Organ network in transparent chip to study how cancer cells spread

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The recent development of the concept of organs on a chip opens the possibility of realistically studying human organs without the use of patients or animal testing. Professor Jaap den Toonder, who gave his inaugural lecture at TU/e on 20 June, even goes one step further: he intends to make microsystems in which multiple 'organs' are connected through 'blood vessels'. That will for example allow precise investigation of how cancer spreads. This could eventually make the development of medical drug much cheaper and faster. TU/e is starting a special microfabrication lab to develop the required technology.

Breast cancer usually spreads to the bone marrow, the brain or the lungs. But it is hard to follow exactly how this process works – it can't be observed directly in the human body. This is exactly the question that Jaap den Toonder, professor of Microsystems, wants to help answer, together with other Dutch institutes. Den Toonder has been involved right from the start in the development of organs on a chip, together with other researchers including Donald Ingber of the Wyss Institute at Harvard.

Metastasis

The TU/e professor is working to develop a microsystem in which different organs are represented as an 'organ on a chip', linked by a system of 'blood vessels'. The sample of breast tissue contains the primary tumor. Because the microsystem is fully transparent, researchers can see with high accuracy how and when the cancer cells spread, or metastasize, to the other organs.

Individual organs on a chip are tiny pieces of cultured live tissue with an artificial blood supply. The aim is to allow the tissue to be studied, for example to investigate how a disease develops or how tissue responds to medicines. However both disease and medicines often involve interaction between multiple organs. A typical example is the interaction between different medicines in the liver, through which substances are produced which could be toxic for other organs. This is the reason to move from one organ on a chip to microsystems with multiple organs. A microsystem typically measures several centimeters and contains a network of channels and microchambers with sizes varying from 1 to 100 micrometers.

No animal testing

Systems of this kind can help to achieve a big reduction in the cost of developing medical drugs. Testing is now often carried out on human cells in Petri dishes, but these do not provide a realistic natural environment. In addition, animal tests are carried out, but these often react differently from humans. In addition, in animal tests it is not possible to observe in real-time exactly what is happening. And the fact that a medicine does not work as expected is often not discovered until it is actually tested on humans, by which time a lot of costly work may already have been done. By using a microsystem with organs on a chip, researchers will in the near future be able to perform tests much more quickly and realistically, without the need to use animals or human test subjects. Den Toonder believes that the first applications will be ready for use within four to eight years.

The microsystems need to provide an environment as is present in the human body to ensure the validity of the test results, Den Toonder explains. The cell environment must for example produce the right bioactive signals, so cells display true (patho-)physiological behavior. Also, the deformation and rigidity of the environment are very important. "There are strong indications that increased rigidity of the environment can make cancer cells trigger to become invasive, which is the first phase of metastasis."

No costly cleanroom

To make the microsystems, Den Toonder uses a technique derived from semiconductor chip production: lithography. He refers to this as 'everyday lithography', because the smallest dimensions are much larger than those in the production of microchips. "Our smallest dimensions are 1 to 10 micrometers. At that scale you don't need a costly cleanroom, and we don't need to use smaller dimensions than that. The smallest scale at which we work is that of red blood cells and micro size blood vessels, and these are of the order of several micrometers." In addition, the fluid flow in such narrow vessels is by definition laminar, so it can easily be monitored.

TU/e will in the near future build a 'microfab lab' specially for the development of microsystems and research with these systems. The 700 square meter lab will be the best equipped facility of its kind in the Netherlands, and represents an investment of more than a million euros.

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