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Taking a drug taxi across the blood-brain barrier

The central nervous system (CNS), which integrates the information it receives from all parts of the body, is perhaps the most sensitive organ we have. As toxic compounds are able to disturb brain function enormously, the brain is separated from circulating blood by a highly selective permeability barrier known as the blood-brain barrier. However, the downside of this protection is that 98 percent of all drugs targeting the CNS cannot pass the barrier. Junior professor Dr. Winfried Römer from the BIOSS Centre for Biological Signalling Studies at the University of Freiburg is studying cellular transport mechanisms for their ability to transport drugs across the blood-brain barrier in a non-invasive way. The project is funded by the Baden-Württemberg Junior Professor Programme for a period of three years. Junior-Prof. Dr. Winfried Römer is seeking to transgress the blood-brain barrier.

All land vertebrates possess a physiological barrier between the circulating blood and the central nervous system designed to control homeostasis, i.e. the exchanges between the blood and the brain. This barrier is known as the blood-brain barrier. The blood-brain barrier is formed by endothelial cells which line all blood vessels that supply the brain with nutrients and oxygen. Endothelial cells are sealed together by tight junctions, thus forming a virtually impermeable barrier. Astrocytes and pericytes also contribute to the tightness of the highly selective filter. While oxygen can pass freely into the brain, most larger molecules need to be actively transported from the blood into the brain. The blood-brain barrier prevents pathogens, toxins and pollutants from reaching the central nervous system, but also prevents many drugs from reaching the brain.

Concepts to overcome the blood-brain barrier are an active field of research, in which Dr. Winfried Römer from the BIOSS cluster of excellence at the University of Freiburg is involved. "The blood-brain barrier is like a border where customs officers, i.e. P-glycoproteins, only allow specific substances to pass through whilst preventing others from crossing. In fact, P-glycoproteins are membrane proteins that actively transport toxic substances out of cells. Very few non-invasive methods targeting the blood-brain barrier are currently available," said Römer.

Pathogens as model

Junior Prof. Dr. Winfried Römer is seeking to transgress the blood-brain barrier.
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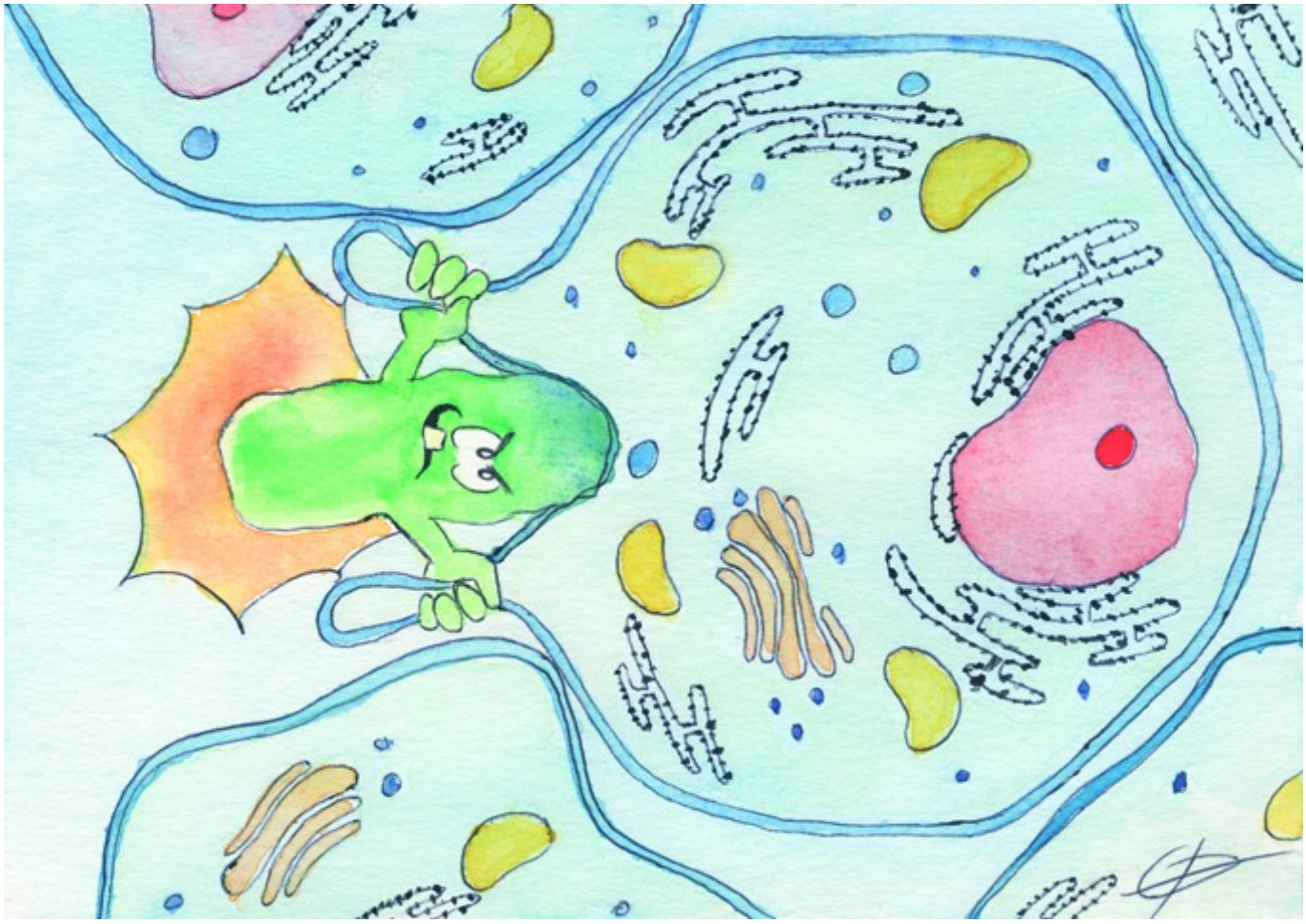
At present, the only clinical methods that can transport drugs into the brain are relatively harsh. Römer is hoping to find methods that are less invasive than needles, which are in standard use for injecting drugs into the brain, and he is particularly focused on exploiting the body's own transport mechanisms to overcome the selectivity of the blood-brain barrier. However, it will take a lot of basic research before this objective can become reality. "First, we need to obtain insights into how to overcome endothelial cells," says Römer highlighting the complexity of the mechanisms he has to deal with.

Römer and his team are studying how viruses and bacteria manage to enter cells, which is the first step in a long process. "The nice thing about pathogens is that we know that all they want to do is to invade cells and infect them," said the biologist. Pathogens use different strategies to enter host cells, one particular strategy is to use the host cells' endocytotic processes for their own purposes. Bacteria produce lectins, carbohydrate-binding substances that can attach to cells. They use these lectins to attach to a host cell's extracellular receptors that expose carbohydrate moieties. This interaction is a highly specific process that follows the typical lock-and-key model. Extracellular receptors differ in their carbohydrate moieties, which affects the interaction with lectin. Slight changes in the glycoproteins' three-dimensional structure reduce the lectin's affinity, preventing it



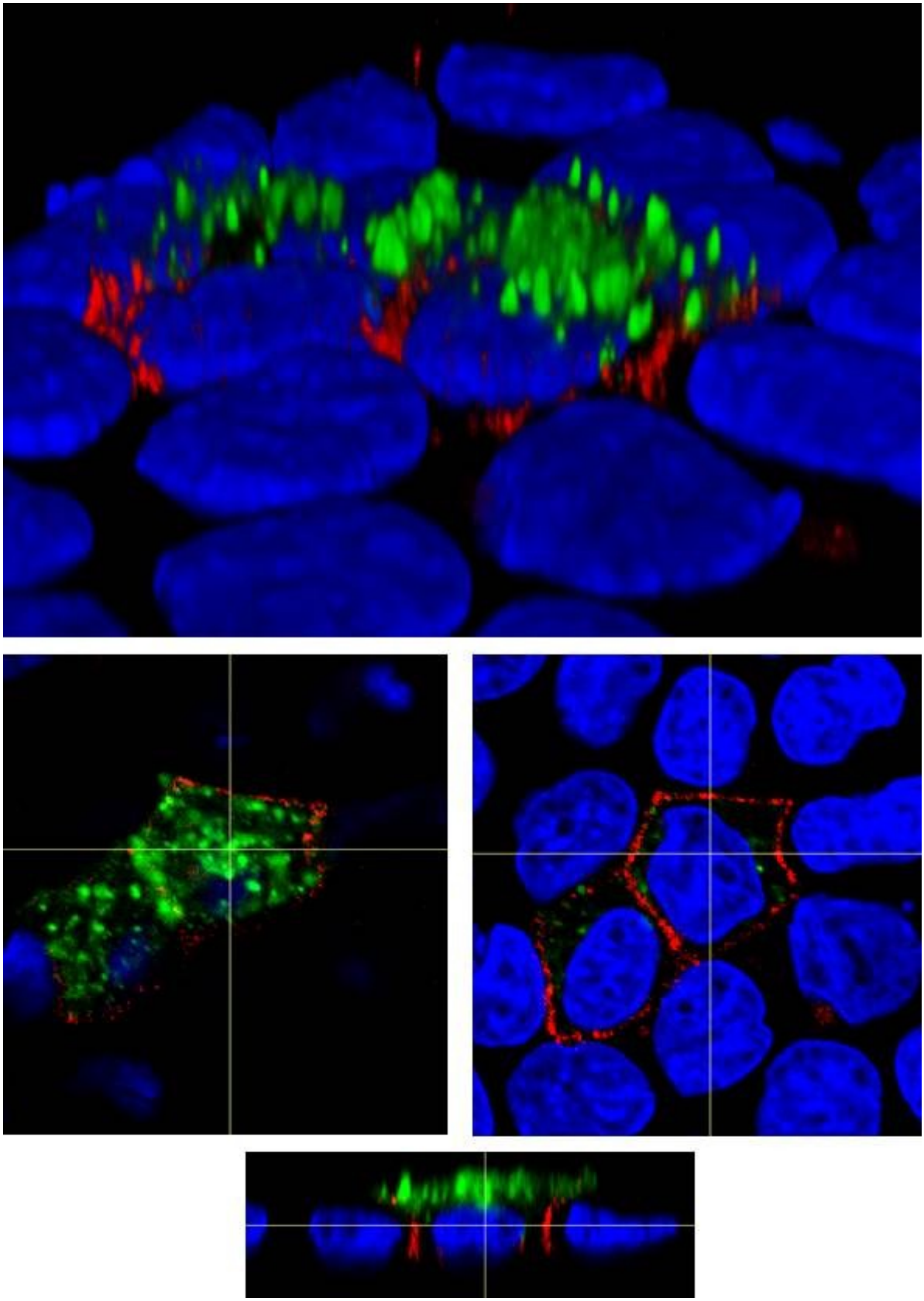
Bacteria provide important insights into how they are able to pass through the cell membrane.

from attaching to the receptor. The successful attachment of bacteria to the host cell membrane induces the invagination of the plasma membrane and internalisation of the pathogen by way of a vesicle that is pinched off.

The Trojan drug horse

Römer and his team are studying these cellular glycoreceptors and the ability of bacterial lectins to attach to them. The researchers hypothesise that specific lectins (i.e. ligands that are recognised by the human body) can be used as "keys" for unlocking the cellular "locks". The next step is even more complicated. The aim is to induce receptor-mediated transcytosis, a process during which a vesicle is formed and transported to the other side of the cell into the brain. However, this process is not yet known in detail. "We are looking for means of transport that enable us to draw substances across the cell," said Römer. He hopes to find out how this works. He is also hoping to use the resulting knowledge to equip the ligand with a kind of a backpack containing pharmaceutical substances that are released by cerebral enzymes once they have reached the brain.

Römer and his team are currently searching for receptors and ligands that would be suitable for the process of receptor-mediated transcytosis. Römer uses MDCK (Madine Darby canine kidney) cells, canine epithelial cells used for in vitro cell permeability studies. He remains fairly optimistic as he has already discovered that certain membrane constituents of polarised cells carry out transcytosis. He wants to use the lectins to identify suitable receptors on the cell membrane, but does not wish to disclose any more about these membrane constituents at present. Little is yet known as to what role these molecules play. They are known to be involved in cell adhesion and interaction and to be vital



Transport of lectin across MDCK cells. Blue: nuclei, green: lectin on apical cell side, red: lectin that has been transported to the basolateral side of the cell.

for the organism, but not for individual cells. Römer and his team have already tested a few ligand taxis and have been able to show that they are suitable for transporting things. However, the researchers do not yet know whether the taxis emerge on the other side of the cell and which receptors are involved.

Strengths and weakness of artificial ingestion

However, it is known that the bacterial lectins attach highly specifically to the receptors, enter the cell and induce – in close cooperation with the host cell – different signalling pathways. The process of receptor-induced transcytosis requires the receptor to be recognised and the receptor to actually induce transcytosis. Römer needs to ensure that the receptor is not digested by cellular lysosomes, but is instead passed through the cell along with ligand and valuable cargo. This seems to be a rather difficult task. "If we are lucky, one out of ten ligands will pass through the cell along with its receptor. This is what I would call a successful project," Römer said.

However, another challenge already awaits Römer on the brain side where specific enzymes are required in order to release the drug from the taxi and convert it into its active form. If all this works, an effective non-invasive tool for transporting drugs across the blood-brain barrier would then be available. As this approach exploits the body's own transport mechanisms, no adverse effects are expected. However, the drug might become heavily diluted on its way from one side of the cell to the other and not reach the brain with sufficient therapeutic concentration.

If the approach works, it could be used for transporting topoisomerase inhibitors for the treatment of small brain tumours that cannot be surgically removed. Topoisomerase inhibitors lead to the arrest of cell division and hence also cell death. Römer's investigations do not yet involve drugs. "We first need to solve all other problems before we can decide which cargo we want to put into the backpack," said Römer. The first tests will most likely be carried out when the project is into its third year.

Further information:

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