**Pipeline Summary**

The Novogen pipeline has 2 distinct oncology drug technology platforms and an early stage degenerative and regenerative disease program. Each program is summarized below with links to each program’s further details. We are scheduled to enter into Clinical Trials for at least two of our programs in 2015. Successful trials of our novel therapeutics will translate into major breakthroughs in the treatment of a wide range of cancer including many areas where there is largely an unmet need. Although our program is diverse, they are all strategically aligned allowing the company to utilise its resources to a high capacity as resources and research can be shared among programs. Our strong partnerships with Yale University, Genea Bio Cells and FSHD Global allow us to further enhance our programs.

The Oncology program has 2 distinct platforms

* **Super-benzopyrans** (SBPs) click to take you to the detailed page
* **Anti-Tropomyosins** (ATMs) click to take you to the detailed page

(Click on the program and it will take you to that section)



**Cantrixil – for the treatment of cancers restricted to the abdomen and Malignant Ascites**

**Overview**

Over the last 40 years there has been little progress in terms of overall patient survival for ovarian cancer patients. Ovarian cancer has the lowest survival rate of all gynaecological cancers with little awareness and no cure. The 5 year survival rate is 40%. Patients with **malignant ascites** survival is very poor, averaging 20 weeks from diagnosis. There is no standard of care for malignant ascites.

**Research**

**Cantrixil** is owned by CanTx Inc, the Connecticut-based, joint venture company between Novogen and Yale University. **Cantrixil** has been developed as a ground-breaking intra-cavity product, to be delivered as a non-irritant anti-cancer agent into the peritoneal and pleural cavities to treat malignancy. **Cantrixil** is a construct of the SBP molecule, **TRX-E-002-1**, in a cyclodextrin (Captisol) polymer. The polymer dissolves within the cavity, releasing the drug molecule. A particular feature of **TRX-E-002-1** is its ability to kill both cancer stem (CD44+ve) cells and their daughter cancer (CD44-ve) cells. For more indepth information view **Cantrixil.**

The primary indication of **Cantrixil** is first-line therapy of ovarian cancer in combination with carboplatin, where this combination in an animal model of intra-peritoneal human ovarian cancer has proved highly effective in providing complete remission of the cancer.

First-in man studies will be conducted in patients with recurrent, late-stage cancers of the abdomen, in particular platinum- and taxane-refractory ovarian cancer, and malignant ascites and peritoneal carcinomatosis associated with colorectal, ovarian, pancreatic and breast cancer. There is no standard of care currently for malignant ascites and peritoneal carcinomatosis and Cantrixil is believed to be the only experimental drug being tested in this area of significant unmet clinical need.

**Market Opportunity and Competitive Advantage**

Ovarian Cancer costs ….

Currently CanTx is filing an IND and clinical trials are expected to commence in 2016

**Trx-7 – Brain Cancer**

**Overview**

**Research**

**Trx-7** is an SBP analog that has been selected for its high cytotoxic activity against prostate cancer cells. It is formulated in the same proprietary formulation developed for Trilexium. It is being developed for the treatment of docetaxel-refractory prostate cancer.

**Trilexium – Brain Cancer**

**Overview**

Brain Cancer kills more children than any other disease in Australia

Brain Cancer kills more people under the age of 40 than any other cancer

Survival rates have hardly changed for 30 years

Approximately 1,600 brain cancers are diagnosed annually in Australia

**Trilexium** is a construct of the SBP drug, **TRX-E-009-1**, in a proprietary formulation that optimizes the bioavailability of the molecule across the gut mucosa. **TRX-E-009-1** has been selected for its potent cytotoxicity against neural cancer stem cells. The primary clinical indications are primary brain cancers of both adults and children and neuroblastoma of children.

**Market Opportunity and Competitive Advantage**

**ATM**

**Overview**

**ATM-001** is the lead ATM drug candidate that is being developed as a treatment for prostate cancer, melanoma and neuroblastoma. The concept is to use ATM-001 in combination with an anti-microtubule drug (vincristine, paclitaxel) in order to deliver comprehensive destruction of the cancer cell’s cytoskeleton, and to be used ultimately in further combination with **Trilexium** or **Trx-7**.

**Market Opportunity and Competitive Advantage**

Current degenerative disease research

A look at recent progress at Novogen

Genistein-related compounds and degenerative disease

Over the last 20 years, Novogen have developed a range of compounds, based on a naturally occurring plant chemical called *genistein*. The most recent generation of these compounds, designed for anti-cancer use, are called the *superbenzopyrans (SBPs)*. Genistein shows natural anti-cancer activity in cells cultured in the laboratory but is no use as a drug molecule itself because it does not survive well through the process of oral ingestion and absorption into the body.

By repeatedly modifying genistein’s chemical structure, Novogen have enhanced and refined these anti-cancer properties to an extraordinary degree, ultimately resulting in the Company’s main SBP drugs *Cantrixil* and *Trilexium*.

An increasingly large body of current research on the properties of genistein shows that it is one of the most versatile compounds ever isolated in nature because it can trigger so many different responses from cells. These different responses are activated by binding of the molecule to a variety of different components within the cell. Imagine a cartwheel with genistein at the hub and a series of spokes radiating from it that contact different individual parts of the cellular machinery.

When genistein is added, the wheel turns and many different cellular components are all pulled at once. While this makes genistein’s action complicated to unpick and comprehend, it also provides multiple opportunities for new clinical applications other than treating cancer. The anti-cancer activity represents only one spoke of the wheel and the cellular contacts of the other spokes are now starting to become clear.

It turns out that some of these spokes make contact with and exert control over critical cell functions such as cell proliferation, energy production, gene activity, stress responses and immune system activation. These are pathways that are central to the development of treatments for a variety of degenerative diseases. The challenge and the opportunity is to isolate these individual modes of action and to enhance and refine their power using the same successful strategy used to develop the anti-cancer compounds.

This process requires two parts; expertise in drug design of genistein-related molecules and high-quality models of disease involving cultured cells or animals to test the compounds on. Novogen have 20 years experience of the former and are establishing collaborations with scientists from some of the leading laboratories in Australia and the world to facilitate the latter.

Based on an up-to-date assessment of published genistein research and the data Novogen have accumulated on the properties of their own compounds, five areas of potential application are currently being researched:

Stem cell regeneration

Neurodegenerative diseases

Muscular dystrophy

Lysosomal storage disorders

Autoimmune disease

**Stem cell regeneration**

Many adult tissues contain pockets of dormant or slowly cycling stem cells that can be activated during damage and disease and will proliferate and repair the lost or diseased tissue. However, sometimes the disease process is so severe that it overwhelms the capacity for regeneration leading to progressive decline (e.g. Duchenne muscular dystrophy).

For reasons that are not clear, stem cells in the brain have limited capacity for proliferation, migration and differentiation that severely limits the capacity for the replacement of dead nerve cells. This is a problem that prevents us from repairing lost tissue after a stroke or severe spinal cord injury.

A chance finding during work on ovarian cancer indicated that one of the main SBP candidates, CS-6, was effective at promoting proliferation and differentiation in cultured stem cells. Encouraging the body’s own capacity to repair itself is a an ideal form of therapy and the regeneration of brain or spinal cord nerve tissue is regarded as the holy grail of neuroscience research.

Novogen have formed a *partnership with Genea Biocells* to screen its library of compounds on models of stem cell repair in adult tissues. Genea Biocells have established cell culture systems that drive the differentiation of human embryonic stem cells to form neurons or muscle cells in culture and the impact of the Company’s compound library is being tested using markers of proliferation and differentiation.

In addition to normal cells, Genea Biocells also have a bank of embryonic stem cells that have been diagnosed with genetic diseases. Parallel studies in neuronal differentiation with cells that have the mutation that causes Down’s syndrome and infantile neuroaxonal dystrophy (IND) will also explore the potential to enhance and normalize these cells. Preliminary studies have already indicated that CS-6 enhances the proportion of differentiated neuronal precursors in IND cells

Similarly, cells with the muscle diseases facioscapulohumeral dystrophy, myotonic dystrophy and nemaline myopathy are being used to test the impact of the compounds on the differentiation of these abnormal cells in the context of muscle disease.

This work with Genea Biocells began at the beginning of September 2014 and the first results are expected in October 2014.

Neurodegenerative diseases

While stem cells offer profound therapeutic potential for regeneration in the central nervous system to replace dead brain cells, neurodegenerative diseases such as Alzheimer’s and Parkinson’s involve a lack of function in affected mature nerve cells while they are still alive. Current research shows that abnormal proteins accumulate in the cell, the energy production system becomes profoundly unbalanced and the crucial synapses with other nerve cells are blocked. The cell loses its capacity to function and enters a semi-vegetative state. Eventually the brain cell dies and localised inflammatory processes are triggered that worsen the damage process.

It is not currently clear what are the spanners that are thrown into the works to stop the cogs inside the neuron from turning or how that leads to a chain of consequences ending in shutdown of the brain cell. Large resources are being invested in addressing these questions. However, it is becoming obvious that while the initiating problem is different in each of the neurodegenerative diseases (e.g. Alzheimer’s, Parkinson’s, motor neuron disease, Huntington’s and frontotemporal dementia), the consequences usually converge on the same set of cellular pathways and the end result is highly predictable.

In what is, virtually, a vacuum of therapeutic options for neurodegenerative disease, any treatment that halts or slows the progress of the disease process would be an unprecedented leap forward of major significance.

Several lines of evidence indicate that genistein-related molecules are strong candidates to achieve this aim. Work on cell culture models of Alzheimer’s disease indicate that genistein can protect cells from death induced by amyloid-beta peptides (thought to be the primary toxin in Alzheimer’s disease) and provides protection from the oxidative stress and mitochondrial dysfunction that seems to be a universal part of neurodegeneration. Phenoxodiol, one of the early anti-cancer drugs produced by Novogen, also shows neuroprotective properties.

One of the contentious issues is how to model these complex diseases ‘in a dish’ in a way that is truly predictive of efficacy against neurodegeneration in humans. In recent years, many drugs that looked promising in cell culture and animal models have failed to meet the primary outcome measures in clinical trials. There has been a strong desire in the neurodegenerative disease research community to focus on protection of cell function rather than the much easier, but probably misleading, assay for protection from cell death.

A powerful drug screening system using a nematode worm called *Caenorhabditis elegans* has emerged that can easily assess the functional consequences of neurodegenerative insults (such as amyloid-beta). As the neurodegenerative toxin accumulates and cell function begins to slow, the mobile worms gradually become paralysed; an effect that is easily visible under the microscope. Agents that can protect the worm’s neuromuscular system from paralysis are potentially predictive of similar benefits against neurodegeneration in the human brain.

Novogen have initiated a preliminary compound screen in these worms at the Florey Institute of Neuroscience Research in Melbourne and the full report is expected in October 2014. Initial indications show that genistein provides functional protection from the paralysing effect of amyloid-beta.

**Muscular dystrophy**

In another joint venture with Genea Biocells, Novogen have begun a research program to investigate the potential use of genistein-related compounds for the treatment of the debilitating muscle disease, *facioscapulohumeral dystrophy (FSHD)*, which is supported by a *New Concept Grant* from the charitable foundation, *FSHD Global*, awarded in July 2014.

Unlike the other muscular dystrophies, which are mostly caused by loss of function mutations in key muscle genes, FSHD is caused by the activation of a gene called *DUX4* that is normally silent in muscle tissue. This gene encodes a transcription factor that regulates other genes and causes the inappropriate activation of abnormal cellular processes. This causes progressive muscle weakness and extreme pain starting in the muscles of the face, the shoulders and the upper arms.

*DUX4* is activated in muscle through the failure of epigenetic control mechanisms that are normally responsible for keeping genes such as *DUX4* locked away from accidental activation. However, changes in the DNA of FSHD patients means that the usual signals for the epigenetic machinery are not present and the gene is left unguarded and available for sporadic activation.

Modulation of the epigenetic machinery turns out to be another spoke of the genistein activity wheel, particularly for the silencing of repetitive DNA regions such as those where *DUX4* is found. Therefore, the aim of this research project is to isolate genistein-related compounds that are effective at silencing *DUX4*.

This work is made possible through an excellent model of early events in the FSHD disease process developed by Genea Biocells. By isolating embryonic stem cells from embryos diagnosed with FSHD and developing methods that allow them to drive such cells into the skeletal muscle pathway, Genea have shown that early FSHD muscle fibres grown in a tissue culture dish switch on *DUX4,* just like in the disease, resulting in smaller and thinner muscle cells with intracellular abnormalities that match the disease process.

The first screen for compounds that might shut down *DUX4* and rescue the cells from these abnormalities will begin in October 2014.

**Lysosomal Storage Disorders (LSDs)**

This class of diseases are caused by genetic mutations in essential cellular enzymes that are part of a production line processing large chemical components of cells. When the proteins are missing, the production line starts to back up and the cell accumulates large amounts of chemical intermediates in spherical bodies called lysosomes where these production lines exist.

These accumulations impact on the normal function of the cells and can lead to abnormalities in various organs of the body. A treatment strategy called enzyme replacement therapy has been effective at controlling disease in some of the LSDs by injecting the missing enzyme into the bloodstream.

Unfortunately, this process only works for cells that are directly exposed to the bloodstream. The brain is protected from direct exposure to the blood by the existence of the blood-brain barrier, which the enzymes cannot cross. Therefore, lysosomal storage disorders such as mucopolysaccharidoses (MPS) type III (Sanfilippo syndrome), principally involving brain cells, currently have no effective treatments.

In cultured cells taken from patients with this disease, genistein has been shown to reduce lysosomal accumulation of the damaging mucopolysaccharides and this has formed the basis of a new therapeutic strategy called substrate reduction therapy. The major advantage of this system is it would utilise small molecule drugs that can cross the blood-brain barrier. Genistein is currently being tested as a treatment for Sanfilippo syndrome in a clinical trial in the UK.

Genistein is unlikely to form the basis of a truly effective drug because it is rapidly altered and degraded when it is taken orally and thus only a small fraction survives intact to be exposed to the abnormal brain cells. Therefore, Novogen have established a collaboration with Professor Grzegorz Wegrzyn in Poland who is responsible for the original concept of treating MPSIII in this way and has high-quality cell models that can be used to test new genistein-related compounds.

An experimental pipeline for drug development has been planned and Novogen are currently seeking funding support to begin work on this project.

**Autoimmune disease**

Autoimmune disease occur when the defence system of the body attacks itself and leads to a range of disorders like diabetes type I, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease.

Many experiments show that genistein-related compounds can selectively suppress the immune system so that levels of activation are reduced without blocking its activity altogether. This is the key desirable outcome that forms the basis of most current treatments for these diseases.

Novogen have previously generated genistein-related compounds that show an ability to suppress T cell responses, which are critical players in autoimmune disease and others that will reduce pathology on rodent models of inflammatory bowel disease.

Accumulating evidence also shows that genistein has the potential to block specific processes in cell culture and rodent models of rheumatoid arthritis and multiple sclerosis that is not directly dependent on direct immunosuppression. Therefore, there are several spokes of genistein action that are applicable within this disease category alone.

Novogen is currently seeking advice from leading experts in the field in how to convert these observations into experimental strategies for drug development.