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VISION RESTORATION INSPIRED BY SOLAR CELLS, LIZARDS AND ALGAE

New ways to treat age-related blindness are being developed using visual prostheses including polymers and graphene, cell reprogramming or optogenetic therapy. Leading experts in Spain, Italy, and France, speaking at the FENS Virtual Forum of Neuroscience today (Saturday 11 July), hope these approaches will help to restore vision in people with conditions such as macular degeneration, retinitis pigmentosa and glaucoma.

Inspired by solar cells that convert the sun's energy into electricity, a team led by **Professor Fabio Benfenati from the Italian Institute of Technology, Genova** is making tiny biological devices, 1/1000mm, made of polymer and implanted onto the diseased retinas of rats. The retina is the layer at the back of the eyeball that contains neurons sensitive to light necessary for the formation of visual images.

Once these engineered nanoparticles are microinjected into a blind eye that has lost photoreceptors, they distribute all over the retina surface and functionally interact with inner retinal neurons that are spared by neurodegeneration. The neuron-nanoparticle interface converts light to an electric current that activates the neurons involved in the ability to see things. "The trick is to stimulate the residual neurons to send messages to the brain," said Professor Benfenati.

They have found that a single microinjection of the nanoparticles rescued and restored the vision in the rats with diseased retinas to be comparable to the visual acuity – the quality of sight - of healthy rats, for up to eight months after administration.

"The great thing about polymers is that they are highly conformable, similar to the flexible plastic of soft contact lenses. They are biocompatible and therefore friendly to the eye tissues. Moreover, they do not activate the immune system and are not damaged or destroyed over time," he said. Tests are now being conducted in the eyes of pigs that are closer in size and geometry to human eyes.

This promising research is being progressed further to make the polymer devices small enough to be injected into the eye without the need for long and laborious surgery. This so-called 'liquid artificial retina' makes it possible to achieve a widespread and effective stimulation of very large areas of the blind retina.

"We are at the start of a new era of tissue electronics, in which light-sensitive molecules and live tissues integrate and intimately interact with each other. We can look ahead to the prospect of producing a new ecosystem of smart organic prosthetics. Working with semiconducting polymer that can activate neurons could, in the future, not only treat degenerative retinal diseases, but

also possibly heal other central nervous system diseases, such as Parkinson's disease, said Professor Benfenati.

Stem cells from bone marrow fused with cells called Müller glial cells, are being reprogrammed and used to regenerate the retina; Müller glial cells are involved in the structure and function of the retina. This is another approach being exploited by **Professor Maria Pia Cosma at the Centre for Genomic Regulation in Barcelona, Spain**.

"Fish and lizard-like salamanders can automatically replace damaged neurons after reprogramming of Müller glial cells, but somehow this ability has been lost in our evolution," said Professor Cosma. "We are trying to push these glial cells to regenerate retinal neurons also in mammals."

Recent research in mice has shown in one experiment that stem cells from bone marrow transplanted into the eye fuse with the Müller glial cells. This fusion generates a hybrid type of cell that is capable of producing photoreceptors - light-sensitive neurons located in the retina that enable vision. "In another experiment we found that stem cells that were not transplanted can somehow find their way from the bone marrow to the damaged retina," she said.

She continued, "Our findings represent an important proof-of-principle that the regenerative potential of mammalian glial cells can be reactivated by cell fusion. This in turn could contribute to the development of new therapies to treat vision impairments and blindness caused by retinitis pigmentosa."

The next stage of the research is to try and reprogramme the body's latent ability to restore vision using retinal human organoids, grown in the laboratory, followed by further experiments in mice that have a form of inherited retinitis pigmentosa. "But we are a very long way from clinical trials," she cautioned.

Optogenetics is a powerful tool in neuroscience whereby neurons are made sensitive to light. Research at the **Vision Institute in Paris, led by Dr Serge Picaud**, uses the DNA of a protein found in unicellular algae that responds to orange light to re-activate the blind retina which then transmits visual information to the brain. After validating this strategy in non-human primates it is now being trialled in four blind patients with inherited retinitis pigmentosa. The patient receives an injection in the eye containing a viral vector – an inactivated virus used to deliver genetic material - that carries the genetic code for the algae protein. The viral vector diffuses into the retina and the retinal ganglion cells (neurons) start expressing the photosensitive algae protein. As a consequence, retinal ganglion cells become photosensitive and send visual signals to the brain.

Tests are currently being carried out to evaluate their visual perception when they wear goggles projecting orange images of high intensities onto the retina.

In parallel, Dr Picaud has been assessing a photovoltaic retinal prosthesis, which converts infrared light into electricity. The implanted prosthesis is a piece of silicon, about 2mm wide, that is completely wireless and powered by near-infrared light. The patient wears goggles with a camera connected to a digital micromirror device (DMD). The DMD projects the infrared light patterns onto the patient's retina to activate the implant. In the quest to restore vision electrical activation of the residual retinal neurons by this photovoltaic prosthesis could one day offer a therapy.

The procedures were first tested on post-mortem primate retinal tissue with the photoreceptors removed, effectively rendering the tissue 'blind'. Once the scientists demonstrated that the tissue could be activated, further tests were carried out in living non-human primates.

"Our tests showed that some vision could be restored to a blind spot in the non-human primates. Their perception was monitored in a behavioural test where the animal was performing an eye movement. At the blind spot of the implant, natural light did not generate the eye movement but infrared light triggered the response," said Dr Picaud. "This gave us sufficient information for us to introduce the procedure into five patients with age-related macular degeneration." The visual acuity – the quality of the vision - with a retinal prosthesis was restored in four patients well enough to enable them to read text.

Dr Picaud is now investigating new materials like graphene to further improve the resolution of such prosthesis. Graphene is highly conductive so even small electrodes should deliver enough charges into the tissue to stimulate the neurons.

"We already believe these techniques could help patients to read text, recognise faces and to be able to move independently, making a real difference to their lives. But we need to make further refinements to fully restore the patient autonomy," he said.

END

Symposia S03: Synthetic vision: new strategies for rescuing visual perception in degenerative blindness
Abstracts: *Fabio Benfenati* - Polymeric light-sensitive interfaces for retinal prosthetics
Maria Cosma - Retinal regeneration via Müller Glia cell reprogramming
Serge Picaud - Primate preclinical validation of an infrared photovoltaic prosthesis and of optogenetic therapy for visual restoration

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Further reading (Benfenati)
Subretinally injected semiconducting polymer nanoparticles rescue vision in a rat model of retinal dystrophy Maya-Vetencourt, J.F., Manfredi, G., Mete, M. Benfenati, F. *et al. Nature Nanotechnology* 2020 **https://doi.org/10.1038/s41565-020-0696-3**

Further Reading (Cosma)

Endogenous Mobilization of Bone-Marrow Cells Into the Murine Retina Induces Fusion-Mediated Reprogramming of Müller Glia Cells. Pesaresi, Bonilla-Pons, Simonte, Sanges, Di Vicino, Cosma. *EBioMedicine* 2018, 30;38-51, **DOI: 10.1016/j.ebiom.2018.02.023**

Dedifferentiation, transdifferentiation and cell fusion: in vivo reprogramming strategies for regenerative medicine. Pesaresi, Sebastian-Perez, Cosma. *The FEBS Journal* 2018, **DOI: 10.1111/febs.14633**

Further Reading (Picaud)

Optogenetic therapy: High spatiotemporal resolution and pattern recognition compatible with vision restoration in non-human primates . G. Gauvain, H. Akolkar, A. Chaffiol, F. Arcizet, M. Khoei, M. Desrosiers, C. Jaillard, R. Caplette, O. Marre, S. Bertin, C.M. Fovet, J. Demilly, V. Forster, E. Brazhnikova, P. Hantraye, P. Pouget, A. Douar, D. Pruneau, J. Chavas, J.A. Sahel, D. Dalkara, J. Duebel, R. Benosman, S. Picaud. *BioRxiv* 2020 **DOI: 10.1101/2020.05.17.100230v1**

Functional efficacy of stimulations with a photovoltaic sub-retinal prosthesis in non-human primates. Prévot P.H., Gehere K., Arcizet F., Akolkar H., Khoei M. A., Blaize K., Oubari O., Daye P., Lanoë M., Valet M., Dalouz S., Langlois P., Esposito E., Forster V., Dubus E., Wattiez N., Brazhnikova E., Nouvel-Jaillard C., LeMer Y., Demilly J., Fovet C.M., Hantraye P., Weissenburger M., Lorach H., Bouillet E., Deterre M., Hornig R., Buc G., Sahel J.A., Chenegros G., Pouget P*., Benosman R*., Picaud S*. 2020 *Nature Biomed. Eng.* 4(2):172-180.

The 12th FENS Virtual Forum of Neuroscience
As a consequence of the COVID-19 pandemic, the FENS Forum 2020 will be held entirely virtually.

The FENS Forum of Neuroscience is the largest basic neuroscience meeting in Europe, organised by the Federation of European Neuroscience Societies and hosted by the British Neuroscience Association. It will attract around 5,000 international delegates. FENS was founded in 1998. With 44 neuroscience member societies across 33 European countries, FENS as an organisation represents 20,000 European neuroscientists with a mission to advance European neuroscience education and research.