

The battle to find a cure for every cancer is evolving

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"THAT'S the thing about cancer; it's all yours – it's entirely, perfectly personalised." So says Kit, a character in *The Quarry*, the final novel by the Scottish writer Iain Banks – who himself died earlier this month from cancer. "An unwilling suicide where... one small part of the body has taken a decision which will lead to the death of the rest."

Kit is right. Outside the lab, or hospital, we continue to talk about "a cure for cancer" as though it was a single disease, with a single cure. But it's an understatement even to say that every case is different: individual tumours in the same person can be quite different, each carrying enormous numbers of distinct genomes (see "[Rapid evolution of tumours may be their Achilles' heel](#)").

That may be why cancer is so difficult to treat. Current treatments are based on the bulk, brute removal of cells – but miss even a few, and evolution will see to it that the cancer returns in a new, often more resistant, form.

Bacteriologists and virologists have long employed evolutionary biology to develop therapies aimed at thwarting adaptation. Now it seems cancer researchers must do the same if we are to find cures for our cancers.

This article appeared in print under the headline "An evolving battle"

Rapid evolution of tumours may be their Achilles' heel

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One man's sacrifice has revealed how his cancer mutated from its emergence to its last lethal change, opening the door to a Darwinian approach to therapy

Editorial: "[The battle to find a cure for every cancer is evolving](#)"

IT WAS the ultimate selfless act. Knowing he had just months to live, and that any knowledge gleaned would be too late to help him, the man known as Patient Two underwent two last painful biopsies. In doing so, he is believed to be the first person to have his cancer's evolution traced from its first appearance to its last, lethal mutation.

Genomic analysis of his tumours over the span of the disease could help figure out how to stop cancer from evolving its deadliest characteristics – its ability to spread throughout the body and its uncanny knack of developing resistance to drugs.

That is the aim of several research groups around the world who are trying to understand the disease by looking at it from a Darwinian perspective. "The fundamental aspects of evolution are at play in tumours – diversity, selection and adaptation," says [Charles Swanton](#) of University College Hospital, London, and Cancer Research UK. "We can influence those things through scientific approaches."

Patient Two was one of eight people with prostate cancer being followed by [Christopher Hovens](#) at the University of Melbourne, Australia, and colleagues. After diagnosis, Patient Two underwent surgery to cut out the tumour, which Hovens then banked. Things looked good until 18 months later, when the cancer returned to his bladder, adjacent to where the primary tumour had been. It had also spread further afield to two places in his pelvis. Again, Hovens's team removed the tumour in his bladder and kept it along with biopsies of the two metastases in his pelvis. Then after hormone therapy failed and Patient Two knew the cancer was terminal, he consented to another biopsy of each metastasis – the last pieces of the puzzle.

This means Hovens has six samples that trace the evolution of the man's cancer from diagnosis, through treatment, to death. For the first time, Hovens should be able to paint a detailed picture of how a cancer evolved and how that evolution was affected by treatment, thanks to whole-genome sequencing, as well as deep-RNA and methylation sequencing – techniques showing when and where genes have been switched on or off.

Preliminary results are already throwing up surprises. Even though the two metastases were sampled at the same time and spread from the same original tumour to the same type of tissue, their genetic make-up is completely different. "In effect, he had two different cancers at the same time," says Hovens. That means there were two different mechanisms driving the metastasis. "If there are multiple redundant ways to drive metastasis, that's very scary, because how are we going to target them?" he says.

Incredible complexity

If confirmed, this is an interesting result, says Carlo Maley, director of the Center for Evolution and Cancer at the University of California, San Francisco. There are probably multiple pathways for metastasis, he says. "I certainly wouldn't put it past cancer to discover them within the same tumour."

The finding tallies with what Swanton found last year when he looked at the genetic diversity of kidney cancer. Even within the same tumour, [different regions carried many different genetic mutations](#).

It is this complexity that seems to drive cancer's incredible ability to become resistant to drugs. "That's why cancer is the emperor of all maladies," Swanton says. By having many different genomes, there's a high chance that genes in a small number of cells will randomly develop resistance. Drugs then kill the other tumour cells, allowing the resistant ones to dominate in a kind of Darwinian selection.

If this is true, it would mean that the more genomically diverse the cancer, the more dangerous it is, so the more aggressively it should be treated. "The hope is that will be a useful patient biomarker to stratify risk," says Swanton. But there's a more ambitious goal too. "By understanding how diversity is initiated, the dream is that we can identify new treatments that can stop diversity once it's occurred – or stop it from ever happening," he says.

Swanton should soon be able to put his theories to the test, in what he calls the "[definitive cancer evolution study](#)". He has started recruiting the first of the proposed 850 people with a type of lung cancer who will make up his study. Each participant will undergo multiple biopsies of their initial tumour. This will be followed up with the sequencing of its different regions and any metastases that develop as the disease progresses, as well as regular sequencing of circulating tumour DNA in the blood.

The study will also look at how the tumours respond to treatment. If the preliminary findings from Hovens's prostate tracking study are anything to go by, this should produce some intriguing results. After hormone therapy, one of Patient Two's metastases became more genetically similar to the second main tumour that had already been cut out, "which paradoxically had not seen any drug treatment", says Hovens. It's a baffling finding and Hovens admits that he's not quite sure what it all means. His team is currently trying to work out just how Patient Two's tumours are related to each other.

If genetic diversity is what makes cancer such an elusive foe, the trick will be to try to minimise that diversity by slowing the evolution of cancer cells, says Maley (see "[Cure in your cupboard](#)"). Evolutionary biologists know what drives the speed of evolution – how fast the cells reproduce, how often they mutate, how big the cell population is and how successful a mutation is in its environment – so the next step will be to measure these in cancer cells, and find ways to manipulate them.

One Darwinian-inspired approach being tried by Robert Gatenby at the Moffitt Cancer Center in Florida is to use current therapies more sparingly, thereby maintaining a stable population of cancer cells that are sensitive to chemotherapy [to compete with any emerging resistant ones](#).

Swanton's hope lies with immunotherapy. Genetic diversity of cancer seems to be why drugs stop working, but with immunotherapy, this may actually be cancer's Achilles' heel, he says. Researchers could try to use the tumour's unusually high mutation rate to alert the immune system that something's not quite right. This might provoke the body into attacking only the tumour, even though it is made of the body's own cells and DNA.

"If this wasn't cancer it would be the most beautiful thing you've ever studied," Swanton says. "What you're looking at is natural selection in a lifetime. You're looking at what Darwin described as happening over billions of years, in 30."

This article appeared in print under the headline "Fighting cancer Darwin's way"

Cure in your cupboard

Chances are there's a [cancer drug lurking in your bathroom cabinet](#)– the humble aspirin. Popping a pill a day seems to [reduce the risk of dying from any type of cancer](#) by more than 30 per cent, if you take the drug for long enough. But why aspirin and other similar non-steroidal anti-inflammatory drugs (NSAIDs) have such a dramatic effect has remained a mystery.

Now a study spanning two decades and borrowing techniques from evolutionary biology has shown that NSAIDs slow cancer's evolution – reducing the rate at which cells mutate. The idea is that this should lower the chance of them becoming cancerous ([PLoS Genetics, doi.org/mv3](#)).

A team led by Carlo Maley from the Center for Evolution and Cancer at the University of

California, San Francisco, studied 13 people who had Barrett's oesophagus, a pre-cancerous condition caused by a build-up of stomach acid. During the study period, the participants spent about six years on average taking the drugs and six years off them. The team took up to 20 biopsies of oesophageal tissue from each person on up to eight occasions. In 11 of the volunteers, taking NSAIDs was associated with a 10-fold decrease in the rate at which new mutations were acquired. Only one of the participants subsequently went on to develop cancer.

However, the direct link between the drugs' affect on mutation rate and risk of cancer has not yet been proven, says [Geoff Macintyre](#) of National ICT Australia, who is part of a team carrying out a cancer evolution tracking study (see main story). "While they show that NSAIDs reduce the mutation rate, there is still not convincing evidence that this lowered mutation rate is directly linked to reduced risk."