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DNA capture molecules wanted for cells

Artificial blood vessels made of special polymers are no longer a pipedream. However, one problem that needs to be solved is that the artificial vessels have to be compatible with tissue. One solution could be to dupe the body into thinking that the artificial vessels are real by coating their inside walls with the patient's own cells. Researchers from Reutlingen have developed a microfluidic chip that identifies molecules that can capture the required cells. These capture molecules then catch vascular precursor cells and attach them to the implant.

The team led by Britta Hagmeyer and Martin Stelzle at the NMI in Reutlingen has developed a microfluidic chip for cell-specific aptamers.
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"Blood clots can form when blood comes into contact with the artificial surfaces of implants," says physicist Martin Stelzle who heads up the research group Bio-Microelectromechanical Systems at the NMI Natural and Medical Sciences Institute at the University of Tübingen in Reutlingen. Stelzle's colleagues in Hans Peter Wendel's team in the Department of Thoracic and Cardiovascular Surgery at the University Hospital in Tübingen came up with the idea of coating the inner wall of artificial blood vessels with molecules that can capture certain stem cells in patients' blood. These cells then differentiate into endothelial cells and mask the artificial surface with a layer of the patient's own cells.

Short single-stranded nucleic acid molecules, so-called aptamers, are seen as promising cell catchers. They fold into specific three-dimensional structures that fit like a key into a particular "lock", for instance by binding specifically to cell surface molecules. "In contrast to antibodies, there are commercially available libraries with quadrillions (a one with 14 zeros) of different molecules that can be used and amplified with PCR," says Stelzle. However, when Wendel's team attempted to search the huge library to find the "needle in a haystack" that would bind to the desired cells, they hit a brick wall.

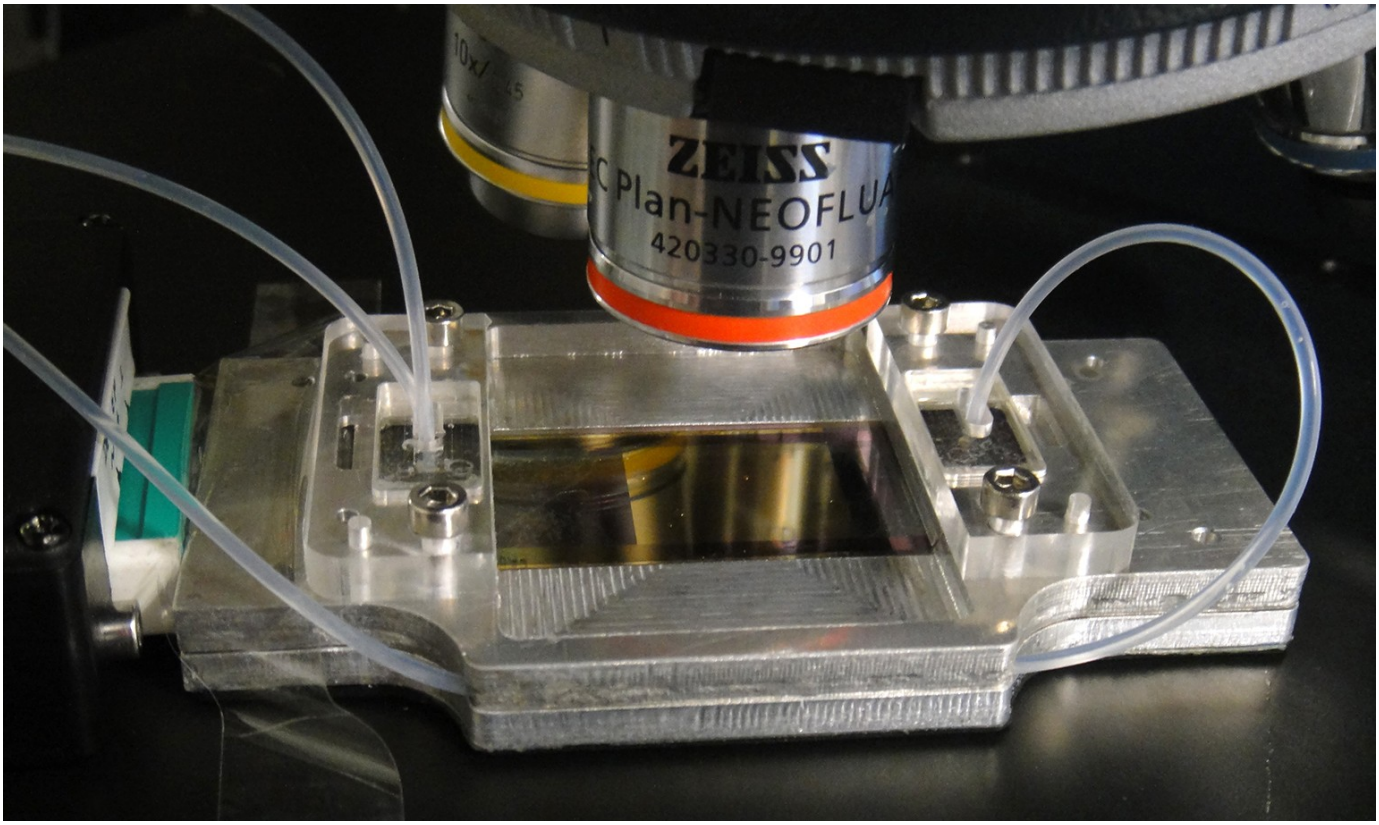
Living cells caught in the electrical field

The problem was that the aptamers that the researchers mixed with a cell preparation in order to

isolate the specifically binding ones, also bound non-specifically to dead cells. Enter Stelzle and his research team. In a cooperative project funded by the "Baden-Württemberg Molecular Bionics" programme, Stelzle's team developed a chip to capture living cells and to which aptamers then bind. "Ion pumps can only maintain different ion concentrations in the intra- and extracellular space in cells that are alive," says Stelzle.

The researchers from Reutlingen exploited this situation by inducing a dipole moment in the cells by way of an electric field. This involved displacing the positive and negative charges in relation to each other, which thus experienced a force in the electric field. By applying alternating voltage, the NMI researchers aligned the polarity of the cell charges according to pulses of the electrical field. Living cells therefore remain in the vicinity of the electrodes on the glass surface of the chip (7.5 x 2.5 cm) and the aptamer suspension can flow around them. Dead cells have a porous membrane, and so do not experience a force in the vicinity of the electrical field; they are washed away.

Breakthrough with the second approach



The researchers used fluorescence microscopes to observe how living cells spread inside the chip channels.

After unbound aptamers had been washed away, the researchers applied a DC field which pulled the negatively charged, weakly bound nucleic acids towards the positively charged electrode in the glass cover of the chip. The researchers then switched off the electrical field and washed the cells with the bound aptamers off the microfluidic chip. These aptamers were then amplified with PCR and used for further selection rounds or coating the implants. Stelzle's and Wendel's research groups have published their results in the journal Biomicrofluidics.

"The first approaches were very different from the one we use now; they were far more complex," says Britta Hagmeyer from the NMI. After nine months of sweat and tears, the researchers eventually discarded their original concept and came up with a new microfluidic chip design. Using

computer simulations, Hagmeyer has optimised the arrangement of the electrodes and the shape of the microfluidic chamber in which the cells are retained. The researchers have also tested a broad range of different materials. The best material must be able to effectively dissipate heat in order to protect cells against damage.

"It is difficult to foresee how a problem can be solved before a project has actually started," says Stelzle. However, the second approach eventually worked. A functional prototype consisting of chip, mount and electronic periphery, pump and control software was produced at the NMI. "The technology we have used in this project can also be used to separate cells, or in systems that are used to isolate rare cells such as circulating tumour cells," concludes Stelzle.

Article

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The article is part of the following dossiers

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