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PORTUGAL

Scientists from the University of Coimbra develop and test new nanoparticle for gene therapy in the brain

A study led by the Center for Neurosciences and Cell Biology at the University of Coimbra (CNC-UC) has developed a new formulation, based on nanoparticles, which has been shown to be able to deliver proteins to the brain in a localized manner. The results presented are intended to respond to the need to find new specific formulations for gene therapy in the brain and may contribute to the development of new safer gene editing therapies.

Gene therapy involves modulating gene expression, making it possible to add a missing or insufficient gene, silence a mutated gene that causes disease or even repair a defective gene. In the brain, despite the advances in the formulations used for gene therapy, there

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are still several limitations in its application, such as the specificity of delivery or the size of the molecules that the formulations deliver.

The study, entitled "Efficient spatially targeted gene editing using a near-infrared activatable protein-conjugated nanoparticle for brain applications", is now published in the prestigious scientific journal *Nature Communications*. For this investigation, the team coordinated by Lino Ferreira, researcher at the CNC-UC and at the Faculty of Medicine of the University of Coimbra (UC), developed and tested nanoparticles (particles whose size is between 1 and 100 nanometers) that are capable of transporting functional enzymes and which, once inside the cells, only release these enzymes when a near infrared light is shined externally, demonstrating the specificity of this technology.

Catarina Rebelo, researcher at CNC-UC and first author of the study, emphasizes that **«these new nanoparticles were developed to respond to the need for specificity in new gene editing therapies»**. About the characteristics of these particles, the researcher explains that «on the surface of these nanoparticles are coupled enzymes that are able to edit and correct the genomic DNA of the cells». For the success of these therapies, Catarina Rebelo reveals that «**it is necessary that the enzymes reach the cell nucleus without being eliminated. For this, we added hydroxychloroquine to the formulation, which prevents the elimination of nanoparticles before their action. Once inside the cells, the enzymes are released by receiving infrared light externally».** In this formulation, the enzymes are linked to the nanoparticles by a blue light sensitive bond. Thus, upon receiving infrared light, **«the particle transforms this low-energy light into blue light and releases the enzymes, allowing them to reach the nucleus»,** she clarifies. The researcher also highlights that, with these properties, **«a very efficient and spatially controlled delivery is possible, and, since infrared light has great penetration into tissues, we have a formulation with great potential for biological applications».**

The high efficiency in the delivery of proteins that the study revealed also allowed to show that it is possible to use significantly less amount of formulation to induce the same effect in cells, compared to products that are commercially available.

Additionally, it allowed the team to test the ability of this formulation to improve existing techniques for modulating neuronal activity, such as optogenetics, which uses light (opto-) to stimulate genetically modified neurons (-genetics). For this, it is necessary that the neurons under study express channels that only open in the presence of light.

Currently, as a rule, in the modulation of neuronal activity, viral vectors are used that infect and transport the message that encodes channels in the target neurons. However, given their infectious nature, these vectors end up infecting and transmitting this message to neurons other than the intended ones, which can lead to misinterpretations of the biological data obtained. In this study conducted by UC scientists, it was possible to ensure that **«the message transmitted by these viral vectors was only read in the neurons that had received the tested formulation, thus increasing the spatial efficiency only for the area of interest, while maintaining its ability to modulate neuronal activity»,** highlights Catarina Rebelo.

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The scientific article can be consulted here.

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