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Current Opinion in Biotechnology

Prosthetic gene networks as an alternative to standard pharmacotherapies for metabolic disorders

Boon Chin Heng[1,2], Dominique Aubel[3] and Martin Fussenegger[2,4]

Synthetic biology makes inroads into clinical therapy with the debut of closed-loop prosthetic gene networks specifically designed to treat human diseases. Prosthetic networks are synthetic sensor/effector devices that could functionally integrate and interface with host metabolism to monitor disease states and coordinate appropriate therapeutic responses in a self-sufficient, timely and automatic manner. Prosthetic networks hold particular promise for the current global epidemic of closely interrelated metabolic disorders encompassing obesity, type 2 diabetes, hypertension and hyperlipidaemia, which arise from the unhealthy lifestyle and dietary factors in the modern urbanised world. This review will critically examine the various attempts at constructing prosthetic gene networks for the treatment of these metabolic disorders, as well as provide insight into future developments in the field.

Addresses
[1] Department of Biological Sciences, Sunway University, Bandar Sunway 47500, Selangor Darul Ehsan, Malaysia
[2] Department of Biosystems Science and Engineering (D-BSSE), ETH Zurich, Mattenstrasse 26, CH-4058 Basel, Switzerland
[3] IUTA Département Génie Biologique, Université Claude Bernard Lyon 1, Boulevard du 11 Novembre 1918, F-69622 Villeurbanne Cedex, France
[4] Faculty of Science, University of Basel, Mattenstrasse 26, CH-4058 Basel, Switzerland

Corresponding author: Fussenegger, Martin (fussenegger@bsse.ethz.ch)

Current Opinion in Biotechnology 2015, **35**:37–45

This review comes from a themed issue on **Pharmaceutical biotechnology**

Edited by **Guillermo de la Cueva-Méndez** and **Dror Seliktar**

http://dx.doi.org/10.1016/j.copbio.2015.01.010

Introduction

Ever since the dawn of medical therapy, the basic concept of pharmacotherapy, that is, the use of specific chemicals or natural products to interfere with critical disease targets to trigger a metabolic bypass reaction or complement a molecular deficiency, has remained the mainstay of therapeutic intervention. Nevertheless, there are inherent conceptual limitations to this common approach to disease therapy. First, as therapy is often initiated after diagnosis, disease is treated rather than prevented. Second, although designed to affect a specific molecular interaction in an extremely complex metabolic network, systemically administered (small-molecule) drugs often exhibit side effect-prone off-target activities.

In recent years, however, rapid advances in molecular biology and bioinformatics have facilitated the development of the new field of synthetic biology, which could potentially offer an alternative to conventional pharmacotherapy of human diseases without its inherent limitations. Synthetic biology involves the syncretic application of computing and engineering principles to molecular biology, which in turn enables the systematic rational construction of desired functionality within biological systems [1,2]. This takes the form of complex application-based synthetic gene circuits or networks [3,4], of which a diverse array has now been constructed, including genetic switches [5–10], oscillators [11–17], filters [18–24] and communication modules [25–29]. These are somewhat analogous to the functions of similarly named electronic devices. Although the field of synthetic biology was initially focused on prokaryotic microbial systems, it is now beginning to be applied to human disease intervention and preclinical research [30,31]. With the advent of bioinformatics and computer-aided design software specifically for applications in synthetic biology [32,33], the pace of progress has greatly accelerated in this field.

From therapeutic synthetic gene circuits triggered by exogenous signals to closed-loop prosthetic gene networks

Therapeutic synthetic gene circuits have been constructed for a diverse range of human diseases, including cancer, immunological disorders, infectious diseases and metabolic disorders [30,31]. As in conventional medical treatment, in which the dosage and timing of drug administration have to be carefully scheduled and tailored to the individual patient's symptoms, there is also a need for precise spatiotemporal control of therapeutic transgene expression by engineering 'smart' trigger systems within synthetic gene circuits, so as to achieve maximal efficacy and optimal treatment outcome. Controlled expression of therapeutic transgene expression could be rewired to exogenous input signals, but the disadvantage

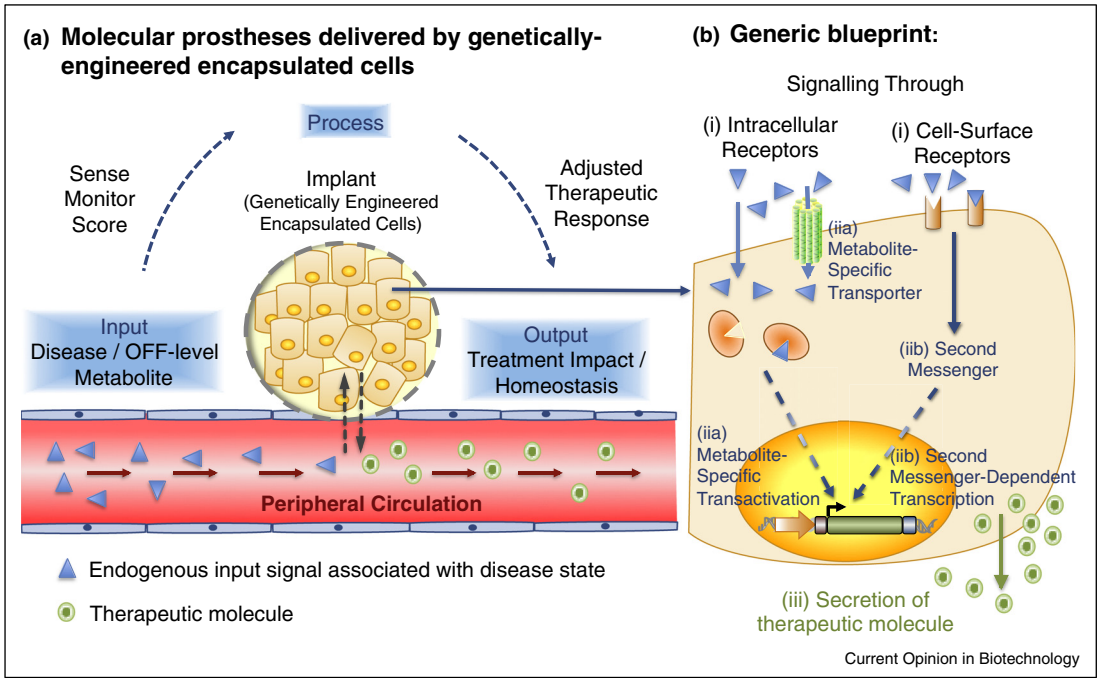
of this approach is that it requires regularly scheduled switching on/off of appropriate input signals, similar to the rigorous dosing regimen associated with the administration of conventional drugs. A better strategy may be to design therapeutic synthetic gene networks to be responsive to endogenous input signals *in vivo*, that is, the presence of specific signalling molecules, metabolites or pathogenic toxins associated with disease states. This would avoid the inconvenience of regularly switching on/off exogenous input signals to control expression of therapeutic transgenes. When the endogenous input signal is directly associated with disease symptoms and is attenuated by the action of the therapeutic transgene, the synthetic gene circuit is referred to as a prosthetic gene network (Figure 1). In essence, this is an autonomous, self-controlled, closed-loop system whereby an endogenous input signal that correlates with the disease state is sensed by the network and automatically corrected.

As systems biology is revealing gene–function correlations and metabolic network dynamics at great pace and synthetic biology enables bottom-up, *de novo* design of genetic devices with predictable behaviour, there is now a real possibility of developing novel treatment strategies with prosthetic gene networks. Upon functional integration and interfacing with the host cell metabolism, prosthetic gene networks could monitor disease-relevant metabolites, restore homeostatic balance of aberrant metabolite concentrations, and coordinate adjusted diagnostic, preventive or therapeutic responses in an automatic and self-sufficient manner, thereby making classic pharmacotherapy (involving taking pills and getting injections in specified dosages at particular time-points) likely to become a thing of the past. This review provides an overview of the progression from therapeutic synthetic gene circuits triggered by exogenous signals to closed-loop prosthetic gene networks. It critically examines the latest research on prosthetic gene networks for treatment of the current global epidemic of human metabolic diseases and speculates on the trajectory of this field in the near future.

Metabolic diseases — a current global epidemic that could be targeted by prosthetic gene networks

Prosthetic gene networks hold particular promise for therapy of metabolic diseases caused by dysfunctional regulation and imbalance of specific metabolites. Currently, the entire spectrum of human metabolic diseases, encompassing diabetes, obesity and high blood pressure, constitutes a global epidemic that is becoming more widespread from year to year due to the unhealthy

Figure 1



Molecular prostheses delivered by genetically engineered encapsulated cells **(a)** could be assembled from similar biological parts following a generic blueprint **(b)**: (i) intracellular or cell-surface receptors specific for disease-related metabolites; (iia) (intracellular receptors only) a validated set of transcription-activation or transcriptional-silencing domains, receptor-specific operator modules, and a metabolite-specific transporter (optional); (iib) (cell-surface receptors only) a set of specific second-messenger-responsive promoters and a collection of cell lines permissive for the desired signal transduction; (iii) an effector gene encoding a therapeutic molecule that degrades the metabolite, triggers competing metabolic pathways or provides diagnostic output.