

NEWS

Cancer patients opt for unapproved drug

An experimental cancer drug shrinks tumours in rats with no apparent side effects. The scientists behind the study plan to do a clinical trial in humans, but it could take years to complete. Meanwhile, dying patients begin taking the unapproved drug and collect their results on the web. Both groups desperately want to save lives: but which is the right route to follow?

This scenario has been playing out in recent weeks for a compound called dichloroacetate (DCA). It taps into long-running issues about whether terminally ill patients should be able to get access to drugs that have not yet had formal approval. Researchers fear that those taking the drug could suffer unanticipated side effects; patients argue they don't have the luxury of waiting for clinical trials to find out.

In January this year, Evangelos Michelakis at the University of Alberta in Edmonton, Canada, and his colleagues reported that DCA has seemingly remarkable anticancer properties (S. Bonnet *et al. Cancer Cell* **11**, 37–51; 2007). DCA is a small molecule that blocks an enzyme in mitochondria — the energy-production centres in cells — causing more glucose to be metabolized in the mitochondria rather than by the different pathway in the cytoplasm. The compound has been in clinical trials for years as a treatment for certain mitochondrial diseases, but it has not yet been approved.

Mitochondria also control cell suicide, and Michelakis wondered whether cancer cells were suppressing these cellular structures to prevent the cells from dying — and so thought DCA might reactivate them. When his team gave DCA to rats that were growing human lung tumours, the tumours stopped growing within a week, and three months later were half the size of those in untreated animals. Other experimental drugs have had similar effects. But DCA stands out because it seems to leave healthy cells untouched, has been relatively safe in human trials, can be taken by mouth and easily penetrates tissues. “If there were a magic bullet,” wrote *Newsweek* about the discovery, “it might be something like dichloroacetate.”

Because DCA has been around for years, its structure can't be patented and Michelakis found that pharmaceutical companies weren't

interested in developing the drug. So he is raising money and hopes to start his own small clinical trial within the next few months.

In the meantime Jim Tassano, who owns a pest-control and marketing company in Sonora, California, came across DCA when researching alternative cancer therapies to help his dying ballroom-dance instructor. He wanted something that was effective, safe and that he could lay his hands on: DCA fit the bill. He ordered some from chemical supply companies, teamed up with a chemist friend and they worked out a way to synthesize the compound themselves. “I couldn't walk away from it,” Tassano says. “It could do so much good for so many people.”

Tassano set up two websites. The first of these (thedcasite.com) hosts information on DCA and a patient chatroom. On the second (buydca.com) Tassano is selling his homemade DCA — labelled for veterinary use, as drugs sold for human use in the United States

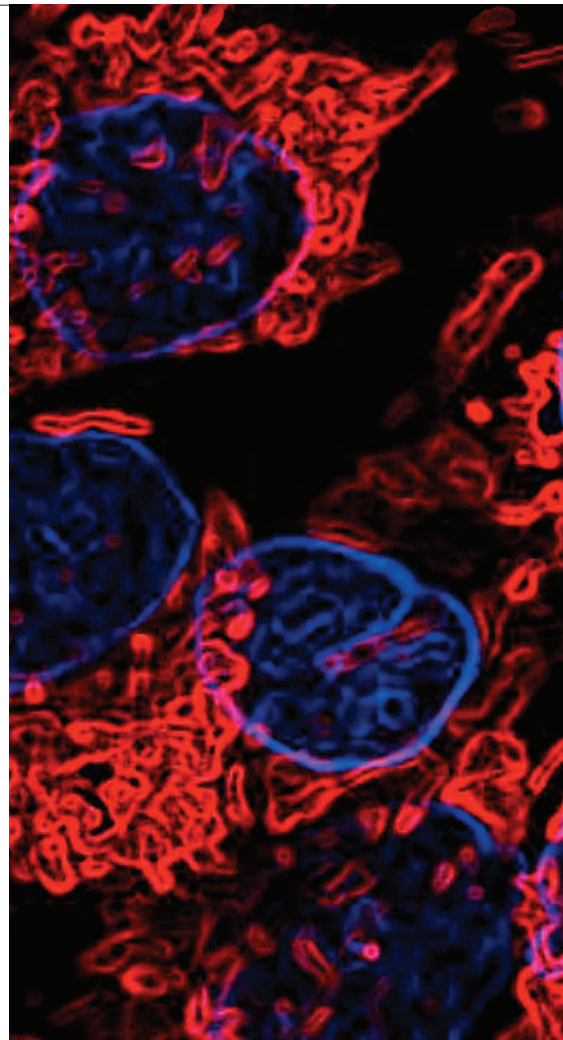
must have approval from the Food and Drug Administration (FDA). Tassano says he is sure patients are buying the drug to use on themselves, and reckons that a couple of hundred of people from around the world have bought from the

site. Many patients taking DCA — acquired from Tassano, chemical companies or other sources — are reporting their progress on thedcasite.com.

Some of these patients plan to set up a database on Tassano's website to collect DCA results in a more organized way. They want people to submit information including the type of cancer they suffer, medical history and the dose they are taking, says Susan Hirasawa in Seattle, Washington, who suffers from late-stage breast cancer and is one of the organizers. The idea is to provide information for others who want to take DCA, she says, but “it's not a real clinical trial”.

Michelakis and other researchers are worried by the development. Although DCA seems safe overall, they point to a clinical trial that was stopped early because those taking the drug developed damage to their peripheral nerves (P. Kaufmann *et al. Neurology* **66**, 324–330; 2006). Without a control group, they point out, it will be impossible to tell whether any improvement in the patients' condition is

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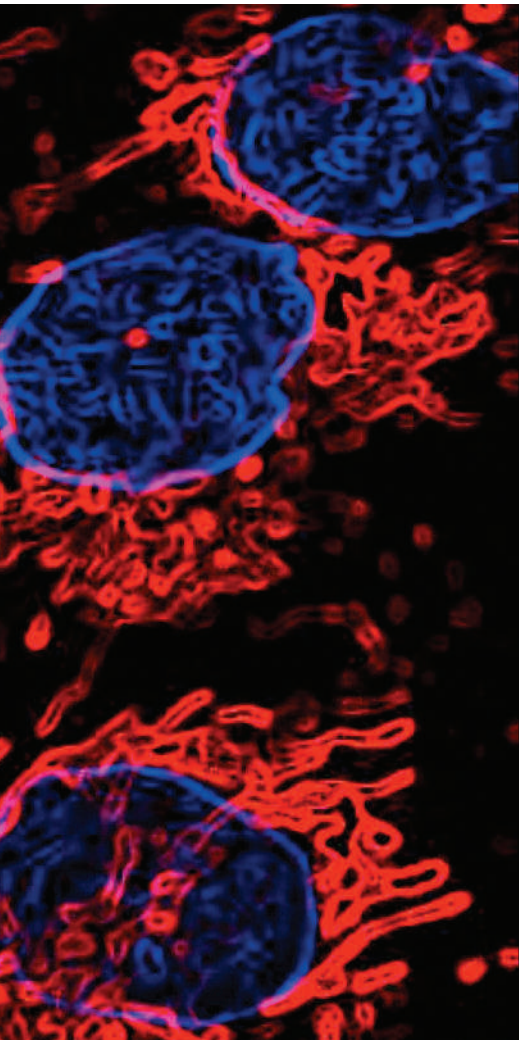


caused by the drug. Patients could also be taking DCA that is not of pharmaceutical grade and might contain harmful impurities.

Michelakis says the patients could end up undermining efforts to do a controlled clinical trial if, for example, some develop harmful side effects and the drug earns a bad reputation. “It's destroying efforts to do this right,” he says. “Any way you look at this, it's a negative development.” An FDA spokesperson told *Nature* that the agency is looking into the matter.

The battle between dying patients who want immediate access to unapproved drugs and doctors who urge trials and caution is a perennial one. Some patients argue that they cannot wait for trials and should have the right to take unapproved drugs, regardless of the risks.

But there are arguments against this. An estimated 95% of cancer drugs that enter clinical trials do not get approval, many because they are ineffective or unsafe, so patients risk shortening their life or making their last days more uncomfortable. “They say what do I have to lose? The truth of the matter is, you have the



E. MICHELAKIS

Reactivating mitochondria seems to trigger cancer cells to commit suicide.

rest of your life to lose," says George Annas, an expert in bioethics at Boston University School of Public Health.

And if patients can access DCA — or other unapproved drugs — there is no incentive for them to enter a clinical trial. So in terms of public health, ethicists argue, more people will be helped if access to unapproved drugs is restricted and proper trials performed.

Peter Jacobsen, an expert in ethics, health and law at the University of Michigan in Ann Arbor, doubts whether any good can come of the patients' efforts. They are so desperate to see results, he says, that there is no way they can report unbiased results and no mechanism to ensure the reports are accurate. "I don't trust the data," he says. "It's hard enough to rely on them in clinical trials, let alone this." ■

Helen Pearson

Database targets Parsi genes

BANGALORE

A biotechnology company in Bangalore has launched a project to build a genetic, genealogical and medical database of India's 69,000-strong Parsi community. Parsis are thought to be particularly genetically homogenous, so researchers hope to use the data to identify genes involved in disease and develop new treatments and diagnostics — in a similar way to a national genetic database already set up in Iceland.

Fleeing persecution by invading Arabs, the Parsis arrived in India from Persia 1,200 years ago, around the same time that a few hundred Vikings arrived in Iceland. They speak a unique Indian dialect and their religion forbids marriage outside the community, so they have remained relatively inbred.

"I realized four years ago that I was sitting on a goldmine or a powder keg," says Viloo Morawala Patell, a Parsi and molecular biologist who founded the biotech company Avesthagen in 1998. Patell says she refers to a powder keg because of the fear that Parsis will soon become extinct because of inbreeding (the population has shrunk to its present size from a high of 115,000 in 1941). But like Iceland, the project could also present a commercial opportunity. In 1999, Iceland's government licensed the genetic information from the national database to deCODE Genetics, a biomedical company that hopes to develop new cures and diagnostic kits.

Hoping to do the same for the Parsis, Patell launched the 1.25-billion-rupee (US\$30-million) project on 21 March.

She plans to create a database that holds genetic data, together with genealogical and medical histories, of at least 50,000 Parsis in five years and eventually of the entire community. Parsis already keep extensive genealogical data, says Patell, and it should be possible to reconstruct their medical records from clinics and hospitals in Mumbai, where more than 90% of Parsis live. The company's genomics and bioinformatics facilities have been upgraded so they can sequence selected markers in



The Parsi community has a unique gene pool.

the participants' DNA.

Avesthagen will provide the initial capital and plans to raise the rest from prosperous sections of the Parsi community and other sources. Patell declines to name potential sources, although Avesthagen already has several international collaborations, including with the French company bioMérieux for the development of diagnostic chips, US company Sequenom for the validation of genetic markers for cancers, and European drug giants AstraZeneca and Novartis.

Patell says that she has been discussing the project with prominent members of the Parsi community for four years, making the case that the information gained will directly benefit the health of the dwindling population. A council

of eminent Parsi figures will manage the project, deciding on matters such as who will own the database and who can access the data.

Vasanth Muthuswamy, deputy chief of the Indian Council of Medical Research (ICMR), says that the government has no problem with the commercialization of the community's genetic information as long as the ICMR's biobanking guidelines are followed. Among other things, these require informed consent and

data confidentiality — issues that overshadowed Iceland's plans to establish a database for the health sector. "After Iceland, this has become a global issue," Muthuswamy told *Nature*. "We have to see what kind of agreement the Parsi community signs with Avesthagen."

Patell says that the genome analysis will focus on genetic defects common in Parsis, such as a deficiency of G6PD (glucose-6-phosphate dehydrogenase) — an enzyme that triggers the sudden destruction of red blood cells. Reduced fertility, ovarian disease, Parkinson's, Alzheimer's and breast cancer are other likely areas of study.

But not everyone is convinced that the project will work. Studies suggest that there has been some mixing of Parsi genes with those of other Indians. "It is a bit of a gamble," says Indraneel Mitra, director of the Bhopal Memorial Hospital and Research Centre in India. "My feeling is that the Parsis are not as pure as Icelanders, and in any case I do not know how fruitful the Icelandic study has been." ■

K. S. Jayaraman



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I. MUKHERJEE/AFP/GETTY