An intelligent system for the storage and controlled release of pharmaceutical substances

It is no longer a pipe dream – a sophisticated reservoir that sits under the skin and dispenses precise quantities of drugs locally and at a particular point in time now exists. What's more, it is also biocompatible. A junior research group from the University of Freiburg's BrainLinks-BrainTools excellence cluster led by Dr. Maria Asplund and her doctoral student Christian Böhler from the Department of Microsystems Engineering (IMTEK) has developed a small storage system made of organic-inorganic hybrid material that can be implanted and used for the controlled release of pharmaceutical substances. The system was developed in cooperation with a team led by Prof. Dr. Margit Zacharias at the IMTEK's Laboratory of Nanotechnology. The researchers hope that the system will be suitable for curbing the inflammatory reactions commonly associated with the implantation of electrodes for controlling prostheses. The system also has the potential to be used in numerous applications for tumour treatment.

A brain-machine interface can be used in many ways, for example helping paralysed patients to control a wheelchair, computer or prosthesis. Arm or leg prostheses are connected directly to existing nerves by way of implantable electrodes, a process that often leads to inflammatory reactions because the body identifies the electrodes and prostheses as foreign. As the inflammation progresses, the signal measured at the electrode gets worse and may be lost completely. If an anti-inflammatory drug could be released at the delicate interface, the system could be kept stable and frequent surgical interventions would therefore no longer be required. Christian Böhler, a doctoral student in a junior research group from the University of Freiburg's BrainLinks-BrainTools excellence cluster and the Department of Microsystems Engineering (IMTEK), came up with the idea of integrating a drug storage system into a multifunctional electrode.

20 times thinner than a strand of hair

Existing drug storage systems are less compact and cannot simultaneously and effectively control and store pharmaceutical substances. Many drug storage systems have drawbacks such as size, risk of infection or lack of controllability. The innovative storage system developed by the team from the University of Freiburg is a promising approach for overcoming the drawbacks of an implantable drug delivery system. The ingenious thing about the new system is that it is separated into two units, one for storage and one for controlled release of molecules. The biocompatible construct is made from hybrid materials and conducting polymers and, with its compact and minimalist architecture, enables simultaneous storage of molecules with different charges. The

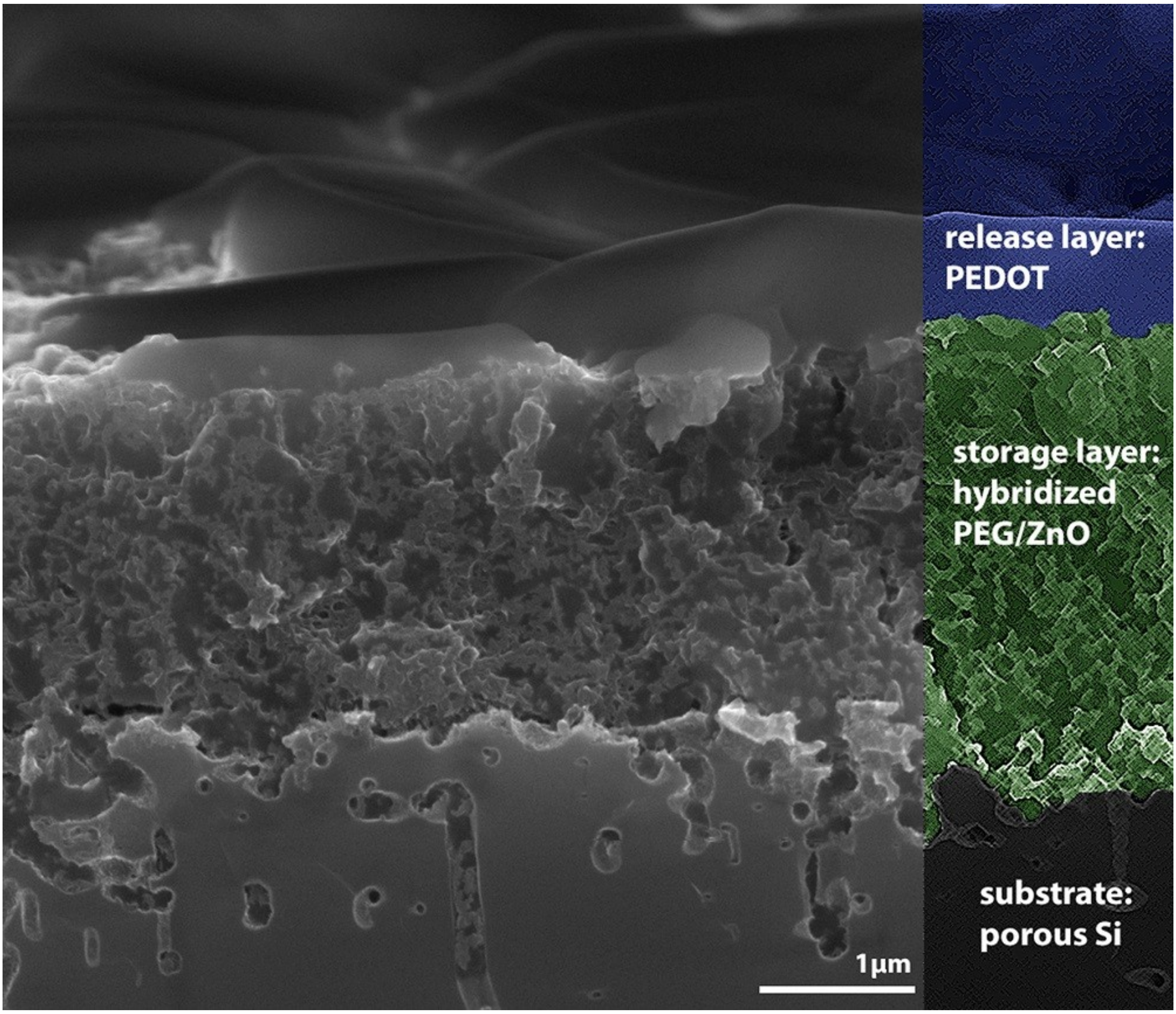
Doctoral student Christian Böhler hopes that the newly developed miniature pharmacy will help control inflammatory reactions associated with implanted electrodes.

miniature pharmacy consists of a storage layer made from organic-inorganic hybrid material, a mixture of polyethylene glycol (PEG) and zinc oxide, in which drugs can be stored. Above this is a release layer made from PEDOT, a conducting polymer that coats the hybrid material with a thin film and changes its pore size when the voltage changes. The system is like a net with holes that release the substance when electrical signals cause the holes to open. It is a layered system that is no more than five micrometres thick, a fraction of the diameter of a human hair. "We wanted to make the system as small and compact as possible, since we work with electrodes that will be implanted," says Böhler, explaining why size is an issue.

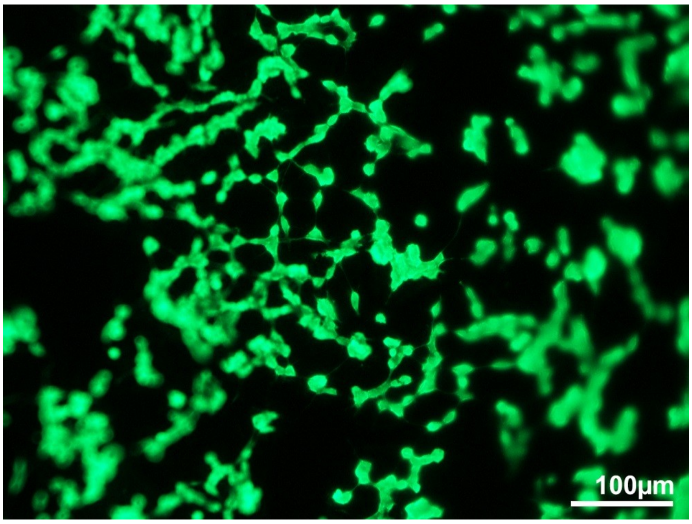
Using atomic layer deposition for producing the hybrid material

The process for producing the hybrid layer is called atomic layer deposition, and has long been used for coating materials. This technique uses diethylzinc and deionised water vapour gases, which are applied alternately to the liquid PEG surface at high temperatures in a vacuum chamber. The gases penetrate into the molecular structure of the material and solidify the plastic layer from the inside as PEG reacts with zinc oxide, resulting in an organic-inorganic compound. The desired bioactive substances (e.g. drugs) are already incorporated into PEG. As they are dispersed in the solidifying layer, any number of substances and different charged and uncharged molecules can be stored in the same matrix. This process is repeated 150 times in order to ensure complete conversion of the synthetic material from a liquid into a solid state. This produces an inorganic matrix that surrounds the organic polymer like a cage. Böhler says it is unlikely to cause irritations because non-toxic materials are used. "PEG and zinc oxide are two biocompatible substances that are already used in medical drug preparations and industry. They can be implanted into the body without causing any adverse reactions," he says.

Modulation of porosity



The individual layers of the drug reservoir can be discerned under a scanning electron microcope: the outer release/control layer (blue, PEDOT), below it, the storage layer consisting of hybridised PEG/ZnO (green), and all this is placed on a porous silicon (porous si) carrier layer.



The hybrid storage layer is coated with a conducting PEDOT polymer film in order to enable controlled release of the drugs. This release/control layer is used for precision delivery of a desired compound into the body. In addition to passive diffusion, the permeability of the layer can be actively modulated by applying electric charge. PEDOT consists of a positively charged matrix to which negative ions are attached. The matrix expands or contracts depending on the charge applied. When a positive charge is applied, the pores become smaller and retain the molecules.

Neuroblastoma cells that grow in the PEDOT surface take up the model substance fluorescein and start to illuminate under UV light.

When a negative charge is applied, the pores enlarge and the molecules can pass through. The researchers used fluorescein, a compound that is widely used as a fluorescent tracer in proof-of-concept experiments, to find out whether the multilayered system exhibits ideal properties for dispensing precise doses of molecules. They demonstrated that the molecules can be electrostatically funneled through the membrane or retained. Since fluorescein is similar in size and charge to anti-inflammatory drugs, the compound is an excellent model substance for this purpose. In a direct contact test in neuroblastoma cell cultures, the researchers have shown that the PEDOT surface is suitable as culture substrate. The cells were viable, spread across the entire pore surface and formed networks. “We were able to prove that the cells took up fluorescein because they started to illuminate when exposed to UV light,” says Böhler.

Anti-inflammatory agents, tumour therapy and lab-on-a-chip applications

Böhler and the team led by Asplund have already received a great deal of feedback on their miniature pharmacy. The next step will be to work with clinical partners to test the clinical application of the system. For example, to use the storage device in cancer therapy for releasing drugs directly onto a tumour from a reservoir under the skin at a particular point over a particular period of time. The technology would also be useful for so-called lab-on-a-chip methods which combine analysis and exchange of analytes in a very small space. “An analyte, blood and urine for example, will flow past chambers from which stored test molecules can be released in a controlled manner, and then produce signals,” says Böhler. However, his favourite application is clearly brain-machine-interfaces. Böhler would like to develop an electrode that connects nerves and prosthesis and can be kept stable for as long as possible, thus preventing inflammatory reactions.

Article

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Further information

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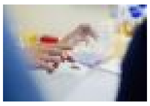

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