Newsletter to Shareholders

8th May 2015

New Director of Research and Development

Following the retirement of Dr Jim Watson, Caldera has appointed a new Director of R&D, Dr Keith Hudson, who will commence work on 1 June 2015. Keith is a gifted New Zealand scientist who has enjoyed an outstanding science career and also has considerable experience in the business of start-up biotech companies. With this background he is a first-class choice for the next phase of Caldera's growth.

Keith received a PhD in immunology from the University of Auckland in 1993, where he studied molecules found on bacteria that act as a decoy for the immune system assisting the spread of bacterial infection. His research resulted in a detailed understanding of the mechanism of these molecules' action, leading to scientific publications in top-rated international journals and five years' postdoctoral research at the University of Oxford, then the University of Birmingham. He studied cytokines, molecules that control whether our white blood cells' immune cells develop immune responses during infection and cancer. Cytokines are termed ligands and must bind to their docking stations or receptors, on or in white cells, to stimulate immune responses. Many modern therapeutics are small molecules designed to inhibit the action of several important cytokines by blocking their binding to their receptors, and Keith's work at that time was a forerunner to such therapeutics.

He returned to New Zealand and joined our largest biotech company, Genesis Research and Development. There he continued his interest in ligand-receptor interactions. While at Genesis he was responsible for developing a major research program on identifying and using plant receptor and ligands for the development of enhanced plant characteristics, work that leveraged one of the most extensive plant DNA databases in existence at the time, developed by Genesis. This research received Government research funding in excess of NZ $6 million and resulted in several patent applications. Keith was also instrumental in developing a powerful software system to turn very early DNA genomic information into useable gene sequences. The heart of this system ended up being sold and developed into a US bioinformatics company.

In 2007, after six years at Genesis, Keith started his own company, Androgenix, to develop new sperm sexing technology for the dairy artificial insemination industry. This company utilised the initial drafts of the entire bovine genome to discover molecules on the surface of sperm that could be used as handles to efficiently sort sperm into those bearing the X or Y chromosome. Although the company was not successful in developing new sperm sorting technology, it did develop new easy processes for modifying the surface of sperm or any cell with a molecule of choice.

Most recently Keith has been developing new diagnostic assays with application to fertility, while also working as Editor of two Springer-Health academic journals, BioDrugs and Molecular Diagnosis and Therapy. The latter is specifically focused in the area of personalised medicine, particularly in the application of next generation sequencing for diagnosis, prognosis and therapeutic intervention guidance. This is extremely relevant to the work he will be carrying out at Caldera.

Project Reviews

At the end of each quarter we take several days to assess progress in the past quarter and refine the product development work plan. This also involves reviewing staff job responsibilities against the changing work plan, providing the Board and Finance Committee with a clear view of financial needs and reviewing the state of what we call “business readiness,” or Caldera’s progress toward major milestones that will underpin our business partnerships and commercial revenues.

Completing Clinical Study 2 remains our priority target. This involves rigorous testing of our RNA biomarkers in diagnostic assays that target prostate cancer diagnosis, using samples from urine, biopsy tissue and prostatectomy tissue. While work has been proceeding for the past two quarters, there is little to report in the way of outcomes until the results of the study are fully collated and analysed. This will start to come together later in the current quarter and extend into Q3 of 2015.

Callaghan Innovation R&D Growth Grant

In 2013 the Government implemented new grants aimed at promoting R&D expenditure in early-stage companies developing new market products as well as encouraging more mature businesses to spend significant funds on their ongoing R&D.

Caldera was awarded a Growth Grant that commenced in July 2014 and expects to be receiving around $80,000 each quarter from the grant, contributing towards the costs of Clinical Study 2. Clinical studies have to be funded, but none of them will generate revenue for the business until they reach the market. Such grants fill an important financial need for Caldera.

Accounting

Michael Laycock our financial controller has migrated Caldera’s accounting system onto the Xero platform. The audit of the previous financial year has commenced and we look for cost benefits for us in this process as the auditors can use the Xero platform to run the entire audit.

Staff

Towards the end of 2014, Dr Nicola Jackson joined the Caldera team. Nicola is a well-trained and experienced scientist with a strong background in immunology and molecular biology from the PhD work she carried out at the University of Auckland. Nicola was then awarded the prestigious Rutherford Foundation Freemasons postdoctoral fellowship which enabled her to go to the University of Cambridge in the United Kingdom for four years. She followed this by taking a job at the Anthony Nolan Research Institute in London. Nicola is currently leading the Caldera project to work out a way of using urine samples for prostate cancer diagnosis.

Our next staff need was to strengthen our in-house analytical processes for interpreting the data that will come from Clinical Study 2. Last month we appointed an experienced biostatistician,

Dr Dug Yeo Han, to join our team. After completing her PhD in Statistics at the University of Auckland, Dug Yeo has been working as a statistical consultant for numerous large research projects, including a large nutrigenomics study in the University of Auckland. She works closely with Dr Kristen Chalmet. We then commenced a collaboration with Professor Chris Triggs from the Statistical Consulting Centre (SCC) at the University of Auckland. Professor Triggs now acts as a consultant to Caldera and brings access to the latest developments in statistical methods, which are vital for our current Clinical Study 2 analysis. Kristen and Dug Yeo will work closely with Professor Triggs, and Keith Hudson also comes with a strong background in handling large data-sets.

This brings our product development team to eight scientists, including Keith, with additional work contracted to the Malaghan Institute for Medical Research in Wellington, and to bioinformatician Dr David Eccles, to provide further analytical input into our D'Cipher software.

We continue to include short articles containing information and commentary about prostate cancer from Jim Watson. The third of these is appended.

Alastair MacCormick
Chairman

Graham Watt
Managing Director

A scientist's view of prostate cancer

Part 3: Modern cancer research in action

Many of you will have read this week that a New Zealand study known as the Midland's Prostate Cancer Study from the University of Auckland reports that two years after diagnosis with metastatic prostate cancer, New Zealand men have only half the chance of Britons of being alive.

"These outcomes are very poor," comments the leader of the study. My personal view is that this situation in New Zealand is unacceptable. There are a number of key reasons for this. At Caldera we know the first reason well – inadequate diagnostic testing for prostate cancer. There is still no accepted alternative to the PSA test, widely criticised for its deficiencies by medical opinion leaders. We lack clear national guidelines for the management of metastatic disease and we do not seem to have a very good understanding of how we might implement the use of a growing list of new drug treatments.

I regard myself as one of the lucky survivors, as today marks the 11th anniversary of my own diagnosis of metastatic prostate cancer. But I am also aware of the steady flow of men who go overseas to get treatment, which they have to pay for, and the gap between those drugs available overseas and those which are Pharmac-approved in New Zealand.

This has led me to think about very recent changes in the prostate cancer field, a story of modern science in action which gives me great hope for cancer treatments.

I start with two cancers, prostate cancer and breast cancer which are regarded as very closely related cancers because their primary drivers are the sex hormones, testosterone, and its companion dihydrotestosterone, for prostate cancer and estrogen for breast cancer.

Testosterone is also called "a male hormone" or an "androgen" but don't let the names mislead you. Both men and women produce androgens, just in differing amounts. In a woman's body, one of the main purposes of androgens is to be converted into female hormones called estrogens.

Testosterone and dihydrotestosterone have long been known as the drivers of prostate cancer. Prostate cancer drugs target both the body's production of these drivers and the receptors, called androgen receptors thereby blocking testosterone binding to the receptors leading to the death of the cancer cell.

In fact many men who have been treated for prostate cancer in New Zealand likely started their treatment with a drug called bicalutamide, which acts by attaching to androgen receptors in the prostate cancer cell, blocking testosterone binding to the receptors.

Interestingly, Pharmac has approved this month in New Zealand, a new drug called Abiraterone or Zytiga which works by blocking the production of testosterone in the body effectively removing the major driver of prostate cancer.

So here we have the two major ways of treating prostate cancer; block the drivers, that is production of testosterone and dihydrotestosterone, or block these drivers from binding to androgen receptors.

A new drug called Enzalutamide has been developed by the pharmaceutical company Medivation for the treatment of metastatic prostate cancer. Like bicalutamide, it binds to the androgen receptor to kill cancer cells, but does so five times more effectively than bicalutamide.

Women with advanced breast cancer now benefit from drugs originally meant for treating prostate cancer in men. Breast cancers are defined by the presence of their own receptor molecules or docking stations. Estrogen and progesterone receptors and HER2 are the most common.

Aggressive forms of breast cancer lack these three receptors (ER, PR and HER2) and are often referred to as triple negatives. It was a complete surprise when a team at the University of Colorado Cancer Centre found some of these triple negative breast cancer cells contain androgen receptors.

Today we know that 75 percent of all breast cancers and about 20 percent of triple negative cancers contain androgen receptors. And this modern science in action story then lead to the discovery that, just as in prostate cancer, both bicalutamide and enzalutamide which both block the androgen receptor, also stop the growth of some triple negative breast cancers.

Men with advanced prostate cancer also benefit from drugs originally meant for breast cancer in women. For example, recent clinical trials show that a new drug, Olaparib, kills breast cancer cells in women with genetic changes known as the BRCA gene mutations (actress Angelina Jolie has this genetic mutation). Up to 30 per cent of men with metastatic prostate cancer have BRCA and appear to respond particularly well to olaparib.

There is another twist to this story. A new study from the Barbara Ann Karmanos Cancer Institute at Wayne State University in Detroit, published online 9 March, 2015 in the journal Cancer, reveals that the family history of prostate cancer may be linked to a woman's risk of breast cancer. More than 78,000 women were enrolled in a Women's Health Initiative Observational Study between 1993 and 1998. At the study start, all were free of breast cancer. When follow-up ended in 2009, more than 3,500 breast cancer cases had been diagnosed. And what fell out was the importance of family history of prostate cancer and breast cancer.

Most women who develop breast cancer have no family history of the disease. However, if women do have a family history of breast cancer, ovarian cancer, or both, these inherited cases of breast cancer are associated with two abnormal genes: BRCA1 (BReast CAncer gene 1) or BRCA2 (BReast CAncer gene 2). Women who inherit a mutation, or abnormal change, in either of these genes — from their mothers or their fathers — have a much higher-than-average lifetime risk of developing breast cancer and ovarian cancer. According to the National Cancer Institute in the US, women with an abnormal BRCA1 or BRCA2 gene have about a 60% risk of being diagnosed with breast cancer during their lifetimes (compared to 12-13% for women overall). These women’s risk of ovarian cancer is also increased. Abnormal BRCA1 or BRCA2 genes are found in 5-10% of all breast cancer cases in the United States.

Men with an abnormal BRCA2 gene are 7 times more likely than men without the abnormal gene to develop prostate cancer. Olaparib is the first cancer drug to target inherited genetic mutations.

There are genetic tests available to determine if someone has an abnormal BRCA1 or BRCA2 gene. But there is no doubt that the next generation sequencing technology Caldera is pioneering for prostate cancer diagnostics will also be widely extended to increased genetic testing for cancer gene mutations.

JD Watson
8 May 2015