New marker substance for cancer cells

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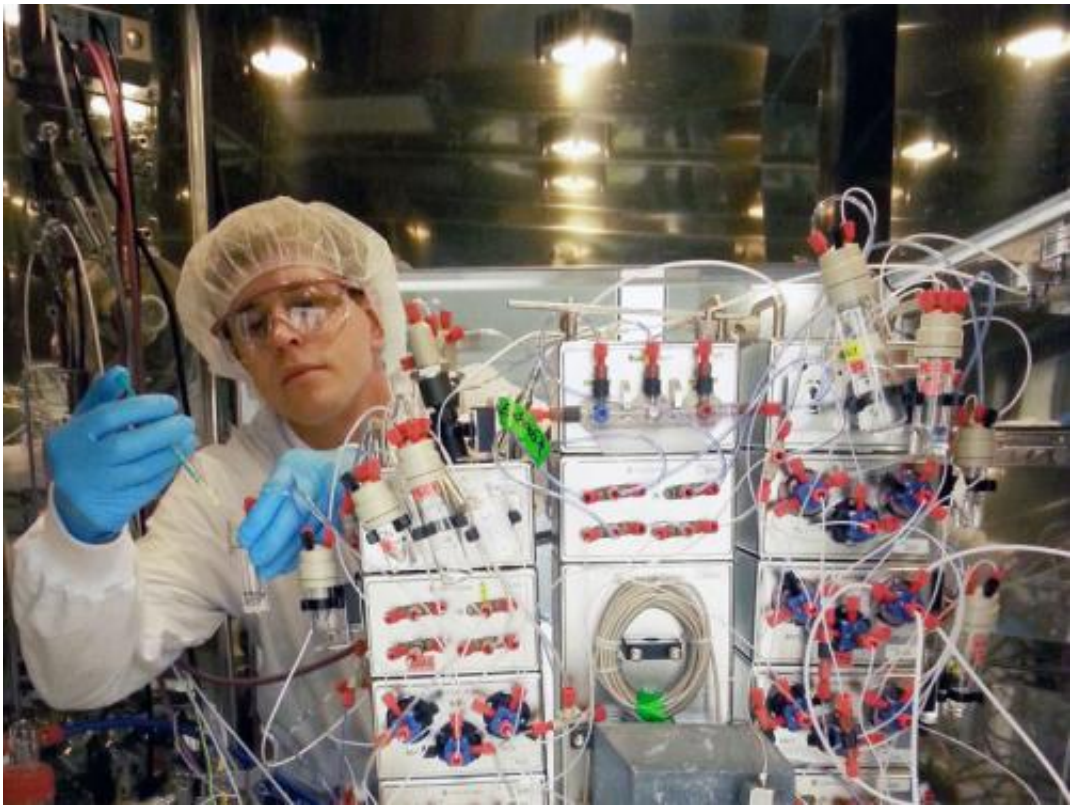

Postdoc Thomas Betzel preparing the synthesis of the newly developed folic acid PET tracer for use on cancer patients. Credit: Gloria Pla / ETH Zurich

Scientists from ETH Zurich have developed a new substance that enables certain tumour types to be rendered visible in high resolution using positron emission tomography. The so-called tracer has successfully been tested in mice. Now the researchers are planning clinical trials in humans.

Imaging techniques in cancer medicine provide far more than merely information on the scale and location of cancerous ulcers. There are modern methods that additionally characterise the tumour cells precisely, for instance by specific molecules they carry on their surface. Such additional information gives doctors key clues as to the precise cancer type and enables them to predict the probability that a patient will respond to a particular form of therapy.

Positron emission tomography (PET) is one such technique. Unlike with computed tomography or magnetic resonance imaging, PET does not render the body tissue visible, but rather radioactively marked molecules – known as tracers – inside the body, which are injected into the patient's bloodstream prior to the scan. Based on the lock-and-key principle, they adhere to certain molecules on the cell surface. Through the radioactive radiation, specifically cell tissue with these surface molecules is visible on the PET scan.

Researchers from ETH Zurich, the Paul Scherrer Institute and company Merck Millipore have now developed a new tracer for PET that binds to the folic acid receptor. This receptor is interesting because it accumulates on the cell surface in many cancer types. The PET scan provides information on the size and location of the tumour and the density of the folic acid receptors on the cell surface.

World's first clinical trial

The team of researchers headed by Simon Ametamey and Roger Schibli, both professors at the Institute of Pharmaceutical Sciences at ETH Zurich, have successfully tested their new substance in mice with cervical tumours. In a next step, the scientists now want to study whether the substance proves equally successful in humans. A pilot study on patients with ovarian, lung and intestinal cancer in several Swiss hospitals, including University Hospital Zurich, is in preparation. It will

be the first clinical trial on a folic acid receptor marker for PET on patients.

If the substance proves suitable, the scientists would like to use it to predict the efficacy of chemotherapy in the future. They primarily have a new generation of cancer medication in mind that also binds to the folic acid receptor, which then channels the drug into the cancer cells, where it unfolds its therapeutic effect.

Personalised medicine

"Our PET tracer provides important additional information for this targeted therapeutic approach with cytotoxic substances," says Ametamey. After all, one difficulty with the new form of therapy is that not in all patients the cancer cells carry the folic acid receptor. In the case of ovarian, cervical and brain tumours, it is nine out of ten patients, with lung cancer around three quarters and with breast cancer about half. In patients without the receptor, the novel chemotherapy is ineffective.

With the aid of the new technique, it could be possible to predict whether a patient will respond to such treatment. Patients whose tumours do not have any folic acid receptors could be spared this therapy and its side effects. Moreover, physicians can use the new PET tracer to better monitor the progress of the therapy and study whether the tumour is shrinking.

Making inflammations visible

However, the new PET tracer is not just interesting for cancer medicine, but also just the ticket for displaying inflammatory responses in the body. After all, the folic acid receptor occurs also at the surface of certain cells of the immune system, the macrophages, and only if these

are in a so-called activated state during an inflammatory response. The new marker substance could thus be used to display inflammatory diseases such as arteriosclerosis, arthritis or inflammatory bowel diseases with PET.

Moreover, a third area of application is also imaginable for the substance: medication development. "If we've got a method to detect chronic inflammatory responses in a non-invasive way, we can test the efficacy of anti-inflammatory medication more effectively," explains Schibli.

Only lab in Switzerland

The work with the radioactive PET marker substance poses special challenges in terms of lab infrastructure. ETH Zurich is home to the only lab in Switzerland to possess the facilities for the development of new radioactive substances and at the same time meet the demands to produce such substances for use in clinical trials on humans. The key is to manufacture the molecules at high purity levels and in sufficient amounts. PET tracers cannot be stored since the radioactive isotope Fluorine-18 used in the study degrades rapidly (it has a half-life of less than two hours). Consequently, the researchers developed a non-radioactive precursor molecule to which they can add the radioactive Fluorine-18 at the last minute. The end product has to be transported to the patient immediately after production and quality control.

More information: Betzel T, Müller C, Groehn V, Müller A, Reber J, Fischer CR, Krämer SD, Schibli R, Ametamey SM: Radiosynthesis and Preclinical Evaluation of 3'-Aza-2'-[18F]fluorofolic Acid: A Novel PET Radiotracer for Folate Receptor Targeting. *Bioconjugate Chemistry*, 2013, 24, 205-214. DOI: 10.1021/bc300483a

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