

## SPECIAL REPORT A cure for cancer?

# Big pharma meets small lab – and the result could change lives of millions

A revolution is brewing on an English business park as scientists harness our natural-born killers – the T cells – to target malign tumours

**Exclusive**

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A single-storey workshop on a nondescript business park in Oxfordshire is not the sort of place where you would expect scientific revolutions to take place. But behind the white-painted walls of this small start-up company, scientists are talking about the impossible – a potential cure for cancer.

For the past 20 years, the former academics who set up Immunocore have worked hard on realising their dream of developing a totally new approach to cancer treatment, and finally it looks as if their endeavours are beginning to pay off. In the past three weeks, the company has signed contracts with two of the biggest players in the pharmaceuticals industry which could lead to hundreds of millions of pounds flowing into the firm's unique research on cancer immunotherapy – using the body's own immune system to fight tumour cells.

Immunocore is probably the only company in the world that has developed a way of harnessing the power of the immune system's natural-born killer cells: the T-cells

of the blood which nature has designed over millions of years of evolution to seek out and kill invading pathogens, such as viruses and bacteria. T-cells are not nearly as good at finding and killing cancer cells, but the hard-nosed executives of the drugs industry – who are notoriously cautious when it comes to investments – believe Immunocore may have found a way around this so that cancer patients in future are able to fend off their disease with their own immune defences.

“Immunotherapy is radically different,” said Bent Jakobsen, the Danish-born chief scientific officer of Immunocore who started to study T-cells 20 years ago while working at the Medical Research Council's Laboratory of Molecular Biology in Cambridge. “It doesn't do away with the other cancer treatments by any means, but it adds something to the arsenal that has one unique feature – it may have the potency to actually cure cancer,” Dr Jakobsen said.

It is this potency that has attracted the attention of Genentech in California, owned by the Swiss giant Roche, and Britain's GlaxoSmith-Kline. Both companies have independently signed deals with Immunocore that could result in up to half a billion pounds being invested in new cancer treatments based on its unique T-cell therapy.

It is no understatement to say that cancer immunotherapy, or immunoncology as it is technically called, represents a sea change in terms of cancer treatment. Cancer in the past has been largely treated by slicing (surgery), poisoning (chemotherapy) or burning (radiotherapy). All are



**POWER OF TWO**  
Bent Jakobsen, left, and James Noble in the Immunocore lab  
TOM PILSTON

burdened with the inherent problem of how to spare healthy tissue from irreparable damage while ensuring that every cancer cell is killed, deactivated or removed.

Now there is another approach based on the immune system, a complex web of cells, tissues and organs that constantly strive to keep the body free of disease, which almost certainly includes keeping cancerous cells in check.

For many years, scientists have realised that the immune system plays a key role in cancer prevention. There is ample evidence of this, not least from patients who are immune-suppressed in some way – they are more likely than other patients to develop cancer.

The immune system has two basic ways of fighting invading pathogens and the body's own cells that have gone awry. One involves the release

**T-CELL THERAPY**

Using the body's immune system to fight cancer is one of the most promising areas of therapy, and could prove particularly helpful in the treatment of metastatic disease, when the cancer has spread from its original site.

The immune system is complex and is composed of many kinds of cells, proteins and chemical messengers that modulate how it works. Scientists are working on ways of exploiting the immune defences to recognise and eliminate cells that have become cancerous.

One of the most interesting

examples is ipilimumab, a “monoclonal antibody” made by Bristol-Myers-Squib. It recognises and binds to a molecule, called CTLA-4, which is found on the T-cells of the immune system. CTLA-4 normally keeps T-cells from proliferating, but in the presence of ipilimumab, it becomes blocked, allowing T-cells to increase in numbers, so leading them to attack cancer cells.

Other drugs based on monoclonal antibodies are designed to attack tumours more directly. When they bind to a cancerous cell, it serves as a signal for other cells of the

immune system to come in and sweep the cancer cells away.

The trouble is that cancer cells are notoriously mutational. Eliminating 99.9 per cent of cancer cells in a patient may be an improvement, but it still leaves 0.1 per cent that could “escape”.

One hope of using T-cells, is that this possibility of escape is narrowed down, or even eliminated. Of course, these are still early days. This is only just beginning to go through the first clinical trials. It could take five or 10 years before we know whether or not they work.

of free-floating proteins, or antibodies, that lock on to an invader, triggering other immune cells to come in and sweep them away.

Many organisations have tried to develop anti-cancer treatments based on antibodies, with limited success, Dr Jakobsen said. Part of the problem is that antibodies are not really designed to recognise cells. What Immunocore has done is to build a therapy around the second arm of the immune system, known as cellular immunity, where T-cells seek out and destroy invading pathogens.

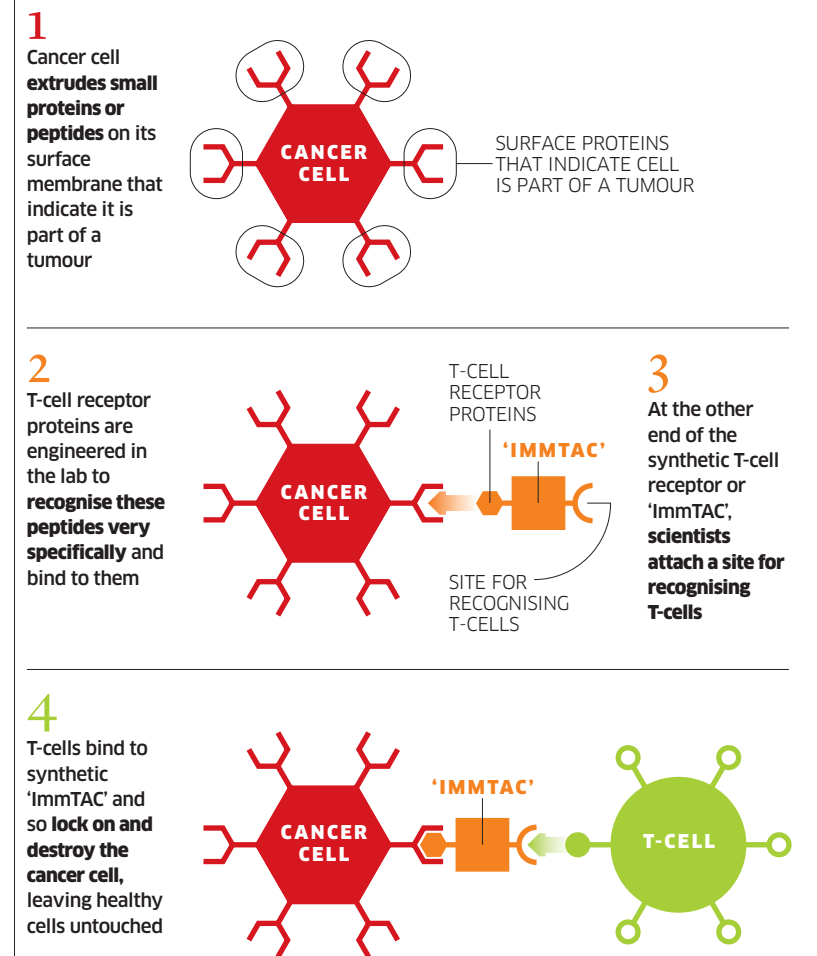
“There are a lot of companies working with antibodies but we are virtually the only company in the world that has managed to work with T-cells. It has taken 20 years and from that point we are unique,” Dr Jakobsen said.

Immunocore has found a way of

designing small protein molecules, which it calls ImmTACs, that effectively act as double-ended glue. At one end they stick to cancer cells, strongly and very specifically, leaving healthy cells untouched. At the other end they stick to T-cells.

The technology is based on the “T-cell receptor”, the protein that sticks out of the surface of the T-cell and binds to its enemy target. Immunocore's ImmTACs are effectively independent T-cell receptors that are “bispecific”, meaning they bind strongly to cancer cells at one end, and T-cells at the other – so introducing cancer cells to their nemesis.

“What we can do is to use that scaffold of the T-cell receptor to make something that is very good at recognising cancer even if it doesn't exist naturally,” said Dr Jakobsen. “Although T-cells are not very keen at recognising cancer, we can force

**HOW IT WORKS**

GRAPHIC – CATH LEVETT

SOURCE – IMMUNOCORE, IGS RESEARCH

them to do so. The potential you have if you can engineer T-cell receptors is quite enormous. You can find any type of cell and any kind of target. This means the approach can in theory be used against any cancer, whether it is tumours of the prostate, breast, liver or the pancreas.

The key to the success of the technique is being able to distinguish between a cancer cell and a normal, healthy cell. Immunocore's drug does this by recognising small proteins or peptides that stick out from the surface membrane of cancer cells. All cells extrude peptides on their membranes and these peptides act like a shop window, telling scientists what is going on within the cell, and whether it is cancerous or not.

“All these little peptides tell you the story of the cell. The forest of them on the cell surface is a sort of display saying ‘I am this kind of cell. This is my identity and this is everything going on inside me’,” Dr Jakobsen explained.

Immunocore is building up a database of peptide targets on cancer cells in order to design T-cell receptors that can target them, leaving healthy cells alone and so minimising possible side effects – or that is the hope.

The first phase clinical trial of the company's therapy, carried out on a small number of patients in Britain and the United States with advanced melanoma, has shown that people can tolerate the drug reasonably well and preliminary results suggest there are “early signs of anti-tumour activity”, the company said.

A danger with deploying T-cells

against cancer is their potency. Yet it is this very potency that it is so exciting because it could lead to a cure for metastatic disease that has spread around the body, Dr Jakobsen said. “You can never make a single-mechanism drug that would come anywhere near a T-cell in terms of its potency.

“If you want to make an impact on cancer you need something that is incredibly potent – but when something goes wrong, it goes badly wrong. I think the honest truth about all cancer treatments is that no matter how much we test and do beforehand, it will continue to go wrong sometimes.”

One infamous case of something going disastrously wrong was a clinical trial in 2006 at Northwick Park Hospital in London where scientists were testing a powerful immunoregulatory drug on six volunteers. All suffered serious side effects caused by the overstimulation of their immune systems.

But Dr Jakobsen said the clinical trial of Immunocore's T-cell drug, as well as future trials, are inherently safe because they are based on incremental rises in dose. All indications suggest it will lead to the expected breakthrough.

He added: “All the pharma companies have come to the realisation that immunotherapy may hold the ultimate key to cancer; it is the missing link in cancer treatment that can give cures.”

“They have seen this technology develop. It has come over the mountain top, if you like. With our melanoma trial they have seen it is safe – and it is working.”