



Upgrading biomaterials with synthetic biological modules for advanced medical applications☆



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ABSTRACT

One key aspect of synthetic biology is the development and characterization of modular biological building blocks that can be assembled to construct integrated cell-based circuits performing computational functions. Likewise, the idea of extracting biological modules from the cellular context has led to the development of *in vitro* operating systems. This principle has attracted substantial interest to extend the repertoire of functional materials by connecting them with modules derived from synthetic biology. In this respect, synthetic biological switches and sensors, as well as biological targeting or structure modules, have been employed to upgrade functions of polymers and solid inorganic material. The resulting systems hold great promise for a variety of applications in diagnosis, tissue engineering, and drug delivery. This review reflects on the most recent developments and critically discusses challenges concerning *in vivo* functionality and tolerance that must be addressed to allow the future translation of such synthetic biology-upgraded materials from the bench to the bedside.

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1. Introduction

The diversity and number of biological modules that nature has evolved is astounding and we have only begun to understand the intriguing complexity that underlies life. Fortunately, the general composition of biological processes can often be subdivided into individual steps, facilitating their investigation. Hereby, the discovery of basic biological modules and the description of their functional principles has opened the doors for the emergence of synthetic biology. At the heart of this relatively young field is the idea of considering biological parts from an engineer's point of view. In simple terms, modules can be extracted, characterized, and assembled to novel "artificial" systems that fulfill desired functions [1,2]. Moreover, in the same way as electronic or computer engineers base their systems on computations, synthetic biologists aim at conceiving biological parts and devices in mathematical terms that allow the modeling and performance prediction of newly developed systems [3,4].

This modular synthetic biology design approach promoted significant innovations in the biomedical [5,6], energy [7,8], environmental [9,10], and chemical [11] sectors. While the impact of synthetic biology in these sectors is summarized elsewhere (see references above), we here review how innovations can emerge by combining synthetic biology tools and principles with concepts from materials sciences. We describe how materials can be interfaced with synthetic biological parts, devices, and systems and how they can be applied for advanced drug delivery.

So far, synergies between synthetic biology and materials sciences have been implemented at three interfaces: (i) the use of synthetic biological organisms to synthesize custom-tailored (cell-containing composite) materials, (ii), the use of materials to regulate synthetic biological networks in cells, and (iii) the application of synthetic biological building blocks, such as sensors and switches, to design interactive materials systems.

At the first interface, polymer design rules are genetically encoded and transferred into engineered cells. This approach has successfully been applied to synthesize defined polymer building blocks (reviewed in [12]) such as polysaccharides [13], defined protein and DNA nanostructures [14–16], inorganic nanoparticles [17] or precursors for polymer synthesis [18]. For example, engineered proteins comprising domains from mussel foot proteins and *E. coli* amyloid curli fibers resulted in hierarchically self-assembling materials with strong underwater adhesive properties outperforming their natural counterparts [19]. The Lu group extended this approach to synthesize environmentally responsive composite materials, composed of bio-based polymers and the organisms required for their production [20]. To this aim, *E. coli* was engineered to synthesize amyloid fibrils that self-assemble to amyloid-based materials allowing either externally controllable or autonomous patterning. The amyloid fibers were further genetically engineered to contain orthogonal anchor motifs that enabled a specific functionalization with gold nanoparticles or quantum dots to synthesize environmentally responsive biofilm-based electrical switches. This study sets a blueprint of how (living, self-renewing) composite materials with desired functionality can be designed [20,21].

At the second interface, polymer materials are applied to control the function of engineered cells in time and space. In a pioneering work, Deans et al. developed a 3D material based on poly(lactic-co-glycolic acid) (PLGA) covalently functionalized with isopropyl β -D-1-thiogalactopyranoside (IPTG) [22]. The ester bond used for coupling IPTG to the polymer backbone hydrolyzed in a defined manner resulting in the controlled release of IPTG into the 3D material. The release rates were adjusted to induce transgene expression in embedded Chinese hamster ovary (CHO) cells engineered with an extremely tight IPTG-responsive gene switch [23]. This system was applied for the local induction of gene expression in mice. A complementary approach was performed by Choi et al. [24] who developed light-guiding hydrogels to illuminate optogenetic, glucagon-like peptide-1 (GLP-1) secreting

cells in diabetic mice to correct blood glucose concentrations [24,25]. Similarly, Liu et al. applied polymer-encapsulated bacteria for building communicating spatially restricted bacterial consortia [26]. These combined materials sciences / synthetic biology strategy set the stage for precise local genetic interventions that are not addressable by classical synthetic biological approaches relying on systemically administered soluble inducers only.

At the third interface, modular synthetic biological building blocks such as sensors, structural motifs, or switches are directly coupled to (polymer) materials to render these inactive chemical structures interactive. This approach requires the transfer of the synthetic biological building blocks to an *in vitro* background and their subsequent functional coupling to the materials framework (Fig. 1).

The feasibility and potential applicability of the first two interfaces have only recently been demonstrated in impressive work that is expected to be followed by further break-throughs and applications. At the third interface, several approaches have already emerged showing a highly attractive application potential in patient-compliant drug delivery. This review gives an overview of these approaches describing (i) how synthetic biological building blocks can be transferred from cells to *in vitro* systems, (ii) how this can be applied to render inactive materials interactive, and (iii) how resulting materials systems can provide novel solutions in drug delivery. We conclude by discussing challenges towards clinical applications that need to be overcome to realize the huge potential of interfacing synthetic biology with materials sciences.

2. Towards cell-free systems

Bacterial, insect, and mammalian cell-free protein expression based on purified components or on cell extracts has been utilized for the synthesis of various proteins, including difficult to express disulfide-bonded constructs such as antibody fragments [27–30]. These systems represent valuable tools for the design and construction of synthetic biological gene networks *in vitro*. The potential of assembling basic biological units in well-defined *ex cellulo* environments was impressively demonstrated by Karzbrun et al., who assembled double-stranded deoxyribonucleic acid (DNA) brushes in silicone compartments to fabricate artificial cells [31]. These cells were connected via diffusive capillaries to a deep-flow channel that supplied an *Escherichia coli* cell extract to provide the necessary ingredients for *in vitro* protein synthesis in the DNA compartments. The system allowed transcriptionally controlled protein expression and, by means of the capillary system, diffusion-based cell-to-cell communication. The elegance of the approach lies in the minimalist functional principle that is a promising basis for predictive assembly and investigation of biological networks. In another recent study, a method was reported for the generation of *in vitro*, paper-based synthetic gene networks [32]. For this, cell-free expression systems were embedded in the cellulose matrix of paper. This principle was applied as an *in vitro* diagnostics platform for the detection of antibiotic resistance genes, glucose, or for rapid prototyping of an Ebola virus sensor as well as more complex transcriptional synthetic gene networks.

These examples clearly illustrate the feasibility of the synthetic biology-based engineering concept of "artificial" biological systems in a cell-independent context. Unaffected by cellular interference, they are expected to be robust and controllable. In parallel to bottom-up approaches for the assembly of novel biological systems, researchers have started to extract minimal structural and functional biological units and, based on their physical and (bio-)chemical properties, have engineered and characterized them from a materialistic point of view. In this respect, nature has produced a plethora of biomaterial modules, selected in their biological context for optimal performance through natural evolution. Hence, it is understandable that distinct biological building blocks and their associated properties are increasingly utilized for the development of synthetic biomaterials. Interestingly, applied

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