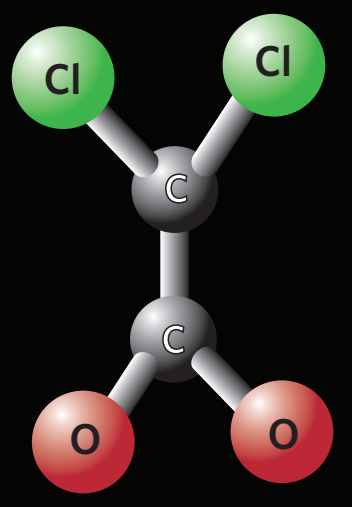
The Road to a Cure

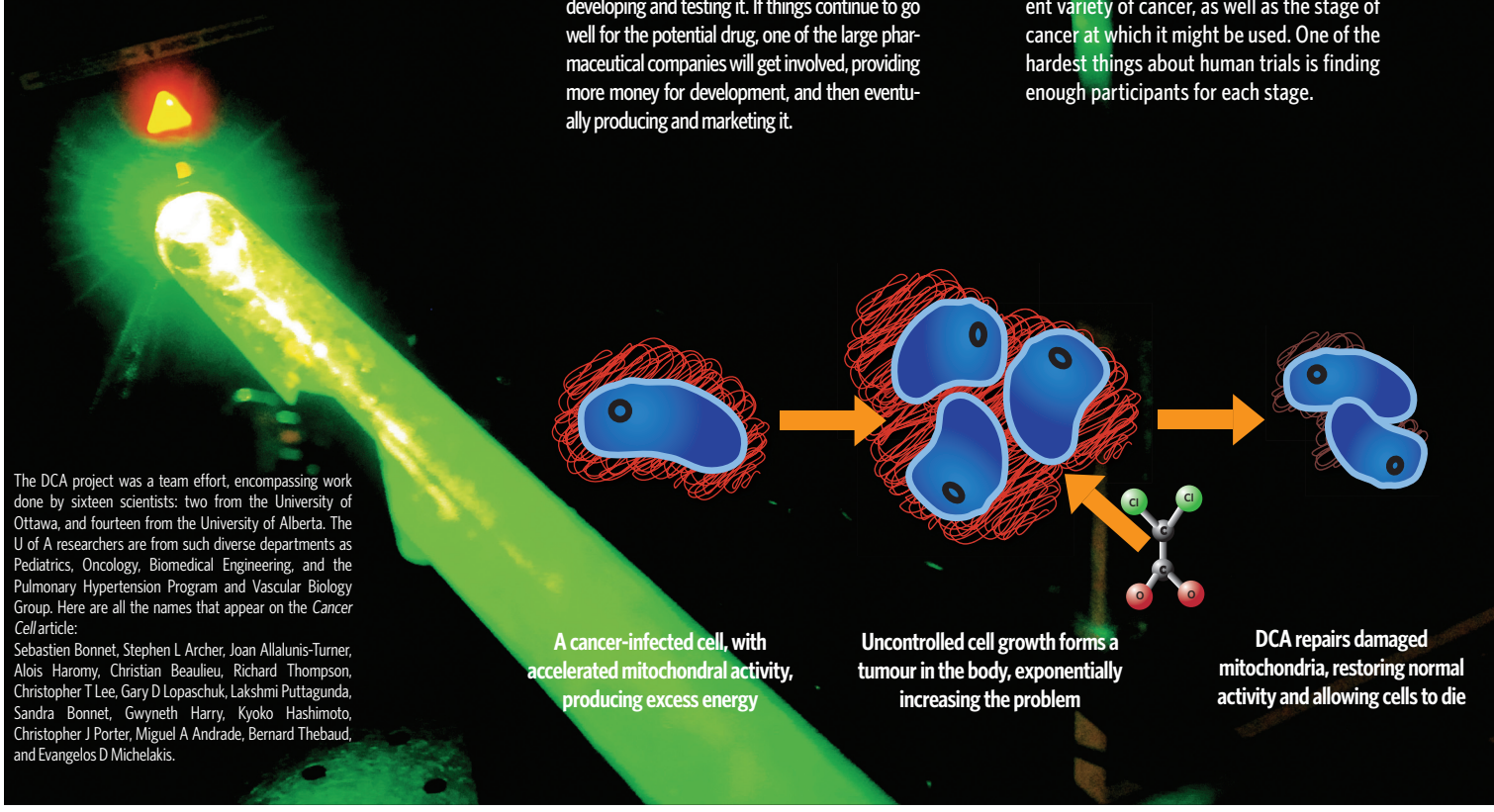
How DCA is paving the way for future research in cancer treatment

When it comes to medical research, universities are where the action is these days. According to Dr Philip Branton, Scientific Director of the Institute for Cancer Research, "the new concepts and drugs virtually all come out of universities." Usually it works like this: researchers at a university will conduct their experiments with funding from government and academic sources (like Canadian Institute of Health Research and the Alberta Heritage Medical Research Fund). Biotech companies might then buy into a drug or molecule that they think shows promise, and keep developing and testing it. If things continue to go well for the potential drug, one of the large pharmaceutical companies will get involved, providing more money for development, and then eventually producing and marketing it.

The clinical human trial process has three phases, and usually takes several years. The first stage is for safety, to see if it has harmful side effects. The second stage is also for safety, but also to see if the drug shows signs of being effective. The third, final stage is treating test patients with the drug as they think they would once it's approved, to see if it's effective. A drug must go through separate trials for each of its possible uses. For example, a cancer drug would have to be tested separately for each different variety of cancer, as well as the stage of cancer at which it might be used. One of the hardest things about human trials is finding enough participants for each stage.



A DCA molecule, the promising remedy



The DCA project was a team effort, encompassing work done by sixteen scientists: two from the University of Ottawa, and fourteen from the University of Alberta. The U of A researchers are from such diverse departments as Pediatrics, Oncology, Biomedical Engineering, and the Pulmonary Hypertension Program and Vascular Biology Group. Here are all the names that appear on the *Cancer Cell* article:
Sebastien Bonnet, Stephen L Archer, Joan Allalunis-Turner, Alois Haromy, Christian Beaulieu, Richard Thompson, Christopher T Lee, Gary D Lopaschuk, Lakshmi Puttagunda, Sandra Bonnet, Gwyneth Harry, Kyoko Hashimoto, Christopher J Porter, Miguel A Andrade, Bernard Thebaud, and Evangelos D Michelakis.

Until now, researchers thought that mitochondria in cancer cells was permanently damaged and that the damage was a result of the cancer—not a cause.

Cancer alters the function of the mitochondria, increasing cell growth and preventing cell death.

DCA activates a critical enzyme in the mitochondria. This normalizes mitochondrial activity, regulating cell growth and more importantly, allowing cells to die so the tumour can shrink.

Drug shows strong results, but researchers caution restraint

Doctors say that the DCA compound, while very promising in rodent studies, is far from being a miracle cure and requires much more testing before it is ready for use in treating human cancer patients

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"What's so intriguing about this work is that it addresses one of the oldest observations in the study of cancer, and takes advantage of this research by using a drug that's already in the clinic," said Dr Philip Branton, scientific director of the Institute of Cancer Research, one of the Canadian Institutes for Health Research, which provided much of this research's funding. "DCA is already used therapeutically, and has been shown to be safe."

So far, all of the DCA experiments have been on laboratory rats injected with cancer cells from human lung, breast or brain tumours. It's still unknown whether the same results will appear when the drug is tested on humans.

"We don't know what the impact will be, other than it is definitely opening another way of looking at cancer because the mitochondria have not before been approached as target for therapy," Michelakis said.

"There are three possibilities for how it could work on humans," Bonnet explained. "DCA is going to kill all the tumour and it won't come back; or DCA will at some point stop working and the tumour will be so small that we can easily take it out with simple surgery; or maybe DCA combined with other chemotherapy agents will kill the tumour. We have a lot of experiments still to do."

Or, it could not work at all. Branton cautioned against people getting their hopes too high based on such preliminary results.

"I've had a whole bunch of people contact me, wanting to know about trials for their parents and for themselves," he said. "But this is really early preclinical work. This is only one drug. There are dozens of good drugs around, and is this better than something else? I don't know."

The next step is to begin human trials—a long, complicated and expensive process. First, researchers must prove that a drug is safe, though that step won't be as difficult with DCA. Then they begin testing for efficacy, experimenting on different types and stages of cancer with varying dosages of the drug.

"That stage is a million times harder," Michelakis said. "You translate what you find in animals to human beings, and it's far more difficult. If you do something in animals that never transfers to humans, it's a big nothing; it's big waste.

"We know it's probably safe, and we know it works on human cancer cell lines in animals, but we don't know if it will work on human beings. We also don't know long-term effects," he explained.

An advantage for Michelakis and colleagues is that they will likely be able to skip traditional first-phase trials, because DCA already known to be safe drug. Unfortunately, DCA's prior use causes another problem: no one wants to invest in it.

Before Michelakis' group began their research, DCA was not under patent. And, since its makeup was generally known, a structural patent could not be filed. During the course of their research, Michelakis and another U of A doctor involved in the project, Dr Stephen Archer, obtained a use patent. This type of patent, relating to the use of a drug rather than its manufacture, is difficult to defend. Investors are therefore wary of putting money into development.

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"If [a drug] is not properly patented, they could never get their money back, because anyone could then make the drug," explained Dr Branton. "A company might invest millions of dollars into clinical trials and then anyone could sell it."

In order to move DCA into the clinical trials stage of development, the research group will probably have to rely on government and other non-profit sources.

"We were looking for investors, and no one was interested," Michelakis said. "That's why we have government, that's why we have groups like the CIHR, the National Cancer Institute, and other agencies and philanthropies. That's why they're there."

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So far, all of the DCA experiments have been on laboratory rats injected with cancer cells from human lung, breast, or brain tumours. It's still unknown whether the same results will appear when the drug is tested on humans. Observers like Branton are particularly optimistic about the success of potential trials because DCA has been used on humans for so long.

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Surgery licks cancer complication

OLESIA PLOKHII
News Writer

Surgeons at the University of Alberta have discovered a technique for repairing speech and swallowing ability in those suffering from mouth and tongue cancer.

Dr Hadi Seikaly and Dr Jeff Harris, the two doctors who have been attributed with this discovery, explained that the new technique is a modification of an old procedure. Doctos have transplanted tissue from the forearm into the mouth after cancer surgery for over 20 years, but a slight change can make the recovery easier.

"The 'beaver-tail modification' involves adding an extra paddle of fat and fascia to the rest of the forearm tissue," explained Dr Dan O'Connell. "This technique is designed for patients that have had the base [or very back]of their tongue removed because of cancer," he said.

O'Connell explained that in the past people who had surgery on these types of cancers would often be crippled in vital abilities pertaining to the mouth.

"It is the extra bulkiness provided by this 'beaver-tail' that preserves the swallowing ability," he said.

O'Connell explained that the paddle of fat and fascia that is the beaver-tail is then rolled up and placed in the base of the tongue defect.

Both the Division of Otolaryngology-Head and Neck Surgery and COMPRU (the Craniofacial Osseointegration and Maxillofacial Prosthetic Rehabilitation Unit) worked together to see 36 patients through this procedure, 90 per cent of which preserved their swallowing and speaking function, O'Connell explained.