BIOSENSOR NEVER MISSES A TUMOUR

A new nanosensor developed by Twente and Wageningen will never miss a single tumour. That is a world first according to WUR Organic Chemistry PhD candidate Pepijn Beekman.

Beekman carefully holds out a Petri dish. In it are two ultrathin chips barely two centimetres wide. No, a photo is out of the question; experts would be able to get information from it, which is not the intention. This chip, the latest product to emerge from Beekman's start-up ECsens, is still a secret. But the sensor is capable of unprecedented things, says Beekman. The chip, a nanosensor, can detect tumour vesicles in the bloodstream, in principle with 100 per cent accuracy. In other words, it never misses a thing. It is looking for what the medical literature calls tumour-derived extracellular vesicles (tdEVs). Body cells are constantly secreting tiny sacs containing nucleic acids, for example, or proteins. They are a bit like parcels that cells use to communicate with one another.

SENSITIVE

Beekman uses those vesicles to detect the presence of cancer cells. That is possible because the surfaces of tumour vesicles contain a protein (epCAM) that is specific for cells that are not normally found in the blood. That makes them good markers for cancer. The sensor uses that protein to differentiate between tumour vesicles and vesicles secreted by other cells. And it turns out to have unprecedented sensitivity.

> **'The question is whether we can improve the chemistry so that it also works in blood plasma'**

'Single-vesicle detection is a world first,' Beekman concludes confidently. 'The data is less than a week old.' The chip that he shows is the follow-up to an earlier version that was announced last month by the University of Twente. Beekman works closely with his colleague at Twente and ECsens co-founder, Dilu Mathew. Twente is responsible for the sensor technology, Wageningen for the chemistry. That first nanosensor had a lower limit of detection (LLD) of 10 tumour vesicles per microlitre (millionth of a litre) of blood.

Beekman and Mathew's announcement of that biosensor made the cover of *Nano Letters*, a leading journal published by the American Chemical Society. 'We're very proud of that,' says the PhD candidate. 'But that sensitivity is not good enough for proper detection. The sensor needs to be at least 100 times more sensitive.' Which they have now managed. So fast? Beekman: 'The article in *Nano Letters* was based on data collected 18 months ago. We have been working further since then.'

NANOLAB ON A CHIP

First, a bit more on how the sensor works. It uses antibodies and electrochemistry. The antibodies make sure that tumour vesicles are selectively detected. An enzyme attached to the antibody then causes an electrical signal to be produced that can be measured. Beekman does not want to disclose much about the improvements they have made. 'We used electrochemistry to make sure the tumour particles gravitate spontaneously towards the detector. That is why you don't miss them anymore.'

The sensor is essentially a nanolab on a chip. The vesicles themselves are less than 100 nanometres across. The electrodes that detect the signal are spaced 120 nanometres apart. 'If you stare at your thumbnail for one minute, it will have grown 100 nanometres': this is Beekman's favourite comparison to show how high-tech the method is. A patent application has been submitted for the technique.

Last autumn, Beekman and Mathew won the 4TU Impact Challenge. That award will take the researchers and their company to the World Expo in Dubai early next year. In the meantime, they already have a quarter of a million euros in grants to perfect the sensor. That means testing it with real blood rather than material from cultivated cell lines. 'The question is whether we can improve the chemistry so that it also works in blood plasma. Plasma contains a lot of biomaterials that could disturb the signal.' **RK**

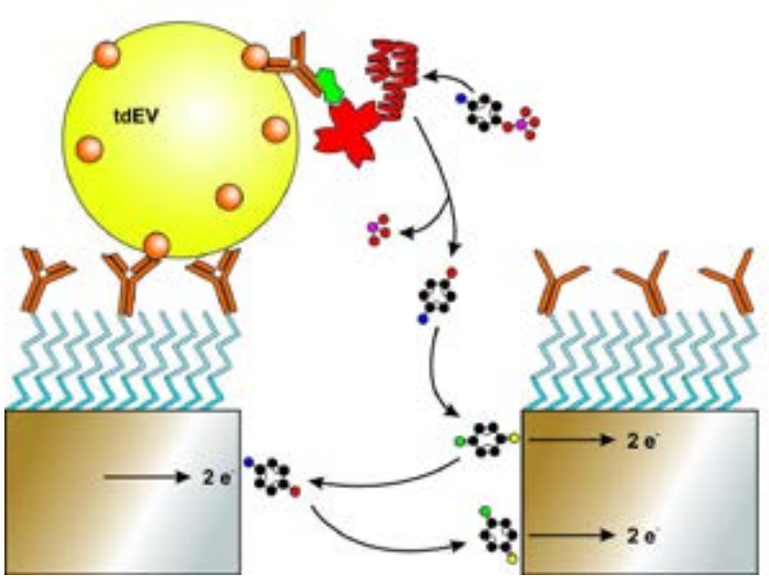

Diagram of the biosensor. Antibodies attached to the sensor (bottom) catch hold of the tumour vesicle (tdEV). Then an identical antibody with an enzyme on it also attaches itself to the vesicle. That enzyme activates a signal molecule (pAPP) by splitting off a phosphate group, causing an electrical signal to be produced between the sensor's electrodes. All the steps are shown here in a single drawing but take place sequentially.

CHLAMYDIA BACTERIA LIVE A LONELY LIFE IN THE ARCTIC OCEAN

Relatives of the *Chlamydia trachomatis* bacterium, which causes the sexually transmitted disease chlamydia, live deep in the Arctic Ocean without a host. This was discovered by an international team of scientists from universities including Wageningen and Uppsala. They published their results on 5 March in *Current Biology*.

Chlamydia bacteria infect not only humans but also koalas and microscopic organisms such as algae and plankton. For a long time, scientists thought chlamydia bacteria could not survive without a host of some sort, but the findings of professor of Microbiology Thijs Ettema's team have changed that. They identified several species of chlamydia bacteria in the Arctic Ocean that seem to survive independently, without a host.

UNDERWATER CASTLE

The team of international scientists discovered the chlamydia bacteria by chance on an expedition to Loki's Castle, a field of active hydrothermal vents in the Arctic Ocean between Iceland, Norway and Spitsbergen. Conditions there, at a depth of three kilometres, are extreme and what with the high pressure and the lack of oxygen, there is hardly any life. 'Finding the chlamydia bacteria in this environment was completely unexpected and we wonder what on earth they are doing there,' says Jennah Dharamshi, a researcher at Uppsala University. Given the large number of chlamydia bacteria in the area, the scientists think they have a big influence on the ecosystem.

EVOLUTION

The scientists took samples of sediments from the seabed in the area of Loki's Castle. Back in the lab, they studied the dna in those sediments, thus discovering the chlamydia bacterium's distant cousin. By comparing the genes of the newly discovered bacterial species with those of the one that causes chlamydia, the researchers gained new insights into how the chlamydia bacterium evolved into an invasive pathogen. Certain genes important for the host-dependent lifestyle turned out to be present in the distant cousin too, causing the researchers to suspect that the Arctic Ocean bacteria do not survived entirely independently. 'We think that they use nutrients from other micro-organisms in their habitat to survive and grow,' says Ettema.
The discovery of the chlamydia bacteria in a remote environment also suggests that they are probably found in other places around the world too, and have been overlooked by previous studies. 'Every time we explore a new environment, we discover micro-organisms that are new for science. That tells us how much there is still to be discovered,' says Ettema. **NvtWH**

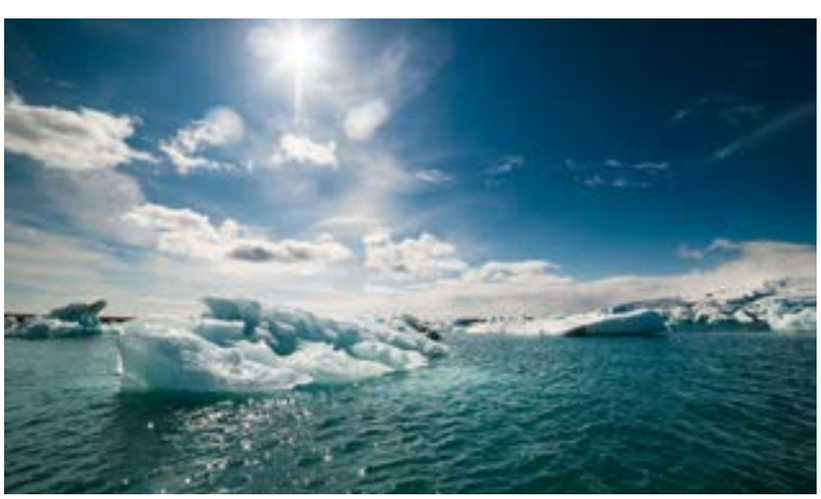

PHOTO: SHUTTERSTOCK.COM

VISION

Concerns about coronavirus

On 9 March, Hans Verhoef, an epidemiologist in the Human Nutrition and Health group at Wageningen, organized a debate in Impulse about COVID-19. 'I am concerned about hospitals' capacity.'

'I don't have all the data on the coronavirus but I am worried. The COVID-19 virus is spreading fast and we don't know how many Dutch people are infected but are not being picked up by the health service. That group can infect other people undetected. Secondly, I am concerned about hospitals' capacity. Dutch hospitals have 2000 intensive care beds, but is that enough in the event of an epidemic? Even now, they barely have enough coronavirus test kits and medical staff.'

This isn't like the flu?
'We don't know yet what the probability is of being infected by the coronavirus nor what the probability is of dying from it but all the evidence points to a virus that is more deadly than the flu virus we are familiar with. The population is vulnerable because it hasn't built up any immunity to this new virus and there is no vaccine as yet. There are also no medicines. What is more, patients remain infectious throughout the period of illness of two to three weeks, which is longer than for the usual flu virus. That lengthy period means the virus is transmitted more often and therefore spreads faster.'

But isn't the virus on its way out in China?
'That's true but that is thanks to the very rapid and stringent measures taken by the Chinese government from the start of the outbreak in December. China's achievement is amazing.'

What can we do?
'We need to be alert and make sure we don't help spread the virus. I am concerned for example about nursing homes with vulnerable old people and about people with chronic diseases such as diabetes and high blood pressure. Are we doing enough to protect them? Above all, we need to wash our hands much more thoroughly and much more often than we do now.' **AS**

If you have questions about the coronavirus and WUR, read the article on page 7 or check out the intranet.