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Fighting cancer head-on

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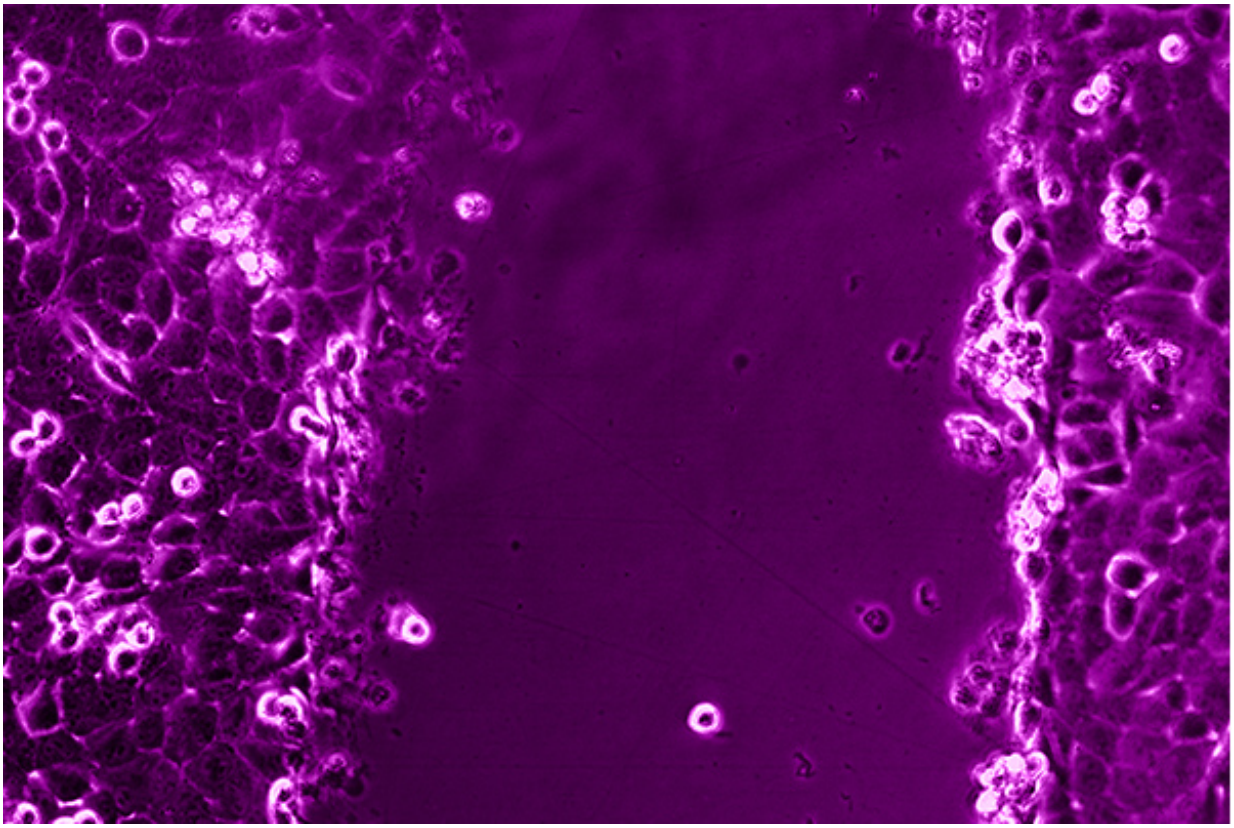

An in vitro scratch assay depicting the migration of head and neck cancer cells. Credit: Pamela Ajuya

Head and neck cancers are the sixth most common malignancies worldwide. Yet few are diagnosed before stage 3 or 4, when the cancer has already spread to the lymph nodes or beyond. New research is helping scientists better understand these cancers and pave the way for

therapies that could improve diagnosis and treatment.

Pain, swelling, a hoarse voice, bad breath; these are some of the common, yet often unknown, symptoms of head and neck cancers. Like many cancers though, symptoms depend on the area affected and when it comes to head and neck cancers that could be the mouth, lips, salivary glands, tongue, tonsils, middle ear, larynx, pharynx, sinus, or any other tissue in the head and neck region.

"We're focusing on this cancer because it has a really bad prognosis and on top of that it tends to be detected at the later stages," explains PhD student Pamela Ajuyah.

Ajuyah is part of the ncRNA Cancer group, run by Nham Tran in UTS's Centre for Health Technologies, which investigates head and neck cancers. For the last three-and-a-half years, Ajuyah's research has focused on small strands of ribonucleic acid (microRNAs) that are continuously created from the human genome.

"MicroRNA are the ultimate gene inhibitors," explains Ajuyah. "And cancer cells can take advantage of this situation. Cancer cells can hijack these microRNAs by suppressing their expression, which prevents their normal function. On the other hand, cancer cells can also increase the expression of specific microRNAs to promote cancer development. When this regulatory system is corrupted, cancers cells may acquire the ability to migrate and metastasis can occur."

"Think of it like a traffic light," says Tran. "The microRNAs are the colours in the traffic light and the cars represent the genes they control. So when the microRNA traffic light becomes red and the traffic stops, this is akin to gene suppression. Conversely, when it turns to green, traffic is allowed to continue and we have gene expression. These regulatory events, which occur daily in a cell, may lead to increased

migration."

And, adds Ajuyah, "When cancer cells have the ability to migrate, they can spread to different parts of the body. This metastasis is the main reason why people succumb to cancer."

The Tran laboratory has identified two microRNAs, known as miR-21 and miR-499, which they believe can promote migration in head and neck cancer cells.

Ajuyah's research has focused on investigating how they do this. Her work has also uncovered the involvement of a tumour suppressor gene known as PDCD4. "These two microRNAs target this gene so it can no longer suppress tumours," she explains. The result is cancer cell migration and metastasis.

For her research, Ajuyah has been comparing normal cells with those from stage 1 to stage 4 cancer patients. She then injects a synthetic version of the microRNAs (a mimic) into the samples. "And, over a period of 24 hours, we were able to show that if you added these microRNAs they would promote migration two-fold and give the cells a more metastatic potential.

"The next step," she says, "is to see if we can inhibit this migration, because that would give us a potential therapeutic. Can you reverse it? Can you stop these cells from metastasising?" Ajuyah plans to spend the last six months of her PhD testing her theory with inhibitors (chemically synthesised ribonucleic acid which stops or slows down the function of microRNAs).

"The idea is these inhibitors will bind to and soak up the microRNA and by doing that it stops the microRNA's normal function. This approach may stop the cells from acquiring a metastatic potential."

Currently, there are no routine screening tests for head and neck cancers, which can be caused by alcohol, tobacco and in some cases, the same subtypes of human papilloma virus that lead to cervical cancer. Ajuyah hopes her research will pave the way for a better understanding of the molecular pathways involved in the development of these cancers.

"These microRNAs are present in the body; everyone has them. In a healthy body they have a certain pattern, they have certain levels, and when things go wrong their levels change. If we can understand the fundamental role of these microRNAs and devise a method to regulate expression we could transform cancer treatment," explains Ajuyah.

However, she cautions, such applications are many years away. "The next part is actually the most difficult. How do you get the microRNA to go to where it needs to go, safely and stably?"

"Delivery is the main barrier in trying to treat human diseases with microRNAs," adds Tran. "One microRNA doesn't just regulate one target, it can regulate thousands of targets, which might have a normal function. So you can imagine, for example, if you give me a microRNA to treat my head and neck cancer it might suppress other genes. It may treat my head and neck cancer, but it might then cause other diseases we haven't even considered."

But it is a start. "The awareness for this kind of cancer is so little that people are almost not even aware that it exists," explains Ajuyah. It's a phenomenon the young scientist has seen first-hand.

Ajuyah's research is partially funded by the Translational Cancer Research Network (TCRN) – a Sydney-based cancer research community that works to translate cancer research into improvements in patient care. As part of their agreement, Ajuyah has met with two head and neck cancer patients.

"They were very interested in what we had to do," she says. "They wanted to know could this have made their lives easier? Could it potentially make other people's lives better?

"For the second lady in particular, getting cancer was quite a surprise because she lived a healthy lifestyle; she wasn't a big drinker, she didn't smoke tobacco.

"The first time she got it, she didn't realise what it was. She went to the dentist several times and he was like, 'Don't worry about it'. But it got worse and eventually she ended up having to go to hospital. At that point she had stage 1 head and neck cancer and they managed to successfully remove it. But it ended up coming back two more times."

Ajuyah says the physical repercussions can be devastating. "Head and neck cancers just eat you up. It affects your teeth, your face – anything that's involved in eating and talking. Patients need a lot of nutritional support because their mouth can be ruined. One of the ladies I met, when she talks she can only move her tongue so much. It's a really serious cancer and we need to do something about it."

Provided by University of Technology, Sydney