Nanobiohybrids: Materials approaches for bioaugmentation

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Nanobiohybrids, synthesized by integrating functional nanomaterials with living systems, have emerged as an exciting branch of research at the interface of materials engineering and biological science. Nanobiohybrids use synthetic nanomaterials to impart organisms with emergent properties outside their scope of evolution. Consequently, they endow new or augmented properties that are either innate or exogenous, such as enhanced tolerance against stress, programmed metabolism and proliferation, artificial photosynthesis, or conductivity. Advances in new materials design and processing technologies made it possible to tailor the physicochemical properties of the nanomaterials coupled with the biological systems. To date, many different types of nanomaterials have been integrated with various biological systems from simple biomolecules to complex multicellular organisms. Here, we provide a critical overview of recent developments of nanobiohybrids that enable new or augmented biological functions that show promise in high-tech applications across many disciplines, including energy harvesting, biocatalysis, biosensing, medicine, and robotics.

INTRODUCTION

For billions of years, life has been constantly evolving to adapt to ever-changing environmental niches on Earth. Changes in nutrient level, geographic location, temperature, pressure, moisture, salinity, or pH can alter biological functions and cause mutations to genetic information, which leads to the evolution of life (1). A fascinating yet challenging-to-overcome example is the antibiotic resistance developed by different strains of deadly bacteria in response to prolonged exposure to antibiotics (2). In the 1970s, genetic engineering was first introduced as a man-made, highly potent strategy for modifying life at the molecular level. Recent developments in precision genome engineering, such as zinc finger proteins (3) and CRISPRs (4), have substantially enhanced the versatility of gene editing. Nevertheless, these techniques still face several challenges including high levels of complexity, noise, epigenetics, and mutations; difficulties in characterization, standardization, and modularity; and a risk of accidental release into the wild, among other things (5). Moreover, ethical boundaries (6) have not yet been agreed on, which recently led to the first embryonic genetic modification of humans (7). In addition, genetic modification is currently irreversible, meaning that genetically modified organisms (GMOs) cannot return to their native state, which has raised notable social concerns, such as the recent debate about GMOs in agriculture (8).

The rapid explosion of materials research and nanotechnology in the past few decades has recently allowed us to explore alternative strategies for enhancing existing, or enabling completely new, functions within biological systems. With careful material design and construction, many synthetic materials have been successfully coupled with biological systems, demonstrating new extrinsic functional properties that surpass many existing natural capabilities of biosystems, such as the adaptation to fatal environments (9–11), the ability to prolong life cycles (12), and photosynthesis in nonphotosynthetic species (13). Biological species have gone through millions of years of evolution to achieve many of their biofunctionalities; however, given the amazing compositional and structural diversity of advanced synthetic materials, it is expected that strategies for the integration of functional synthetic materials with biological systems for the design and engineering of nanobiohybrids are a more rapid, powerful, and cost-effective alternative than natural evolution or genetic engineering.

Notable effort in the past decade has been devoted to the design of nanobiohybrid systems, which broadly encompasses composite materials that have both a biologically derived component and a synthetic component. The biological component can be anything from purified biomolecules (14) (e.g., DNA and proteins) to complex biological systems (11, 15) (e.g., living cells, tissues, and organisms), while the synthetic component can be inorganic materials (16, 17) (e.g., carbon materials, CaCO₃, SiO₂, Au, and iron oxide), organic materials (18, 19) (e.g., polymers and lipids), or hybrid materials (14, 20) [e.g., metal-organic frameworks (MOFs) and metal-phenolic networks (MPNs)]. In these nanobiohybrid systems, the choice of both biological and synthetic components has an impact on different aspects of the final biofunctionality (Fig. 1).

Here, we investigate the recent synthetic materials and engineering efforts surrounding the construction of advanced nanobiohybrid systems for augmenting biofunctionality. Although many functional materials have been widely exploited for biotechnological applications such as biosensing and in vivo drug delivery (e.g., inorganic or hydrogel particles hosting bioactive macromolecules), in this review, we instead primarily focus on materials that introduce novel functionalities to endow or augment the properties of the biological component. Construction of nanobiohybrids generally follows two routes: (i) endogenous (internal) bioaugmentation: engineering synthetic materials inside biosystems, and (ii) exogenous (external) bioaugmentation: engineering synthetic materials outside biosystems (Fig. 1). In the first section, we focus on the materials used for constructing nanobiohybrid systems, ranging from inorganic materials to polymers to hybrid materials, while in the second section, we focus on the enhanced/novel biological functionality arising from the nanobiohybrid systems (see table S1). In the last section, we provide an

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overview and outlook of the possible synthetic methods and technologies that could be adapted for future bioaugmentation applications.

**SYNTHETIC STRATEGIES AND MATERIALS FOR CONSTRUCTING NANOBIOHYBRIDS**

**Inorganic materials**

Because of the inherent stability, robustness, and diverse functionalities, a variety of inorganic nanomaterials have been applied in constructing nanobiohybrid systems. In particular, the outstanding mechanical strength, ultrahigh surface area, and excellent electrical and thermal conductivity of low-dimensional carbon materials, such as graphene oxide (GO) and carbon nanotubes (CNTs), are promising candidates for constructing advanced nanobiohybrids, which could enable previously unknown solar-biochemical or solar-chemical pathways not possible with either natural or artificial systems alone and therefore has found vast potential (21). In addition, other inorganic nanomaterials, such as hydroxyapatite minerals and calcium carbonates, have been applied in the nanobiohybrid systems due to their extreme thermostability and biocompatibility.

**Exogenous bioaugmentation**

In a pioneering work of interfacing CNTs with living cells, a glycopolymer, poly(methyl vinyl ketone) backbone (C18) decorated with α-N-acetylgalactosamine residues, was coated onto CNTs. The sugar polymer mimics cell surface mucin glycoproteins, while the C18 tail provides a hydrophobic anchor for CNT surface assembly (25). To interface CNTs with cells, the authors introduced *Helix pomatia* agglutinin (HPA) to cross-link the cells and the glycopolymer-functionalized CNTs. Two-dimensional (2D), carbon-based materials have also been used to augment living cells. To interface GO with living cells, a multistep coating approach was used, which allowed the fine tuning of the thickness and surface charge of the GO-coated cells (26). Using this approach, the layer-by-layer (LbL) consecutive assembly of alternatively charged GO (GO-COO− and amine-functionalized GO) can be achieved on the living yeast cells (27).

In Tang and co-workers’ report (22), a biocompatible and noncytotoxic coating composed of positively charged poly(diallyldimethylammonium chloride) (PDADMAC) and negatively charged poly(styrene sulfonate) (PSS) was built on living cyanobacteria in a LbL fashion. PDADMAC could then induce the in situ silicification within 30 min (Fig. 2A) (22). Choi and co-workers (28) reported coating of mammalian cells with silica, where the nanobiohybrids could be potentially used as drug carriers or cell-based sensors. The cytoprotective silicification
around HeLa cells required a catalytic template poly(ethyleneimine) as a primary layer on the cell surface, and the silica shell was formed with a mixture of tetramethyl orthosilicate and 3-mercaptopropyl trimethoxysilane. To introduce extrinsic cellular functionalities, Choi and co-workers (29) synthesized nanocoating of poly(norepinephrine) and inorganic silica on living yeast cells for cytoprotection against lytic enzymes and ultraviolet (UV) irradiation. In a follow-up study, the same group applied iron oxide magnetic nanoparticle-functionalized silica coatings on living cells (30).

In Yang and co-workers’ work (31), a nanobiohybrid system was constructed by precipitating CdS semiconductor nanoparticles from \( \text{Cd(NO}_3\text{)}_2 \) onto the surface of nonphotosynthetic, \( \text{CO}_2 \)-reducing bacterium \textit{Moorella thermoacetica}. Interfacing CdS with the bacteria allowed for the generation of an electron and hole pair from the cell surface-attached CdS under light irradiation, which, in turn, activated the Wood-Ljungdahl pathway to synthesize acetic acid from \( \text{CO}_2 \). The CdS-functionalized \textit{M. thermoacetica} system was also reported to oxidize disulfide form cysteine from the thiol amino acid cysteine using tandem reactions, highlighting that nanobiohybrids can carry out complex, artificial biochemical cascades (32). Yang and co-workers (33) reported using a semiconductor nanowire bacteria nanobiohybrid system to convert carbon dioxide to value-added chemicals. The silicon nanowire arrays, which acted as light-capturing units, were passivated by a TiO\textsubscript{2} protection layer. The anaerobic homoaocetogen, \textit{Sporomusa ovata}, acted as the cellular catalyst and was directly interfaced with the arrays.

**Fig. 2. Materials and synthetic strategies for biohybrid systems.** (A) Silica coating on cyanobacteria through LbL deposition of PDADMAC and PSS (22). (B) Illustration of single-walled CNT (SWCNT) augmentation (86). (C) SWCNT transport through the chloroplast double membrane envelope (39). (D) Schematics showing different strategies of LbL self-assembly for cell encapsulation (44). (E) Illustration of basic plant physiology and their analogy to electronics (48). (F) Poly(3,4-ethylenedioxythiophene) (PEDOT) infusion into leaves by a syringe (48). (G) Schematic illustration of the biomimetic EV-MOF protein nanoparticles and the intracellular delivery of proteins (78). (H) Schematic illustration of biomimetic crystallization of cytoprotective MOF coatings on living yeast cells (11). (I) Schematic illustration of the MOF monolayer wrapped \textit{M. thermoacetica} and decomposing of reactive oxygen species (80). (J) Schematic illustration of the MPN shell on individual yeast cells (62). (K) Illustration of MOF formation inside of living plants (15). Reproduced with permissions from the Royal Society of Chemistry (22), American Chemical Society (78, 86) Springer Nature (39), Wiley-VCH (11, 15, 44, 62), National Academy of Sciences (80), and American Association for the Advancement of Science (48).
Another nanobiohybrid system was recently reported by interfacing efficient light-harvesting InP nanoparticles and genetically engineered Saccharomyces cerevisiae (34). The photoexcited electrons produced from InP activate reduced form of nicotinamide adenine dinucleotide phosphate regeneration, fueling the ultimate conversion of 3-dehydroshikimic acid to shikimic acid by the hybrid cells.

Fakhrrulinn and Minullina (35) reported the encapsulation of individual living yeast cells with CaCO₃. The inorganic CaCO₃ shell can be introduced by simply soaking living yeast cells in a super-saturated solution of Ca²⁺ and CO₃²⁻ ions (35). TiO₂ was also used as artificial cell coatings, which allowed for the introduction of various functional groups via bioinspired catechol chemistry (36).

Maheshwari and co-workers (37) reported a direct nanoparticle deposition method on living cell surfaces without the aid of peptides or lipids. Gold (Au) nanoparticles were incorporated onto the relatively neutral surface of yeast cells using calcium ions (Ca²⁺) as the mediator, which reactivated the ion binding sites of the cell surface through the continuous uptake of Ca²⁺. In another work, lanthanide-based La₄0.20Ce₀.45Tb₀.35PO₄ coating was synthesized on the chorion (eggshell surrounding embryo) of zebrafish, which enabled the hybrid cells with UVB-resistant properties (38).

**Endogenous bioaugmentation**

Strano and co-workers reported several pioneering works by augmenting living plants with carbon-based nanomaterials (39, 40). In one study, single-walled CNT (SWCNT) was inserted into the lipid envelope of extracted plant chloroplasts (39), demonstrating how nanomaterials can specifically interface with plant organelles ex vivo and in vivo to enhance biofunctions. In a follow-up study, the plant leaf mesophylls were engineered with NIR fluorescent nanosensors composed of SWCNTs conjugated to bomblitin II (Fig. 2, B and C) (40).

**Polymers**

Polymers can be readily synthesized from a vast range of natural and synthetic monomers, allowing fine tuning of their functionality and physicochemical properties. Polymeric materials can be designed with specific responses to stimuli such as light, electricity, heat, and pH, which have attracted diverse interest in energy, environment, and biomedical applications. Different polymer assembly techniques—such as LbL, polymerization, and grafting—have been used along with a variety of different polymers, such as polydopamine, biomaterials, synthetic linear polymers, covalent organic frameworks (COFs), etc. So far, polymers are the most exploited material for constructing nanobiohybrids and manipulating the biological properties of the organisms.

**Exogenous bioaugmentation**

Several techniques are available for incorporating polymers outside cells or organisms, including grafting from (e.g., in situ polymerization) and grafting to (e.g., LbL sequential polymer deposition) (41). Direct polymerization offers the versatility and ease of interfacing polymeric materials with biosystems; however, sequential polymer deposition can afford more precise tuning of the physicochemical properties at a molecular scale.

Polymer coatings can be directly synthesized from the cell surface using a grafting from approach (9). For example, Yang and co-workers (42) synthesized an artificial polymer cell coating using surface-initiated atom transfer radical polymerization (ATRP). A dopamine-based ATRP initiator allowed for uniform and dense coverage of the initiator on the cell surface using the material-independent coating property of catechols. Moreover, the initiator simultaneously protected the cells from radical attack during polymerization by the radical-scavenging properties of dopamine.

Sequential deposition using LbL assembly provides a highly controlled method for growing ultrathin polymer coating on diverse surfaces. LbL polymer coatings can be formed on living cells via a range of interactions such as electrostatic interactions, hydrogen bonding, van der Waals interactions, covalent bonding, or combinations of interactions (19). LbL assembly provides high-precision control over the layer thickness, density, morphology, surface charge, and material composition (43). Because of these outstanding features, LbL polymer assembly has been widely studied for augmenting biological systems, particularly living cells, for applications including cell protection, enhancing cell viability, cell proliferation, and cell surface functionalization (44). LbL cell encapsulation mainly consists of two strategies (Fig. 2D) in which “direct cell encapsulation” refers to the sequential deposition of polymer layers and “indirect cell encapsulation” involves an initial hydrogel encapsulation step before polymer deposition (44).

Hasan et al. (46) interfaced plant chloroplasts with a redox polymer to create photobioelectrochemical cells for photosynthetic energy conversion. A naphthoquinone-functionalized linear poly(ethyleneimine) redox polymer was used as both the immobilization matrix and an electron transfer mediator for intact chloroplasts.

Indirect cell encapsulation refers to the initial encapsulation of cells within a biocompatible, sacrificial template, followed by polymer coatings on the template (44). Mano and co-workers (47) reported an external coating consisting of PLL, alginate, and chitosan on alginate macroparticle templates containing poly(-l-lactic acid) (PLLA) microparticles and living cells. The alginate macrotemplates were formed by ionotropic gelation between Ca²⁺ and the PLLA micro-particles in the enclosed environment acted as cell adhesion sites to support cellular functions of anchorage-dependent cells.

**Endogenous bioaugmentation**

Recent studies have shown that extrinsic functions can be introduced into biological systems by directly incorporating polymeric materials inside of living systems. For example, Berggren and co-workers (48) reported an inspiring nanobiohybrid by integrating conductive polymers with living plants. In that work, a garden rose was augmented by immersing the freshly cut stem in an aqueous poly(3,4-ethylenedioxythiophene) (PEDOT)–S:H (self-doped via a covalently attached anionic side group) solution for 24 hours (Fig. 2E). As a result, the PEDOT polymer was taken up by liquid transport into the xylem vascular channels. Similarly, a picked leaf was placed in PSS-doped PEDOT solution combined with nanofibrillar cellulose (PEDOT:PSS-NFC) in a syringe. The syringe was pulled up to create negative pressure, which resulted in the evacuation of the gas inside the spongy mesophyll. When the piston was returned to its initial position, the environment returned to the standard pressure and PEDOT:PSS-NFC was infused through the stomata, filling the spongy mesophyll between the veins (Fig. 2F) (48). In a later study, the same group reported using conjugated oligomers as the electronic materials that could reach every part of the xylem vascular tissue of a cut flower to form long-range conducting wires that can be used as supercapacitors (49).

**Organic-inorganic hybrid materials**

Hybrid organic-inorganic coordination networks were reported as early as the 1950s due to their interesting and tailorable physical and
chemical properties through the adjustment of metal ions and organic linkers and their common use in many historical applications, such as ohaguro (50). Their unique properties—including tunable pore size, volume, and dimensions—have led to various applications in health, biotechnology, energy, and the environment (51). In terms of bioaugmentation, the two most investigated coordination materials are MOFs and MPNs (11, 50).

MOFs (also called porous coordination polymers) are a class of coordination network materials constructed with various fascinating structural topologies from metal ions or clusters and organic linkers through coordination interactions. Since the 1990s, MOFs have been actively investigated as next-generation gas storage (52), in which the most active two are carbon dioxide capture and separation technology (53) and hydrogen storage (54). Besides gas storage, their excellent chemical and structural designability and tunability have allowed MOFs to be exploited in more diverse applications outside their original scope. Presently, the application of these porous materials is spreading to other fields including proton and electron conductance, molecular sensing and recognition, ferroelectrics, catalysis, and biotechnology (55, 56). The porosity and pore dimensions of MOFs can be precisely designed at angstrom resolution and can be constructed from biofriendly components and/or under biocompatible conditions (57); therefore, the development of MOFs for bioaugmentation is rapidly emerging.

MPNs are a class of conformal coordination networks synthesized from coordination complexes of natural and synthetic polyphenols and metal ions. Initially assembled on substrates and interfaces, these amorphous MPNs demonstrate superior properties to crystalline coordination compounds such as MOFs in some aspects (50, 58). Because of the flexibility and diverse chelation ability of polyphenols, they can be coordinated to more than 18 different metal ions so far—including aluminum, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, zirconium, molybdenum, ruthenium, rhodium, cadmium, cerium, europium, gadolinium, and terbium—to generate robust MPN films with diverse functional capabilities (59). Moreover, the MPN coating is substrate independent, i.e., it can be formed on almost any type of surfaces due to the nonspecific binding of polyphenols with various surfaces and the simultaneous cross-linking of polyphenols by metal ions. In addition, the MPN-coating morphology, roughness, thickness, degradation profiles, and surface functionalities can be engineered through choice of the building blocks (51, 60, 61). Owing to their excellent biocompatibility, MPN coatings have also been exploited at the interface of bioentities such as proteins, alkaloids, polysaccharides, and even living cells and tissues under physiological conditions (62).

**Exogenous bioaugmentation**

Inspired by the natural sporulation process of certain bacteria and fungi strains, MOFs and MPNs have been used as new functional coatings for biological organisms to combat against physical and chemical stresses (10, 11, 63). Various driving forces and synthetic conditions have been exploited for growing MOFs around biological species under diverse conditions without imparting their biological functions. Different interactions and synthesis conditions between MOFs and the biological species have been exploited such as van der Waals interaction, covalent bonding and electrostatic interactions (64), synthesis temperature and time (65), and growth strategies, such as depositing to, growing from, and interfacial reactions (66).

Initial developments have been oriented around fabricating MOF coatings around biomacromolecules. Although biomolecules are not considered living organisms, the research developed around MOF-coated biomolecules has shed light on fundamentals surrounding the developments of MOF-based nanobiohybrids using living cells and organisms in later studies. Enzymes are one of the most popular biomacromolecules being investigated since retaining their biological activity under diverse conditions is highly desired. A widely used technique for enzyme protection is by inserting the enzymes in the presynthesized MOF particles through pore insertion (67). The post-infiltration method is sufficiently reported to accommodate various biomacromolecules with different sizes in a range of MOFs (20, 68, 69).

One substantial drawback of this approach is that biomolecules significantly larger than the pore size of the host could not be encapsulated. To address this challenge, a number of recent works focus on exploiting biomolecules’ intrinsic ability to initiate an in situ growth of MOFs and end up encapsulated in the framework analogs to natural biomineralization process (70–74). In this approach, biomolecules are situated inside the MOFs by generating macromolecular defects during MOF crystallization, which eliminates the pore size limitation of the presynthesized MOFs.

The intrinsic pores of MOFs act as channels to allow trafficking of small molecules, while the large guest molecules are prevented from leaching out. Commonly used ZIF-8 (zeolitic imidazolate frameworks 8) (including ZIF-L) and ZIF-90 frameworks are reported for encapsulating the desired guest biomolecules in aqueous solution under extremely mild synthetic conditions (70, 73, 75, 76). Multiple enzymes can also be incorporated with one MOF particle in situ using similar preparation method (77). The model cascade enzyme system of lactase, glucose oxidase (GOx), and horseradish peroxidase can be immobilized in ZIF-8 by simply mixing ZIF precursors and the enzymes at room temperature. In a very recent work, Zheng and co-workers interfaced lipid vesicles with protein/MOF particles (Fig. 2G) (78). By mixing the extracellular vesicles (e.g., exosomes) with the protein/ZIF-8 particles under ultrasonication and then extrusion, the surface of the MOFs was decorated with the lipid bilayer membrane (78).

MPNs have also been used at the interface of biomolecules. One of the most extensively studied MPNs, composed of tannic acid and iron [TA-Fe(III)], can be formed around protein-enriched proteinosomes as a cell wall–like shell (14).

Recent work on integrating hybrid materials with living systems has focused on imparting enhanced or completely new functionalities to organisms beyond what evolution offers. The first exploration of MOFs with living organisms involves S. cerevisiae (baker’s yeast) and the bacterium Micrococcus luteus coated by ZIF-8 shells (Fig. 2H) (11). The tendency of MOF particles to crystallize on the cell’s surface originates from interactions between the biomolecule-rich cell surface and the MOF precursors under aqueous conditions (11). The highly efficient heterogeneous nucleation sites on the cell surface lead to the rapid buildup of MOF coatings in which the living cells remain viable. In that work, the MOF coatings were synthesized by simply immersing living cells in aqueous solutions containing 2-methylimidazole (HmIm) and zinc acetate. In a later work, which pioneered the integration of functional biological components into cell-coating materials, an exogenous enzyme lactase was first adsorbed on the surface of yeast cells, followed by the ZIF-8 coating. The presence of lactase allowed the conversion of lactose into glucose, which was then used as the nutrient for cell survival (79).

Recently, Yaghi and co-workers (80) reported a MOF monolayer wrapped around the bacterium M. thermoacетica (Fig. 2I). The MOF Zr6O4(OH)4(HTBT)2(OH)6(H2O)6 [1,3,5-benzenetricarbonylazate (BTB)]
was presynthesized and wrapped spontaneously around the newly
grown cell surface through coordination bonds between the zirconium
cluster and teichoic acid. In terms of multicellular-scale augmenta-
tion, Richardson and Liang reported the growth of ZIF-8 (and its
derivative) and Eu and Tb2(bdc)3 inside and outside living plants (15).
Using intact plant and plant clippings, they showed that aqueous
solutions containing the MOF precursors can be taken up into the
xylem through the plant’s active liquid uptake mechanism, where
the rich polysaccharide-containing plant linings could induce the
rapid MOF nucleation and growth in situ both inside and outside of
organism for the construction of advanced nanobiohybrid systems.

For example, Zhou and co-workers (87) showed that enzyme-loaded
MOF nanoparticles can be uptaken into living cells, which contrasts
with the extensive work performed on traditional bioaugmentation
routes such as calcium phosphate, calcium carbonate, silica, gold, or graphene coatings (29, 37), and it
is expected that new MOFs will be studied to greatly expand their
integration with biological systems.

MPNs have also been augmented with living cells (50). MPN cell
coating was introduced during the original study on MPNs (50);
howerver, Park and co-workers extended this and reported artificial
stimulus-responsive TA-Fe(III) shells around S. cerevisiae (Fig. 2J)
(62). Qu and co-workers (81) reported MPN coatings around yeast
cells to protect against UV irradiation and reactive oxygen damage.

Caruso and co-workers (82) showed that poly(ethylene glycol)
(PEG)–functionalized polyphenol decorated MPN capsules formed
around human cervical carcinoma cells could endow the cells with
reduced nonspecific protein adsorption and cell association.

MPN complexes have also been applied as preservatives for more
complex, multicellular biological objects by forming nanometer-scale
thin coatings on a range of fruits with spray-assisted coating method
(83). The coating process was carried out by dissolving ferric chloride
and TA in deionized water, and the solutions were sprayed with air-
brush at a pressure of 10.5 liters/min.

Apart from coordination-based hybrid materials, Su and co-workers
(84) reported an artificial self-repairing shell around eukaryotic and
prokaryotic cells with biohybrid aggregates composed of Au nano-
particles and l-cysteine molecules. Yeast cells were selected as the model
eukaryotic cells, and the presynthesized Au@l-cysteine hybrid ag-
gregates were condensed around the cells through gentle shaking at
room temperature. Pahrullin and co-workers (85) described several
methods of magnetizing living yeast cells with the polyelectrolyte-
mediated deposition of superparamagnetic iron oxide nanoparticles.
In one approach, the yeast cells were coated with poly(allylamine
hydrochloride) (PAH) and PSS to form LbL PAH/PSS/PAH coatings
before incorporating the magnetic nanoparticles as a layer. The cells
were then coated with two additional polyelectrolyte layers. In another
approach, PAH-stabilized nanoparticles were directly mixed with
native yeast cells. Because of the functional magnetic coating on the cell
surface, the cells can be successfully manipulated by an external mag-
netic field, which could be applied in microfluidic devices.

**Endogenous bioaugmentation**

Modifying or altering the cell or organism to take up functional ma-
terials, or by synthesizing the material inside of living systems, rep-
resents an emerging yet challenging branch of augmentation with
potential applications in sensing, electronics, catalysis, and robotics
(39, 48, 86). Recently, preformed MOFs were placed inside the cell and
organisms for the construction of advanced nanobiohybrid systems.
For example, Zhou and co-workers (87) showed that enzyme-loaded
MOF nanoparticles can be uptaken into living cells as nanofactories or
artificial cell machineries. In that approach, two enzymes, catalase and
superoxide dismutase, were incorporated in sequence to occupy the
heterogeneous pores in a high stable MOF, nano–PCN-333.

We recently showed that the in situ formation of MOFs inside
living plants can be achieved without affecting the plant’s viability,
which turned the plant into a living chemical sensor (Fig. 2K) (15).
Taking advantage of the rapid liquid transport mechanism of liv-
ing plants, aqueous solutions containing the metal ions and organic
linkers could be easily transported inside the xylem from the root of
the plant through the cohesive and adhesive forces. With this method,
functional MOFs can be implanted inside intact plants without the
restriction of the size limitation of plant vasculatures, showing in-
spiration of MOF assisted bioaugmentation toward advanced sens-
ing applications.

**AUGMENTED/NEW BIOLOGICAL FUNCTIONS ENABLED
BY NANOBIOHYBRIDS**

Augmenting biological functions with man-made materials is not a
new idea. For thousands of years, humans have been improving their
survivability and livability using external enhancements, e.g., using
clothes, shoes, houses, weapons, and, more recently, the internet, com-
puters, cars, and smart phones. However, bioaugmentation at the
molecular and cellular level is an emerging concept, largely owing to the
rapid progress in materials research and nanotechnology in the past
decade. Hitherto, advanced functional materials have been applied
at the molecular, single cellular, and simple multicellular levels for
enhancing biosynthetic enzymes such as the biostability and biocatalytic
efficiency and introducing extrinsic functionalities such as new
metabolic pathways, electrical conductivity, and optical properties
to living systems (Fig. 3).

**Enhancing the functionality of biomacromolecules
Preserving enzymatic activity**

Biocatalysis is widely studied because of its high molecular and chiral
specificity, unrivaled activity under mild conditions, high turnover
number, and biodegradability (88). However, the further utilization
of biocatalysts, such as enzymes, is limited by their intrinsic insta-
bility, including low thermal stability, narrow optimum pH ranges, low
tolerance to most organic solvents, and many metal ions (68), which
leads to difficulties in their production, processing, storage, and uti-
лизation. Therefore, high-integrity enzymes are in high demand to
realize their full potential as biocatalysts both in vitro and in vivo. Re-
cent studies showed that protecting these biomolecules in a porous
matrix could improve their structural stability. For example, porous
silica has been widely investigated as solid supports for biocatalysts
(89). More recently, coordination network materials such as MPNs
and MOFs have been exploited as these materials offer much tailor-
able pore environments for hosting biocatalysts.

Porous MOFs have been studied as protective coatings for en-
zymes using numerous methods including physical adsorption, co-
valent cross-linking, pore insertion, and in situ synthesis (64).

The immobilization helped retain the catalytic activity of en-
zymes from harsh environments without significantly hindering
the diffusion of analytes. COFs have also been explored as matrices for
stabilizing enzymes. In the work reported by Banerjee and co-workers
(90), the chemically stable hollow spherical COF (DhaTab) was used
for trypsin immobilization. Although most of the microporous COFs
synthesized to date do not have pores large enough to accommodate
large biomolecules, the enzyme was found to be able to adjust its
conformation to fit the pore size due to its soft characteristics. The enzyme-loading capacity of the COF-DhaTab and the catalytic activity of the enzyme-loaded COF are comparable to other literature-reported values for porous materials, thereby showing great potential for biosensors and biocatalysis applications.

**Enhancing biomacromolecules stability**

In Wang and co-workers’ work, CaP was engineered around Human enterovirus type 71 (EV71) (91). Biomimetic nucleating peptides were integrated onto the capsid of EV71 through standard DNA recombination technology. The self-biomineralized vaccine was stable at 26°C for more than 9 days and stable at 37°C for roughly 1 week (Fig. 4A) (91). In another work, Zhou and co-workers (87) showed that two enzyme-loaded nanofactories prolonged the intracellular enzymatic activity and protected the cells from oxidative stress through biocascade reaction (Fig. 4B).

We exploited the concept of biomineralization to synthesize a library of bio-MOF nanocomposites and showed that these MOF materials can provide excellent protection for biomolecules against various conditions. A range of biomolecules including amino acids, proteins, enzymes, DNA, and polysaccharides can attract MOF building blocks in aqueous environments, leading to the rapid MOF mineralization around these biomolecules (70, 74, 92). This versatile method overcomes the pore size restriction of the MOFs for hosting biomolecules, and the protected biomolecules showed up to 10-fold enhanced stability compared to free biomolecules. Our study revealed that there exists an exclusive synergistic stability effect of both the biomolecule guest and MOF host, enabled from the unique, new coordination bonds between the host and guest molecules (Fig. 4C) (74).

Peng and the co-workers (93) reported protecting single-stranded DNA (ssDNA) by incorporating in the nanoporous Ni-IRMOF-74 MOF matrix. The pore sizes of the MOFs were optimized (from 2.2 to 4.2 nm) to satisfy the high loading of ssDNA, and the interior structure of Ni-IRMOF-74 showed interactions with the ssDNA that helped the carrier bind to target sequences. The incorporated ssDNA showed enhanced stability in fetal bovine serum with a survival percentage of more than 95% in 24 hours compared to quick degradation of bare DNA. The series of MOFs also showed augmented DNA transfection efficiency in mammalian cells (Fig. 4D).

Antibodies have emerged as a crucial category of biomolecule and biopharmaceuticals for medical diagnosis and disease treatment due to their unprecedented selectivity and sensitivity. However, most antibodies display poor stability and a tendency to undergo aggregation, which significantly limits their practical applications. To address this challenge, extra protective coatings were applied to preserve the biorecognition functionalities of the antibodies (94, 95). In Singamaneni and co-workers’ report, ZIF-8 was directly coated on antibody-functionalized gold nanorod biosensors (94). The MOF-protected immunoglobulin G (IgG) biosensors retained more than 70% functionality after 1 week of storage in air compared to the complete inactivity of unprotected samples (Fig. 4E) (94). In a follow-up work by Feng et al. (95), free IgG was encapsulated by ZIF-90 and ZIF-8. The MOF coating significantly enhanced antibody resistance against heat, organic solvents, or mechanical stress and can survive for long-term storage (>3 weeks) under temperature cycling test at fast ramp rates.

The MPN shell has several important characteristics including high cytocompatibility, on-demand facile degradability, and the flexibility of further functionalization (96). In a work reported by Huang and co-workers (14), the uncoated proteosome degraded completely within 5 min in the presence of protease, while the MPN-coated proteosomes could be well preserved for 30 min even under a high protease concentration (Fig. 4F). The MPN shell was found to be
Fig. 4. Synthesis and performance of biomacromolecule-based nanobiophybrids. (A) Schematic of CaP coating on the mutant viral protein and in vitro tests of virus thermostability. Thermal inactivation kinetics were determined at 26° and 37°C (91). PFU, plaque-forming units. (B) Catalase (CAT) and superoxide dismutase (SOD) insertion into FNPCN-333 and the relative enzymatic activities of several SOD formulations. The fluorescence cell images showing the internalized FNPCN-333 particles in living cells. (C) Schematic diagram showing the new coordination bond formed between the carboxylate groups from catalase and Zn in ZIF-L. Retention of the biocatalytic efficiency of catalase@ZIF-L with different treatments (74). (D) Illustration of intracellular delivery of single-stranded DNA (ssDNA) with and without MOF as vectors. Comparison of the intracellular delivery efficiency of ssDNA with and without MOFs using MCF-7 human breast cancer cells (93). cDNA, complementary DNA; DAPI, 4′,6-diamidino-2-phenylindole; FAM, 6-carboxyfluorescein. (E) Schematic of reversible MOF coating on antibody-functionalized DNA nanoparticles. Graph shows the retained recognition capability of MOF-coated biosensors on glass substrates stored at room temperature (RT), 40°, and 60°C for different durations and the retained recognition capability of the MOF-coated biosensor stored at room temperature for 3 days (94). (F) Microscopy images showing the stability of a bare proteinosome and MPN-protected proteinosome (14). (G) Schematic representation of the microfluidic device used to encapsulate individual exosomes. A generic term, EV, was used for all secreted vesicles including exosomes and microvesicles (97). (H) Schematic of the approach for wrapping a virus in a metal-organic molecular net with two-step preparation and evaporation of water that leaves the virus partially hydrated for further analysis in vacuum or air (98). Reproduced with permissions from the National Academy of Sciences (91), Springer Nature (87, 93), Elsevier (74), Wiley-VCH (94, 97), and the Royal Society of Chemistry (14, 98).
stable under physiological conditions for more than 24 hours. Kumar and co-workers (97) reported MPNs coatings around exosomes against plasma membrane rupturing from UVC irradiation and thermal treatment (Fig. 4G). The supramolecular complexed nanofilm was capable of preserving the native structure of the intrinsical exosomes and surface modification with Au nanoparticles and cancer-targeting ligand for tumor targeting and pH-responsive drug release. In another work reported by Delalande and co-workers (98), the MPN was constructed around the bromo mosaic virus particle as a protective coating (Fig. 4H). The wrapping sufficiently rendered the viruses resistant to air and vacuum environment without dehydration.

### Living cells

Interfacing functional materials with living cells can endow enhanced cellular functions and even lead to the generation of previously unknown biological functions. Recent advancements in nanobionic research have greatly broadened the material choice for integration with living cells. These novel bionic constructs have shown new prospects in preservation of cellular function, sensing, delivery, and advanced cell manipulation.

#### Preserving cell viability

Polymer coatings have been widely studied as a protective material for shielding living cells against various stress conditions (99). Polydopamine is a popular choice for coating cells due to its versatile polymerization process and cytoprotective nature. In one study, polydopamine was readily formed around living yeast cells (Fig. 5A) (9). The cells retained good viability, and the polydopamine coating enabled the cells to have stronger resistance against harsh environments, such as digestive enzymes (e.g., lyticase). The coating could be further functionalized with streptavidin for additional biofunctionalization and in situ targeting. Coordination network–based hybrid materials such as MOFs and MPNs have also been exploited as nanoporous coatings to protect living cells from physical and chemical stressors. These coordination network coatings significantly enhanced the cell viability by allowing access to small essential nutrient molecules while excluding large cytotoxic agents (11, 62).

#### Enhancing cell stability

Cell surface modification with chemical moieties is another viable strategy to induce functional polymer coatings. In a recent work by Soh and co-workers, polymer coating was directly synthesized on living cell’s surface by living radical polymerization in situ, which provides a bottom-up strategy for polymerization on cell surfaces with enhanced precision. Cell aggregation could be controlled by the interaction of PEG-functionalized cells with tannic acid, which demonstrates a previously unknown method for manipulating cell stability (Fig. 5B) (18).

Inorganic materials such as graphene sheets were used as ultrathin coating materials due to their high modularity and thermal conductivity. Calcium ion and Au nanoparticle–modified chemically reduced GO could partially encapsulate cells endowed with enhanced cell stability against osmotic stresses and an electrical and thermal conducting pathway on the surface, which enabled the direct imaging of cells under an electron beam (100).

#### Cell interaction

Cell surfaces have receptors and targeting molecules that regulate many cellular processes such as cell–cell recognition, adhesion, proliferation, and differentiation. It is obvious that cell coatings alter the cell surface chemistry and, therefore, controlling cell-cell interactions with artificial coatings presents an elegant strategy for manipulating biological functions. A primary example of controlling the cell surface chemistry is the formation of polymer coatings around islets (Fig. 5C) (12). Azide or phosphine-decorated alginate and PEG-based polymers deposited around islets showed no detrimental effect to the underlying murine primary pancreatic islets. The coating masked the surface of the islets and hence prevented recognition by the immune system in an allograft murine model.

The LbL-coated erythrocytes with alginate (AL), chitosan–graft-phosphorylcholine (CH–PC), and PLL–PEG showed optimized viability and immune camouflage against their respective antibodies (101). The multilayered shell was permeable to oxygen, with the uptake kinetics similar with uncoated ones (12% versus 15%). The immune camouflage effect was verified in the presence of the ABO/D (Rh) blood group antigens, and no sign of agglutination was found for the coated red blood cells with the addition of the respective antibodies.

#### Manipulating cell fate

Stem cells have the unique capability of differentiating into various cell types (102). Among them, mesenchymal stem cells are capable of differentiating into different types of functional tissue, and this differentiation can be controlled by the stiffness of the substrate (103). To manipulate stem cells for cell therapies, we investigated synthetic polymer substrates for cell attachment enhancement and oxygen gradient minimization. Pluripotent stem cells (PSCs) are promising candidates for therapy of lethal myocardial infarction. Inspired by nature, Zhao and co-workers (104) encapsulated PSCs within a semi-permeable alginate hydrogel shell, mimicking the zona pellucida in vitro and predifferentiated into early cardiac lineage (Fig. 5D). This encapsulation method yields core stem cells with immunosuppression effects and in situ cardiac cell regeneration, resulting in over six times higher viability in cell therapy compared to conventional injection methods (104). Barron and co-workers (105) investigated the effect of COOH-functionalized SWCNTs on human mesenchymal stem cells for controlling cell renewal, metabolic activity, and differentiation. The incorporation of SWCNTs showed no interference with cell differentiation to adipogenesis, osteogenesis, or chondrogenesis. In a recent work, He and co-workers (106) fabricated hybrid multilayer CNT films over neural stem cells. The CNT–multilayered nanocomposites provided a potent regulatory signal, including cell adhesion, viability, differentiation, neurite outgrowth, and electro-physiological maturation of neural stem cells (NSCs)–derived neurons. The dynamic molecular mechanisms in the NSC differentiation involved the integrin-mediated interactions between NSCs and the CNT multilayers, thereby activating focal adhesion kinase and subsequently triggering downstream signaling events to regulate neuronal differentiation and synapse formation.

### Advanced nanobionics

#### Nanobionic cells

In 2017, we reported a new concept of engineering single-cell nanobionics by interfacing bioactive MOFs with living cells. In that work, a nanocoating composed of a β-galactosidase (β-gal) inner layer and a ZIF-8 outer layer was synthesized around individual yeast cells (Fig. 6A) (79). β-Gal is capable of converting non-nutrients (i.e., lactose) from the environment into essential nutrients (i.e., glucose) for cell metabolism, while the external MOF layer acted as selective barriers against cytotoxic compounds but allowing for the diffusion of substrates for β-gal conversion into cell nutrients. This coating strategy allowed the yeast to survive for more than 7 days in a glucose-deficient environment by converting lactose to glucose in situ.
Fig. 5. Synthesis and performance of cell-based nanobiohybrids. (A) Schematic of polydopamine encapsulation and surface functionalization of individual yeast cells and the transmission electron microscopy micrograph of microtome-sliced hybrid cells. Reproduced with permission (9). (B) Schematic of modification of the cell surface using chain-transfer agent (CTA) lipids and subsequent cell surface–initiated polymerization and the cell viability after polymerization. Reproduced with permission (18). (C) Schematic of coating scheme for aminated beads and islet cell clusters and the multisliced projection confocal images of coated islets 48 hours after coating (12). Cluster diameter is of order 150 μm. NHS, N-hydroxysuccinimide. (D) Schematic showing the preparation of zona pellucida–like nanobiohybrid stem cells for implantation in the uterus wall (104). Reproduced with permissions from the American Chemical Society (9), Springer Nature (18, 104), and Wiley-VCH (12).
Nanobiohybrid supermaterials

Produced naturally by Bombyx mori larval silkworms, silk is widely applied in the textile industry and for wearable sensors due to its high elastic property and extensibility (107). To enhance the mechanical properties of silk, carbon nanomaterials such as SWCNTs and graphene were fed directly to silkworms (104). The resulted hybrid silks showed enhanced fracture strength and elongation, as well as electrical conductivity. A similar method could also be used on spiders for mechanically enhanced spidersilk by exposing spiders to CNTs or graphene dispersions (108). These synthetic recombination methods pave the way for higher-efficiency reinforced biofibers and can endow conventional materials with innovative applications.

Nanobiorobotics

Natural biological tissues are sensitive to subtle changes in the environment, which can induce complex responses. Primary examples include chromatophoric regulation, self-healing, and self-replication (109). In a pioneering work reported by Parker and co-workers (110), neonatal rat ventricular cardiomyocytes were cultured on polydimethylsiloxane thin films to fabricate actuators and powering devices. Three kinds of 2D myocardial tissues were fabricated including isotropic, anisotropic, and an array of discrete muscle fibers, and the tissue structure was proven to be important to potentiating motility by comparing the anguilliform swimming motion of triangles. In another work, the same group reported using rat tissue and silicone polymer for the construction of synthetic jellyfish (Fig. 6B) (111). The artificial jellyfish generated thrust during the power stroke and fed currents during the recovery stroke, exhibiting similar pumping performance to real jellyfish.

Superior to cardiac muscle with uncontrolled autonomous contraction, skeletal muscle is also widely studied because of its capacity of sensing and responding to external signals with motion. Building a hydrogel-based biobot with engineered mammalian skeletal muscle strip by 3D printing could reach an impressive maximum velocity of the locomotion of 156 μm/s (112). Recently, the same group reported another nanobiomaterial with an intricate protocol by building modular skeletal muscle actuators with 3D printing (113), which could...
convert the input stimuli to tensile force. The locomotive speed increased along with exercise training, including static mechanical stretch and dynamic optical pulse stimuli, and stimulation frequency.

**Implantable nanobionics**

Insects such as mosquitoes, bed bugs, and some beetle species can use portions of the infrared spectrum for vision; however, it is outside mammals’ visible spectrum. In Xue and co-workers’ report (114), a mouse could gain NIR vision by interfacing the eyeballs of a mouse with upconversion nanoparticles (UCNPs). The synthesized and surface-functionalized NaYF<sub>4</sub>:20%Yb,2%Er@β-NaYF<sub>4</sub> core/shell photoreceptor-binding UCNPs act as miniature energy transducers that can transform NIR light into short wavelength visible emissions without the need of further energy input. (Fig. 6C).

**Plant nanobionics**

Plants are ideal candidates for bioaugmentation and bionics due to their vascular network and use of passive forces for transporting fluids and molecules or particles dispersed in fluids. Because of these unique biological properties and their robust nature, various research efforts have been undertaken to enhance or augment plant biofunctions with synthetic materials. Hitherto, different kinds of nanomaterials have been studied, and these artificial materials endowed extrinsic functions to the plants and contributed to the development of new bionic materials for extrinsic applications such as light harvesting and biochemical detection with regenerative properties and enhanced efficiency.

**Fluorescence and biosensing**

Taking advantages of the unique biological functions of living plants, such as energy harvesting and self-healing, Strano and co-workers (13) reported the incorporation of inorganic, polymeric, and semiconductor nanoparticles in the leaf mesophyll and stomata guard cells to produce light-emitting plants (Fig. 6D). The resulting plant emitted more than 1.44 × 10<sup>12</sup> photons/s, and the luminescence was controlled by the presence of dehydroluciferin and coenzyme A.

SWCNTs could be directly augmented via leaf lamina infiltration through the abaxial surface, which is suitable for endowing plant-based biosensors due to their fluorescence in the NIR region while avoiding the autofluorescence wavelengths from plant tissues. This bioaugmentation method is expected to be generalizable to other chemicals, thus showing great potential for developing plant sensors for infrared communication in diverse environments (40). Apart from fluorothermocouples detection, SWCNT plant nanobionics were also used to detect nitric oxide, which enabled NIR fluorescence monitoring both ex vivo and in vivo (39). Therefore, the plants incorporated with CNTs could be augmented to function as a photonic chemical sensor. Using this method, living spinach plants were engineered to serve as a photonic chemical sensor (39). It was found that tens of chloroplasts could be encapsulated into one protocell by simple mechanical agitation and the encapsulated intact chloroplasts retained their structural and functional integrity within the protocell phase. Compared with bare chloroplasts in buffer, the immobilized ones showed similar half-life and photosynthetic capability and even higher efficiency at low concentrations of photoproduction agents. Furthermore, acoustic devices could be used to trap the organelle-containing droplets under water at the nodes of the acoustic pressure field, which led to highly uniform droplets sizes and dispersion of encapsulated chloroplasts.

**Conductivity**

Special attempts have been made to engineer electronics in and around plants, which will allow real-time recording of physiological events, photosynthetic harvesting, and nongenetically modified plant optimization. In Berggren and co-workers’ report, conductive polymers were incorporated into plant clippings for the in situ fabrication of bioelectronic circuits (Fig. 2E) (48). The augmented plant tissue showed an impressive long-range electron (hole) conductivity on the order of 0.1 S/cm in plant’s xylem. Similarly, conductive polymer was also introduced into the leaf through vacuum infiltration (Fig. 2F). The augmented leaves showed field-induced electrochromic gradients with higher hole conductivity in isolated compartments but higher ionic conductivity in the whole leaf. This bioaugmentation method paved the way for new applications in organic electronics and plants in general, aiming at synthesizing functional plants for electrochemical fuel cells, charge transport, and storage systems that convert sugar produced from photosynthesis into electricity in vivo (48).

**Photosynthesis**

To mimic the unique structure of green leaves with high light-harvesting efficiency, Ogawa and co-workers (115) replicated the natural structures of chloroplasts with morph-structured TiO<sub>2</sub> through a two-step infiltration process (Fig. 6E). The biomimetic leaves showed higher visible light absorbance intensity of more than 200% compared to natural leaves and a red shift in the bandgap absorption onset. In a follow-up study, the same group reported photochemical hydrogen production with an artificial inorganic leaf using a similar biomimetic construct (Fig. 6F) (116). Platinum nanoparticles (2 weight %) were doped in the artificial hierarchical structures for water splitting under UV and visible light irradiation and showed higher light-harvesting performance and photocatalytic efficiency. Although these studies did not directly involve living plants but rather used plant materials as templates, they opened up new avenues of materials engineering and highlight new possibilities in interfacing plants with advanced synthetic materials.

In another work, Strano and co-workers (39) implanted SWCNTs inside the plant chloroplasts by vacuum infiltration. The bandgap of SWCNTs enabled conversion of solar energy into excitons, which could later transfer electrons to the photosynthetic machinery. The amount of light absorbed by immobilized SWCNTs surpassed the chloroplast antenna pigments and were found to be able to promote over three times higher photosynthetic activity than the blank leaves. The nanobiobybrid assemblies also showed more efficient electron transportation in vivo due to the higher photosorption enabled by the SWCNTs. The nanomaterial implantation was found to enhance plant solar energy conversion through augmented light reactions of photosynthesis and reactive oxygen species scavenging while imparting extrinsic sensing capabilities to the living plants.

PDADMAC and carboxymethyl-dextran coacervate microdroplets or protocells could be used as artificial photosynthetic protocol matrices (117). It was found that tens of chloroplasts could be encapsulated into one protocell by simple mechanical agitation and the encapsulated intact chloroplasts retained their structural and functional integrity within the coacervate phase. Compared with bare chloroplasts in buffer, the immobilized ones showed similar half-life and photosynthetic capability and even higher efficiency at low concentrations of photoproduction agents. Furthermore, acoustic devices could be used to trap the organelle-containing droplets under water at the nodes of the acoustic pressure field, which led to highly uniform droplets sizes and dispersion of encapsulated chloroplasts.

**OUTLOOK**

In this review, we systematically introduce recent research efforts in nanobiobionic constructs ranging from materials choice and construction at the nanobiointerface to emerging applications that are aimed at enhancing or enabling new biological functions. The rapid explosion of nanomaterial research in the past two decades has enabled a material “toolbox” including diverse choices of organic,
inorganic, and hybrid materials to be exploited together with biological systems. From a fundamental scientific viewpoint, these nanobiobybrid systems have unveiled extrinsic biological behaviors in response to their environments, and they have also been instrumental for providing insights into the underlying molecular and cellular mechanisms for cell–material interactions by interweaving micro/nanoengineering and materials science with cell biology. From a translational science viewpoint, the advent of nanobiobybrid constructs has provided previously unknown ideas and methodologies into the fields of energy generation and storage, catalysis, sensing, and biomedicine. For example, recent success in integrating individual living cells with nanomaterials has opened up new avenues for controlling cell functions as an alternative but sometimes more powerful tool than genetic engineering.

At present, the full promise of nanobiobybrid constructs to real-world applications has still not been met as the field has only recently begun to mature. Many fundamental questions surrounding the biological functioning of the constructs, such as the genomic level understanding of the impact of functional nanomaterials, remained unanswered, likely because of the field emergence from engineering disciplines rather than biological disciplines. Besides the substantial work still needed to be performed in the biological space (gene expression, up/down-regulation, etc.), there is still work to be performed on flushing out new techniques for integrating nanomaterials with biological systems. Another important consideration in engineering these hybrid structures is the interface between synthetic nanomaterials and biological systems not only from a biocompatibility perspective but also from a functional compatibility perspective. Therefore, it is important to develop noble nanomaterials with unique physicochemical properties and morphological stability compatible with biological systems. The current techniques generally revolve around self-assembly and infiltration, but materials science uses numerous other techniques, such as vapor deposition, etching, slicing, lithography, and micromolding. As a current research trend, coupling functional nanomaterials that can mimic biological functions with biological systems would provide a previously unknown solution to augmentation engineering. For example, inspired by the natural energy conversion in photosynthesis, MOFs containing chlorophyll analogs have been reported to facilitate artificial light harvesting for higher solar energy conversion efficiency (118). These materials could theoretically be immobilized inside leaves to promote the reorganization of chlorophores in a well-defined manner and prevent the photoexcitons from quenching. In addition, the optimization of materials properties—such as size, morphology, geometry, and crystallinity—has been shown to influence the performances of materials and therefore should play a role in guiding or enhancing biological function when integrated with living systems. It is anticipated that advancements in these areas will lead to an improved ability in understanding, designing, and optimizing material biointerfaces to enable improved or new applications.

REFERENCES AND NOTES


SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/12/eaaz0330/DC1

Table S1. Choice of nanomaterials, biosystems, and the corresponding nanobiobybrid construction routes. References (119–127)


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