We think of the cornea as a windscreen for the eye. But this transparent layer of tissue is far more complex than a simple protective covering. Stefan Schrader and Sonja Mertsch are pursuing new approaches to treating diseases of the ocular surface.

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Mertsch has already developed a procedure that makes these cells grow into thin layers or “sheets”. The advantage of these so-called “cell sheets” is that they resemble natural corneal tissue, much more closely than the biomaterials currently in use.

Unusually high numbers of nerve cells

After just three weeks the cell sheets are around forty micrometres thick, that is four hundredths of a millimetre, and after one year they grow to a thickness of approximately 150 micrometres. In the future, patients could potentially have their own fibroblasts removed to make tissue for corneal reconstruction. “This would minimise the risk of rejection,” Schrader says. Tests have produced positive results so far: the new material is extremely transparent, strong enough to withstand an operation, and corneal cells have no problem growing on it. The team’s current objective is to use growth factors – special molecules that stimulate cellular growth and proliferation – to reduce the time the tissue needs to reach the desired level of thickness to about three months.

Whether or not a transplant using artificial or donor tissue succeeds also depends on the nerve cells in the eye: “The cornea has an unusually high number of nerve cells,” Schrader explains. We only become aware of the functionality of these neurons when, say, we get a fly in our eye when cycling. We immediately feel a burning pain. The eyelid closes and lacrimal fluid shoots into the eye. “The nerve cells trigger a blinking reflex to keep the ocular surface intact. They also control secretion of the lacrimal glands and other glands which moisten the eye surface,” the researcher explains.

After a corneal transplant, the nerve cells grow into the new tissue again, but even twenty years later their numbers still won’t reach the original levels in many patients, Mertsch says. The problem here is the close interaction between nerve cells and corneal cells. If the nerve cells are not working properly, the cells on the surface of the cornea will atrophy. In the worst case they will die, and this can result in further damage to the eye surface. Herpes infections, laser operations on the cornea, brain tumours and diseases like diabetes or multiple sclerosis can also negatively impact nerve function to such a degree that the outer layer of the cornea is damaged. “This is why we are trying to find drugs that stimulate nerve growth in the cornea,” Mertsch explains.

To do this the researchers need a proper model of the corneal tissue. After years of research the neurobiologist has succeeded in reproducing the tissue in the lab – using as a basis the collagen gel that gave such good results as a wound bandage. To this base all the main cell types from the various layers of the cornea are added. “We have combined all the individual components into a unified structure and this has given us a model of the cornea as a whole,” Mertsch says. The trickiest part was to get the nerve cells to grow in the lab. Using state-of-the-art molecular biological methods, the researchers are now studying which drugs influence nerve growth and which metabolic processes play a key role. They have already tracked down a number of interesting substances, the neurobiologist says.

To test the effectiveness of these substances the team is conducting various experiments, some of them on mice. Here the researchers operate the mice cornea just as they do for a human corneal transplant, and follow up with a four-week course of eye drops. “Through these tests we have identified an active substance that is particularly effective in stimulating regeneration in damaged nerves,” Mertsch says. “This substance has already been approved as a drug for another eye disease. This is a lucky break for us because it means we will soon be able to start performing patient studies,” Mertsch adds.

In the search for new treatment methods the scientists contemplate the so-called “cell sheets” as a new biomaterial for the cornea. In the Wechloy lab they produce this artificial tissue, analyse its function and structure, and test drugs.

But here, too, the neurobiologists have come up with some promising approaches.

**Stem cells for the lacrimal gland**

The researchers are using mesenchymal stem cells, for instance. These cells are found in the bone marrow or fatty tissue of human adults and, like embryonic stem cells, they can divide and transform into other cell types. Jana Dietrich, a doctoral student in the lab for experimental ophthalmology, has already shown in her doctoral thesis that these stem cells have a therapeutic effect on the damaged lacrimal gland in mice. To verify these results the researchers now plan to work with human mesenchymal stem cells. They are able to get these cells from a stem cell bank.

Alongside the work with stem cells, the researchers are trying to replace the lacrimal gland with artificial tissue, as they did with the cornea. As a scaffold for their experiments they are using sections of pig intestines from which all animal cells have been removed. The idea is to grow human cells on it in a special bioreactor. The researchers have already succeeded in delivering a constant supply of nutrients to the constructs in the bioreactor under special cultivation conditions, similar to what takes place in the body via the blood vessels. This cultivation ensures that the lacrimal gland cells grow on the construct in several layers and are functionally active. “That was a major breakthrough,” Mertsch says. “The new tissue even produced a form of lacrimal fluid.” One challenge the researchers have yet to overcome, however, is the different conditions for growth which the many different types of cells of the lacrimal gland require. But these are not the only reasons why an artificial organ is still a distant goal: porcine intestinal tissue is simply too large to provide a good basis for a human lacrimal gland. Moreover, an artificial gland would need to be connected to nerves that control tissue activity. “This is definitely a long-term project,” Mertsch emphasizes. But the researchers are optimistic. In their new laboratory site Sonja Mertsch and Stefan Schrader have everything they need to work on their many research questions. And they are clearly focused on their objective: to help and maintain vision in patients for whom conventional corneal transplants are out of the question.