

Central Research Facility case study: Melanoma

Researchers at the University of Leicester have played a significant role in the development of a new drug which can potentially double survival times for patients with advanced melanoma skin cancer.

Vemurafenib, also known as Zelboraf, is a drug therapy that works as a cancer growth blocker. It targets a particular protein – called BRAF – which is produced by cells and controls their ability to grow and divide. When the BRAF gene is damaged in cancers such as melanomas, the BRAF protein is permanently active and locked in the “on” state. As a result, cell growth is deregulated, causing tumours to develop.

More than 12,000 people were diagnosed with malignant melanoma in the UK in 2010, and around half of all melanomas occur due to a change in the BRAF gene.

Melanomas can be relatively easy to treat when diagnosed early. However, after it has had time to spread to other parts of the body, it becomes very hard to tackle and is likely to limit patients’ life expectancy to less than one year. The development of the drug has improved the outcomes for advanced melanoma patients by relieving symptoms and extending life expectancy.

Vemurafenib, which is sold by pharmaceutical company Roche, has been approved by the USA’s Food and Drug Administration (FDA) agency and will be available to the 70,000 people who are diagnosed with melanoma in the USA each year. Although the drug has not yet been licensed in the UK, the National Institute for Health and Clinical Excellence (NICE) is reviewing whether the treatment can be introduced by the NHS.

Research into BRAF-induced melanoma has been carried out at the University of Leicester since 2002, shortly after a first draft of the human genome DNA sequence was published. Once it was established that damage to the BRAF gene was responsible for many melanomas, more research was needed to make the findings applicable to clinical trials and the development of treatment.

An essential part of this process was to use animal models. Models were used to determine the effect of damage to the BRAF gene on melanocyte growth and also to determine the efficacy of vemurafenib in preventing melanoma progression. This research also showed that the drug must be restricted to the 50 per cent of melanoma patients with damage to the BRAF gene and actually makes the cancers worse if the BRAF gene is not damaged.

The results allowed the researchers to transfer findings from the lab to the clinic. The treatment is now being used to significantly prolong the lives of melanoma patients around the world.

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Central Research Facility case study: Coronary stents

The University of Leicester's role in the development of coronary stents has been highly beneficial to coronary artery disease patients around the world.

Stents are used in coronary angioplasty to widen arteries in the heart which have become narrow or blocked. These arteries are extremely important, as they are responsible for supplying blood to the heart muscles, allowing the heart to pump blood to the rest of the body. When they become narrowed or blocked, patients can face angina symptoms such as chest pains and breathlessness, or even heart attacks and strokes if the restriction of the blood supply grows too severe.

To combat this, a coronary stent – normally a drug-coated or bare-metal tube - can be placed inside the artery to prop open the passage, increasing blood flow to heart muscles and reducing the risk of angina and more serious heart conditions.

Angioplasty has a number of advantages over coronary artery bypass graft surgery, an alternative treatment, the most important of which is that there is no need for a major heart operation. Not all patients can have stents, and by-pass surgery still has an important role in the management of patients with more complex narrowings. However, over 83,000 patients had angioplasty and 19,000 had by-pass surgery in 2010 - so angioplasty is clearly an important procedure.

Researchers at the University of Leicester have made a significant contribution to the development of both bare-metal and drug-eluting stents over the last two decades. Drug-eluting stents have the added benefit of suppressing the body's natural scar response to the stent, reducing the amount of scar tissue which builds up inside the stent which could have caused the artery to narrow again. This reduces the likelihood that patients will need to return to hospital for further procedures following the angioplasty - from 12% with bare metal stents to 5% with drug releasing stents.

To get to this point, researchers needed to spend years testing and developing the treatment in labs on the bench tops to determine the efficacy of stents before they could be trialled on humans. To test for safety - to ensure the drug and the polymer coating over the struts of the stent didn't cause the stent to block off suddenly and cause heart attacks and death - these stents were tested around the world, including in University Hospitals of Leicester, in an animal model of stenting. The results have helped make these devices fit for human use, and while studies continue to improve drug eluting stents, they are now used to the benefit of up to 3 million people worldwide each year.

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Central Research Facility case study: Liver Cancer Hope

Research involving the University of Leicester has already saved more than 100 lives of „terminally ill“ patients with a revolutionary cancer treatment.

The University has been involved on developing a way of eliminating liver tumours, by inserting a probe into them and blasting them with microwaves. It is a technique he has developed over seven years.

The academic leading the project is the only person in the world carrying out this treatment, and his techniques have attracted attention from major cancer institutes around the world. He expects the process which, to date, has saved just over 100 lives will quite soon be saving thousands.

“Two million people in the western world and in Asia are dying each year from liver cancer,” he said. “It is a massive problem. In the past doctors have used electricity and lasers against liver cancer, but these have not proved very effective. Microwave technology has the potential for fast destruction and can be used on big tumours. It is extremely safe, very effective, easy to use and is proving to be a significant advance in the treatment of liver cancer.”

In 95 per cent of patients treated with the microwave technology the cancer has disappeared, with the best results coming from patients also receiving chemotherapy to reduce the chance of cancer recurring elsewhere in their body.

At the research stage, the team had to design a study, knowing it could have fantastic potential for humans. They successfully tried it first on dead liver from an abattoir, but they needed to know what would happen in living tissue, with blood flowing through. Would the patient’s heart stop? How safe was it?

There was no option to use a computer model to test its safety, and the research team were not working with cells or molecules but on a major organ. By operating first on rats and later pigs they were able to demonstrate that the technique worked and the animals recovered well.

Of the patients who have been treated so far, none of whom were predicted to live beyond one year, more than half are alive after three years.

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Central Research Facility case study: Improving Life Expectancy for Patients with Heart Disease

The repair of damaged heart muscle is a new, promising therapy to improve the quality of life and long-term prognosis of patients with heart attacks leading to heart failure. One million people suffer from heart disease in the UK, of which 140,000 die each year.

A group in the University's Department of Cardiovascular Sciences has been one of the first to show that stem cells obtained from patients' own bone marrow can improve contractile function of the scarred heart muscle.

While other research groups have also provided evidence that bone marrow cells and other stem cell types are improving heart function after a heart attack, the mechanism of this benefit is unclear. It is not known whether the benefit is obtained by differentiation of the stem cells into cardiomyocytes, by stimulation of proliferation of cardiac resident progenitor cells or by reduction of the death of heart tissue.

"The knowledge of the mechanism by which stem cells induce repair of the heart is essential to improve and refine the treatment with these cells and to identify the group of patients that can benefit most," say the researchers. "This knowledge cannot be obtained from human studies only, and animal research is fundamental to elucidate the mechanism of healing of the heart by stem cells.

"As well as clinical studies, my group is performing mechanistic studies in mice that we hope will provide us with the necessary information to further advance the treatment of the failing heart and bring about an improvement in the quality of life and life expectancy of these patients."

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Central Research Facility case study: Alleviating the suffering of Huntington's patients

Huntington's disease is a debilitating, incurable, inherited, neurological condition. Physical and mental symptoms include uncontrolled movements and memory loss, which become progressively worse over time.

About 6,000 people in the UK are known to have Huntington's disease although many more remain undiagnosed as symptoms rarely appear before the age of 30. For sufferers of this condition, their children (who stand a 50% chance of inheriting the gene), and their carers, there is currently no hope.

In 1993 the cause was identified as a faulty gene which produces the protein htt and we know, at a molecular level, how faulty htt interferes with brain cells – leading to the unstoppable symptoms of Huntington's disease.

University of Leicester researchers are seeking to discover a way to correct this, in order to alleviate the suffering of Huntington's patients and prevent the disease recurring in future generations. This research is only possible through the use of genetically engineered mice.

Advances in genetic modification are the principal reason for the increase in UK animal experiments in recent years, more than counteracting the concurrent reduction in other animal procedures. By adding human genes to non-human organisms, medical researchers can examine in great detail the precise effects of potential drugs.

Essential research like this starts with one of the simplest organisms on the planet: baker's yeast.

Drugs which show positive effects in „transgenic“ yeast are then tested in the fruit fly

Drosophila, one of the most commonly used research animals.

It would be both unethical and dangerous to move from fruit flies straight to human trials so another level of research is required, which involves tissue samples from specially bred transgenic mice. The mice are raised in a clean environment as healthy, happy animals – distressed or ill mice would be useless as subjects – then humanely killed so that their brain cells can be removed and cultured in a lab. There is no way to study these brain cells in a living creature.

Because the mice used are genetically identical „clones“ many factors which might adversely affect the results can be eliminated. Furthermore, mice have a very short life cycle, allowing scientists to study the effects in subsequent generations. This would clearly not be possible in human subjects, especially with a condition which can take 30 years or more to appear.

Some people believe that animals do not make valid research subjects for human conditions because of differences between species. Genetic modification means that aspects of human health can be tested, using other organisms, in ways which would be impossible with human subjects. From yeast to flies to mice, more potential drugs are discarded at each stage so that only the most likely candidates need be tested on human volunteers.

All data from the experimental cultures of mice cells is collected and made available to reduce the need for similar experiments in the future. In fact every aspect of this potentially life-saving research has been designed to minimise the need for animal subjects.

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