Mimicking evolution to treat cancer

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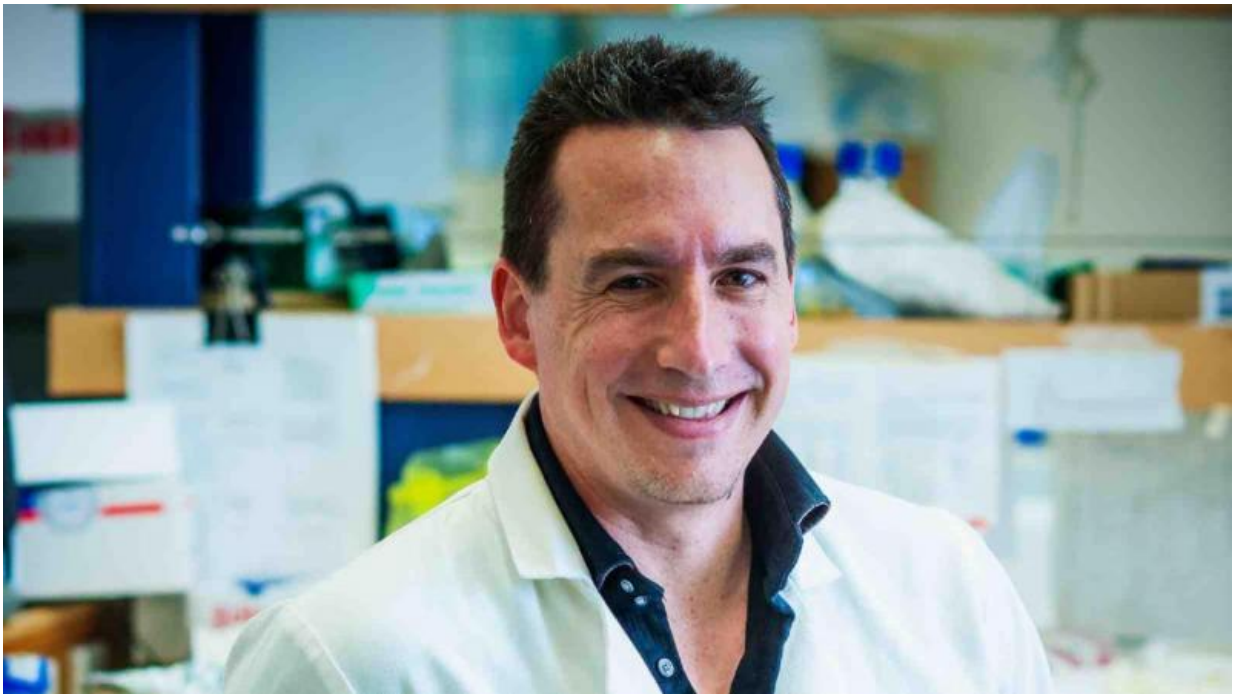

Associate Professor David Ackerley. Credit: Victoria University

Research led by Associate Professor David Ackerley, director of Victoria's Biotechnology programme, has underpinned the development of a new form of chemotherapy that exclusively targets cancer cells.

A key goal of this chemotherapy is a more targeted treatment method that results in fewer side effects for cancer patients.

To achieve this goal, Associate Professor Ackerley and his team engineered enzymes that can transform a relatively safe and non-toxic compound (a "pro-drug") into a drug that is highly toxic to cancer cells.

The genes encoding these enzymes are delivered to cancer cells using viruses or bacteria that are only able to replicate in tumours.

The pro-drug the team worked with is called PR-104A, and was developed by scientists at the University of Auckland, including Associate Professor Ackerley's collaborators on this study, Associate Professor Adam Patterson and Dr Jeff Smaill.

"The enzyme we started with was moderately active with PR-104A," says Associate Professor Ackerley. "However, this was purely by chance—nature has never evolved enzymes to recognise these very artificial types of molecules.

"We reasoned that by mimicking evolution in the laboratory—by introducing random mutations into the gene encoding our target enzyme, then selecting the tiny minority of variants where chance mutations had improved activity—we might eventually achieve a more specialised enzyme that could more effectively activate PR-104A."

Not only is the team's artificially evolved enzyme significantly better at activating PR-104A within living cells, it also addresses another major problem—how to keep track of the microbes in patients to make sure they are only infecting cancerous cells.

"A unique aspect of our work is that our enzymes can also trap radioactive molecules called 'positron emission tomography (PET) probes'," says Associate Professor Ackerley. "We hope that this will allow a clinician to put a patient in a full body PET scanner to safely identify the regions where the microbes are replicating."

The team's research has been published in this month's edition of high-profile research journal *Cell Chemical Biology*, and has been supported by several New Zealand funding agencies including the Marsden Fund managed by the Royal Society of New Zealand, the Health Research Council of New Zealand and the New Zealand Cancer Society.

In ongoing work, Dr Smaill and Associate Professor Patterson have been developing more effective pro-drugs to partner with Associate Professor Ackerley's enzymes. The team has been collaborating with groups at the University of Nottingham in the United Kingdom and Maastricht University in the Netherlands, aiming to progress the therapy into clinical trials in cancer patients.

More information: Janine N. Copp et al. Engineering a Multifunctional Nitroreductase for Improved Activation of Prodrugs and PET Probes for Cancer Gene Therapy, *Cell Chemical Biology* (2017). DOI: 10.1016/j.chembiol.2017.02.005

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