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Review Article

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Publication date:
2022-06

Permanent link:
https://doi.org/10.3929/ethz-b-000547194

Originally published in:
Current Opinion in Chemical Biology 68, https://doi.org/10.1016/j.cbpa.2022.102151

Funding acknowledgement:
785800 - Electrogenetics - Shaping Electrogenetic Interfaces for Closed-Loop Voltage-Controlled Gene Expression (EC)

Available online at www.sciencedirect.com

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Current Opinion in Chemical Biology

Electrogenetics: Bridging synthetic biology and electronics to remotely control the behavior of mammalian designer cells

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Abstract

Electrogenetics, the combination of electronics and genetics, is an emerging field of mammalian synthetic biology in which electrostimulation is used to remotely program user-designed genetic elements within designer cells to generate desired outputs. Here, we describe recent advances in electro-induced therapeutic gene expression and therapeutic protein secretion in engineered mammalian cells. We also review available tools and strategies to engineer electro-sensitive therapeutic designer cells that are able to sense electrical pulses and produce appropriate clinically relevant outputs in response. We highlight current limitations facing mammalian electrogenetics and suggest potential future directions for research.

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Current Opinion in Chemical Biology 2022, **68**:102151

This review comes from a themed issue on **Synthetic Biology (2022)**

Edited by **Wilfried Weber** and **Martin Fussenegger**

For complete overview of the section, please refer to the article collection Synthetic Biology (2022)

Available online 25 April 2022

https://doi.org/10.1016/j.cbpa.2022.102151

Keywords

Synthetic biology, Therapeutic cell engineering, Traceless switch control, Electrostimulation, Electrogenetics.

Introduction

Synthetic biology-inspired cell-based therapy relies on engineered designer cells that are able to "sense" a customized input, "process" it according to a user-designed plan, and finally "produce" a specified therapeutic output [1]. This "sense-process-produce" functionality is often constructed by using genetically encoded elements that can be delivered into suitable cells to either improve their natural function or introduce a non-native function [2,3]. The process of sensing can be done by engineering a "receiver" platform or "receptor" which can be expressed on the surface, or in the cytoplasm or nucleus, of the designer cells to recognize the exogenous signal with high sensitivity and specificity [4,5]. Such receptors use the input signal to activate a biological pathway via recruitment of appropriate downstream molecules to initiate either a customized orthogonal pathway or an endogenous pathway within the cell, leading to the production of a biological output at a programmable level with desired kinetics [6].

The input signal can be either chemical or physical. Organic and inorganic compounds (e.g., rapamycin [7]), disease-related biomarkers (e.g., high levels of glucose in diabetes [8]), stimulatory peptides (e.g., interleukins [9]) and odorants (e.g., volatile spearmint aroma [10]) have been extensively used as chemical inducers for timely control of therapeutic designer cells. However, they can have disadvantages such as limited bioavailability, inappropriate pharmacodynamics, and a broad biodistribution that may lead to unwanted side-effects or lack of precision in the delivery of the therapeutic output. In contrast, physical stimuli such as light, temperature, mechanical disturbances, and magnetic fields offer an efficient, safe and non-invasive traceless approach that enables wireless induction of therapeutic engineered cells with high spatiotemporal precision [6].

Electrogenetics uses electrical fields to control the function of engineered cells [11]. In contrast to other physical inducers, electrostimulation can be done with comparatively simple, affordable, and widely used electronic devices (e.g., smart phones or rechargeable batteries). Electrogenetics can provide a co-factor free approach with possibility of using micron-scale electrodes enabling creation of more miniaturized and compact device, which might not be possible with other physical stimulus like light.

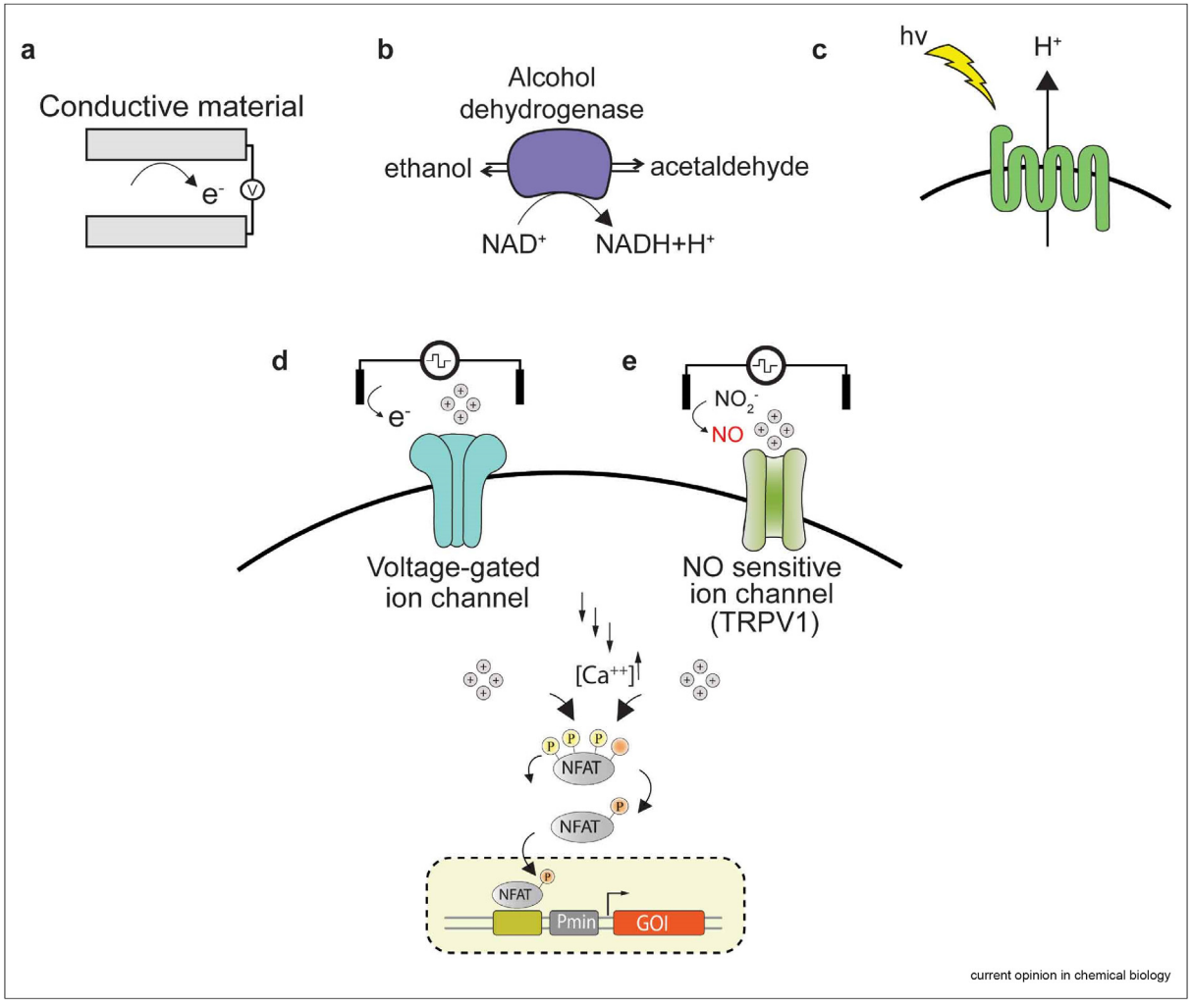
The roots of electrogenetics lie in microbial biotechnology; for example, it was shown that the Arc regulator system in electrochemically active bacteria (EAB) regulates the expression of diverse catabolic genes by sensing electrical potential [7]. However, in this review, we focus

only on the new field of mammalian electrogenetics, in which electrical fields are used to remotely control therapeutic gene expression and protein release in mammalian designer cells. We also introduce the range of molecular tools available for constructing electro-sensitive mammalian designer cells and briefly discuss recently developed bioelectronic implants that mediate the interaction between electrical fields and designer cells. Current limitations and potential developments in mammalian electrogenetics are also discussed.

Strategies for engineering of electro-sensitive mammalian designer cells

Electrogenetics relies on a generated electric field to transfer free electrons for programming designer cells. In general, electrons can be harvested from two sources: conductive materials (e.g., platinum [12]) or molecular proteins (e.g., catalytic proteins [13]) (Figure 1a–c). The electrons may activate designer cells either directly or indirectly (Figure 1d–e). In the direct approach, engineered cells respond to the electrical field itself, whereas the indirect approach involves an intermediate biological or chemical product generated by the electrical field. In the direct strategy, the receptor platform implemented in designer cells is sensitive to electrical pulses and responds with a conformational change. Examples include the voltage-gated ion channels that normally regulate polarization of the plasma membrane in excitable cells such as neurons. A change in transmembrane potential of the cells is detected by voltage-

Figure 1



Tools and strategies for generation of electro-sensitive designer cells. **a-c**) Source of electrons in electrogenetics. **a**) Transfer of electrons through conducting materials for cell induction. **b**) Molecular enzymes can produce H^+ ions and electrons upon enzymatic reaction. **c**) Bacterial proton pumps can pump protons inwardly or outwardly across the plasma membrane to change the cell membrane potential. **d-e**) Strategies for generation of electro-sensitive designer cells. **d**) Direct approach: electrons transferred by an electric field can be directly sensed by designer cells to initiate a planned signaling pathway (e.g., calcium influx) and trigger expression of a specified gene. **e**) Indirect strategy: an applied electric field produces an electro-chemical stimulus (e.g, nitric oxide, NO) which can activate designer cells expressing a suitable receptor (e.g., TRPV1 channel). Receptor activation can be rewired to express a transgene. GOI; gene of interest.

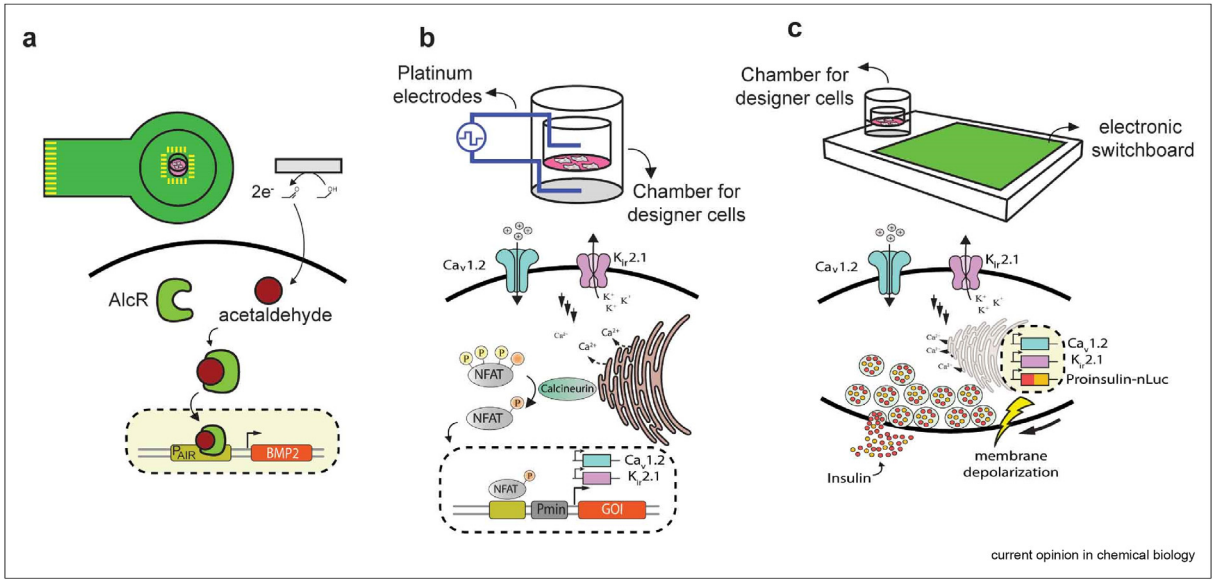
sensing domains that open and close the pore of the voltage-gated ion channels, regulating the passage of selected inorganic ions across the cell membrane [14]. In the indirect strategy, cells do not sense the electrical field directly, but are equipped with a receiver platform enabling them to sense a product of electrostimulation. This "electrochemical" approach is exemplified by the generation of nitric oxide (NO) [15] or reactive oxygen species (ROS) [16] in response to electrical pulses; then, these species activate downstream units (e.g., transcription factors), eventually triggering an engineered pathway to deliver the desired output. In addition, electrochemical reagents (e.g., redox reagents) can directly activate a synthetic promoter within electro-sensitive mammalian cells to induce transgene expression [17,18].

Mammalian electro-cells: Electric field-induced gene expression and protein release in designer cells

Synthetic biology-inspired, electrogenetically mediated gene expression in mammalian cells was initially achieved by implementing an electronic transcription control circuit that linked production of acetaldehyde from electrochemical oxidation of ethanol to acetaldehyde-inducible transgene expression [19]. Here, production of acetaldehyde was facilitated by platinum anode and cathode electrodes at an acidic pH. The produced acetaldehyde binds to a receiver platform, acetaldehyde-dependent transactivator AlcR, in the cytoplasm of designer cells, and the complex activates the acetaldehyde-inducible promoter P_{AIR}, triggering transgene expression (Figure 2a). This system has been used for expression of bone morphogenetic protein-2 (BMP-2) in engineered rat cardiomyocytes, and it successfully increased the contraction frequency (tachycardia). However, this interface was neither direct nor useable under physiological conditions.

The first bioelectronic interface for direct electrical conduction between electrodes and electro-sensitive mammalian designer cells to induce a specified therapeutic protein under physiological conditions was implemented in $_{Electro}$HEK cells [20]. These cells were engineered to ectopically express an electrosensitive L-type voltage-gated calcium channel ($Ca_V1.2$) consisting of α1, α2, δ, and β subunits, which are essential for the functioning of cardiomyocytes, neurons, and endocrine cells [21]. Expression of $Ca_V1.2$ enabled $_{Electro}$HEK cells to convert electrical input via depolarization of the

Figure 2



Mammalian electro-cells. **a**) Production of acetaldehyde by electrochemical oxidation of ethanol via electrodes triggers an acetaldehyde-inducible gene expression system in CHO cells. Generated acetaldehyde diffuses into the designer cells and binds to its receptor (AlcR), thereby activating transcription of BMP-2 gene from an acetaldehyde-responsive promoter. **b**) $_{Electro}$HEK cells. These electro-sensitive designer cells ectopically express a $Ca_v1.2/K_{ir}2.1$ ion channel circuit that triggers calcium influx into the designer cells upon electrostimulation induced by a free-hanging electrode system. The change of calcium level induces dephosphorylation of NFAT transcription factor, causing its translocation to the nucleus, where it triggers transcription of the target gene in the presence of a synthetic expression unit containing NFAT-responsive elements. **c**) $_{Electro}$β cells are engineered to express $Ca_v1.2/K_{ir}2.1$ channel as well as a proinsulin-nLuc construct. Insulin and nLuc are produced as interconnected prohormone thats that traverses the endoplasmic reticulum and the Golgi apparatus before reaching the secretory vesicles where the prohormone convertases 2 and 1/3 create process it into distinct insulin and nLuc molecules. In the unstimulated condition, insulin and nLuc remain inside the secretory vesicles within the designer cells. Electro-stimulation triggers plasma membrane depolarization, which leads to insulin release in as short a period as 10 min after stimulation.

plasma membrane, thereby enabling calcium influx into the cell upon electrostimulation with a free-hanging electrode system (Figure 2b). The change in intracellular calcium concentration was rewired to express a transgene from a synthetic expression unit containing binding sites for activated NFAT transcription factor. In order to reduce the leakiness of the system, $_{Electro}$HEK cells were also co-transfected with an inwardly rectifying potassium channel ($K_{ir}2.1$) to reduce the resting membrane potential. This $Ca_V1.2/K_{ir}2.1$ voltage-gated circuit decreased basal expression of the target gene and improved the overall induction profile of electrosensitive HEK cells. Fine-tuning of transgene expression by altering the voltage or adjusting the electrical pulse length demonstrated that $_{Electro}$HEK cells provide a robust, programmable and reversible electro-inducible gene expression system.

$_{Electro}$HEK is a transcription-based electrogenetics system that induces transgene expression in a time frame of ~7 h after electrostimulation. To develop electrically responsive designer cells with faster kinetics, a similar voltage-gated genetic circuit was introduced into a pancreatic β cell line [22,23] to afford $_{Electro}$β cells [20]. In addition to expressing the voltage-gated channel circuit ($Ca_V1.2/K_{ir}2.1$), $_{Electro}$β cells constitutively express a synthetic proinsulin-nLuc construct that mediates co-secretion of equimolar amounts of insulin and nLuc. In the unstimulated condition, $_{Electro}$β cells produce and store proinsulin-nluc within granular vesicles. These granules release insulin to their surroundings only upon electrostimulation, irrespective of the glucose concentration in the vicinity (Figure 2c). In $_{Electro}$β cells, the peak of insulin release can be reached within 10 min after electrostimulation. In a proof-of-concept study to demonstrate the ability of electro-responsive designer cells to treat experimental diabetes, a miniaturized wireless-powered bioelectronic implant containing electrodes on either side of a semipermeable membrane was placed subcutaneously on the dorsal side of an alloxan-induced type-1 diabetic mouse model. An extracorporeal field generator provided wireless energy transmission for electric field activation. Rapid insulin secretion by the electrostimulated $_{Electro}$β cells reversed hyperglycemia in the mouse model.

Mammalian electrogenetics; advantages, limitations and future possibilities

Using an electronic device to activate therapeutic cells requires translating an electrical signal into a form that can be recognized by living cells [20,24]. Although physical stimuli such as heat [25] and light [26,27] have been used by electronic devices to program designer cells, they are associated with some major challenges, including cytotoxicity [28], the need for sophisticated chemical or inorganic cofactors [29], and the need for a considerable amount of energy to operate the light or heat source [25,30,31]. Therefore, developing designer cells that rely on a wirelessly delivered cofactor-free electric field is expected to revolutionize future human therapies by combining minimal cytotoxicity with high efficiency. However, some problems remain in translating therapeutic electrosensitive designer mammalian cells for human therapy. First and foremost, the electro-chips used for stimulation of designer cells are still too large; there is an urgent need for miniaturized biocompatible electronic devices that can be easily operated within the body with minimal side-effects, such as inflammation, upon implantation [32]. Second, the number of the cells that can be plated on electro-chips is currently quite limited. Although the number of $_{Electro}$β cells that could be used was sufficient for the treatment of type-1-diabetic mice [20], humans would require a much larger number of transplanted cells. Therefore, research to increase the number of electro-designer cells that can be transplanted is necessary. Cell encapsulation is a standard technique for cell transplantation [33], so encapsulation of electro-designer cells in conductive polymers might be one way to tackle this problem [34]. Third, an extracorporeal field generator was used to wirelessly power and control the bioelectronic implants containing $_{Electro}$HEK and $_{Electro}$β cells [20]. Interestingly, it would be useful to link miniaturized extracorporeal field generator interface to readily available wearable electronic devices such as smartphones and smartwatches, which can bridge electrogenetics to mobile health technologies [35]. Such wearable electronic devices are often already equipped with health-related biosensors that can monitor various physiological parameters of patients. They can also communicate with other ingestible or implantable devices to transfer biological data through the internet of things (IOT), and even analyze the data [36] and helps self-disease management. A good example of these wearable electronic devices is the artificial pancreas, which can sense the level of glucose in the blood of diabetic patients and automatically inject the correct amount of insulin into the body through an integrated insulin pump [37]. Akin to the artificial pancreas, next-generation mammalian bioelectronics may sense disease-related biomarker(s) with an electronic device (instead of designer cells) and then electronically stimulate designer cells to produce therapeutic agent(s) in an autonomous way. Such an electrogenetically mediated closed loop system could not only provide a digital-based biosensor platform to sense biomarkers, but also routinely transfer biological data to a physician or care person for disease management.

We believe mammalian electrogenetics can revolutionize real-time diagnostic-driven therapies in the near future. In addition, electrogenetic-based therapy in combination of other already existing well established traceless strategies (e.g., thermogenetics, optogenetics, magnetogenetics, mechanogenetics) may have the potential to create multi-tasking cells in which each

function is separately programmable by a different wireless control system. Translation of such devices to the clinic will require the cooperation of electronic engineers, synthetic biologists and physicians to develop new bioelectronic devices and sensitive electro-inducible designer cells that can recognize disease-related biomarkers and deliver an appropriate therapeutic output in a timely manner.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Work in the laboratory of M.F. is financially supported in part through a European Research Council advanced grant (ElectroGene, no. 785800) and in part by the National Centre of Competence in Research (NCCR) for Molecular Systems Engineering. The authors would like to thank Preetam Guha Ray for helpful discussions and critical comments on the manuscript.

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