Summary of the research project

This avant-garde project is managed through a collaborative work between University College London and Kings College London. It started financed by us, in 2010, first results being recently published in Science. Second phase of the project is starting now through a co financing with Motor Neuron Association. 

This project involves a novel approach to restore muscle function following motor neuron loss, using a combination of stem cell based replacement of motor neurons and the revolutionary technique of optogenetics.

Briefly, we have shown that embryonic stem cell-derived motor neurons (ESC-MNs) can be transplanted into injured peripheral nerves that have lost their endogenous motor neuron axons and that these ESC-MNs can then reinnervate the target muscles (See Bryson et al, 2012, Science). Moreover, we genetically manipulated these ESC-MNs to express the light-sensitive ion channel, channelrhodopsin-2 (ChR2), so that when we optically stimulate these ESC-MNs with blue light, they can induce finely-controlled contraction of reinnervated muscles.

The schematic illustrates the transplantation of embryonic stem cell-derived motor neurons into specific branches of an injured sciatic nerve. After 35 days, the transplanted motor neuron axons grow towards the muscles in the hind-limb to reinnervate them. At this time point, the nerve in the mid-thigh region was exposed and a blue light-source was used to ‘optogenetically’ activate the transplanted motor neurons, which resulted in finely controlled muscle contractions.
This approach has the potential to overcome the normally permanent atrophy and paralysis of skeletal muscles that can occur as a result of diseases such as ALS as well as by traumatic neurological injury (e.g. spinal cord injury). Our long-term aim is to use this approach to maintain function of the diaphragm muscle in models of ALS, since loss of function of this respiratory muscle is the main cause of death in ALS patients. To accomplish this, we are currently investigating whether it is possible to restore muscle function in the long term in mouse models of ALS, using an implantable optical stimulator device.

In order to fully evaluate the translational potential of this strategy for ALS patients, and to model the potentially toxic environment that may exist within the neuromuscular system of ALS patients, we now plan to develop this technique using the SOD1G93A mouse model of ALS. We have preliminary evidence that that these ESC-MNs can survive and innervate muscles in SOD1G93A mice in vivo, up until late-stage disease. In addition to establishing whether ESC-MNs also survive and functionally innervate target muscles in SOD1G93A mice, we also aim to develop a technique to optically stimulate muscles chronically in vivo, which will require the use of an implantable optical stimulator.

A near-term application of this technique would be to restore diaphragm muscle function in ALS patients suffering from respiratory insufficiency, using an implanted optical pacemaker, thereby enabling them to breathe without a mechanical ventilator.

This would not only greatly improve the quality of life of these patients, but could also prevent diaphragm muscle atrophy and may even reduce the risk of ventilator-associated pneumonia which is a common cause of death in ventilator-dependent patients. Ultimately, the ability of this novel biological interface to control complex motor functions is only limited by the sophistication of the optical control device.

**Diagram of the ultimate clinical application of this research**

Schematic representation of light-activated motor neuron transplants combined with an implantable optical pacemaker, which will enable ALS patients with compromised respiratory function to breathe without the need for mechanical ventilation.
2014 Call for projects

Optogenetically-Controlled Restoration of Muscle Function in ALS

Relevant research articles for this project are:


link to the lab website:

[http://www.ucl.ac.uk/ion/departments/sobell/Research/LGreensmith](http://www.ucl.ac.uk/ion/departments/sobell/Research/LGreensmith)

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His 5 most relevant publications are:


