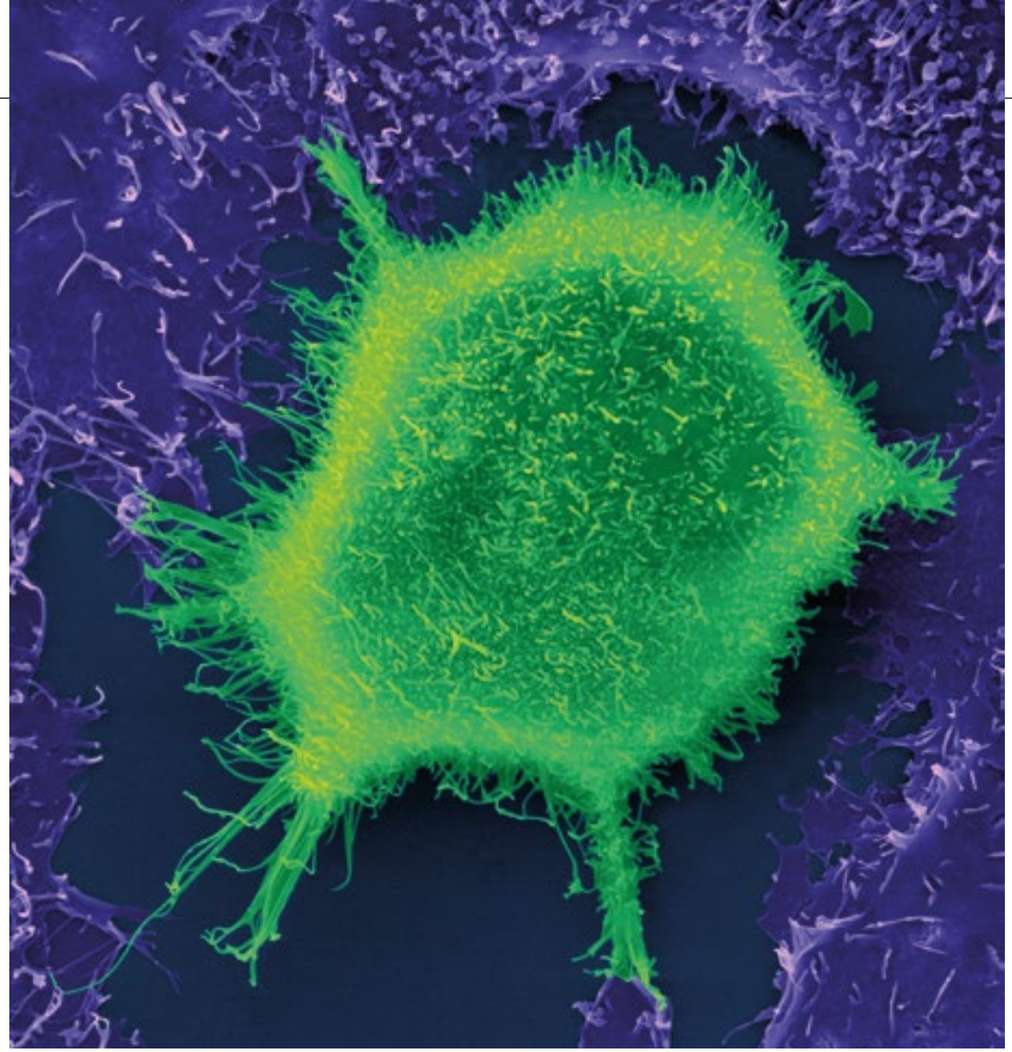
CAPTURING TUMOUR CELLS

Could new advances mean that blood tests may replace biopsies in cancer care? **Zhonglin Hao** explains his work.



Left. Human lung epithelial cancer cell among healthy epithelial cells, coloured scanning electron micrograph (SEM). Original magnification x600.

IMAGE: SCIENCE PHOTO LIBRARY

"Biopsy is the cornerstone of modern cancer care," says Zhonglin Hao, Associate Professor of Medicine at Georgia Cancer Center at the University of Augusta in the US. "However, biopsy is an invasive procedure, which can lead to complications, such as collapsed lung in the case of lung biopsy, for example."

Consider, then, an alternative to traditional biopsy: a way of extracting and examining cancer cells without needing to remove tissue from the body – by analysing a blood sample. That is what fascinates Zhonglin and drives his research, and it is known as liquid biopsy.

Zhonglin's most recent findings in this field were published in *Lab on a Chip* in August 2017. The research focused on capturing circulating tumour cells (CTCs), cells that have detached from the original site of the tumour and found their way into the blood. "Our aim was to recover them and then study them either immediately or after amplification *in vivo*," Zhonglin says.

This has been tried before with limited success. Some previous approaches had low throughput and low viability because they relied on using the cancer cells' surface markers to separate them out. But surface markers don't necessarily remain constant as cancer cells themselves are liable to change. Zhonglin and his collaborators' research relied instead on separating out cells based on cell size difference in biocompatible ferrofluids.

Again, this isn't the first time this technique has been tried, but Zhonglin found a way to do it efficiently through close collaboration with colleagues in chemistry, medicine, biochemistry and – crucially – engineering. They developed a laminar-flow microfluidic ferrohydrodynamic cell separation device that could enrich rare CTCs from patients' blood.

Zhonglin says: "Our paper describes a high-throughput method to separate and recover CTCs from as few as 10cc of patient blood. The throughput can process about 6ml of blood per hour with a recovery rate reaching 93%. And the cells recovered can be further cultured because they have excellent viability – more than 80%. This will provide good assurance of downstream applications, such as enabling culture and establishing tumours in animal models. And this will enable us to do further molecular analysis and drug sensitivity testing."

In terms of real-world applications for his results, he believes at the very least it should eventually improve the experience of cancer patients.

"I hope from this study to develop a very low-cost, easily-applicable-in-the-community system where we have a cancer patient on treatment, we draw a tube of blood a few weeks into treatment and, after we analyse the blood, we'll be able to tell the patient how they are responding to treatment," Zhonglin says. It should reduce the need for CT scans, which are costly – US$1,300 per scan in the US, he says – and carry some risk to the patient in terms of radiation exposure and complications relating to the use of contrast dye.

"Besides this monitoring," he says, "the overarching goal is to be able to culture the cells *in vivo* in a test tube or in petri dishes or in animals, so we can test them. A lot of tumours in the end become resistant to prior treatment – that's how cancer progresses. It could help us to pick out the drugs that will work for that patient."

The analysis specifically of CTCs is also a vital part of cancer research. "CTCs are cells that have detached from the original tumour sites and have got into the blood circulation," Zhonglin says. "They circulate until they reach a place that is friendly to their settling as a colony, where they will form metastatic foci. In late stages of cancer these are associated with treatment fatality and death. Therefore, studying the biology and finding out an effective way to prevent CTCs from settling down is very meaningful."

The next stage of Zhonglin's work in this area is to make the process even more efficient. "The next question we want to address is to further improve the throughput," he says. "We are also working on the downstream applications, and to amplify the tumour cells after we lure them out and capture them with the device so that we can further analyse using modern molecular analytic technology. We could potentially test them for drug sensitivity. In the next few years I anticipate some other device will be approved for general use by the Food and Drug Administration after a big-scale clinical trial probing CTC research's relevance at least in patient treatment efficacy monitoring."

Zhonglin hasn't spent his whole career in cancer research, although it is where he started out. Immediately after his masters he worked in a cancer research institute in China, where his focus was lung cancer.

He was also involved in introducing the first tissue of origin tests in the country. But when he first arrived in the US following his PhD in Japan, he helped to develop a contraceptive vaccine, a byproduct of which was a consumer fertility product that analyses sperm health. He realised, however, that his calling was cancer research and returned to that field via positions in universities in Georgia, before settling at the Georgia Cancer Center in Augusta, GA.

Neither is CTC research the main focus of Zhonglin's work. Liquid biopsy also includes cell-free DNA detection and amplification, another way of monitoring treatment efficacy. "I want to be in this area because the promise is so huge. In cancer research we have so many unknowns," he says. DNS

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ABOUT ZHONGLIN

- ✔ Born in China, first degree from Inner Mongolia Medical College then Masters in Medical Science at Tianjin Medical University
- ✔ Moved to Japan for five years to complete his PhD at the University of Tokyo. Was involved in cell cycle research following groundwork by Nobel prizewinners Paul Nurse and Tim Hunt
- ✔ 38 published papers; five currently being reviewed
- ✔ Some of the cancer research early in his career involved tumour analysis and required the use of synaptophysin protein from the adrenal glands of cows which he collected himself from a slaughterhouse in Tianjin, China.
- ✔ Plays table tennis and badminton; fluent in Mandarin Chinese (mother tongue), English and Japanese.