

Target Analysis—Toll-like Receptors

Welcome to the monthly newsletter for *Pharmaprojects*, the Update Analysis. This issue contains an analysis of Toll-like Receptors and the potential they hold as a therapeutic target for many diseases. All the usual *Pharmaprojects* highlights follow, including details of four 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 search for miRNA therapeutics.

It is well-established that the innate immune system is essential to human survival, providing the first line of defence by recognizing and responding to pathogenic threats when microorganisms breach the body's barriers. For many years, the signalling pathways involved in this system were unknown, but recent work using positional cloning and knockout animal models has provided us with knowledge of some of the most powerful receptors involved in innate immunity - the Toll-like receptors (TLRs).

With the discovery of endogenous ligands for TLRs and other pattern recognition receptors (PRPs), it has become increasingly evident that TLRs may not only be involved in recognizing the threat from invading pathogens, but also in sensing tissue damage due to disease or injury as well as having a key role in initiating cellular repair mechanisms.

A greater understanding of the immune system holds huge potential for the development of therapeutics for bacterial and viral infections, allergies and cancer, and also to limit the damage caused by autoimmune disorders. Additionally, the role of TLRs in tissue repair and regeneration provides a further avenue for drug targeting. However, developing therapeutics based on manipulation of Toll signalling is not straightforward. The fine balance of cell signalling these receptors participate in has wide-ranging and powerful effects on gene expression affecting thousands of individual genes; clearly, the issue of side-effects could be quite an obstacle.

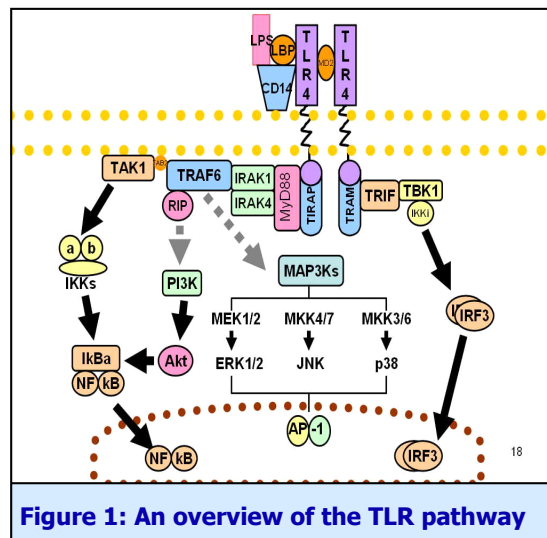


Figure 1: An overview of the TLR pathway

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Toll-like Receptors – meet the family.

In 1985 the *Drosophila melanogaster* Toll gene was discovered. Originally identified as having a developmental role, it was later found that the protein encoded by Toll is involved in the synthesis of antimicrobial peptides, and therefore vital to the functioning of the fly's immune system. TLR1, the first reported human TLR, was discovered by Nomura *et al* in 1994. This was followed by the discovery by Bruce A Beutler's group that mice lacking functional TLR4, another member of the family, were unable to respond to challenge with bacterial lipopolysaccharide (LPS), suggesting a role for these receptors in 'recognition and response' to pathogenic threat. In all, ten human TLRs have been identified, each with their own ligand specificities and downstream signalling pathways, adding a further layer of complexity to the function of TLRs. Additionally, these receptors were found to exist on very specific cell types, depending on their roles in innate immunity.

TLRs are type I transmembrane receptors with a single membrane-spanning domain, as well as an extracellular ligand-binding domain that contains leucine-rich repeats, and an intracellular Toll/interleukin-1 receptor domain. Each of the human TLRs, acting either as homo- or heterodimers, recognises a specific set of pathogen-associated molecular patterns (PAMPs) essential for pathogen survival. Table 1 shows examples of PAMPs and the TLRs they activate.

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TLRs are non-catalytic, and ligand binding induces conformational changes that lead to cytosolic signal transduction via a number of adaptor molecules such as MyD88, an adaptor common to all TLRs. Subsequent activation of protein kinases such as IRAK1 leads to signal amplification, and ultimately result in a stimulatory or inhibitory effect on gene expression and the production of cytokines.

Figure 1 shows an example of a Toll signalling pathway, resulting from recognition of LPS from Gram negative bacteria such as Escherichia coli by TLR4. LPS bound to LPS-binding protein (LBP) is presented to CD14. CD14 manoeuvres the LPS-LBP complex to TLR4, and LPS, in combination with MD22, activates TLR4 signalling. Following ligand binding, the cytoplasmic domain of TLR4 recruits an adaptor molecule such as MyD88 or TRIF, which activates protein kinases and propagates the signal.

Whilst TLRs are able to recognize viral PAMPs, the situation is rather more complex. Some viral proteins are able to subvert TLR pathways, aiding viral entry into cells, whereas others actually suppress TLR function.

Interestingly, it is not only molecules from externally-derived pathogens that are able to elicit Toll-signalling. A number of host molecules have also been identified as ligands for TLRs. Breakdown products from the extracellular matrix, such as hyaluron, intracellular components released when cells rupture, and products of proteolytic cascades are all able to stimulate TLRs, suggesting their role in sensing tissue damage signals caused by disease or injury. Recognition of these products by TLRs leads to the activation/recruitment of immune cells and cytokines that repair the tissue damage. There are already drugs in the pipeline for tissue regeneration applications, such as Clinquest's TLR3 agonist CQ-07001, currently in preclinical trials.

PAMP	Receptor
Leipoteichoic acid Bacterial lipoproteins Zymosan	TLR2
Double-stranded RNA	TLR3
Lipopolysaccharide Heat shock proteins	TLR4
Flagellin	TLR5
Single-stranded viral RNA	TLR7/8
Unmethylated CpG motifs from bacterial DNA	TLR9

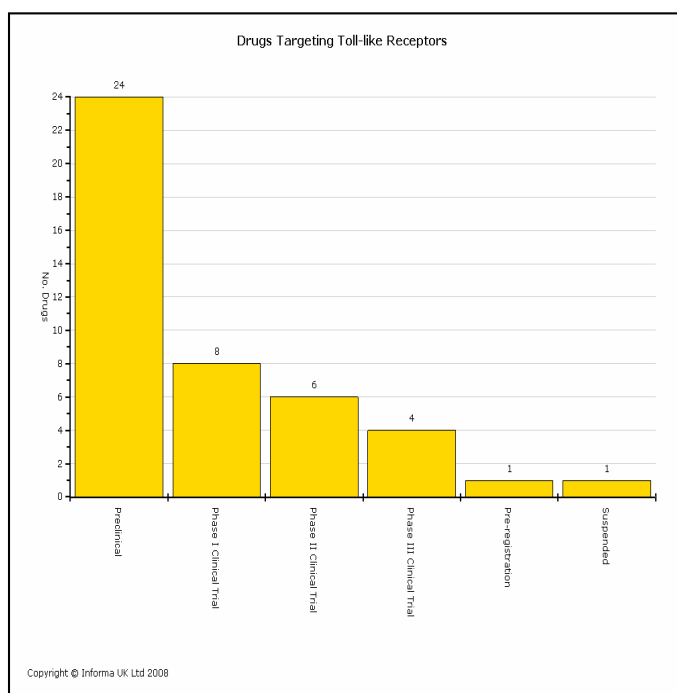
Table 1: Toll-like Receptors and the PAMPs which activate them

Drugs in development acting on TLRs

Development of novel therapeutics in the area of TLRs is at quite an early stage at present. There are currently 24 drugs in preclinical development, with a further 18 in clinical trials (Graph 1). Aptly-named Innate Pharma is developing IPH-32XX, a series of TLR7 modulators for the treatment of cancer, autoimmune and infectious diseases. Also in Innate's pipeline is IPH-31XX, a double-stranded RNA which is the natural ligand of TLR3, usually detected during viral infection. Activation of the TLR3 pathway leads to the activation of NF-κB and the production of type I interferons, and it is hoped that this will be an effective method of destroying cancerous cells present in melanoma and breast cancer. Both of Innate's TLR candidates are in the very early stages of development, so it will be interesting to see how they perform in the clinic.

Pfizer's agatolimod is a CpG oligonucleotide which mimics the natural ligand of TLR9 - unmethylated bacterial CpG DNA - and activates the TLR9 immunostimulatory cascade. This product is more advanced than Innate's TLR-targeted drugs and is in Phase II trials in breast and renal cancers, asthma, allergies and hepatitis-B virus infection. However, this drug has not been without setbacks, and development for advanced nslc was discontinued after an independent DSMC found that trial data did not show increased efficacy over standard chemotherapy alone. This is not the only CpG oligonucleotide targeting TLR9 that has failed to live up to expectations for Pfizer; CpG-10101 was suspended at Phase II, when it failed to show efficacy in treating hepatitis-C.

To date, Pfizer has had more success using oligonucleotide TLR9 agonists as vaccine adjuvants; its vaccine adjuvant CpG-TLR9 is currently in Phase III trials with GlaxoSmithKline's MAGE-A3 cancer vaccine. It has been argued by some that use as adjuvants is the most promising avenue for TLR agonists, as lower doses would be required which could avoid certain side-effects that may be associated with



Graph 1: World status of Toll-like Receptor therapeutics in active development

Generic Name	Originator	Any Pharmacology Description	Primary Indication	Primary Indication Status
Ampligen	Hemispherx Biopharma	TLR3 agonist	Chronic fatigue syndrome	Pre-registration
eritoran tetrasodium	Eisai	TLR4 antagonist	Sepsis	Phase III Clinical Trial
CpG-TLR9	Pfizer	TLR9 agonist	Vaccine adjunct	Phase III Clinical Trial
resatorvid	Takeda	TLR4 antagonist	Sepsis	Phase III Clinical Trial
PF-676	Pfizer	TLR9 agonist	Cancer, lung, non-small cell	Phase III Clinical Trial
agatolimod	Pfizer	TLR9 agonist	Cancer, breast	Phase II Clinical Trial
resiquimod	3M Pharmaceuticals	TLR7 & TLR8 agonist	Infection, hepatitis-C virus	Phase II Clinical Trial
IMO-2055	Idera Pharmaceuticals	TLR9 agonist	Cancer, renal	Phase II Clinical Trial
non-Hodgkin's therapy, Dynavax	Dynavax Technologies	TLR9 agonist	Cancer, lymphoma, non-Hodgkin's	Phase II Clinical Trial
poly-ICLC, Oncovir	Oncovir	TLR3 agonist	Cancer, brain	Phase II Clinical Trial
852A	Pfizer	TLR7 agonist	Cancer, melanoma	Phase II Clinical Trial
TLR-9 agonist, cancer, Dynavax	Dynavax Technologies	TLR9 agonist	Cancer, colorectal	Phase I Clinical Trial
IMO-2125	Idera Pharmaceuticals	TLR9 agonist	Infection, hepatitis-C virus	Phase I Clinical Trial
ANA-773	Anadys Pharmaceuticals	TLR7 agonist	Cancer, lymphoma, general	Phase I Clinical Trial
SD-101	Dynavax Technologies	TLR9 agonist	Infection, hepatitis-C virus	Phase I Clinical Trial
HspE7-2nd gen + poly-ICLC, Nve	Nventa	Immunostimulant HPV16 E7 inhibitor TLR3 agonist	Infection, human papilloma virus	Phase I Clinical Trial
CPG-52364	Pfizer	TLR7 antagonist TLR8 antagonist TLR9 antagonist	Lupus erythematosus, systemic	Phase I Clinical Trial
DSP-3025	Dainippon Sumitomo Pharma	TLR7 agonist	Asthma	Phase I Clinical Trial
peanut allergy ther, Dynavax	Dynavax Technologies	T cell stimulant ToLR9 agonist	Allergy, food	Preclinical
GSK-675	GlaxoSmithKline	TLR4 agonist	Rhinitis, allergic, seasonal	Preclinical
IPH-31XX	Innate Pharma	TLR3 agonist	Cancer, breast	Preclinical
IMO-3100	Idera Pharmaceuticals	TLR7 antagonist TLR8 antagonist TLR9 antagonist	Lupus erythematosus, general	Preclinical
vaccine adjuvants, Idera	Idera Pharmaceuticals	TLR7 agonist TLR8 agonist TLR9 agonist	Vaccine adjunct	Preclinical
IPH-32XX	Innate Pharma	TLR7 agonist TLR7 antagonist	Unspecified	Preclinical
TLR7 agonist, Pfizer	Pfizer	TLR7 agonist	Infection, hepatitis-C virus	Preclinical
IRS-954	Dynavax Technologies	TLR7 antagonist TLR9 antagonist Interferon alpha antagonist	Lupus erythematosus, systemic	Preclinical
CQ-07001	Clinquest	TLR3 agonist	Unspecified	Preclinical
VTX-463	Array BioPharma	TLR7 agonist TLR8 agonist	Allergy, general	Preclinical
NPI-503	ViroGenomics	TLR9 agonist TLR4 agonist TLR7 agonist TLR8 agonist	Ischaemia, cerebral	Preclinical

Table 2: Details of TLR therapeutics currently under development

immunotherapeutics. This suggestion is borne out of the discontinuation of the TLR7 agonist ANA-975, which was under development by Anadys Pharmaceuticals as an anti-viral but had unacceptable toxicity in animals. It produced intense immune stimulation, so chronic administration of this drug would have been inadvisable.

Other than use as vaccine adjuvants, another way around the problem of toxicity could be via a non-systemic route of administration. Array BioPharma's TLR7/8 agonist VTX-463, under development for the treatment of allergy, has shown efficacy in animal models of ragweed allergy. In sensitized beagles, intranasal administration of VTX-463 increased the size of the nasal cavity, and caused a selective decrease in eosinophils and nasal congestion.

Initially it may seem counterintuitive to stimulate an immune response for the treatment of allergy. However, there are differences between the types of immune response elicited by allergens and invading microorganisms. An important component of the immune system is the T-helper cell. These cells are differentiated into either Th1 helper cells, or Th2 helper cells and both subdivisions produce different cytokines. The Th1 response relies on the production of interferon- γ , which is a pro-inflammatory cytokine that eliminates pathogens. The Th2 response involves the production of interleukins 4, 5 and 13 that promote IgE production and eosinophilic responses, which form part of the pathology of allergic diseases. It is thought that restoring the balance between these responses in favour of the Th1 response, possibly via activation of TLRs, is likely to alleviate the symptoms of allergic hypersensitivity, and this is the approach being taken by Array BioPharma with VTX-463.

As well as TLR agonists there are also a number of antagonists in development for various indications. Systemic lupus erythamatosus (SLE) is an autoimmune disorder in which it is thought that an immune complex of autoantibodies and protein-bound DNA interacts with dendritic cells and subsequently leads to the activation of intracellular TLR9. Current therapies for SLE are general immunosuppressants which can of course lead to a host of unwanted and potentially dangerous side-effects. TLR-targeted therapies may thus represent a more specific approach. Dynavax Technologies' TLR7/9 antagonist, IRS-954, has already shown early signs of efficacy; in a murine model of lupus, it reduced serum levels of nucleic acid-specific antibodies and decreased proteinurea, glomerularnephritis and end-organ damage, producing an overall survival benefit.

A more advanced TLR antagonist is Eisai's eritoran tetrasodium, which targets TLR4 and has reached Phase III trials for the treatment of sepsis and septic shock. In Phase I trials it proved its ability to dose-dependently inhibit TNF- α production, although the results from Phase II trials were not outstanding - 28-day all-cause mortality rates in 293 patients with severe sepsis were 26.9 and 32% on 105mg eritoran tetrasodium every 6 days and 45mg every 6 days, respectively, compared with 33.3% on placebo. However, the trial in question was not sized to show significance, so it remains to be seen how the drug will perform in the larger-scale Phase III trial.

It is clear that a great many attempts to use TLR manipulation for the treatment of infectious, allergic and autoimmune diseases, as well as cancer, are in the very early stages of

development, and so far clinical trials have presented a mixed bag of results. Table 2 shows a snapshot of drugs currently in development that target TLR signalling. Today, the most successful TLR candidate in development is Ampligen, a mismatched, double-stranded RNA which activates TLR3 and is currently awaiting registration in the US for the treatment of chronic fatigue syndrome, an illness that is not fully understood, but often seems to be associated with viral infection. Ampligen is also in Phase II development for HIV and hepatitis infections, as well as for the treatment of cancer.

As we begin to understand more about innate immunity, including the role of TLRs, both for defending the body against invading pathogens, and for repairing damage caused by disease or injury, perhaps we will learn to harness this knowledge in the development of effective therapeutics. There have already been some successes, but this field of immunology is still relatively new and as such it will be exciting to see what the future holds!

*Leanne Coyne
Pharmaprojects Analyst*

Search strategies

In Drug Profile Search:

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([Any Pharmacology code] = TLR+  
OR [Any Pharmacology code] = TLR-  
OR [Any Pharmacology code] = TLR2+  
OR [Any Pharmacology code] = TLR3+  
OR [Any Pharmacology code] = TLR4+  
OR [Any Pharmacology code] = TLR4-  
OR [Any Pharmacology code] = TLR7+  
OR [Any Pharmacology code] = TLR7-  
OR [Any Pharmacology code] = TLR8+  
OR [Any Pharmacology code] = TLR8-  
OR [Any Pharmacology code] = TLR9+  
OR [Any Pharmacology code] = TLR9-)  
And [Active, Ceased, Fully Launched] = Active
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Graph by World Status

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MD7046

New Targets

integral membrane protein 2B

Integral membrane protein 2B (ITM2B or BRI2) is a putative type II transmembrane protein believed to interact with amyloid precursor protein and regulate amyloid- β production. Defects in ITM2B have been linked with Familial British and Danish Dementias.

RemeGenix is developing peptides derived from the BRI2, to reduce the toxic impact of Amyloid beta, for the treatment of Alzheimer's disease.

Its Entrez Gene ID is **9445**.

microRNA 208a

Also known as MIRN208A this microRNA is encoded by an intron of the MYH6 gene and is expressed in cardiac tissue. Overexpression induces cardiomyocyte hypertrophy, fibrosis and β -MHC expression. Knockout mice lacking this miRNA did not develop heart failure following thoracic aortic banding.

Miragen is developing inhibitors of endogenous microRNAs for the treatment of heart failure. One of the targets under investigation is MIRN208A.

Its Entrez Gene ID is **406990**.

ras homologue gene family, member C

This member of the Rho family of small GTPases is more commonly referred to as RHOC and is believed to play a role in cell locomotion. Interactions with DIAPH1, ROCK1, ROCK2, RTKN and AKAP13 have been demonstrated and research suggests involvement in tumour cell invasion. Over-expression of RHOC has been shown to enhance metastasis.

CompleGen is developing RHOC inhibitors as anticancers.

Its Entrez Gene ID is **389**.

TIMP metalloproteinase inhibitor 3

This member of the tissue inhibitor of metalloproteinase (TIMP) family is more commonly referred to as TIMP3. It complexes with, and permanently inactivates, matrix metalloproteinases, a group of endopeptidases involved in the degradation of the extracellular matrix. Mutations in TIMP3 cause Sorsby's fundus dystrophy (SFD), a macular degenerative disease.

Oscotec is developing orally-administered TIMP-3 secretion inducers for the treatment of osteoarthritis.

TIMP3 belongs to the **Enzyme>Protease/peptidase** Target Family Groups and its EC number is **3.4.24.17**. Its Entrez Gene ID is **7078**.

New Drug Development Strategies

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

Utrophin stimulant

Faust Pharmaceuticals, OSI Pharmaceuticals and Summit are developing utrophin stimulants for the treatment of muscular dystrophy.

Utrophin stimulants are coded in *Pharmaprojects* as **UTROPH+**.

Oligoadenylate synthetase stimulant

Cubist Pharmaceuticals is developing an oligoadenylate synthetase stimulant for the treatment of hepatitis-C virus (HCV) and other RNA virus infections.

Oligoadenylate synthetase stimulants are coded in *Pharmaprojects* as **SY-OA+**.

Companies New to *Pharmaprojects*

Abeome is a biotech outfit investigating high-affinity monoclonal antibodies.

Adienne is an integrated biopharmaceutical company dedicated to the treatment of rare and severe diseases.

Altair Therapeutics was formed to develop **Isis Pharmaceuticals'** antisense drugs for respiratory disease.

Amplimmune is developing immune-based biologics to treat patients in the areas of cancer, autoimmunity, transplantation and infectious diseases.

Aprea is developing anticancer apoptosis inducers that work via p53-dependent pathways.

Asklepion Pharmaceuticals is focusing on hepatic diseases.

Auckland UniServices is the research and knowledge transfer company for the University of Auckland, New Zealand.

Bioceros is a biotech company working in the fields of allergy, autoimmunity, inflammation and cancer.

BioSceptre is developing anticancer antibodies.

Cancer Innovations is focused on the development of therapeutics targeting cryptic elements within malignant tumours.

CellNexus is developing therapies for the treatment of cancer-related anaemia.

CompleGen is working on the treatment of various indications.

Connexios Life Sciences is an Indian company focused on chronic disease management.

Cornerstone Pharmaceuticals is developing anticancers based on exploiting metabolic pathways common to cancer cells.

Cortria is focused on therapeutics for cardiovascular disease.

Coserix was spun-out of **Serenex** and is developing treatments for unmet medical needs.

Danish company **Drugrecure** reprofiles marketed drugs for new indications.

Endoceutics specialises in late-stage Phase III trial and commercialisation of products.

Ensemble Discovery is developing macrocyclic therapeutics and bioassays using its proprietary DNA-Programmed Chemistry platform.

Expergen is an Austrian company with an anticancer under development.

Galantos is developing galatamine-based drugs for the treatment of Alzheimer's disease.

GlycoForm was spun-out of Oxford University to develop novel synthetic glycoproteins.

Hansa Medical is commercialising projects from Malmö University, Sweden, including proteins and peptides for sepsis and autoimmune diseases.

Icon Bioscience is developing novel ophthalmic pharmaceuticals using its Verisome drug delivery platform.

ImmunSystem is developing IgY antibodies for use in a number of disease areas.

Inbiopro is performing research on purification methods for recombinant proteins, high-expression stable cell lines and protein modification techniques.

InCode BioPharmaceutics is developing drugs for the complement-related pathologies in autoimmune and inflammatory diseases.

Innate Pharmaceuticals is developing novel antibiotics.

InvivoGen Therapeutics is developing gene therapies and immunotherapeutics using in-house plasmid vectors.

MagForce Nanotechnologies is developing nanomolecular cancer therapies.

Miragen is developing microRNA-targeting drugs for cardiovascular disease and related muscle disorders.

NatureWise is developing medicines based on traditional Chinese medicine.

NeuroNascent is developing therapies based on neurogenesis for the treatment of Alzheimer's disease, depression and stroke.

Pharmena is based in Poland and is initially focusing on cardioprotectives.

RemeGenix is a biopharmaceutical company developing therapies for neurodegenerative diseases.

Reviva Pharmaceuticals has a portfolio of drugs discovered through an integrated chemical genomics platform.

Spring Bank Pharmaceuticals is using natural nucleotides as templates for small molecules for use in diverse therapeutic areas.

TauRx Therapeutics is a Singapore-based company focused on neurodegenerative disease.

Telormedix is developing immunoselective drugs.

ValiRx is developing technologies and products for the analysis and treatment of cancer.

Mergers, Acquisitions, Name Changes and Joint-Ventures

Stiefel Laboratories has acquired **Barrier Therapeutics**, which will remain as a subsidiary.

Bentley spun-out all of its drug delivery products to **Cpex**.

Intercell has acquired **Iomai**.

Raven Biotechnologies has been acquired by **MacroGenics**.

Further Information

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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.

First ever approval for Freidreich's Ataxia therapeutic

Santhera Pharmaceuticals has received the first marketing authorisation in the world for a Freidreich's Ataxia therapy, following a conditional approval by Health Canada for Catena (ibedenone). Launch is expected in at the end of October. The product is also under review by health authorities in the EU and Switzerland.

Catena demonstrated significant efficacy and clinically relevant improvements in Friedrich's Ataxia patients; however, Santhera also agreed to submit additional data from an ongoing US Phase III trial in around 60 patients to confirm efficacy. It is also in Phase II trials for Duchenne muscular dystrophy and Leber's hereditary optic neuropathy, and has European and US orphan drug status for all three indications.

Ibedenone was previously developed and launched by Takeda for improving cerebral energy metabolism and treating sequelae of cerebral apoplexy, such as stroke. It is a small molecule optimised to facilitate the balance and flow of electrons within mitochondria. Through preserving mitochondrial function and protecting cells from oxidative stress, it is thought to prevent cell damage and increase energy production within impaired nerve and muscle tissue.

Intercell acquires Iomai

Austrian-based Intercell has acquired the American biotechnology firm Iomai for US\$189 million, in a deal that closed at least one month ahead of schedule. Intercell managed to edge ahead of competitors to purchase Iomai, which will now become a subsidiary of Intercell. Intercell completed the purchase for 1.44 million of its shares and US\$116 million in cash, despite which it is expecting to remain profitable in 2008. The closing price on the day the deal was first disclosed was US\$2.92; however, the stock was worth US\$6.59 a share when the deal closed, placing it within a cent of the valued US\$6.60 price.

The acquisition has a great deal of synergy, with Intercell developing vaccines for the prevention of infectious diseases and Iomai focused on needle-free delivery of vaccines. Iomai's transcutaneous immunization technology has the potential to deliver novel vaccines, boost the efficacy of existing vaccines, and facilitate administration of currently-available vaccines. It acts by leveraging immune system cells in the skin to deliver vaccines.

With the acquisition of Iomai, Intercell has also gained a pipeline including clinical-stage pandemic influenza vaccines and a needle-free patch delivery vaccine against traveller's diarrhoea. The latter has demonstrated efficacy in preliminary trials, significantly reducing both occurrences as well as severity of diarrhoea. Intercell intends to develop this alongside its own Japanese encephalitis vaccine in a portfolio of vaccines for travellers. Intercell's vaccine is awaiting approval in Australia, Canada, the EU and US, and is expected to launch this year.

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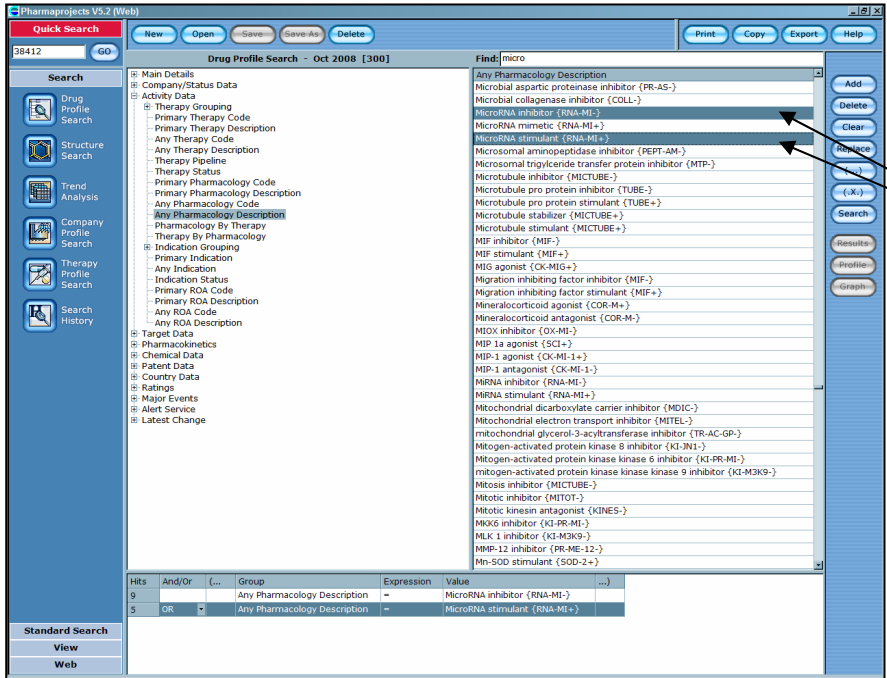
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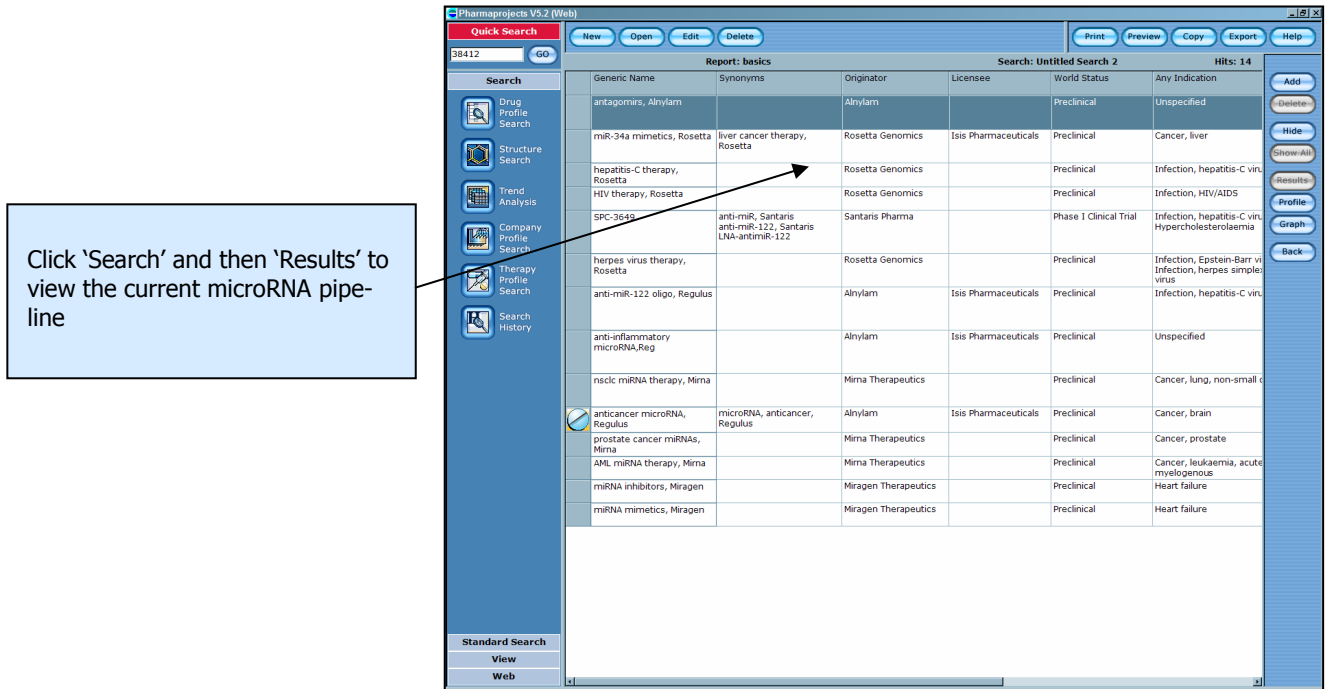
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Search Tip of the Month - Search for an miRNA Pipeline

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 drugs in development which act on miRNAs.



In the Drug Profile Search, add the pharmacologies MicroRNA inhibitor and/or MicroRNA stimulant



Click 'Search' and then 'Results' to view the current microRNA pipeline

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