Photosynthetic semiconductor biohybrids for solar-driven biocatalysis

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Abstract

Photosynthetic biohybrid systems combine the best attributes of biological whole-cell catalysts and semiconducting nanomaterials. Enzymatic machinery enveloped in its native cellular environment offers exquisite product selectivity and low substrate activation barriers while semiconducting nanomaterials harvest light energy stably and more efficiently than biomolecules. In this topical review, we illustrate the evolution and advances of photosynthetic biohybrid systems focusing on the conversion of CO_2 to value-added chemicals. We begin by considering the potential of this nascent field to meet global energy challenges while comparing it to alternate approaches. This is followed by a discussion of the advantageous coupling of electrotrophic organisms with light-active electrodes for solar-to-chemical conversion. We detail the dynamic investigation of photosensitized microorganisms creating direct light harvesting within unicellular organisms while describing complementary developments in cytoprotection and understanding of charge transfer mechanisms. Lastly, we focus on trends and improvements needed of photosynthetic biohybrid systems in order to address future challenges and enhance their widespread adoption for the production of solar fuels and chemicals.

Introduction

Societal and industrial development has yielded a plethora of benefits for a quickly expanding and interconnected global population. While our quality of life has vastly improved over the last century, it has come at a cost exemplified by depletion of finite energy reserves as well as release of harmful greenhouse gases into the atmosphere contributing to increasingly erratic climatic patterns.[1] The finite supply of hydrocarbon fuels is further aggravated by their loss of usefulness once consumed, as the carbon ends up as dilute and nearly inert CO_2. In order to prevent further environmental deterioration and secure a lasting energy source, we must find a deployable strategy to simultaneously tap into renewable energy and close the carbon cycle.

In regard to renewable energy, sunlight provides an unparalleled abundance of energy on earth with one hour of solar energy matching our yearly global consumption.[2,3] It is no coincidence that earth's biomass is largely derived from solar energy. Although electricity obtained from photovoltaics has gained a foothold in the energy landscape, carbon-based liquid drop-in fuels remain critically important for their stability and high-energy density. Overcoming our global energy challenge will undoubtedly require the development of strategies to harvest and store solar power.[4]

Nature has provided a blueprint for capturing and storing solar energy in chemical bonds in photosynthesis.[5] However, our energy demands realistically outmatch the short-term capability of this natural process.[6] Attempts to directly use plant biomass have resulted in noncompetitive economics and deviation of resources from agricultural needs.[7] Overall, nature does not perform satisfactorily at solar capture as conventional crops only have a 1-2% solar-to-biomass conversion efficiency.[8]

In contrast, inorganic materials, in particular devices consisting of doped semiconductors, have benefited from decades of intense research and technological development. Commercial silicon-based photovoltaic cells routinely reach 20% solar-to-electricity conversion rates even securing profitability.[9] Advantageously, inorganic light harvesters do not suffer from photodamage and can be engineered to scale to specific light environments. Biological organisms, on the other hand, require a stable light source, and an appropriate climatic environment.[10] Although the benefits of inorganic materials for light capture are significant, they do not hold the upper hand over biology in regard to

CO_2 fixation. Most semiconducting materials are not suitable catalysts for CO_2 reduction.[11] Therefore, light capture and charge transfer to CO_2 must occur on different platforms. Despite the fact that catalysts for CO_2 reduction have progressed expediently, the catalytic understanding necessary for solar-to-chemical conversion is not fully mature.[12] Photoelectrochemical reactors for CO_2 reduction have produced mostly C_1 compounds such as carbon monoxide, methane, methanol and formate.[13,14,15] These devices also suffer from low product selectivity, often employ rare metals and long-term stability has not been fulfilled. By comparison biological organisms engage a symphony of enzymes and reductive pathways to produce long-chain hydrocarbons from simple building blocks including CO_2, N_2 and H_2O. Enzymes and proteins within the metabolic pathways of cells benefit from an ingrained building code in genetic information and are repaired and replicated as necessary. For these reasons, the combination of inorganic light-harvesters and whole-cell biocatalysts would exploit the best attributes of each component. In particular, semiconducting nanomaterials are highly configurable, pair well with cellular organisms due to similar lengths scales and provide exceptional light capture. In this review, we illustrate advances in photosynthetic biohybrid systems on three fronts: i) biocatalyst integration in photoelectrochemical devices, ii) introduction of membrane-bound light-harvesting nanoparticles in whole-cell microorganisms, accompanying cytoprotective strategies and iii) understanding of the interface between charge-donating inorganic materials and cells.

Semi-artificial Photosynthesis

Economic expansion has rendered the worldwide carbon flux unidirectional with CO_2 serving as a final carbon sink following the utilization of fossil fuels. Nature is the single biggest contributor to atmospheric CO_2 fixation through photosynthesis, however our energy demands vastly outmatch nature's time-scale. Artificial photosynthesis aims to mimic the conversion of CO_2 into value-added carbon products powered by solar energy.[16] Recent advances in semiconductor materials enable broadband light absorption and high photoconversion rates.[17] Photoelectrochemical (PEC) systems integrating light-harvesting semiconducting materials with catalysts primed for CO_2 reduction have been

documented.[18,19] These systems obtain light energy from semiconducting electrode materials or external light-harvesters and couple the photoreaction with appropriate catalysts that bind and transfer electrons to CO_2.[12] Nevertheless, even among state-of-the-art CO_2 catalyst selectivity remains poor.[20] Additionally, faradaic efficiencies for C_{2+} chemicals are low. Natural organisms have evolved to rely on enzymes to convert CO_2 to upgradeable intermediates such as acetyl-CoA and pyruvic acid with exquisite selectivity.[21] Enzymes undertake conformational changes to create local hydrophobic environments and promote steric effects to aid in reaction selectivity.[22] Additionally, dangling amino acid residues mediate electron and proton transfers while stabilizing reactive intermediates.[23] However, combining proteins *in vitro* within a PEC setup results in stability issues.[24] Enzymes inhabit unique protective environments and often operate synergistically with other proteins and organelles; therefore coupling purified enzymes with electrodes is nontrivial. In light of these complications, exploiting the enzymatic machinery within whole cells could improve stability by preserving innate replication and healing mechanisms.[25] Pairing whole cells biocatalysts with artificial light-capturing PEC systems could enhance product selectivity and lower energetic barriers of CO_2 activation.

At the outset, the integration of whole-cell biocatalysts with inorganic electrodes forged multiple avenues for powering microbial metabolism for the synthesis of desired chemicals from CO_2, N_2 and H_2O.[26] An early demonstration of microbial electrosynthesis consisted of pairing acetogen *Sporomusa ovata* (*S. ovata*) with a graphite cathode.[27] The reducing equivalents transferred to *S. ovata* facilitated the reduction of CO_2 into carbon compounds via the Wood-Ljungdahl pathway (WLP).[28] Conveniently, acetate is a byproduct of the WLP as CO_2 is converted to acetyl-CoA, which is oxidized to acetate in ATP phosphorylation. The faradaic efficiency of acetate, as calculated by accounting for the fraction of electrons consumed to produce acetate, was found to be over 85%. After the initial demonstration of microbial electrosynthesis for the production of multicarbon organic compounds from CO_2, different approaches have been undertaken to improve performance and product selection including optimization of electrode geometry[29], electrode surface engineering[30,31] as well as bacteria adaptation[32], enrichment[33] and genetic modification.[34] Though auspicious, these strategies did not fulfill the mission of

semi-artificial photosynthesis, namely coupling natural biocatalysts with artificial light-harvesting materials.

In a first of its kind study, Liu *et al*. realized solar-to-chemical microbial electrosynthesis by loading *S. ovata* into a light-harvesting nanowire PEC cell (**Fig. 1 A**).[35] Si and TiO_2 photoactive nanowires capture simulated sunlight and provide *S. ovata* with electrons to drive CO_2 reduction. The Si nanowire substrate can accommodate higher loading of *S. ovata* than planar substrates per unit reactor volume. The high-surface-area nanowire platform allows for greater interface between the bacteria and cathode. Additionally, the nanowire electrodes create a local anaerobic environment that maintains the viability of *S. ovata* even with oxygenic headspace gas. Significantly, the *S. ovata* – nanowire biohybrid system was completely operated under simulated sunlight without an external bias achieving a CO_2-reducing current density of -0.35 mA/cm^2 with circa 90% faradaic efficiency. The acetate was upgraded to value-added multicarbon products, such as *n*-butanol, polyhydroxybutyrate (PHB), and isoprenoid by genetically altered *Escherichia coli* (*E. coli*) (**Fig. 1 A**). Altogether this study demonstrates the ability of biohybrid systems to replicate photosynthesis by combining CO_2, sunlight and H_2O into fuels, polymers and pharmaceuticals.

Autotrophic organisms can also utilize H_2 as a form of reducing equivalent. Therefore, H_2 can be considered as a mediator to facilitate microbial electrosynthesis. In this case the cathode may be used as an electrolyzer to reduce water (**Fig. 1 B**). Accordingly, appropriate cathodic materials with catalytic activity need to be selected. Nichols and colleagues paired platinum and nickel based H_2 electrocatalysts with *Methanosarcina barkeri* to convert CO_2 to methane.[36] The faradaic efficiency of this device was tabulated at 86% over seven days. Additionally, the electrodes were substituted with an indium phosphide photocathode and a titanium dioxide photoanode to create a solar-driven system. Moreover, Liu *et al.* illustrate that cobalt-based H_2 catalysts can be used in conjunction with genetically engineered *Ralstonia eutropha* to produce biomass and alcohols from CO_2.[37] The biocompatible cobalt phosphate electrodes produce H_2 and O_2 under low driving voltage while minimizing reactive oxygen species (ROS) generation, which had previously inhibited microbial growth.[34] Notably, these electrodes were used in a following study with *Xanthobacter autotrophicus* (*X.*

autotrophicus) to fix N_2 gas into NH_3 and nitrogenous biomass.[38] Nevertheless, the low solubility of H_2 in aqueous media as a mediator limits the efficiency of microbial electrosynthesis. Recently, Rodrigues *et al*. employed a biocompatible perfluorocarbon nanoemulsion as an H_2 carrier thus increasing the solubility of H_2.[39] This strategy was successfully combined with *S. ovata* helping the model system achieve an average acetate titer of ~6.4 g/L in four days with close to 100% faradaic efficiency.

Whole-cell Photosensitization

A key aim of the nascent field of biohybrid photocatalysis has been to expand beyond the limitations set forth by PEC systems. These systems, which are best suited for purely inorganic photocatalysis, may require a strong light flux and variable pH conditions incompatible with living organisms. Furthermore, extracellular electron transfer can be a bottleneck limiting the rate of photoreduction by bacteria. While the interface between inorganic cathodic materials and bacteria is actively under investigation, small changes in the local environment can have deleterious effects. For instance, current density of a biohybrid photoelectrochemical device is restricted by the resulting local change in pH near the cathode, which creates an inhospitable environment for microbes. Leaching of toxic metals from the electrodes as well as ROS generation present an engineering challenge. For these reasons, it has been a pressing need to devise of a novel semiconductor-cell interface that overcomes these limitations.

In a landmark discovery, Sakimoto *et al.* enhanced a model acetogen *Moorella thermoacetica* (*M. thermoacetica*) with light-absorbing cadmium sulfide (CdS) nanoparticles (**Fig. 2 A**).[40] While the precipitation of inorganic nanoparticles within microorganisms is a well-known protective response to toxic metal ions[41], the ability of these nanoparticles to absorb light within the host microorganism had not been thoroughly studied. Cysteine desulfhydrase, an enzyme found in *M. thermoacetica* among other microorganisms, produces sulfide from cysteine.[42,43] Sulfide reacts with metal ions such as Cd^{2+} introduced to cell culture media to form high quality and homogenous CdS nanoparticles. The nanoparticles are primarily anchored in the cell

membrane. Most interestingly, illumination drives autotrophic CO_2 conversion to multicarbon acetate in the *M. thermoacetica* – CdS constructs. *M. thermoacetica* consumes the photogenerated reducing equivalents produced by illuminated CdS nanoparticles to power their innate CO_2-fixing metabolism. Under the WLP CO_2 is enzymatically reduced to acetyl-CoA, which is then either used for protein biosynthesis or oxidized to acetate to obtain ATP. Cysteine not only provides a source of sulfur but also serves as a hole scavenger. Charge separation at the inorganic nanoparticle interface is namely aided by the oxidation of cysteine to cystine. Further spectroscopic examination of the charge transfer and uptake pathway is needed in order to elucidate the molecular mechanism of this photoreaction. Overall, the *M. thermoacetica* - CdS constructs generated ~1.2mM acetic acid from CO_2 in three days under low-intensity simulated sunlight. The discovery of photosensitized microorganisms for CO_2 reduction effectively realizes a novel line of investigation. Although quantum dots and nanostructures have been introduced in cells for fluorescent labeling[44] and drug delivery[45] for well over two decades, light-absorbing nanostructures had not been used to drive reactions inside of cells. Photosensitized microorganisms not only epitomize an innovative strategy for photocatalysis but also present a unique opportunity for investigating the interface between light-activated nanomaterials and whole-cell organisms.

Further self-photosensitization with CdS nanoparticles of varied microorganisms for photocatalysis has been reported. Wang *et al.* presented a biohybrid system consisting of *Rhodopseudomas palustris* (*R. palustris*) and CdS.[46] While *R. palustris* is a non-sulfur purple photosynthetic bacterium, it still requires a source of reducing equivalents as it only expresses for the machinery required for photosystem II. *R. palustris* – CdS biohybrids fix CO_2 through the Calvin cycle into biomass, carotenoids and poly-β-hydroxybutyrate (PHB) under illumination. The production of these C_{2+} compounds is increased by nearly 50% by the *R. palustris* – CdS constructs. Moreover, Chen and colleagues complemented denitrifying bacterium *Thiobacillus denitrficans* (*T. denitrificans*) with self-precipitated CdS nanoparticles.[47] *T. denitrificans* – CdS use photogenerated reducing equivalents to reduce NO_3^- to N_2O. The authors also confirmed

that the relative transcript abundance of genes encoding for denitrifying proteins is upregulated in biohybrid *T. denitrificans* – CdS after illumination.

CdS nanoparticles, while an effective semiconducting nanomaterial, may limit the efficiency of the CO_2 photoreduction as they induce oxidative stress and are thus cytotoxic to anaerobic bacteria like *M. thermoacetica*.[48,49] Furthermore, they pose a known environmental hazard that limits their applicability in CO_2 recycling.[50] Gold nanoclusters (AuNCs) are sub 3nm nanoparticles consisting of a precise number of atoms bound into a network by organic ligands.[51] These AuNCs have garnered interest due to their unique optical and electronic properties based on both number of atoms and overall arrangement.[52] In addition, choice of surface ligands enables exquisite control over their biochemical properties.[53,] In particular, thiol-protected AuNCs displaying chromophore-like discrete energy states have been applied in catalysis[54], optics[55] and for solar energy harvesting.[56,57] $Au_{22}(SG)_{18}$ (SG is glutathione) is both water soluble and exhibits high luminescence which makes it a candidate for microorganism photosensitization.[58] Zhang *et al*. document that over 90% of $Au_{22}(SG)_{18}$ is taken up by *M. thermoacetica* when added to a pre-exponential culture and $Au_{22}(SG)_{18}$ retains its luminescence over a period of seven days (**Fig. 2 B**).[59] Importantly, $Au_{22}(SG)_{18}$ does not hinder cell proliferation at optimal concentrations. In fact, $Au_{22}(SG)_{18}$ quenches photoexcited radicals including ROS in contrast to CdS. This advantageous effect translates to higher viability of *M. thermoacetica* – AuNCs cultures than in *M. thermoacetica* – CdS. The diminutive size of AuNCs allows for increased interface between the light-absorbing particle and cell machinery. The improved interface and biocompatibility in *M. thermoacetica* – AuNCs resulted in an appreciably higher rate of acetate production from CO_2 under simulated sunlight. The overall quantum yield of *M. thermoacetica* - AuNCs was 2.86 ± 0.38% compared to that of *M. thermoacetica* – CdS at 2.44 ± 0.62%.

Photosensitization of *M. thermoacetica* with CdS nanoparticles or AuNCs offers a new approach for combining the selectivity and replication of biology with the light-harvesting capability of inorganic semiconductors for photocatalysis.[60] However, autotrophic bacteria are disadvantaged by slow reproduction times, high oxygen

sensitivity and are limited to few exogenous products.[61] Organisms such as *E. coli* and yeast serve as workhorses of synthetic biology, as significant progress has been made to tailor their metabolic pathways.[62, 63] Therefore, devising of strategies to augment these microorganisms with light-absorption capabilities would signify an important advance in the field. Wei and coworkers report on the enhancement of genetically engineered *E. coli* with CdS nanoparticles.[64] Interestingly, the authors utilize PbrR, a membrane-bound protein with cysteine residues that selectively adsorbs lead and cadmium ions to precipitate CdS nanoparticles. As cysteine desulfhydrase, the enzyme responsible for sulfide production and CdS precipitation in *M. thermoacetica* is not present in all bacterial strains, PbrR and similar proteins could be exploited to generate nanoparticles in a wider spectrum of cells. The *E. coli* in this study is genetically engineered to synthesize hydrogenase and under illumination the *E. coli* - CdS constructs produce hydrogen. This solar-to-chemical scheme is, however, hampered by the inherent oxygen sensitivity of hydrogenase.

Moreover, Guo and colleagues functionalized genetically engineered yeast with light-absorbing indium phosphide (InP) nanoparticles (**Fig. 2 C-F**).[65] *Saccharomyces cerevisiae* (*S. cerevisiae*) operates heterotrophically utilizing hexose sugar as a substrate for biomass, energy and target metabolites. Low yields of sugar to target metabolites, exemplarily shikimic acid, a precursor molecule in biomanufacturing, can be attributed to the loss of carbon as CO_2 in the oxidative generation of NADPH. However, NADPH is needed as a reducing equivalent in most cell functions. Deletion of the pentose phosphate pathway in *S. cerevisiae* decreases the availability of NADPH but also halts the loss of carbon. The authors claim that InP nanoparticles enable the regeneration of NADPH without the oxidation of hexose in genetically engineered *S. cerevisiae*. Therefore, *S. cerevisiae* decorated with broadly absorbing InP nanoparticles consume hexose substrate more efficiently while streamlining carbon flux toward shikimic acid production. S. cerevisiae – InP hybrids effectively decouple biosynthesis and NADPH regeneration. These highlighted studies involving *E. coli* and yeast respectively provide blueprints for combining workhorse microorganisms with light-absorbing nanoparticles for the solar-powered production of fuels and fine chemicals.

Although the field encompassing the coupling of whole-cell organisms with light-absorbing nanomaterials for photocatalysis is rapidly expanding, no study had yet to systematically match the bandgap energy of light-absorbing nanoparticles with the redox potential of target enzymes. Ding *et al*. newly report on the synthesis of semiconducting nanoparticles with finely tuned bandgaps for biohybrid photocatalysis.[66] Seven different core-shell quantum dots (QDs) were produced each with different bandgap energies for wide-ranging utilization of the solar spectrum. The surface chemistries of the QDs with CdS, CdSe, InP and Cu_2ZnSnS_4 cores were tailored to biocompatibly bind to enzymes in *Azotobacter vinelandii* (*A. vinelandii*) and *Cupriavidus necator* (*C. necator*). The authors found that a zinc sulfide shell has a strong binding affinity to histidine-tagged MoFe nitrogenase and Fe-S clusters in hydrogenase in cell lysates. They further modified the surface of the QDs with zwitterion cysteine in order to improve the association of the QDs with the bacteria. However, it is not demonstrated whether this ligand has an effect on enzyme binding. Finally, the *C. necator* – QDs constructs provide a platform for the solar generation of a plethora of carbon-based products including methyl ketones, butanediol, ethylene, PHB and propanol. *A. vinelandii* – QDs hybrids were used to generate NH_3/H_2 and formic acid. Altogether, these results indicate that the tunability of electronic properties as well as the modifiable surface chemistry of nanomaterials can be leveraged to operate synergistically with biological catalysts. **Figure 3** and **table 2** offer an overview and summary respectively of reported cell-photosensitizer pairings.

Cytoprotection

Photosensitization of microorganisms offers a promising platform for the light-driven catalytic conversion of CO_2, N_2 and H_2O into fuels and value-added chemicals.[67] However, autotrophic organisms equipped with specialized metabolic pathways, such as *M. thermoacetica* cannot sustain the high photon flux required for photosynthesis. In addition, enzymes responsible for reduction and hydrogenation like RuBisCO, hydrogenase and nitrogenase are sensitive to oxygen.[68] Furthermore, sacrificial hole scavengers used to maximize charge separation of the photoexcited nanoparticles become depleted throughout the course of photosynthesis. Accordingly, a model strategy has been

devised in which cystine is reduced back to cysteine by photoactive TiO_2 nanocatalysts.[69] Although this approach boosts the overall yield of acetate from CO_2 through an increase in the availability of cysteine, the photoanodic TiO_2 nanocatalysts are also responsible for creating additional ROS.[70] In order to promote the applicability of photosensitized whole-cell organisms for solar-to-chemical conversion, it is imperative to devise of cytoprotective strategies to enable long-term stability even in oxidative environments.

Nature provides ample inspiration for cytoprotection. Diatoms, for instance, shield themselves with siliceous exoskeletons from environmental stressors.[71] Photosynthetic cyanobacteria extrude extracellular polymers that contain molecules absorbing in the UV-range.[72] Therefore, approaches consisting of coating charged polymers[73], inorganic materials[74,75], and metal-framework materials (MOFs)[76] directly onto cell membranes have provided protection against radiation, thermal and mechanical stresses.[77] As previously described hydrogenase-expressing *E. coli* was photosensitized with CdS nanoparticles for the solar-driven production of hydrogen.[64] Since hydrogenase is sensitive to oxygen, the *E. coli* – CdS biohybrids were encapsulated in silica. Oppositely charged polymers were deposited on the membrane of the cells thus offering scaffolding for silica synthesized from silicic acid. This enhancement resulted in the generation of a locally anaerobic microenvironment within the cell core, which allowed for the long-term stability of the photosynthetic biohybrid system. (**Fig. 4 A, B**).

A further strategy consists of the complete encapsulation of a unit of photosensitized cells in a hydrogel. Alginate hydrogel, for example, allows for the unencumbered proliferation of cells as its soft structure develops microvoids.[78] The alginate may scavenge and attenuate the concentration of superoxides, hypochlorites and peroxides.[79,80] *M. thermoacetica* – AuNCs encapsulated in hydrogel microspheres demonstrated lower levels of internal ROS which led to an increase in acetate produced during photosynthesis.[81]

MOFs are a class of microporous materials synthesized from modular building blocks that can be optimized to enhance biocompatibility.[82,83] Their exceptional thermal and chemical robustness have shown to facilitate gas absorption with exemplary applications in mixed gas sequestration and CO_2 electrocatalysis.[84,85] Liang and coworkers have demonstrated the *in vitro* precipitation of a MOF on yeast.[76] The

biomolecule-rich yeast membrane serves as a nucleation point for the MOF when other precursors are present in the media. Remarkably, the crystallized MOF prolongs the overall viability of yeast under adverse environments as shown in **figure 4 C**. However, the stiff attachment of this MOF to the yeast membrane can prevent cell proliferation and induce dormant states. Additionally, this method may yield incomplete membrane coverage. Ji *et al*. developed a technique to uniformly wrap *M. thermoacetica* in flexible MOF nanosheets.[86] Phosphate residues on the cell surface act as anchoring points for zirconium clusters in the MOF nanosheets (**Fig. 4 D**). Therefore, this ultrathin MOF material allows the mechanical dynamics required during cell division to occur. As compared to bare *M. thermoacetica*, the wrapped *M. thermoacetica* sustains a remarkably lower rate of inhibition when exposed to H_2O_2, a model ROS. The decomposition of ROS can be attributed to the catalytic ability of the zirconium clusters. Consequently, the MOF-wrapped *M. thermoacetica* – CdS can continuously undertake CO_2 photoreduction even under oxidative stress achieving a 200% increase in acetate yield over the bare biohybrids. Cytoprotection by MOF nanosheets containing zirconium clusters improves on the design of photosensitized organisms. This material allows for the creation of a complete cell factory, realizing artificial photosynthesis with simultaneous CO_2 reduction and redox shuttle regeneration.

Charge Transfer

Bacteria accept photogenerated reducing equivalents from either poised electrodes or light-absorbing nanoparticles.[87] These reducing equivalents serve to jumpstart the metabolic pathways involved in the reduction of building blocks such as CO_2 and N_2, as well as provide energy to regenerate redox mediators like ATP and NADH. The charge transfer mechanism between a poised electrode and electrotrophic bacteria has been investigated.[88] Although autotrophic bacteria can commonly use H_2 as a source of energy, many organisms have also evolved the ability to establish direct electrical contact. Membrane-bound proteins can shuttle electrons across the cell membrane.[89] Surface displayed cytochromes and flavins are commonly involved in this process but evolving research constantly yields new information on charge uptake pathways.[90] The oxidation

of inorganic mineral oxides mediated by electrostatic interactions is carried out by surface-displayed hemoproteins. Fukushima *et al.* report that extracellular electron transfer protein MtrF, a terminal protein in cytochrome c from *Shewanella oneidensis* MR-1 binds to mineral oxides by creating a three-dimensional positively charged pocket of specific residues (**Fig. 5 A**).[91] Moreover, electrotrophic bacteria may also secrete proteins and small molecules that act as redox shuttles as well as extracellular polymers, coined as microbial nanowires.[92,93] Cryoelectron microscopy was used to discern the structure of microbial nanowires in *Geobacter sulfurreducens* responsible for long-range electron transport (**Fig. 5 B**).[94] It was determined that the nanowires consists of hexaheme cytochrome OmcS with hemes assembled within 3-6Å of each other (**Fig. 5 C**). Electron conduction occurs through the core of the filaments over the tightly packed metal-cluster hemes.

The platform established by cell-nanoparticle hybrids offers an additional benefit for the study of charge transfer between biotic-inorganic interfaces. The translucent and light-activated biohybrid samples facilitate their *in situ* observation by spectroscopic means. Transmittance-based transient absorption (TA) and time-resolved infrared spectroscopy (TRIR) were employed to elucidate charge carrier lifetimes in *M. thermoacetica* – CdS (**Fig. 5 D**).[95] The photoexcited reducing equivalents may be taken up by hydrogenase or directly as electrons by membrane-bound proteins. Through appropriate experimental design, the biochemical activity of proteins involved with charge uptake was correlated with charge carrier lifetimes. *M. thermoacetica* – CdS constructs were incubated with hydrogen pre-photosynthesis for varying lengths of time in order to ramp up hydrogenase activity. The rate of acetate production was higher in the first three hours for those samples with no hydrogen incubation but the average rate of acetate production was higher in the samples with the longest hydrogen incubation time. TA results showed that bare CdS had the slowest decay kinetics followed by *M. thermoacetica* – CdS with no hydrogen incubation while *M. thermoacetica* – CdS with hydrogen incubation exhibited the fastest decay. These observations indicate that a CdS-to-hydrogenase electron transfer pathway may be established. Interestingly, the TRIR spectra highlight a change in vibrational range of CO and CN double and triple bonds corresponding to amino acid residues. These changes occur on the same time scale as the

TA signal. While the spectral changes in the TRIR spectra occur in hydrogen and non-hydrogen incubated samples, slight differences point to two charge uptake mechanisms. Photoexcited electrons feed directly into proteins accelerating acetate production in samples with limited hydrogenase activity but cannot maintain long-term metabolic activity due to lack of high energy reducing equivalents. Whereas a CdS-to-hydrogenase electron transfer pathway is established in samples with sufficient hydrogenase activity to produce high energy reducing equivalents.

Outlook

The coupling of whole-cell biocatalysts and semiconducting nanomaterials has allowed for the light-driven conversion of CO_2, H_2O and N_2 into value-added products. Research has centered around the biotic-abiotic interface, namely to create a functional flux of reducing equivalents either by direct electron transfer or through a mediator like H_2. Although there have been significant developments in this field of research, there is room for improvement.

Direct electron transfer to microorganisms is hindered by the change in pH of the microenvironment at the cathode and the relatively low extracellular electron transfer rate. The first limitation can be addressed by using a better buffering system and by designing an electrochemical cell with superior mass transport. Furthermore, upgrading from a primarily batch to a flow system could enhance biocompatibility. Flow-based microbial fuel cells with markedly improved performance have been reported.[96] With thorough understanding of extracellular electron transfer, bacteria could be genetically engineered to overexpress proteins responsible for charge uptake. This would greatly complement electrochemical adaptation studies. Non-electroactive workhorse bacteria with wide product arrays could even be engineered to accept charge. For instance, S. cerevisiae had not shown indices of electroactivity but S. cerevisiae – InP hybrids successfully regenerated NADPH.[65] Moreover, microorganisms rarely exist in monocultures in nature. In fact, communities of organisms join forces to symbiotically exploit available sources of energy. Co-cultured organisms demonstrate synergistic effects as higher resiliency to

stresses and overall increase in biomass.[97,98] Employing a diverse community of organisms could enhance the rate of microbial electrosynthesis.[99] Furthermore, a study by Lu and colleagues demonstrates that bacterial communities derive photoexcited reducing equivalents from illuminated Mn and Fe oxides. This report provides an account of light-induced bacterial electrotrophy in nature and indicates that there is the need for further investigation into the synergistic relationship between light, cells and semiconducting materials.

Some of the highest current densities of microbial CO_2 reduction have been achieved by using H_2 as a reducing equivalent.[39] Taking this into consideration, solar power could provide the necessary H_2 for biocatalysts by coupling HER catalysts with light-absorbing materials. High (>20%) solar-to-hydrogen efficiency has been attained by photovoltaic electrolysis systems.[100] The challenge persists, however of maintaining a biocompatible environment. Fewer studies on N_2 assimilation by microbial electrosynthesis have surfaced. The reason for this might be that nitrogen-fixing bacteria quickly consume valuable NH_3. Liu *et al* were forced to inhibit protein biosynthesis in order draw extracellular NH_3. Therefore, nitrogenous biomass accumulation and NH_3 production could not be observed simultaneously. This points to a root challenge with microbial electrosynthesis - competition with biocatalysts for access to products may arise.[101]

Moreover, improvements on the purely biological aspect of semi-artificial photosynthesis are necessary to match advances on the bio-inorganic interface. The rate of carbon assimilation in autotrophic microbes needs to increase in order to compete with purely inorganic catalysts. This could be done through metabolic engineering of autotrophic organisms[102] or by constructing CO_2-fixing pathways in highly active organisms such as *E. coli.*[103] Although whole cell biocatalysts possess unrivaled selectivity of many desirable natural products and biofuels[104], yield and generation rate of these products needs to be optimized. This may be addressed by redesigning metabolic pathways.[105]

Photosensitized microorganisms have achieved direct solar-to-chemical conversion. However, most of these systems rely on hole scavengers. TiO_2 nanoparticles have been used to regenerate cysteine, a common scavenger. But as TiO_2 is intrinsically

cytotoxic[106] better approaches for scavenger regeneration are needed. Further in-depth study of the interaction between whole cells and light-active nanoparticles could provide more insight into the molecular pathway of charge uptake. Spectroscopic analyses could be combined with biochemical assays such as transposon sequencing.[107] Moreover, the field of nanocarrier-based drug delivery has solidified the paramount of role of surface chemistry in nanomaterial-cell interaction.[108] More exploration on the effect of surface chemistry of light-absorbing nanomaterials for photosensitization could continue to yield similarly interesting results.

Altogether, the union of biology and nanomaterials has shown extraordinary promise to fulfill the mission of artificial photosynthesis. The illustrated biohybrid approaches play to the strengths of each component: the replication, self-healing and specificity of whole organisms and the remarkable solar energy capture of semiconducting nanomaterials. The advent of photosynthetic biohybrid systems has begun to enable to conversion of sunlight into liquid fuels and value-added chemicals. With steady improvements, we can envision a future in which engineered inorganic materials work in concert with the natural world.

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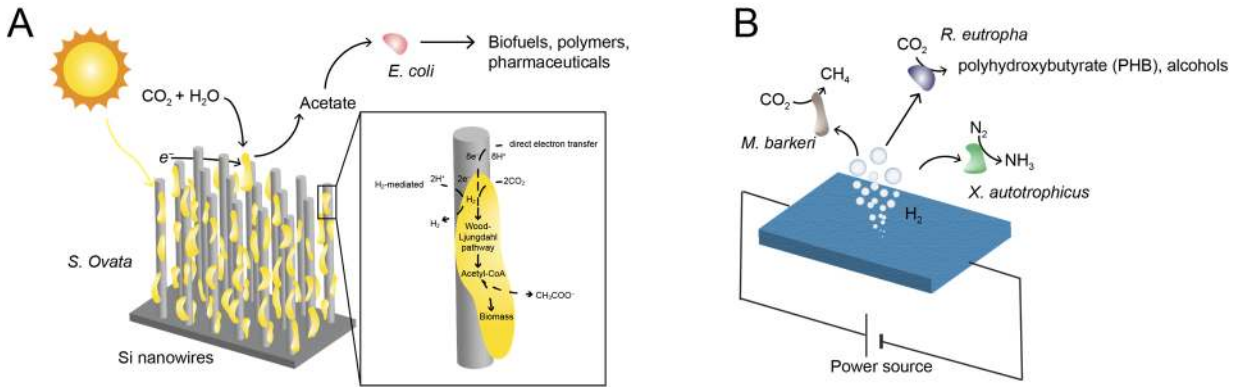

Figure 1. Semi-artificial Photosynthesis. A. *S. ovata* loaded on light-harvesting nanowires arrays undertake CO_2 to acetate conversion. Genetically engineered E. coli upgrade acetate to value-added products. Inset shows the Wood-Ljungdahl pathway leading to acetogenesis. **B. A contrasting strategy consists of** water electrolysis producing H_2 . Microbes utilize H_2 as a feedstock to generate CH_4, NH_3, alcohols and PHB.

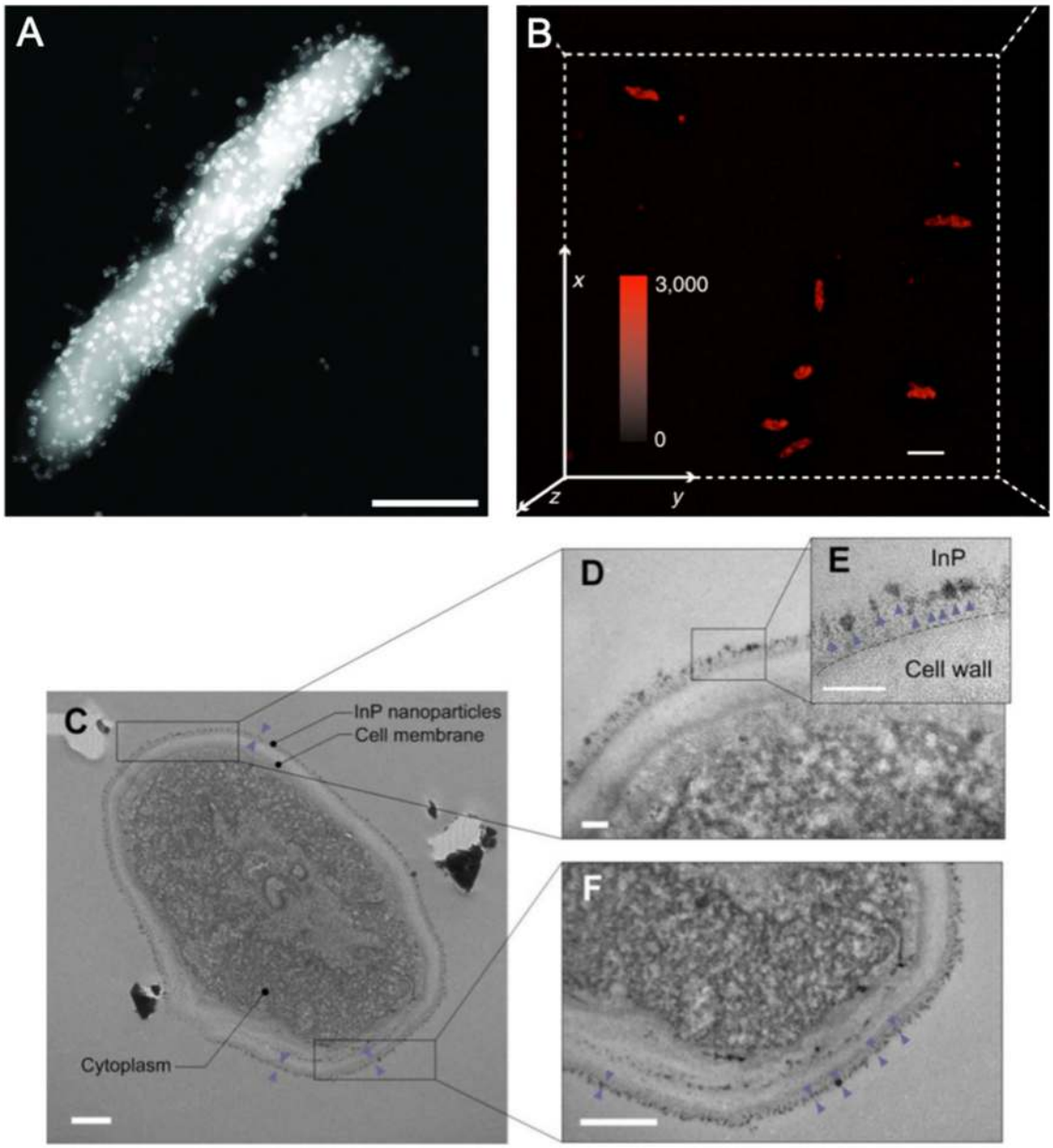

Figure 2. Three methods for visualization of light-active nanoparticles on cells. A. High-angle annular dark field STEM image illustrating the association of CdS nanoparticles on the membrane of *M. thermoacetica*. **B.** Fluorescence intensity measured by structure illumination microscopy confirms the presence of AuNCs on *M. thermoacetica*. **C.** Cross-sectional TEM image of *S. cerevisiae* – InP hybrid with InP assembled on the cell membrane (Scale bar is 500nm). **D-F.** Magnified images show higher detail of the nanoparticle attachment on the cell membrane (Scale bars are 100 nm (D,E) and 500 nm (F)). *Reproduced with permission.*

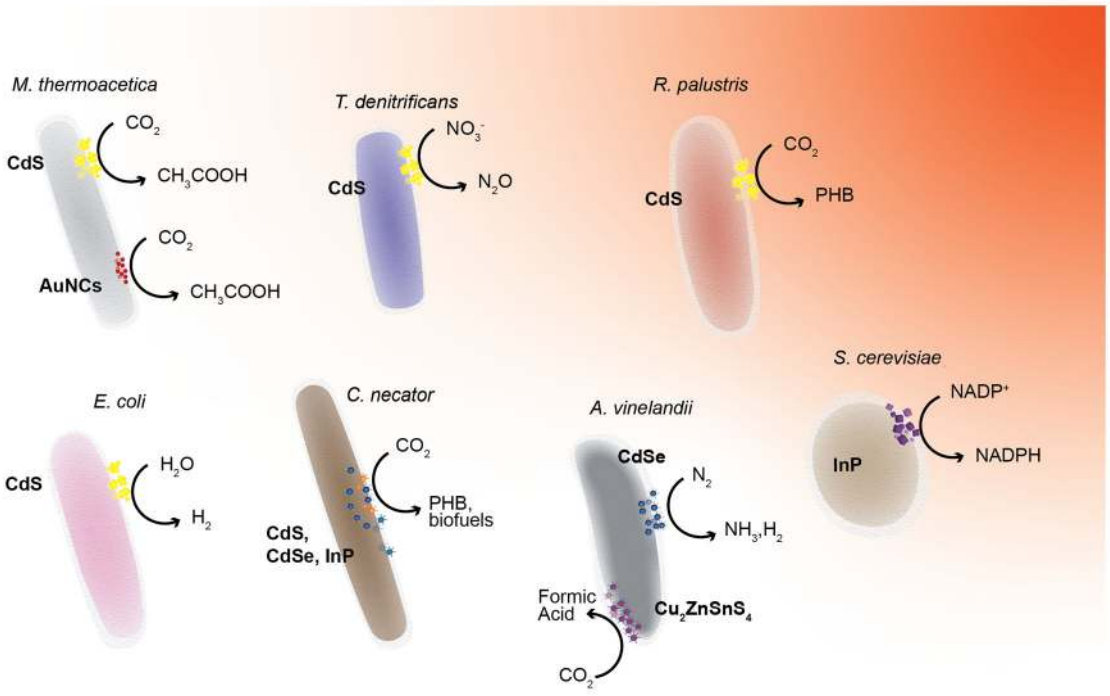

Figure 3. Map of photosensitized microorganisms. Photosensitizer-microbes pairings enable the synthesis of C_{2+}, H_2 and NH_3 from CO_2, H_2O and light. InP nanoparticles photoregenerate NADPH in *S. cerevisiae*.

Host Organism	Photosensitizer (Bandgap [eV])	Substrate/ Product	Reference
M. thermoacetica	CdS (2.51)	CO_2 / acetate	[40]
R. palustris	CdS (not reported)	CO_2 / PHB, carotenoids	[46]
T. denitrificans	CdS (not reported)	NO_3^- / N_2O	[47]
M. thermoacetica	$Au_{22}(SG)_{18}$ (not reported)	CO_2 / acetate	[59]
E. coli	CdS (2.92)	H_2O / H_2	[64]
S. cerevisiae	InP (1.34)	Hexose / shikimic acid	[65]
A. vinelandii	CdSe (2.30) Cu_2ZnSnS_4 (1.55)	N_2 / NH_3 CO_2 / formic acid	[66]
C. necator	CdS (2.98, 2.90) CdSe (2.48, 2.17) InP (1.72)	CO_2 / methyl ketones, butanediol, ethylene, PHB, propanol	[66]

Table 1

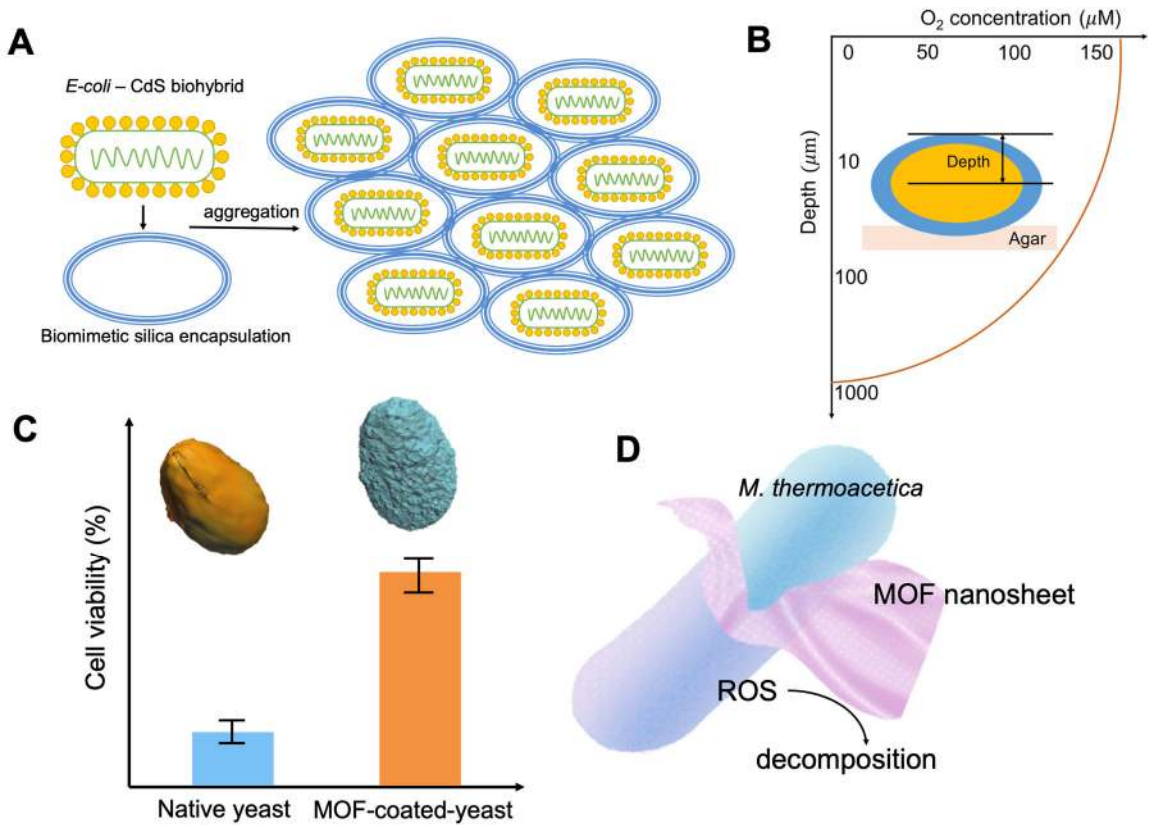

Figure 4. Cytoprotective strategies for unicellular organisms. A. *E. coli* – CdS biohybrids are encapsulated in silica shells to maintain a local anaerobic environment. **B.** Microsensor-based measurements display a sharp decrease in O_2 concentration with increasing depth. **C.** Schematic illustration of biomimetic crystallization of cytoprotective MOF coatings on living cells. Bar graph indicates the relative culture viabilities (%) of native yeast (blue) and MOF-coated yeast (orange) under lysing conditions. **D.** Schematic of dynamic MOF nanosheet covering *M. thermoacetica* while catalyzing ROS decomposition. *Reproduced with permission.*

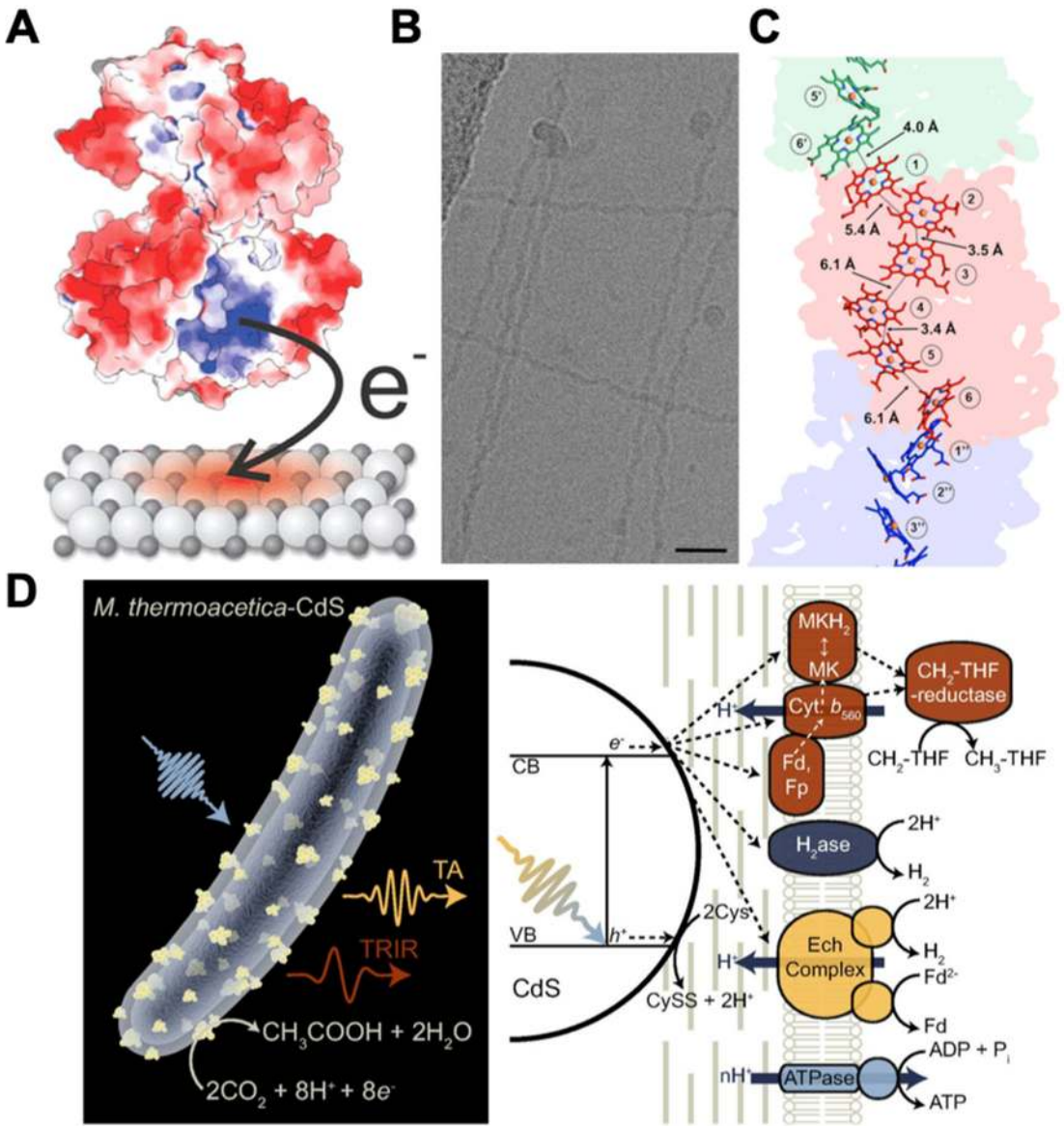

Figure 5. Exploration of charge transfer mechanisms in microbial cells. A. MtrF mediates electron transport on the membrane of *Shewanella oneidensis* MR-1. **B.** Cryo-EM image depicting conducting microbial nanowires from *Geobacter sulfurreducens* (Scale bar is 200Å). **C.** Scheme showing close-packed metal cluster hemes in the core of microbial nanowires. **D.** Translucent *M. thermoacetica – CdS* hybrids allow for transient absorption and time-resolved infrared spectroscopy. Dual charge uptake mechanisms are proposed, either by membrane-bound proteins or through hydrogenase. *Reproduced with permission.*