Cell marking opens up a window into the body, could reduce animal experiments

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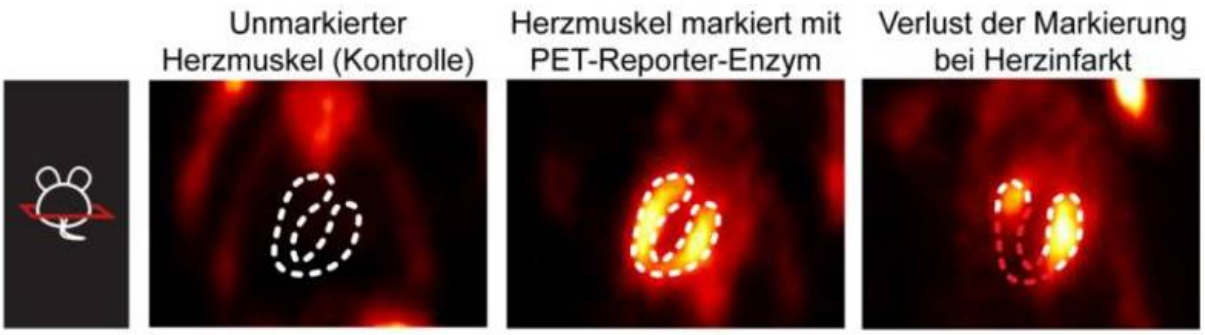

Credit: Robert Feil and Bernd Pichler / University of Tübingen

A new and particularly reliable method for marking cells can simplify research into diseases such as myocardial infarction, diabetes or Alzheimer's and reduce the use of test animals: Scientists from the University of Tübingen have developed a method by which they can target specific cell types in mice and monitor their behavior using positron emission tomography (PET). PET-based cell tracking allows scientists to observe complex life processes in the body without subjecting test animals to invasive methods.

"The ability to actively observe the behavior of selected cell populations in vivo without invasive methods opens up new avenues for research, detection and treatment of diseases. At the same time, it reduces the

burden and number of animals required in comparison to previous methods," explains Professor Robert Feil. Professor Feil and his team from the Interfaculty Institute of Biochemistry (IFIB) at the University of Tübingen conducted the study together with the Werner Siemens Imaging Center and the Departments of Cardiology, Pathology and Physiology at University Hospital Tübingen and researchers in Nuclear Medicine at the Münster University Hospital. Their results have now been published in the journal *Nature Communications*.

Tissues and organs consist of many different cell types, such as blood, bone, liver, muscle or nerve cells. The migration or change in the number of specific cell types is a normal process in the body, but is also linked to many diseases. For example, the proliferation and migration of immune cells leads to inflammation, uncontrolled cell growth triggers cancer or arteriosclerosis and the loss of certain cell populations is the cause of diabetes mellitus or Alzheimer's disease. These processes are based on complex interactions of different cell types. In order to understand them, the entire organism must be studied.

The new cell tracking method is based on an artificial PET reporter enzyme, which can be produced by a genetic trick in each cell type of the mouse (for example, only in T-cells of the immune system). The enzyme

Using a PET device, the marked cells become visible on the screen. Credit: Christoph Reichelt / Universität Tübingen

causes a radioactive substance, the PET tracer, to accumulate in these specific cells. The radiation is harmless to the animal and can be detected with a positron emission tomograph and shown on screen. The PET method has been used in humans for a long time and as a non-invasive procedure, it causes less burden than other diagnostic methods.

Until now investigating cell behavior in mice necessitated stressful or harmful procedures which are only suitable for a few cell types or may require the sacrifice of experimental animals. "By using modern imaging techniques, we can achieve a reduction in the number of test animals by up to 80 percent," says Dr. Martin Thunemann, first author of the study,

who is now researching at the University of California in San Diego. "The marked cell populations can be monitored non-invasively in living mice for many weeks, so that the same group of animals can be examined repeatedly." In the study, the authors marked blood platelets, myocardial cells, or T cells in experimental mice, and then followed their behavior in myocardial infarction or inflammatory reactions.

The newly developed imaging method can be used to represent any cell type and be combined with any disease model, as Feil explains. It is therefore suitable for many applications in biomedical research and the investigation of diseases. "Among many other applications, the non-invasive analysis of cardiac disease, diabetes, inflammation, tumor formation and metastasis is conceivable. In addition, the development of transplanted cells could be monitored in regenerative medicine. The technology is also interesting for the pharmaceutical industry for testing new drugs and treatment methods."

The research on PET-based cell tracking is relevant to the "Principles of animal protection and animal experiments at the University of Tübingen". In these principles, the university establishes rules and targets for the responsible handling of animal experiments and encourages research on new methods. Even though the alternatives have been substantially improved, life sciences cannot completely dispense with animal experiments in the foreseeable future. For research on the complex interaction of cells, tissues and organs in the whole organism, as well as new drugs and therapeutic strategies, animal experiments will continue to be necessary. Therefore, it is important to optimize the methods of investigation to reduce the burden and number of test animals. Procedures need to be developed that increase the quantity and quality of the data collected per animal and whose results can easily be transferred to humans.

More information: Martin Thunemann et al. Cre/lox-assisted non-

invasive in vivo tracking of specific cell populations by positron emission tomography, *Nature Communications* (2017). DOI: 10.1038/s41467-017-00482-y