Bio-electronic cell based implant to deliver beta interferon

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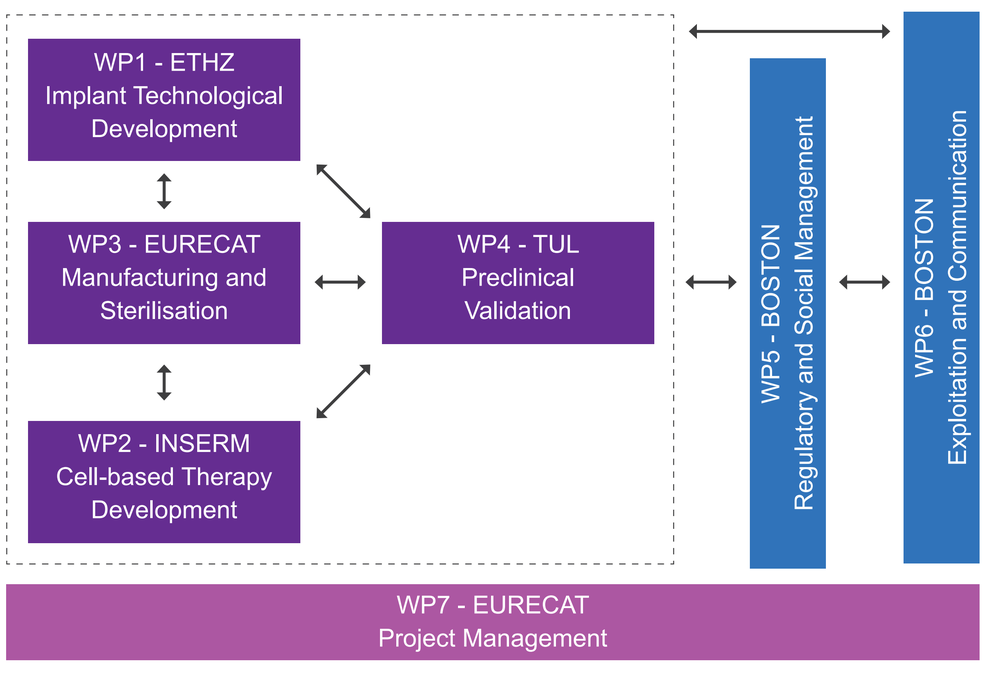
ABSTRACT

New emerging advanced therapies invest in genetic, electronics and cell-based therapy for addressing unmet needs for the caregivers and the patient. Optogenerapy, a synergy between optogenetic and gene therapy holds promise of a new modern syringe era capable of producing a drug of interest at will directly inside the patient. Inside a bio-electronic implant, electronics and optogenetics are interfaced by light as a traceless inducer signal. By controlling a synthetic optogenetic pathway in the cell, therapeutics delivery can be fine-tuned with a precise spatiotemporal control.

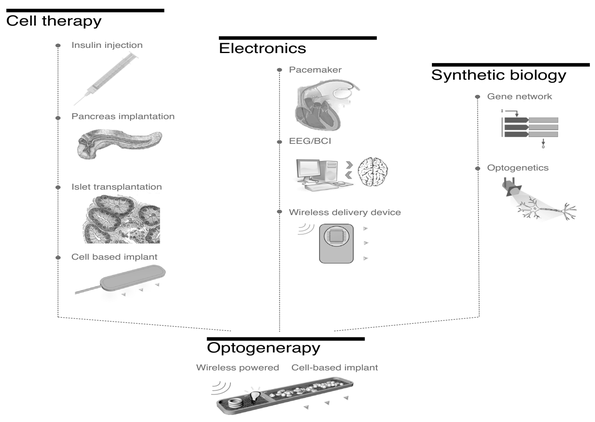
The device is built as a wireless-powered optogenetic implant, with a highly modular interface that couples electronics with living cells and enables electronic devices to directly and remotely control gene expression using Near Infrared Light (NIR). The novelty lies in the delivery of beta interferon (IFN-ß) through a membrane, overcoming current limitations of short drug half-life in vivo, adverse immune reactions, pain and irritation at the site of local injection.

The main objective of the Optogenerapy consortium is to develop the manufacturing of a new optogenetics cell-based implant to bring a pre-clinical proof of concept of a controlled beta interferon (IFN-ß) protein delivery for treating patients suffering from multiple sclerosis. The therapeutic optogenetic cell-line are developed (ETHZ and INSERM) for long term delivery of a recombinant glycosylated form of IFN-β. Manufacturing aspects of the implant integrating the cell chamber, the optoelectronics and the injection moulding are addressed (EURECAT, BOSTON SCIENTIFIC) together with the suitable sterilization protocol (TUL, Lodz University of Technology) including materials modelling and a clear business case for exploitation (BOSTON SCIENTIFIC).



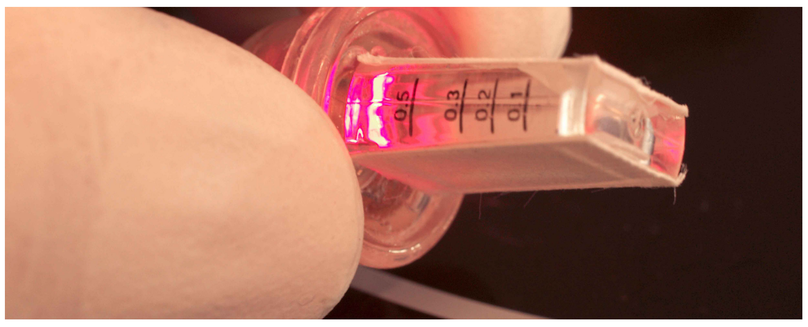
METHODS

Optogenerapy: an innovative cell-based implant to orchestrate the administration of biologics.



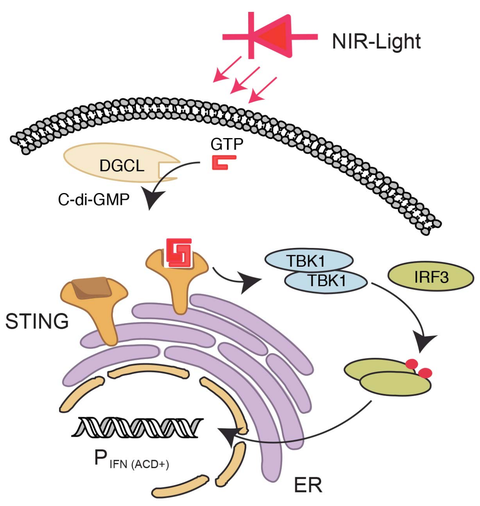
F.Michel, M.Folcher Porto Biomed.J. 2017

The concept of optogenerapy emerged subsequent to the development of the domains of cell therapy, electronics and synthetic biology. Cell therapy, guided by the progress on encapsulated cells for diabetes therapy, opens the path of cell-based implant. Electronic medical devices characterized by the development of pacemakers leaded to devices capable of releasing therapeutics wirelessly. The Optogenerapy approach is based on the subcutaneous implantation of genetically engineered cells in a semi-permeable membrane that enables diffusion of small molecules and proteins. The physical integrity of the implant allows the device to be easily implanted or removed. At the same time, this membrane acts to prevent immuno-rejection and offers long-term safety with regards to the biological agent associated with the therapeutic protein delivery.



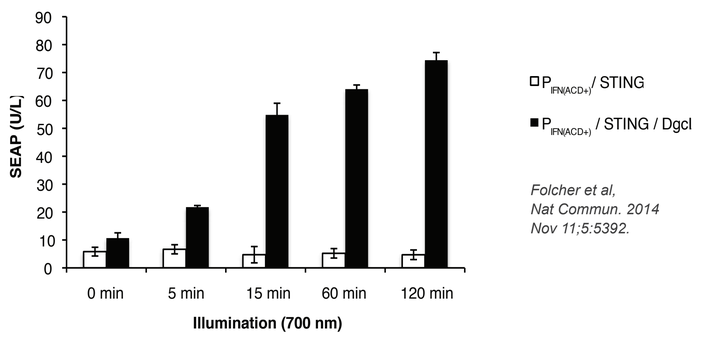
Synthetic biology and optogenetic permit the control of cells protein production simply by light.

SYNTHETIC BIOLOGY APPROACH



M.Folcher et al. Nat. Commun. 2014

The figure illustrates the optogenetic pathway in engineered mammalian cells proposed in the project: NIR light activates an engineered light dependent bacterial phytochrome-associated diguanylate cyclase (DGCL), which converts the mammalian cytosol guanosine triphosphate (GTP) to second messenger cyclic diguanylate monophosphate (c-di-GMP). c-di-GMP binds and activates the Stimulator of Interferon response Gene (STING) at the Endoplasmic Reticulum (ER) and specifies Tank-Binding Kinase 1 (TBK1)-mediated phosphorylation of the interferon regulatory transcription factor IRF3. Phosphorylated IRF3 translocates to the nucleus, binds cognate IRF3-specific operators and induces transcription of the optimized type-1 interferon promoters (PIFN-β) and thus, a recombinant glycosylated form of IFN-β therapeutic protein can be secreted.



Folcher et al, Nat Commun. 2014 Nov 11;5:5392.

HEK-293T cells were co-transfected with pSO4 (PhCMV-DGCL-pA), pSTING (PhCMV-STING-pA) and pSO3 (PIFN(ACD.)-SEAP-pA) and illuminated with NIR light (700 nm) for different periods of time before profiling the reporter secreted alkaline phosphatase (SEAP) in the culture supernatant after 24 h.

CONCLUSION

The Optogenerapy consortium will further develop the manufacturing process and test the optogenetic cell-based implant in rodent model of multiple sclerosis. Further cell engineering research will be performed to define the best engraftment and neo-vascularization parameters that are essential for the success of implanted bio-electronic devices. The ultimate goal is to validate the bioavaibility of protein based therapeutic controlled delivery by the Optogenerapy bio-electronic cell based implant.

OPTOGENERAPY CONSORTIUM

This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 720694

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