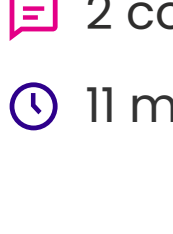


Hacking cancer cell metabolism


by **Cancer Research UK** | In depth
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2 comments

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Restricting specific amino acids from cancer cells has been shown to slow tumour growth and sharpen the effects of chemotherapy and radiotherapy in studies using mice and cell lines. Now, startup Faeth Therapeutics want to create precision diets to test whether modulating specific metabolic pathways could enhance the effects of existing cancer treatments. We spoke with Professor Oliver Maddocks to find out how the startup came about, and how he thinks hacking cancer metabolism with targeted dietary interventions could help cancer treatments work better.

It was way back in the 1920s when cancer metabolism was first identified as a possible therapeutic target.

[Otto Warburg](#) had observed that cancer cells prefer to metabolise glucose anaerobically, even when oxygen is present. Later, in the 1940s, [Sidney Farber](#) discovered that a folate antagonist could block nucleotide synthesis. Folate antagonists and other “antimetabolite” drugs became the vanguard of the chemotherapy era and improved survival for millions of people with cancer. In subsequent years, however, [genomics took centre-stage](#) in cancer research. It was, of course, a successful approach leading to effective drugs targeted at faulty gene products. More recently though, largely thanks to the advent of metabolomics, cancer metabolism is once again being turned to.

Professor Oliver Maddocks and his then-supervisor Professor Karen Vousden, former chief scientific officer at Cancer Research UK – now running her lab at the Francis Crick Institute in London – found that starving cancer of selected amino acids *in vitro* and in mice slowed tumour growth and improved survival, with landmark *Nature* papers in [2012](#) and [2017](#).

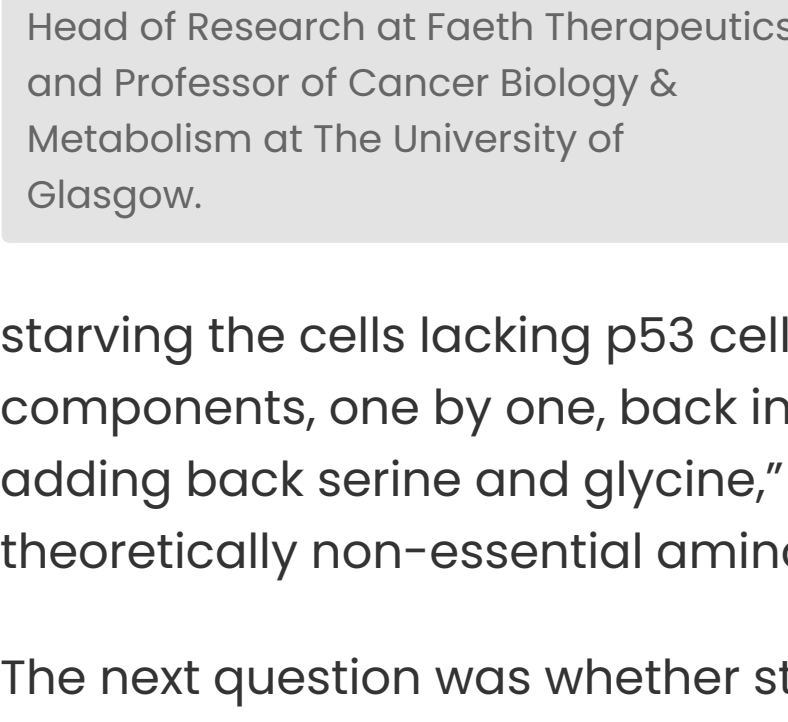
Around the same time, two other leading cancer research groups in the UK and US were coming to similar conclusions – that specific nutrition alterations could selectively hit the metabolism of cancer cells hard enough to slow growth and to make them more sensitive to standard therapies.

“There was a natural coming together of these three groups of scientists,” says Maddocks. “There were nine of us around the table, saying we all think this is fundamentally important, we need to start a company to translate this.”

This transatlantic meeting of minds gave birth to [Faeth Therapeutics](#) in 2019. The startup has three routes that it hopes will take advantage of cancer metabolism – pairing existing anti-cancer drugs with precision diets restricted for specific amino acids to weaken the cancer, along with a digital app with direct dietician support to help patients stick with the diet. Fast forward to today, and the start-up has three early-phase clinical trials ongoing, a busy R&D department stocking up the pipeline, and \$67 million of investment to make it all happen. It’s early days and the clinical trials are designed to first test whether this approach is safe and acceptable to patients, and then to detect any early signs that it actually has an effect on the cancer.

Mind the metabolism

Originally a pharmacist, Maddocks spent 18 months as a Fulbright scholar in the US before returning to the UK in 2010 to start a postdoc in Vousden’s lab at the CRUK Beatson Institute in Glasgow. The lab was focussed on the p53 tumour suppressor gene and was getting more interested in cancer metabolism just as Maddocks arrived.



Dr Oliver Maddocks is Co-Founder & Head of Research at Faeth Therapeutics and Professor of Cancer Biology & Metabolism at The University of Glasgow.

Maddocks started with *in vitro* work by concocting a minimal essential media, with the bare minimum amount of ingredients needed to culture cells. “I immediately saw cells lacking p53 did not grow, but the p53 wild type cells could,” he says. Clearly, he was

starving the cells lacking p53 cells of something important. Maddocks started adding components, one by one, back into the media. “What immediately rescued the cells was adding back serine and glycine,” he says. This was an overwhelming observation; that this theoretically non-essential amino acid could control growth to such an extent.

The next question was whether starving mice of serine and glycine would impact cancer growth. This went against conventional wisdom at the time. There was no point removing serine and glycine from the diet, so the dogma went, since the organism could synthesize them anyway and was not reliant on sourcing these non-essential amino acids from the diet. They forged ahead anyway.

“The way Karen and I thought about this was, let’s assume we don’t know the answer before we talk ourselves out of doing an experiment,” says Maddocks.

He formulated a tailored diet with a similar nutrient profile to the cell culture media and fed it to mice. “Lo and behold, just [changing two small parts of the diet really slowed tumour growth and allowed the mice to survive for longer](#),” he says.

Liquid chromatography-mass spectrometry (LC-MS) analysis of the serum from mice fed the restricted diet showed that levels of serine and glycine halved – evidence that dietary depletion had an impact in the mice, despite the ability to manufacture the amino acids elsewhere in the body.

Using *in vitro* work, tumour organoids and mice, Maddocks and Vousden filled in various [mechanistic elements](#) of the story over the next few years, continuing to collaborate after Maddocks received funding from CRUK to set up his own cancer metabolism lab at the University of Glasgow in 2015. Maddocks and Vousden were already convinced that their discovery could be translated into a treatment. Together with the commercialisation arm of CRUK, Cancer Research Horizons, they patented the process of selectively starving cancer cells of certain amino acids.

“You start off as a young scientist quite idealistic, thinking you should just publish findings, not worry about patents, and let the whole world have them,” says Maddocks, “but you learn that if you can’t patent, it becomes really difficult to translate because the clinical translation process is so resource intensive.”

Converging towards a common conclusion

Despite their breakthrough academic discoveries in how selective amino acid depletion can starve cancer cells, Maddocks and Vousden were feeling a little lonely in the years between 2010 and 2017, with few other groups working in the space. “It was too far outside many people’s comfort zone,” says Maddocks.

However, things began to change in 2018, when star US cancer researcher Lew Cantley showed that, in mice, specific alterations in [systemic metabolism were responsible](#) for blunting the response to PI3K inhibitors. By suppressing the insulin feedback loop responsible with a low-carbohydrate diet, it significantly boosted effectiveness of anti-cancer PI3K inhibitors.

Around the same time, Greg Hannon’s functional genomics lab at the CRUK Cambridge Institute showed using *in vitro* and mouse breast cancer models, that metastasis [is influenced by the availability of the non-essential amino acid asparagine](#), and that limiting asparagine in the diet of mice reduced metastasis.

“The three groups, when you put it all together, provided a thematic discovery around selective diet, tumour metabolism, systemic metabolism, targeted therapies and chemotherapies,” says Maddocks.

Faeth takes form

When the three research groups decided to form a startup, an immediate challenge was: who among the nine cofounders would take the lead to push the company forward into existence? As an early career principal investigator, a pharmacist, and with some previous experience in industry, Maddocks was ideally placed to take some time aside from his academic research to lead the fledgling company.

“I have this pharmacy background, molecular biology of cancer and then cancer metabolism, which gave me a translational way of thinking about things,” he says. Plus, he says, bringing a startup to life was an itch he just had to scratch.

The following months and years were a whirlwind of conversations with venture capitalists until they secured enough seed investment in 2019 to get off the ground. “To begin with, it was about trying to get the funding, having conversations about raising money, putting a deck together to present to potential investors. And also, figuring out how you actually start and incorporate a company.”

Throughout all of this, Maddocks was juggling his academic research and setting up the company. Not to mention two young kids and a pandemic. This was a lot of work, admits Maddocks. “However, success is very little about how bright you are,” he says, “and much more about how hard you work.”

A thumbs up from CRUK and the university to spend a portion of his time on the new company helped. So much so in fact that, when needed, Maddocks took a sabbatical from research to concentrate fully on the endeavour. The new transatlantic company was founded in 2019, and was aptly named Faeth, meaning “nutrition” in Welsh. Getting CEO & Co-Founder Anand Parikh onboard early was a critical step forward, says Maddocks, who then took on the role of chief scientific officer.

The Faeth approach

There are three main aspects to the treatment approach Faeth wants to test: therapy, diet and digital support. “Instead of just giving someone a drug, they will get the therapeutic, they will get food tailored to their treatment regimen, delivered to their door,” says Maddocks. “And they get a digital health app, which will coach them through the diet, learn about their preferences, help them comply.”

Each diet is precision engineered to selectively deplete certain key amino acids, with the aim of weakening a patient’s particular cancer so that standard treatments become more effective – and that will be tested in clinical trials, in specific cancer types, looking at safety and signals of drug efficacy and whether a patient’s genetic makeup affects these. This is where Faeth differs from the myriad of dubious diets and food supplements that claim to treat cancer.

“People have come up with ideas about nutrients, and then applied it in a very non-targeted way across a bunch of different cancers or different genotypes, without that real mechanistic insight into if, or why, that dietary intervention works,” says Maddocks. Faeth wants to change that. “We’re bringing our molecular biology, cancer metabolism, genetically-driven focus to this question of diet,” explains Maddocks, “We’re not going to prescribe or suggest things for people unless we know it’s validated through clinical trials for that particular type of cancer.”

Three clinical trials are already underway. Two are investigating standard care medications for [metastatic pancreatic cancer](#) and [metastatic colorectal cancer](#) in combination with a nonessential amino acid restriction diet. In this diet, patients receive a very low protein diet composed of whole foods, supplemented by a specially formulated shake that is free from certain amino acids.

The third trial is an example of Faeth’s alternative approach – testing an investigational drug in combination with a personalised diet. In this phase Ib trial, Faeth is investigating the anticancer ability of an in-licensed experimental PI3K inhibitor called [serabelisib, combined with an insulin suppressing diet](#) in people with advanced solid tumours with PIK3CA mutations.

Stocking the pipeline

As the team wait for results from the clinical trials, Faeth’s R&D department – supported by Vousden and the other scientific co-founders – are busy designing possible future studies. Their discovery platform, dubbed MetabOS, combines functional genomics, metabolomics and machine learning. The platform zooms in a tumour’s genotype and organ to figure out which nutrients can be selectively deleted to sensitise the tumour to a therapy. “We’re already bringing new programmes through preclinical research,” says Maddocks.

Faeth’s multidisciplinary team certainly has an uncommon profile. “It’s a unique company, where you have molecular biologists working in labs doing cancer metabolism, doing molecular biology, but you also have dieticians and chefs,” says Maddocks.

Molecular biologists can take the results of a nutrient starvation experiment, go straight to the dieticians who assess whether humans can tolerate depletion of the nutrient in the diet, and from there work with the company chefs who will start creating meals, recipes and menus for initial taste-testing by the rest of the company. “You have to iterate many times around that until you get a diet that actually does the thing you want it to do,” says Maddocks.

Time will tell if Faeth’s clinical trials show positive results – but it’s clear that translation of discovery science is absolutely vital to have an impact on patients. As such, it is equally vital to support researchers as they embark on their entrepreneurial endeavours.

Explore how Cancer Research Horizons can help you [translate your work](#)

Disclaimer

As there is currently no evidence in humans that a restricted diet has benefits, it is not recommended that cancer patients self-administer a restricted diet. The research of Dr Maddocks and the rest of the Faeth Therapeutics team has not been shown to work in human cancer patients. There are clinical trials underway to establish if a nonessential amino acid restriction diet alongside conventional cancer therapy will improve the efficacy of those treatments in human cancer patients.

Click [here](#) for more on diet and cancer.



Author:
Fiona Dunlevy is a freelance medical writer. She has been medical writing since 2010, following doctoral and postdoctoral research in respiratory biology.

Comments

Lea 12 February 2023

Sounds brilliant, but then find out it’s only in the USA 🇺🇸

Ceejay 31 January 2023

Like many other cancer patients I am interested in this concept of dietary modification to attack cancer cells via metabolism alongside conventional therapy. But considering this is CRUK article, promoting UK scientists role, it was very disappointing to then click onto Faeth website and see all the current clinical trial locations are only in USA.