NORWOOD ABBEY

Norwood Abbey Ltd ABN 20 085 162 456
63 Wells Road, Chelsea Heights Victoria 3196 Australia
Telephone 61 3 9782 7333
Facsimile: 61 3 9782 7334
norwood@norwoodabbey.com.au
www.norwoodabbey.com

Dear Fellow Shareholder,

As many of you will be aware, the Immunology Project currently being carried out by Norwood Abbey Ltd and its research partner, Monash University, has recently received a significant amount of favourable exposure in the press.

Like all listed companies, Norwood keeps the market fully informed of its activities by way of "ASX announcements". The difficulty with such announcements is that they really do not create an ideal forum for shareholders to completely understand the background and/or the consequences of the notice.

I have therefore taken this opportunity to write to you to explain a little more about the Immunology work being conducted by our Company and Monash University and enclose a detailed briefing document.

We are currently conducting four human clinical studies at two major Melbourne hospitals to investigate the effects of using an existing class of drugs, known as **GnRH analogues**, to stimulate the possible re-growth of the thymus gland. The thymus gland is responsible for the production of **T cells**, which are a major cellular component of the immune system. In particular, we are monitoring the extent and type of new T cells produced as a consequence of thymus growth.

The initial human study, which commenced late in 2000, is investigating a group of prostate cancer patients. This patient group are receiving a GnRH analogue drug as a normal part of their prostate cancer therapy. We are monitoring their improvement in thymic function and T cell production.

Whilst the data from this study has not yet been published, we have reported that a significant number of these patients have shown a clinically important increase in their T cell count. Furthermore, the new T cell production is of the "naïve" (or "new") T cell type. (This is important because such T cells are most able to assist in immune deficiency situations such as cancer, organ transplantation and auto-immune diseases).

As a consequence of this encouraging human data we applied, early in 2001, to conduct a number of additional human studies, to investigate specific groups of patients suffering from life threatening diseases, and who were likely to benefit significantly from the proposed therapy.

These studies are investigating the following patient groups:

- **Immunosuppressed Cancer patients.** These patients have advanced cancer and the treatments they have received have resulted in them having a very poor immune system.
- **Bone Marrow Transplant patients.** This group will receive a transplant of bone marrow, as part of the therapy for their cancer. In order to prevent transplant rejection, these patients are given immunosuppressive drugs.
- **HIV/AIDS patients.** As a consequence of their illness, they have a very low number of T cells. This group are also receiving anti-viral drugs as part of their therapy.

The GnRH analogue drugs have been extensively studied over a long period of time and there is over a decade of clinical experience with their current therapeutic applications. It should be noted that these studies are investigating new uses for this group of drugs.

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For these reasons, the proposed new use for the GnRH analogue drugs will not need to go through the usually lengthy processes associated with pre-clinical evaluation and toxicology. Associate Professor Richard Boyd's group at Monash has generated complete and detailed animal data concerning the proposed new uses for this drug class, which is integral to obtaining regulatory approvals for the new uses.

Norwood and Monash University have an extensive patent position on the proposed new immunological use of GnRH analogue drugs. It is the Company's belief that, other than with the agreement of Norwood, these drugs cannot be registered for the proposed new clinical indications, without infringing Norwood's patent position.

The clinical studies being conducted on our behalf are advanced human studies, investigating drugs with known toxicity, but for a new use. The purpose of these clinical trials is to determine whether the previously observed T cell increase in animal groups and human prostate cancer patients is also reflected in other patients, particularly those with critical immune deficiencies.

All patients enrolled in our studies are undergoing extensive blood analysis. Although it is currently expected that these patients will be monitored through until 2002, the Company, and its research colleagues expect to be in a position to announce initial clinical data results prior to the end of November 2001.

We are often asked why our newly discovered use for the GnRH analogue drugs was not previously known. In essence, it is because the first GnRH analogue drugs on the market were biologically and clinically evaluated prior to the structure, function and activity of T cells being fully appreciated.

Subject to the results of the clinical trials, the research being carried out by Norwood and Monash University has the potential to impact on the treatment of a number of diseases related to the immune system. These include cancer, HIV/AIDS, organ transplants, and auto-immune diseases such as multiple sclerosis, psoriasis and rheumatoid arthritis.

Discussions with potential Pharmaceutical partners:

As previously advised, discussions are well advanced with a number of interested international 'pharmaceutical' parties.

Given the most probable commercial arrangements would be based on the combination of Norwood's Science with relevant drugs from a pharmaceutical partner, the eventual structure of any joint venture and/or licensing arrangements could take a number of different forms.

The Directors of Norwood are cognisant of their duty to develop a relationship which is of long term benefit for all shareholders. To that end, we are proceeding carefully with all discussions.

It is possible that the Company will be in a position to announce the successful formation of a suitable business relationship prior to the initial results of our clinical trials being publicly available.

Thank you for your continued support in our first year as a listed Company.

Yours sincerely

Peter Hansen

EXECUTIVE CHAIRMAN

Enclosure

1 Investor briefing

Immunology Breakthrough

In the second edition of Norwood Abbey News we announced details of our research partnership with Monash University and Associate Professor Richard Boyd. This briefing is designed to provide the background to this project by introducing you to some of the basic concepts in immunology and the potential application of the Norwood Abbey technology to the treatment of a number of diseases.

INTRODUCTION

The immune system is the name given to the organs and special cells that work together to protect the body against attack from bacteria, viruses, parasites, other "foreign" intruders, and cancers.
The immune system is the body's defence system and the study of this system is known as immunology.

The immune system has many ways to fight disease, ranging from physical specific barriers to germs, such as the skin, to the production of cells that destroy foreign attackers.

When foreign particles, also known as antigens, enter the body the immune system responds in two steps. The first involves the body "recognising" these foreign cells and the second is the mobilisation and production of specialised cells to eliminate antigens.

Cells that will destroy foreign cells are known as lymphocytes and include B cells and T cells. These cells are in very small numbers until the presence of the specific invader is recognised. When that happens the cells are able to call on the body to create many more cells specifically to destroy the invader.

SELF AND NON-SELF

The concept that the immune system must be able to distinguish between cells that are "self" (and against which it should not interact) and "non-self" (foreign to the body) was first described by Sir MacFarlane Burnet and Peter Medawar in the early 1960s. Working at the Walter and Eliza Hall Institute in Melbourne, Australia, Burnet was awarded the Nobel Prize for this work in 1964.

To distinguish "self" from "non-self", the human body uses a complex mechanism whereby it produces T cells that **are only capable of recognising and reacting against non-self (or foreign) cells.** The production of T cells that can only recognise "non-self" **occurs in the thymus**. Once these T cells recognise a foreign invader, including "non-normal" or cancer cells, they will then eliminate it.

This system is essential so that the body does not destroy itself.

Obviously, a fully functional immune system that can readily seek out and destroy foreign material is **vital** to our health and well-being. Abnormalities in the immune system, at any level, can be devastating. For example, a poorly working, or suppressed, immune system cannot easily fight off viruses and other invading micro-organisms, or, more seriously, will allow uncontrollable growth of abnormal cells leading to tumour formation. A suppressed immune system can result from chemotherapy and diseases such as HIV/AIDS. On the other hand, if the immune system is overactive, contact with common things like dust, pollen or animal hair is seen as a serious threat and the body mobilises all of its defences. Examples of this are allergic reactions, such as hayfever, and asthma.

1 Investor briefing

Organs and cells of the immune system

The two major organs of the immune system are the thymus and bone marrow. (Other organs include the lymph nodes, spleen, tonsils and appendix). The thymus is located near the heart, and bone marrow is found in the centre of bone. Bone marrow produces haemopoietic stem cells (HSC), which can develop into B cells or other white blood cells. Some of the HSC also move from the marrow, through the bloodstream, to the thymus. In the thymus they develop into T cells.

- **B Cells:** These cells produce **antibodies** and other chemicals to fight off any invasion of the body by **bacteria, fungi or protozoa**. When a certain antigen is detected in the body, the specific B cell will produce antibodies, which surround the antigen and mark it as foreign. Each B cell will only make one specific antibody. These cells are extremely good at localised immune defence, e.g. at the site of an infection.
- **T Cells:** These cells are designed to deal primarily with infections inside cells such as **viruses and parasites**, and with any other **foreign cells** within the body.

  They are of two main types: **T helper cells,** which initiate virtually every response, and **T cytotoxic cells,** which kill the infected cells, those cells marked by the antibodies or tumour cells. (Interestingly, tumour cells are "foreign" to the body, in that they are not normal cells. T cells actively try to remove them). Without these T cells, the individual is highly susceptible to disease, and can die from infection.

  The T cells and the B cells interact with each other and other specialised cells termed antigen presenting cells (APC) to provide us with a strong and comprehensive defence mechanism against numerous foreign or "non-self" invaders.

ROLE OF THE THYMUS

Despite the vital importance of the thymus for maintaining good health, one of the most intriguing features of the immune system is that after puberty the increased production of the sex hormones (oestrogen in women, testosterone in men) causes the active part of the thymus to shrink dramatically to less than 1% of its young size and function. Prior to puberty the thymus is about the size of two small apples and can weigh up to 35 grams; in adults the active section can be smaller than a pea.

An interesting question to ask is "why would the body cause its own defence system to slow down as we age?"

A fundamental feature of evolution is that nature provides a number of ways to enable individual members of a species to reach sexual maturity. Reproduction ensures that the species does not die out. The most important mechanism by which humans are protected throughout life is the immune system. Therefore, pre-pubescent children are given maximum protection against infection because they have a fully sized, fully functional thymus – producing T cells in abundance. As a corollary to this, once sexual maturity has been reached, the protective mechanisms required for survival are not (at least from the viewpoint of enabling the species to reproduce) needed any more. Indeed, too much long-term protection might mean that members of the species live for too long, resulting in a drain on the food chain.

Although the active part of the thymus shrinks during adulthood, the **normal** adult has enough functioning T cells to cope with most immunological problems. For many people, the decrease in thymus activity after puberty is not all that important, although with increasing age, the lack of new T cells does start to present serious and significant medical problems. In particular, following destruction of T cells by chemotherapy for example, young children will recover their cell-mediated immunity within one or two months but adults may require one or two years. In the absence of full immune protection, the individual is very susceptible to diseases, particularly viral infections which often lead to death.

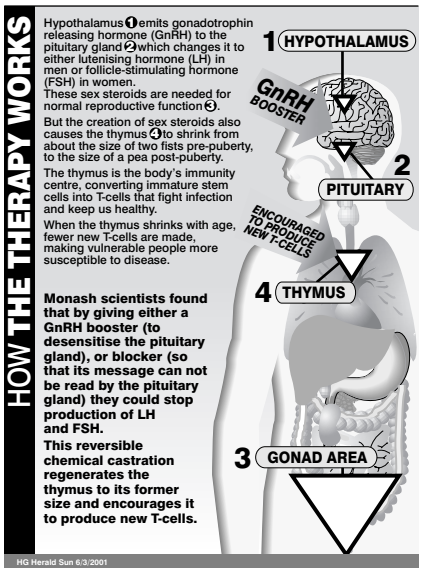
T CELLS AND THEIR ROLE IN MEDICINE

Many diseases that generate publicity and community interest are either diseases of the immune system or those whose treatment has a severe impact on the immune system. T cells can play a role in the treatment of all of these diseases.

Cancer:

Cancer therapies try to eliminate cancer cells from the body using chemotherapy (drug treatment), radiation, surgical removal or a combination of these.

Unfortunately, the use of chemotherapy and radiation regimens is restricted because both treatments significantly lower the number of T cells in the body.



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Indeed, cancer therapies are a balance between killing the cancer cells, risking infection because of the serious decrease in T cell levels, poisoning the patient (overdosage), and not killing the cancer (underdosage). By promoting the production of new T cells, the cancer patient will be less likely to develop infections, giving an improved quality of life over the course of the treatment. Adequate and active T cells are also a major defence mechanism against cancer because they can recognise and eliminate any newly growing cancer.

AIDS:

Acquired Immune Deficiency Syndrome (AIDS) presents as a consequence of an infection by the Human Immunodeficiency Virus (HIV). This virus infects and destroys T cells. Invariably, the low number of T cells results in the HIV patient, who develops AIDS, dying from the complications of infections that they would normally have no difficulty in fighting off. Boosting the number of T cells in the AIDS patient's body will help defend them against developing life-threatening infections.

Auto-immune diseases:

With increasing age, and in some abnormal situations, the body mistakes "self" for "non-self" and a form of self-destructive immune response is initiated. This is called an **auto-immune response** – where the body literally destroys its own tissue. Diseases such as Multiple Sclerosis, Rheumatoid Arthritis, Diabetes and Lupus are examples of auto-immune diseases. In Multiple Sclerosis, for example, the body mistakenly produces T cells that destroy the protective coating surrounding nerve cells, leading to the loss of control of nerve function. In normal circumstances these nerve cells would not be recognised as being "non-self". The reason such autoreactive T cells are produced is poorly understood. Producing new T cells that will not destroy the body's own tissue will limit the effect of these diseases.

Tissue (organ) transplants:

Replacement of diseased organs with functional organs (such as heart, lungs and kidneys) from a donor has become an almost routine part of modern medical practice.

Unfortunately, organs from other people (except for identical twins) will be recognised as foreign (or "non-self"), and the T cells will begin to destroy them. This is referred to as rejection following tissue transplantation. To counteract such rejection, we administer **immunosuppressive drugs**, which stop the production of T cells. Unfortunately, without T cells to fight other infections, the patients become very susceptible to any diseases and viruses, and can die. By producing new T cells that can recognise both the body and the donor organ tissue, we hope to limit the possibility of transplant rejection without the need for high dosages of immunosuppressive drugs.

IMPROVING T CELL FUNCTION

Improvements in the number and the function of T cells in adults is now seen medically to be a most desirable phenomenon in virtually all immune-based disease conditions. Until now, no one has been able to achieve this, primarily because the active thymus, in adults, has decreased in size to an extent where improved T cell production has not been possible. Some drug treatments (eg. Interferon, Interleukins etc.) are available to improve T cell function, but these often do not produce the required effect and can have side-effects such as headaches, fever and joint pain.

A NEW WAY OF THINKING

Associate Professor Richard Boyd and his group at Monash University and the Alfred Hospital in Melbourne will soon publish data demonstrating that the thymus can be regrown in humans and that this thymus can create a new set of T cells.

The technique, **which is now extensively patented as part of Norwood Abbey's patent portfolio**, uses a class of medicines that have been used to treat some breast and prostate cancers and endometriosis. These drugs (known as GnRH analogues) have been marketed in most Western countries for more than a decade. The GnRH drugs work by blocking the production of the sex hormones (oestrogen and testosterone), which slows the growth of these particular cancers. The overall effect is to produce a state of "chemical castration", which is **reversible** when the GnRH analogue treatment is ceased.

The sex hormones are produced by a mechanism that originates in the brain and is shown in the diagram, above, left.

As already stated, it is the sex hormones that cause the thymus to shrink from puberty onwards and the number and function of T cells produced to diminish.

What was not fully appreciated, until the studies by Richard Boyd, was that stopping the production of sex hormones caused the thymus to regrow to a form identical to that in the young. This creates the optimal environment for the production of a new set (known as a repertoire) of T cells.

Whilst Richard Boyd and his colleagues have studied this technique extensively in animal model systems, it is only recently that these studies have been extended to humans. They have demonstrated, in patients being treated for prostate cancer, that the thymus **does regrow and that this is often accompanied by a significant increase in T cell number in the patients studied**.

Further, they have demonstrated that the new T cells thus created, are of the type required (naïve T cells, which have never been presented with an antigen) to potentially provide significant medical benefits to many patients suffering from the above-mentioned disease states.

NORWOOD ABBEY'S STRONG POSITION IN IMMUNOLOGY

Norwood Abbey is superbly placed to take advantage of this breakthrough in the treatment of disease. The strength of our position is confirmed by the following facts:

- Immunology concepts have potential clinical relevance in the management of cancer, AIDS and auto-immune diseases (e.g. Multiple Sclerosis) and in increasing the success of organ transplantation surgery.
- Norwood's patent applications cover all of these expanded uses.
- Results of clinical studies will be known before the end of 2001.
- Norwood does not have to develop a new drug, as our technology uses an existing "approved" class of drugs that have been on the market (for other uses) for many years.
- Regulatory approval process for the use of existing drugs for a new "indication" (use) is significantly less complex and faster than for a new drug.
- Patented concepts create significant new market potential for the existing drugs.
- Norwood has received significant interest from prospective pharmaceutical partners.
- Opportunities for Norwood's pressure wave technology to be used in "genetically" enhancing new T cells in organ transplantation.

AUSTRALIANS AND BIOMEDICAL BREAKTHROUGHS

There is no doubting the major contributions made by Australians, working in Australia and throughout the world, to advancing the field of medicine. In many cases the discoveries have changed forever the way in which we approach the treatment and understanding of human disease.

Some of the major medical developments are:

- **Antibiotics.** The discovery of the effects of Penicillin by Lord Florey completely revolutionised the treatment of bacterial diseases, and led us into the so-called "Antibiotic Age".
- **Organ Transplants.** Sir MacFarlane Burnet discovered that the human immune system was able to differentiate between "self" and "non-self" (or foreign). This fundamental knowledge explained the action of T cells and has led people to describe him as the "father" of immunology.
- **Stomach Ulcers.** Dr Barry Marshall discovered that stomach ulcers were actually caused by bacteria. This completely overturned the conventional wisdom that ulcers were caused by stress or poor diet and resulted in the prescribing of more effective drugs for ulcer treatment.
- **Colony Stimulating Factor.** The discovery of Colony Stimulating Factor by Dr Don Metcalf enabled a new set of treatments to be developed for cancer therapy.
- **Influenza.** The first effective cure for Influenza was discovered by Dr Peter Colman and Dr Wen Yang Wu, and has resulted in the worldwide sale of the drug Relenza.

Norwood Abbey is excited to be working alongside Richard Boyd in the development of treatments resulting from regrowth of the thymus. Clinical research trials, sponsored by Norwood, have commenced in Melbourne with a number of collaborating hospitals and research institutions. The human clinical trials are investigating the effectiveness of the use of GnRH analogues in a number of conditions where T cell levels are seriously reduced.

These studies will include groups of HIV/AIDS sufferers, bone marrow transplant patients and immunosuppressed cancer patients. It is expected that the initial results from these studies will be available in six months.

It is our ambition that, in the future, the rebirth of the thymus and the work of Richard Boyd can be a worthy addition to the list of Australian contributions to the advancement of medicine.

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