The social stigma associated with drug addicts reflects the poor public perception of addiction, directly related to a lack of scientific knowledge and understanding. Just as mental illness was seen as a social problem instead of a medical issue until the last several decades, drug addiction continues to be incorrectly viewed as a character flaw instead of as the biological problem that it is.

Rewarding behaviour, but at what cost?

The neurochemistry associated with drug use and addiction is complex and involves many interrelated pathways. However, all drugs of addiction have one thing in common - they produce a sensation in the user that is pleasurable, the so-called 'high'. The common factor for all abused drugs is that they stimulate the mesolimbic reward pathway in the brain, with the neurotransmitter dopamine a key element. This chemical is released naturally by the brain in response to stimuli such as food or sex, but it is also released by drugs of abuse. Substances which activate the reward pathway are positively reinforcing - that is to say, the pleasurable effects experienced by the user when the pathway is stimulated drives them to repeat the experience. It is when this reinforcement becomes aberrant and the user engages in compulsive drug-seeking behaviour, that true addiction sets in. To compound the problem, tolerance to the effects of a drug builds up over time, often by the reduction in dopamine receptors on the dendrites of neurons. The user therefore requires more and more to achieve the desired effects and when the drug is no longer available, such as when an effort is made to quit, an addict will go through a period of withdrawal. The over-stimulated reward pathway is no longer active and a dysphoric state ensues. This often leads to relapse.

The involvement of neurotransmitters has been explored scientifically throughout the last century and many scientists now implicate the neurotransmitters 5-HT (serotonin), noradrenaline and glutamate in the process of addiction. Perhaps the most addictive of drugs is cocaine, which is linked to not only the dopamine pathway of the midbrain, but also the glutamate and the noradrenaline pathway, which activates the fight-or-flight response triggering an

increase in heart rate, blood pressure, body temperature and dilation of the pupils. Cocaine binds to the dopamine reuptake transporters, thus blocking functionality and as a result, dopamine levels increase in the synapse, so the receiving neuron is continuously stimulated - this constant firing of the neurons leads to a feeling of euphoria. Another factor in the reinforcement of cocaine use lies in the fact that after cocaine administration, dopamine levels fall significantly below normal, pre-consumption levels. The user therefore feels a "low," and the immediate response to alleviate this low is to consume more cocaine to raise the level once again. Being a key player in memory regulation, it is theorized that glutamate is directly linked to trigger memories that lead to relapse. In one study, researchers stimulated a memory-related brain area that is rich with glutamate, which caused rats weaned off of cocaine to frantically press a lever that previously dispensed the drug. In essence it caused a relapse, and blocking glutamate activity subsequently blocked the response.

Generally, the neurochemistry of addiction is heavily theorized and not yet fully understood, and the addictive nature of drugs varies from substance to substance, and from individual to individual. Owing to their neurochemical effects, drugs such as codeine or alcohol, typically require many more exposures to addict their users than drugs such as heroin or cocaine. Likewise, a person who is psychologically or genetically predisposed to addiction is much more likely to suffer from it. There are anecdotal reports of psychological addiction to recreational stimulants such as MDMA (ecstasy) and a dissociative psychedelic ketamine, but it is thought that pills sold on the street as 'ecstasy' often contain adulterants, which may be the addictive compound.

Road to recovery - drugs for drugs

Treatment of drug addiction is usually multifactorial, with a combination of counselling, psychotherapy and pharmacotherapy often employed, depending on the substance involved. Pharmacotherapy for drug addiction, particularly as the neurochemical basis of addiction and reward becomes further elucidated, is becoming more and more common, and below we will look at some of the various therapies available and in development for some common drug addictions. The traditional approach is to give a compound that mimics a drug's action but does not provide the same intense 'high', thus satisfying cravings and avoiding withdrawal whilst drug use can be tapered off. More novel strategies are also under investigation such as compounds and vaccines that block the activity of a drug completely. As would be expected, the pharmaceutical industry has focused most of its efforts where the biggest potential rewards are to be made.

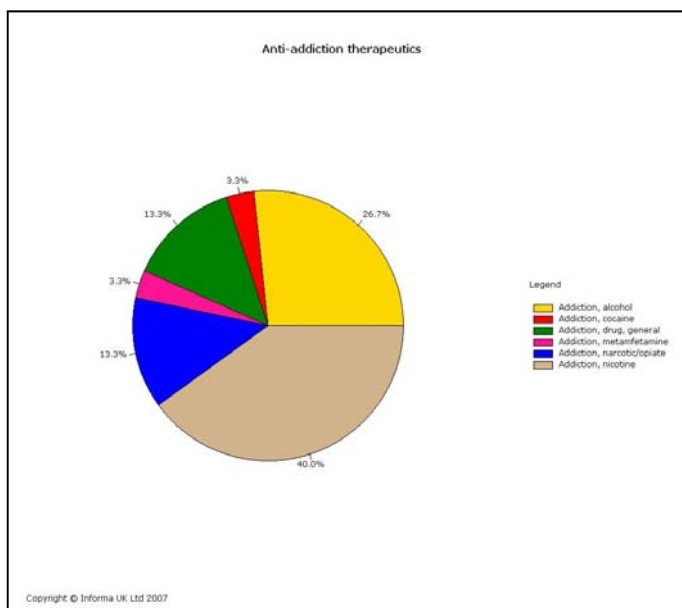
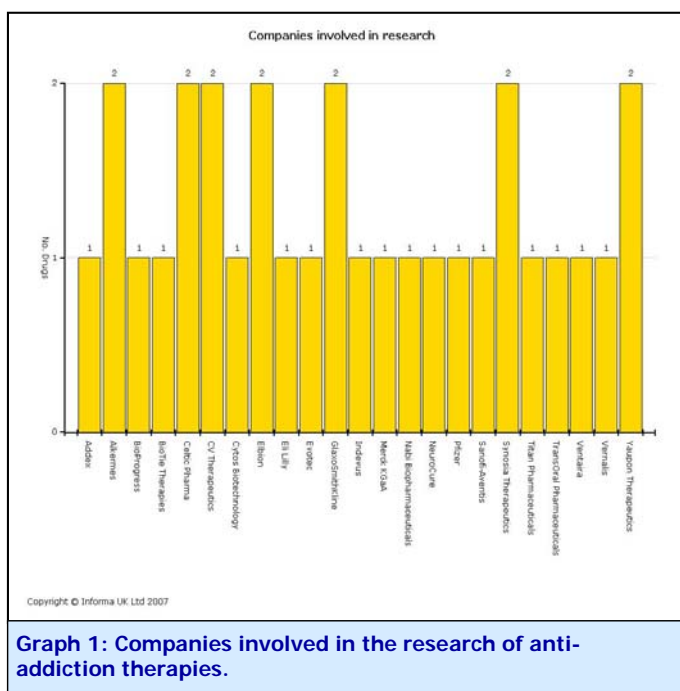


Chart 1: A pie chart to demonstrate the development of anti-addiction therapies.



Indeed, our data shows that of all the drugs in active development for a variety of drug addictions, it is clear that smoking is the main focus of much of this research, followed by drugs to treat alcohol addiction (Chart 1).

Smoking and alcohol

Even tobacco companies no longer dispute the addictive nature of nicotine, found in all tobacco products. It leads to rapid activation of the dopamine reward system, particularly because smoking provides the perfect drug delivery vehicle. The field of smoking cessation therapies is already crowded, with multiple OTC products such as nicotine gums and patches available for the individual trying to quit. These therapies simply replace the nicotine a smoker would have received from cigarettes. For those who fail to kick the habit using this approach, the standard non-nicotine drug therapy until recently had been a sustained-release formulation of the antidepressant bupropion, marketed as Zyban by GlaxoSmithKline. Whilst the exact mechanism by which it produces anti-smoking effects is unknown, it is a weak inhibitor of both dopamine and noradrenaline reuptake. Recently, a second drug has become available, with Pfizer's launch of Champix/Chantix (varenicline tartrate), a partial agonist at the $\alpha 4\beta 2$ nicotine receptor. Useful as these compounds are, they still only produce quit rates of less than 50%, and so drug development in this area continues apace. In late-stage trials currently are GlaxoSmithKline's GW-468816, an NMDA glycine site antagonist, and dianicline (SSR-591813), a nicotinic $\alpha 4\beta 2$ partial agonist under development by Sanofi-Aventis. Using a very different approach, Celtic Pharma is developing an immunotherapy, TA-NIC. This vaccine induces production of antibodies against nicotine, thus preventing the nicotine from crossing the blood-brain

barrier and hence removing the positively reinforcing effect. Acting in a similar fashion is Cytos Biotechnology's CYT002-NicQb, a nicotine vaccine in Phase II and recently partnered with Novartis.

In cases of chronic alcohol abuse, the standard drug therapy is the opioid receptor antagonist naltrexone (which is also used to treat opiate addiction, see later). It has been shown to reduce the frequency and severity of relapse to drinking, mediated, it is presumed, through modulation of the dopaminergic system usually activated by ethanol. A sustained-release formulation of naltrexone developed by Alkermes is also just becoming available in various markets, and BioTie's nalmefene tablet formulation is also waiting in the wings. A second drug currently prescribed for alcohol addiction is acamprosate. This acts in a very different way - it increases GABA-ergic transmission in the brain through the inhibition of EAA receptors. Much further back in the pipeline, CV Therapeutics is developing an aldehyde dehydrogenase 2 antagonist for the treatment of alcohol dependence, which is hoped to be an improvement on standard aversion therapy drugs such as disulfiram.

Narcotics

The opiate narcotic heroin (the street name of diamorphine) activates mu opioid receptors in the brain that are usually activated by endogenous substances. The stimulation of these opioid receptors from heroin leads to feelings of intense euphoria, known as a rush, accompanied with flushing of the skin, and heavy extremities. This is also linked to an increase in the neuronal firing of dopaminergic cells. Following this rush, the user experiences an alternately wakeful and drowsy state due to the clouding of mental functioning due to the depression of the central nervous system.

Long-term effects occur after a long period of repeated use, and chronic users may develop infection of the heart lining and valves, abscesses, collapsed veins and liver disease. In a similar way to other drugs, mainly cocaine, repeated heroin use is triggered by its often devastating physical withdrawal effects. This withdrawal may occur as early as a few hours after the last administration in regular abusers and includes restlessness, muscle and bone pain, insomnia, cold flashes with goose bumps, kicking movements and diarrhoea and vomiting, which all produce drug craving.

In addition to the use of a replacement therapy, such as methadone, opioid antagonists such as naltrexone are commonly used to treat opiate addiction. Currently in Phase III trials for the 6mth treatment of opioid addiction is Titan Pharmaceuticals' subcutaneous formulation of buprenorphine, Probuphine, and Indevus has an extended release formulation of naltrexone in Phase II trials.

Cocaine and methamphetamine

As explained previously, cocaine inhibits the reuptake of dopamine, increasing the availability of dopamine in the synapse and increasing dopamine's action on the postsynaptic neurons. The 'high' is short-lived, meaning that users repeatedly administer cocaine to repeat the effect. Methamphetamine is a dopaminergic and adrenergic reuptake inhibitor. It rapidly enters the brain causing a cascading release of norepinephrine, dopamine and 5-HT. Both cocaine and methamphetamine use is on the rise in the Western world, which would suggest that these drug addictions may soon be more on the radar of the pharmaceutical industry. At present, there are no drugs specifically approved for the treatment of these addictions, and the usual approach is to administer drugs to deal with the effects of the different phases of withdrawal, such as sedatives or antidepressants, and offer counselling. Similar to its nicotine vaccine discussed above, Celtic Pharma is also developing a vaccine against cocaine use, TA-CD that has reached Phase II development. For methamphetamine addiction, Yaupon Therapeutics is collaborating with the US NIH on the development of the first specific pharmacological treatment - an alkaloid from Indian tobacco called lobeline.

The future?

The development pipeline for pharmacotherapeutics for drug addiction (Graph 1) shows that there are many companies active in this area, including some traditional big pharma such as Pfizer, Eli Lilly and Merck KGaA, as well as a host of small-to-middle size pharma and biotech enterprises. Indeed, no one company dominates the area and there is still much room for improvement

over existing therapies. As has been seen, much of the research is currently focused on improved formulations of existing drugs. With drug use a continuing social and economic problem worldwide, it is hoped that as the mechanisms of addiction are further elucidated, new pharmacological strategies will be developed.

Andrew Benson

Search strategies

In Drug Profile Search:

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(
  [Primary Indication] = Addiction, alcohol
OR  [Primary Indication] = Addiction, amphetamine
OR  [Primary Indication] = Addiction, cocaine
OR  [Primary Indication] = Addiction, drug, general
OR  [Primary Indication] = Addiction, metamphetamine
OR  [Primary Indication] = Addiction, narcotic/opiate
OR  [Primary Indication] = Addiction, nicotine )
AND [Active, Ceased, Fully Launched] = Active
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Graph by:

Chart 1— Primary Indication, pie chart

Graph 1—Originator, line graph

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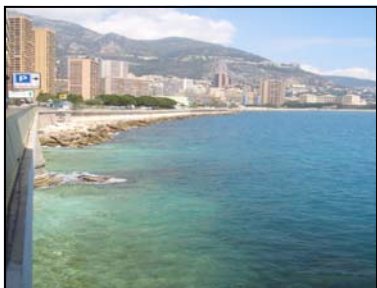
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Meeting Reports

The 4th Rodman and Renshaw Global Healthcare Conference, Monte Carlo, Monaco, 14th-15th May 2007

As Monte Carlo prepared itself for the excitement of the 65th Monaco Grand Prix, it played the perfect host to the 4th Acumen BioFin Rodman & Renshaw Global Healthcare Conference.



Set in such a glamorous location, and with the high expectations associated with Rodman and Renshaw, it is no surprise the event commenced with style and finesse - with a string quartet serenading attendees at the 'Riviera Chic'-themed welcome reception held at the conference hotel's Sea Club. Company Executive Officers were then treated to a cabaret dinner at the Monte Carlo Casino.

Presentations began early on the Monday, with Aus Bio providing a detailed pipeline update including mechanism of action details and preclinical data for its novel diabetic therapy, MD-960. By targeting the associated leucocyte antigen-related protein tyrosine phosphatases, it demonstrated reproducible efficacy in combating insulin resistance, allowing simultaneously administered insulin to control glucose levels. Oncology-focused OncoVista spoke of its clinical-stage drug cordycepin, advising that an IND for a Phase I/II trial in 100 patients with chronic myelogenous leukaemia, acute myelogenous leukaemia and acute lymphatic leukaemia has been approved. OncoVista hopes to register the molecule in 2009. Another interesting presentation came from Glycadia, which advised that by preventing proteins such as albumin from becoming glycosylated, its novel compound, GLY-230, could prevent kidney diseases such as proteinuria, which is commonly developed by diabetics. A single-ascending dose Phase I trial in 54 patients has demonstrated no serious adverse events as well as predictable dose-dependent pharmacokinetics. An ongoing Phase Ib/IIa trial in healthy and diabetic patients is expected to produce results by the end of 2007.

Afternoon presentations included those from Hemi-spherix, Idera and Wilex, as well as from the recently renamed 'Silence Therapeutics' - the final result of the merger between Atugen and SR Pharma. Silence is concentrating on its patent-protected siRNA technique that it states could potentially be applied to all pharmaceutical targets. With their catalytic characteristics, siRNAs have up to a 1000-fold greater potency compared to their stoichiometric molecular targeting equivalents, and with their faster development schedule, successful

products could provide longer on-patent sales periods. The Gala dinner proved a perfect, if somewhat surreal, break in this successful conference. The spectacular arrangement offered top-class food from the Salle Des Etiolles Summer Sporting Club, free flowing champagne, and musical entertainment from Diana Ross, who looked spectacular in a continually changing wardrobe of red, black and white dresses with matching feather boas. The electric atmosphere gave executives the perfect chance to unwind, reflect on the business opportunities of the last day and discuss the potential of the next in an environment of laughter and excitement. With a classic rendition of 'Ain't no mountain high enough,' and an encore of 'I will survive', Ms Ross dazzled the crowd for over an hour and a half with non-stop enthusiasm, and in a magnificent finale, the ballroom's roof-top opened to reveal a firework extravaganza! After this fantastic event, the night continued below at Jimmy's night club, where the 70s-style dance floor proved the perfect opportunity for many executives to dance the night away.

Tuesday was filled with a number of captivating presentations, many of which began with a humorous anecdote from the night before. Cylene gave a fascinating presentation explaining its motives behind targeting the nucleolus to develop novel anticancers. It advised that its leading nucleolus-disrupter, CX-3543, has demonstrated widespread systemic infiltration, post-administration, but has also demonstrated inactivity in healthy tissue such as bone marrow, suggesting great potential as a non-toxic therapeutic. In preclinical studies in animals, PET scans have demonstrated that CX-3543 can reduce tumours to a necrotic core in just 2 days.

In a private meeting, the CEO of Hunter-Fleming, Mike Capaldi, discussed his company's Phase II candidate, HF-0220, a naturally-occurring steroid containing a 7 β -hydroxy group that has potential in Alzheimer's disease, colitis and rheumatoid arthritis. Mr Capaldi explained that by indirectly upregulating 15d-PGJ2, a natural steroid that appears to be absent in the brains of Alzheimer's patients, HF-0220 might have considerable therapeutic benefits. Hunter-Fleming plans to out-license the development of the oral formulation of the compound to a large partner for development in such indications, whilst retaining development of a topical version for itself. With 2nd generation HF-1220 compounds already in development, as well 6 patents granted and further patents pending for the mechanism of action, the company looks set for a successful year.

The closing reception was held on the sunny terrace of the Monte Carlo Bay Hotel & Resort, with cellists providing the perfect musical background as attendees bade their final goodbyes. This year's Rodman and Renshaw

Annual Global conference was once again an excellent opportunity to network in style, and quite aptly, it was the calming sound of the lapping of Mediterranean waves that marked the end of this highly anticipated meeting.

Samantha Richards

Digestive Disease Week, Washington, DC, USA, 19th – 24th May 2007

In the bustling hubbub of downtown Washington, DC, attendees gathered at the Convention Center for the 2007 Digestive Disease Week. Sponsored by the combined strength of the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA), the American Society for Gastrointestinal Endoscopy (ASGE) and the Society for Surgery of the Alimentary Tract (SSAT), the much-anticipated DDW meeting proved once again to be the largest assembly of intellectuals in the field of gastroenterology and hepatology.

It seemed that a great deal of the conference this year was focused on diagnosis and surgical treatment of gastrointestinal disorders. Various clinical update sessions, research forums and symposia where sub-divided into specific themes, including irritable bowel syndrome (IBS), non-alcoholic fatty liver disease, various cancers, and the possible links between obesity and gastrointestinal disorders. Another area of development that was a common theme was the utilisation of probiotics and their efficacy in various conditions, particularly irritable bowel disease. In fact, many of the presenters in the large underground exhibit hall were offering various pro and prebiotic drinks, snacks and advice.



In a notable press conference on Sunday entitled 'New Approaches to Managing Hepatitis', results of a Phase II trial of celgosovir in combination with peginterferon- α 2b and ribavirin were presented. The trial, in chronic hepatitis-C genotype-1 patients who were either partial or non-responders, showed an early viral response in non-responders of 42%, compared with only 10% for patients on peginterferon- α 2b and ribavirin alone. The addition of celgosovir to the regime also decreased the mean viral load.

In the same press conference, researchers also reported on the retrospective analysis of trials in hepatitis-C patients who were also administered a statin at some

point during their treatment. Currently, the US FDA and other health authorities worldwide suggest the use of statins in patients with 'active liver disease' as potentially unsafe. This ruling was initially instigated due to the possible link between alanine transaminase (ALT) levels and liver damage. It has since come to light that ALT levels are not an accurate measure of severity of liver disease, and as such levels of total bilirubin were measured as a better indicator. In a 14-day study, fluvastatin had no effect on bilirubin in patients with normal ALT levels and actually improved levels in 92% of patients with abnormal ALT levels. A further study, where patients had taken peginterferon and ribavirin with either simvastatin, lovastatin, atorvastatin or fluvastatin, showed an improvement in sustained viral response (SVR): without the use of a statin, the SVR was 37% and with the use of statins SVR was 63%. During this analysis, the only statin which seemed of no use in this circumstance was pravastatin.

Another key area for development was highlighted in a section entitled 'Progress in 2007: Important New Therapies for IBD and IBS', during which researchers presented details on a variety of treatments for an assortment of conditions. GlaxoSmithKline presented efficacy data for rosiglitazone, a drug launched for Type II diabetes, in the treatment of mild-to-moderately active ulcerative colitis, which is refractory or intolerant to 5-aminosalicylic acid. After 12 weeks of treatment, 44% had achieved a clinical response with a higher rate of clinical remission and improvements in quality of life also evident. In another presentation, Microbia reported the use of linaclotide acetate in the treatment of constipation-predominant IBS. Currently in Phase II trials, this product effectively accelerated colonic transit and bowel habits with no evident safety issues. Sucampo Pharmaceuticals also released interesting data on lubiprostone, which is currently only launched in the US for constipation. In 2 Phase III trials in IBS, it demonstrated superiority versus placebo and side-effects were comparable, with discontinuation rates higher in the placebo group.

This year's Digestive Disease Week also showcased an abundance of other kinds of activities. With over 300 companies and 1000 booths filling the exhibition hall, offering anything from massage sessions to computer simulation games of drug action, and the profusion of captivating posters filling another large hall, the conference was a busy hive of activity for the week. Add to this various presentations, sponsored dinners and focused sessions in some of the most prestigious hotels in Washington, DC, DDW once again lived up to its reputation as the cornerstone of gastrointestinal conferences.

Rebecca Bridge

The next Digestive Disease Week will be held in San Diego, CA, USA 17th - 22nd May 2008.

9th Annual C21 BioVentures, Monterey, CA, USA, 22nd – 24th May 2007

The Monterey Plaza Hotel & Spa was the luxurious venue for the 9th Annual C21 BioVentures. Located on Cannery Row, it could not possibly be compared to John Steinbeck's depiction of the land near a sardine fishery during the Great Depression, in his 1945 novel of the same name.

C21 BioVentures is a meeting that aims to bring private life science companies together, and to provide insights into the trends driving growth and development in the bioscience industry in the 21st century. Robert Lee Kilpatrick, a partner of Technology Vision Group LLC which organizes the conference, welcomed over 350 attendees, including representatives from more than 225 companies. President of the North Californian biotech association BayBio, Matt Gardner, extended the greetings and a positive outlook for next year's gathering

in Napa, highlighting the meeting's importance. However, he also made mention of the fact that the life science "industry is challenged by government", and has obstacles to overcome. Held over three days, the 2007 meeting consisted of leadership sessions and three streams of company presentations, together with tabletop presentations and one-to-one meetings.

CG Pharmaceuticals, the US operation of S Korean company CrystalGenomics, took a morning slot to begin the 54 private and emerging company presentations. Under development for osteoarthritis and rheumatoid arthritis (RA), its drug CG-100649 protects blood vessels and renal tissues from the negative effects of traditional cyclooxygenase inhibitors by acting as a dual COX-2 and carbonic anhydrase inhibitor. In completed UK Phase I trials, this compound showed superior efficacy and improved safety to celecoxib. Two US Phase Ib trials are underway, with completion expected in 2008. CG also discussed its hypoxia inducible factor (HIF) stabilizers, including CG-0089 and CG-0086, noting that seven novel scaffolds are to undergo optimization to achieve a targeted IND filing in the second half of 2008. A partner is sought with expertise in HIF for these erythropoietin-stimulating therapeutics.

Located north of Monterey Bay in Menlo Park, CA is Colby Pharmaceuticals, a new addition to Pharmaprojects. CEO Dr David Zarling gave an insight into Colby's targeted antioxidants, with an emphasis on prostate cancer. Colby offered four projects – 3 of which have been exclusively in-licensed worldwide – that target oxygen free radicals and oxidative stress. Its lead compound CPC-100, an androgen receptor binding antioxidant, is in late preclinical studies and is slated to enter a

Phase I/IIa trial in 2008. The trial will enroll men who have failed androgen ablation therapy and who are resistant to Casodex (bicalutamide), and a Phase IIb trial expected to follow two years later. Colby's second most advanced compound CPC-200 is a prostate-targeted oxidase inhibitor, which produced a greater than 50% reduction in mortality in mice by week 20: a Phase I trial is expected in 2009. Under development for advanced metastatic hormone-refractory prostate adenocarcinoma, CPC-300 is a natural product that also has utility in pancreatic cancer, and a Phase I/IIa trial is planned for 2010. Discovered by Colby and its collaborators, CPC-410 is a new chemical entity (NCE) nitron, consisting of a large cation with a +32mV charge, that is a mitochondria-targeted superoxide dismutase mimic. It displayed efficacy in both LNCaP and PC-3 prostate cancer models, in addition to increasing motor activity and survival in a mouse model of amyotrophic lateral sclerosis (ALS).

Wednesday's proceedings came to an end with conference attendees visiting the Château Julien Wine Estate, not only for delectable wine tasting but also to continue with significant networking opportunities. If deals had not met their conclusion by the time the sun was leisurely setting behind the hills of the Carmel Valley accompanied by the jazz music entertainment, there was still the poker evening hosted by Square 1 Bank to continue the discussions and secure the trade.

With a focus on biotherapeutics that modulate receptor tyrosine kinases, Receptor BioLogix gave a snap shot of its pipeline on Thursday afternoon. Acquired from Aphoton, its lead product Gastrimmune is in Phase III development for gastric cancer. This synthetic peptide stimulates the production of antibodies that neutralize endogenous gastrin, which in turn inhibits growth signalling. Intron Fusion Proteins (IFPs) that included Hermodulins for nsclc, and angiogenesis programmes derived from the Tie-1 receptor and fibroblast growth factor receptor (FGFR) for RA, were also presented. Receptor BioLogix is seeking partners worldwide for all of its programmes.

The C21 BioVentures ended with a drinks reception on the terrace overlooking Monterey Bay and the Pacific Ocean for one final opportunity to network, and to reflect on the successful three days of partnering, deal making and financing. With a continued rise in attendees, the 10th Annual C21 BioVentures will relocate back to its 1999 foundations in Napa, California. With a greater than 50% increase in capacity promised, it is hoped that the number of partnering opportunities and financing will also be maximised.

Jo Woodcock

The 10th Annual C21 BioVentures will be held at the Meritage Resort, Napa, CA, the US, 20th – 22nd May 2008.

New Targets

integrin, alpha E (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide)

Integrins are a family of cell surface adhesion molecules that play a major role in morphogenesis, haemostasis, leucocyte activation and cellular adhesion. Immune responses at mucosal sites are mediated by lymphocytes associated with mammary glands and the gastrointestinal, genitourinary, and respiratory tracts. Integrin, alpha E is preferentially expressed on human intestinal intraepithelial lymphocytes (IEL), and in addition to adhesion, it may serve as an accessory molecule for IEL activation.

LigoCyte is developing a compound targeting CD103 for the treatment of asthma, COPD and rheumatoid arthritis.

Integrin, alpha E belongs to the Receptor Target Family Group. Its Entrez Gene ID is **3682**.

hepatocyte erythrocyte protein 17 kDa, Plasmodium yoelii

hepatocyte erythrocyte protein 17 kDa, Plasmodium yoelii is a target of protective antibodies and T-cells. It induces antigen-specific immune responses and protects against sporozoite challenge.

Alza (Johnson & Johnson) and Inovio are developing a DNA malaria vaccine encoding CSP and HEP17 antigens to be delivered by in vivo electroporation-enhanced injection.

The Entrez Gene ID for hepatocyte erythrocyte protein 17 kDa, Plasmodium yoelii is **3790041**.

v-raf murine sarcoma 3611 viral oncogene homologue

v-raf murine sarcoma 3611 viral oncogene homologue (a-raf) is a member of the v-raf oncogene involved in the transduction of mitogenic signals from the cell membrane to the nucleus.

Novartis is developing a small-molecule Raf and VEGFR kinase inhibitor for the treatment of cancer.

a-raf belongs to the Enzyme > Kinase Target Family Group. Its Entrez Gene ID is **369**.

circumsporozoite protein, Plasmodium yoelii

Circumsporozoite protein, Plasmodium yoelii is the most prominent surface antigen on the sporozoite of the malaria parasite, Plasmodium spp. The sporozoite is the infectious stage in the Plasmodium life cycle, the form in which malaria is passed from the mosquito vector to the mammalian host. Antibodies to this protein have been used in the field to detect exposure to malaria.

Alza (Johnson & Johnson) and Inovio are developing a DNA malaria vaccine encoding CSP and HEP17 antigens to be delivered by in vivo electroporation-enhanced injection.

The Entrez Gene ID for circumsporozoite protein, Plasmodium yoelii is **3830374**.

potassium inwardly-rectifying channel, subfamily J, member 2

Potassium inwardly-rectifying channel, subfamily J, member 2 (KCNJ2) is an integral membrane protein that has a greater tendency to allow potassium to flow into, rather than out of a cell. It is thought to participate in establishing action potential waveform and excitability of neuronal and muscle tissues.

Intrexon is developing gene therapies for progressive neural disorders.

KCNJ2 is a member of the Ion Channel > Potassium channel Target Family Group. Its Entrez Gene ID is **3759**.

peripherin 2 (retinal degeneration, slow)

Peripherin 2 is a member of the tetraspanin family of proteins that mediate signal transduction events, which play a role in the regulation of cell development, activation, growth and motility. Peripherin 2 is a cell surface glycoprotein found in the outer segment of both rod and cone photoreceptor cells. It may function as an adhesion molecule involved in stabilization and compaction of outer segment disks or in the maintenance of the curvature of the rim. It is essential for disk morphogenesis and defects in this gene are associated with both central and peripheral retinal degenerations. Some of the various phenotypically different disorders are autosomal dominant retinitis pigmentosa, progressive macular degeneration, macular dystrophy and retinitis pigmentosa digenic.

Copernicus Therapeutics is developing gene therapy systems for the treatment of retinal degeneration conditions, using non-viral compacted DNA-nanoparticle vectors.

The Entrez Gene ID for peripherin 2 is **5961**.

KeyNeurotek, in collaboration with the Max Planck Society, Munich, Germany, is developing inhibitors of FKBP38 as a neuroprotective following stroke.

FK506BP belongs to the Enzyme > Isomerase Target Family Group. Its Entrez Gene ID is **23770**.

FK506 binding protein 8, 38kDa

FK binding proteins (FKBPs) are of central importance for the folding and functionality of proteins. FKBP38 is a member of the FKBP506 family and has been shown to reduce nerve cell death following strokes. The FKBP/FK506 complex exerts its immunosuppressive effects by inhibiting calcineurin and calmodulin-dependent serine/threonine phosphatase that functions as a critical signaling molecule during T-cell activation.

New Drug Development Strategies

The following new drug development strategies are also new to the July edition of *Pharmaprojects*.

Interleukin-34 agonist

Five Prime is developing interleukin-34 agonists as an immunostimulant in cancer, inflammation and infectious diseases.

Interleukin-34 agonists are coded in *Pharmaprojects* as **IL-34+**

Casein kinase antagonist

Cylene is developing casein kinase antagonists for the treatment of cancer.

Casein kinase antagonists are coded in *Pharmaprojects* as **KI-CA-2-**

Companies New to *Pharmaprojects*

Amkor Pharma is a virtual company that in-licenses and develops compounds for diverse clinical applications.

British-based **Apitope Technology** develops novel vaccines for the treatment of autoimmune diseases and allergies.

French biotechnology company **Collectis** develops meganucleases for pharmaceutical and industrial applications.

Cequent Pharmaceuticals develops novel therapeutics using its TransKingdom RNA interference (tkRNAi) technology to treat and prevent a wide variety of diseases.

Colby Pharmaceutical Company develops targeted antioxidants for the treatment of prostate cancer.

Conatus Pharmaceuticals is a privately-owned company, developing compounds for the treatment of inflammation and liver disease.

Coronado Biosciences is engaged in developing novel and proprietary cancer therapeutics.

Effector Cell Institute is developing novel therapeutics that regulate leucocyte activity, for the treatment of cancer and inflammatory diseases.

UK-based **Epistem** has a pipeline of protein therapeutics that regulate adult stem cells, for the treatment of ulcers and cancer.

Established in 1988, **Glycadia Pharmaceuticals** develops novel therapies targeting upstream diabetes-specific abnormalities.

Intrexon Corporation is developing multifunctional genes and gene activation products for the treatment of complex, intractable diseases.

LipoNova is a German company, developing autologous cell therapies for the treatment of cancer.

Using its dominant negative ligand drug discovery system, **Molecular LogiX** develops protein-based cancer therapeutics called anticancer ligands (ACLs).

Osprey Pharmaceuticals is engaged in the development of therapeutic proteins for chronic diseases.

OsteoGenix is developing products for the acceleration of bone repair and bone growth.

Established in 2004, French-based **Pharmaxon** focuses on cell mobility control.

Verona Pharma discovers and develops new therapeutic drugs for the treatment of allergic rhinitis and other chronic respiratory diseases, such as asthma and COPD.

Xcovery is developing kinase therapeutics for the treatment of inflammation and cancer.

Mergers, Acquisitions, Name Changes and Joint-Ventures

Boston Life Sciences has changed its name to **Alseres Pharmaceuticals**.

Cytec has acquired **Adeza**, a biotech company focused primarily on the diagnosis of pregnancy-related and female reproductive disorders.

NeuroMedix has been acquired by **Transition Therapeutics**, a company developing therapeutics for unmet medical needs.

India-based **Orchid Pharmaceuticals** has acquired **Bexel Pharmaceuticals**, which will remain as a subsidiary.

Gene therapy company **Oxford BioMedica** has acquired **Oxxon Therapeutics**.

Pfizer has acquired privately-owned biopharmaceutical company **BioRexis**.

Sheffield Pharmaceuticals merged with **Pipex Therapeutics** and changed its name to **Pipex Pharmaceuticals**.

VIA Pharmaceuticals has merged with fellow US-based **Corautus Genetics**.

Specialist pharmaceuticals and devices company **Maelor** has acquired **Acorus Therapeutics**.

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Pharmaprojects News Digest

The following news stories are a selection of those listed on our new *Pharmaprojects* website. Go to www.pharmaprojects.com for more of the same, and to subscribe to our e-mail alert service.

Safety concerns over GSK's Avandia

GlaxoSmithKline (GSK) is fighting for the reputation of its second best-selling drug, Type 2 diabetes therapy Avandia (rosiglitazone maleate), after the emergence of meta-analysis data suggesting that it could increase the risk of heart attacks by 43%.

The FDA had already revised the product labelling for the drug in 2006, to include a warning about a potential increase in heart-related chest pain and heart attacks, but the meta-analysis conducted by leading cardiologist, Steve Nissen from the Cleveland Clinic Foundation in Ohio, prompted the FDA to look again at the safety profile. Nissen and his co-author Kathy Wolski, reviewed 42 trials all listed in the public domain, and concluded that Avandia may raise a patient's risk of heart attack by 43% and increase the risk of death from all cardiovascular causes by 64%.

GSK strongly disagrees with the report's conclusions, pointing out that comparable rates of cardiovascular deaths were observed in patients receiving Avandia, compared to non-treatment arms, in two of its long-term studies, ADOPT and DREAM. Ronald Krall, GSK's Medical Director, added, "We are confident of the safety profile of Avandia and believe in its benefits for Type 2 diabetic patients."

Despite the view of the FDA, that the risks of Avandia are not yet clear, the share price is already down by 8%, with analysts predicting a 35% fall in Avandia sales due to negative publicity. The FDA is currently conducting its own analysis and plans to take the data to an advisory committee meeting as soon as possible.

China sentences former drugs chief to death

A Chinese court has sentenced to death the former director of the State Food and Drug Administration (SFDA) on charges of corruption.

Zheng Xiaoyu had headed China's pharmaceutical watchdog agency from 1998 to 2005, after rising through the ranks of state-owned pharmaceutical companies. Following a 2 week trial, he was convicted of accepting bribes and gifts to the value of almost half a million British pounds to fast-track some drugs. Additionally, eight companies were allowed to circumvent the approval process. Investigators also found that Zheng lowered standards in renewing drug

production licences which led to the manufacture of fake drugs.

In one example from 2006, an antibiotic approved by his agency killed at least 10 patients before it was taken off the market. The transgressions were not restricted to drugs however, and included other contaminated goods.

The severe sentence comes amidst growing domestic as well as international concern about the quality and regulation of Chinese goods.

Johnson & Johnson offers up a money-back deal for Velcade

Johnson and Johnson's (J&J) multiple myeloma drug Velcade (bortezomib) finally looks set to become available in England, after the UK's National Institute for Clinical Excellence (NICE) reached a deal with J&J, to make the drug 'cost-effective' for prescription by the UK National Health Service (NHS) in England. Velcade will now be recommended for use in the English NHS, and under the terms of the agreement, the NHS will pick up the bill for patients who respond well and continue their treatment. However, those showing a minimal or no response will be taken off treatment, and the drug's costs (around £18,000/year) will be refunded by J&J. This scheme is the first of its kind and could signal a new era for the health service, allowing wider patient access to novel drugs and greater value for money for the NHS. Velcade had previously been unavailable in England, despite being available throughout the remainder of the UK.

Every year in the UK there are more than 2,400 multiple myeloma-related deaths. Velcade was the first anticancer proteasome inhibitor to reach the clinic and has advanced rapidly through registration and launch — since 2003, it has been launched in Asia, Australasia, Europe and the US. It has proven efficacy in refractory and relapsed myeloma patients, and demonstrated superiority over dexamethasone by nearly doubling the median time to disease progression and reducing the risk of death by 41%. In its earlier review, NICE had agreed that it was efficacious, but restricted availability to use in clinical trials only due its cost.

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:

For **Europe & ROW:**

For **The Americas:**

For **Japan:**

Guy Morris at guy.morris@informa.com

Anthony Stewart at astewart@pharmabooks.com

Mr T Hirata at info@shiryoken.co.jp

Dates	Conference	Details
IBC's Drug Discovery Tech-		
6-9 August	Drug Discovery and Innovative Therapeutics World Congress	World Trade Center and the Seaport Hotel, Boston, USA For information: http://www.drugdisc.com/ <i>Our Product Development Manager, Alex Westbury will be presenting about trends in pharmaceutical R&D at this meeting.</i>

Further Information

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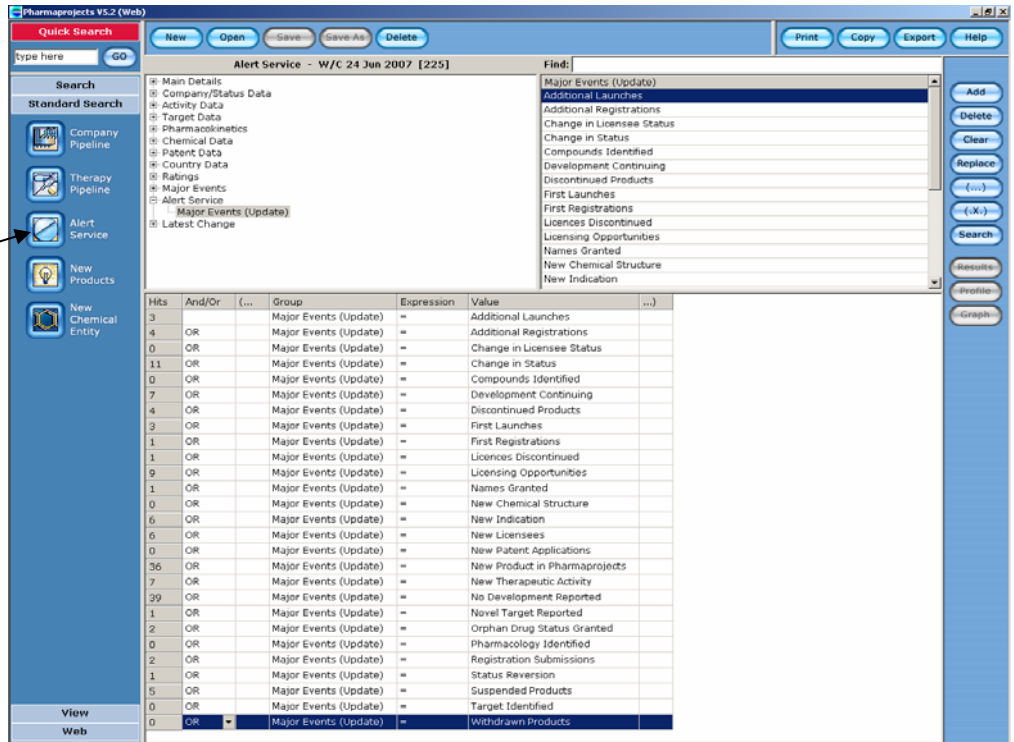
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Search Tip of the Month - Major events in a specific therapy area

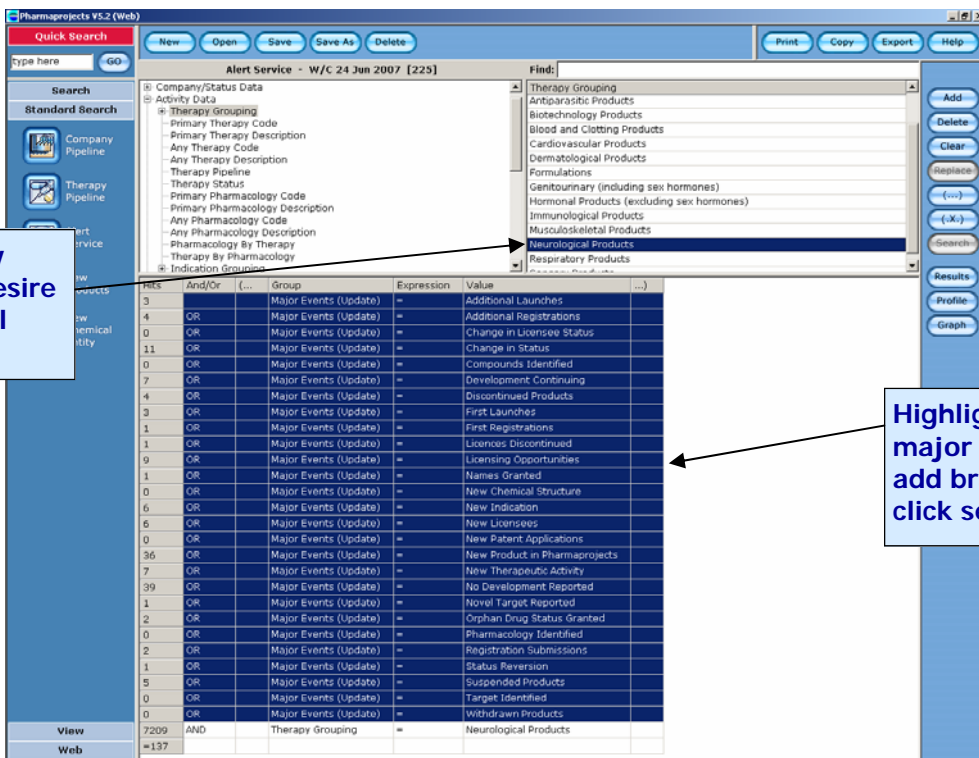
The powerful search facilities available on *Pharmaprojects* can be used for a variety of business purposes. This month's search describes how to search for all neurological drugs which have experienced a Major Event during the past update week/month.

In the standard search, click on the Alert service button.



Add the therapy grouping you desire eg. Neurological products.

Highlight all of the major events and add brackets and click search.



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