receptor (EGFR), but over time the tumour became resistant. We did a whole-genome analysis and found that the tumour had an amplification of the *MET* gene, which provides an alternative route for tumours to grow even in the presence of the EGFR blockade. In that case, we identified not only a mechanism of resistance but also a new potential avenue of therapy, because a number of *MET* inhibitors are now available or in clinical trials.

How can ctDNA aid the early detection of cancer?

One example is the early detection of disease recurrence. If you knew soon after surgery by using a liquid-biopsy test that the patient still had residual cancer, you could give some type of targeted therapy to help clear out the remaining cancer. Ultimately, liquid biopsies could make it practical to look at blood from apparently healthy individuals and try to determine whether they have a certain type of cancer. We should be cautious about this, though, because the levels of ctDNA in very-early-stage cancer might be below the limits of detection. But it will be an exciting avenue to investigate because a substantial fraction of patients with early, potentially curable disease are likely to be detectable in this way.

We are also seeing progress in the analysis of circulating tumour cells — cells shed from the tumour into the bloodstream that are still intact, as opposed to fragments of DNA. Are the roles of these two liquid-biopsy approaches becoming clear?

Yes, I think they are complementary. In some settings, ctDNA will be more sensitive for diagnostic purposes. On the other hand, circulating tumour cells are an extremely powerful source of tumour cells when you don't have access to the tumour itself. The challenge is to grow them and propagate them effectively outside the body. They could be a great avenue for testing new therapies.

Are drug companies starting to adopt ctDNA analyses?

There is a lot of interest from pharmaceutical companies, and liquid biopsies are beginning to be used as entry criteria for clinical trials. Companies are also interested in using liquid biopsies to monitor responses to therapy. If the analyses they do in their clinical trials are successful, companies may want to convert some of those tests into companion diagnostics. When they do, it is important for these diagnostic approaches to have the same rigour as the therapies. Like any approach, these liquid-biopsy genetic tests, and the regulatory framework guiding their use, won't be perfect. But we should not let the perfect become the enemy of the good. ■

INTERVIEW BY ERIC BENDER

Q&A Victor Velculescu Out for blood

Oncologist Victor Velculescu, co-director of cancer biology at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland, describes how circulating tumour DNA can be used to improve the detection and treatment of colorectal cancer.

What is circulating tumour DNA (ctDNA) and how might it help in cancer therapy?

In ctDNA, fragments of DNA that escape from tumours into the bloodstream provide genetic clues that help us to detect and analyse the disease. These clues are especially valuable when tissue biopsies are not available, both at the start of treatment and when monitoring patients as therapy progresses.

Is ctDNA research still mainly in the lab?

We are moving to clinical applications. One application is looking at late-stage cancers. In many cases, tissue analysis is difficult or impossible, so a blood-based biopsy could be very helpful. We have shown in colorectal cancer that a liquid-biopsy approach allows us to identify patients with amplification of the HER2/neu receptor — a target of the drug trastuzumab (Herceptin). A small percentage of people with colon cancer have dramatic amplification of HER2/neu, and there are ongoing clinical trials that will figure out if it is a good target in colon cancer, and whether it will provide a therapeutic option for these patients.

Are you also looking at monitoring patients' responses to treatment?

Many patients are in clinical trials for a long time, and it may not be obvious whether they are responding to the investigational agent. A liquid biopsy makes it possible to get a measure of tumour burden that very nicely tracks disease over time. Clinical trials are extraordinarily expensive, and often we have to wait until the end to see if the therapy has worked. Monitoring subjects over the course of the trial by using liquid biopsies could provide insight into therapeutic responses much more quickly.

Can these liquid biopsies help us to understand resistance to drug therapy, by picking up clues about new mutations?

Yes, they allow us to study drug resistance, which arises from genetic alterations that occur in the tumour over time as it responds to the evolutionary pressure of the therapy. For example, we looked at a person with colon cancer who initially responded to inhibition of a protein called epidermal growth factor