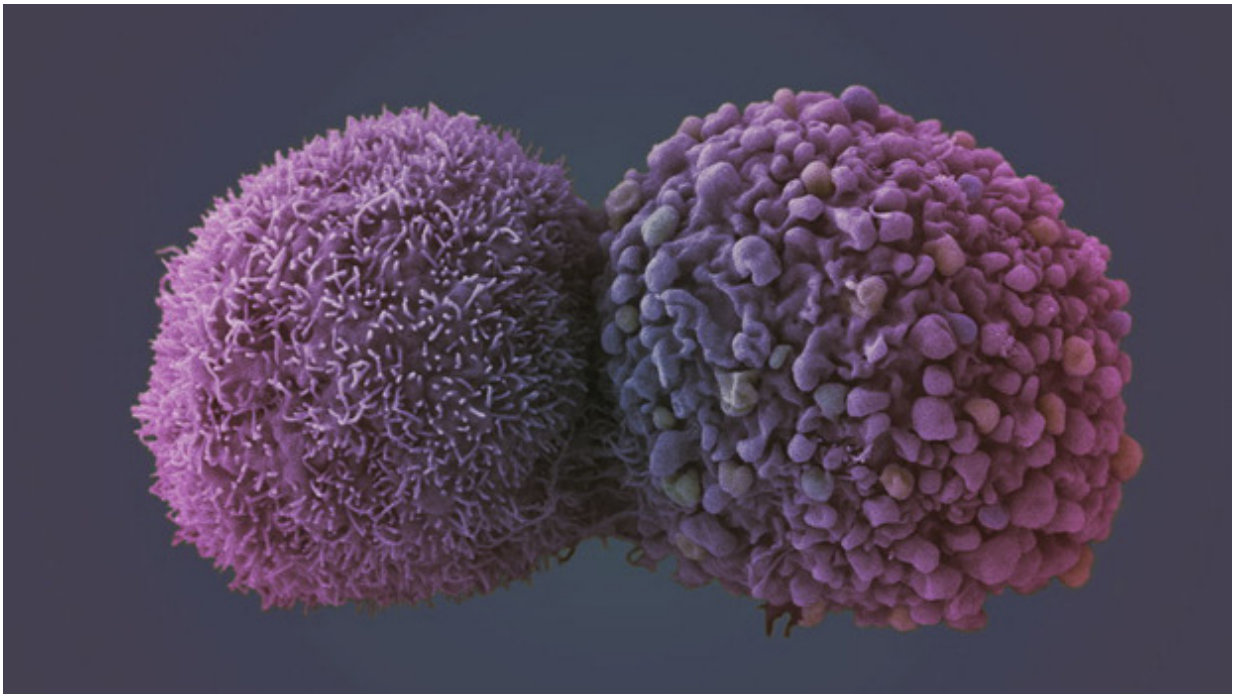
Fishing for clues – how 'liquid biopsies' are uncovering cancer's secrets

July 2 2015, by Nick Peel



Lung cancer cells (image courtesy of the London Research Institute EM unit)

It takes just three minutes for a precious 10 millilitre blood sample to be carried from the specialist cancer wards of the Christie Hospital in Manchester, down a corridor, and into a lab housing several large, white machines.

But before arriving in the fluorescent light of the Cancer Research UK

Manchester Institute, the blood was on a different journey: flowing around a cancer patient's body – and potentially collecting some unwelcome passengers along the way.

The stowaways are cancer cells that have broken away from a tumour and escaped into the blood. They're wily and difficult to target, and can lodge in nooks and crannies in the patients' body, and spawning the secondary tumours that sadly claim so many lives.

Yet, Professor Caroline Dive and her team – along with colleagues from the Cancer Research UK Lung Cancer Centre of Excellence – believe these rogue cells could hold the key to stopping this process in its tracks.

The team's work is part of a fast-flowing area of research, moving away from a need for invasive tissue samples, called biopsies, to gather precious research material.

Instead, they're turning to blood-based 'liquid biopsies' – searching for crucial information floating in a patient's blood.

It's in the blood

Caroline's team is focussing on lung cancer, the world's biggest cancer killer.

"One of the problems is we detect very few lung cancers early enough," she tells us from her office just down the corridor from the lab. "And once the cancer has spread around the body, it becomes very difficult to treat."

The symptoms can mimic other common conditions, and sadly this translates into a stark statistic: more than two thirds of people see their lung cancer diagnosed at a late stage.

This means lung cancer survival remains stubbornly low: for every 100 people diagnosed in England and Wales, just five are alive 10 years later.

"We need to understand the biology far better, so we can develop drugs to treat the disease more effectively," Caroline explains.

But to compile this more comprehensive picture, the team need samples. And gathering these has, until now, proved difficult.

"Biopsying patients with lung cancer can be problematic, and really very challenging," Caroline stresses.

"And often when a biopsy is produced, it's quite small. By the time it's gone to the pathology team for a diagnosis there's not much left for researchers like me to study."

But the team believe they've found a way around this.

The 'American fridge'

Over in the lab, Caroline's team – one of the world's best at tracking down circulating cancer cells – is hard at work, preparing the latest round of blood samples for an elaborate cellular fishing trip.

Their lab is littered with pristine white machines, each exquisitely engineered to hook out circulating cells using different features that tell them apart from healthy blood cells.

For example, circulating tumour cells are often bigger, allowing different filtering devices to catch them. They're also less 'squidgy' than healthy blood cells, so the researchers can trap them in small networks of tubes.

But one particular machine – CellSearch – has been the lab's dominant focus for some time.

CellSearch – a futuristic sounding name for what's essentially yet another plain white box – relies on magnets to catch rogue cancer cells in a patient's blood sample.

But these lung cancer cells are rare in the blood.

A recent study by Caroline's team found only around 200 of these tumour cells in 1 millilitre of patient blood – and this was the highest number they saw across six patients with small cell lung cancer. Compared to the estimated five billion red blood cells in that same volume of blood and you start to get an idea of how challenging they are to find.

So to catch them, the team need to use some specialised bait.

Circulating cancer cells carry a particular molecular on their surface, called EPCAM. And when the team prepares a blood sample, they use antibodies to attach microscopic metal beads to the EPCAM molecules on the cancer cells' surface. This allows the magnets to fish for these cells, pulling them away from others in the sample. But it's not perfect – some blood cells also get trapped among the cancer cells.

"You've enriched the circulating tumour cells, you haven't purified them," Caroline explains. "There are still way too many blood cells to do any molecular testing."

So, as the video below shows – and as Caroline's team will demonstrate at this year's Royal Society Summer Science Exhibition – the samples are placed into a second big white box called the DEPArray (or the 'American fridge', as the team call it) that will painstakingly pick out the

cancer cells, one by one, for analysis.

With the cells isolated, the team are now using them to solve one of the biggest challenges in cancer: how cancers become resistant to drugs.

Irresistible force

Progress in understanding drug resistance has been slow, chiefly because the tissue samples used to study lung cancer tend to be taken before a patient starts treatment.

"Getting a biopsy when a patient is first diagnosed is doable, but challenging. Getting multiple biopsies, as the patient's cancer goes from being drug sensitive to drug resistant, is really much more difficult," says Caroline.

"So I think the real challenge has been that we can't look at drug-resistant disease," she explains. "And now with these blood samples we can. That's the step-change, that's the game changer."

Caroline believes that isolating and studying the rogue cancer cells in a patient's blood could give crucial new information to help monitor and understand how drug resistance develops.

"What we can do now is just ask for a small volume of the patient's blood to tackle those important questions about the biology of drug resistant disease."

And the team is already using this technique to explore more uncharted territory. They have been able to grow lung cancer cells taken from patient's blood in laboratory animals, and have shown they respond to treatment in the same way the patient they came from did. And the team has also found a way to grow the circulating cells in the lab.

This is a big deal, particularly for research on lung cancer.

"Now we can grow a patient's circulating tumour cells in the lab we can test a variety of combinations of drugs, to see which are the best at killing the cells," says Caroline.

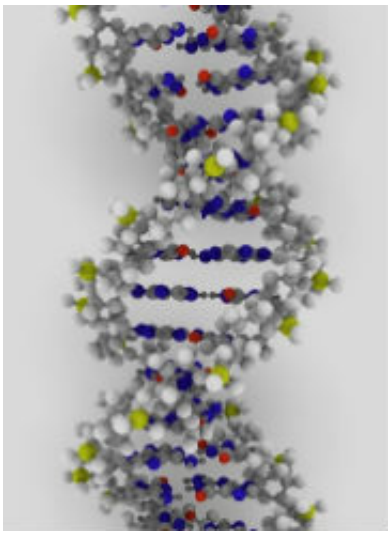
And by doing this – alongside other ground-breaking research projects like the Cancer Research UK-funded TRACERx study – Caroline and her colleagues hope to map the genetic twists and turns a tumour takes as it develops, becomes resistant to treatment and, in some cases, spreads around the body. There are years of work ahead to piece together this complex picture, but it's a crucial part of finding new ways to stop it.

It will also involve cracking open these single circulating cells, reading their entire genetic code, and comparing this to other cells to see what's different. This research holds great promise, but it isn't easy, and it isn't cheap.

Caroline is quick to caution that the technique is still in its early stages. "There are lots of reasons why information from circulating tumour cells is going to be really important in the future. But is it a quick, easy test right now? Not yet," she says.

But looking for entire, intact cancer cells isn't the only way of fishing for cancer clues in the blood.

The floating code



Researchers are also studying blood-borne fragments of cancer's DNA

When cancer cells die – which they do constantly as a tumour grows and multiplies – they release fragments of DNA code into a patient's blood. And Professor Jacqui Shaw, from the University of Leicester, is trying to work out if cracking this code can help patients.

"We're looking at circulating DNA from several different types of tumour, including breast and pancreatic cancers," Jacqui tells us. "And we're also handling the circulating DNA analysis for the TRACERx study in lung cancer."

Her team is scouring these circulating DNA fragments for faults linked to the rapid growth of the cancer cells.

And they believe that analysing these chunks of DNA could potentially offer a real-time 'snap-shot' of these faults, as well as a way of monitoring how the disease changes over time.

This could help researchers and doctors get a handle on something called

'tumour heterogeneity' – a complex phenomenon mirroring Darwin's own theory of evolution. Groups of cells within the same tumour can be genetically very different from each other. And when the disease spreads around the body these cells can become more different still.

This means that relying on a single tissue biopsy gives an incomplete picture of a patient's disease.

Jacqui believes that circulating DNA could help track tumour heterogeneity, "identifying genetic faults that might be missed by analysing a single tumour biopsy". And this could one day help doctors make more informed decisions about which treatments to offer their patients.

But just as with Caroline's circulating cell studies, the field of circulating tumour DNA is still in its relative infancy.

"We don't yet know which tumours are the most 'leaky'," explains Jacqui. Understanding why these chunks of DNA end up in the blood – and what useful information they hold – are a big focus of the team's research.

And they are combining this with work on circulating tumour cells to help find out more. "Circulating DNA and tumour cells can be analysed from the same blood sample," says Jacqui. "So we need to do more studies to better understand the relationship between both of these 'liquid biopsies'."

One journey starts, another begins

Although it's easy to talk of a 'simple blood test' for cancer, the reality is a lot more complex – and a long way off.

But through research on rogue tumour cells and circulating DNA, the secrets held in a patient's blood are beginning to come into focus.

And researchers like Caroline, Jacqui and their colleagues are revealing a never-before-seen level of complexity within different tumours.

The promise is a kinder way to gather this information, and use it to make crucial decisions about how a patient's disease should be treated. But that's a long journey we're only just beginning to tread.

For now this means a regular three-minute walk for our scientists collecting blood samples from one the busiest lung cancer wards in the country.

But in time this could become the three minutes a patient and their family might spend walking to the hospital car park or waiting for the next bus across the road. For them that short walk could mark the start of a different journey free from cancer.

Let's hope that just 10 millilitres of blood could one day help them get there.

More information: "Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer." *Nature Medicine* 20, 897–903 (2014) DOI: 10.1038/nm.3600

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