

Electrogenetics: a new avenue in precision medicine

- ◆ Electrogenetics is an emerging field in synthetic biology that uses electrical or electrochemical stimulation to control gene expression
- ◆ Benefits include precise control over treatment delivery, dynamic dose control, and the potential for patients to self-manage their conditions when combined with bioelectronic implants or wearable devices
- ◆ One ambition is to develop ways to use electrogenetics to correct certain gene disorders, including chronic diseases such as type 1 diabetes
- ◆ While there is a need for sensitive, effective, non-toxic, and durable electrogenetic-based products, there are no products ready for clinical use at present. However, there are promising clinical applications currently being developed within research settings

Developing electrogenetic cells

Electronic and biological systems need [a functional interface](#) to communicate with each other. Electrogenetics, a sub-field of synthetic biology, provides the necessary toolkit to create special cells that can interpret electrical signals and activate a gene of interest. These cells can be implanted in the body where needed, and the desired gene can be activated when an electrical signal is applied, allowing ‘spatiotemporal’ control over gene expression.

The inspiration for electrogenetics as a tool for controlling gene expression emerged from the study of electrochemically active bacteria, first conducted in the 1970s.¹ Unlike mammalian cells, these bacteria can control gene expression in response to electrical stimuli. To develop mammalian electrogenetic cells, adding specifically engineered components such as electro-sensitive receptors were necessary.²

Advances in the fields of genetics, engineering, and electronics have driven ambitions for designing human cells that can interpret electrical signals. For example, we can now imagine a cell designed to release insulin in response to an electrical stimulus – an exciting prospect for patients with type 1 diabetes. As these fields progress, they offer the prospect of building better electrogenetic systems suitable for clinical use.

At the time of this briefing, electrogenetic approaches to disease management remain in the research domain.

Box 1: Components of an electrogenetic system

Input: the source of electrostimulation derived from conductive materials, such as palladium, or chemical reactions

Designer cell: a special cell modified to contain the appropriate electro-sensitive receptors, and the target which is a gene that produces the desired therapeutic effect

Output: a biological product such as a transcript or a protein produced via the expression of the target gene in response to electrostimulation

The ambitions for electrogenetics in patient care

Put simply, the hope is to implant engineered electrogenetic cells in patients whose own genetic makeup is unable to produce the necessary transcript or protein to allow normal functioning.

There are alternative methods to control gene expression, for example using heat, light or a magnetic field but compared to an electrical field, these can be more toxic to the cell, consume more energy, and require additional components to support effective stimulation of designer cells.³

Indications are that electrogenetics could support clinicians and patients to manage diseases through:

- ◆ **Precise control over treatment delivery:** electrogenetic cells deliver therapeutic outputs precisely where and when needed, enhancing their appeal over traditional medications taken at specific time points
- ◆ **Dynamic dose control:** the intensity and duration of the electrical signal can be adjusted to control the amount of therapeutic output, thereby ensuring patients do not overmedicate
- ◆ **Self-management of disease:** for example, when combined with biomarker monitoring systems such as glucose monitors, electrogenetic systems could be used to trigger insulin release as needed, enabling diabetic patients to manage their condition with minimal clinician intervention. This approach could be beneficial for managing a range of conditions, including chronic pain, cardiovascular disorders, and hormonal imbalances such as hypothyroidism⁴

Integrating electrogenetics with bioelectronic implants

Unlike other cell-based therapy approaches, electrogenetic systems do not require a virus-based vector or editing of the patient genome, minimising unwanted immune response, genetic errors, or off-target effects. However, electrogenetic systems need to be suitably packaged into implants or even wearable devices before they can be used for patients. This may be achieved through:

- ◆ **Bioelectronic implants:** containing electrogenetic cells on one side of the implant and electronic components on the other. These are implanted under a patient's skin and an external power source is used to activate the implant wirelessly

- ◆ [Direct current \(DC\)-actuated regulation technology \(DART\)](#): direct current is used to generate non-toxic levels of reactive oxygen species (ROS) which the cell recognises as electrostimulation. Electrogenetic cells, encased within biopolymers to prevent rejection by the patient's immune system, are implanted in a patient. As most wearables use DC batteries, adding small needles that function as electrodes to the base of wearables and placing them next to implanted electrogenetic cells could allow linking wearables with the DART system
- ◆ [Piezoelectric device](#): Piezoelectric materials produce electricity in response to a change in their shape. When this device – which is about the size of a five pence coin and implanted beneath a patient's skin – is pushed, the force causes the piezoelectric membrane to bend and produce electricity, providing the necessary electrostimulation

Box 2: Electrogenetics to control release of pre-stored proteins

In addition to therapeutic gene outputs, electrogenetics can be used to trigger the release of pre-produced proteins stored within vesicles inside designer cells. Protein-based electrogenetic systems offer faster treatment delivery – within 10 minutes of electrostimulation, compared to gene-based methods which may take several hours. Read: [Electrogenetic systems for type 1 diabetes](#).

Barriers to clinical implementation

To enable clinical uptake of electrogenetic systems, further research and evidence is needed into:^{3,4,5}

- ◆ **Ensuring safety of outputs**: that any output from an electrogenetic system is non-toxic and within normal physiological levels. For example, if the stimuli lead to the release of excessively high insulin levels, this could pose risks to patients
- ◆ **Biocompatible implants**: developing bioelectronic implants with long shelf lives that do not trigger the immune system and risk being rejected by the patient's body
- ◆ **Minimising leakiness**: where genes are activated even when the threshold for electrostimulation has not been met. Optimising receptor numbers to increase the sensitivity of electrogenetic systems and minimising leakiness is an ongoing challenge
- ◆ **Increasing the number of cells on electro-chips**: mouse models require electro-chips with up to 3 million electrogenetic cells, but for use in human subjects, significantly larger numbers - potentially 150 times more – and electro-chips capable of supporting such large number of cells will be needed
- ◆ **Miniaturising bioelectronic chips**: using smaller chips to hold electrogenetic cells could minimise potential side-effects upon implantation
- ◆ **Miniaturisation of the electric field source**: developing compact electric field sources for electrogenetic systems to facilitate integration with existing wearables

Regulation of electrogenetic systems

Without a product ready for clinical use, it is difficult to define what regulations might govern the use of electrogenetic systems. It seems likely that they will be classified as combined Advanced Therapy Medicinal Products (ATMPs) as these electrogenetic systems comprise modified cells integrated with bioelectronic implants. They will therefore need to adhere to [ATMP regulations](#) and may require additional evidence demonstrating that the device meets essential requirements as outlined in the UK Medical Devices Regulations and, where available, the results of an assessment by an approved body.

Box 3: Further ahead

Artificial intelligence (AI) is likely to have applications within electrogenetic systems. If electrogenetic bioelectronic implants are combined with wearables, AI could automate treatment delivery by monitoring biomarkers through the wearable and adjusting dosage through the electrogenetic system. Currently people with diabetes may be offered a [bionic pancreas](#) to monitor glucose levels which uses AI to administer insulin. Further research could be done to assess whether electrogenetic systems could be incorporated as an insulin source.

Another avenue to explore could be combining electrogenetics with other wireless technologies such as magnetogenetics and optogenetics. This might enable the development of multi-stimuli responsive designer cells capable of addressing several patient deficiencies simultaneously, further advancing this promising field in precision medicine.³

Where are we now?

Integration of electrogenetic systems with bioelectronic implants and even wearables will be essential for the feasibility of electrogenetics as a tool for management of diseases. That wearable and implant technologies are already undergoing evaluation in clinical settings may facilitate clinical uptake of electrogenetics.

However, work to bring electrogenetics into healthcare is yet to move beyond the research and innovation space. While human cell-based electrogenetic systems have been successfully engineered, their functionality has primarily been tested in mouse models. Key challenges include ensuring safety, preventing immune rejection, minimizing 'leakiness', and scaling systems for human use. The clinical utility of electrogenetic systems for patient care also remains to be determined.

While electrogenetics is still in development, its therapeutic applications are exciting. From self-managing chronic conditions to allowing dynamic dose control of treatment, this field holds potential to offer novel and safer ways to treat genetic disorders.

References

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