

Therapy Analysis—microRNA

Welcome to the monthly newsletter for *Pharmaprojects*, the Update Analysis. This issue contains an analysis of microRNA and the potential this holds as a therapeutic target, and we also review this year's BIO meeting. All the usual *Pharmaprojects* highlights follow, including details of seven new targets, and a selection of the free news stories published on our website in our News Digest section. This month's Search Tip shows you how to query *Pharmaprojects* to view entire therapy pipelines.

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Managing Editor Ian Lloyd

Editor Thomas Stirzaker

Subeditor Sophie Green

Writers Janet Beal
Amir Hakim

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MICRO-MANAGEMENT

How microRNA could revolutionize traditional thinking on targeted drug development

Perhaps this is a time for turning old ideas on their heads. Novelty may create value, but has been slow to create blockbusters. An accidental discovery can bypass years of painstaking research. And DNA may make RNA (sometimes) – but RNA can do a great many other things besides making protein. The Human Genome Project yielded data on hundreds of hitherto unknown proteins, ripe for investigation as therapeutic targets – but this was not the end of the story. Hidden among the previously-unfashionable realm of 'non-coding' sequences lay what may emerge as the real master-regulators of biological systems, opening up a whole new area for pharmaceutical R&D, and one which seriously challenges our preconceptions regarding specificity of drug targeting.

MicroRNA (also known as miRNA), once disregarded simply as a part of 'junk' RNA, was first encountered in 1993 by Victor Ambros and his colleagues Rosalind Lee and Rhonda Feinbaum at Harvard University, while studying developmental mutants of the nematode *Caenorhabditis elegans*. When homing in on a putative 'protein', *lin-4*, a sequence regulating heterochronic temporal control of development, the research team was surprised to find that *lin-4* was no protein, but actually a short hairpin RNA with powerful regulatory functions.

As with many seminal discoveries of this sort, the wider implications did not become immediately apparent. It was not until 2001 that short RNA sequences of the type discovered by Ambros's team were found to be widely distributed in many species, including *Drosophila* and humans, following extensive studies in Ambros's own group and the laboratories of David Bartel and Thomas Tuschl at the MIT, and the term 'microRNA' was coined. At that point it became apparent that these sequences, only 17-24 nucleotides long, were highly conserved, and had profound and complex regulatory functions in their host organisms. In 2005, it was conservatively estimated that miRNAs could influence the expression of 30% of all human genes, and latest calculations have predicted the presence of some 1,000 human miRNAs, around 500 of which have already been isolated, and a few have been characterized in considerable detail.

These sequences are produced within the cell by transcription from individual miRNA genes, from introns within protein genes, or from polycistronic clusters of closely related miRNA genes. The initial transcripts, pri-miRNAs, are several thousand bases long. These are then processed within the nucleus by a 'microprocessor complex' containing a double-stranded RNA-specific ribonuclease known as Drosha, and its binding partner Pasha, to

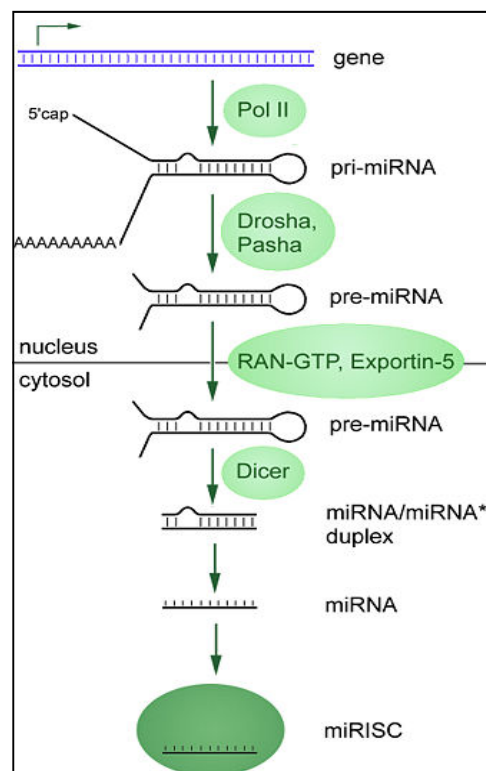


Fig. 1: An overview of microRNA processing in animals, from transcription to the formation of the effector complex

give hairpin RNA precursors known as pre-miRNAs, which are then transported to the cytoplasm using Exportin-5. Cleavage by the endonuclease Dicer results in a double-stranded miRNA, which is then incorporated into an RNA-induced silencing complex (RISC), similar to that involved in the related (but distinct) process of RNA interference. Once there, a single mature miRNA strand is selected and the other is degraded, and the mature strand is then in a position to manipulate gene expression (Fig 1).

The resulting active miRNAs down-regulate gene expression by translational repression and/or messenger RNA (mRNA) cleavage, mediated by the RISC, in a manner strikingly similar to the much-documented gene silencing/RNA interference effects of agents such as short interfering RNA (siRNA). However, although siRNAs also silence expression via RISC, there are some crucial differences from miRNAs. For instance, naturally-occurring siRNAs have not been documented in mammals, in contrast to the wide prevalence of endogenous miRNAs. And most notably, siRNAs are highly complementary to their target gene transcripts, whereas miRNAs are not – in fact, miRNAs only have complementarity in a crucial ‘seed’ region 2-8 bases long in the 5’ region. This can make it possible for some miRNAs to pair with hundreds of high- and low-affinity mRNA targets (one-to-many), and conversely, multiple miRNAs may target a single mRNA (many-to-one). Thus, the precise one-to-one specificities of siRNAs for their targets can be contrasted with much more far-reaching effects of a single miRNA on expression of many genes, with some individual miRNAs affecting entire pathways or disease mechanisms.

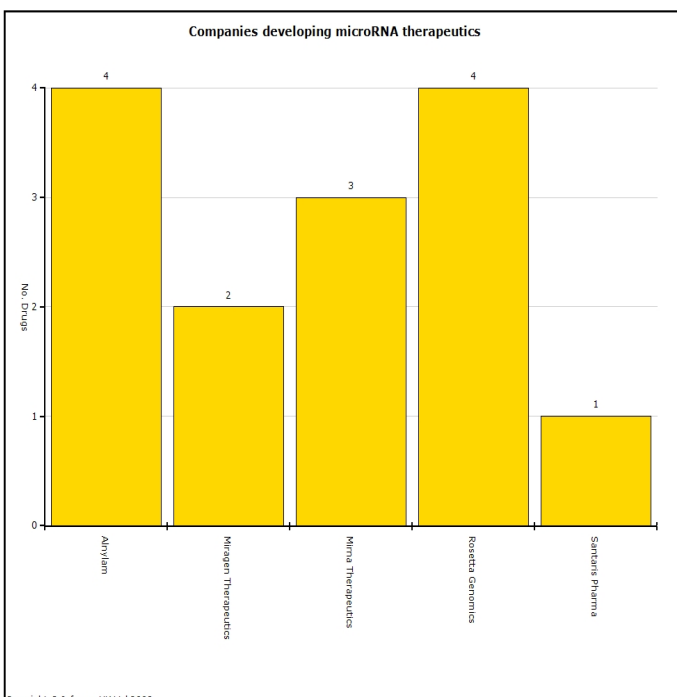
This intriguing natural mechanism seems to be evolutionarily ancient, having been detected throughout plant and animal systems in various forms, and even in viruses. The sequences involved appear to be highly conserved between individuals and indeed species, but their populations and compositions within cells correlate very strongly with specific cell or tissue

types, developmental stages and/or disease states. Thus, profiling of these populations as biomarkers should be a very powerful diagnostic and prognostic tool, and the technology for detecting and analyzing miRNAs within cells has already advanced rapidly to accommodate this possibility, with notable successes in the profiling of metastatic cancers. But what about their implications as therapeutic targets? To answer that, one must consider their natural function and how it may be exploited.

The function of a cell’s miRNA population may be compared to a ‘master-switch’ – but one involved in fine tuning rather than a crude on-off mechanism. Following transcription, the fate of a nascent mRNA transcript is not just dependent on its stability – it can be prey to one or more of the population of miRNAs within that particular cell, or none. The result is that even highly-transcribed genes may never be translated, their levels may be up- or down-regulated highly precisely, or translation may be allowed to proceed unhindered. Thus, in theory, inhibition of a particular miRNA linked to disease can remove the block against expression of a therapeutic protein – and conversely, administration of a miRNA mimetic can boost the endogenous miRNA population repressing a detrimental gene. However, just to complicate things, one must remember that blocking or boosting one miRNA may impact on expression of many genes rather than just one, some in completely different tissues or affecting entire pathways – giving a whole new dimension to the idea of ‘off-target effects’. Clearly this new branch of drug development requires a radical new way of thinking.

This last fact has not deterred a pioneering group of specialist companies from embracing the new development and tackling the finicky problem of creating viable therapeutic candidates – some miRNA inhibitors and some miRNA mimetics – in fields as diverse as cancer, cardiovascular disease, neurological disorders and viral infection. The drug candidates in question are all DNA-based therapeutics, since no anti-miRNA small molecules are yet on the radar. The new players in this select area have been fired up, maybe, by the high-speed development of therapeutic siRNAs – with the first siRNA candidate (bevasiranib sodium for wet AMD) reaching Phase III within four short years of initial research – and, amazingly, the first miRNA inhibitor has already reached the clinic, with more set to follow (Table 1).

The company with the honour of the first-to-clinic candidate is a Danish outfit with well-established credentials in the therapeutic DNA field – Santaris Pharma. Santaris, formed in 2003 by the long-established players Cureon and Pantheco (founded in 1998-99), is focused on the therapeutic applications of its proprietary DNA analogues, particularly its Locked Nucleic Acid (LNA) technology, which produces next-generation antisense oligonucleotide drugs with very high specificity and potency. Adapting this technology to target a miRNA, rather than a conventional gene, is one attractive route to generating miRNA inhibitors. This has resulted in a class of compounds referred to by Santaris as ‘LNA-antimiRs’, which function via an advanced antisense mechanism to block endogenous miRNAs. The lead LNA-antimiR is SPC-3649, which targets the liver-specific miRNA 122. This miRNA has the intriguing effect of binding to hepatitis-C virus (HCV) RNA and stimulating its replication – and thus blocking it opens up a brand-new avenue of HCV treatment. It has not escaped Santaris’ attention that this target miRNA is also involved in regulating genes implicated in hypercholesterolaemia – and indeed *in vivo* murine studies have confirmed the potential of



Graph 1: Distribution of the companies involved in microRNA therapeutics

SPC-3649 as a cholesterol-lowering agent. GlaxoSmithKline has an option on this project, which one presumes it must be monitoring with quite some interest.

Although Santaris can claim to be the first past the post to the clinic, it is by no means the longest-established specialist company in the miRNA arena. This distinction belongs to Rosetta Genomics, based in Israel and established in 2000 at the birth of the miRNA revolution. An early and far-sighted focus on high-throughput discovery and validation of miRNA sequences resulted in the integrated scanning of the entire human genome for miRNAs in 2005, and the company has now validated around 400 of the known human miRNAs. Rosetta has divided its interests between the development of miRNA-based diagnostic systems for cancer, already a lucrative area, and the development of its own pipeline of miRNA-based therapeutics, with both miRNA inhibitors and mimetics under scrutiny as drug candidates. The company has a formidable IP position, covering miRNA validation methodologies, specific sequences and therapeutic applications.

It would have been hard to keep the major players in the RNA interference and antisense fields out of a field which impinges so closely on their territory. In September 2007, Alnylam, which dominates the RNA interference field in terms of IP (notably holding the Tuschl II, Kreutzer-Limmer and Crooke patents), joined forces with Isis Pharmaceuticals, the historical leader in antisense-based therapeutics, to form the US-based joint venture Regulus Therapeutics, with the aim of exploiting miRNA targets in the development of both novel siRNA- and antisense-based therapeutics. Interestingly, one of the first key projects of the collaboration has been an antisense targeting miRNA 122, the same as that for Santaris' Phase I LNA project, for HCV and cardiovascular applications – although Regulus is also casting its net much wider into anti-inflammatory and anticancer fields. It is clear that Isis is perhaps hoping that this strategy may revive the previously flagging field of antisense therapeutics, which it pioneered with the only antisense product ever launched (fomivirsen sodium for CMV retinitis, back in 1998), but for which further true successes have remained elusive over two decades.

Generic Name	Originator	Status	Pharmacology	Target	Indication
SPC-3649	Santaris Pharma	Phase I	MicroRNA inhibitor	microRNA 122	Infection, hepatitis-C virus Hypercholesterolaemia
antagomirs, Alnylam	Alnylam	Preclinical	MicroRNA inhibitor	Unspecified	Unspecified
anti-inflammatory mi-croRNA,Reg	Alnylam*	Preclinical	MicroRNA inhibitor	Unspecified	Unspecified
anticancer microRNA, Regulus	Alnylam*	Preclinical	MicroRNA inhibitor	Unspecified	Unspecified
anti-miR-122 oligo, Regulus	Alnylam*	Preclinical	MicroRNA inhibitor	microRNA 122	Infection, hepatitis-C virus
miRNA inhibitors, Miragen	Miragen Therapeutics	Preclinical	MicroRNA inhibitor	microRNA 208a	Heart failure
miRNA mimetics, Miragen	Miragen Therapeutics	Preclinical	MicroRNA stimulant	Unspecified	Heart failure
prostate cancer miRNAs, Mirna	Mirna Therapeutics	Preclinical	MicroRNA stimulant	Unspecified	Cancer, prostate
AML miRNA therapy, Mirna	Mirna Therapeutics	Preclinical	MicroRNA stimulant	Unspecified	Cancer, leukaemia, acute myelogenous
nscL miRNA therapy, Mirna	Mirna Therapeutics	Preclinical	MicroRNA stimulant	microRNA let-7a-1	Cancer, lung, non-small cell
herpes virus therapy, Rosetta	Rosetta Genomics	Preclinical	MicroRNA inhibitor	Unspecified	Infection, Epstein-Barr virus Infection, herpes simplex virus
miR-34a mimetics, Rosetta	Rosetta Genomics	Preclinical	MicroRNA stimulant p53 stimulant Apoptosis agonist	microRNA 34a tumour protein p53	Cancer, liver
hepatitis-C therapy, Rosetta	Rosetta Genomics	Preclinical	MicroRNA inhibitor	Unspecified	Infection, hepatitis-C virus
HIV therapy, Rosetta	Rosetta Genomics	Preclinical	MicroRNA inhibitor	Unspecified	Infection, HIV/AIDS

*Alnylam/Isis Pharmaceuticals joint-venture

Table 1: Details of microRNAs currently under development

Aside from these major players, start-ups keen to broadcast their specialization in miRNA have already begun to appear. It must have been quite a coup for a company to secure the highly desirable (and descriptive) name of Mirna Therapeutics – and this Texas-based concern has focused its efforts on the development of miRNA mimetics rather than inhibitors, concentrating on cancers where the targeted miRNAs are naturally down-regulated. And hot on its heels, another US start-up, Miragen, is carving a niche for itself in the contrasting area of cardiovascular drugs, developing both miRNA inhibitors and mimetics, with an initial focus on heart failure. It will be interesting to see whether the pipelines of these companies, and the inevitable further start-ups to follow, can compete with the larger players.

In the chequered history of nucleic acid therapeutics, many 'next-big-thing' technologies have come and gone, and only a handful of therapeutics have struggled through to the market. Despite over two decades of intense research effort, only two vector-based gene therapies have ever been launched (one in China, one in the Philippines), and the track record for therapeutic oligonucleotides is equally disappointing – one antisense drug and one aptamer. However, the advances in DNA delivery technology resulting from this massive research effort have not been in vain – the lack of visible success on the market belies an increasingly robust late-stage pipeline for gene and oligonucleotide therapies – and certainly the rapid progress of a siRNA therapeutic to Phase III development within a four-year space would never have been achieved with 'old' oligonucleotide technologies. Thus it may be a prime time for miRNA inhibitors and mimetics to succeed on the back of these advances.

On the flip side, the very mechanism by which miRNA operates is doubtless destined to turn a few drug development ideas upside-down. The relentless emphasis over the last few decades on increased precision in drug targeting as being the most desirable way forward could certainly be revisited – the smallest fragments of DNA may have the most profound and far-reaching implications in fine-tuning and control in multiple tissues and disease processes. Perhaps we should have been looking *between* the genes all along, rather than directly at them.

Janet Beal

Image Courtesy of Narayanes under the GNU free documentation license 1.2

Search strategies

In Drug Profile Search

[Any Pharmacology Description] = microRNA mimetic
OR [Any Pharmacology Description] = microRNA inhibitor

Graph By: Originator

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

(You would if you read RAJ Pharma)

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Meeting Report

BIO Biotechnology Convention, San Diego, US, 17th-20th June 2008.

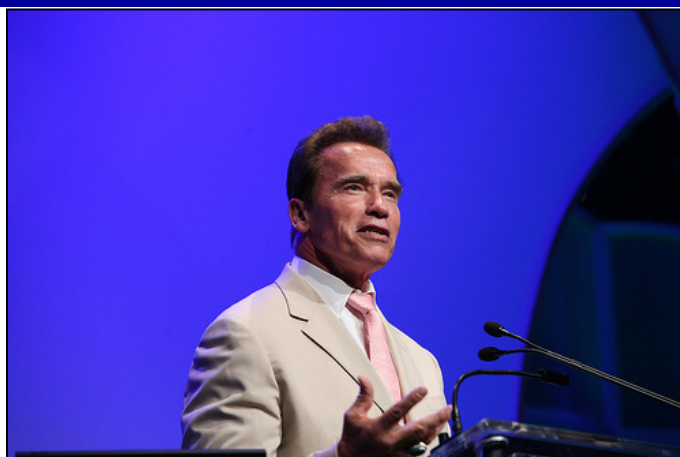
The world's largest and most anticipated biotechnology event, BIO 2008, was held in California, attracting more than 20,000 attendees. With nearly half of all spending on biotech research and development occurring in California, a staggering US\$4.3 billion in 2007, it was only fitting to hold this event in downtown San Diego.

BIO 2008 certainly pulled out all the stops. This year, the event kicked off with a spectacular firework display and welcome reception on board the USS Midway, America's longest serving naval ship, followed by enchanting animal shows at the world-famous San Diego Zoo. And if that was not enough, there was also a block party on 5th Avenue in the glamorous Gaslamp Quarter.

Once again there was an all all-star keynote line up, with speeches from Dr Craig J. Venter, President of the Venter Institute, Colin Powell and the governor of California, Arnold Schwarzenegger. First up, Dr Venter discussed the translation of his early successes of mapping the genome into potentially life-saving breakthroughs. He was followed by the star attraction, Gov. Schwarzenegger, who praised the world's biotechnology industry particularly for tackling currently untreatable diseases. He urged the BIO community to speed up the translation of research and discovery into meaningful patient-relevant advances. He ended with a heart-rending account of his father-in-law's battle with Alzheimer's disease, stating "I've witnessed the disease first hand, along with millions of others, and know that changes need to be made".

A topic that resonated throughout BIO was stem cell research and its huge potential. The capacity of stem cells to differentiate into a diverse range of specialized cell types to treat diseases that cause death of life-sustaining cells is rapidly becoming a driving force in biotechnology and a central focus in medicine. Amongst the first to present was NOXXON Pharma, an early stage biopharmaceutical company boasting a pipeline of novel and highly potent therapeutics capable of blocking protein-protein interactions, known as spiegelmers. Spiegelmers are synthetic L-nucleic acids, mirrors of natural D-nucleic acids, that bind to their target molecules with incredible specificity, with the added advantage of being biostable. In addition, they combine the favourable characteristics of both antibodies and small molecules, and are non-immunogenic and non-toxic. NOXXON has multi-year drug discovery collaborations with Pfizer and Hoffmann-La Roche, and intends to enter its first clinical trials in the 1st half of 2009 in two indications.

Representing the diversity of biotech on show was Magforce, a company developing anticancer nanoparticles coated with an intelligent aminosilane structure which provides stabilization against agglomeration and sedimentation, thus maximizing particle concentration within a tumour. These nanoparticles then heat the tumour from within, rather than introduce a heat source from outside the body, helping to ensure surrounding healthy tissue is spared. The company reported on the success of the first clinical study in March 2003 in 14 patients with malignant brain tumours, and has since been pushing the research forward into many other indications. Currently it is in 2 Phase II trials for glioblastoma multiforme and prostate carcinoma, with filings expected in 2009.



Governor Arnold Schwarzenegger treated delegates to a rousing and personal speech

Also presenting was DSX Therapeutics, an early-stage biotech outfit developing monoclonal antibodies to treat sepsis. If successful, it will have the first pharmaceutical to treat the early-stage pathology of sepsis and tap into a US\$19 billion annual therapeutic market. Whilst conducting IVD clinical trials, DSX discovered plasma microvesicle-associated particulate inducible nitric oxide synthase (iNOS) was only present in the plasma of septic patients. In further preclinical studies, isolated iNOS-containing microvesicles from septic patients induced hemodynamic collapse, thus confirming particulate iNOS as a therapeutic target. Additionally, administration of a lead candidate, a chimaeric anti-iNOS antibody, rescued up to 80% of challenged animals from death by sepsis. This antibody is currently in preclinical development with Phase I safety studies planned.

Profectus BioSciences captivated the audience with its breakthrough antiviral therapy that combines antiviral agents with specific immune-modulating drugs to solve challenges that ultimately lead to therapy failure, such as adverse events and drug resistance. Currently there are two platforms in the programme, namely antivirals and cell cycle inhibitors, using both antibody and small molecule approaches. Profectus, established in 2004, primarily focuses on developing cutting-edge products and technologies for HIV/AIDS.

BIO is renowned for record-breaking numbers and this year was no exception. There were more than 2,100 companies presenting, and over 208,000 sq. feet of exhibition space, the largest ever at the convention. And at the centre of it all were the 14,500 one-on-one partnering meetings. The comprehensiveness of BIO 2008 certainly surpassed all expectations and next year we hope that the resounding success that is BIO will be back.

Amir Hakim

The next BIO International Convention will be held May 17-20 2009 at the Georgia World Congress Center, Atlanta, Georgia, the US.

New Targets

klotho beta

Klotho beta (KLB) is a member of the glycosidase I superfamily. It is expressed in the liver, pancreas and adipose tissue and is thought to negatively regulate bile acid synthesis through mediating the interaction of FGF-15 with FRG receptor 4. Research has also suggested a role in lipid metabolism as a cofactor for the interaction of FGF-21 with FGF Receptor 1c in adipocytes.

Amgen is developing recombinant FGF-21 which activates FGF receptor tyrosine kinase and beta klotho for the treatment of obesity, steatohepatitis and insulin resistance.

Klotho beta belongs to the **Enzyme** Target Family Group. Its Entrez Gene ID is **152831**.

glutaminyl-peptide cyclotransferase (glutaminyl cyclase)

More commonly known as glutaminyl cyclase, this transferase converts glutaminyl peptides to cyclic pyroglutamyl peptides and is responsible for the presence of pyroglutamyl residues in many neuroendocrine peptides.

Probiodrug is developing glutaminyl cyclase inhibitors for the treatment of Alzheimer's disease.

Glutaminyl cyclase belongs to the **Enzyme>Transferase** Target Family Group and its EC number is **2.3.2.5** Its Entrez Gene ID is **25797**.

Glutaminyl-peptide cyclotransferase inhibitors are coded in Pharmaprojects as TR-GLU-CYC-

prominin 1

Also known as CD133, prominin 1 is a pentaspan transmembrane glycoprotein. It was initially found to be expressed on primitive hematopoietic stem and progenitor cells and retinoblastoma. No naturally-occurring ligand has been found for CD133.

ImmunoCellular Therapeutics is developing peptide vaccines that elicit a T-cell response targeting CD133-positive cancer stem cells, for the treatment of gliomas.

Its Entrez Gene ID is **8842**.

nonstructural polyprotein, Norwalk virus

This protein is a viral protease similar to the picornavirus 3C protease and cleaves the first ORF polyprotein into non structural proteins.

Microbial Novoteqs is developing inhibitors of Norwalk virus 3CL protease.

Its Entrez Gene ID is **1491970**.

triggering receptor expressed on myeloid cells 2

More commonly referred to as TREM2, this membrane protein forms a receptor signalling complex with TYRO protein tyrosine kinase binding protein (TYROBP or DAP12) and triggers an immune response in macrophages and dendritic cells. Loss of function mutations in either TREM2 or TYROBP are a known cause of polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOS).

Amgen is developing recombinant FGF-21 which activates FGF receptor tyrosine kinase and beta klotho for the treatment of obesity, steatohepatitis and insulin resistance.

Klotho beta belongs to the **Enzyme** Target Family Group. Its Entrez Gene ID is **152831**.

CD300 molecule-like family member g

Like other members of the CD300L family, CD300 molecule-like family member g (CD300LG or TREM4) is a type I cell surface glycoprotein widely expressed on haematopoietic cells. Research suggests IgA and IgM as possible ligands.

BioXell is developing therapeutics that target CD300LG for the treatment of inflammatory, neurodegenerative and metabolic disorders.

CD300LG belongs to the **Receptor** Target Family Group. Its Entrez Gene ID is **146894**.

CD300 molecule-like family member b

Like other members of the CD300L family, CD300 molecule-like family member b (CD300LB or TREM5) is a type I cell surface glycoprotein widely expressed on haematopoietic cells. Research has shown interactions with TYRO protein tyrosine kinase binding protein (TYROBP or DAP12).

BioXell is developing therapeutics that target CD300LG for the treatment of inflammatory, neurodegenerative and metabolic disorders.

CD300LG belongs to the **Receptor** Target Family Group. Its Entrez Gene ID is **124599**.

New Drug Development Strategies

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

Fibroblast growth factor receptor tyrosine kinase stimulant

Amgen is developing fibroblast growth factor receptor tyrosine kinase stimulants as a treatment for obesity, steatohepatitis and insulin resistance.

Fibroblast growth factor receptor tyrosine kinase stimulants are coded in *Pharmaprojects* as **KI-GFFN+**.

CD-91 antagonist

Ophthalmopharm is developing CD-91 antagonists as a treatment for age-related macular degeneration.

CD-91 antagonists are coded in *Pharmaprojects* as **CD-91-**.

Companies New to *Pharmaprojects*

AdAlta is a biotechnology company, spun out from EvoGenix, focusing on the discovery and development of peptide diagnostics and therapeutics.

A&G Pharmaceutical is engaged in the development of cancer-specific targets with therapeutic and diagnostic uses.

Activus Pharma combines organic chemistry, biological redox measurement and nano-particulation technology for creating new therapies for the control of diseases.

Alopexx is developing novel products for the treatment and prevention of MRSA and other serious infections.

Altheus Therapeutics identifies and implements pharmaceutical strategies for the treatment of inflammatory bowel disease.

Amulet Pharmaceuticals is focused on developing safer and more effective drugs by engineering nitric oxide release into well established, commercially successful therapeutics with known safety and efficacy profiles.

Anaeropharma Science is a gene therapy company focused on anticancer treatments using bifidobacteria.

AndroBioSys is a biotechnology company developing novel treatments for prostate cancer.

Archer Biosciences is a New-York based pharmaceutical company, focused on the development of anticancer therapeutics.

Arcion Therapeutics is a biotechnology company engaged in the development of targeted treatments for severe pain.

Armgo Pharma is developing small-molecule therapeutics, known as 'rycals', which target the ryanodine receptor/calcium release channel for the treatment of cardiac, muscular and neurological disorders.

Arthritis Relief Plus is developing a transdermal osteoarthritis therapy.

Bacilligen is a privately-owned early-stage biotechnology company developing therapies for cancer and infectious disease.

BaroFold is engaged in developing improved biopharmaceuticals for patients suffering from chronic immunological disorders.

Black Lion Pharmaceuticals is developing oncology drugs with reduced side-effects.

Privately-owned **Blue Note Pharmaceuticals** is focused on undervalued drug development candidates with the potential to more effectively treat or help major medical conditions.

Centrose utilizes sugars to increase the activity and decrease the toxicity of certain drugs.

Celentyx uses its NCIP application to identify candidate drugs for the treatment of immune-related disorders.

Cempra Pharmaceuticals discovers and develops well differentiated medicines for the treatment of bacterial infections.

DelSite Biotechnologies is a drug delivery/biotechnology company developing novel drug delivery solutions for proteins and peptides.

Dilafor is engaged in the development of pharmaceuticals from heparin derivatives with low anticoagulant activities.

DSX Therapeutics is an early-stage company that investigates novel scientific treatments for sepsis.

Eribis is a Swedish outfit that develops drugs for the treatment of cardiovascular disorders.

EyeCyte is focused on stem cell-/progenitor cell-based therapies for ophthalmological diseases.

f-star is an antibody engineering company developing improved therapeutic antibodies and antibody fragments based on its Modular Antibody Technology.

Fina Biotech is a spin-off from Laboratorios Indas, focused on the development of biotechnology products.

GlycoMar is a marine biotechnology company, focused on the discovery, development and commercialization of novel anti-inflammatory drug candidates.

Gradalis is a Texas-based gene therapy company developing innovative anticancer therapies involving antisense and RNAi mechanisms.

Hepasome Pharmaceuticals develops hepatocyte-directed drug formulations for the treatment of hepatitis.

ImmuneWorks is a biotechnology company committed to developing novel therapeutics for autoimmune diseases of the lung.

Immunomic Therapeutics is engaged in the development of DNA vaccines based on its 'LAMP' technology.

IntelGenx is a drug delivery company focused on improving existing medications by incorporating proprietary, advanced controlled-release technologies.

International Drug Development researches and develops healthcare products and cosmetics.

International Stem Cell Corporation develops treatments for diseases such as diabetes, liver disease and retinal disease, using stem cells. It derives therapeutic cells from human parthenogenetic stem cells.

Link Medicine identifies and develops disease-modifying therapies for neurodegenerative diseases.

Meritage Pharma develops therapeutics for unmet medical needs.

MyeloRx is developing compounds derived from natural products, for the treatment of cancer and autoimmune diseases.

Founded in 2003, **Northern Antibiotics** is a biotechnology company developing novel compounds which are highly effective against difficult-to-treat Gram negative bacteria.

Obura develops treatments for neurodegenerative disorders.

Pathway Therapeutics is engaged in the development of anticancer therapeutics.

Pear Tree Pharmaceuticals is focused on the development of products that address the needs of aging women.

PhytoHealth Corporation develops adjuvants for cancer and vaccine administration, cough treatment, osteoporosis, diabetes, hepatitis-C and pain control.

Profectus Biosciences develops therapeutic and vaccine technologies to treat and prevent viral diseases, with focus on HIV/AIDS.

PsychoGenics specializes in preclinical neurobiology, with in-house efforts focused on psychiatric indications.

RaQualia was spun out from Pfizer's former central research laboratories in Japan.

RXi is a biotechnology company focused on the development of RNAi therapeutics for the treatment of neurological and metabolic diseases and cancer.

Spaltudaq creates human therapeutic antibodies from IgG memory B-cells for the treatment and/or prevention of debilitating diseases.

TGR BioScience discovers and develops therapies for oral and gastrointestinal health and skin and tissue repair.

Valens Pharma is developing biopharmaceuticals based on a novel class of energy metabolism agents known as PDK blockers.

ValiRx develops technologies and products for the analysis and treatment of oncology indications.

Vivendy Therapeutics is focused on the development of an enzyme replacement therapy for the treatment of mucopolysaccharidosis IVA.

VLST is a privately held biotechnology company dedicated to the discovery and development of novel therapeutics for the treatment of autoimmune and inflammatory disorders.

Mergers, Acquisitions, Name Changes and Joint-Ventures

Antisoma has acquired **Xanthus Pharmaceuticals**.

Bristol-Myers Squibb has acquired **Kosan Biosciences**. Kosan will remain a wholly-owned subsidiary.

Daiichi Sankyo has acquired **U3 Pharma**.

Jubilant Organosys has acquired **Draxis Health**.

Nastech has changed its name to **MDRNA**.

Novartis has acquired a majority shareholding of **Speedel**.

Synthetic Blood International has changed its name to **Oxygen Biotherapeutics**.

Pharmaprojects News Digest

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

Myriad terminates Phase III Alzheimer's therapy

US-based Myriad Genetics has announced that it has discontinued development of tarenflurbil (Flurizan), its first-in-class gamma secretase inhibitor for the treatment of Alzheimer's disease (AD).

The decision to discontinue Flurizan followed the results of an 18-month randomized, double-blind, placebo-controlled Phase III trial in 1684 mild AD patients, in which 800mg of Flurizan twice-daily failed to meet either of its primary endpoints of improvement in cognitive function and activities of daily living. Adverse events were those expected in the study population.

The failure of Flurizan reflects a continued poor success rate for AD therapies in 2008. In June, Wyeth's bapineuzumab, currently in Phase III trials, failed to reach its primary endpoints in a Phase II trial in 240 mild-to-moderate AD patients. And in April, Phase II trials of Wyeth and Elan's beta-amyloid immunoconjugate ACC-001 were briefly suspended after a patient developed vasculitis.

President and CEO of Myriad, Peter Meldrum said, "The discontinuation of Flurizan will reduce our pharmaceutical development spend substantially and should enable Myriad to achieve profitability next year".

Myriad Genetics has invested US\$60 million in the development of Flurizan in 2008, with further projected expenses of \$8 million over the next two fiscal quarters.

First organ-specific MRI contrast agent approved in the US in over a decade

The US FDA has granted Bayer Schering Pharma marketing approval for its magnetic resonance imaging (MRI) contrast agent, gadoxetate disodium, for the detection and characterisation of liver lesions. The product is currently launched as Primovist in several markets, including Australia, Germany and Switzerland, and is approved in over 40 countries worldwide.

Administered via intravenous injection, gadoxetate disodium is specifically taken up by hepatocytes, enhancing healthy liver tissue. Cancerous tissue is not enhanced, therefore allowing detection of hepatocellular carcinomas, as well as liver metastases and cysts. In addition, its high contrast imaging properties allow identification of tumour structure and intrahepatic vessels, giving an advantage in surgical planning over existing contrast agents.

Dr Gunnar Riemann, of Bayer Schering Pharma said gadoxetate disodium offered the "unique benefit of being able to simultaneously detect, locate and distinguish various types of liver lesions".

Gadoxetate disodium now becomes the first organ-specific MRI contrast agent to gain US approval for over a decade. It will be marketed as Eovist in the US, with launch planned for mid- 2008.

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TrialTrove is the leading source for real-time clinical trials intelligence. We track planned, ongoing, and completed clinical trials on a detailed trial-by-trial basis to give you the most up-to-date and complete picture of your competitors' clinical development programs.

To see a guided tour of the **TrialTrove** system simply go to www.informahealthcare.com/trialtrovedemo/

Alternatively call +1 707 237 3647 for a product demonstration.

TrialTrove

Real-Time Clinical
Trials Intelligence

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:** Guy Morris at guy.morris@informa.com
 For **The Americas:** Sean McDonnell at sean.mcdonnell@informa.com
 For **Japan:** Mr T Hirata at info@shiryoken.co.jp

Dates	Conference	Details
August 4-7	Drug Discovery and Innovative Therapeutics World Congress	World Trade Center Boston and The Seaport Hotel, Boston MA For information: http://www.drugdisc.com/ Delegates can attend a presentation by <i>Pharmaprojects'</i> Biotech Editor Janet Beal on 'Pharma R&D—The Big Picture' at 4:30 on Wednesday 6th August

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@informa.com

For product information contact:

Michael Aplin Marketing Manager, *Pharmaprojects*
 Telephone +44 (0)20 7017 6949
 Facsimile +44 (0)20 7017 6985
 E-mail michael.aplin@informa.com

Thomas Stirzaker Editor, *Pharmaprojects Update Analysis*
 Telephone +44 (0)20 7017 7660
 Facsimile +44 (0)20 7017 6898
 E-mail thomas.stirzaker@informa.com

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Search Tip of the Month - Search by Therapy Pipeline

The powerful search facilities available on *Pharmaprojects* can be used for a variety of research purposes. This month we show you how to query the database to view the pipeline for one or more therapeutic areas.

In standard search, click on the therapy pipeline button.

Once you have added your particular therapeutic area of interest just hit 'Results' to view the whole pipeline, or 'Graph' for a visual overview

Hits	And/Or	(...)	Group	Expression	Value	(...)
193			Therapy Pipeline	=	ABA3 (Obesity)	
=193						

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