

# Cheap, safe drug kills most cancers

ANDY COGHLAN

IT SOUNDS almost too good to be true: a cheap and simple drug that kills almost all cancers by switching off their "immortality". The drug, dichloroacetate (DCA), has already been used for years to treat rare metabolic disorders and so is known to be relatively safe. It also has no patent, meaning it could be manufactured for a fraction of the cost of newly developed drugs.

Evangelos Michelakis of the University of Alberta in Edmonton, Canada, and his colleagues tested DCA on human cells cultured outside the body and found that it killed lung, breast and brain cancer cells, but not healthy cells. Tumours in rats deliberately infected with human cancer also shrank drastically when they were fed DCA-laced water for several weeks.

DCA attacks a unique feature

of cancer cells: the fact that they make their energy throughout the main body of the cell, rather than in distinct organelles called mitochondria. This process, called glycolysis, is inefficient and uses up vast amounts of sugar. Until now it had been assumed that cancer cells used glycolysis because their mitochondria were irreparably damaged. However, Michelakis's experiments prove this is not the case, because DCA reawakened the mitochondria in cancer cells. The cells then withered and died (*Cancer Cell*, DOI: 10.1016/j.ccr.2006.10.020).

Michelakis suggests that the switch to glycolysis as an energy source occurs when cells in the middle of an abnormal but benign lump don't get enough oxygen for their mitochondria to work properly (see Diagram). In order to survive, they switch off their mitochondria and start producing energy through glycolysis.

Crucially, though, mitochondria do another job in cells: they activate apoptosis, the process by which abnormal cells self-destruct. When cells switch mitochondria off, they become "immortal", outliving other cells in the tumour and so becoming dominant. Once reawakened by DCA, mitochondria reactivate apoptosis and order the abnormal cells to die.

"The results are intriguing because they point to a critical role that mitochondria play: they impart a unique trait to cancer cells that can be exploited for cancer therapy," says Dario Altieri, director of the University of Massachusetts Cancer Center in Worcester.

The phenomenon might also explain how secondary cancers form. Glycolysis generates lactic acid, which can break down the collagen matrix holding cells together. This means abnormal cells can be released and float to other parts of the body, where

**"Once reawakened by DCA, mitochondria order the abnormal cancer cells in a tumour to die"**

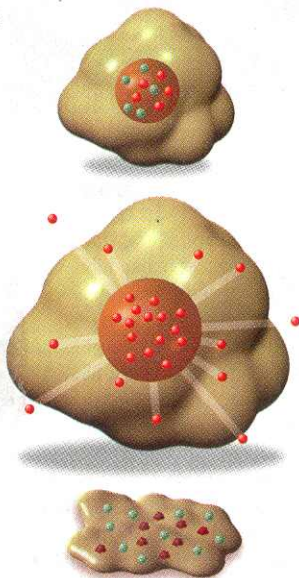
## KILLING CANCER

What makes cancer cells different - and how to kill them

Normal cells (blue) in the middle of a benign growth are starved of oxygen but can survive by switching to glycolysis, a different way of making energy. In the process the mitochondria, which contain the cells' self-destruct mechanism, switch off. This makes the cells "immortal" and cancerous (red), so they carry on replicating and the tumour grows

Glycolysis also generates lactic acid, which lets the cancer cells eat through tissue, escape and form secondary cancers elsewhere in the body

A drug called dichloroacetate switches the mitochondria in the cancer cells back on (blue) so they halt glycolysis and start making energy in mitochondria again. The self-destruct mechanism is then activated, and the cells wither and die (brown)



they seed new tumours.

DCA can cause pain, numbness and gait disturbances in some patients, but this may be a price worth paying if it turns out to be effective against all cancers. The next step is to run clinical trials of DCA in people with cancer. These may have to be funded by charities, universities and governments: pharmaceutical companies are unlikely to pay because they can't make money on unpatented medicines. The pay-off is that if DCA does work, it will be easy to manufacture and dirt cheap.

Paul Clarke, a cancer cell biologist at the University of Dundee in the UK, says the findings challenge the current assumption that mutations, not metabolism, spark off cancers. "The question is: which comes first?" he says. ●