APP Securities Company Research

13 September 2016

Noxopharm Limited

Pharmaceuticals & Biotechnology

A$0.14 **TARGET PRICE** A$0.35

Speculative Buy

Noxopharm Limited is seeking to engage in the treatment of cancer, As such Noxopharm has created a new dosage form of idronoxil which is a cancer treatment called NO66 that it aims to test with a clinical study starting in 2016. It has patents pending on this new dosage form of idronoxill.

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Asia Pacific
Prudential Securities

Trialling a potential cure for cancer

In Australia, 1 in 2 men and 1 in 3 women will be diagnosed with a potentially lethal cancer before the age of 85 and 40% of these patients will die from that cancer within 5 years of diagnosis.

Overwhelmingly, those deaths stem from the problem of drug resistance, with the cancer either failing to respond to treatment form the start, or responding and then becoming resistant.

Once resistant, the cancer is invariably fatal.

Chemotherapy with cytotoxic (cell-damaging) drugs remains the backbone of cancer therapy and in general has made a major difference in the survival prospects of some cancers. But clearly is not delivering to the extent that patients and their doctors would like.

The search for ways to overcome drug resistance mechanisms in cancer cells has been a high priority in medical research for many years, unfortunately with very little to show for it.

With 1 in 3 of us likely to die from cancer, finding a way to make current drugs work better is one of the most urgent needs we face as a community.

It also is a major investment opportunity.

20 years ago, experimental drug, idronoxil, was being hailed as one of the best prospects to deliver on that need and opportunity. Despite its early promise, it faltered and failed at the last step.

Noxopharm is confident that it has discovered why it failed and how to make it work.

Resistance mechanisms are part of a cancer cell's over-expression of survival mechanisms. Those mechanisms include switching somes genes OFF and others ON through a set of central master signalling switch boxes known as PI3 kinase/Akt/NF-kB/mTOR.

Idronoxil works because it does not target these switchboards directly.

As such Noxopharm has created NO66 as a new dosage form of idronoxil (patents pending) and aims to put that confidence to the test with a clinical study starting in 2016.

If NOX66 delivers on its promise, the rewards for both patients and investors could be extraordinary.

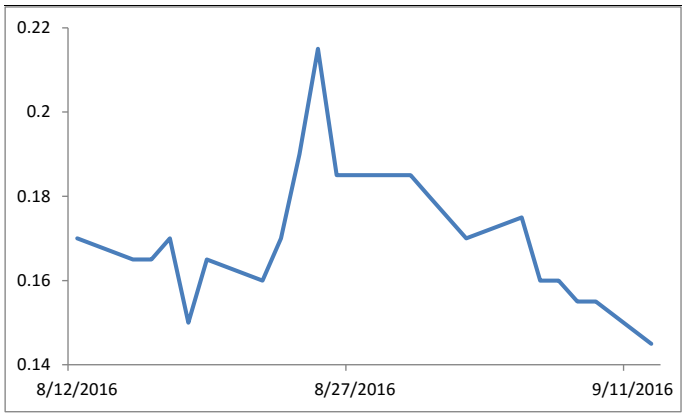
Disclaimer: APP Securities Pty Ltd acted as Lead Manager in Equity Placement as part of the Noxopharm Limited Initial Public Offering announced by the ASX on 9 August 2016, for which it received fees.

Company Data

Number of shares	75.2M
Market capitalisation	$12.08M
Free Float (%)	43.8
12 month high/low	$0.215/$0.15
Average Daily Turnover ($M)	0.1
% S&P/ASX 200	N/A
% All Ordinaries	N/A
DDM Ranking	N/A
ESG Score (Ranking)	N/A
GICS Industry Group	Healthcare

Data Source: Factset, APP Securities

Share Price Performance



Source: APP Securities, Company Reports.

APP Securities contributes all company estimates to Bloomberg, Thomson Reuters, FactSet and Capital IQ.

Note: Numbers displayed are a sub-set

The ESG (Environmental, Social, Governance) score is a measure of the sustainability and ethical impact of an investment in this company or product. ESG scores range from 0.1 (min) to 100 (max). ESG scores are provided to AAP Securities by Bloomberg and are only available for those companies that disclose ESG data to Bloomberg.

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COMPANY OVERVIEW

Noxopharm believes that it has a realistic chance of making a difference to the survival prospects of people with many types of life-threatening cancers. If it is right, it would propel this Company onto the international stage.

Noxopharm is the brainchild of Dr Graham Kelly, the recently departed CEO of Australian/US biotech company, Novogen. Kelly founded Novogen in 1994, leaving it in 2007, then returning by way of a reverse takeover of Novogen in December 2012, before leaving again in July last year.

Between 1998 and 2008, the focus of Novogen's and Kelly's attention was the drug candidate, idronoxol (better known to most people as phenoxodiol). Idronoxil was originally discovered by Kelly while working as an academic medical researcher, and subsequently shown in the laboratory to greatly increase the sensitivity of cancer cells to most of the commonly used cytotoxic chemotherapy drugs. Kelly said at the time that he believed idronoxil was the most powerful drug of its kind …something that he still believes.

Novogen had focused on ovarian cancer, based on laboratory studies showing that idronoxol was able to restore sensitivity in ovarian cancer cells to standard-of-care drugs carboplatin and paclitaxel, even after those cancer cells became highly resistant to those drugs. Yale University was a great supporter of idronoxil. They said publically that they believed that idronoxil represented a real chance to finally do something about the appalling survival prospects of women diagnosed late with ovarian cancer.

Idronoxil went all the way into a multi-national Phase 3 study (known as OVATURE), being given as an oral dose form in conjunction with carboplatin to women with carboplatin-resistant ovarian cancer. But the study was abandoned before it was fully recruited due to lack of any meaningful clinical benefit.

At that stage, idronoxil (phenoxodiol) was bundled up with all of Novogen's remaining assets and on-sold to US biotech, MEI Pharma Inc (MEIP). At that point, MEIP put idronoxil back on the shelf and that could have been the last that the world would hear of idronoxil.

But Kelly didn't let it go. Convinced that the problem lay with a lack of understanding of how to use the compound rather than an inherent weakness in the compound itself, he eventually in mid-2012 came up with what he believed to be the problem, and with that, a solution. The 'problem,' he believed, lay with the way the human body metabolised idronoxil, effectively rendering it completely inactive. Mice, where idronoxil had originally been tested to great effect, treated these class of compounds in a completely different way, leaving enough drug untouched that enabled it to work. The 'solution', Kelly believed, was a new way of delivering idronoxil that would protect the drug from the body's attempts to destroy it. NOX66 is the result.

Noxopharm plans on bringing NOX66 into the clinic in 2016, testing its ability to increase the effectiveness of a standard therapeutic combination of carboplatin and paclitaxel in patients with late-stage cancers. The Company is using this first study simply to confirm that the new formulation is working as predicted. They have not at this stage confirmed the type(s) of cancer that they then will focus on, although prostate, ovarian and cervical cancer look the most likely.

Noxopharm intends to run on a virtual business model with minimal overheads, with a small team of scientists and project managers overseeing clinical and R&D projects being conducted by external contractors.

INDUSTRY SNAPSHOT

Drug resistance

Resistance to chemotherapy and radiotherapy is often said to be the greatest hurdle preventing more successful management of cancer.

Most life-threatening cancers respond to these therapies initially, but then over time become less responsive until they eventually stop responding.

Where a cancer shows little or no response initially, this is referred to as primary resistance; where it happens after multiple lines of therapy it is known as acquired resistance.

The mechanisms involved in both forms of resistance are thought to be similar involving highly-resistant cancer stem cells, elevated levels of pro-survival mechanisms, and the development within the cell of means of ejecting the drug before it can work.

Drug resistance mechanisms might be overcome to some degree if chemotherapy and radiotherapy could be given at sufficiently high dosages. But they can't, because they cause too much collateral damage to healthy tissues.

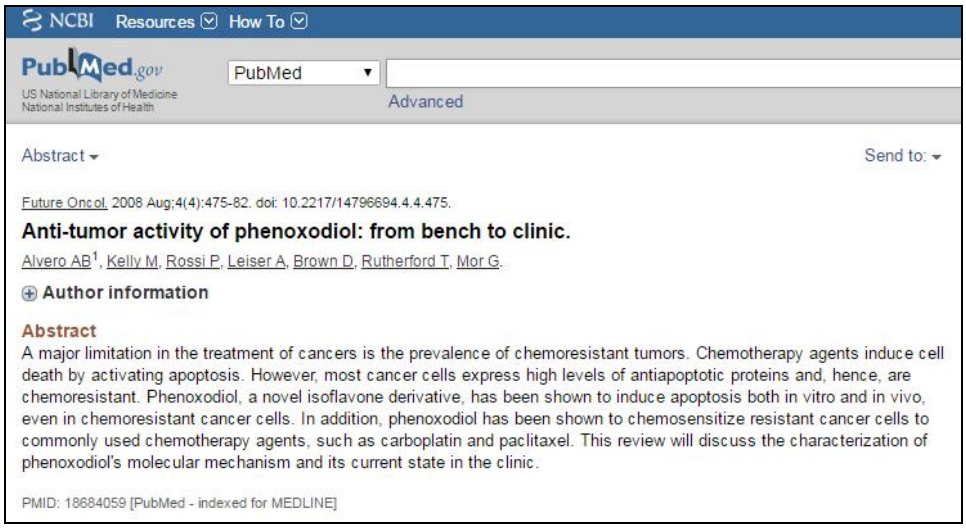
Some progress in this field has been made by packing toxic drugs into various constructs that tend to target cancer cells preferentially, or delivering radiation more selectively to cancer tissues. And while these approaches certainly have had some effect on reducing the problem of side-effects, they have not been able to block the ability of the cancer cell to develop eventual resistance to chemotherapy or radiotherapy.

This is the field that idronoxil proposes to enter. The concept behind idronoxil is a two-fold approach:

- to elevate the toxic effects of standard therapies on cancer cells without affecting healthy tissues. *In other words, to make current dosages of chemotherapy more effective. This is called chemo-sensitising.*
- to destroy the resistance mechanisms that make cancer cells able to withstand standard therapies.

Idronoxil

Idronoxil has been extensively studied, with >50 scientific research publications. There are 2 review articles that nicely summarise its properties: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Future Oncol. 2008 Aug;4(4):475-82. doi: 10.2217/14796694.4.4.475.

Anti-tumor activity of phenoxodiol: from bench to clinic.

Alvero AB[1], Kelly M, Rossi P, Leiser A, Brown D, Rutherford T, Mor G.

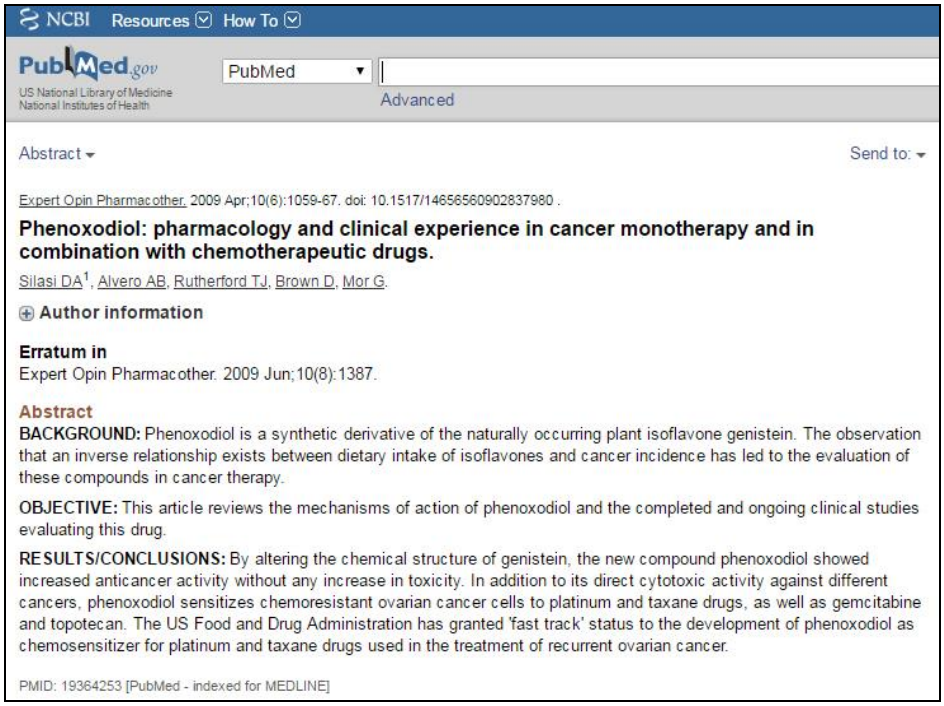
Author information

Abstract

A major limitation in the treatment of cancers is the prevalence of chemoresistant tumors. Chemotherapy agents induce cell death by activating apoptosis. However, most cancer cells express high levels of antiapoptotic proteins and, hence, are chemoresistant. Phenoxodiol, a novel isoflavone derivative, has been shown to induce apoptosis both in vitro and in vivo, even in chemoresistant cancer cells. In addition, phenoxodiol has been shown to chemosensitize resistant cancer cells to commonly used chemotherapy agents, such as carboplatin and paclitaxel. This review will discuss the characterization of phenoxodiol's molecular mechanism and its current state in the clinic.

PMID: 18684059 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/18684059



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Abstract Send to:

Expert Opin Pharmacother. 2009 Apr;10(6):1059-67. doi: 10.1517/14656560902837980 .

Phenoxodiol: pharmacology and clinical experience in cancer monotherapy and in combination with chemotherapeutic drugs.

Silasi DA[1], Alvero AB, Rutherford TJ, Brown D, Mor G.

Author information

Erratum in
Expert Opin Pharmacother. 2009 Jun;10(8):1387.

Abstract

BACKGROUND: Phenoxodiol is a synthetic derivative of the naturally occurring plant isoflavone genistein. The observation that an inverse relationship exists between dietary intake of isoflavones and cancer incidence has led to the evaluation of these compounds in cancer therapy.

OBJECTIVE: This article reviews the mechanisms of action of phenoxodiol and the completed and ongoing clinical studies evaluating this drug.

RESULTS/CONCLUSIONS: By altering the chemical structure of genistein, the new compound phenoxodiol showed increased anticancer activity without any increase in toxicity. In addition to its direct cytotoxic activity against different cancers, phenoxodiol sensitizes chemoresistant ovarian cancer cells to platinum and taxane drugs, as well as gemcitabine and topotecan. The US Food and Drug Administration has granted 'fast track' status to the development of phenoxodiol as chemosensitizer for platinum and taxane drugs used in the treatment of recurrent ovarian cancer.

PMID: 19364253 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/19364253

Idronoxil is a synthetic derivative of naturally-occurring plant isoflavone, genistein, itself the subject of considerable research and attempts to bring it into the clinic for its anti-cancer properties.

The target of idronoxil is a protein found on the outer membrane of all cancer cells and known as ENOX. ENOX is responsible for regulating the pump (proton pump) that moves waste hydrogen ions out of the cell. Inhibiting ENOX disables the pump which causes toxic levels of hydrogen ions to build up in the cell.

Human cells have the ability to make two closely related forms of ENOX known as ENOX1 and ENOX2. Healthy cells only make ENOX1; once a cell becomes cancerous, it switches to making ENOX2.

Idronoxil only targets ENOX2 and has no effect on ENOX1.

The reliance of all cancer cells on ENOX2 explains why idronoxil works against all forms of cancer, and the absence of ENOX2 on healthy cells explains why idronoxil only targets cancer cells.

The toxic levels of hydrogen ions within the cancer cell has a number of knock-on effects, but the main one is a shift in sphingolipid metabolism in the cancer cell's plasma membrane, leading to a dramatic fall in levels of sphingosine-1-phosphate (S1P).

S1P is a powerful pro-survival factor, typically over-expressed in cancer cells, and responsible for down-regulating cancer-suppressing genes and up-regulating cancer-promoting genes. S1P also promotes the ability of the cancer cell to develop drug-resistance mechanisms.

Idronoxil is able to kill cancer cells in its own right, as evidenced by its ability to retard the growth of human cancer xenografts in mice when used on its own.

But its most valuable property appears to be its ability to make cancer cells respond better to standard chemotherapies that kill cancer cells by damaging them.

The effect of idronoxil in lowering the cancer cell's S!P levels means that the cell is less able to repair the damage caused by the other drugs and less able to exercise those mechanisms it has developed to eliminate the other drugs.

In both the test tube and in animal studies, idronoxil has proven to be a powerful sensitiser of all major standard cytotoxic chemotherapy drugs including cisplatin, carboplatin, paclitaxel, gemcitabine and doxorubicin.

NOX66

NOX66 is a new form of delivery of idronoxil designed to avoid the problems associated with the oral and intravenous dosage forms used to date.

Noxopharm believes that the problem to date has been that idronoxil is subjected to virtually complete metabolism by Phase 2 metabolic enzymes, a classic response of the body to the presence of water-insoluble drugs, seeking to make them more water-soluble by attaching them to another compound so that they can be excreted in the kidneys.

The effect of this is to render the drug inactive.

The same process happens to a number of commonly-used drugs such as paracetamol and codeine. But with those drugs, healthy tissues (such as the brain in the case of paracetamol and codeine) have the capacity to remove the attaching compound, liberating the free drug so that it can work.

The problem for idronoxil, however, is that its target is cancer tissue and not healthy tissue. Noxopharm believes that cancer tissue is not able to liberate the drug, meaning that its ability to seek out and kill cancer cells is considerably compromised.

NOX66 is the dosage form that Noxopharm has come up with to solve this problem.

The Company has filed patents on this approach, and remains under wraps for the moment until the patents progress a bit further.

But we understand that it is designed to protect the drug from exposure to Phase 2 metabolic processes, keeping as much of the drug as possible in a free form that can readily seek out and bind to cancer cells.

CLINICAL PROGRAM

NOX66 is set to come into the clinic. We understand that this is scheduled to happen before the end of 2016 and will be a Phase Ia/Ib study involving patients with late-state solid tumours who either have failed to respond to standard of care therapies or who have declined such therapies.

The study will be conducted in Europe at several sites.

At the stage the Company is not indicating what clinical indication will be looked at in the next step.

They are giving themselves to chance to see in the Phase I study if any particular cancer type is a stand-out in terms of response, although using NOX66 to increase the sensitivity of such cancers as prostate cancer, ovarian cancer and pancreatic cancer to standard therapies seems a logical progression given the history of idronoxil.

What we find interesting, however, is that the Phase I study involves using the drug in combination with carboplatin and paclitaxel.

It is highly unusual to do anything more than use the test drug on its own in Phase I, so the fact that they are going from NOX66 on its own as a first step to NOX66 + other drugs as a second step within the one study, points to a degree of confidence over the drug and its safety and efficacy.

CLINICAL PROGRAM UPDATE

NOXOPHARM TO INITIATE RADIOTHERAPY CLINICAL STUDIES.

- NOX 66 to extend reach from potentiating chemotherapy to potentiating radiotherapy
- Guidance to market on major program initiative

As foreshadowed in the Company's recent Prospectus, the company's post OPO intended to expand its clinical pipeline and clinical assets.

Noxopharm today announced that it has initiated a major research program testing the ability of NOX66 to promote the anti-cancer effects of radiotherapy. The program will involve clinical trials in Australia and overseas. This program will run in parallel with the Phase 1a/1b/2a study being established in Europe where NOX 66 is being tested in combination with chemotherapy.

The details of the clinical studies will be released in due course, but involve the use of NOX66 with radiotherapy in specific cancer types including metastatic prostate cancer, particularly where multiple tumours are present and irradiation of all tumours is impractical, and where the dosage of the radiotherapy is palliative because of the advanced nature of the disease.

Radiotherapy suffers the same challenge as chemotherapy= cancer cells learn how to survive the therapy. Nay of the mechanisms that lead to chemotherapy drug resistance are the same that lead the cell to resist radiotherapy (radio-resistance). The ability of the active ingredient of NOX66, idronoxil, to cancel cancer drug- resistance mechanisms is believed to have the potential to provide the same benefit for radiotherapy.

Noxopharm CEO, Graham Kelly, said, "We have good reason to believe that idronoxil possesses a potent ability to overturn radio resistance mechanisms. One of the major benefits that we for this effect is the ability to turn dosages of radiotherapy only intended to provide a temporary anti-cancer effect, into a far more meaningful and cancer effect. Our Objective is to bring to market the first drug capable of providing this urgently needed benefit across multiple cancer types and which does not compromise the safety of the patient."

"The main benefits that we see in expanding our clinical program in this way are the dual effects of t de-risking the company's commercial position while at the same time broadening the commercial potential of NOX66. Having the same drug able to provide a potent benefit for the two main frontline anty0cancer therapies opens up an extraordinary and unique market opportunity"

The program is based around pilot clinical studies in several countries including Australia involving relatively small numbers of patients with specific cancer types. The company currently Is putting in place the infra-structure to support and expanded clinical program. The cost of the program is within the company's budgeted expenditure for the next 18 months.

MARKET OPPORTUNITY/SIZE

The fact that idronoxil in pre-clinical studies has proven to both sensitise a wide range of cancer types to the most commonly-used chemotherapy drugs as well as reversing resistance in those same cancer types to the same drugs, points to a potentially very broad use in the field of cancer management.

This is not a case with the great majority of biotech companies developing a drug that will find a niche in one particular type of cancer. Rather, we see it having considerable potential to become a standard drug to be used in the majority of patients with life-threatening solid cancers.

That fact alone distinguishes Noxopharm in a very busy investment opportunity space.

Taking prostate cancer as just one example…

Just over 300,000 men are estimated to have died from prostate cancer globally last year; this includes 3,300 in Australia and 27,500 in the US.

Overwhelmingly, these figures relate to men where the cancer is inoperable at the time of diagnosis and has spread beyond the gland. Once spread, the cancer is almost invariably fatal.

The standard treatment of inoperable prostate cancer involves a three-pronged attack, typically in the following order of:

- Radiotherapy
- Androgen ablation therapy
- Chemotherapy.

Radiotherapy is a common first-line of treatment, attempting to destroy as many of the cancer cells in and around the prostate gland as possible. It also is used later in the disease process when the cancer has spread to bones or lymph nodes to slow down the rate of growth in specific locations.

Androgen ablation therapy is designed to block the manufacture of testosterone by the body or to block the ability of testosterone to promote the growth of prostate cancer cells.

Chemotherapy (typically docetaxel in combination with prednisone) is commonly used as the last-line to therapy.

Each of these 3 standard therapies generally is regarded as little more than palliative, attempting to slow down the rate of growth and spread to the skeleton.

There are a number of opportunities to introduce a drug into this management process in order to increase the effectiveness of therapy.

The first opportunity is to sensitise the cancer cells to radiation, both first-line radiotherapy to the pelvic region and second-line therapy to treat specific secondaries.

The second opportunity is to sensitise the cancer to the effects of cytotoxic drug therapy. Docetaxel (Taxotere) remains the most effective drug for prostate cancer, although its benefits are limited.

Approximately 1:4 men respond to docetaxel with shrinkage of their tumour, although the overall survival benefit is in the order of months.

This scenario is perfectly suited to a drug such as idronoxil, with a potential ability

- to increase the response rate from the current 25%, and
- increase the individual degree of response beyond partial shrinkage for a matter of months.

KEY RISKS

The Company is subject to a number of risks and other factors that may impact its future performance, the market price at which its shares trade and the outcome of any investment in the company.

Business Risk Factors

Notion Risk	The Company must overcome the notion that a cure for cancer cannot be found that utilises its technology.
Competitive risk	The desire to find a cure for cancer exposes the company to increasing domestic and global competition.
Intellectual risk	There may be third party (or related) companies that challenge the Company's intellectual property right.
Political and legal risk	The Company will look to sell its prodcuts globally which will make it subject to local laws and regulations. The Company's operations may be subject to any regulations that may hinder or delay the cash flow, incur increased fees and costs.
Security Risk	The company may be vulnerable to potential hacking, data loss, theft or corruption to some extent
Additional requirements for capital	If the company is unable to obtain additional financing as needed, it may be required to reduce the scope of its operations and scale back its expansion and development programs.
Existing Shareholders Shares	The potential future sale of shares that are subject to restriction agreements and escrow arrangements could adversely affect the price of shares in the company.

Investment Risk Factors

Stock Market Fluctuations	The shares are to be quoted on ASX, where their price may rise or fall in relation to the offer price.
Economic Conditions	Operating and financial performance influenced by a variety of general economic and business conditions.
Share market risk	Share market is a volatile market that is exposed to many domestic and foreign factors. It may be affected by but not limited to economic outlook, interest and inflation rates, currency fluctuation, changes in demand and supply,
Taxation Issues	There will be taxation consequences for every acquisition and disposal of Shares. The Company accepts no responsibility in regards to taxation consequences hence it is advised that all potential investments should obtain independent financial advice.

ASX-LISTED COMPETITORS

ASX Code	Companies	Description
IMU	*Imugene Limited*	Imugene is an Australian biopharmaceutical company developing HER-2+ gastric and breast cancer immunotherapies. **HER-Vaxx** Specifically, the Company's lead product is the HER-2+ cancer immunotherapy HER-Vaxx, which will shortly enter Phase II clinical trials for gastric cancer. HER-Vaxx is a HER-2+ cancer immunotherapy that mobilizes a polyclonal antibody response against the tumour receptor HER-2. The HER-2 receptor is expressed on the surface of tumours including gastric, breast, ovarian and pancreatic cancers. This is the same receptor targeted by the monoclonal antibody Herceptin®, which has been successfully marketed for several years in the treatment of cancers expressing this receptor. HER-Vaxx, since it mobilises the innate immune system of the patient, is expected to exert a more effective and more durable anti-tumour response than Herceptin® at an anticipated lower cost. HER-Vaxx has already completed a Phase I trial in breast cancer where it was shown to be safe and tolerable and gave strong indications of immunogenicity. A Phase II trial in gastric cancer is now in preparation. **Mimotope** Imugene has an option on a specific Mimotope technology, using peptide mimics of conformational epitopes that are commonly recognized by an antibody with antitumor activity, for use in cancer vaccines. These are currently in early research stages. Imugene acquired HER-Vaxx and the Mimotope technology through the acquisition of Biolife Science Qld Limited in late 2013.
IPD	*Impedimed Limited*	ImpediMed develops bioimpedance devices with a focus on medical applications in the fluid status area. Primary to this is the L-Dex U400 which measures extracellular fluid differences in the limbs for unilateral lymphedema. The company is pioneering the use of next generation bioimpedance technology in BIS (Bioimpedance Spectroscopy). BIS is the gold standard in bioimpedance. ImpediMed's products are unique in the field of BIS. They scan the full frequency range from 3kHz to 1000kHz taking readings from 256 points to make them the most accurate bioimpedance devices available. In BIS, ImpediMed has developed devices which are the most accurate and clinically useful in this field. ImpediMed is respected in the BIS field for the strong scientific foundation of its approach to BIS. The Group consists of three entities: • ImepdiMed Limited, the Parent company operating in medical markets in regions outside the US; incorporated in 1999 and listed on the ASX on 24 October 2007. • ImpediMed, Inc. a Delaware corporation operating in medical markets in North America. • XiTRON Technologies, Inc. a California coporation operating in power test and measurement markets globally. XiTRON Technologies, Inc was acquired by ImpediMed Limited on 1 October 2007.

NRT	*Novogen Pharmaceuticals Limited*	Novogen is a dual listed (ASX (NRT) and NASDAQ (NVGN)) drug discovery and development Company. The most powerful and most effective anti-cancer agents ever developed are known as cytotoxic drugs, meaning that they kill cancer cells by inflicting lethal damage. Cytotoxic chemotherapy has been the mainstay of cancer therapy for the past 40 years and is set to continue to hold that position for the foreseeable future. But cytotoxic chemotherapy has hit a roadblock. It has not advanced in any meaningful way in the last 20 years for two fundamental reasons: First, it has no effect on cancer stem cells, those minority cells within a tumor that are responsible for perpetuating the tumor. So that even where initial response to therapy has occurred, malignant cancer almost always returns; Second, most forms of cancer either have from the start or quickly develop drug-resistance mechanisms that render them insensitive to cytotoxic drugs. Novogen has focused on breaking through this roadblock. Novogen's objective has been to find ways both to kill the cancer stem cells, as well as augmenting the cytotoxic effect of standard drugs in their ability to kill the regular cancer cell. The Company has two main drug technology platforms: super-benzopyrans (SBPs) and anti-tropomyosins (ATMs). **SBP technology** Cantrixil is an intra-peritoneal anti-cancer agent. This means that it can be administered directly into the peritoneal cavity to fight cancer. Cantrixil is being developed for the treatment of ovarian cancer,and other abdominal malignancies. TRXE-009 (Trilexium) is highly active against cancers of cells that originate in the neural crest. This includes brain cancers, neuroblastoma and melanoma. **ATM Technology** Anisina synergises with the taxanes and vinca alkaloid families of anti-cancer drugs to achieve significant anti-cancer activity against cancer cells with little or no sensitivity to cytotoxic chemotherapies. Melanoma and prostate cancer in adults and pediatric cancers are the indications to be tested.

OSL	*Oncosil Medical Limited*	OncoSil Medical's core technology uses radioactive phosphorous (P32) with the intent to control tumour growth. OncoSil™ is a patent protected proprietary medical device (class III) that creates a localised stream of beta radiation. The product is created by melting up to 5% phosphorous in liquid silicon in a furnace. The resultant molten liquid is shattered into small particles using sterile water. The particles are graded by size and 30 micron particles are selected for further use. Particle size is an important product design feature, related to localisation capability. The 30 micron particles are etched with acid to make them porous and placed into a special reactor to give the phosphorous a radioactive charge. The resulting radioactive phosphorous (P32) produces radioactive beta particles that can be emitted for up to three months. Patients with unresectable pancreatic cancer have few treatment options. The current standard of care is to provide intravenous chemotherapy, and in some cases external beam radiation. The OncoSil™ is intended to complement existing standard of care chemotherapy.
PTX	*Prescient Therapeutics Limited*	Prescient Therapeutics is a clinical stage oncology company developing novel drugs that show great promise as potential new therapies to treat a range of cancers that have become resistant to front line chemotherapy. Lead drug candidate PTX-200 inhibits an important tumor survival pathway known as AKT, which plays a key role in the development of many cancers, including breast and ovarian cancer, as well as leukemia. This highly promising compound is the focus of three PTX clinical trials. The first is a Phase 1b/2 study examining PTX-200 in breast cancer patients at the prestigious Montefiore Cancer Center/Albert Einstein College of Medicine in New York and the Moffitt Cancer Center and Research Institute in Tampa, Florida. A Phase 1b/2 trial of PTX-200 in combination with current standard of care carboplatin is also underway in patients with recurrent or persistent platinum resistant ovarian cancer at Moffitt Cancer Center. In addition, a Phase 1b/2 trial evaluating PTX-200 incombination with citarabine in acute myeloid leukemia is scheduled to begin accrual in mid-2016. Prescient's second novel drug candidate, PTX-100, is a first in class drug that kills cancer cells by blocking geranylgeranyl ransferase-1 (GGT-1), a protein required for the cancer-causing activity of Ral and Rho, that are in turn required for the cancer-causing protein Ras. PTX-100 was well tolerated and achieved stable disease in a Phase 1 trial in advanced solid tumors. Prescient expects to commence Phase 1b/2 clinical trials in breast cancer and multiple myeloma in Q4 2016. At the same time, Prescient plans to develop its novel p27 cancer biomarker as a companion diagnostic that will potentially identify those patients that are most likely to respond to PTX-100 therapy. Prescient has licensed access to its Co-X-Gene™ platform technology to French biotechnology company Transgene for use in two immunotherapeutic products.

RAC	*Race Oncology LTD*	Race Oncology is a specialty pharmaceutical company, whose business model is to pursue later stage drug assets, principally in the cancer field. Its first important asset is a chemotherapy drug, called Bisantrene, which was the subject of more than 40 phase II clinical studies, before it was lost in a series of pharmaceutical mergers during the 1990s. Race Oncology is rediscovering Bisantrene. RAC own recent patent filings on Bisantrene and have secured Orphan Drug Designation in the US. Now RAC's goal is to complete final development of Bisantree and bring this valuable cancer drug to market.
SPL	*Starpharma Holdings Limited*	Starpharma Holdings Limited is focused on the development of dendrimer products for pharmaceutical, life science and other applications. Starpharma's underlying technology is built around dendrimers – a type of synthetic nanoscale polymer that is highly regular in size and structure and well suited to pharmaceutical and medical uses. Starpharma has three core development programs: VivaGel® portfolio, DEP™ drug delivery, and agrochemicals with the Company developing a number of products internally and others via commercial partnerships. Starpharma's lead products are based on : **VivaGel** **VivaGel®** (SPL7013, astodrimer sodium), a proprietary dendrimer which has antimicrobial properties. VivaGel® formulated as a water based gel and delivered vaginally now has EU regulatory approval for topical treatment and rapid relief of bacterial vaginosis (BV) and is under clinical development for the prevention of recurrent BV. **DEP™ drug delivery** A number of dendrimer-enhanced, or DEP® versions of existing drugs are under development. The most advanced of these is DEP® docetaxel, a dendrimer-enhanced version of docetaxel (Taxotere®), which is in clinical development in patients with solid tumours. In preclinical studies DEP® docetaxel has shown significant tumour-targeting and superior anti-cancer effects across a range of important cancer types including breast, prostate, lung and ovarian tumour, when compared to Taxotere® (docetaxel). **Agrochemicals** In agrochemicals Starpharma has a series of partnerships with leading industry players including global leader Adama (formerly Makhteshim Agan) as well as internal programs including an enhanced version of glyphosate (the active ingredient in Roundup®)..
SRX	*Sirtex Limited*	Sirtex Medical Limited is an Australian company with an approved cancer treatment supplied globally. Sirtex's main commercialised product is a targeted radioactive treatment for liver cancer called SIR-Spheres® Y-90 resin microspheres. Approximately 55,000 doses of SIR-Spheres Y-90 resin microspheres have been supplied to treat liver cancer patients in over 900 medical centres in over 40 countries. This product has PMA approval from the U.S. Food & Drug Administration (FDA), the European Union (CE Mark) and Australia's Therapeutic Goods Administration (TGA). **SIR-Spheres Y-90 resin microspheres** SIR-Spheres Y-90 resin microspheres are used to deliver targeted internal radiation therapy directly to liver tumours via the hepatic artery. This therapy is called Selective Internal Radiation Therapy (SIRT) and is performed using minimally invasive surgical techniques by an interventional radiologist.

		Where SIR-Spheres Y-90 resin microspheres are used, the available clinical evidence suggests SIR-Spheres Y-90 resin microspheres may approximately double the rate of tumour shrinkage and tumour remission. The evidence also suggests it may be capable of improving the life expectancy of patients.
VLA	*Viralytics Limited*	Viralytics is focused on the development and commercialisation of oncolytic immunotherapies that harness the power of certain viruses to preferentially infect and kill cancer cells. **Viralytics'** lead product candidate is CAVATAKTM, a proprietary formulation of the common cold Coxsackievirus Type A21 (CVA21), now being evaluated in Phase 1 and 2 clinical trials. CAVATAK binds to specific receptor proteins highly expressed on a range of cancer cell types, and acts to destroy local as well as metastatic tumour cells through cell lysis and the potential generation of a specific immune response against the cancer cells. Through these selective mechanisms of action, our therapies are designed to provide greater tolerability and efficacy, offering hope of an improved quality of life to patients with cancers that are difficult to treat with current therapeutic approaches.

NON-ASX-LISTED COMPETITORS

	QBiotics Limited	QBiotics is an Australian public unlisted lifesciences company. QBiotics are in the business of development and commercialisation of pharmaceutical products that have the potential to address major health problems for humans and companion animals (dogs, cats and horses). QBIOtic's products are new chemical entities which are sourced from Australia's pristine tropical rainforests. EBC-46 is a novel natural product small molecule with anticancer activity being developed as a local treatment for solid tumours in humans and companion animals (dogs, cats and horses). EBC-46 was discovered by applying the EcoLogic™ approach to drug discovery from the tropical rainforests of Far North Queensland. EcoLogic™ was developed by QBiotics' parent entity EcoBiotics. QBiotics plans to develop EBC-46 as a human pharmaceutical to Clinical Phase II and then seek a development partner for final development and marketing of the drug. QBiotics has already demonstrated very compelling proof-of-concept of the drug's efficacy and safety by successfully treating advanced, spontaneous tumours in companion animals that were considered untreatable with current standards of care. As the principles behind the development of cancer in animals and humans are analogous, it is likely that EBC-46 will have similar effects in humans as in animals. QBiotics is continuing to conduct clinical trials for EBC-46, a novel molecule with anti-cancer properties. QBiotics has previously reported significant efficacy of EBC-46 in the treatment of most cell tumours and soft tissue sarcomans in dogs. More recently, QBiotics has also conducted multi-centre human clinical trials in Australia.

OTHER RECENT CANCER DRUGS - Provenge

Provenge is the **Vaccine Sipuleucel-T** (APC8015 **Provenge**), manufactured by Dendreon Corporation.

It is a cell-based cancer immunotherapy for prostate cancer (CaP). It is a personalized treatment that works by programming each patient's immune system to seek out cancer and attack it as if it were foreign.

While referred to as a therapeutic vaccine rather than a preventive vaccine that prevents infectious disease, sipuleucel-T is instead an immunostimulant.

On February 20, 2015, Valeant Pharmaceuticals received approval to purchase all Dendreon assets (including Provenge).

The treatment cost $93,000 at FDA approval, rising to over $100,000 in 2014.

Treatment method

A course of treatment consists of three basic steps:

The patient's white blood cells, primarily dendritic cells, a type of antigen-presenting cells (APCs), are extracted in a leukapheresis procedure.

The blood product is sent to a production facility and incubated with a fusion protein (PA2024) consisting of two parts:

1. The antigen prostatic acid phosphatase (PAP), which is present in 95% of prostate cancer cells and
2. An immune signaling factor granulocyte-macrophage colony stimulating factor (GM-CSF) that helps the APCs to mature.

The activated blood product (APC8015) is returned from the production facility to the infusion center and reinfused into the patient.

A complete sipuleucel-T treatment includes three courses at two week intervals.

Use

Sipuleucel-T is used to treat people with metastatic, asymptomatic, hormone-refractory prostate cancer (HRPC). Other names for this stage are metastatic castrate-resistant (mCRPC) and androgen independent (AI) or (AIPC). This stage leads to mCRPC with lymph node involvement and distal (distant) tumors; this is the lethal stage of CaP. The prostate cancer staging designation is T4,N1,M1c.

Clinical trials - Completed

Sipuleucel-T showed overall survival (OS) benefit to patients in three double-blind randomized phase III clinical trials, D9901, D9902a, and IMPACT

The IMPACT trial served as the basis for FDA licensing. This trial enrolled 512 patients with asymptomatic or minimally symptomatic metastatic HRPC randomized in a 2:1 ratio. The median survival time for sipuleucel-T patients was 25.8 months comparing to 21.7 months for placebo-treated patients, an increase of 4.1 months 31.7% of treated patients survived for 36 months vs. 23.0% in the control arm. Overall survival was statistically significant (P=0.032). The longer survival without tumor shrinkage or change in progression is surprising. This may suggest the effect of an unmeasured variable. The trial was conducted pursuant to a FDA Special Protocol Assessment (SPA), a set of guidelines binding trial investigators to specific agreed-upon parameters with respect to trial design, procedures and endpoints; compliance ensured overall scientific integrity and accelerated FDA approval.

The D9901 trial enrolled 127 patients with asymptomatic metastatic HRPC randomized in a 2:1 ratio. The median survival time for patients treated with sipuleucel-T was 25.9 months comparing to 21.4 months for placebo-treated patients. Overall survival was statistically significant ([[P-value | P=0.01]]).

The D9902a trial was designed like the D9901 trial but enrolled 98 patients. The median survival time for patients treated with sipuleucel-T was 19.0 months comparing to 15.3 months for placebo-treated patients, but did not reach statistical significance.

Clinical trials - In progress

As of August 2014, the PRO Treatment and Early Cancer Treatment (PROTECT) trial, a phase IIIB clinical trial started in 2001, was tracking subjects but no longer enrolling new subjects. Its purpose is to test efficacy for patients whose CaP is still controlled by either suppression of testosterone by hormone treatment or by surgical castration. Such patients have usually failed primary treatment of either surgical removal of the prostate, (EBRT), internal radiation, BNCT or (HIFU) for curative intent. Such failure is called biochemical failure and is defined as a PSA reading of 2.0 ng/mL above nadir (the lowest reading taken post primary treatment).

As of August 2014, a clinical trial administering sipuleucel-T in conjunction with ipilimumab (Yervoy) was tracking subjects but no longer enrolling new subjects; the trial evaluates the clinical safety and anti-cancer effects (quantified in PSA, radiographic and T cell response) of the combination therapy in patients with advanced prostate cancer.

Side effects

Common side effects include: bladder pain; bloating or swelling of the face, arms, hands, lower legs, or feet; bloody or cloudy urine; body aches or pain; chest pain; chills; confusion; cough; diarrhoea; difficult, burning, or painful urination; difficulty with breathing; difficulty with speaking up to inability to speak; double vision; sleeplessness; and inability to move the arms, legs, or facial muscles.

Regulatory approval and reimbursement

Sipuleucel-T was approved by the U.S. Food and Drug Administration (FDA) on April 29, 2010, to treat asymptomatic or minimally symptomatic metastatic HRPC.

Shortly afterward, sipuleucel-T was added to the compendium of cancer treatments published by the National Comprehensive Cancer Network (NCCN) as a "category 1" (highest recommendation) treatment for HRPC. The NCCN Compendium is used by Medicare and major health care insurance providers to decide whether a treatment should be reimbursed

Source: Wikipedia

OTHER RECENT CANCER DRUGS - Keytruda

Pembrolizumab is a **Monoclonal antibody** with the formula: $C_{6534}H_{10004}N_{1716}O_{2036}S_{46}$(peptide)

Pembrolizumab (formerly MK-3475 and lambrolizumab, trade name Keytruda) is a humanized antibody used in cancer immunotherapy. It targets the programmed cell death 1(PD-1) receptor.[The drug was initially used in treating metastatic melanoma

Pembrolizumab was invented by Gregory Carven, Hans van Eenennaam and John Dulos at Organon Biosciences.[5] MRC Technology humanized the antibody pembrolizumab for Organon in 2016.

On September 4, 2014 the US Food and Drug Administration (FDA) approved pembrolizumab under the FDA Fast Track Development Program It is approved for use following treatment with ipilimumab, or after treatment with Ipilimumab and a BRAF inhibitor in advanced melanoma patients who carry a BRAF mutation. It is marketed by Merck.

On October 2, 2015, the FDA approved pembrolizumab for the treatment of metastatic non-small cell lung cancer in patients whose tumors express PD-L1 and who have failed treatment with other chemotherapeutic agents

Mechanism of action

Pembrolizumab is a therapeutic antibody that blocks the inhibitory ligand of programmed cell death 1 receptor. This receptor is responsible for inhibiting the immune response to cancer cells. Normally, this effect is necessary to avoid inappropriate overreaction, such as an auto-immune disease, in healthy individuals.

In cancer patients antibody blockade against this receptor such as with Pembrolizumab reinvigorates the immune system, allowing it to target and destroy cancer cells.

Pembrolizumab is one of a number of closely related therapies dubbed checkpoint therapy.

Clinical trials

As of 2015 a large phase I clinical trial produced response rates of 37–38% in patients with advanced melanoma and an overall response rate of 26% in patients who had progressive disease after treatment with Ipilimuma.

Also in 2015 the drug was in Phase II clinical trials for non-small-cell lung cancer (NSCLC) in patients with oligometastatic diseases.

Keytruda was going to be the answer to the treatment of melanoma and was going to change the face of chemotherapy.

Apparently, the oncologists Graham Kelly has talked to are now expressing their disappointment with Keytruda.

According to Graham Kelly, Keytruda only works in about 20% of melanoma patients and they get a survival benefit ranging from a couple of months to a couple of years but this is at the expense of all patients suffering severe side-effects (such as destroying the bowel).

Source: Wikipedia

BOARD OF DIRECTORS

Mr Graham Kelly BSc (Vet) (Hons), BVSc (Hons) PhD Chief Executive Officer

Graham has a PhD in the area of drug development from the Faculty of Medicine at The University of Sydney. Twenty-five years in medical research then followed in the fields of organ transplantation, surgical research, cancer research and isoflavonoid metabolism which culminated in Graham leaving academia in 1994 to found the company that became Novogen Limited.

Novogen focussed on isoflavonoid drug development, with Graham playing a key role in the clinical programme.

A spin-off subsidiary, MEI Inc was formed in 2000, with Graham as Executive Chairman, eventually listing on NASDAQ in 2003 as an anti-cancer drug development company.

Graham retired from Novogen in 2006 but returned in 2012 when he orchestrated a reverse takeover of Novogen by a small private company. Graham remained as CEO and Executive Chairman of Novogen Limited until July 2015.

He was awarded an Adjunct Professorship by The University of Sydney.

Graham brings to the role of CEO of **Noxopharm** considerable experience in the establishment and management of public companies; in the regulatory requirements of public companies; in shareholder relations; in general drug development and isoflavonoid drugs in particular, and in the conduct of clinical trials

Mr Peter Marks BEc LLB Grad. Dip. Comm. Law MBA Chairman Independent under ASX, SEC and NASDAQ

Peter Marks holds a Bachelor of Economics, Bachelor of Laws and a Graduate Diploma in Commercial Law from Monash University, Australia. He also holds an MBA from the University Of Edinburgh, Scotland.

Peter brings over 30 years' experience in corporate finance, specialising in capital raisings (for listed and unlisted companies), underwriting, IPO's and venture capital transactions, including KPMG Corporate Finance Ltd (Australia) and Merrill Lynch. Peter has acted as Director and Chairman for a number of listed entities on the ASX and AIM.

Peter is currently a director of Prana Biotechnology Ltd (ASX & Nasdaq listed) since 2005, Rivus TV Ltd (unlisted) and Watermark Global Plc (AIM listed) where he has been a director since the company listed in early 2006 and Chairman since 2009.

Dr Ian E. Dixon PhD, MBA, MAICD

Director

Ian is an experienced technology entrepreneur and business builder – and has been a hands-on founder, executive and angel investor in a number of successful technology-based enterprises since 1987.

To date, four technologies Ian has originated have been acquired by Australian Stock Exchange (ASX) - listed companies:

1. Ian is the original co-founder/Director of **Cynata Therapeutics Ltd** (ASX-CYP) in early 2011- Cynata Inc. (www.cynata.com);
2. co-Founder and executive Director of **Genscreen Pty Ltd** (www.genscreen.com.au) formed in 2003 - a privately-held Melbourne-based biotechnology accelerator with drug discovery/development programs being progressed towards the clinic – addressing needs in cancer, neurodegeneration and autoimmune disease. In 2013, Genscreen licensed the anti-Tms project to **Novogen Ltd** – an ASX- and NASDAQ-listed therapeutics company (www.novogen.com). Novogen presently has a market capitalisation of $45m..

Ian has a PhD in Biomedical engineering from Monash University (monash.edu.au), formal qualifications in engineering (mechanical and electronics) and an MBA. Ian takes a hands-on role in developing new technologies and inventing.

With a career spanning 30 years working in Australia, Europe, USA, China and Asia/Pacific, Ian has extensive experience in technology innovation and commercialising technology and has an extensive network of industry contacts and colleagues.

Appendix 1- Idronoxil

Drugs of the Future 2008, 33(10): 844-860

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.10.1260120

Idronoxil

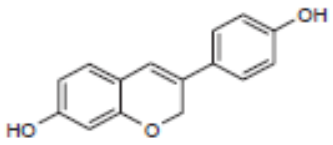
Rec INN; USAN

Proapoptotic Agent
Oncolytic

Phenoxodiol
NV-06

3-(4-Hydroxyphenyl)-2H-1-benzopyran-7-ol

InChI=1/C15H12O3/c16-13-4-1-10(2-5-13)12-7-11-3-6-14(17)8-15(11)18-9-12/h1-8,16-17H,9H2



$C_{15}H_{12}O_3$
Mol wt: 240.254

CAS: 81267-65-4

EN: 273285

Abstract

Idronoxil (phenoxodiol) is being developed as a novel anticancer therapeutic both as a single agent and as a chemosensitizer in late-stage cancers resistant or refractory to other approved chemotherapies. Idronoxil targets dysregulated prosurvival pathways mediated via Akt, FLIP and XIAP in cancer cells, restoring caspase-mediated apoptosis. Pharmacological studies demonstrated that idronoxil was able to sensitize cancer cells to a range of cytotoxic agents, and in particular to potently sensitize platinum-resistant ovarian cancer cells. Further studies have demonstrated that idronoxil also possesses antiangiogenic properties. Idronoxil has been evaluated in several clinical studies, with the major adverse events being low-grade nausea, minor hypersensitivity reactions and transient thrombocytopenia when delivered i.v., attributed to the cyclodextrin excipient used in that formulation. For orally delivered idronoxil, an MTD of 800 mg t.i.d. was observed, manifesting as mild diarrhea in a small number of patients. Idronoxil has demonstrated efficacy as monotherapy in phase II studies in late-stage hormone-refractory prostate cancer, and as a chemosensitizing agent in platinum-resistant ovarian cancer when used in combination with cisplatin and paclitaxel. Idronoxil is currently being evaluated in a phase III multicenter, randomized, double-blind trial in platinum-resistant or -refractory late-stage epithelial ovarian, fallopian or primary peritoneal cancer patients following at least second-line platinum therapy, as an oral formulation in combination with carboplatin.

Synthesis

Idronoxil is synthesized by a linear synthetic strategy starting from either very simple starting materials or from commercially available highly elaborated intermediates. The availability of this intact carbon scaffold allows for a simple functional group modification synthetic strategy. The key highly elaborated intermediate daidzein (I) is protected as the bis-acetate using acetic anhydride and triethylamine. Diacetyldaidzein (II) is smoothly reduced to diacetyltetrahydrodaidzein (III) by catalytic heterogeneous low-pressure hydrogenation. Diacetyltetrahydrodaidzein is dehydrated efficiently by benzoyl chloride in refluxing dimethylformamide. The resulting diacetyldehydroequol (IV) is deacetylated by sodium methoxide in methanol to afford idronoxil in high yield. Scheme 1.

Daidzein is a readily available starting material and affords a very cost-effective and efficient means of synthesizing idronoxil. In order to complete advanced ADME studies, labeled idronoxil was prepared. [^{14}C]-Labeled idronoxil was prepared from [^{14}C]-labeled 4-hydroxyphenylacetic acid. The condensation of labeled 4-hydroxyphenylacetic acid (V) with resorcinol (VI) was completed using boron triflouride diethyletherate. The resulting labeled benzoin (VII) was cyclized using modified Haak conditions: boron trifluoride in dimethylformamide with methanesulfonyl chloride. The resulting labeled daidzein (VIII) was then progressed through the standard protection–hydrogenation–dehydration–deprotection strategy to afford labeled idronoxil. Scheme 2.

Background

Idronoxil (phenoxodiol) is an analogue of the naturally occurring plant isoflavone genistein. Genistein is a pan-protein tyrosine kinase inhibitor, inducing mitotic arrest, terminal differentiation and apoptosis of human cancer

David M. Brown, Andrew Heaton, Alan J. Husband*. Marshall Edwards, Inc., 140 Wicks Road, North Ryde, NSW Australia 2113. *Correspondence: Alan.Husband@novogen.com.

Appendix 2 – Novogen CEO Graham Kelly says he will make an anti-cancer drug at affordable price – May 5, 2014

AN Australian drug company chief has made the astounding vow he'll deliver a breakthrough new cancer drug at a price families can afford without mortgaging their home.

Big pharmaceutical companies claim you can't develop a breakthrough cancer treatment for less than $1.5 billion but Novogen chief Graham Kelly, who is using his own experimental cancer medicine on himself to beat his aggressive prostate cancer, accuses them of "obscene" price gouging.

He says it will cost just $50 million to take his new anti-cancer drug from the test tube to the clinic. Big drug companies are charging thousands of dollars for some medicines that cost between $5-$20 to manufacture and package, he says.

"It is one of the closely guarded secrets of the industry," Mr Kelly said.

And he believes many breakthrough new cancer medicines which have huge price tags over $100,000 deliver only an extra 6-10 months of life.

"The price of drugs is based on what the market can bear rather than what is a fair price," he told News Corp Australia.

"The way we are going the Federal Government will soon say we can't afford these medicines.

"We believe innovative medicine can be developed without the obscene price tags that make families mortgage their homes or strain federal health budgets."

Novogen has developed a world first drug technology designed to selectively kill cancer stem cells without the side effects associated with existing chemotherapy.

The drug is set to be trialled on children with neuroblastoma, women with ovarian cancer, men with prostate cancer and melanoma patients in 2015.

The company believes if it is successful it should eventually be able to be used in all types of cancer.

University NSW Professor Peter Gunning spent 30 years researching the architecture of cancer cells until had a light bulb moment in 2006 led to the development of the anti-tropomyosin treatment that is part of the new drug.

Australia's National Health and Medical Research Council funded his research for 22 years and the charity the Kids Cancer Project will spend $8 million on upcoming clinical trials of the new combination drug.

Gunning says changes in the US Food and Drug Administrations's regulatory process has changed the dynamics of the pharmacy industry and will make it cheaper to get new drugs onto the market.

He says drug companies are no longer doing their own medical research but waiting until university or charitably funded researchers identify new drugs and then buy in to the development process.

Mr Kelly will present his company's new cancer therapy to a panel of global philanthropic investors at an event hosted by the United Nations today (5/4/14). "If we are right, we will change the face of cancer treatment and end up with some of the largest selling oncology drugs in history," he said.

Source: News Corp Australia

Appendix 3 – Researchers identify a new mode of drug resistance to emerging therapies in prostate cancer – EurekAlert 17 November 2015

SEATTLE -- Advanced prostate cancer is a disease notoriously resistant to treatment. New research by scientists at Fred Hutchinson Cancer Research Center and the University of California, San Francisco sheds light on a new mode of drug resistance to emerging therapies in metastatic prostate cancer. This discovery ultimately may help predict which patients may benefit most from treatment.

As one of the most commonly corrupted signaling networks in human cancer, the PI3K-AKT-mTOR pathway is a tempting target for scientists developing new cancer drugs. Many molecules currently in clinical trials have been designed to disrupt aberrations in this cellular activity as a potential treatment, albeit with limited success. In practice, cancer patients are often resistant to these therapies, a class of drugs called mTOR inhibitors.

Now, a new study co-led by Dr. Andrew Hsieh, a cancer biologist and assistant member of the Human Biology Division at Fred Hutch, and Dr. Davide Ruggero of the University of California, San Francisco has identified a mechanism that may help cancer cells escape the effects of these drugs. Described this week in the journal Science Signaling, specific populations of prostate cancer cells are uniquely resistant to inhibitors of the PI3K pathway.

This alarming population of drug-resistant cells was found to harbor high levels of a protein known as 4EBP1, an important player in protein production. The authors found that high 4EBP1 levels decrease protein synthesis within cancer cells and make them immune to PI3K pathway inhibitors.

When the researchers genetically manipulated these cells to reduce 4EBP1, protein production was restored and the tumor cells once again became sensitive to drug treatment.

"By measuring 4EBP1 and protein-synthesis rates, we can potentially identify tumors that are resistant to PI3K pathway inhibitors," Hsieh said. This could be used to predict which prostate cancer patients might benefit most from this class of drugs and those who should not waste precious time with treatments that are likely to fail.

Using tumor samples from an ongoing clinical trial led by Dr. Won Kim at the University of California, San Francisco that is testing an experimental PI3K pathway inhibitor known as buparlisib, orBKM120, for men with prostate cancer, the researchers saw that 4EBP1 levels jumped in tumors following treatment. Hsieh points to these findings as substantiation of the clinical relevance of their discoveries in the laboratory in mouse models and cancer cell lines.

According to Hsieh, "the next step is to understand how high levels of 4EBP1 and low protein-synthesis rates drive drug resistance," and to develop new treatment strategies that either increase protein production rates to drug-sensitive levels or suppress them to levels intolerable to cancers.

Their findings also add to a growing field of knowledge showing that how cancer cells make proteins -- the cells' building blocks -- matters for disease progression. Until recently, the cancer research community has primarily viewed changes in DNA and RNA as the instigators of human malignancies, while protein production has been seen as a static and subservient process. However, this dogma is steadily changing to encompass a more complex dynamic in cell activities. "Our findings show that the process of making proteins is just as, if not more so, important than changes in DNA and RNA alone in determining the fate of cancer cells," Hsieh said.

These perniciously difficult-to-treat cells studied by Hsieh and Ruggero's labs won't be able to depend on 4EBP1 to evade cancer therapies indefinitely. Hsieh believes that exciting new therapeutics are on the horizon to target this unique form of protein synthesis in cancer. "There are a number of companies and laboratories worldwide, including our own, that are pushing the envelope to develop new strategies to drug this critical cellular process."

Indeed, the findings from these studies aren't just limited to advanced prostate cancer but could point to how targeting aberrant protein synthesis can potentially be a death knell to all tumors that exhibit this once-overlooked process in cancer cell activity.

Appendix 4 – Pfizer to buy Medivation in $US14b deal

Pfizer agreed to buy biotech Medivation for about $US14 billion, in a move that adds one of the crown jewels of the multibillion-dollar market for cancer drugs to Pfizer's portfolio.

The deal ended months of bidding for San Francisco's Medivation, one of the most desired independent biotechs because it sells a leading prostate-cancer drug.

Pfizer will pay $US81.50 a share, a 21 per cent premium to Medivation's closing stock price Friday. Medivation shares traded up 20 per cent to $US80.47 in early trading as Pfizer shares fell 5 cents to $US34.92.

Medivation's drug, Xtandi, already generates about $US2 billion in yearly sales and has the potential to more than double, according to analysts.

Pfizer said the deal would add 5 cents to earnings in the first full year after closing and isn't expected to affect its 2016 financial guidance. Pfizer said it plans to finance the transaction with its cash holdings.

Pfizer has been seeking to expand its line-up of such oncology treatments. Xtandi would give the New York drug company a beachhead in prostate cancer complementing its breast-cancer treatment Ibrance, which is on track to be a blockbuster.

Medivation's drugs in development could also complement Pfizer's efforts to develop combinations of cancer agents with so-called immunotherapies, which deploy the immune system in the fight against cancer.

The deal is expected to close in the third or fourth quarter of 2016 and is subject to customary closing conditions and US antitrust clearance.

Pfizer agreed to take over Allergan PLC late last year in a $US150 billion deal, but the two companies parted ways in April after the Obama administration targeted the proposed combination with new rules.

Mr Read has said Pfizer would decide by year's end whether to split into two, with one company selling fast-growing brand-name drugs like Ibrance and another selling drugs that have lost patent protection — a move that has often been discussed in recent years.

Some analysts have said Pfizer needs to do more deals to add patent-protected drugs if that side of the company was to develop the critical mass of revenue it would need to function on its own.

Cancer is one of the pharmaceutical industry's biggest markets with worldwide sales amounting to roughly $US80 billion a year and growing more than 10 per cent annually, according to EvaluatePharma.

Despite charging high prices often surpassing $US100,000 a year per patient, companies haven't faced the challenges securing reimbursement that have limited sales of new drugs for other diseases.

Medivation is one of the few independent biotechs left with a cancer treatment that is already approved and selling well. CEO David Hung says he decided to found the company after watching a 28-year-old breast-cancer patient die during his oncology fellowship.

Xtandi has held its own against a rival prostate-cancer treatment from Johnson & Johnson called Zytiga. Xtandi, which Astellas Pharma Inc. also sells, could be one of the top-selling cancer drugs by 2020, according to EvaluateSHYPharma.

But J&J is developing a new prostate-cancer drug that could pose a threat to Xtandi, according to analysts.

Medivation was put in play after French drug company Sanofi SA made an unsolicited proposal of $US52.50 a share in cash, which the biotech rejected in April, saying the offer substantially undervalued the company. Medivation shares were trading as low as $US26.41 in February.

Following Sanofi's proposal, a bidding war resulted. With Pfizer's deal, Medivation is fetching more than double the $US6 billion it was valued earlier in the year.

On Monday, Sanofi said that while it saw benefits to a potential deal with Medivation, "we are first and foremost a disciplined acquirer and remain committed to acting in the best interests of Sanofi shareholders."

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Contact with **Noxopharm Limited** has been made during the preparation of this report for assistance with verification of facts.

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