SCHOOL PROJECT MATERIAL

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VICTOR CHANG RESEARCH LABORATORIES

The Victor Chang Cardiac Research Institute
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THE VICTOR CHANG CARDIAC RESEARCH INSTITUTE

BACKGROUND

When Dr Victor Chang established a national heart transplant program in 1984 at St Vincent's Hospital, he pioneered the future of cardiothoracic surgery and research in Australia.

It is now 13 years since Victor's tragic death but his vision lives on through the research conducted at the Victor Chang Cardiac Research Institute (VCCRI).

In Australia, cardiovascular diseases claimed the lives of 128,500 people in the last 12 months alone – over one-third of them aged less than 60.

Although only operational for 10 years, the VCCRI has succeeded in recruiting faculty and staff of international stature, who have already made world-class research discoveries, spanning from clinical medicine to basic molecular, cellular and developmental biology.

The VCCRI also plays a major role in biomedical research training and in the translation of basic science advances to bedside clinical treatments.

Despite the profound importance of heart disease and despite the VCCRI's achievements, it continues to be heavily dependent for its daily operations on charitable donations.

The Victor Chang Cardiac Research Institute has as its mission "the relief of pain and suffering and the promotion of well-being through an understanding of the fundamental mechanisms of cardiovascular diseases". In particular it has as a major emphasis the prevention diagnosis and treatment of heart muscle disease.

The following are the research projects currently being undertaken by the Institute.

Computational Biology & Bioinformatics Program

Much of our information on the structure and function of molecules affecting function and growth of heart, or interfering with cardiac function, is now available in an electronic or generally symbolic form, in public or private databases (e.g. the human genome). One of the roles of the Biocomputing Unit is, to translate this information into three dimensional structural models that can aid, and even guide, experimental work. In the past year, the Unit was involved in modelling, analysing and interpreting structures of adrenergic receptors; lamins, proteins that likely regulate cellular functions within the nucleus; the transcriptional activation factor, NKx2-5; and human Delta 3 ligand, an important signalling molecule.

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Cardiac Mechanics Program
(Professor Michael Feneley, Head)

The contractile function of the heart is the focus of Michael Feneley's research group. Many things including blood pressure, hormones and ageing affect the mechanical function of the heart and may cause changes in the heart muscle itself. Using animal models of heart disease, sophisticated clinical and research techniques are utilised including echocardiography and ultrasonography in order to determine very early changes in heart function. In addition, by examining electrically-paced single heart cells, very minor changes in contractile function can be assessed. These approaches should provide new insight into the initial changes in heart muscle function, which ultimately lead to heart disease and failure.

A/Professor David Muller
(Head)

Coronary artery disease remains the major cause of death from heart disease. Although dilating and reaming out clogged coronary arteries is effective for improving blood supply to the heart, not infrequently the arteries rapidly reclog, a process called restenosis. This is due to excessive growth of the smooth muscle cells in the coronary artery, and even with the use of stents (a wire mesh placed in the arteries to hold them open) cannot be entirely prevented. Dr Muller's group are investigating the mechanisms and treatments of coronary artery restenosis.

Developmental Biology Program

(Professor Richard Harvey, Head)

Understanding heart development is relevant not only to problems causing congenital heart disease, but also to adult heart disease. Interestingly, when the heart is stressed it begins to produce proteins that are otherwise only found in the immature developing heart. This response may allow heart function to be preserved during stress. Understanding the mechanisms of heart development is the focus of Richard Harvey's group.

A/Prof Peter Currie
(Laboratory Head)

A/Prof Peter Currie is one of only a small group of researchers world-wide, who use zebrafish as a model to understand fundamental biological processes, such as muscle development. Zebrafish are a unique research model because their transparency allows the development of their organs, such as their heart, to be readily visualised, and because they reproduce rapidly over a short period of time. Moreover, the genes controlling organ development in the zebrafish, which closely mimic those in humans, can be fairly readily isolated and studied.

Dr Sally Dunwoodie
(Laboratory Head)

Abnormal development of the heart and vasculature underlie a large number of birth defects, and can contribute to the onset of heart failure later in life. Many of these defects are due to mutations in genes that are crucial for normal development of the heart and vasculature in the embryo. Sally Dunwoodie's group is defining the role of novel genes during embryonic development in order to understand how heart defects arise.

Victor Chang
Cardiac Research Institute

<u>**Electrophysiology and Biophysics Program**</u>
(Professor Terry Campbell, Head)

The co-ordinated spread of electrical impulses down the heart is required for it to pump blood efficiently. If this process becomes disordered the heart pumps inefficiently or may even stop, resulting in sudden death. Indeed, such an event is the eventual cause of death in approximately 50% of people with heart failure and at present there is no way to predict which of these people is particularly at risk. Terry Campbell's group focuses on the mechanisms by which the normal electrical activity is produced. The group is also very interested in genetic abnormalities of these physiological systems and in the mechanisms by which various drugs can either be used to treat electrical disturbances of the heart or in some cases can aggravate these disturbances.

Dr Jamie Vandenberg
(Laboratory Head)

The underlying rhythm of the heartbeat is controlled by the passage of electrically charged atoms ("ions"), through special pore-forming proteins in the membrane surrounding each cell in the heart. These pores open and close in response to changes in the voltage across the cell membrane and hence are known as voltage-gated ion channels. One of the most important members of this family of proteins is the HERG potassium channel, which plays a significant role in preventing the triggering of abnormal heart rhythms. This is the main focus of Dr Jamie Vandenberg's research.

Molecular Genetics Program

(Professor David Martin, Head)

At birth heart muscle cells lose their ability to divide. When injured, the heart has only a limited ability to repair itself and its pump-function is reduced. This often results in heart failure. The inability of heart muscle cells to divide is due to the shutting off of certain genes. David Martin's laboratory is interested in the precise mechanisms determining which genes are active and why certain genes are inactivated.

Dr Thomas Preiss

(Laboratory Head)

Dr Preiss's research is aimed at understanding the fundamental mechanisms whereby 'the messages of life' contained in our genes, are translated into 'the workers of the cell', proteins. This research has enormous and direct relevance to our understanding of how the heart changes its properties and functions in the face of stresses, such as high blood pressure or diseases of the heart valves, which require the heart to work harder under an increased load, and therefore causes deleterious, excessive thickening of heart muscle.

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Molecular Cardiology Program

(Professor Robert M Graham, Head)

Both the moment-to-moment and long-term regulation of heart function are controlled by hormones and growth factors. Abnormalities in these systems as well as in the genes regulating heart muscle cell growth and contractility can cause excessive enlargement of heart muscle and eventually hart failure. Robert Graham, Diane Fatkin and their colleagues study the molecular mechanisms regulating heart function and the genes responsible for familial causes of heart enlargement and failure.

Dr Diane Fatkin

(Laboratory Head)

The major focus of research in this laboratory is the study of cardiomyopathies – disorders of heart muscle that not uncommonly lead to heart failure and even death. The primary objectives of the research are the identification of known gene defects, as well as the discovery and characterisation of new disease-causing genes. Currently over 30 families are being evaluated in whom candidate gene screening is being performed.

Another objective is to find out more about how gene mutations actually result in heart muscle disease. Although many genes are identified as disease-causing, the characteristics of the genes themselves and the function of the abnormal proteins produced by these genes are frequently unknown.

The third objective is to apply molecular genetics to patient management by developing new drug therapies specifically designed to entirely prevent or at least halt the progression of the disease.

Tranplant Program

(A/Professor Anne Keogh and A/Professor Peter Macdonald, Joint Heads)

Heart transplantation remains a major treatment for patients with end-stage heart failure. However, obstruction or blockage of the arteries of the heart, resulting from long-term attack of the transplanted heart by the patient's immune system, remains a major limitation to long-term survival. Trials with immuno-suppressive drugs conducted within the unit over the past 3 years, have gone a long way toward impacting this impediment to long-term survival.

The reduction Australia-wide (and indeed worldwide) in cardiac organ donation, has forced us to focus on alternatives to transplantation, and particularly on pulmonary arterial hypertension (which would otherwise have required a heart and 2 lungs to be transplanted).

We are optimistic, that the Transplant program is actively evaluating new drug therapies for pulmonary arterial hypertension that appear to delay or to completely prevent, the need for transplantation in the future.

Ventricular-Vascular Interactions Program

(Professor Michael O'Rourke, Head)

Each time the heart pumps the blood vessels stretch to accommodate the ejected blood. This causes a pressure wave to be reflected back against the heart. Pioneering work by Michael O'Rourke and his colleagues showed that as we age our blood vessels stiffen. This reduced ability to stretch, increases the pressure reflected back onto the heart, which eventually causes it to fail. The mechanisms leading to arterial stiffness and the influence of hormonal and other factors on the progression of this problem, are the focus of the ventricular-vascular unit.

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