Electrotransfer for drug delivery – from bench to bedside

Professor Richard Heller, Professor and Director of the Frank Reidy Research Center for Biotechnology at Old Dominion University has over 25 years’ research experience into the effects of electric pulses on biological systems. His pioneering research uses pulses of high-voltage electric fields to enable drug and gene delivery. His work centres on optimising these gene therapy tools with a view to developing exciting therapeutics for a wide range of diseases.

Gene transfer or gene therapy is a form of treatment that involves inserting one or more genes (the basic biological unit of heredity) into a patient’s cells. Once inside the host cell, the new gene (or DNA) makes its way to the cells nucleus where the cell machinery then alters the levels of proteins coded by that gene. The altered levels of proteins can then correct or control disease. An exciting and active area of research, the potential for gene therapy is immense, holding huge promise for immunisation as well as a therapeutic tool for a range of diseases, including haemophilia, muscular dystrophy, immune deficiencies and types of cancer.

UNLOCKING THE POWER OF GENE THERAPY

Drugs and proteins can be targeted using electroporation. In this method, high-voltage electric pulses are supplied to target host cells allowing the uptake of molecules. The electrical treatment causes a transient increase in the permeability of cell membranes, allowing drugs and genes to be taken up by the cell. Professor Heller’s early studies showed that the increase in permeability is temporary and has no effect on cell viability. Subsequent clinical studies have demonstrated its safety and efficiency.

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Electrotransfer is a medical procedure that enables the delivery of DNA to a patient’s cells, allowing them to express new genes and produce new proteins. The electrotransfer device is designed to deliver DNA to experimental cells, Professor Heller and his research team have developed the electrotransfer tool for in vivo use, meaning that the genes are transferred directly into the cells inside the patient’s body.

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Professor Heller’s team realised that successful gene transfer depends on achieving a precise therapeutic protein dose. Although controlling the administered dose of the gene is achievable, controlling levels of the resultant expressed protein is far more challenging. Through his research, Professor Heller is developing new approaches to improve delivery and therefore impart more control on protein expression. His non-invasive electrotransfer, the multi-electrode array (MEA), efficiently delivers high levels of genes in the skin for up to 15 days after treatment. By exploring parameters including electric field strength, pulse duration, pulse number, electrode geometry and configuration, and also the delivery area, Heller’s team can control the onset, level, and duration of protein expression of the transgene. The researchers are also exploring the use of moderate heat controlled through an exogenous source to improve gene delivery in vivo. In this way, their approach can be fine-tuned to control the levels and duration of expression of the new gene, allowing a tailored approach, specific for the patient.

Pre-heat cell/tissue increased membrane fluidity

Low/moderate exogenous pre-heating of target could enhance transfer by compensating for the reduced electric field between the electrodes.

Figure 1. Thermally Assisted Electro Gene Therapy

Figure 2. Blood Flow within the Heart. Coronary perfusion before and after treatment was determined using the SPIRIT Intraoperative Perfusion Assessment System (Naviscan, Technologies Inc., Burlington, MA). Fluorescent microspheres are injected intravenously and fluorescent intensity measured with a camera. The SPIRIT system enables the user to image, capture, and view dynamic fluorescence images of the myocardium. The level of perfusion has been shown to be directly related to changes in the intensity of fluorescence. The post-occlusion image was taken immediately after blocking the left anterior descending artery. The post-reperfusion image was taken two weeks after treatment with plasmid VEGF and gene electrotransfer.
GENE DELIVERY OF VACCINES
Prof. Heller's team evaluated the MCA tool to effectively deliver a DNA vaccine against B. anthracis, the bacteria responsible for causing anthrax. By adjusting the voltage, amount of DNA and number of treatments, the team optimised the tool to safely administrate the vaccine in mice in vivo. Changing the voltage in particular, the team found that mice raised levels of protective antibody from the vaccination and generated a protective immune response, suggesting that MCA could be established as a non-invasive way to vaccinate against anthrax.

A NOVEL APPROACH FOR MALIGNANT MELANOMA
Much gene transfer research aims to push the expression of genes to the highest level. Prof. Heller's team, however, takes a different approach. By determining the optimum dose of the expressed gene, the researchers work out the delivery method to achieve this. This is not an easy task - although controlling the administered dose of the gene is relatively straightforward, controlling the levels of expressed protein is much harder. Prof. Heller believes that the best clinical outcomes can be achieved by first optimising the expression profile. In this way, the team has developed a successful protocol for the treatment of malignant melanoma. The deadliest form of skin cancer, occurring with increasing frequency, malignant melanoma will be diagnosed in an estimated 75,000 new patients in 2014. A major health concern, melanoma does not respond well to standard chemotherapeutic agents and is currently ineffective for treatment of advanced disease, which occurs in 20% of cases. Gene therapy offers therapeutic hope for this aggressive disease and unlike current therapies, has the potential to eliminate cancer cells without damaging normal, healthy tissue.

The team first tested the electroporation method in mice with melanoma. Mice were treated with the gene for interleukin-12 (IL-12), which stimulates the immune system to fight the cancer. A powerful immune system stimulates, previous studies investigating IL-12 protein, which produced the desired therapeutic response. Their hope is that with correct delivery and expression of DNA, not only can they achieve a favourable outcome on the primary tumour but also provoke an increased response at distant sites (i.e., on the spreading secondary tumours), through the activation of specialised immune cells.

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FUTURE RESEARCH
Prof. Heller's team are now building on their exciting results in malignant melanoma, paving the way for further clinical trials. The researchers are testing the idea that if IL-12 DNA is delivered under appropriate conditions (i.e. at the right dose and location), a change in the tumour microenvironment will occur that can be associated with an appropriate therapeutic response. Their goal is to characterise the response and identify potential markers that can indicate appropriate delivery and expression - a specific pattern of response. Their hope is that with correct delivery and expression of DNA, not only can they achieve a favourable outcome on the primary tumour but also provoke an increased response at distant sites (i.e., on the spreading secondary tumours), through the activation of specialised immune cells.

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Reference


Personal Response

Your research has significantly advanced the development of in vivo gene electrotransfer as a therapeutic tool. What originally sparked your interest in this area of research?

In the 1990s, we had success delivering chemotherapeutic agents directly to tumours with electroporation. This was a localised response and the oncologists testing the therapy asked if we could enhance it to include effective treatment of distant metastases. The critical aspect was to develop a potentially effective, non-toxic and inexpensive option. We found that gene delivery with electrotrode allows sufficient control of the expressed protein levels, which produced the desired therapeutic result. This led to testing this concept for other potential therapies including cervical and peripheral ischemia, wound healing and DNA vaccine delivery.