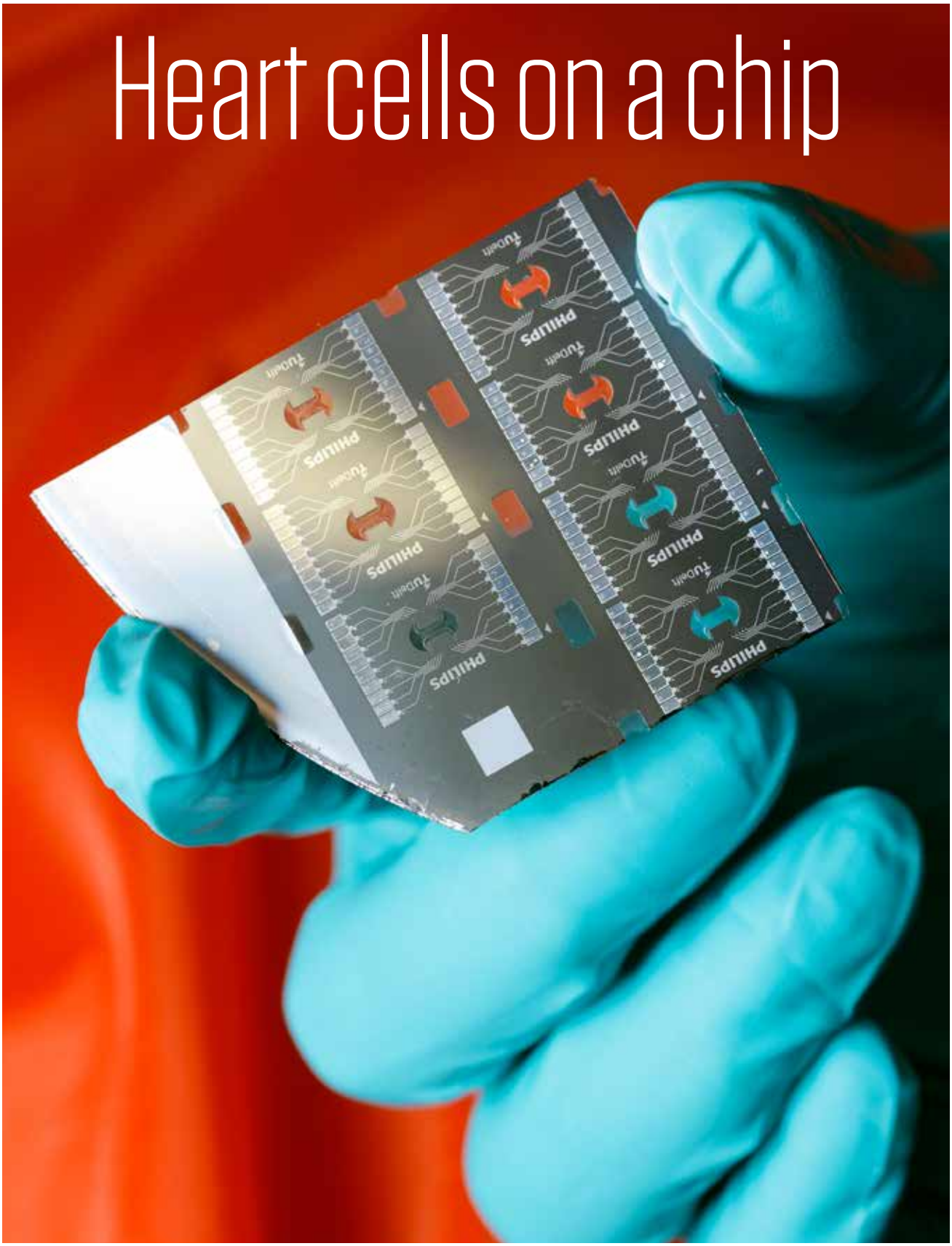
AUTHOR: TOMAS VAN DIJK
PHOTOS: SAM RENTMEESTER

Heart cells on a chip



Beating human heart cells are expected to give a significant boost to drug research. Researchers at TU Delft are working to develop such a chip: an electronically readable mini-organ.

It is a strange sight. At first glance, the invention of ir. Saeed Khoshfetrat Pakazad looks like the type of bone dogs gnaw on in cartoons and comics. It is tiny, however, only three millimetres in length, and it beats like a heart – literally. The PhD candidate plays a video clip showing human heart cells going up and down in a synchronised fashion. They form a thin layer of tissue on a rubber membrane shaped like a bone. In turn, the membrane is mounted on a silicon chip.

The tissue is attached to electrodes in dozens of places. With this miniature organ, all sides of which can be measured, Pakazad hopes to identify adverse side effects of drugs in an early stage. Drugs are regularly taken off the market after having been found to cause cardiac arrhythmia or even cardiac arrest in a few cases.

A thorough investigation of the side effects of new medication requires experimenting with living and beating human heart cells. This makes it possible to establish whether individuals with certain genetic traits are more sensitive to side effects than others. This is the idea behind the research programme on human organ and disease model technologies (HDMT). Pakazad's chip is the first tangible outcome of this project. Apart from TU Delft, project partners include Philips, the other two universities of technology, VU University and the universities of Utrecht and Leiden.

Euphoric

Pakazad conducted most of his work at Philips, under the supervision of Professor of Electronics ir. Ronald Dekker. Dekker also holds a part-time position in the faculty of Electrical Engineering, Mathematics and Computer Sciences. He conducted the experiments with heart cells in collaboration with the Leiden-based biotechnology company Pluriomics.

The high point of his research was when Pakazad recorded the first electrical signals from the heart cells. 'I was euphoric. I had temporarily transferred to the research group of stem cell biologist Christine Mummery at Utrecht University, to measure a special signal amplifier attached to my cells. After a long period of experimentation, a mini-electrocardiogram finally emerged from the computer. It showed the same pattern as the ECG of an actual heart.'

The next step will be to apply medication to the cells with a pipette to see how they react. If the shape of the electrical signals changes, this could indicate cardiotoxicity. Pakazad will no longer have time to do these tests. He defended his dissertation on 15 June.

'After a long period of experimentation, a mini-electrocardiogram emerged from the computer'

Professor of Micro-Electronics ir. Lina Sarro (EEMCS) will be continuing his work at TU Delft. 'We would like to further improve the readout of the electrical signals,' she notes. 'And we'll start developing a range of miniaturised sensors. Examples include sensors for measuring the force with which the cells contract and sensors for measuring the presence of certain ions. The more we can measure electronically, the easier it will be to analyse the data.'

Reliable measurements require replicating all of the forces to which heart cells are normally exposed as accurately as possible. A tiny pump underneath the cells inflates the membrane, causing the cells to rise, fall and stretch, just like in a real heart.

Stretchable wiring

It took considerable effort to create this chip. Pakazad built on research work done by Ronald Dekker and Nikolai Böker, whose 2009 graduation projects dealt with this topic and who had also developed a prototype. What the chip lacked was the stretchable wiring.

How can you build electrodes that can be stretched? 'In the past, researchers have experimented with liquid metal alloys for use as electrode material, with elastic conductors and electrodes in the form of flexible coils (much like telephone cords). None of these methods were suitable for mass production. This is a prerequisite, however. To get the attention of the pharmaceutical industry, you need to be able to produce hundreds of thousands of chips at a low price.'

Pakazad discovered that shaping the membrane like a bone creates zones that hardly stretch at all when the membrane is inflated. Because of the characteristic shape, forces are not distributed equally. Pakazad uses this to his advantage. He installed the largest electrodes in those areas that are hardly stretched.

Stem cell technology

Many research groups around the world are working on the replication of organs on chips. The fact that this research has taken off in recent years can be put down to three factors. First, the pharmaceutical field is reaching its limits. The drug industry does not have suitable models for studying the behaviour of organs. In addition, better polymers have been developed for cells >>

Saeed Khoshfetrat Pakazad: 'I am the first to create an electronically readable heart on a chip that is also able to stretch.'

Professor of Micro-electronics ir. Ronald Dekker has been working for years to develop chips containing beating heart cells.

Professor of Micro-electronics ir. Lina Sarro (EEMCS) will be continuing the work of doctoral candidate Pakazad at TU Delft. 'We would like to further improve the readout of the electrical signals.'

to thrive on. The most important factor, however, was the 2006 breakthrough in stem cell technology.
In that year, Shinya Yamanaka from Japan and John Gurdon from the UK developed the Induced Pluripotent Stem cell (IPS) technology, which is used to reshape specialised cells back into stem cells. Until that time, it had been quite difficult to obtain human cells for experiments. Specialised cells (e.g. heart cells, lung cells and neurons) have lost their ability to divide and, in theory, cannot be cultivated. With IPS technology, however, it is possible to take a piece of skin and reprogram the skin cells to become stem cells, which can then be grown into any desired type of body cell.
As a result, experiments with human tissue became easier to reproduce. It is now possible to conduct countless experiments with tissue from a single individual, with cells that are genetically identical. Ronald Dekker sums up the power of this technology in a few words. 'In the past, we would take a biopsy of a heart, conduct an experiment, and that was the end of it. It was possible to take a biopsy from someone else as well, but that would introduce genetic differences.'
The group that created the greatest stir with its mini-organs is the Wyss Institute at Harvard University. Several years ago, researchers at this facility replicated a type of lung. On one side of the membrane, they grew lung epithelium cells, while growing blood vessel endothelial cells on the other side. With this system, they investigated the effects of fine dust on the lungs, among other things.
'Those guys are pioneers,' says Pakazad. 'What they are doing is so impressive. But an electronically readable heart on a chip, and one that can stretch, they'd not been able to produce that,' he adds with a smile.

HDMT

The official kick-off for the collaborative partnership in human organ and disease model technologies took place on 16 March. The researchers had already been working together for years in a less formal partnership. After the official launch, it is hoped that the pharmaceutical industry will join efforts, thus bringing in additional money.
In addition to cardiac research, HDMT has two other research lines. Twente University and VU University in Amsterdam are at the forefront of blood-vessel research. They will attempt to replicate vessels on chips, after which they will conduct research on such topics as thrombosis and blood vessel infections. Biochemists at TU Eindhoven are hoping to cultivate cancer cells on a chip.