



The Philadelphia experiment

AN ADELAIDE RESEARCH INSTITUTE HAS BEEN QUIETLY LEADING THE FIELD IN CHRONIC MYELOID LEUKAEMIA, HELPING TRANSFORM IT FROM A TERMINAL INTO A CHRONIC ILLNESS. LOUISA DEASEY REPORTS.

PHOTO CREDIT: EAMON GALLAGHER

Professor Timothy Hughes has long held a fascination with chronic myeloid leukaemia (CML).

In 1989 as a leukaemia research fellow at London's Hammersmith Hospital, the Director of Haematology Research at Adelaide's Institute of Medical and Veterinary Science (IMVS) was given the opportunity to work with the world leader in CML research, John Goldman.

Eighteen years later, Professor Hughes and his team at the Institute are considered world leaders themselves, at the forefront of groundbreaking research into treatment of the disease.

In Australia, CML currently afflicts about 200 new patients per year. It is a cancer of the bone marrow, caused by a mutation within a single bone marrow cell. This mutation is an unusual rearrangement

of chromosomes 9 and 22, called the Philadelphia chromosome.

The fusion of chromosomes 9 and 22 causes two important genes to come together, producing a fused gene, BCR-ABL. This new gene produces the BCR-ABL protein that is responsible for driving abnormal growth of this mutated cell, which rapidly divides to produce billions of copies of itself. All of the abnormal behaviour of these leukaemic cells can be attributed to the BCR-ABL protein. This protein is an overactive tyrosine kinase enzyme that signals the cells to keep dividing.

CML treatment in the 1990s involved interferon therapy (which left patients feeling like they permanently had the flu) or bone marrow transplants, which can cure some patients but are high risk.

Both were unsatisfactory treatments compared to a breakthrough discovery in 1998.

The development of the tyrosine kinase inhibitor Glivec (imatinib mesylate) sparked an exciting time in CML research. The drug, manufactured by Novartis, worked by blocking the tyrosine kinase protein that drove the disease, and was one of the first 'kinase inhibitor' agents found to be effective in cancer therapy.

This discovery saw many new areas of CML investigation open up, and Glivec turned out to be all the researchers had hoped, offering a 90% success rate in blocking disease progression.

Five years after the first group of patients started taking it, 90% of them were still alive. The challenge now is to increase the response rate closer to 100%. >

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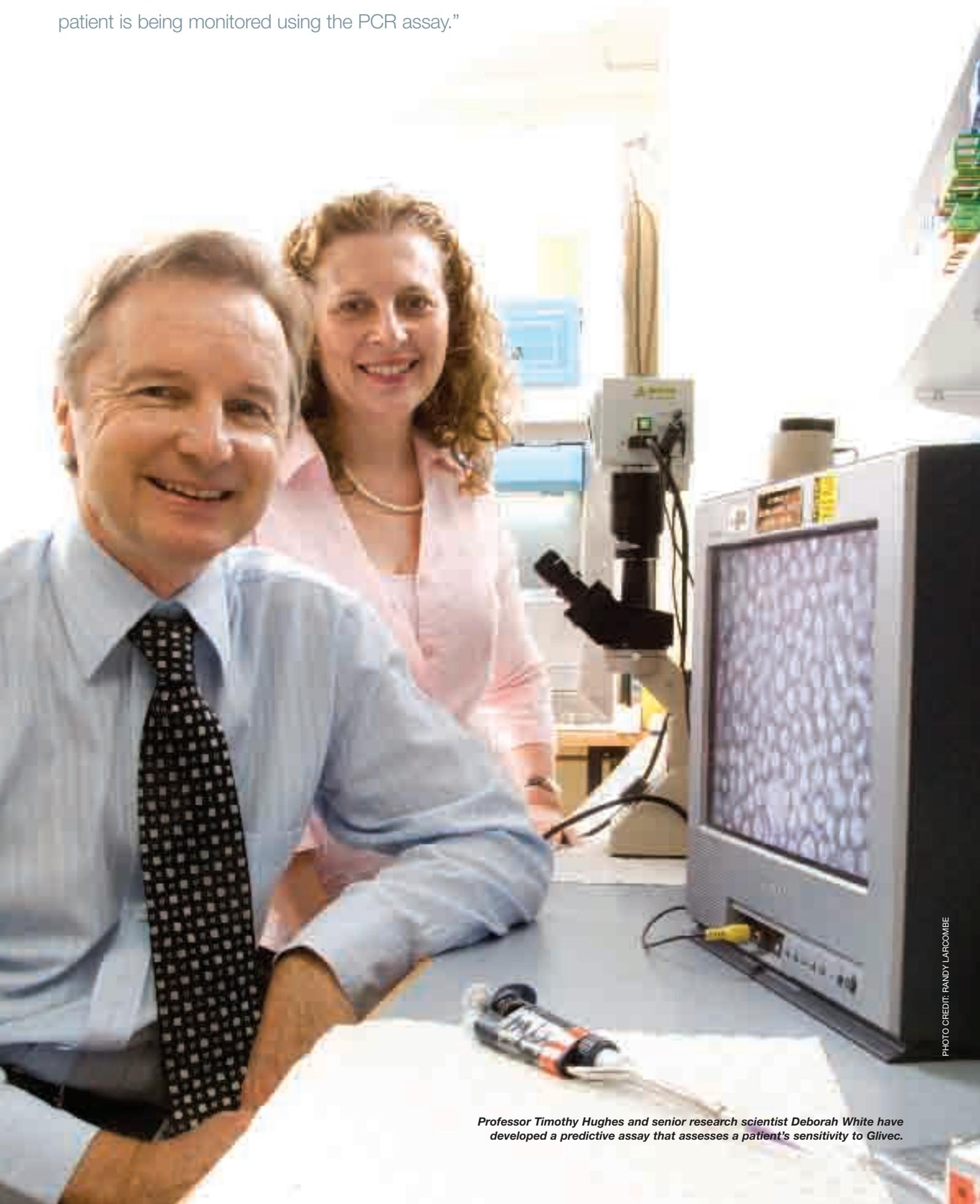


PHOTO CREDIT: RANDY LARCOMBE

Professor Timothy Hughes and senior research scientist Deborah White have developed a predictive assay that assesses a patient's sensitivity to Glivec.

The Institute's molecular breakthroughs

Because of his previous work on CML, Professor Hughes had been busy forming a team to focus on molecular research into the disease. So when patients in Australia and around the globe began taking Glivec in 1999, the Institute had already started diagnostic research into monitoring treatment response and predicting drug resistance and relapse.

It was a case of perfect timing.

The Institute's CML laboratory was specialised and set up so that as soon as patients started taking the new drug, the team was monitoring exactly how it worked, when it didn't, and how this could translate into predicting patient outcomes on the drug.

In 1997, Dr Susan Branford (PhD) had formed the Institute's CML molecular laboratory, to work on developing a highly accurate and sensitive molecular assay, which tested the levels of the BCR-ABL gene using polymerase chain reaction (PCR) tests and thus monitored a patient's response to treatment.

Over two years, Dr Branford worked with Professor Hughes (an RCPA fellow), developing this sensitive PCR assay, which is now at the forefront of global CML monitoring and research.

Senior research scientist Deborah White, who has worked at the Institute for 25 years, manages the CML research laboratory. With Professor Hughes she developed a predictive assay that assesses an individual patient's sensitivity to Glivec therapy.

She explains the mechanism of action for this predictive assay:

"In cases of CML there is a phosphorylated form of a protein called CRKL. By then giving the drug to the cells in a test tube, we look at changes in the level of phosphorylated CRKL with drug exposure.

"It essentially means at diagnosis we can predict, with a reasonable degree of certainty, how a patient is going to respond and whether they'll need a dose increase, or whether they'd be better on a different drug."

To a patient, this knowledge can mean receiving the most appropriate therapy right from the start, rather than waiting for a poor response to standard therapy before making a change.

Knowing that resistance to Glivec is mainly due to mutations of the BCR-ABL gene has led the researchers to theorise that second- and third-generation kinase inhibitors currently under development might be able to specifically target these mutations and offer an even more successful treatment option for patients.

Most patients in Australia enrolled in clinical trials of the newer kinase inhibitors for CML are monitored by Professor Hughes and his team using the assays they have developed. As well as Australian patients, the Institute oversees CML patients undergoing clinical trials from Asia, South Africa and North and South America.

Achievements honoured

Since starting at the Institute, Professor Hughes and his team have produced a number of internationally published papers on their work. Their laboratory was one of only three in the world to conduct a study monitoring the impact of Glivec on newly diagnosed CML (N Engl J Med 2003;349:1423-32), which proved the drug's effectiveness in reducing BCR-ABL levels for those with CML, compared to interferon therapy.

The Institute's laboratory testing, analysis and quantitative research into CML was also recognised last year, with Professor Hughes receiving the Eric Susman award for the most outstanding contribution to the knowledge of any branch of internal medicine by a fellow of the Royal Australasian College of Physicians.

But there is still more work to be done. The Institute's PCR assay to measure serum levels of BCR-ABL is still not a standardised test across the world. In an effort to make this happen, Professor Hughes and his team recently published a paper on the accuracy and benefits of BCR-ABL testing in Blood (2006;108:28-37).

"America has been very slow to adopt PCR monitoring for patients," Professor Hughes says.

"A physician in New York recently told me that a patient in New York could not get a BCR-ABL assay for CML. They are still relying on an assay developed 50 years ago to monitor their patients. In Australia, virtually every patient is being monitored using the PCR assay.

"The first thing I look at when I see a patient is their PCR result. Without PCR monitoring, we only know the patient is in trouble when resistance is already quite advanced."

Though it may be a year or two off from standardising the assay internationally, the Institute is currently standardising 16 other laboratories around Australia.

These are exciting times for the Institute and for CML research in general as we teeter on the brink of even more dramatic developments in leukaemia research.

"Some patients have had dramatic responses to Glivec where we can't detect any leukaemia in their blood or bone marrow for several years," Professor Hughes says.

"The question then becomes, do they actually need to take Glivec anymore? We're now conducting a study in Australia where patients who have had negative PCR assays on every single occasion for two years and who want to be part of the study, stop the drug and then we follow them closely with PCR tests."

To have reached this point after the drug has only been available in Australia for seven years is very much due to the work of Professor Hughes and his team. But he says haematologists from all around Australia have contributed to the research effort, through the Australasian Leukaemia and Lymphoma Group.

Associate Professor Andrew Grigg, deputy head of the Royal Melbourne Hospital haematology department, says: "The IMVS is a world-class centre conducting groundbreaking research which has been published in a number of front-line journals. On a global level, they're up there with the best of them."

Perhaps the most exciting aspect about our new knowledge of CML is the long-term benefit for patients, Professor Hughes says.

"Those of us working in CML have been riding a wave of exciting progress that has turned a terminal illness into a chronic one, and provides hope that a cure based on drug therapy alone may be around the corner." 🙌

Declaration of interest: Professor Hughes and his team receive research funding support from the Leukaemia Foundation of Australia, the Cancer Council of Australia, the NHMRC, and several pharmaceutical manufacturers including Novartis.