



Update Analysis

October 2004, Volume 25, Issue 4

Welcome to the monthly *Pharmaprojects* newsletter, the *Update Analysis*. The October issue contains an analysis of one of the hottest developmental strategies around, RNA interference, a report from the 228th ACS meeting and all the usual *Pharmaprojects* highlights you have come to expect from the UA.

CONTENTS

Therapy Analysis	1
Meeting Reports	4
New Drug Development Strategies	6
New Companies	8
Mergers, Acquisitions, Name Changes & Joint-ventures	10
Exhibition Calendar	11
News Headlines and Updates	12
Office Relocation	12
Search Tip of the Month	13
Copyright Information	14
Further Information	14

Managing Editor Ian Lloyd
Editor Elizabeth Cairns
Writers Jan Beal
Jo Woodcock
Lynne Kincaid

Update Analysis is also available electronically, in full colour, via email.

Please contact
hayley.mckechnie@pjbpubs.com

Therapy Analysis

Silence is golden: Can RNA interference therapeutics deliver?

'I like your silence: it the more shows off your wonder'

Paulina, *"The Winter's Tale"* by William Shakespeare

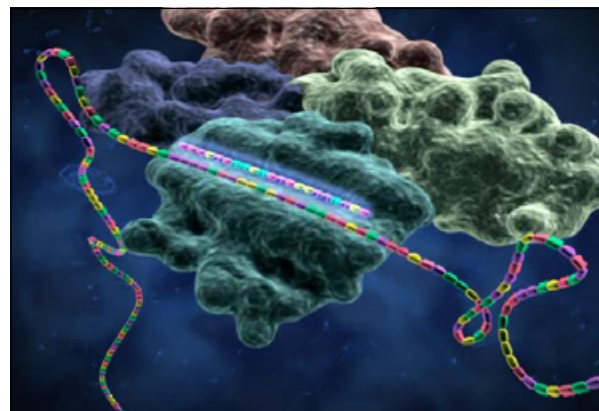
Short-lived crazes come and go in the biopharmaceutical industry, particularly when it comes to anything which might fit the description of a 'magic bullet'. Immunotoxins, gene therapies, antisense agents and ribozymes have all been hailed as the 'next generation of therapeutics', but, after years of intensive research effort, each has arguably failed to fulfil its initial promise. This is doubly frustrating with the advent of the human genome project, and the increased understanding of genes linked to human disease, ripe for targeting.

So what has the current flavour of the month, RNA interference (RNAi), or gene silencing, got to offer, and is it different from previous gene-based technologies? RNAi works by blocking expression of specific proteins

within the cell at the messenger RNA (mRNA) level, using short nucleic acid fragments - which at first glance, seems a remarkably similar strategy to those tried-and-tested warhorses of biotech, antisense and ribozyme technologies. After years of extensive preclinical and clinical study, neither of the latter strategies has yet met with significant commercial success, being plagued by delivery problems, inefficiency and doubts about precise mechanisms of action.

The main advantage of RNAi over these techniques is that it appears to be a much more robust and efficient technology. In addition, it is based on a natural process, which may work in favour of clinical success and public acceptance.

RNAi was discovered relatively recently, and in grand Hollywood tradition, was stumbled on almost by accident. In the late 1980s, Dr Richard Jorgensen and researchers at the University of Arizona working on transgenic plants noted an unusual effect when two separate transgenes interacted, resulting in inhibition rather than stimulation of gene expression. The effect was particularly striking in a study aimed at deepening flower colour in petunias. The introduction of a gene encoding a pigment-producing enzyme - chalcone synthase - resulted in the flowers *losing* their colour, becoming variegated or white (see picture overleaf).



An RNA silencing complex

RNAi is based on a natural process, and works by blocking expression of specific proteins within the cell at the messenger RNA (mRNA) level, using short nucleic acid fragments

Elucidation of the actual mechanism responsible for this effect had to wait until 1998, and a study by Andrew Fire and his colleagues at Stanford University. Instead of plants, they were investigating gene silencing in the nematode *Caenorhabditis elegans*, and found that short stretches of double-stranded RNA were capable of blocking gene expression sequence-specifically. Silencing was later demonstrated in a wide variety of species, including mammals - in which it is presumed to have evolved as a mechanism of protection against viral RNA.



A variegated petunia, created using gene silencing

The mechanism of RNAi, while more sophisticated than conventional direct hybridization (antisense) or RNA cleavage (ribozyme) strategies, is still relatively simple. Short double-stranded RNA fragments (around 22 nucleotides long) are the key agents, the most commonly-used type being known as small

interfering RNA (siRNA). In nature, these fragments are produced from longer strands by an enzyme known as Dicer. However, in the laboratory, they tend to be produced synthetically or from a vector.

siRNAs contain a sequence which is complementary to a target mRNA. On entering the cell, these fragments bind to cellular proteins to form an RNA-induced silencing complex (RISC). Within the complex, the two RNA strands separate, and the whole complex is guided to the target mRNA by the complementary sequence on the siRNA. On binding to the target, the complex cleaves and completely degrades the target mRNA, abolishing expression of the encoded protein.

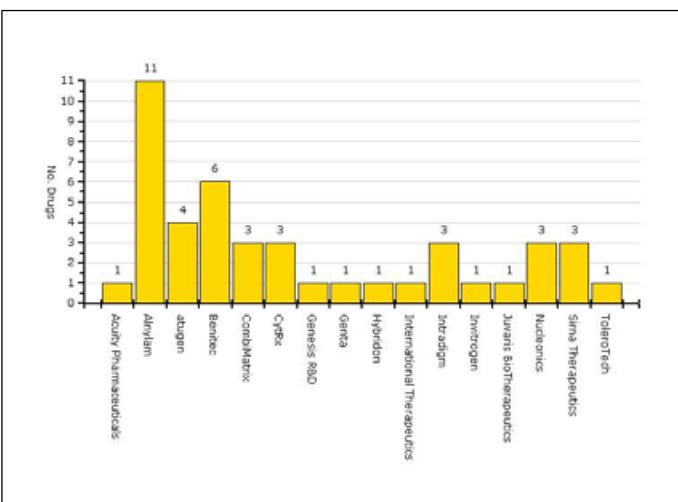
This highly efficient 'knockdown' effect can be used to block expression of any specific protein rapidly, precisely and stably. Expression blocking is normally around 70%, which means that the system may be used on essential genes without lethal effects, and is controlled and reversible. As a result, RNAi has rapidly gained popularity as a technique for producing stable loss-of-function mutant model organisms, from nematodes to rodents, for use as research tools and disease models in drug target discovery and validation.

This has precipitated the first RNAi revolution - researchers can now choose any gene of interest (including those encoding proteins of unknown function), construct an siRNA, and observe the effects when expression is silenced in living cells or a knockdown animal model. An RNAi knockdown model may be produced in a fraction of the time and cost required using previous antisense 'knockout mouse' technologies, and as a result these have been largely superseded by RNAi-based systems in a very short time.

Due to its flexibility and reversibility, this type of system lends itself readily to high-throughput screening to identify not only functions of unknown genes, but possible targets for future drugs. If silencing a particular gene has a therapeutic effect, chances are that a drug acting on the gene product will have a head start on its way to the clinic.

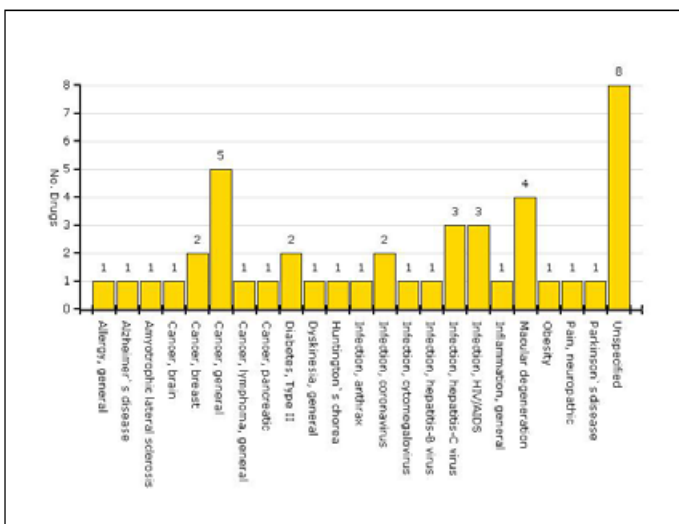
Naturally, it has not escaped the notice of drug developers that the siRNAs which produce therapeutic effects in models are prime drug candidates in themselves - and several specialist companies have sprung up to exploit this (Graph 1). Theoretically, an siRNA drug may be designed and developed against virtually any protein target, whether druggable by conventional molecules or not, and its precise mechanism of action reduces the potential for side-effects. The only major obstacles are delivery and intracellular stability of the siRNA agents - and these are being tackled using vectors, protein or liposome conjugates and RNA modification. The broad spectrum of possibilities for RNAi therapeutics is illustrated by the wide variety of lead indications currently under study (Graph 2).

From Graph 1, it is fairly clear which is the current major player in RNAi therapeutics - Alnylam, founded in 2002 by siRNA pioneer Thomas Tuschl and Nobel Laureate Philip Sharp. This impressive set of credentials was further strengthened by the acquisition of valuable RNAi patent rights through a merger with Ribopharma, making Alnylam a formidable player in this sector. The ambitions of the company are reflected in its offbeat choice of name: Alnylam is the central star on the belt of the constellation Orion (the hunter), and has a luminosity 250,000 times greater than the sun.



Graph 1
Companies developing RNAi therapeutics

Alnylam's lead project is an anti-VEGF siRNA for age-related macular degeneration (AMD), and is expected to enter the clinic next year in collaboration with Merck & Co. Furthermore, the company has a rich variety of other projects against a wide selection of indications,



Graph 2
Lead indications for therapeutic RNAi projects

some notably involving targets previously deemed undruggable by conventional small molecules. A prime example of this is a siRNA targeting α -synuclein, an important disease-modifying target for Parkinson's disease.

The more prosaically-named Sirna Therapeutics has had a somewhat different history. It was born when Ribozyme Pharmaceuticals shifted its pipeline away from ribozyme therapies and jumped on the RNAi bandwagon, necessitating a name change. However, the time spent on ribozymes was not wasted - the company's considerable expertise in RNA modification for therapeutic use should stand it in good stead for the development of stable siRNAs suitable for the clinic.

Indeed, Sirna may be one of the first companies to initiate human trials with RNAi, since an IND has already been filed for its lead AMD treatment Sirna-027 - also an anti-VEGF siRNA oligonucleotide - and Phase I trials are due by the end of the year.

The Australian company Benitec has carved an important niche for itself in RNAi using DNA vectors rather than oligonucleotides, and holds a dominant patent position in this area. This is a version of gene therapy, which may have certain advantages over siRNA oligonucleotides in delivery, stability and efficacy - however, since the gene therapy sector itself has been fraught with difficulties, commercialization is no more certain than with other RNAi strategies.

Table 1 shows some key RNAi projects expected to enter the clinic in the next couple of years. It is interesting to note that the race to be the first to enter clinical trials has been hotly contested between two (possibly three) VEGF-targeting siRNAs against the same ocular disorder; there is no current therapy for AMD.

In contrast to the big players, a small Philadelphia-based company, Acuity Pharmaceuticals, has achieved two major milestones so far. Its anti-AMD oligonucleotide, Cand5, was the first RNAi therapy to show efficacy in a primate model. Acuity then became the first company to file an IND in this area, and trial initiation is imminent. Sirna Therapeutics is hot on its heels, and the dominant RNAi company, Alnylam, is ready to begin trials next year with its anti-AMD siRNA. The next race will be to find out which will make it to market.

Product	Company	Indication(s)	Status
Sirna-027	Sirna Therapeutics	Macular degeneration	IND filed; Phase I trials due in 2004
Cand5	Acuity Pharmaceuticals	Macular degeneration Diabetic retinopathy	IND filed; Phase I trials due in 2004
ALS RNAi therapy	CytRx	Amyotrophic lateral sclerosis	Phase I trials due in 2005
BLT-HCV*	Benitec	Hepatitis-C	Phase I trials due in 2005
Ocular siRNA therapy	Alnylam/Merck & Co	Macular degeneration	Phase I trials due in 2005
RNAi HIV therapy*	Benitec/City of Hope	HIV/AIDS	Phase I trials due in 2005
RNA interference	Genesis R&D	Allergy	Phase I trials due in 2006
BLT-HIV*	Benitec	HIV-related lymphoma	IND filing due in 2004
ToleroVax*	ToleroTech	Autoimmune disease Transplant rejection	IND filing due in 2005
Diabetes therapy	atugen	Type II diabetes	IND filing due in 2005/6

Table 1
RNAi therapeutics in late preclinical development

* denotes gene therapies using vectors—other products are synthetic oligonucleotides

Benitec has other investigations underway: RNAi therapeutics for HIV-related lymphoma, diabetes, hepatitis-C and breast cancer can be found in its pipeline. Many other small companies are emerging. If the technology is not scuppered by safety issues or delivery problems, a huge expansion in the RNAi therapeutics sector is likely over the next couple of years. However, it is as well to remember the gene therapy debacle. Gene therapy was hailed as a panacea and became very popular over the last decade, only to dissolve into disappointment and frustration as efficacy and safety concerns halted project after project, with only one minor marketed product emerging thus far.

The Human Genome Project has given RNAi developers a goldmine of untapped therapeutic targets on which to test their new technology. Unhampered by the need to develop small molecules through traditional means, and with RNAi technology itself generating screening models for each new target, the generation of actual drug candidates seems almost too easy. This may be a rare example of a newcomer living up to its advance publicity - the moment of truth will be the arrival of the first

RNAi drug on the market, and its commercial success. Only then will RNAi overcome the most important target for silencing: the sceptics.

Jan Beal

Image of RNAi silencing complex courtesy of Sirna Therapeutics

Image of petunia courtesy of Dr Richard Jorgensen, Department of Plant Sciences, University of Arizona, AZ, the US

Search strategy 1

In Tree Search:

```

([Detailed Information] = "RNA Interference"
OR [Detailed Information] = "Interfering RNA")
AND ([Any Therapy Description] = Gene Therapy {T4A}
OR [Any Therapy Description] = Non-Antisense Oligonucleotide
{T4E})

```

Graph by: Originator

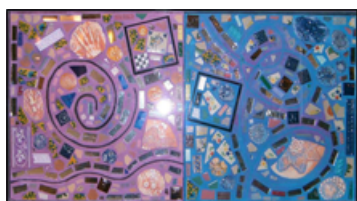
Search strategy 2

Perform the search shown above. Graph by Primary Indication.

Meeting Reports

228th Meeting of the American Chemical Society, Philadelphia, PA, USA, 22nd - 26th August 2004

Philadelphia, America's capital from 1790-1800 and birthplace of the Declaration of Independence, provided the stage for the 228th meeting of the ACS. Philadelphia is the epitome of old-meets-new; reminders of Philadelphia's historic past include the Liberty Bell and City Hall's statue of founder William Penn, and its future is represented by the glass-domed architectural splendour of the Kimmel Center for the Performing Arts.



Housed in the former location of the Reading Terminal Train Station, the Pennsylvania Convention Center offered lavish seating areas where the 14000 dele-

gates and exhibitors could discuss their thoughts on chemistry whilst pondering the myriad of art on display, including Evolution 2001 (inset) by Isaiah Zagar, creator of South Street's famous Magic Garden.

Some of the themes of the autumn meeting echoed the old/new harmony of the city: new strategies to treat diseases of the old. These included Alzheimer's disease and arthritis, as well as the consequences of the Western harder-faster-better lifestyle: obesity, cardiovascular disease, anxiety and depression. An array of anticancer

compounds and those for the treatment of hepatitis-B and -C were also presented; however the salient topic was the development of compounds to treat the effects of the burger 'n' fries culture.

In the antiobesity therapy symposium, Pfizer expostulated the potential of its acetyl-CoA carboxylase inhibitor CP-640186, an antidiabetic compound - first presented at the 64th meeting of the American Diabetes Association in June - as a therapy for obesity. The preclinical results presented demonstrated a significant and selective reduction in body fat; and the development of analogues, including the more potent CP-640188. In the same session, melanocortin-4 receptor (MC4R) agonists were presented by Amgen, as part of its concerted effort to develop antiobesity therapies following the presentation of melanocortin-1 receptor agonists at the 227th ACS meeting in the spring. The melanocortin-4 receptor is expressed in the hypothalamus and is involved in the regulation of appetite and energy homeostasis. These agonists decreased food intake in rodent models and had favourable pharmacokinetic properties.

Taisho introduced a series of piperazine derivatives also targeting the MC4R; however, in a deviation from the conventional application of the target, it disclosed MC4R antagonists, including MCL-0129. These hold promise for the treatment of anxiety and depression, with MCL-0129 exhibiting dose-dependent activity in numerous rodent models.

A series of compounds conceived via a collaboration between Arena and Taisho were discussed in both oral and poster sessions; ATC-0175 and ATC-065, both melanin concentrating hormone-receptor 1 (MCH-R1) antagonists were evaluated. These incorporate antiobesity, antidepressant and anxiolytic activity. Optimization of compounds in the series is ongoing and further in vivo pharmacology results will be presented at the Neuroscience 2004 meeting in San Diego in October.



Philadelphia City Hall

A new addition to Target data on *Pharmaprojects* was provided by Synaptic Pharmaceutical (a Lundbeck subsidiary), which disclosed SNAP-98529, an azo analogue in a series of galanin receptor 3 (GalR3) antago-

nists. Although a specific indication for this series of compounds was not disclosed, SNAP-98529 had high selectivity for GalR3 compared to GalR1 and GalR2, thus demonstrating potential as a therapy in treating undesirable cognitive and affective behaviours for which GalR3 has implicated involvement.

As with previous ACS meetings, the 228th invited a broad array of companies to disclose their current efforts and progress in the development of synthetic compounds. The meeting also provided the opportunity to meet with competitors and collaborators, and to share knowledge. Many of the delegates also reflected on the sad passing and celebrated the achievements of Dr David Robertson (1955-2003), the Texan discoverer of Lilly's blockbuster Cymbalta (duloxetine hydrochloride).

The 229th meeting of the ACS will be held in San Diego, CA, USA, 13-17th March 2005

Joanne Woodcock

14th Congress of the European Respiratory Society, Glasgow, Scotland, 3rd - 7th September 2004

The 14th Annual Congress of the European Respiratory Society (ERS) was held in Glasgow, Scotland, last month. With an estimated 14000 conference-goers, this meeting rivalled the scale of the traditionally larger American conferences. An audience of this size fully utilized the Scottish Exhibition and Conference Centre (SECC); the adjacent Clyde Auditorium (known locally as 'the armadillo'); and the nearby Moat House Hotel. Glasgow's ability to cater for such a large event highlights its transition from a heavily industrial city to an international business centre.

Subjects ranged from new research into respiratory devices to pharmaceuticals and epidemiology. Most oral presentations, symposia and posters were presented by medical and academic research organisations, but the pharmaceutical industry featured prominently in the exhibition hall and some companies sponsored evening symposia. Most of the information presented was additional clinical data for products that have recently reached the marketplace.

Novartis held a press conference to release new data from trials of omalizumab, a monoclonal antibody developed by itself, Genentech and Tanox, for the treatment of asthma. Omalizumab binds IgE, the antibody involved in triggering the hypersensitive immune response that results in the clinical symptoms of allergy. The Phase III trial, INNOVATE, involved patients with inadequately-controlled, severe, persistent asthma. Results showed that omalizumab significantly lowered asthma exacerbations in this patient population. Dr

Yamo Deniz of Genentech confirmed the next phase of development of this product: omalizumab has recently started enrollment in Phase II trials in the UK and the US, as a therapy for peanut allergy. It is the first IgE inhibitor to reach the marketplace, and has potential to treat all allergic diseases.

Altana presented results from the RECORD Phase III trial of the oral phosphodiesterase IV inhibitor roflumilast, showing additional evidence for use in the treatment of COPD. The trial revealed a dose-related response rate and confirmed the conclusions of previous studies which showed a reduction in COPD exacerbation rates. Furthermore,



Glasgow Clyde Auditorium

Altana reported Phase I trial results for the same drug, in which it was shown to be safe and well tolerated when administered with erythromycin. Successful clinical trials were also reported for cilomilast,

GlaxoSmithKline's new phosphodiesterase IV inhibitor which is awaiting approval in the US for the maintenance of lung function in COPD. Additional data from a previous Phase III trial demonstrated maintenance of expiration volume and reduced exacerbation rates in cilomilast-treated patients, when compared with placebo.

There were sporadic presentations of new data for developmental drugs, including LL-37, an LPS-binding peptide under development by OctoPlus for the treat-

ment of chronic upper respiratory tract infections. Preclinical studies of this molecule proved it to be a chemo-attractant of eosinophils and neutrophils, and demonstrated that the chemotaxis could be inhibited by certain formyl peptide antagonists. Another early-stage product is Ruzam, a lipopeptide extract from a thermophilic strain of *Staphylococcus aureus*, and a new entry to *Pharmaprojects*. It is under development by the Pulmonary Research Institute, based in Moscow, Russia,

for the treatment of asthma and allergic rhinitis, and has shown promising results in Phase II trials in both indications.

The 15th Annual Congress of the European Respiratory Society will be held in Copenhagen, Denmark, 17th - 21st September 2005.

Lynne Kincaid

New Drug Development Strategies

Interleukin-10 antagonist

Interleukin 10 (IL-10) is an anti-inflammatory cytokine that has a role in controlling and dampening immune response. It suppresses the maturation and cytokine production of dendritic cells, reduces lytic activity of CD4 and CD8 cells, and prevents the activation of naïve T-cells and their polarization towards γ -interferon-producing effectors. These processes are important to switch off inflammatory mechanisms and to protect the body from hyperactive immune responses.

Conversely, the action of IL-10 has been implicated in the pathogenesis of infectious disease; IL-10-induced CD4 and CD8 suppression is suspected of increasing mycobacterial resistance in tuberculosis. Intriguingly, cytomegalovirus is thought to subvert the induction of antiviral responses by the production of an IL-10 homologue.

Tumour cells deactivate monocytes and decrease their secretion of proinflammatory factors, TNF- α and IL-12, and increase production of IL-10. Inhibition of IL-10 is a promising new approach to the treatment of cancer as it will increase the function of the immune system, giving the body a better chance to heal itself.

Neovacs is developing an anticancer vaccine that induces the production of antibodies against interleukin 10.

Interleukin-10 antagonists are coded on *Pharmaprojects* as **IL-10-**.

SDF-1 antagonist

Stromal cell-derived factor 1 (SDF-1) is a pleiotropic α -chemokine which binds to G-protein coupled CXCR4 and plays an important role in the trafficking of CXCR4-expressing haematopoietic and lymphopoietic cells. It is involved in the homing of CXCR4-expressing cells to related organs and their retention at that site. The processes of chemoattraction, locomotion, and adhesion are all essential to tumour metastasis.

SDF-1 has recently become a popular target for research into metastasis, and has been implicated in the metastasis of head and neck squamous cell carcinoma to the lymph nodes. It has also been shown to reduce apoptosis in acute myelocytic leukaemia cells. Thus, SDF-1 antagonists have the potential to prevent or decrease metastasis.

Pharmaprojects has a number of related entries that act upon SDF-1's receptor, CXCR4 (see pharmacology CK-CR-4-). These include HIV therapeutics and a similar anticancer therapy.

Chemokine Therapeutics is developing CTCE-9908, an SDF-1 inhibitor, for the treatment of grade 2-3 metastatic lung, breast, uterine or bone cancer.

SDF-1 antagonists are coded on *Pharmaprojects* as **CK-SD-1-**.

β 1 integrin antagonist

β 1 integrins are cell-surface receptors that mediate cell-cell and cell-matrix interactions. Cell-matrix interactions mediated through the β 1 integrin pathway help regulate cell survival, proliferation, adhesion and migration. Disrupting abnormal cell-ECM interactions by inhibiting β 1 integrin is an effective mechanism for advancing breast cancer therapy and shows promise as a means of enhancing the therapeutic efficacy of ionizing radiation.

Research has shown that β 1 integrin specifically modifies response to chemotherapy in lung, leukaemia, and colon cancers. In vitro studies have demonstrated that it also increases the sensitivity of tumours to radiation. Studies with mice implanted with invasive human breast cancer cell lines show that antibodies against β 1 integrin inhibit formation of tumours and significantly

enhance apoptosis and decrease proliferation. In addition, when 3-D cultured malignant cell lines are treated with ionizing radiation combined with anti- β 1 integrin therapy, the effects are enhanced by up to 50% compared to the use of ionizing radiation alone.

Berkeley Lab is developing β 1 integrin antagonists, for sensitizing cancer to ionizing radiation.

β 1 integrin antagonists are coded on *Pharmaprojects* as **ITG-B1-**.

tRNA synthetase inhibitor

Transfer RNA (tRNA) molecules are short-chain RNA molecules, active during cell replication. During protein translation, a tRNA molecule attaches to an amino acid and acts as an enzyme to catalyse the formation of protein strands. The enzymes which catalyse the attachment of each tRNA to its amino acid are aminoacyl tRNA synthetases.

In most human cells, there is a different synthetase enzyme for each amino acid (that is, 20 synthetases in all). However, in bacteria, the same synthetase is responsible for coupling more than one amino acid to the appropriate tRNAs. Furthermore, bacterial tRNA synthetases are different in structure from their human equivalents, enabling the designing of inhibitors with much greater affinity for the tRNA synthetase enzymes found in bacteria than those in human cells.

Replidyne is developing tRNA synthetase inhibitors for the treatment of bacterial infections.

tRNA synthetase inhibitors are coded on *Pharmaprojects* as **SY-RNA-**.

Sheddase inhibitor

The signaling pathways that utilize the receptors and ligands of the epidermal growth factor receptor (EGFR) family play a key role in the growth and survival of multiple tumour types, including breast, colorectal, and non-small cell lung cancers, and are often overexpressed in cancer cells. EGFR family ligands must be cleaved from larger, cell-attached proteins in order to be released in their soluble active form. EGFR family receptors are also subject to cleavage, which in this case results in a constantly activated receptor that does not require the presence of the corresponding ligand for signalling. Sheddase is a protease which appears to act to cleave EGFRs and their ligands, thus contributing to

the growth and metastasis of breast and possibly other cancers. Inhibition of sheddase could interfere with epidermal growth factor receptor family signalling in multiple tumour types, and consequently would be of use as an anticancer therapeutic.

Incyte is developing INCB-7839, a small, orally-bioavailable sheddase inhibitor, for the treatment of cancer.

Sheddase inhibitors are coded on *Pharmaprojects* as **PR-SH-**.

Bombesin receptor 3 antagonist

Bombesin is a tetradecapeptide originally obtained from the orange and yellow skin of two toad species, *Bombina bombina* and *Bombina variegata*.

Human bombesin receptor subtype 3 (BRS-3) is an orphan receptor, found predominantly in the central nervous system and gastrointestinal tract. The role of BRS-3 in physiological or pathological processes is obscure due to the lack of selective ligands or identification of its endogenous ligand. Bombesin-like peptides are involved in the growth regulation of various cancers. Expression of BRS-3 in human tumours was found preferentially in the neuroendocrine tumours of the lung (bronchial carcinoids, small-cell lung cancer cell lines and large cell neuroendocrine carcinoma), indicating that BRS-3 could serve as a therapeutic target for human lung carcinoma.

BioFocus is investigating a series of human receptor bombesin 3 subtype antagonists for the treatment of lung cancer.

Bombesin receptor 3 antagonists are coded on *Pharmaprojects* as **BOMB-3-**.

Bruton's tyrosine kinase inhibitor

Named after a doctor in the US Army, Colonel Ogden C. Bruton, Bruton's tyrosine kinase (Btk) is an intracellular kinase expressed in B-lymphocytes, mast cells, and macrophages. It plays critical roles in immune system development and function, being essential for activation of inflammatory pathways through the B-lymphocyte receptor, as well as for macrophage activation and IgE-mediated mast cell activation, which leads to the release of TNF- α and other inflammatory cytokines. Because B-lymphocytes and macrophages play central

roles in autoimmunity and inflammation, Btk represents a compelling target for multiple autoimmune and inflammatory diseases, including rheumatoid arthritis, SLE, and vasculitis. Moreover, Btk's dual role in both mast cell and B-cell activation also makes it a highly attractive target for a novel therapeutic for the treatment of asthma. Thus, a Btk small molecule kinase inhibitor could have broad applications across multiple large clinical indications.

Cellular Genomics is developing a small-molecule Btk inhibitor for the treatment of autoimmune and inflammatory diseases. It has potential in rheumatoid arthritis, systemic lupus erythematosus, vasculitis and asthma.

Bruton's tyrosine kinase inhibitors are coded on *Pharmaprojects* as **KI-TY-BTK-**.

Companies New to *Pharmaprojects*

Aerovance is a biopharmaceutical spin-off from Bayer, focused exclusively on the development and commercialization of biologics for the treatment of respiratory and inflammatory diseases.

Danish firm **ALK-Abello** specializes in treatments for common allergies, including grass pollen allergy and house dust mite allergy. These use fast-dissolving sublingual tablet technology, thought to be advantageous as the treatment can be administered by the patients themselves at home, unlike subcutaneous injections, and dosage is more accurate than with sublingual drops.

Alzhyne is a biopharmaceutical company investigating the treatment of Alzheimer's disease. Its proprietary technology is based on the discovery that a series of small peptide antagonists can simultaneously reduce the neurotoxicity and enhance the clearance of β -amyloid from the brain.

Amazon Biotech primarily develops immune modulating drugs, based on the plants used in the traditional medicines of populations indigenous to the Amazon basin.

Founded in 2001, **Amphora** uses small-volume, high-throughput, microfluidics-based assays to validate SARs of pharmaceutically-relevant biological targets, including kinases, proteases, ion channels and G-protein coupled receptors, to construct fully-characterized drug-like libraries.

Tokyo-based **Aphoenix** is a chemical genomics company, using its proprietary 'reverse targeting' technology to develop drugs against novel targets. Drugs or other compounds with unknown mechanisms of action are used as probes for target discovery, using proprietary bead affinity chromatography methods. Resulting validated targets are then used as the subjects of collaborations or drug development projects.

APT Therapeutics is developing enzymatic anti-platelet therapeutics using its proprietary knowledge-

based and computer-aided drug discovery and optimization technology. Core areas of this include protein informatics, protein engineering and chemoinformatics, and resulting drugs are intended for the treatment of vascular occlusive diseases such as stroke, pulmonary embolism, deep vein thrombosis, acute coronary syndrome, peripheral arterial occlusion and myocardial infarction.

Auvation is developing therapeutics and diagnostics for cancer and other diseases, based on intellectual property relating to cytochrome P450 and angiogenesis control. The company was originally formed for the licensing of intellectual property related to the CYP1B1 tumour marker, from the University of Aberdeen, the UK. Auvation also conducts contract research, and licenses out tumour-associated antigen targets isolated from proprietary human tumour tissue banks.

AviGenics is a Greek company, specializing in protein-based therapies using its avian biotechnology. It uses proprietary vectors and microinjection to produce therapeutic proteins in the eggs of transgenic birds. AviGenics operates in three distinct business areas; improving versions of marketed therapeutics, developing new therapeutics, and co-developing partnered therapeutics whereby AviGenics is able to offer the avian biotechnology.

Beijing Tri-Prime Genetic Engineering is a Chinese biotechnology company engaged in the development, production and commercialization of biomedical products and technology, including genetically-engineered medicines, vaccines and diagnostic reagents, as well as the related technology, trade and technical services.

Berolina Drug Development (BDD) is a small life-science company based in Berlin, Germany, developing improved drugs from existing products using its atomic substitution platform. Compounds improved by the platform are then patented as NCEs. BDD is also active in three other areas; new indications for existing drugs, developing innovative products, and contract licensing for generics.

Cellular Genomics aims to develop signal transduction-based small-molecule drugs through comprehensive integration of biology, chemistry and informatics. It has proprietary kinase-focused compound libraries and chemical genetics technology.

Chipscreen has a proprietary chemical genomics approach to accelerate the discovery of new small-molecule medicines from its collection of natural products, traditional Chinese medicines and synthetic chemical libraries. It also provides services, including assay development, microarray analysis and combinatorial chemistry.

Compugen, a genomics-based drug and diagnostic discovery company, increases the probability of successful development of novel drug and diagnostic products by incorporating ideas and methods from mathematics, computer science, and physics into the disciplines of biology, organic chemistry, and medicine.

Creabilis Therapeutics investigates novel therapeutics through research into DNA-binding proteins. Its proprietary technology is directed firstly toward the generation of a series of bent duplex DNA/PNA hybrids or DNA/PNA chimeras or PNA sequences, and secondly to the identification of new DNA-binding protein targets.

Cologne, Germany-based **DIREVO Biotech** specializes in the screening-based directed evolution of genes and proteins. The company has worked on proprietary technology to allow the efficient and accurate designing of proteins. DIREVO creates and optimises proteins for use in industrial, agricultural and personal care, in addition to its protein therapeutics interests.

DMI BioSciences is a biopharmaceutical company engaged in the discovery and development of small-molecule and peptide-based pharmaceuticals and biomarkers for acute and chronic inflammation. DMI focuses on immunologic, vascular and CNS diseases, including acute coronary syndrome, multiple sclerosis, Alzheimer's disease, asthma and cancer.

Erimos examines small molecules, particularly for viral infections and cancer. The company has licensed several patents from Johns Hopkins University, Baltimore, MD, the US, and intends to conduct early-stage development in-house, and seek partners at Phase II for late development.

Halozyme has a pipeline of recombinant human enzymes for the treatment of infertility, cancer and ophthalmic diseases. The company researches recombinant hyaluronidase in particular, as an alternative to animal-derived products with associated risks. Halozyme intends to outsource manufacturing, marketing and legal activities.

IC-MedTech (Indian Creek Medical Technologies) is dedicated to the development of novel technologies and biotherapeutics for the treatment of cancer.

Intercept Pharmaceuticals is focused on the creation of small-molecule drugs for the treatment of chronic liver and metabolic diseases. The company intends to lead in the advancement of drug candidates which act on farnesoid X receptors.

Israeli firm **Jexys Pharmaceuticals** is a private company developing drugs that inhibit MAP kinase target proteins. It has developed a novel, high-throughput technology system in yeast allowing cost-effective in vivo drug discovery.

LifeCycle Pharma is a Lundbeck spin-off developing drug formulations with improved water solubility and oral bioavailability. LifeCycle's MeltDose technology involves formation of tablets from solid solutions in a melted carrier, using no water or organic solvents. LifeCycle is developing internal products to the preclinical proof-of-concept stage, followed by out-licensing for clinical development, and will also undertake reformulation of in-licensed products.

Momenta Pharmaceuticals is part of the ever-expanding Cambridge, Massachusetts biotech cluster. Its putative therapeutic products are based on complex sugars; Momenta's proprietary technology allows the company to correlate specific sugar sequences with biological activity.

Mpex specializes in antibacterials with activity against multidrug-resistant pathogens, particularly for hospital- and community-acquired infections. It is investigating compounds which inhibit bacterial resistance mechanisms, in order to increase the activity of existing broad-spectrum antibiotics, particularly for Gram negative bacterial pathogens.

Neurophoxia is a pharmaceutical company concerned with the discovery and early-stage development of treatments for severe neonatal disorders. It is affiliated with the Wilhelmina Children's Hospital and the University Medical Centre, Utrecht, the Netherlands, and will seek partnerships with larger pharmaceutical companies for late-stage product development.

NexBio is a two-year-old biopharmaceutical company, developing broad-spectrum prophylactic and therapeutic anti-infectives to combat life-threatening respiratory diseases, including influenza and SARS.

Novagali Pharma is a pharmaceutical company which develops innovative drug delivery technologies for use in ophthalmology and oncology. The company's technology platform is based on cationic nanoemulsions which can be applied in various delivery applications.

PBL Therapeutics is a biotechnology company evaluating next-generation interferon molecules. Using its discovery platform, it can identify interferon variants that are produced naturally in cancer cells. It then formulates these, using its SuRe-PD technology to deliver them locally and release them over time. It also has phosphorylation technology, used primarily to radiolabel monoclonal antibodies.

PediaMed Pharmaceuticals is a pharma company specializing in paediatric medicine. Childhood respiratory, gastroenterological and central nervous system diseases are the main focus of the firm, with anti-infective drugs for the treatment of paediatric patients also on the agenda.

Established in 2000, **Phico Therapeutics** is developing a novel platform technology, SASPject, which has the potential to produce antibacterials active against all species of bacteria. The technology combines a very broad spectrum antibacterial protein (SASP) with a delivery vector that can be programmed to target selected bacteria.

Portola Pharmaceuticals is a spin-off of Millennium Pharmaceuticals, and focuses on novel therapeutics for the treatment and prevention of severe cardiovascular diseases, through comprehensive understanding of platelet physiology and vascular thrombosis.

Proton Therapeutics intends to aid the treatment of vascular diseases using proprietary vascular remodelling technology. This involves the use of agents that modify the extracellular matrix of blood vessels, leading to immediate and persistent vessel enlargement.

Sirtris is investigating the biology, biochemistry and regulation of class III protein deacetylases, known as sirtuins, for the treatment of metabolic diseases.

Spherics, a spin-out from Brown University, the US, focuses on the application of its proprietary bioadhesive drug delivery systems (BDDS) to develop significantly-improved therapies in large pharmaceutical markets. Spherics has developed a number of complementary advanced drug delivery technologies mainly targeting oral delivery: Bioadhesive, biocompatible, and bio-erodable polymer-based spheres for drug encapsulation; Bioadhesive enhancers and coatings; and Phase Inversion Nanoencapsulation (PIN), a process to create minute drug carriers for systemic absorption of difficult to absorb drugs.

Symbigene hopes to improve the cost-benefit profiles of biopharmaceutical products using its Symbiotix and Oncomax technology platforms. Its technologies take advantage of the microorganisms that naturally inhabit organs within the human body and benefit human health.

French company **Vaxon Biotech** was established in January of this year to develop innovative therapeutic vaccines for the treatment of cancer; especially prostate cancer. It is developing modified cell-surface antigens to stimulate the immune system.

Mergers, Acquisitions, Name Changes and Joint-Ventures

In the largest and most dramatic change in the industry this year, European pharma giants **Sanofi-Synthelabo** and **Aventis** (including **Aventis-Pasteur**), have merged. The resulting company - the third largest pharmaceutical firm in the world - is named **Sanofi-Aventis**.

The world's largest biotechnology company, **Amgen**, has acquired cell-signalling specialist **Tularik**.

Canadian company **Micrologix Biotech** has acquired the US-based **Mitokor**, also a biotechnology firm.

Frankfurt, Germany-based **MediGene** has acquired its compatriot company **Munich Biotech**.

Protein Therapeutics has been acquired by Kentuckian paediatric specialist firm **Pediamed Pharmaceuticals**.

Belgian chemicals and pharmaceuticals firm **UCB** has acquired the UK's largest biotech company, **Celltech**.

Cephalon has acquired **CIMA LABS**, which will remain a wholly-owned subsidiary.

Epix Medical has changed its name to **Epix Pharmaceuticals**, as its lead pharmaceutical compound is approaching commercialization.

Galen has changed its name to **Warner-Chilcott**. Its UK subsidiary will remain known as Galen.

Hudson Health Sciences has changed its name to **Hana Biosciences**, following a restructuring of the company.

Northern Therapeutics is a 50%-owned subsidiary of **United Therapeutics**, specializing in gene therapy.

Exhibition Calendar

Our team of experienced account managers will be demonstrating and promoting the full capabilities of *Pharmaprojects* and other online services from PJB Publications Ltd 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:**

Alana Berger at alana.berger@pjbpubs.com

Damian Parker at damianp@pharmabooks.com

Mr T Hirata at info@shiryoken.co.jp

Date	Conference	Details
5-7 October	Biotech Forum + ScanLab	Bella Center, Copenhagen, Denmark For information visit www.biotechforum.se/conference
18-19 October	FT Global Pharmaceutical Conference	Hotel Intercontinental, London, UK For information visit www.ftconferences.com/healthcare
20 October	FT Global Biotech Conference	Royal Garden Hotel, London, UK For information visit www.ftconferences.com/healthcare
18-20 October	Drug Discovery to Manufacturing: Global Partnering & New Science	Renaissance Mumbai Hotel & Convention centre - Mumbai, India For information visit www.drugdisc.com/USC3067
15-17 November	Phase I Clinical Trials	DoubleTree Hotel Philadelphia, PA, USA For information visit www.ibclifesciences.com/3089
7-9 December	CPhI Worldwide & ICSE 2004	Brussels Expo, Brussels, Belgium For information visit www.ICSEexpo.com
9 December	Genesis IV - the UK's largest one-day biotechnology conference	Queen Elizabeth II Conference Centre - London, UK For information visit www.one-events.com or call Anita Howard on +44 (0)20 7801 0900

News Headlines

In order to help *Pharmaprojects* subscribers to get the most out of the database, the News Headlines highlight some of the most important developments that have occurred in the industry over the past month. These and other news headlines appear on the *Pharmaprojects* website. Please visit www.pjbpubs.com/pharmaprojects/weekly_news.htm to ensure you are updated with all the latest developments. This month's news includes:

- Two head trauma drugs granted orphan drug status
- TopoTarget to develop NeuroSearch's glioblastoma drug
- Joint-development candidates for transcription factor decoys sought
- German atomic substitution company seeking partners
- Ranbaxy's lead antimalarial enters Phase I
- Genmab gains orphan drug status for mycosis fungoides MAb
- Sumitomo confirms discontinuation of pimilprost
- Cellular Genomics finds novel target for autoimmune disease therapy
- Phase II trials for α -fetoprotein in RA
- Vesicare enters several EU markets
- Lilly's new antidepressant launched in the US
- Sankyo seeking partner for antifungal after Fujisawa pulls out
- First filing for a RapidMist formulation
- UK market entrance for Telzir
- Lyrica launch for Pfizer
- Serono licenses in two musculoskeletal drugs from ZymoGenetics
- Myriad Genetics' amyloid-lowering compound makes clinical phase advance
- US orphan drug status for antineoplastons
- Bayer and Schering-Plough in marketing deals
- Kyowa Hakko's asthma drug fails in Phase II

Also updated this month:

684 Products with Major Events	16 Discontinued Products
266 New Products	16 Licensing Deals
52 New Chemical Structures	3 Licences Discontinued
3 First Registrations	84 Licensing Opportunities
4 Registration Submissions	8 Novel Target Reported
3 First Launches	5 Target Identified

Products that have undergone Major Events can be located on the Web and CD-ROM versions by clicking on the alert button of the Standard Search options. An additional **3631** entries have had minor changes, giving a total of **4315** entries updated this month.

Announcements

Our London office has moved!

Please note that as of 1 September 2004, *Pharmaprojects* is based in new offices. Our new address is: Telephone House, 69-77 Paul Street, London, EC2A 4LQ. New telephone and facsimile numbers are below. Our e-mail addresses are unchanged.

Helpdesk	Marketing	Editorial
Telephone: +44 (0) 20 7017 6868	Telephone: +44 (0) 20 7017 6900	Telephone: +44 (0) 20 7017 6878
Facsimile: +44 (0) 20 7017 6905	Facsimile: +44 (0) 20 7017 6880	Facsimile: +44 (0) 20 7017 6898



An International Conference for Attendees from the USA, Europe and Asia-Pacific

October 18-20, 2004 • Renaissance Mumbai Hotel & Convention Centre • Mumbai (Bombay), India • www.drugdisc.com

Search Tip of the Month - Use of NOT logic

A recent query from a subscriber involved an infrequently-used logic function: how to ensure that a specified term is *not* found by a search.

The client wanted to find out what proportion of the newly-formed Sanofi-Aventis pipeline was made up of New Active Substances, also known as New Molecular Entities. Essentially, this is a search for everything except previously-developed drugs that have been reformulated by Sanofi-Aventis.

This search uses Boolean logic. Boolean logic refers to the logical relationship among search terms, and is named after the Irish mathematician George Boole. Put simply, the NOT expression excludes the term it refers to from the search. Thus, changing the expression of the Therapy Grouping to "NOT" means the search below will be find all molecules under development for the first time.

The screenshot shows the Pharmaprojects V5.1 (Web) interface. The search criteria are defined in a table below the search tree:

Hits	And/Or	(...)	Group	Expression	Value	(...)
221			Company R&D Pipeline	=	Sanofi-Aventis	
28933	AND		Therapy Grouping	NOT=	Formulations	
=206						

Entries in *Pharmaprojects* which fall into the Formulations therapy grouping are those which have previously been developed, but have been reformulated to change their delivery; for example, to extend their release duration.

The NOT expression is little-used, but can be a very effective search tool.

To further refine the search to find only New Chemical Entities, add a further line:
AND Therapy Grouping NOT= Biotechnology Products.
 This will exclude molecules derived from biological sources.

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

Copyright Information

Copyright in this issue of *Update Analysis* is held by PJB Publications Ltd © 2004. You may copy this issue as many times as you wish in whole or part and in any format provided this is for internal use at the same mailing address as the one to which PJB has sent the copy you are reading.

Otherwise this issue is supplied on the same terms as apply to *Pharmaprojects*: save as provided herein, material may not be sent to any other part of the subscriber's organisation and save for any use authorised by those terms and conditions this material may not be reproduced, distributed, leased or resold or otherwise made available to any third party.

Further Information

For further information on any aspect of the *Pharmaprojects* service, or if you would like to receive the *Pharmaprojects Update Analysis* by e-mail to facilitate internal distribution, please contact your local agent or one of the following:

For editorial information contact:

Ian Lloyd Managing Editor, *Pharmaprojects*
Telephone +44 (0)20 7017 6886
Facsimile +44 (0)20 7017 6898
E-mail ian.lloyd@pjbpubs.com

For product information contact:

Hayley McKechnie Marketing Supervisor, *Pharmaprojects*
Telephone +44 (0)20 7017 6900
Facsimile +44 (0)20 7017 6880
E-mail hayley.mckechnie@pjbpubs.com

Elizabeth Cairns Editor, *Pharmaprojects Update Analysis*
Telephone +44 (0)20 7017 6863
Facsimile +44 (0)20 7017 6898
E-mail liz.cairns@pjbpubs.com