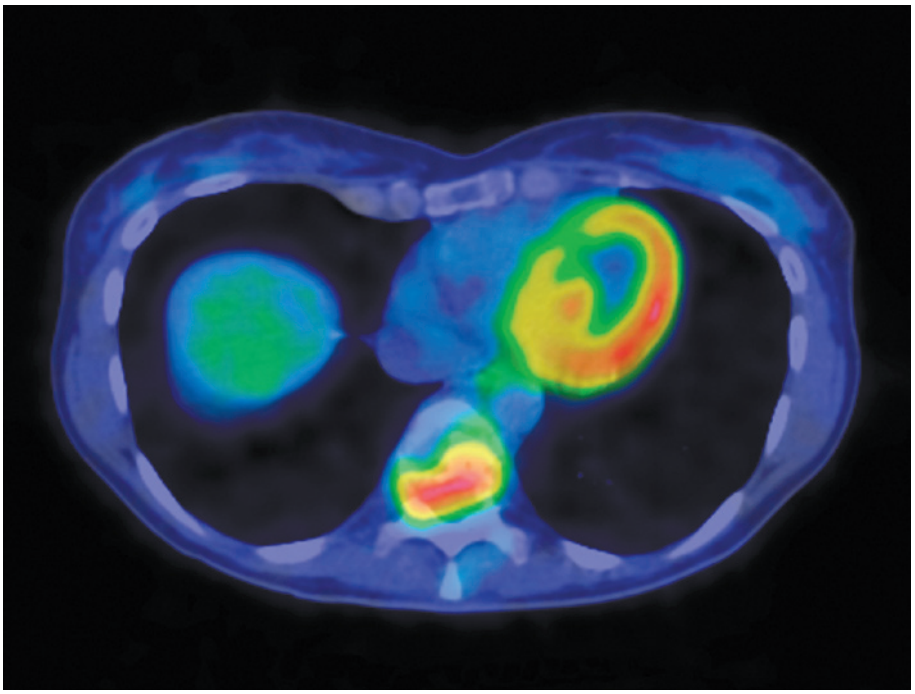


CENTRE JEAN PERRIN, ISM/SPL

Preferential uptake of glucose by cancer cells allows tumours, here shown in the spine, to be imaged.

CANCER

Metabolic quirks yield tumour hope

Early clinical-trial results show promise for targeting cancer-related biochemical pathways.

BY HEIDI LEDFORD

One of cancer's deadly sins — gluttony — is turning out to be one of its key vulnerabilities.

Cancer cells harness unusual metabolic pathways to obtain the energy and molecular building blocks that they need for their relentless proliferation. Many potential drugs have tried to take advantage of this hunger. Early results for a genetically targeted drug, unveiled this week at the annual meeting of the American Association for Cancer Research in San Diego, California, suggest that the approach could pay off.

"The field is at a turning point," says Almut Schulze, a cancer researcher at the University of Würzburg in Germany.

In some ways, the findings send cancer research back to its roots. For much of the twentieth century, the disease was considered a metabolic malady — an idea that arose in the 1920s, when the German biochemist Otto Warburg showed that cancer cells have an outsized appetite for glucose. The glucose is broken down, yielding energy in the form of ATP, produced in the cell's mitochondria, as well as components of amino acids, lipids and other compounds needed to build new cells.

The phenomenon, called the Warburg effect, quickly led to techniques that image tumours by tracking radioactively labelled glucose molecules taken up by cancer cells. It also suggested a path to new therapies, says Nissim Hay, a cancer biologist at the University of Illinois in Chicago: "If we can selectively detect cancer cells, why can't we selectively target them?"

"It's very interesting biology that's been neglected for over 30 years."

In the 1970s, the discovery of chromosomal abnormalities and cancer-causing mutations shifted focus to the disease's genetic origins. Cancer's odd metabolism was ruled an effect, rather than a cause, and researchers largely sidelined its study. But over the past decade, they have come to realize that the mutations alter a handful of key metabolic systems from which cancer derives its energy. These metabolic pathways are potential targets for drugs. "That was the wake-up call," says Matthew Vander Heiden, a cancer researcher at the Massachusetts Institute of Technology in Cambridge.

The clinical work announced at the meeting stems from two targets that were characterized in 2009 by researchers at Cambridge-based Agios Pharmaceuticals. The team reported on the effect of mutations in genes called *IDH1* and *IDH2* that had already been associated with some forms of leukaemia and brain cancer.

The genes encode enzymes that act in an energy-producing metabolic pathway called the citric acid cycle. The Agios team found that the mutations lead to unusually high production of a cancer-promoting compound called 2-hydroxyglutarate (L. Dang *et al. Nature* **462,** 739–744; 2009). This compound, which is produced at only low levels in normal cells, allows cancer cells to proliferate by keeping them in an immature state.

TREATMENT RESPONSE

On 6 April, Agios reported the first clinical-trial results for a drug designed to inhibit the mutant IDH2 enzyme. The trial was small, involving ten patients who had acute myeloid leukaemia with *IDH2* mutations. Three of the patients were removed from the trial after developing infections, a common consequence of advanced leukaemia. But of the remaining seven patients, six responded to treatment. The drug, called AG-221, eradicated cancer cells in five of them.

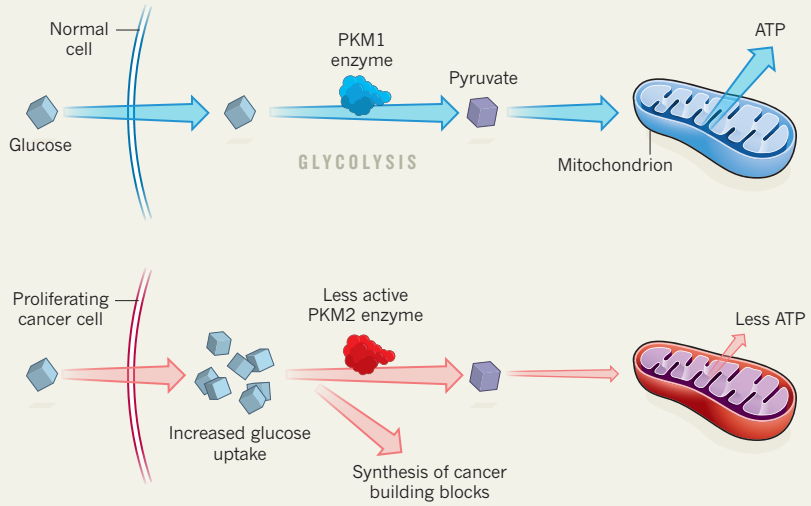
The results are encouraging, says John Byrd, director of haematology at the Ohio State University Wexner Medical Center in Columbus, who was not involved in the study. The patients in the trial were very sick, he notes, and had already undergone multiple therapies. "This is very impressive," he says.

The patients have been on the drug for five months or less, and so it is too early to say how long the effects will last, says Agios chief executive David Schenkein. Tumours quickly become resistant to many drugs that target a single cancer mutation, and metabolic pathways are remarkably plastic, notes Navdeep Chandel, a mitochondrial biochemist at Northwestern University in Chicago. "If a cell needs certain metabolites to grow, it will find a way."

Other drugs based on the quirky metabolism of cancer cells are making their way into the clinic. In February, Calithera BioSciences of South San Francisco, California, launched two trials of a drug that capitalizes on the penchant of some cancer cells to mop up huge amounts of the amino acid glutamine, which they use to make proteins and to fuel the citric acid cycle. The company has produced a

ENERGY HUNGRY

Researchers are trying to find targets within cancer's metabolic cycles, such as one that breaks down glucose.



drug that blocks glutaminase, the enzyme that converts glutamine to glutamate, a key step in the cycle. The hope, says Calithera chief executive Susan Molineaux, is that because of cancer cells' strong dependence on glutamine, concentrations of the inhibitor can be found that will halt cancerous growth without damaging healthy cells.

But finding that sweet spot poses a challenge, because the metabolic oddities associated with cancer are sometimes found in normal cells that need to proliferate rapidly, such as immune cells. Agios was able to sidestep that hurdle by targeting an abnormal form of the IDH2 enzyme associated with cancer.

ENZYME CONUNDRUM

Other approaches have not had the benefit of such a clear target, and have suffered as a result. Several companies, including Agios, have studied an enzyme called pyruvate kinase that helps to break down glucose in the Warburg effect. Most normal cells produce a form of the enzyme called PKM1, but cancer cells tend to favour a less active form, PKM2. That pattern suggested that a drug blocking PKM2 could halt cancer growth.

But Vander Heiden and his colleagues found that tumours grew faster, not more slowly, in mice that lacked PKM2 (W. J. Israelsen *et al. Cell* **155,** 397–409; 2013). To explain this strange result, the researchers hypothesize that multiplying cancer cells may prefer the less active PKM2 — or even no pyruvate kinase at all — because it allows glucose breakdown products to be shunted into pathways that generate molecules needed to build new cancer cells (see 'Energy hungry'). Although that would result in less ATP generated per molecule of glucose broken down, the cells can compensate by taking up more glucose. Nevertheless, the results cast doubt on PKM2 as a drug target. "Initially, people were very excited about PKM2," says Hay. "But then it turned out to be more complicated than expected."

Although Chandel is glad that cancer-metabolism research is taking centre stage, he thinks that expectations for drugs based on the research might be too high — most attempts will not succeed. Even so, he adds, the fervour should lead to a better understanding of metabolic processes in both healthy and diseased cells. "These are good days for studying metabolism," he adds. "It's very interesting biology that's been neglected for over 30 years." ■

PUBLIC HEALTH

E-cigarettes affect cells

Questions raised over health effects of devices.

BY DANIEL CRESSEY

Electronic cigarettes can change gene expression in a similar way to tobacco, according to one of the first studies to investigate the biological effects of the devices.

Presented at the American Association for Cancer Research annual meeting on 6 April in San Diego, California, the research looked at human bronchial cells that contained some mutations found in smokers at risk of lung cancer. The cells were immortalized, grown in culture medium that had been exposed to e-cigarette vapour and their gene expression profiled.

The researchers found that the cells grown in medium exposed to the vapour of e-cigarettes showed a similar pattern of gene expression to those grown in a medium exposed to tobacco smoke (S. J. Park *et al. Clin. Cancer Res.* **20,** B16; 2014).

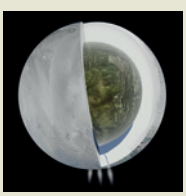
The changes are not identical, says study researcher Avrum Spira, who works on genomics and lung cancer at Boston University in Massachusetts. But "there are some striking similarities", he says. The team is now evaluating whether the alterations mean that cells behave more like cancer cells in culture.

The work is at a very early stage and therefore cannot establish that e-cigarettes can cause cancer *in vitro*, let alone *in vivo*. "They may be safer [than tobacco], but our preliminary studies suggest that they may not be benign," says Spira.

E-cigarettes are extremely controversial. Because they vaporize liquid containing nicotine, rather than burning tobacco, some researchers believe that the devices could greatly reduce the damage done to health by smoking; others, however, argue that they are simply 'renormalizing' smoking. ■

MORE ONLINE

TOP NEWS



NASA/JPL-CALTECH

Saturn's moon Enceladus hides huge water ocean under its south pole go.nature.com/vijdmf

MORE NEWS

- Public disclosure leads to more retractions of flawed publications go.nature.com/rwos3y
- Europe urged to relax text-mining access go.nature.com/gpdekt
- How Earth got its tectonic plates go.nature.com/715d6y

NATURE PODCAST

Flooding the Colorado River; being an IPCC contributor; and amoebae eating nature.com/nature/podcast