Newsletter to Shareholders

17 November, 2014

New Premises

In mid-October Caldera moved to new premises at 74 Leonard Road, Penrose. We have now a first-class laboratory facility with more laboratory, office and meeting space than our previous facilities.

Shareholders will have an opportunity to view our premises at the Annual Meeting in two weeks' time.

Clinical Study 2

Completing Clinical Study 2 is our immediate target. While work is proceeding according to plan and budget, there will be little to report in the way of outcomes until the results of the study start to come together later in Q1 of 2015. We can, however, let you know that results to date are encouraging on two fronts. Firstly, we have established that RNA suitable for the RBAS technology can be extracted from urine. Secondly, we have demonstrated that patient urine samples can be stabilised with a preservation process suitable for clinical use. These satisfy two critical conditions that will enable broad application of a urine diagnostic test for prostate cancer.

New Investment

Our existing funding will carry Caldera to the end of 2014, with directors currently seeking funding to carry the company through to the end of Clinical Study 2, targeted for April, 2015.

Investors in biotech compare this sector, often unfavourably, to the IT industry with its faster growth profile. It's relatively easy and can be relatively quick for a software company to start with a few thousand dollars, hire a programmer to translate a software-as-a-service idea into code, and start selling its first product. Then, as they get feedback and revenues from customers, they can tweak the software, release new and better versions of it over time, and consequently attract more customers and earn more revenues. IT lends itself to an incremental improvement model.

Unfortunately, the timeframe to market is much slower for a biotech company. It's not possible to develop a new diagnostic, drug, biologic, or medical device prototype in short time periods, market it immediately to the public, and then make small adjustments along the way based on how it is received. That would be very risky, not to mention unethical and potentially illegal! To get a diagnostic, drug or medical device to market, a series of incrementally bigger and more expensive clinical studies have to be designed, approved and conducted. All of these activities have to be funded, yet none of them will generate revenue for the business. Importantly, potential commercial partners follow progress as each study de-risks their investment in new technology. This model can be described as cumulative risk mitigation.

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Caldera's commercial strategy remains the same: we are targeting multinational diagnostic companies to find the best partner to support our dual aims of providing Caldera with funding and shared resources to rapidly develop the technology to its full potential, and also with the capability to achieve clinical uptake and global laboratory sales reach.

Accounting

The annual accounts for the year ended 31 March 2014 have been audited by Ernst and Young, and Caldera has migrated its accounting system onto Xero.

Staff

Last week we welcomed Dr Bianca Dobson Robin to the Caldera team. Bianca holds a BSc (Hons) from Otago University and has recently completed a PhD from the Australian National University in Canberra. She has a passion for molecular biology and clinical science, and her skills complement those of our other staff. This brings our lab staff to seven scientists 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, which is the back-end of the RBAS process providing the results.

Annual Meeting

We remind shareholders our 2014 Annual Meeting will be held Wednesday 3 December at our premises at 74 Leonard Road, Penrose, at 4.00pm. Parking is readily available.

As we send you further newsletters we will continue to include short articles containing information and commentary about prostate cancer from Jim Watson. The second of these is appended.

Alastair MacCormick
Chairman

Graham Watt
Managing Director

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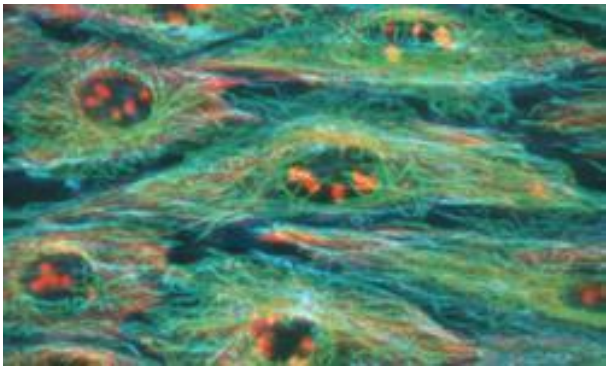
A scientist's view of prostate cancer

Part 2: Going forward from the Gleason Score

Caldera is a biotech company focused on developing novel diagnostics for detecting and staging prostate cancer with the aim of bringing these to market. To understand how these tools work and what use they are, it's necessary to understand a little about cancer itself.

Cancer is a term used for diseases in which abnormal cells divide without control and where many are able to invade other tissues, spreading from their point of origin to other parts of the body through the blood and lymph systems. There are more than 100 different types of cancer which are often named for the organ or type of cell in which they start. Prostate cancer, for example, begins in the prostate gland, but can often migrate to bone and other organs.

Each cancer starts with changes in one cell or a small group of cells. These changes are gene changes and it may be many years before a symptom such as a lump is felt, by which time the cells have started to divide uncontrollably.



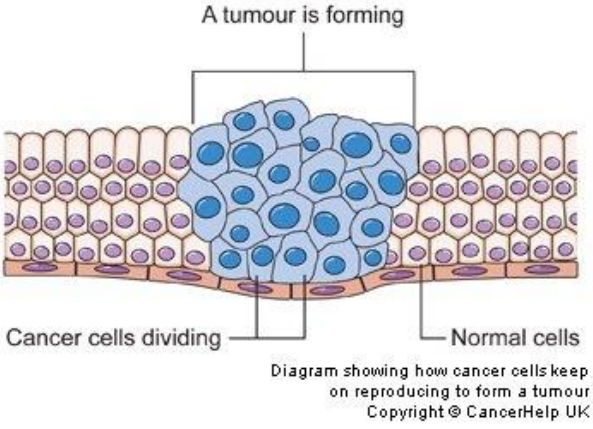


Diagram showing how cancer cells keep on reproducing to form a tumour

Different scientists and physicians approach the diagnosis of early cancer in different ways. One way is by using imaging technologies which look at what's going on inside the body. These technologies began with the harnessing of **x-rays** to invent CT scans. Other technologies followed. These include **MRI** (Magnetic Resonance Imaging) **scans**, which use magnetism rather than x-rays to build up a picture of the inside of the body. **PET** (Positron Emission Tomography) **scans** are a relatively new technology and are available in several hospitals in New Zealand. And there are **Ultrasound** scans, which use sound waves. These technologies have evolved over long-time frames: x-rays were discovered in 1895; CT scanners were invented in 1972.

While these technologies are extremely valuable, they are not yet alone, primary diagnostic tests. Rather they are supporting tools, as they do not give any insight into why the same cancer in different patients can present as very different clinically, that is, they look very different.

These advances since the discovery of the structure of DNA in 1953 have resulted in an explosion in technology development today. The completion of the sequencing of the human genome in 2000 showed how DNA carries a code for living organisms. The total DNA of each

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person forms their genome, and a copy of the entire genome can be found in most cells of the body. The code that the genome carries can be broken down into some 25,000 different genes. These genes are coded sets of instructions inside a cell that tell it how to behave. Each gene codes for one protein, and different genes tell the cell how to make different proteins. Each cell has many genes and can therefore make many different proteins. Every person has a unique variation some of these genes. Although gene variation between individuals generally has no effect on health, some changes lead to disease.

Other teams of scientists approach the diagnosis of cancer by looking for small variations in the DNA code, or mutations, in different individuals. They focus on people and families said to have a genetic predisposition to a certain type of cancer. This means they are more likely to develop that type of cancer than most other people. They are more at risk of cancer because they have been born with one of the mutations that starts to make a cell cancerous. More than one mutation is needed for a cancer to develop, as there are many steps in the process of a normal cell becoming a cancer cell. But some people with particular mutations appear to be naturally further along the road towards getting certain types of cancer than people who don't have the mutation.

Other scientists, like those in our Caldera team, believe that in the study of diseases like cancer, it's not enough to know whether a gene is mutated or normal—it's also important to know whether that gene is expressed and how it is expressed. That's because many mutations in DNA have no effect on healthy cells.

RNA expression profiling was developed as a logical next step after DNA sequencing to determine whether a particular gene is expressed and how it is expressed. The first RNA profiling technology was developed in 2001. It is based on the fact that the instructions found in each gene code are copied as messenger RNA (mRNA), and this acts as a template for making a protein. At any particular moment each cell makes mRNA from only a fraction of the genes it carries. If a gene is being used to produce mRNA, it is considered switched on; if not it is switched off. Many factors determine whether a gene is switched on or off, such as the time of day, whether or not the cell is actively dividing, its local environment, and chemical signals from other cells. For instance, skin cells, liver cells and nerve cells switch on somewhat different genes and that is what makes them different. An RNA expression profile of each of these cell types allows scientists to deduce a cell's type, state, environment, and so on. Similarly, when a healthy cell becomes cancerous it also switches on different genes.

When a gene is switched on it allows the instructions carried by the gene to be copied into molecules of mRNA, and a cell uses these to make particular protein. Some proteins act as on and off switches that help to control how a cell behaves. For example, a hormone signal acts on a protein in or on the cell. The protein then sends a series of signals which tell the cell to reproduce by dividing into two. For example, such a signalling protein may be permanently switched on. Or other proteins, whose job is to control and limit cell division, may be permanently switched off.

Caldera is comparing mRNA expression profiles of healthy prostate cells and prostate cancer cells. We have developed RBAS technology to measure the relative amount of mRNA made by the same genes in these healthy prostate cells and prostate cancer cells. For example, if prostate cancer cells express higher levels of mRNA associated with a particular receptor than

healthy cells do, it might be that this receptor plays a role in prostate cancer. Caldera's RBAS diagnostic technology identifies which RNAs are involved with healthy cells and which with cancer cells. There are more than 100 types of cancer, and we know from the differences between healthy and cancer cells that cancer cells seem to lose a number of vital systems that control how often cells divide.

Our RNA biomarkers are designed to target only those mRNA that are involved in these control systems. Our core commercial products will be combinations of the RNA biomarkers that identify a gene fingerprint or "signature" of prostate cancer. This is what we are testing in our clinical studies.

What is most exciting here is the potential to use RNA profiling to identify key gene expression changes shared by different cancers, regardless of where they arise in the body. Such information is driving research to develop more individualised approaches, called personalised medicine, for helping people with cancer. For example, if a patient's cancer has a signature of genes indicating the cancer is likely to spread to other areas of the body, or metastasize, physicians may suggest a more aggressive treatment strategy than they would for a patient whose cancer had a profile for a non-metastatic cancer.

The next step for our technology is into personalised medicine. Gene expression variation among people is seen in responsiveness to drugs, for example, in men with prostate cancer. Today it is common for physicians to use a trial and error strategy until they find the treatment therapy that is most effective for their patient. In broad terms cancer drugs are effective for some 25% of patients, and it is important to determine quickly which drugs an individual patient may respond to. Physicians need to have more detailed information that will guide them in treatment prescriptions to make them more cost-effective and accurate.

As scientific paper, *Pharmacogenomics: The Promise of Personalized Medicine*, said it best: "therapy with the right drug at the right dose in the right patient" is a great description of how personalised medicine will affect the future of treatment.

In considering that fundamental question, the future of treatment I am reminded of a question put to me recently by a rather knowledgeable investor in the biotechnology sector. "Where are the *biotechies* today who really believe in themselves, and are willing to bet everything that they will beat the odds and do something remarkable?" he asked.

Well, at Caldera we are backing RNA expression profiling.

In my next article, I will explain the technical hurdles we have faced in moving through our clinical studies and how we understand our competitors' progress.

JD Watson
17 November, 2014