

# phenolic hormones . 2000

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## NV-06

### **NV-06 in human anti-cancer trials**

Ongoing laboratory studies continue to confirm that NV-06 has potent and novel anti-cancer actions.

These studies have demonstrated that NV-06 targets within the human cell, a range of enzyme systems whose activities are thought to play key roles in allowing a cell to transform from normal to cancerous.

Switching these enzymes off has long been a key objective of anti-cancer therapy. NV-06 is very effective at doing this, suggesting that it is able to target the most fundamental processes within the cell that control the cancer process. For the scientifically-minded, NV-06 is, among other things, a potent inhibitor of protein tyrosine kinases, topoisomerases and 5- $\alpha$ -reductase.

Beyond the ability of NV-06 to inhibit multiplication selectively within cancer cells, the compound has the ability to reverse a number of the cancer changes within cells. Cancer cells exposed to N-V06 display a range of behaviours normally associated with normal cells such as the expression of differentiation antigens and apoptosis.

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### **Human phenolic hormones reveal their secrets**

In this issue, we report progress on the three leading phenolic hormone compounds – NV-06, NV-04 and NV-07. The Australian Government has recognized the potential for this program by granting over \$6 million to expedite the development of the compounds.

NV-06 shows potent and equivalent activity against a wide range of human cancers from solid tumours (prostate, breast, colon and melanoma) through to dispersed tumours (leukaemias).

Novogen has decided to concentrate in its clinical testing program initially on prostate cancer. The effectiveness of NV-06 against prostate cancer is exemplified by a recent animal study using oral NV-06. In athymic mice transplanted with vigorously-growing human prostate cancer cells, oral NV-06 resulted in an 80 per cent reduction in tumour growth.

NV-06 recently took an important step in its path of development as an anti-cancer drug by entering a

Phase 1 clinical trial. This trial is being conducted at an Australian teaching hospital and involves patients with malignant cancer. The NV-06 is being administered in the form of an intravenous solution in order to provide sensitive control over the levels of NV-06 in the blood stream. The purpose of this trial is to gain a better understanding of the safety profile of the drug in humans and the duration of therapy required to achieve an anti-cancer effect.

The Phase 1 program consists of a number of separate studies, and is expected to conclude in the second half of 2000. Novogen is also preparing a submission to the United States FDA to carry out clinical trialing under its auspices.

# NV-07

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## **NV-07 shows early promise as an anti-inflammatory compound**

Anti-inflammatory drugs are important pharmaceuticals because they are required to treat such common conditions as rheumatoid arthritis, inflammatory bowel disease and eczema. While a range of such drugs are available, they all suffer from the disadvantage of having undesirable side-effects which limit their long-term usefulness.

NV-07 is being developed as an effective, well-tolerated anti-inflammatory drug.

Ideally, anti-inflammatory drugs should be active across a range of different mechanisms in order to ensure their effectiveness across a range of different disease states.

Currently, the most broadly acting anti-inflammatory drugs are those that are derived from the body's anti-inflammatory hormones – corticosteroids (eg. cortisone and prednisone). However, these hormones also have other functions in the body other than anti-inflammation and it is these other functions that can cause problems with long-term use.

Alternatives to corticosteroids have been produced in order to make them safer and these are known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs, although better tolerated, are still associated with adverse effects. They also are more restrictive in how they work, so limiting their effectiveness.

Phenolic hormones tested by Novogen have proven to have broad-ranging effects against the different mechanisms involved in inflammation and to include effects against mechanisms not affected by corticosteroids or NSAIDs.

NV-07 has been selected as the most effective anti-inflammatory phenolic hormone. To date, NV-07 has not demonstrated any of the adverse side-effects associated with corticosteroids or NSAIDs.

NV-07 is to be developed as a classic anti-inflammatory drug for use in diseases such as rheumatoid arthritis.

However, its potential for certain other novel applications has been suggested by recent studies.

One such application is the prevention of both acute and long-term skin damage associated with sun exposure. In a human subject, NV-07 prepared as a cream and applied to skin following exposure to a burning dose of sunlight, reduced significantly the normal burning effect 2-3 days later. This effect is due to the ability of NV-07 to reduce the inflammation within the skin as a result of the burning and is not associated with a sun-screening effect.

Apart from burning, repeated, long-term inflammation within the skin produces three other important outcomes.

These are:

- the skin becomes thicker and wrinkled;
- the immune function of the skin is depressed;
- the skin is predisposed to skin cancer.

In animal studies recently completed, NV-07 was applied in a cream base in very small amounts to the skin of hairless mice exposed to sunlight. NV-07 treatment reduced the skin thickness, helped maintain normal immune function and reduced the rate of skin cancer development.

These results suggest that NV-07 offers the opportunity to pursue an entirely new approach to the problem of chronic skin damage associated with long-term sun exposure.

# NV-04

## NV-04 program achieves major milestone

The NV-04 drug development program is targeting cardiovascular disease.

The laboratory results obtained to date support the Company's belief that a prime function of phenolic hormones in the body is the regulation of the function of the cardiovascular system.

This includes functions such as controlling blood pressure, controlling the activity of smooth muscle cells in artery walls, protecting cholesterol from oxidation in artery walls, and preserving the integrity of the endothelium (the lining of blood vessels).

The development of drug therapies that will prevent or reverse cardiovascular disease is a major priority in medicine. Novogen's aim is to treat the underlying disease process of cardiovascular disease, in contrast to the limitations of current therapies which treat some of the symptoms of the disease but do little to reverse the disease process.

The NV-04 program has been conducted with the assistance of the Baker Medical Research Institute (Melbourne, Australia) and the Heart Research Institute (Sydney, Australia).

A key milestone has been the confirmation that NV-04 exerts actions that suggest that it might target the underlying disease processes of cardiovascular disease and that the actions of NV-04 would be sufficiently potent to suggest that they might be clinically relevant. NV-04 now is confirmed in the laboratory and in animals as having potent and wide-ranging effects on the cardiovascular system.

The main effects are to:

- protect cholesterol from oxidation;
- lower blood pressure (anti-hypertensive effect);
- inhibit the proliferation of vascular smooth muscle cells.

The last two effects are very important in preventing and treating heart disease as high blood pressure and over-activity of vascular smooth muscle cells in the walls of arteries are two important risk factors in the development of heart disease.

Various drugs are available or are being developed that target individual risk factors of heart disease, but what makes NV-04 a particularly exciting drug prospect and unique is that it targets such a wide range of risk factors and does so without apparent side-effects.

The NV-04 pre-clinical program now has been accelerated with the aim of having the drug in human clinical trials by 2002.

NOVOGEN

## Rimostil™

Natural isoflavones for the maintenance of post-menopausal health and well-being. Each Rimostil tablet contains 57 mg of standardised Clovone, a proprietary ratio of four isoflavone plant hormones.

**30 tablets – take one daily**

with natural Clovone™



## Rimostil prepares for market launch

Rimostil is Novogen's new isoflavone product for post-menopausal women. Rimostil contains Clovone, a proprietary ratio of four isoflavones.

Novogen scientists discovered that the ability of isoflavones to stimulate human bone cells to make new bone and to stimulate the body to make HDL (the 'good') cholesterol was related to a particular ratio of certain isoflavones.

Clovone has that ratio, and is the result of that discovery.

In a clinical trial conducted at a major Australian teaching hospital in post-menopausal women aged in their late 50s, Rimostil produced a mean 28 per cent rise in HDL cholesterol and a 4 per cent rise in the density of cortical bone, the type of bone that dominates in load-bearing bone such as the hip joint.

Significantly, these effects were obtained with no reported adverse side-effects and in particular no increase in the thickness of the endometrium.

Rimostil will be launched mid 2000 initially in Australia and Canada

## Promensil delivers important health benefits in clinical studies

Promensil, currently is the subject of a large number of clinical studies around the world. These studies are building on clinical experiences derived from early studies and are particularly aimed at confirming the range of health benefits of Promensil in middle-aged women.

Two studies in particular have been announced in recent months.

One involved the use of Promensil to manage vasomotor symptoms ('hot flushes') in women entering menopause. This was a double-blind, placebo-controlled study conducted by the Institute of Gynecology and Reproduction in Lima, Peru and involved 30 menopausal women. After 4 months' therapy with Promensil, the average hot flush count was reduced from 7 down to 3, a highly statistically significant ( $p < 0.001$ ) effect compared to the control group.

The second study, a Phase 2 study, was conducted at the Queen Elizabeth II Hospital in Perth, Australia. This also was double-blind, placebo-controlled study involving 18 pre-menopausal with severe cyclical mastalgia (fibrocystic breast disease). This condition is thought to be one of the manifestations of pre-menstrual syndrome and displays as pain and swelling of the breasts during the menstrual cycle. It is thought to be associated with excessive estrogen function within the breast tissue since anti-estrogen drugs usually provide effective relief.

In this study, nine of the twelve women on Promensil treatment showed worthwhile improvement in their pain, compared with only two of the six on placebo. The average reduction in pain was 12 per cent for placebo and 44 per cent for one Promensil tablet per day.

These two studies, taken together with the considerable amount of clinical data generated from other Promensil clinical studies, indicate that Promensil offers considerable health benefits to peri-menopausal women.

## Novogen moves up in Nasdaq

Nasdaq is the US technology stock market where Novogen has been listed since early 1999.

At that time the Company was listed under the "Small Cap" heading as the initial volumes of trades and number of stock holders were assessed.

However, Nasdaq has announced that from May 2000, Novogen will be listed on the more widely reported Nasdaq National Market.

This has occurred because the volume of trading in Novogen stock in the US and the number of holders has now increased to the point where the Company meets the criteria for the National Market.

Novogen's US stock will continue to be traded in the form of American Depositary Receipts (ADRs). One ADR will remain equal to five ordinary shares. The Company's US trading symbol is NVGN.

Novogen's original and primary stock listing is with the Australian Stock Exchange (ASX) where the Company trades under the symbol of NRT.

In April 2000, the ASX announced that due to the increase in the Company's market capitalisation and the volume of trading in the stock, Novogen would be included in the ASX200 which is the index of the top 200 listed companies in Australia.