PROTECTION OF LABORATORY ANIMALS

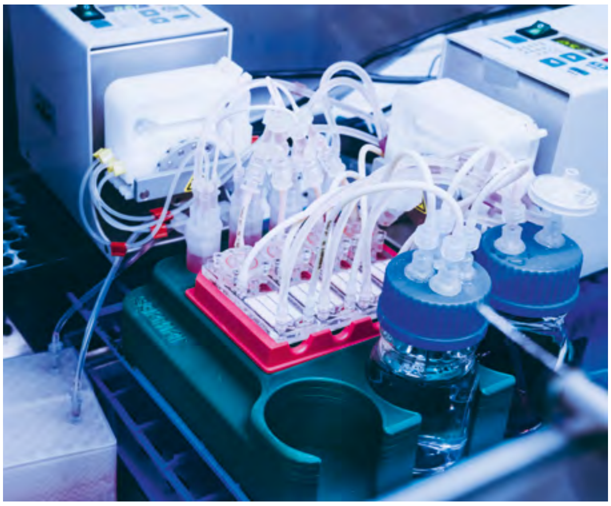
Bone on a chip

GERMAN CENTRE
FOR THE PROTECTION OF LABORATORY ANIMALS

BfR
Bundesinstitut für Risikobewertung

Miniature bones

Dr. Frank Schulze grows bone-forming cells on plastic chips. These "organoids", which are only a few millimetres in size, can help replace animal experiments.



Rows of vials containing reddish nutrient fluid, from which tubes lead to small pumps, plus measuring instruments, containers with nutrient solution and chips made of transparent plastic with round cavities. Each chip is about the size of a microscope slide. What looks like a small-scale biochemical factory is an experimental set-up for growing and researching bone tissue – a "bone-on-a-chip". The bone cells, which are supplied with liquid nutrition and oxygen, are kept in the cavities on the plastic chip, which are called culture chambers. Here they are carefully monitored, kept at the right temperature and provided with the exact conditions they are exposed to in humans.

A bone-on-a-chip? How does that fit together? And what is it all for? We are in the laboratory of biotechnology engineer Dr. Frank Schulze at the German Centre for the Protection of Laboratory Animals, which is part of the BfR at the Berlin-Marienfelde site. Schulze's miniature bone model was conceived and built by him and his team. The chip they designed was manufactured by a specialised company in Jena and the team produced other parts of the system themselves using a 3D printer. However, the technology to grow tiny organs – be it bones, liver, brain or kidneys – is uncharted territory that will need tinkering for further development.

No shoulder blade to order

However, we have to abandon the idea that a small shoulder blade or coccyx will grow on a semiconductor chip. The notion that it will soon be possible to grow an entire organ, whatever the size, is unrealistic. An organ-on-a-chip can only ever mimic structure and function in a very limited way. This is why it is also known as an organoid, which means organ-like structure.

Nonetheless, these models represent a big leap forward. While a conventional cell culture remains two-dimensional – the cells form a flat lawn in the Petri dish – the organoid is a three-dimensional structure. Research is flourishing worldwide, including that on bone organoids. Bone-on-a-chip – it sounds as if electronics and life, cells and semiconductors are connected here. That is not actually the case. After all, it is a chip made of plastic and not silicon. This design makes it easier to simulate and study the life processes in the organ. Frank Schulze's bone model aims to adapt the oxygen supply to natural conditions. Moreover, the cells are exposed to a fixed mechanical strain, as is the case in real life. The bone is "under pressure" and is exposed to stress in real life, too.

Bone tissue is very much alive. It has a strong blood supply, nerves and a variety of tasks. This is how bones enable movement. They protect the internal organs, are part the mineral metabolism and the place where blood is formed. Old bone material is constantly being broken down and new bone built up.

Donor cells from bone marrow

There are different types of cells that can be cultivated in bone organoids. Frank Schulze's "bone chips" are populated with osteoblasts. Their task is to produce osteoid – the soft basic substance for new bone – and then to mineralise it, in other words, to harden it. Schulze's team obtains the cells from a hospital in Berlin. They come from donors whose bone marrow has been taken during surgery. They are osteoblasts from adults, which only proliferate to a limited extent and have a limited lifespan. "For this, we have a wide genetic range and level of realism because of the different donors," explains Schulze. The team is working on keeping the cells alive as long as possible under realistic conditions. Precise control of the oxygen level is important. A lot of handiwork is needed to improve the model. "As an engineer, I love it," says Schulze. "Combining technology and biology is an exciting challenge."

Culture with a low germ count: the cells are monitored and grown by Frank Schulze and his team in a sterile workbench.

Bones atrophy in space

The principle of organoid systems is to simplify the complicated, to imitate an organ's variety of tasks in a simple system. For example, Schulze is interested in how bone reacts to mechanical stress. Generally speaking, training promotes bone formation, known as osteogenesis – but zero gravity conditions do not. Astronauts' bones waste away despite training. The bone chip can help to understand such processes.

Schulze sees future uses for the system that include testing chemical substances or potential drugs. Another topic is the wear and tear of implants, such as artificial hip joints, which react with the tissue and can lead to the implant becoming loose. "If the chip performs as intended, we can start the first substance tests this year," says the scientist. "We hope that this approach will provide a scientifically useful alternative to animal experiments." The advantage of the organoids is that they consist of human cells and, therefore, provide more realistic conditions in the organism. There's no doubt that big tasks await these little bones.

More information:

Schulze, F., M. R. Schneider. 2019. Hoffnung oder Humbug? Organ-on-a-chip in der biomedizinischen Forschung und als Alternative zum Tierversuch. Deutsches Tierärzteblatt (10) 67: 1,402-1,405 (in German)

Imprint
Extract from the BfR Science Magazine BfR2GO, Issue 1/2021, p. 40–42

Publisher: German Federal Institute for Risk Assessment
Edited by: BfR Press and Public Relations Unit
Photos: p. 03 picture Schulze: BfR/Sara Graetz, others: BfR/Norman Erytch
Layout: Studio GOOD, Berlin
Translation: Kern AG Sprachendienste, Frankfurt am Main

This text version is a translation of the original German text which is the only legally binding version.

BfR2GO 1/2021
ISSN 2567-8949 (Print)
ISSN 2567-8957 (Online)

BfR2GO is published twice a year.
Free subscription www.bfr.bund.de/en

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The German Centre for the Protection of Laboratory Animals at the BfR

The Centre combines the various areas of alternative method research on a national level in line with the 3R principle. The Centre coordinates activities all over Germany with the goals of restricting experiments with animals to a level which is absolutely necessary and affording laboratory animals the best possible protection. In addition, impetus is to be given to national and international research activities through the work of the Centre while encouraging scientific dialogue at the same time. The German Centre for the Protection of Laboratory Animals was established in 2015 in the course of the Animal Welfare Initiative of the Federal Ministry of Food and Agriculture. It is an integral component of the BfR which is subdivided into five areas of competence.

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BfR 2 GO
The Science Magazine of the German Federal Institute for Risk Assessment