17 April 2013

ASX RELEASE

Novogen releases newsletter to coincide with General Meeting

Novogen today has posted on its website its inaugural newsletter which is intended to inform shareholders of its strategy in developing CS-6 and its analogs as comprehensive cancer therapies.

About Novogen

Novogen Ltd is a public Australian biotechnology company whose shares trade on both the Australian Stock Exchange (symbol 'NRT') and NASDAQ (symbol 'NVGN'). The Company is based in Sydney, Australia and is focused on the development of a family of novel anti-cancer drugs based on comprehensive anti-cancer activity against both cancer cells and cancer stem cells. The Company's inaugural drug candidate is CS-6.

About CS-6

CS-6 belongs to a new class of drug candidates intended to treat most forms of cancer in a comprehensive manner, targeting both cancer cells and their progenitor cells, cancer stem cells. CS-6 shows broad anti-proliferative and cytotoxic activity against human cancer cells and ovarian cancer stem cells. CS-6 also has been designed deliberately to meet the major known criteria for crossing the blood-brain barrier, and for that reason is being developed as a first-line for the treatment of glioblastoma multiforme, the main form of primary brain cancer.

About Cancer Stem Cells

Cancer stem cells (CSC) (or tumour-initiating cells) are believed to be a subpopulation of cells within many types of cancer that are responsible for driving the growth and spread of the cancer. CSC typically are resistant to radiotherapy and chemotherapy and are thought to be responsible for cancer recurrence following therapy. Targeting CSC is a new direction in oncology drug development as a means of preventing cancer recurrence.

Further information
Contact Dr Graham Kelly, Chief Executive Officer.

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Please note that the Company currently is relocating offices and that the original phone numbers no longer are in use. New contact details will be available shortly.

Further information is available on the Company's web site, www.novogen.com

NOVOGEN

Our Mission: To bring the ability to conquer cancer into the reach of the common man

Newsletter

April 2013

Number 1

In this issue:

What it means to have the technology to make CS-6 and CS-6 analogs

The significance of CS-6 lies not just in the drug and the clinical and commercial opportunities that it holds. It lies deeper in the breakthrough technology that led to its discovery.

Behind the difference between the *simple benzopyran* structure of the first generation Novogen isoflavonoid drugs (phenoxodiol, NV-128, NV-143 etc) and the *super-benzopyran* drugs in the Company's current pipeline lies a major development that has implications well beyond that of the benzopyrans. When time and resources permit, we will look at applying that development to other types of drugs, but for the moment the opportunity that lies ahead in the field of oncology is more than enough.

At its simplest, the breakthrough development is an ability to 'bend' molecules that have an inherent rigidity, where that rigidity or inflexibility acts as a natural barrier to making more powerful versions of the molecule. Think of the difference between a one-dimensional on paper and three-dimensional computer graphics, and you get some way to understanding the scope of our breakthrough design and manufacturing technology.

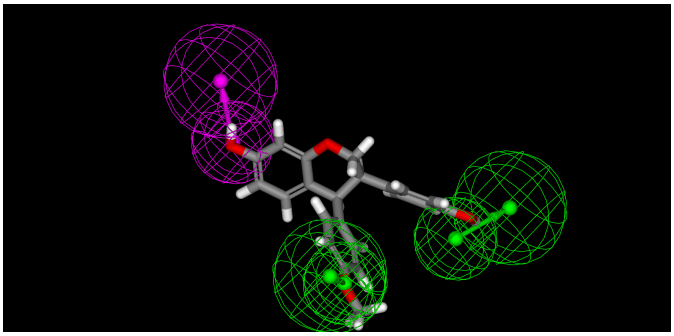
CS-6 represents the first example of that new technology. It is entirely possible that we have by accident stumbled upon the best example of that new technology and will never better it. But we don't believe so. We are continuing with an analog program that we expect will deliver designs even more active than CS-6 or with anti-cancer activities to complement that of CS-6.

The advantage of the *super-benzopyran* design is evident in two features. The first

is what we believe will lead to a major improvement in the bio-availability of the drug. This refers to the ability of a drug to leave the bloodstream and to enter the cancer cell. For all the early promise of the *simple benzopyran* drugs, in the end this emerged as a potential problem in the clinic. The flexibility of the new manufacturing process has meant that we can change the electron field force of the *benzopyran* molecule to help the molecule avoid the cancer cell's ability to repel it. We refer to this ability as 'Stealth technology' and will be bolted onto every *super-benzopyran* drug we make.

A second distinctive benefit of the technology is the increase in potency it has delivered. The amount of drug required to kill cancer cells in the test-tube can be expressed in two ways – either as mg of drug per milliliter of culture medium, or molarity, which refers to the number of molecules of the drug per milliliter of culture medium. Both terms amount to the same thing.

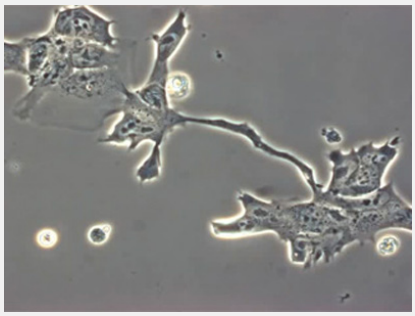
The first generation Novogen drugs (simple *benzopyrans*) generally were active at **micro-molar** levels. One thousand times below that is **nano-molar** and one thousand times below that again is **pico-molar**. CS-6 is active against cancer cells down to pico-molar levels. In other words, CS-6 requires 1 million times fewer molecules than the simple *benzopyrans* to achieve the same anti-cancer effect, highlighting the extraordinary potency of this molecule.



The (coloured) electron fields of the *super-benzopyran* molecule that have been modified to overcome a cancer cell's ability to avoid the drug.

Comprehensive cancer therapy explained

Most people by now would have heard of stem cells. These are the basis of the new science of regenerative medicine – the use of progenitor cells to restore function to a damaged spinal cord or to a heart after a severe heart attack. Stem cells are the cells from which all other cells derive. There are two basic forms of stem cells – embryonic and adult. Embryonic stem cells are referred to as *pluripotent* – that is, each has the capacity to differentiate into a range of different tissue types. Adult stem cells are more focused, typically leading to one tissue type only.



Embryonic stem cells

In the same way that normal, healthy tissue derives from tissue stem cells, so cancer tissue is thought to derive from those same tissue stem cells that have become cancerous. These cancer stem cells are believed to provide all the various cell types present in a tumor (including blood vessels), to be responsible for the spread of the cancer (metastasis), and for recurrence of the tumor following therapy.

Cancer stem cells have been identified in a range of common cancer types including prostate cancer, brain cancer and ovarian cancer. The notion of the cancer stem cell being the key to the

cancer process is not universally held, although the weight of evidence inexorably is pointing to the critical role of cancer stem cells in the start of the cancer process and in tumor recurrence following anti-cancer therapy.

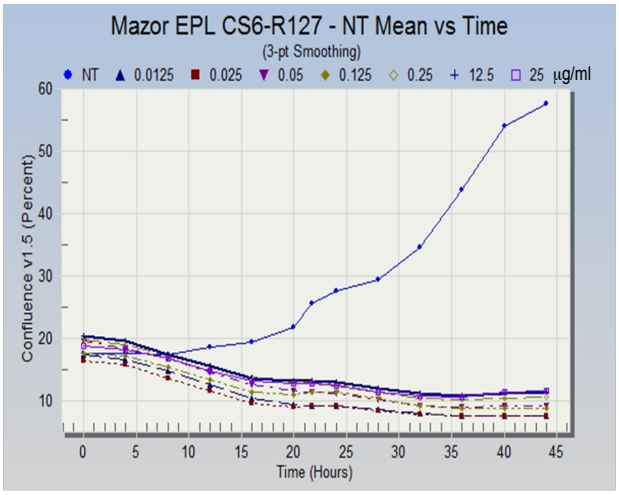
A common feature of the different types of cancer stem cells so far isolated is that they are highly resistant to radiotherapy and chemotherapy. It is that resistance that allows them to survive an extensive therapeutic onslaught, and then to go on to repopulate the tumor. But this time the new population of tumor cells are different to the original ones…these new cells now bear the resistance characteristics of their parent stem cells. Follow-up radio- or chemo-therapy now is met either with a much-reduced response or no response.

This is the challenge that Novogen has set itself – to go beyond the current horizon of attacking just the regular cancer cells, and to attack the source of the cancer – the cancer stem cells. And on the basis of what we have seen so far, we are confident that we have the technology to achieve this goal.

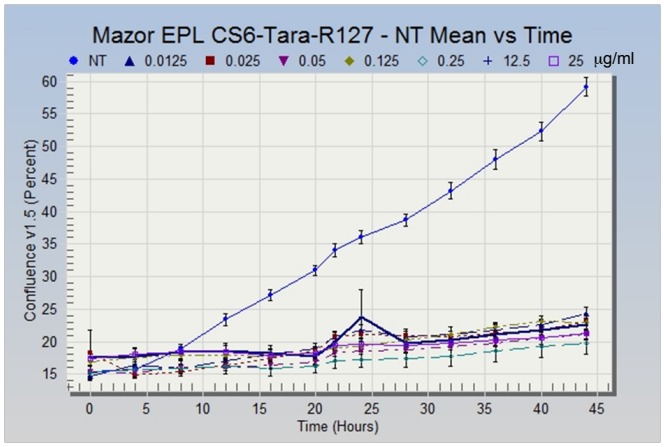
Going from (first generation) *simple benzopyrans* to (second generation) *super-benzopyrans* had led to a vast increase in activity against regular cancer cells. It was a natural thing therefore to ask the question whether we would see the same jump in activity against cancer stem cells.

What you are looking at in both graphs is the rate at which cancer cells grow to confluence on a culture plate. In other words, the rate at which they divide to eventually cover the entire surface of the plate. The top graph is a line of highly-resistant ovarian cancer stem cells (R127). The bottom graph is the progeny of R127 cells (Tara-R127). These progeny cells are obtained by growing R127 in athymic mice, treating the mice with carboplatin and paclitaxel, and then waiting for the tumor to recur. This is as close to the clinical situation of late-stage ovarian cancer as it is possible to get to in the laboratory.

The blue line (NT) in each graph represents No Treatment (no CS-6). As shown, CS-6 inhibited the growth of both the ovarian cancer stem cells and their progeny cells at all drug concentrations tested, including down to nanomolar levels (0.0125 ug/mL). **Thus confirming this drug's equivalent high potency against both the regular cancer cell and its cancer stem cell parent.**



CS-6 inhibiting the growth of ovarian cancer stem cell line R-127



CS-6 inhibiting the growth of the daughter cells of R-127

That is the basis of the concept of comprehensive anti-cancer therapy – the ability to shrink a tumor through death of the regular cancer cells comprising the bulk of the tumor, PLUS the death of the cancer stem cells, thereby retarding or completely inhibiting the likelihood of the tumor recurring.

Bringing CS-6 into the clinic

We have set ourselves the target of having CS-6 complete a Phase 1a study by May 2014. To that end, we have commissioned a clinical research organization to conduct a full pre-clinical program embracing pharmacokinetics, ADME, toxicology and xenograft efficacy. That study is underway and is expected to provide all relevant data necessary to support a Phase 1a study to be conducted in an Australian hospital.

At this stage we are planning on pursuing two clinical indications in Phase 1b studies.

(a) Late-stage ovarian cancer

The choice of this indication speaks for itself. The extraordinary potency of CS-6 against both regular ovarian cancer cells and a library of ovarian cancer stem cells points to a strong prospect of finally being able to make a difference to the lives of women with late-stage ovarian cancer.

A key pre-clinical milestone lies ahead of us in this objective. That is to use an ovarian cancer stem cell line considered by the Yale group to represent the most chemo-resistant and most aggressive of all of their library of ovarian cancer stem cells and which has never responded yet to experimental treatment in their xenograft mouse model. That represents their gold standard and our first milestone of 2013.

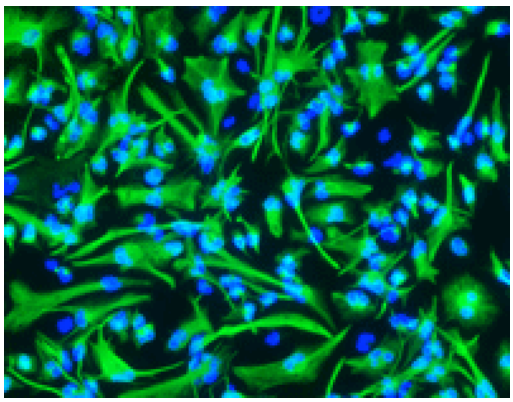
Success in that model would provide all the justification required to proceed into a Phase 1b study in late-stage, carboplatin-refractory ovarian cancer, the design of which will be in the hands of a scientific advisory panel comprising leading OBGYN oncologists.

(b) Glioblastoma multiforme

The choice of this indication lies in two observations. The first is the finding that CS-6 shows extraordinarily high potency against gliomablastoma cells in the laboratory. The second is that the chemical structure of CS-6 shows all the hallmarks of being able to cross the blood-brain barrier, something that was deliberately designed into its structure.

We are starting with the standard model of growing tumor cells, including brain cancer stem cells, under the skin of mice and looking for evidence of growth inhibition. We then will progress onto an orthotopic model where the same cancer cells are injected into the brain of athymic mice and the ability of CS-6 to inhibit the growth of those cells a clear indicator of the drug's ability to cross the blood-brain barrier. That is our second major pre-clinical milestone ahead of us this year.

Studies also are getting underway to establish if CS-6 shows the same anti-cancer activity against brain cancer stem cells that it does against ovarian cancer stem cells. We anticipate that it will, but that remains to be determined.



Brain cancer stem cells growing in culture.

Reproduced with kind permission of Dr Steve Pollard, UCL Cancer Institute

Breakthrough Therapy Designation

CS-6

Aiming for Breakthrough Therapy designation

The traditional pathway to market for an anti-cancer drug, or any drug for that matter, has been the classic Phase 1-2-3 approach.

A Phase 1a is a small study usually conducted in 6 subjects or less, typically healthy volunteers, where a very small amount of the new drug is applied and the pharmacokinetic and pharmacodynamics of the drug determined. Those data inform the best way to use the drug (eg. once a day, twice a day etc).

A Phase 1b study normally has one objective – to determine the safety profile of the drug and the highest dose that it is possible to give safely (maximum tolerable dose). This usually is conducted in patients with late-stage cancers of any type.

Phase 2 studies generally are conducted in patients on an intent-to-treat basis, meaning that you now use patients with the form of cancer being targeted. It is not unusual to conduct more than one Phase 2 study in order to determine the appropriate dose and appropriate clinical end-points.

A Phase 3 study is the pivotal study on which the FDA (or any regulatory authority) bases their approval to market the drug.

The criticism over the years from patient advocacy groups is that while this approach may be appropriate for drugs being developed for non-lethal indications, many cancer patients don't have time to wait the 8-10 years it usually takes to get a promising new drug through the system.

The FDA has addressed this criticism in the past through a number of approval devices such as Orphan Drug Status, Fast-Track Status and Accelerated Approval Status, all of which provide a degree of shortening of the approval process.

But in February of this year the FDA announced a significant change to their approval process, offering the opportunity to substantially shorten the approval process for drugs with early clinical promise and which are intended for areas of substantial unmet clinical need.

This new process is known as Breakthrough Therapy Designation and was created by the FDA to expedite the development and review of a potential new medicine if it is "intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence suggests that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints."

A more complete history and review of this matter is available at the following link: http://www.focr.org/rpm-report-qbreakthrough-therapyq-new-pathway-in-fdasia-may-point-the-way-to-future-reforms.html

On the basis that we believe that CS-6 will meet the key criteria for Breakthrough Therapy status, we propose to move directly from a Phase 1a study into Phase 1b/2a studies using CS-6 on an intent-to-treat basis in patients meeting strict inclusion criteria for either late-stage ovarian cancer Temozolomide-resistant glioblastoma multiforme.

Novogen management has extensive experience in pharmaceutical patents and patent strategies. A Provisional Patent Application has been lodged for CS-6 and the underlying technology and it is anticipated that a series of patents will ensue over the coming years as the limits of the technology are explored.

A recent change to patent rules and regulations demands that any inventions be "reduced to practice". That is, the international patent office will only grant patents on those inventions that can be manufactured. This stops inventors making ambit claims for millions of compounds that may not be able to be manufactured by the proposed technology. Through collaborators in Switzerland, we are currently manufacturing a wide series of new compounds that are closely related to CS-6. This ensures optimal patent protection of CS-6 and its background manufacturing technology. In addition, the manufacture of a range of wider analogs will allow us to generate new lead compounds potentially over a variety of cancer indications.

The first library of *super-benzopyrans* afforded the lead compound CS-6. Deeper analysis of the how certain compounds acted against key cancer cell lines allowed Novogen scientists to identify "Stealth technology". Stealth technology was identified as a sub-unit group of atoms in the parent *super-benzopyran* structure that allowed compounds to avoid a cancer cell's natural defense mechanisms.

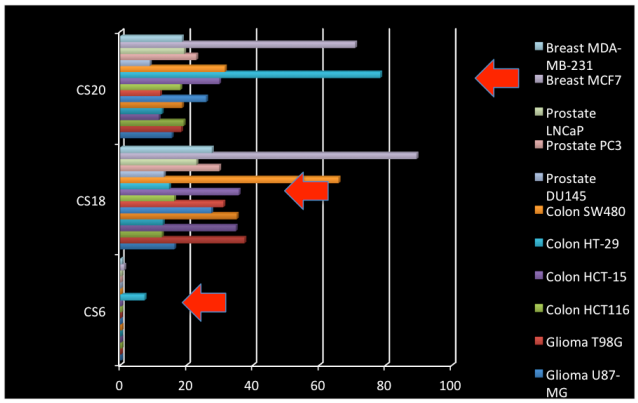
We now are making the next family of molecules leveraging off this Stealth technology, allowing us to understand exactly how it works and determine if we can further improve it. We have already synthesized the next library of molecules, some of which contain "double Stealth technology". These compounds are being screened for their activity against cancer cells and their ability to avoid key cancer cell defense mechanisms.

The libraries have been designed to allow fine-tuning of the current *super-benzopyrans* to cancer types alongside ovarian cancer and brain cancer. These libraries represent the next logical step in generation of this family of drug candidates.

As the new CS-6 technology platform represented a significant step forward in the generation of *super-benzopyrans*, so we are also developing the next step forward to go beyond *super-benzopyrans*. The initial work on this next important discovery technology platform is projected to be completed by March 2014.

Novogen is committed to not only ensuring a solid patent background for CS-6, but to elaborating the technology in a number of parallel streams. This approach will ensure that we have a fruitful pipeline with the potential to bring at least one new compound to the clinic every year.

The Pipeline



'Stealth Technology' identified on CS-6 has the same effect on other drug candidates. When the stealth technology sub-unit was bolted onto CS-20, the new molecule (CS-18) demonstrated an ability to avoid the detoxifying enzymes over-expressed by the colorectal cell line HT-29.

Fully-owned subsidiary Novogen (North America) Inc has been established.

The role of the Company will be:

- To be available to respond to US-based shareholders and to the market generally
- To respond to the SEC and NASDAQ in real time
- To coordinate applications to the FDA and the US Patent Office
- To help coordinate the growing chain of collaborating research groups world-wide
- To help promote the Company in North America.

Dr Andrew Heaton is relocating to the US to head up this new entity in June 2013. He will be President and CEO. The Company will be based in Ithaca, New York. The contact details of the new Company will be made available shortly.

Novogen (North America) Inc