

Super-benzopyrans (SBPs) Some whys and wherefores

Our super-benzopyran (SBP) drug technology is distinguished by its ability to kill cancer stem cells. To date we have tested the technology against two libraries of cancer stem cells - ovarian cancer (Yale University) and glioblastoma (Weill Cornell Medical School). These are libraries of cells from patients who have become completely resistant to standard chemotherapy, and the cancer stem cells isolated from these patients show the same level of chemo-resistance in the laboratory as they did in the patient.

For the first time, researchers are seeing these cancer stem cells responding to a drug and dying within 24 hours. On the basis that the technology has worked so remarkably against the first two cancer types we have tested it against, we assume that they will be active against cancer stem cells from many other cancer types.

These findings generate two common questions:

Q. Why is killing cancer stem cells so important?

A. It's important because the cancer stem cells are the cells that initiate the tumor and then keep it being propagated. These cells to date have proven to be impervious to chemotherapy and radiotherapy. When a tumor responds to chemotherapy and shrinks, it is their daughter cells that have responded. But the parent (cancer stem) cells survive the chemical onslaught and produce a second generation of daughter cells that now inherit their parent's chemo-resistance, thus producing recurrent disease. Recurrent disease is unresponsive to therapy.

Killing cancer stem cells is the key to preventing recurrent disease, and progress in improving the survival prospects of most cancers has been hindered by an inability to prevent tumor recurrence. Our ability to kill the cancer stem cell so effectively at least brings some hope to this enormous area of need.

Q. How are SBPs different to other drugs being developed against cancer stem cells?

A. Novogen is not alone in this endeavour, but its approach is unique.

The approach being taken by almost all other companies is called 'targeted therapy.' This involves developing drugs that target a specific protein called CD44 found on the surface of cancer stem cells. We have chosen not to go down this path for a variety of reasons: e.g. the importance of CD44 to many forms of non-cancer cells, the great variety of different forms of CD44, and the general lack of success of targeted therapy in cancer therapy. Trying to pick the lottery of which particular form of CD44 you need to target, along with the renowned ability of cancer cells to detour around affected pathways, seemed to us to be too great a challenge.

SBPs do not rely on the presence of CD44. They kill both CD44-positive as well as CD44-negative cancer cells. SBPs target a protein that is critical to the survival of the cancer cell, rather than the target being incidental to the cell.

OVERVIEW

Since our last newsletter, Novogen has made substantial progress in all facets of drug discovery and development. In these pages, I hope that shareholders will come to appreciate the growing strength of their company.

We are sitting on two novel, exciting drug technology platforms, each capable of transforming medicine. Our priority over the last year has been to ensure that we have exclusive ownership over both assets for at least the next 20 years, and a solid strategy of how to manage our opportunities.

After 18 months of intensive drug development, our super-benzopyran (SBP) drug technology is poised to enter the clinic. The focus of our studies has been how to make these experimental drugs more powerful and how to improve their access to the tumor tissue. We have already announced our discovery of how to make the basic benzopyran structure more complex, yielding compounds up to 100-times more powerful than earlier benzopyrans. The details of how to increase the access of these more complex drugs into tumor tissue is the subject of ongoing patent lodgments and will be detailed soon.

We are focusing the SBP technology on three areas – cancers restricted to the abdomen, cancers of neural origin, and other systemic cancers. In each case, we have identified SBP molecules that are the most appropriate. Ovarian cancer, glioblastoma, neuroblastoma and prostate cancer are the immediate clinical targets. Having determined which drugs and which indications to pursue, we now have embarked on a program to bring all three drugs into the clinic in 2015.

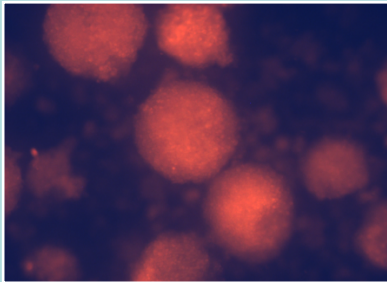
Progress has also been rapid and substantial with the anti-tropomyosin (ATM) program, our second drug platform. Under the direction of Justine Stehn, PhD, a co-founder of the technology, and with some clever in-house medicinal chemistry, the ATM team has taken an emerging technology from concept to a point where we believe we have the potential to replace anti-mitotic drugs as one of the most prescribed drugs in oncology. All that in just nine months.

The next 12 months is shaping up as an exciting and extraordinarily busy time. It's a time that will see the Company make the transition from a pre-clinical to a clinical stage company.

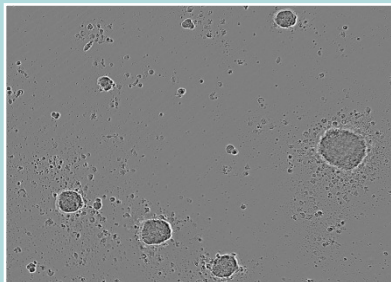
I am proud to lead such a committed team of scientists and support staff working tirelessly on your behalf. We are determined to turn Novogen into a global biotechnology company.

Dr Graham Kelly, CEO

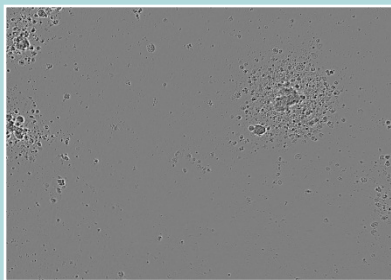
CanTx announces effectiveness of a new approach to the treatment of ovarian cancer



Spheroids of human ovarian cancer stem cells



Spheroids before ↑
and after ↓ exposure to Trx-1



Novogen-Yale joint venture company, CanTx, announced recently that it has provided proof-of-concept evidence in an animal model that the experimental drug, Cantrixil had a significant effect in blocking the growth of ovarian cancer stem cells responsible for post chemotherapy tumor recurrence.

This is the first evidence yet obtained, raising the possibility of improving survival of ovarian cancer patients by wiping out cancer stem cells, the cells responsible for spreading and perpetuating the cancer. We have to eradicate these cells to have any chance of bringing successful cancer therapy to the general population.

About 85% of ovarian cancers respond to first-line therapy. A response typically means several years relatively free from disease, but the majority of these cases eventually relapse, and recurrent disease eventually fails to respond to further chemotherapy.

The CanTx goal is to find a way of preventing the development of recurrent disease. This means killing the full range of cells within the ovarian cancer, both the parent (stem) cancer cells as well as their daughter cancer cells. Our objective is to wipe out primary disease so that we don't have the challenge of dealing with recurrent disease.

We hope that our first product, Cantrixil, will help achieve that goal. Cantrixil is a construct of the drug candidate, Trx-1, encapsulated in the cyclodextrin carrier, Captisol. Cantrixil will be administered into the peritoneal cavity of patients, where the Captisol will dissolve, releasing Trx-1 to seek out and destroy the cancer stem cells.

With cancers like ovarian cancer that are confined to the abdominal cavity, the cancer stem cells also are largely confined there, migrating as small clusters known as spheroids to seed new tumors on various organs.

By injecting Trx-1 into the peritoneal cavity, we are concentrating the drug where it is going to be the most effective in locating these spheroids. Trx-1 also is active against the daughter cancer cells, but we find that when we combine Trx-1 therapy with that of a standard of care drug such as carboplatin, the across-the-board killing of all ovarian cancer cells (parent + daughter) is complete.

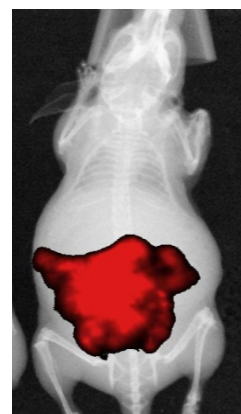
The three diagrams (above left) show that Trx-1 is highly effective at killing human ovarian cancer stem cell spheroids.

When we took Cantrixil into animals, the data that we announced in June suggests that we're well on track to reach our goal.

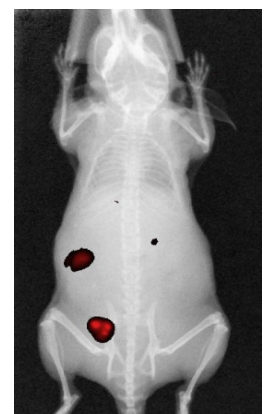
The animal model used is highly representative of human ovarian cancer. Human ovarian cancer stem cells are injected into the abdomen of mice, where they quickly develop into highly aggressive tumors that spread throughout the abdomen. The accompanying fluoroscopy photos of anaesthetized mice show what happened. Ten days after the injection of the cancer cells, the tumors in control mice receiving no drug grew into a significant tumor mass. Those mice receiving Cantrixil had tumors that either didn't progress or had completely regressed.

Cantrixil is the first experimental drug to provide any meaningful anti-cancer effect in this highly aggressive tumor model. We believe that it bodes well for a similar effect in humans.

This clears the way for the Investigational New Drug (IND) application process. With that now underway, we look forward to being in a Phase 1 study within one year.



Control



Cantrixil

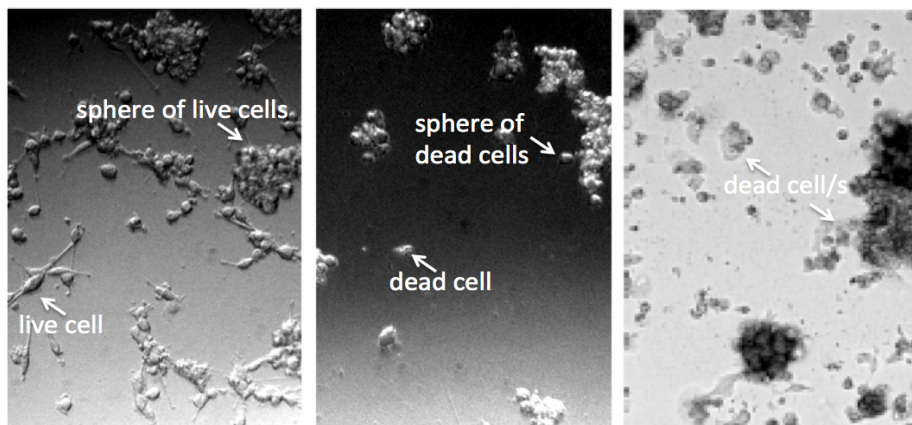
Trilexium*

Facing final test before heading into the clinic for the treatment of glioblastoma

Novogen recently welcomed Eleanor Ager, Ph.D., who recently completed a post-doctoral appointment at Harvard Medical School/Massachusetts General Hospital, to head up the Trilexium program. Trilexium is the brain cancer equivalent of Cantrixil*.

The active drug candidate in Trilexium, TRX-E-009-1, has been selected for its high level of activity against

cancer stem cells collected from glioblastoma multiforme (GBM). GBM, the immediate clinical focus of the Trilexium program, is the most common and aggressive form of primary brain cancer in adults. Even with aggressive combination therapy, GBM patients rarely survive more than two years after diagnosis and only three to nine months once tumors recur after treatment.



The image on the left shows cancer stem cells collected from a patient whose GBM tumor recurred after initial chemotherapy. The central image shows those same cells 24 hr after treatment with TRX-E-009-1 with over 75% of cancer cells dying after 48 hr. The image on the right shows the cancer cells after several weeks of continuous culture showing that they retain sensitivity to TRX-E-009-1, indicating lack of recovery (tumor recurrence) after treatment with this drug.

Courtesy Dr Moonsoo Jin, Weill Cornell Medical School

We have been able to show that TRX-E-009-1 is effective at killing a panel of highly chemo-resistant GBM cancer stem cells generated from biopsies of brain tumors that had recurred after chemotherapy, as shown in the accompanying photomicrographs.

Most of the cell cultures employed in these studies were collected from patients whose tumors had recurred following standard of care. The responsiveness of these cells to TRX-E-009-1 gives us hope that we might be able to make a difference for patients who currently have survival outcomes measured in months.

Additional studies conducted through the University of Hong Kong have confirmed that GBM cells that fail to respond to the only currently approved first-line chemotherapy, Temozolomide, are sensitive to TRX-E-009-1, further demonstrating the potential of TRX-E-009-1 to provide particular benefit to GBM patients failing current care.

In the same way that Cantrixil is a construct of drug in a delivery vehicle, so Trilexium is a construct of TRX-E-009-1 in a form designed to maximize its ability to cross

the blood-brain barrier. The details of this construct will be revealed once the appropriate patents are in place.

We have shown Trilexium can work in animals with implanted human tumors. The next step, beginning in August 2014, is to test Trilexium in so-called orthotopic studies where human GBM cells are implanted directly into the brains of mice. Success in that model will be the trigger point to initiate the IND process for this drug product.

The promise of TRX-E-009-1 against neural-cell derived cancer stem cells has instigated the process of evaluating the effect of TRX-E-009-1 on a range of other primary neural cell-derived cancers, including medulloblastomas and neuroblastomas in children.

Dr Ager is running a busy program involving a number of US and Australian Hospitals and research institutions, all of which are collaborating in this potentially promising approach to cancers that to date have defied any improvement in patient survival prospects.

* Trademark registration in progress for Trilexium and Cantrixil.

Novogen welcomes Dr. Stephen Palmer to drive its Degenerative Diseases Program

So how did a drug technology focused on cancer, spin off an opportunity to treat Alzheimer's disease, cystic fibrosis and/or muscular dystrophy?

One of the benefits of experimental research is the occasional surprising observation that you weren't looking for or expecting. One of these unexpected moments occurred during an experiment we commissioned to test the effect of one of our early SBP molecules, CS-6, on ovarian cancer stem cells. At the doses we anticipated using in the clinic, the drug had its predicted effect, killing ovarian cancer stem cells. When the dosage was lowered to levels where we would not have expected to see any effect, instead of killing the cancer stem cells, CS-6 actually increased stem cell numbers and promoted cell differentiation, making the cancer stem cells start to look and behave more like normal ovarian stem cells. This led us to ask the question that if we saw the same effect in malfunctioning stem cells associated with forms of degenerative disease other than cancer, then it could form the basis for an entirely new treatment approach. We would be assisting the capacity of the body's own stem cells to self-repair, a novel and potentially curative approach to many vexing problems.

The first step was a study conducted with Genea Biocells, a company with pluripotent stem cells isolated from embryos with a wide range of genetic abnormalities. Working with stem cell isolates from embryos with nemaline myopathy and infantile neuroaxonal dystrophy, Genea Biocells found that CS-6 appeared to select sub-populations of the affected stem cells and promote their development, as evidenced by the expression of surface markers of cellular differentiation.

You don't ignore an exciting result like this, particularly given its therapeutic potential, and so the Company made a commitment to extend its SBP technology drug discovery program into degenerative diseases. Stephen is conducting this research in collaboration with a range of researchers with specific expertise and resources across a range of diseases.

One of those collaborations is with Genea Biocells. Novogen is accessing stem cells carrying various

genetic disorders along with the laboratory models that mimic the human diseases. This program is focusing on three neurodegenerative diseases (Alzheimer's, amyotrophic lateral sclerosis, infantile neuroaxonal dystrophy) and two musculodegenerative diseases (fascioscapulohumeral dystrophy and Becker muscular dystrophy). The purpose of this work is to generate the basic evidence that we are going to need to attract the investment interest of the large foundations who support work into the various degenerative diseases.

To give you some idea of the scope of this program, Novogen also is working with the Florey Institute of Neurosciences in Melbourne, Australia, in a study that utilizes a tiny nematode worm as a model of Alzheimer's disease. These worms have been genetically modified to produce one of the damaging truncated proteins found in the human disease and, as

a result, become paralysed by the same cellular mechanisms that block the activity of human brain cells. The characteristics of these worms mean that large libraries of chemicals can be easily tested for their capacity to rescue the worms from paralysis and thus narrow down a handful of lead compounds for second tier pre-clinical studies in mouse models.

But the promise of the SBP technology and stem cells doesn't stop at killing cancer stem cells or recovering genetically-damaged embryonic stem cells. Twelve years ago, we looked at the likelihood that the benzopyran molecule might be capable of protecting

peripheral nerves from the damaging effects of the chemotherapy, cisplatin. Peripheral neuropathy is a dose-limiting side-effect of cisplatin therapy, with peripheral nerves essentially shrinking because they lose the ability to make neurites, the extensions that allow them to connect with neighbouring nerve cells. We found that some benzopyran molecules did in fact protect nerve cells from cisplatin toxicity.

www.ncbi.nlm.nih.gov/pmc/articles/PMC1950519/

With this in mind, we have begun work with an Australian university group that has developed a cutting-edge model to test the impact of drug compounds on the capacity of neural stem cells within the brains of mice to repair a localized injury. Drugs are added to enhance the repair process and the outcomes

Stephen Palmer PhD joins Novogen after a distinguished career in medical research in various fields of degenerative diseases. He will be heading our Degenerative Diseases Program, which although young, already is showing signs of growing into a surprise major strength of the Company.

are monitored by tracking the fate of the neural stem cells and by examining the restoration of normal motor function in the mice. Endogenous neuronal stem cell repair is regarded by many as the 'Holy Grail' in medical neuroscience and could open the door to new treatments for neuro-degenerative diseases, traumatic brain injury and stroke.

A summary of our experience with benzopyrans and neural cells is:

- ✚ Simple benzopyrans such as phenoxodiol can protect normal neural cells from toxic damage.
- ✚ Complex super-benzopyrans such as TRX-E-009-1 are capable of targeting neural cancer stem cells and killing them.

- ✚ Super-benzopyrans such as CS-6 can influence stem cell proliferation and differentiation in a way that could enhance regenerative mechanisms in the brain.

Together what all of this suggests is that within this broad family of compounds there appears to lie an ability to manipulate neural stem cells in a way that no other family of compounds is reported to do.

The task we have set ourselves is to harness this ability and to bring to market a range of drugs across a wide spectrum of neurodegenerative diseases, musculodegenerative diseases, and neurological injuries.

Anti-Tropomyosin (ATM) Drug Program: Our second exciting technology platform

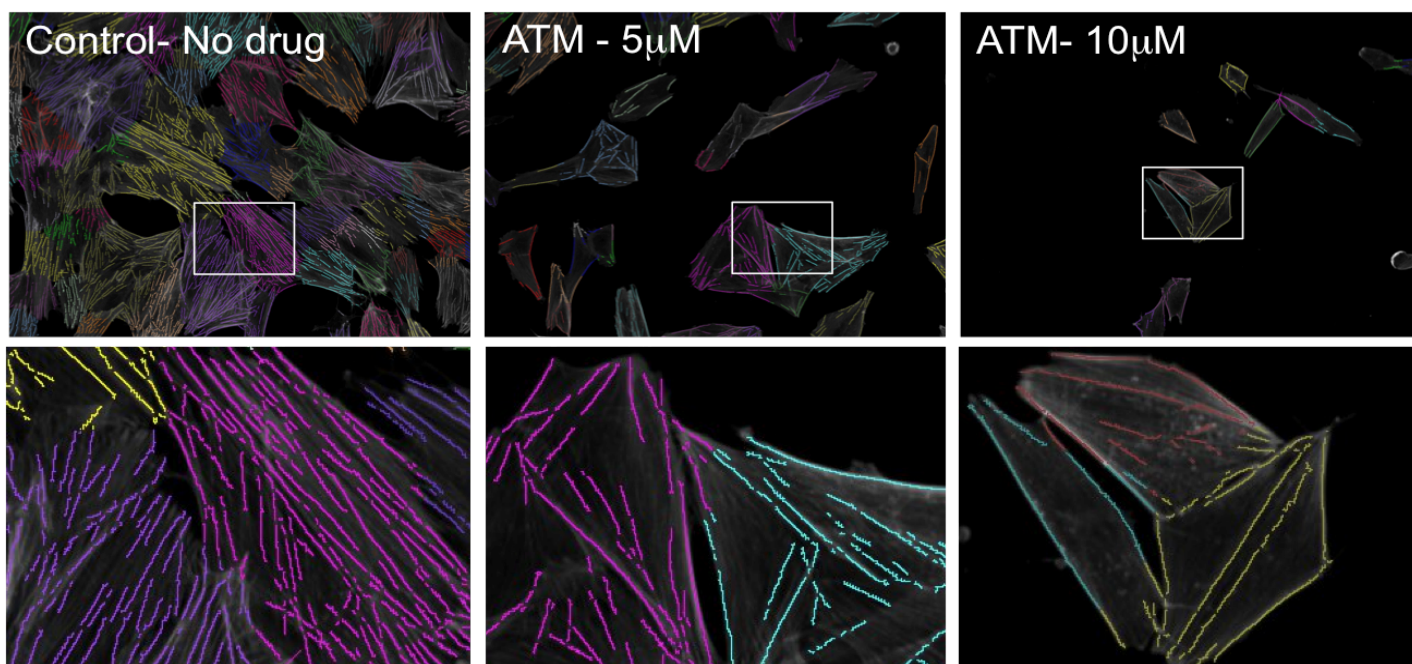
Our second drug technology platform is on the verge of identifying its lead candidate compound. The program has identified a family of 20 active compounds, with the task now to identify the preferred compound.

The program, is headed by Dr Justine Stehn who, along with Professor Peter Gunning, co-discovered this drug technology while conducting research into the role of the cell cytoskeleton in cancer at the University of New South Wales in Australia.

The tropomyosin isoform, Tm5NM1, is a new anti-cancer target. It's one of over 40 different types (isoforms) of tropomyosin found in human cells, all of which form part of the cell's skeletal structure known as micro-filaments, and which plays such a key role in

how a cell moves and attaches to its neighbours and how it transmits signals both internally and externally.

In normal cells, Tm5NM1 is just one of many tropomyosin isoforms that the cell employs. The crucial discovery of Gunning and Stehn was to show that cancer cells have come to rely on Tm5NM1 for their function and survival in a way that normal cells have not. Tm5NM1 is a major component of the cancer cell's skeleton. Shown below are some images of a cancer cell that has been treated with increasing amounts of an ATM compound. The microfilaments of the cells are highlighted with coloured lines. Blocking the ability of the target protein, Tm5NM1, to form microfilaments effectively causes the structure of these cells to disintegrate and the cancer cell to die.



Targeting the cytoskeleton of the cancer cell is not a new approach. Some of the longest-serving and most widely used chemotherapy drugs target the cytoskeleton. Drugs such as the taxanes (paclitaxel, docetaxel) and the vinca alkaloids (vincristine, vinblastine) remain among the most widely used drugs in oncology, being used in the treatment of cancers of the breast, prostate, lung, ovaries, stomach and head and neck (taxanes) and various leukemias (vinca alkaloids).

The cell's skeleton has two main components – the microfilaments and the microtubules. Think of it in terms of the two main components of the body's skeleton – bones and joints. They each do different things, but they each need each other, and together they form a single structure.

The taxanes and the vinca alkaloids target the microtubules. These drugs are very potent but have limitations in that they do not distinguish between the microtubules of a cancer cell and a normal cell. The result is a significant amount of toxicity and hence an inability to use the drugs at dosages that might be far more effective. Cancer cells also quickly adapt and become resistant to treatment, again limiting their clinical application to first-line therapy.

The success of the microtubules as a target in cancer therapy inevitably brought the microfilaments into play as a potential target as well many years ago. Despite extensive interest, no such drug was ever developed and brought into the clinic. The reason is very clear – among a wide range of functions, the microfilaments are essential for muscular contraction, which meant that certain other cells in the body, such as cardiac muscle cells, were adversely affected when drugs targeting the whole microfilament were tested in animals.

Until now there has been no drug able to discriminate between the microfilaments in specialized cells such as heart muscle cells and those in cancer cells. The breakthrough was the discovery by Gunning and Stehn that microfilaments in cancer cells differed from those in normal cells in being highly dependent on the tropomyosin isoform, Tm5NM1, for their survival. By targeting the Tm5NM1 component of the microfilaments, we are able to destroy specifically the structure of a cancer cell, leaving specialized cells, such as heart cells fully functional. This improved specificity is what makes the ATMs a very powerful new class of anti-cancer drug.

We have been running an intensive ATM drug discovery program over the past six months. One of the outcomes of that program has been the identification of six different patent families of compounds. This provides us with a wealth of molecules to work with in the future for all sorts of potential therapeutic applications outside the cancer field. But it has also meant having to work our way through a lot of compounds and in the course of that process a large number of highly active compounds have been identified. The task has been to pick a winner from this large library of actives, a task that is within weeks of being complete.

The clinical indications we are focusing on for the ATMs are two adult cancer indications, melanoma and prostate cancer and a childhood indication, neuroblastoma. We are projecting that it will be 3Q15 when our lead ATM makes its way into the clinic.

Instead of replacing taxanes and vinca alkaloids in the clinic, we see the most likely role for ATMs in cancer therapy as being in combination with those older drugs. In combination, these drugs are delivering a killer-blow to cancer cells. By knocking out both microtubules and microfilaments, the cancer cell has no capacity to detour its signalling processes. The result is complete disintegration of the cytoskeleton.

Novogen Programs Summary Table

Therapeutic Field	Drug Candidate & Program	Discovery	Preclinical	Clinical
Oncology	Cantrixil Ovarian Cancer			Q3 2015
	Trx-7 Prostate Cancer			Q3 2015
	Trilexium Neural Cancer			Q4 2015
	ATM Program Melanoma			Q4 2015
Degenerative Diseases	Neurodegenerative Diseases			TBA
	Musculodegenerative Diseases			TBA
	Neural Injury			TBA

**KEY DATES**

September 8-11
Rodman & Renshaw Annual
healthcare Conference
New York, USA

Sept 30 – October 1
14th Annual Biotech in Europe Forum
Basel, Switzerland

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