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N2B-patch: circumventing the blood-brain barrier

There are many medications for treating central nervous system diseases. However, only a fraction of the active pharmaceutical ingredients actually reaches the site where they are needed. The reason for this is the blood-brain barrier that protects the brain and thus prevents many drugs used to treat neurological diseases from effectively penetrating the brain. Researchers from the Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB are part of the international N2B-patch consortium that is developing a drug delivery technology for treating multiple sclerosis that enables the active ingredient to reach the brain directly via the nasal mucosa.

In order for a drug to be highly effective, the active pharmaceutical ingredient (API) must reach the site where it is needed as quickly and as fully as possible. After application, the API is transported via the bloodstream to the diseased cells where it exerts its action. Depending on the tissue, this is more or less efficient. It is particularly difficult for APIs to enter the brain. This is due to the blood-brain barrier - a selective physiological barrier that efficiently protects our body's central control centre against pathogens and toxic substances and that is therefore difficult or even impossible for the majority of neuropharmaceuticals to overcome.

This applies equally to multiple sclerosis (MS) drugs. MS is a chronic inflammatory disease of the central nervous system. Although therapies are available for treating the disease, better treatment results could be obtained if the blood-brain barrier could be bypassed, enabling all the administered drug to enter the brain. The same also applies to drugs for treating many other neurological disorders such as Alzheimer's disease.

Via the olfactory mucosa into the brain

With this issue in mind, scientists from the Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB in Stuttgart, together with colleagues from the Biberach University of Applied Sciences, came up with the idea of bypassing the blood and transferring APIs into the brain via the nose (N2B: "Nose2Brain"). Instead of applying APIs via the respiratory epithelium using a nasal spray the researchers decided to apply the drug to the nasal olfactory region. This olfactory epithelium, i.e. the olfactory mucosa, is only separated from the brain and its surrounding fluid by the ethmoid bone and a few layers of cells. APIs can penetrate this area relatively easily and thus enter the brain via the shortest possible route. “However, it is not quite as easy as it sounds. A formulation that is suitable for application to this nasal region is required. In addition, a medical device from which the drug can be released is also needed. Neither is yet available,” explains Dr. Carmen Gruber-Traub, who is coordinating the research at the IGB.

The international N2B-patch project consortium met at the Fraunhofer IGB in Stuttgart to kick off the project.
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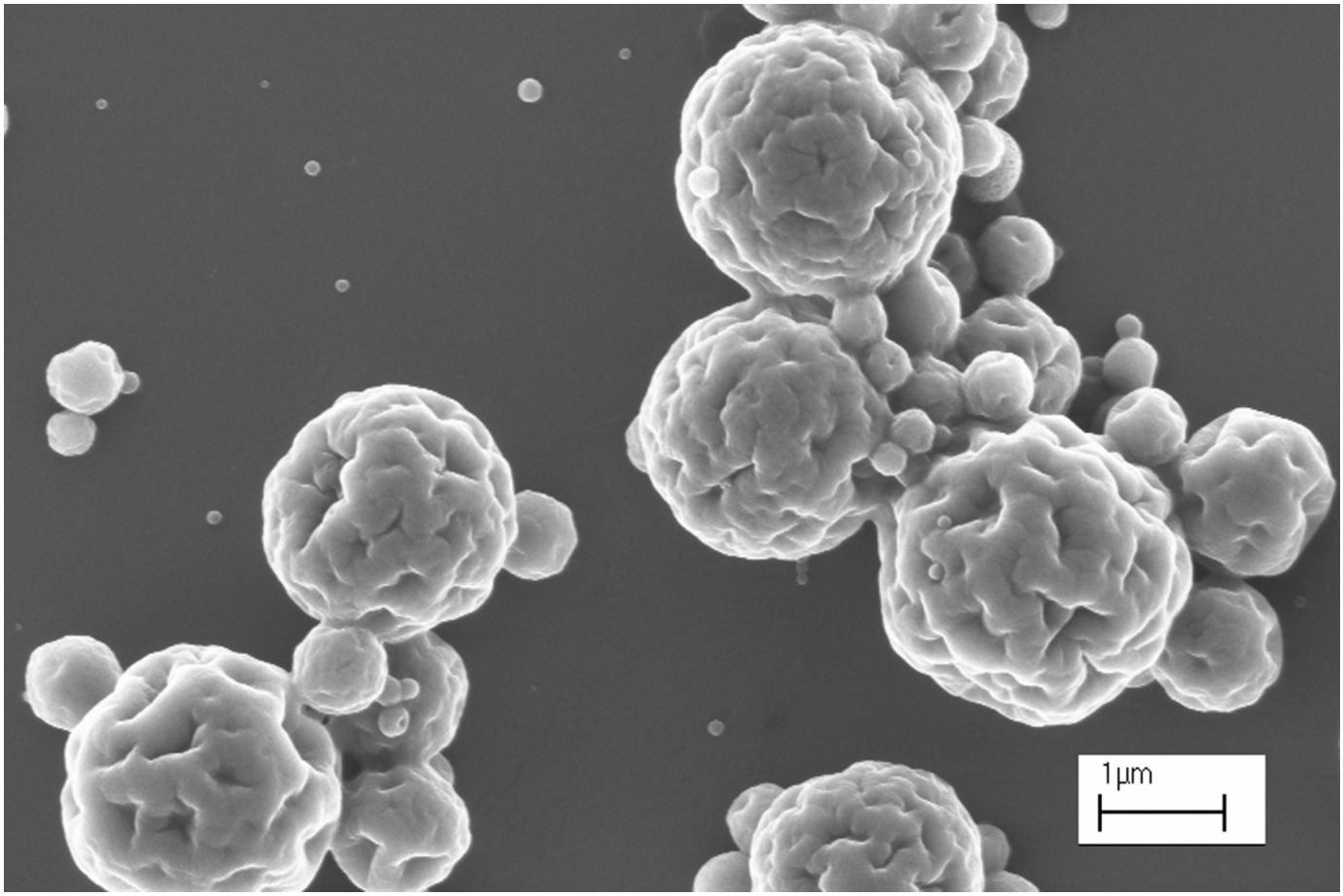
Last year, the IGB researchers came across an EU call that suited their research idea; they founded a consortium and their application was successful. Since January 2017, a total of eleven international partners have been working together in an EU-funded collaborative project called N2B-patch aimed at developing a drug delivery technology to administer drugs via the olfactory region, starting with drugs to treat MS. The task of the IGB researchers in Stuttgart is to find out how the AIP, i.e. an antibody that stimulates the regeneration of nerve cells, can be integrated into a stable container. This involves developing a suitable drug formulation. A company called MJR Pharmjet GmbH, another member of the consortium based in the Saarland, is also working on the development of drug formulations. “At this important point, we want to use a two-pronged approach, and will decide at a later stage which of the two approaches is more appropriate for the envisaged purpose,” explains Gruber-Traub. MJR Pharmjet GmbH will at some stage in the future also be in a position to work on the upscaling of the formulation under GMP conditions.

The IGB researchers will initially focus on the formulation of chitosan: “We believe that this is a good approach because chitosan adheres well to mucous membranes,” says the chemist. “We only use basic materials that are approved for medical applications by the health authorities. The approach would otherwise become far too complicated and it makes no sense to explore two unknowns.” The researchers have also planned to test other commercially available pharmaceutical polymers such as EUDRAGIT® for their suitability as N2B patches.

Miniature gel patch for the olfactory nerve

Once the formulation consisting of drug-loaded biodegradable polymer particles, is available, the



Microscope image of chitosan particles: the first miniature gel patches will be made of chitosan from marine animals that adheres well to mucous membranes.

researchers will embed it into a biodegradable hydrogel matrix that is currently being developed by one of the six partner companies. The hydrogel matrix will be only a few millimetres in size and will be in the form of a patch in the olfactory region where it will adhere to the olfactory nerve. Gruber-Traub comments: "The hydrogel patch will remain on the olfactory mucosa for a few days only after which it will spontaneously dissolve." Treatment will involve placing a new hydrogel patch in the olfactory region at three- to four-week intervals."

Another project partner, a company called Beiter GmbH & Co. KG from the south of Baden-Württemberg, is developing a device for applying the gel patch to the inside of the nose. The patch will most likely have to be applied by a doctor. "The patch is very small, and care must be taken to not interfere with a person's sense of smell," says Gruber-Traub. "There is an ENT doctor on the consortium's advisory board who will help us optimise the application of the patch into the nose. The nasal cavity is a very sensitive area, and many people have probably experienced the unpleasant sensation of water entering the nose when jumping into the water. Nobody will accept the therapy if the application of the patch feels too unpleasant."

Focus on obtaining marketing authorisation from the word go

The consortium is specifically planning to have developed a suitable formulation in three years' time. There are many questions that need to be resolved In the meantime. For example, how large can the particles be, and how much drug can be integrated into the particles? "At present, such drugs are applied via the spinal cord; and the quantity administered is much different than that contained in the patch under development," says the scientist. "Apart from having adverse effects, the AIP is

rather expensive. It goes without saying that healthcare costs would have to be affordable." Gruber-Traub also highlighted that the olfactory system is one of the first attempts to use the new technology. “Little research has been conducted in this area. Model substances have so far only been tested in animals. However, the situation in animals is completely different from that in humans. For example, the olfactory epithelium of animals is much larger than that of humans.” However, the N2B-patch researchers will also carry out tests with animal tissues. For this purpose, the Biberach University of Applied Sciences is currently developing a test system based on pig epithelium derived from slaughterhouse waste.

The AIP is an antibody that is being co-developed and made available by a young biotechnology start-up. However, before the precious AIP can be integrated into the particles, the appropriate formulation will have to be developed as far as possible using model substances and dyes. In parallel to this work, the scientists are already focusing on obtaining marketing authorisation. “We are well aware that we will not have obtained marketing authorisation by the time the project ends. However, we will be able to demonstrate in a relevant environment that the therapy works,” says Gruber-Traub. “As the ultimate goal is to obtain marketing authorisation, it is key for us to do everything right from the word go. This is also why the entire process is being accompanied by a pharmaceutical consultancy firm from the UK that are supporting us on our journey from research to the marketplace."

Universal platform for central nervous diseases

The researchers originally thought of using a different AIP for their new platform, i.e. one for treating Alzheimer’s rather than MS. Gruber-Traub highlighted the potential of adapting the formulation to other AIPs and use the innovative hydrogel matrix and particle combinations to deliver AIPs for treating a broad range of neurological diseases in the brain – a universal N2B platform.

Article

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Dr. Petra Neis-Beeckmann

Further information

Dr. Carmen Gruber-Traub
Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB
Nobelstr. 12
70569 Stuttgart
Phone: +49 (0)711 970-4034
E-mail: carmen.gruber-traub(at)igb.fraunhofer.de

- Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB

The article is part of the following dossiers

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Neurodegenerative diseases

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