Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Biomedical Engineering

Synthetic biology – Engineering cell-based biomedical devices

Viktor Haellman[1] and Martin Fussenegger[1,2]

Abstract

Synthetic biology applies rational bottom-up engineering principles to create cell-based biological systems with novel and enhanced functionality to address currently unmet clinical needs. In this review, we provide a brief overview of the state-of-the-art in cell-based therapeutic solutions, focussing on how these integrated biological devices can enhance and complement the natural functionality of cells in order to provide novel treatments. We also highlight some blueprints for synthetic biology-inspired approaches to developing cell-based cancer therapies, and briefly discuss their future clinical potential.

Addresses

[1] Department of Biosystems Science and Engineering, ETH Zurich, Mattenstrasse 26, CH-4058 Basel, Switzerland

[2] Faculty of Science, University of Basel, Mattenstrasse 26, CH-4058 Basel, Switzerland

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

Current Opinion in Biomedical Engineering 2017, **4**:50–56

This review comes from a themed issue on **Synthetic Biology and Biomedical Engineering**

Edited by **Charlie A. Gersbach**

Received 12 June 2017, revised 22 September 2017, accepted 26 September 2017

https://doi.org/10.1016/j.cobme.2017.09.010

Keywords

Synthetic biology, Engineered mammalian cells, Theranostics, Personalized medicine, Cell therapy.

Introduction

Despite continuous advances in the field of biomedicine, diagnostic tools such as point-of-care technologies are still unable to reliably interpret the intricate relationship between genotypes and disease onset or progression, or predict and control the therapeutic efficacy of pharmaceutical agents based on individual patients' needs. Consequently, modern medicine is currently shifting focus towards personalized treatment strategies, where therapeutic strategies are designed in a bottom-up and patient-specific way. In this context, the interdisciplinary field of synthetic biology has entered the limelight as a field that interprets biology from the mind-set of computer programmers, developing rational and tuneable genetic programs that plug seamlessly into the core architecture of cells to regulate natural and synthetic cellular processes in a predetermined way. By applying this analogy to clinical issues and interpreting cells as individual nodes in a higher-order machine (i.e., the human body), synthetic biology aims to leverage biology by creating cell-based biomedical devices for disease diagnostics and even to directly elicit a beneficial response with superior specificity, timing, and therapeutic dosage control compared to traditional pharmacological treatment strategies. Indeed, synthetic biology opens up the possibility of linking disease diagnostics with autonomously regulated *thera*peutic action to create cell-based theranostic solutions within a single integrated system, thereby inaugurating a new era of precision medicines with customizable solutions according to the needs of each individual patient.

Engineering cell-based biomedical devices

The core architecture of engineered genetic systems consists of discrete sensory modules that serve to access and process relevant endogenous or exogenous data. These core biological sensors are then integrated into transcriptional-control modules through cell and tissue-specific promoters, as well as synthetic trigger-regulated transcriptional response systems, hence allowing user-defined targeting and/or induction of transgene expression in response to diffusible molecules [1–8]. Thus, synthetic systems can be engineered to express a therapeutic gene in a tissue-specific manner (e.g., for gene therapy) or employed as diagnostic devices by linking the sensor component to an easily detectable extracellular or systemic signalling molecule [9–11]. For example, by forcing a tumour-specific promoter to express a user-defined reporter construct, this approach effectively transforms cancer cells into diagnostic devices signalling their own presence in the body [12•]. Further, the ability to customize such genetic sensors to integrate individual endogenous signal transduction events and expression of transcription factors enables the functional rewiring of endogenous cellular processes to a user-defined output [13–15,16•,17••].

Encoding synthetic sensory devices into core regulatory domains of RNA molecules and proteins further enables fast-acting functional control of translational and post-translational events that can be fine-tuned in response to user-defined endogenous or exogenous inputs [18–20,21•,22,23•,24•]. However, whereas intracellular sensory devices are limited to a relatively small range of intracellular and diffusible molecular inputs, cells also

naturally possess a vast range of surface receptors that can be harnessed to control distinct intercellular functions. For instance, by developing engineered transcriptional control devices that capture receptor activation through their specific intracellular signalling cascades, synthetic biology has demonstrated that the natural sensing ability of cell-surface receptors can be functionally rewired to trigger quantitative expression of a reporter gene (i.e., a diagnostic device) or a therapeutic protein (i.e., a therapeutic device) [13–15]. To further expand the repertoire of sensory devices that integrate arbitrary inputs and trigger a user-defined output, substantial effort has been dedicated to design synthetic receptors with novel sensory and signal transduction capabilities [25–28]. A prominent example is the chimeric antigen receptors (CARs) used to engineer T cells that specifically target cancer cells. These synthetic receptors consist of an antigen-specific single-chain variable fragment (scFv) derived from a monoclonal antibody fused to the core intracellular signalling domain from the T cell receptor (TCR; CD3ζ) to trigger T cell activation, and various costimulatory domains to rewire intracellular signal transduction to auxiliary immunological functions (e.g. cytotoxicity, proliferation, cytokine production, and survival) [29]. Notably, although CARs allow for flexible user-defined retargeting simply by swapping the ligand-binding scFv domain, intracellular processing and signal transduction are limited to endogenous signalling cascades. To facilitate discrete user-defined signal transduction and cell reprogramming without interfering with endogenous processes, two platforms recently developed by Leonard and colleagues, and Lim and colleagues hold great promise as universal synthetic sensory systems for soluble and surface ligands, respectively [30•,31••,32••]. The first example, by Leonard and colleagues, is based on a modular extracellular sensor architecture (MESA), consisting of two transmembrane chains, each bearing a scFv that is fused to either an intracellular protease chain or a target chain containing the protease ligand and a synthetic transcription factor [30•]. Upon binding to the target ligand, the two receptor fragments dimerize and trigger proteolytic shedding of the synthetic transcription factor, initiating an exogenous transcriptional response. Additionally, by integrating the programmable clustered regular interspaced short palindromic repeats (CRISPR) genome regulation system [33,34], MESA can directly reprogram endogenous cellular processes in response to a user-defined input [31••]. Analogously, Lim and colleagues demonstrated that by using a minimal synthetic Notch (synNotch) construct with interchangeable ligand-binding and signal transduction domains, cells can be programmed to transduce user-defined cell-surface ligand recognition through a discrete signal transduction event [32••].

Cell-based theranostic devices

By linking the output from endogenous or synthetic sensory devices to a clinically beneficial action, cells can be genetically programmed to function as therapeutic effectors. This approach aims to create cell-based theranostic solutions within a single integrated system that continuously and quantitatively synchronizes disease diagnostics with an autonomously regulated therapeutic action to attenuate and prevent disease-related symptoms in real-time (Fig. 1a) [3,4,13–15,17••,35••–37]. An illustrative example by Bai and colleagues recently showed how a cell-based theranostic device can be engineered to function as an integrated protective system against liver failure (Fig. 1b) [35••]. By functionally rewiring the human G-protein-coupled bile acid receptor TGR5 to initiate production of hepatocyte growth factor (HGF), they demonstrated how the systems could be tuned to integrate liver injury-associated pathophysiological bile acid levels and to generate dose-dependent protection against acute drug-induced liver failure in mice. Theranostic devices have also been developed to identify unrelated higher-order biological functions (e.g., emotional state) or complex immune disorders (e.g., pro-inflammatory cytokines) and provide vital treatment options at optimal time-points [14,15].

Synthetic cell-based theranostic systems have also been deployed to functionally complement, bypass, and even reconstitute defective body functions by integrating disease-related molecular or physiological cues. For example, Saxena and colleagues developed a cell-based system that restored the pituitary-thyroid feedback loop in an experimental Graves' disease model (Fig. 1c) [36••]. Since the otherwise tightly controlled thyroid hormone homeostasis is disrupted in Graves' disease by autoantibodies targeting the thyroid-stimulating hormone receptor, the natural regulatory function of the pituitary-thyroid feedback control is lost, resulting in unpredictable pathophysiological thyroid levels. They rewired the nuclear thyroid hormone receptor to the expression of a thyroid-stimulating hormone receptor agonist that competes with the autoantibodies, and showed that this synthetic theranostic system could effectively act as an intermediate functional node that successfully restored the endogenous network regulating thyroid hormone homeostasis. Analogously, Ye and colleagues created a cell-based system to manage prediabetic insulin resistance (Fig. 1d) [37]. By rewiring the signalling cascade of human insulin receptor to a synthetic hybrid transcription factor driving the expression of adiponectin – a protein hormone that stimulates insulin-sensitivity in target tissues such as skeletal muscles or adipose tissue, they were able to reverse the insulin resistance syndrome and prevent the development of type-2 diabetes in a mouse model of diet-induced obesity.