Microrobots: 21st century eye surgeons

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Vision is perceived to be the most important human sense. For people, this is the main tool for learning because we use it to get 80% of the information we need. However, over time, vision deteriorates or is lost due to age-related, genetic or unpredictable factors such as trauma. Therefore, it is very important for us to have technologies for effective treatment of diseases that lead to vision loss. This article introduces the reader to a new and promising method of treating eye pathologies using microrobots.

How important is the vision?

In total, humans have five recognized senses: sight, hearing, smell, touch and taste. All of them have sensors with a common function: collecting signals from the external environment and converting them into human-readable information. But are they all equally important?

In a survey conducted in 2019, participants were asked to imagine losing one of their senses. The vast majority of people claimed that losing vision would be the scariest for them (74%).

In another experiment, scientists evaluated the area of the cortex that is involved in the processing of visual information. It turned out that vision accounts for more than 50% of the entire area of the cortex and only a small part of the tactile (11%) and auditory (3%) processing.

But despite the fact that vision is the most important sense, no one is safe from losing it.

What are the pathologies of vision and their causes?

In 2013, 12 research centres around the world joined together to make a systematic analysis of data on the causes of blindness. They evaluated all available cases in 1990 and 2010 and found that the leading diseases of vision loss were cataract (in 1990: 39% and in 2010: 33%), uncorrected refractive error (20% and 21% in 1990 and 2010, respectively) and macular degeneration (5% and 7% in 1990 and 2010, respectively). Many of them are associated with retinal disorders.

The main cause of these diseases is age. People over the age of 75 have been shown to have a very high risk of blindness.

The second highest risk factor is genetics. Researchers have demonstrated that the presence of cataracts in childhood is associated with the presence of chromosomal abnormalities or gene rearrangements, such as Down syndrome or myotonic dystrophy. Therefore, it is extremely important to have effective ways to treat such diseases.

What are the treatments for blindness?

Most diseases that lead to blindness are associated with retinal disorders. This light-sensitive layer is located in the back of the eye, making it much more difficult to treat with therapies than the front area. Current strategies for treating such pathologies include topical administration of drugs, intravitreal injections (inside the vitreous body of the eye) and laser surgery (Figure 1). The effectiveness of externally administered drops or ointments in the eye is very low due to their rapid release together with lacrimal fluids. Another obstacle to drug delivery in this way is the retina–blood barrier that prevents drugs from entering. The use of intravitreal injections has more advantages over conventional drops since most of the drug reaches the retina. But regular doses lead to patient discomfort and side effects in the form of infections or retinal detachment.

Laser surgery is the third type of retinal therapy. Its essence is to cause local blood clotting in abnormal blood vessels. But this method is quite painful, as it can damage healthy areas of the retina. Indeed, all these methods are invasive, ineffective and have undesirable side effects. Now, researchers have begun to investigate a novel method of micro- and nanotechnology to treat eye diseases, using mobile microrobots (Figures 1d and 2).

What are microrobots?

Microrobots (microbots) are controlled devices that can both convert different types of energy into motion and perform specific types of tasks. For example, they can detect cancer cells in the human body or neutralize toxic substances from the oceans.

But how can they be used in eye therapy?

As mentioned above, the main problem in ophthalmology is the ineffective delivery of drugs to the retina. Microrobots offer a new approach for targeted drug delivery. Due to their controllability and ability to

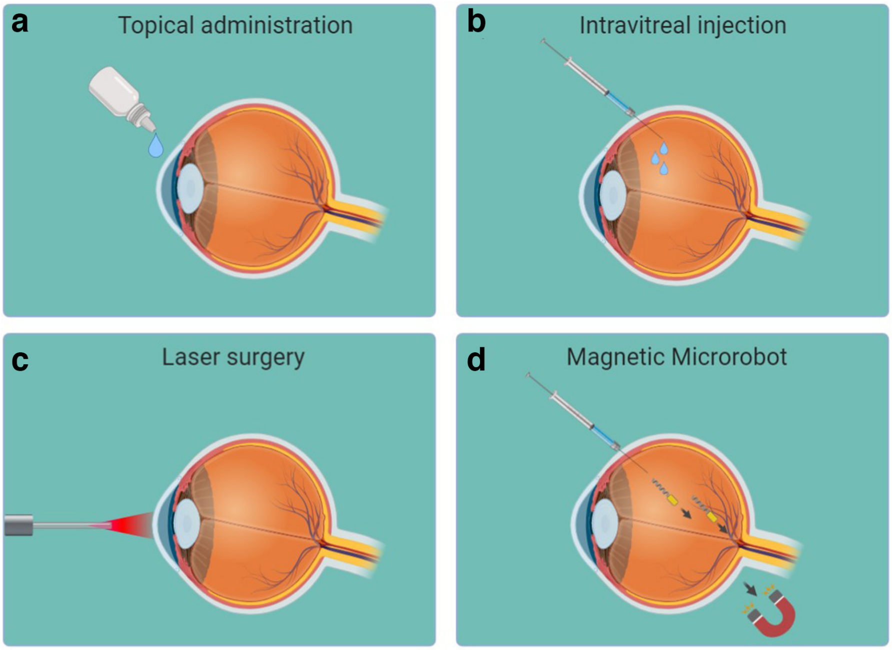

Figure 1. Methods of treatment of retinal diseases

move actively in a liquid environment, they can deliver various loads accurately and quickly.

In 2015, researchers from ETH Zurich were the first to apply the technology of microbots in eye therapy. To do this, they created a magnetic tubular microrobot with a sharp tip (Figure 2). The tube-like shape allowed for the maximum amount of medicine to be loaded inside, whilst the pointed end of the device reduced friction in the viscous medium of the vitreous body of the eye and ensured its high speed.

The idea was that after injecting a microbot inside the eye, it could move quickly and in a controlled manner to the retina and deliver the drug to its target. Works published earlier have already shown the effectiveness of such devices, but issues around immunogenicity and the required surgery for their introduction remained. Therefore, in this case, the researchers changed the design of the experiment. They chose the most biocompatible alloy with the highest magnetization (cobalt–nickel) and also reduced the size of the device, which made the procedure minimally invasive (Figure 2). For more information about the experiment, see Figure 3.

To demonstrate the possibility of using the device in a clinical setting, the scientists tested it in the eyes of an anaesthetized rabbit (Figure 4). By injecting a microrobot into the centre of the eye, they were able to test its manoeuverability and experiment on targeted drug delivery and release. The results showed high efficiency and accuracy of the microbot, which is very unusual for the first *in vivo* study in this field.

However, this device still had some limitations. There was significant discomfort for the patient when walking with this implant, and although the method is minimally invasive compared to the laser, it is not very pleasant, since it requires injection at the beginning and end of the procedure. These shortcomings prompted another team of scientists to come up with a new idea.

Can we do better?

Researchers from the Max Planck Institute for Intelligent Systems considered whether better solutions could be found. They came up with a number of proposals. First, they noticed that it is very difficult to take a microrobot

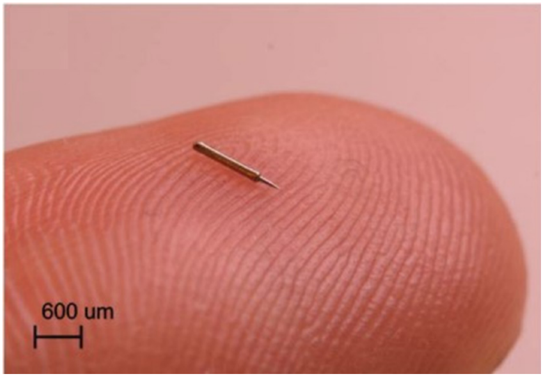

Figure 2. The appearance of the microrobot. The device size is 350 μm × 3.4 mm. Reused with permission from the Creative Commons Attribution License (License Number: 4855911247659).

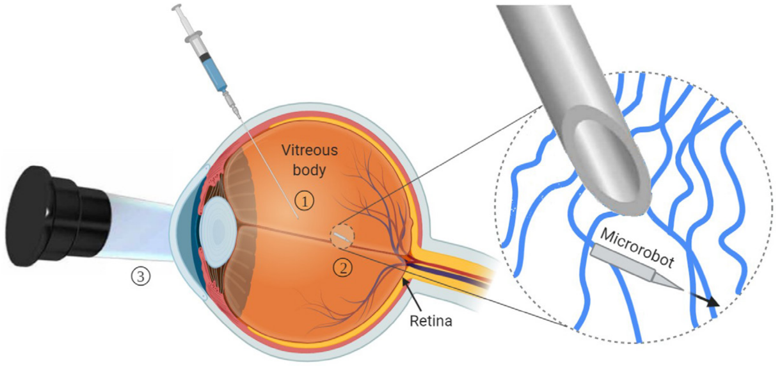

Figure 3. Schematic of the experiment. Microrobot injection into the eye using a thin needle (1). Magnetic control and movement of the device in the direction of the retina (2). Observation using optical tomography (3). After performing its function, the microbot was oriented in the direction of the needle and extracted using it.

from the eye, which poses great risks for the patient. So, scientists changed the design of the device: instead of a single large microrobot, they created millions of tiny micropropellers that do not need to be extracted from the eye. Their diameter was about 500 nm, which is 700 times smaller than those used in the previous experiment. This size not only accelerated their movement in the porous environment of the eye, but also forced researchers to

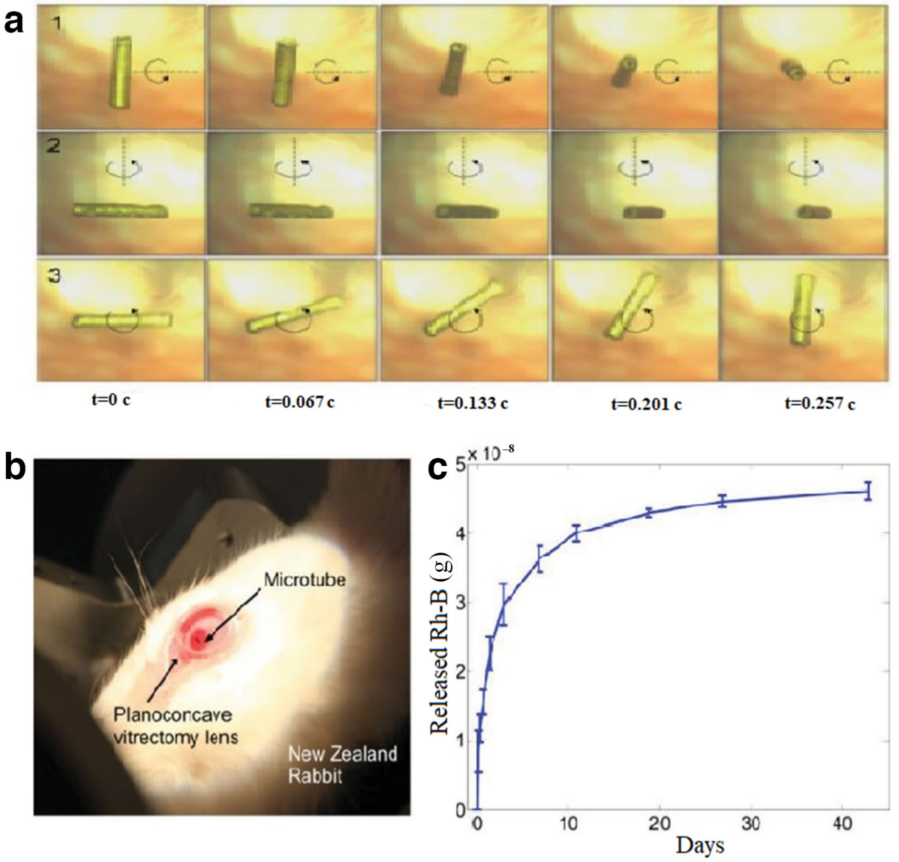

Figure 4. The results of the experiments. Microrobot quickly and accurately performs movement inside the viscous environment of the eye (**a**) Implantation of a microbot inside the eyeball of an anaesthetized rabbit (**b**) The rate of release of the model drug, Rhodamine B, to the retina (**c**) The substance was gradually released from the device within 42 days, which proves its long-term effect and high efficiency. Reused with permission from the Creative Commons Attribution License (License Number: 4855911247659).

use the most biocompatible materials. Silicon was used as the frame of the structure – having been classified as a safe material and approved for eye surgery. The special coating, which we will discuss later, was also non-toxic. The magnetic part consisted of iron (Fe) due to its high magnetization and compatibility.

Another feature of these microbots in the presence of a sliding layer of perfluorocarbon. This special coating greatly reduced the interaction of the device with the biopolymer network inside the eye, including dense collagen fibres. This improvement was inspired by the slippery surface of the carnivorous plant *Nepenthes*, which it uses to catch insects. A further innovation is the helical shape of the micropropeller (Figure 5). The researchers selected the optimal structure and length of the tail of the device, which made its movement faster.

In general, this structure had many advantages over the first microrobot: the small size and slippery shell greatly reduced the operation time. The procedure of working with the device did not require its reverse extraction with a needle, so it was less invasive. And all the materials were biocompatible and approved for surgery.

This strategy of using the device was unusual and previously unexplored. Therefore, scientists did not rush to test them on living organisms and began with individual pig eyes. The choice of this animal was due to the high anatomical similarity of their eyes with human ones.

The scheme of the experiment was very similar to the previous work (Figure 3), but there were small changes. For example, the model dye Rhodamine B was replaced with nanodiamonds for more accurate fluorescent imaging of microbots. The results were surprising: in a viscous environment, the devices moved at a speed of 10 μm/second and reached the retina in 30 minutes. This was 12 times faster than passive drug delivery using nanoparticles. Another great advantage of these microrobots was almost complete biodegradability inside the eye after 2–3 days. This means that the devices were destroyed and they disappeared after performing their function.

Experiments have shown that micropropellers are able to efficiently deliver drugs to the retina in an accurate and safe manner. More good news from this study is that such devices are universal. In addition to their ability to actively move inside the eye, they can also move in any other porous biological tissue such as the brain, liver or lungs.

In the future, researchers want to improve the effectiveness of microbots because only 95% of them were able to reach the retina. The rest got stuck in the pores and did not reach their target. After that, they are going to test the devices on animals and then on people. Scientists believe that this technology will save many human eyes from complete blindness.

Conclusions, gaps and perspectives

The 21st century is shaping to be the heyday for micro/nanotechnologies. Even now, scientists and engineers are beginning to create and domesticate the inhabitants of the microworld to use them for the benefit of humanity.

In ophthalmology, microrobots show huge advantages over existing methods for ocular drug delivery. They are able to quickly and accurately deliver cargo to the most difficult and important area of the eye — the retina. Moreover, the entire procedure does not require surgery, and the materials from which microbots are made are safe and approved by the medical community.

Despite this, it will take a long time before such devices are introduced into humans. But to bring this moment closer, we need to overcome the difficulties of today. For example, expensive and cumbersome equipment for conducting experiments severely restricts

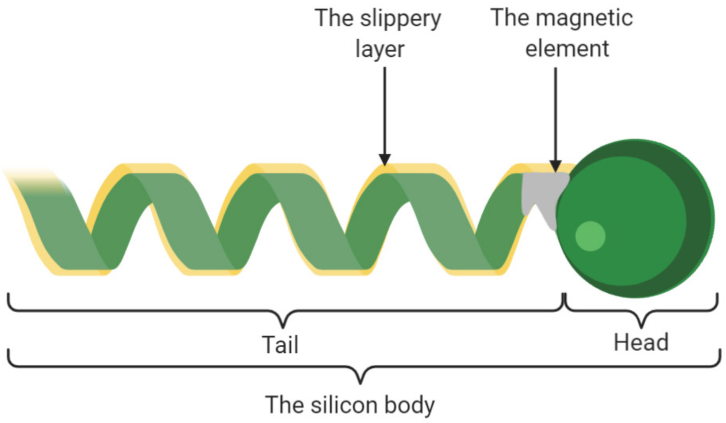

Figure 5. Structure of the micropropeller

such research. Another problem is the time-consuming production of microrobots. We also need more research on animals and humans to get more accurate and reliable data on the effectiveness of devices. Surmounting these problems will open up new horizons for us not only in ophthalmology, but also in understanding our entire world.

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Further reading

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