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REVIEW

The Cross-Species Implantable ATP Battery Inspired by Photosynthesis for Application in Diseases

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Abstract: Insufficient cellular energy and reducing equivalents critically disrupt physiological homeostasis, compromising the body's intrinsic repair mechanisms and posing a major challenge for treating many diseases. This review aims to explore the cross-species implantable ATP battery inspired by photosynthesis for application in diseases. This technology is designed to autonomously regenerate ATP within compromised human cells, directly countering the metabolic deficits underlying disease progression. We systematically delineate the three foundational components of this artificial photosynthetic system: the photooxidation module, responsible for transducing light energy into an electrochemical proton gradient; the photophosphorylation module, which harnesses this gradient to power ATP synthesis; and the encapsulation system, essential for spatial organization, functional integrity, and targeted cellular delivery. The coordinated operation of these modules enables sustained, light-powered ATP production within human cells, establishing a functional mimicry of natural photosynthesis at the cellular level. Moreover, we evaluate the therapeutic feasibility of this platform across diverse pathological contexts, including the hypoxic tumor microenvironment, metabolically impaired tissue regenerations, and energy-deficient neurons. This technology platform integrates synthetic biology, materials science, and targeted delivery strategies. By directly restoring cellular bioenergetics and facilitating reparative processes, it holds transformative potential for treating diverse diseases. Thereby, it represents a pioneering step towards establishing metabolic reprogramming and precision energy restoration as a core clinical therapeutic modality in human diseases.

Keywords: synthetic biology, artificial photosynthesis system, cross-species drug transportation, energy battery, human diseases

Introduction

In many pathological states, cells experience a critical insufficiency of energy and reducing equivalents, which disrupts their physiological functions and self-repair capabilities.[1] This defect impedes cells from fulfilling their corresponding physiological functions, let alone synthesizing sufficient proteins to facilitate intracellular self-rescue mechanisms.[2–6] Initial strategies to correct this imbalance focused on modulating the tricarboxylic acid cycle, a central pathway for ATP production. However, its integration into broader metabolic networks makes targeted intervention difficult, often leading to off-target effects or even cell death.[7–9] An alternative approach, the exogenous administration of ATP, is also ineffective due to its poor cellular uptake and rapid degradation in vivo. Consequently, a third strategy has emerged: the construction of a controllable, self-sustaining system capable of autonomously generating both ATP and NADPH to directly support cellular function and repair. The principle of adapting solutions from nature has driven innovations ranging from submarine ballast systems based on fish swim bladders to aircraft wings designed to counter vibration

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phenomena observed in insects.[10,11] This review extends this principle into biomedicine. While the biomedical field remains focused on human-derived therapeutics, we propose a paradigm shift: to harness photosynthesis by introducing a non-human, light-driven system into the body.[12,13]

The field of biohybrid systems is rapidly advancing, typically integrating three key elements: a light-harvesting component, a biological catalyst, and a mechanism for energy transduction.[14,15] This study builds upon this foundation by integrating advanced photosensitizers with functional biological units such as ATP synthase (ATPase) within a designed carrier system. 1) The photooxidation module functions analogously to an artificial photosensitive system, responsible for light capture and proton pumping. Upon light absorption, it initiates a specific photochemical reaction such as pumping protons across a membrane to generate an electrochemical gradient. Natural photosynthesis provides the fundamental blueprint, wherein Photosystems I and II operate in cascade to synthesize ATP and NADPH. This principle inspires the design of analogous, simplified systems for intracellular function.[16,17] 2) The core of the phosphorylation module is ATPase, an enzymatic nanomotor that synthesizes ATP by harnessing the energy of protons flowing down their electrochemical gradient. 3) The encapsulation system serves a dual purpose: it provides a confined compartment essential for maintaining the proton gradient that drives ATPase, while also functioning as a delivery vehicle to introduce the entire functional complex into human cells. Furthermore, in synthetic biology, established strategies for coupling donor-acceptor functional units provide a theoretical framework for effectively linking the light-harvesting and ATP-synthesis modules.[18,19]

Photooxidation Module in Artificial Photosynthesis System

Photosynthetic organisms utilize photooxidation to convert light energy into a potential difference, which can then be harnessed for subsequent utilisation. Similarly, in an implantable photosynthesis system, the photooxidation module serves as the fundamental component. The fundamental definition of a photooxidation module can be outlined as a type of energy conversion device that facilitates the conversion of light energy into an electrochemical gradient.[20,21] Currently, four types of photooxidation devices are available: microbial rhodopsin (MR), photosystem II complex (PSII), photoacid generators and photobase generators (PAGs & PBGs), and artificial photooxidation device (Figure 1).

Microbial Rhodopsin

MR is a bacterial pigment protein. As a chromophore, it contains one retinal-like rhodopsin molecule. Its chemical properties are analogous to those of rhodopsin, and it is therefore designated as bacterial rhodopsin. The earliest documented example of MR is the well-characterized bacterial rhodopsin, which functions as a light-driven proton pump. In 1971, the protein was successfully extracted from the purple membrane.[22] Since that time, bacteriorhodopsin has been the subject of numerous biophysical experiments.[23–26]

Although MR can function as a pump, channel, and light sensor, they all share a common structural organization, which is typical of all members of the rhodopsin superfamily. This organization involves the chromophore retina covalently binding to an internal pocket formed by alpha helices embedded in seven membranes of the opsin apolipoprotein.[25] The absorption of light induces isomerization from all-trans retina to 13-cis retina in MR, which ultimately results in protein conformational changes and the activation of rhodopsin.[27,28] Once activated, MR can act as a proton pump to generate an electrochemical gradient, thereby functioning as a highly effective photosensitizer.[24,29,30]

A system for the synthesis of ATP based on MR has been successfully developed. In a pioneering study, Choi et al introduced a light energy conversion building block into an artificial environment for the first time.[31] The functions of MR and ATPase were integrated into a polymer composed of ABA triblock copolymers, thereby constructing an artificial photooxidation device. In order to create the requisite artificial environment for membrane-bound proteins, self-assembled amphiphilic ABA triblock copolymers have been proposed as a potential building material for novel biomimetic membranes. The polymers in question comprise a hydrophobic layer situated between two hydrophilic layers, a configuration analogous to that of a typical lipid bilayer. The artificial biocompatible polymer film has demonstrated the requisite stability for long-term organic/inorganic hybrid systems. A biomimetic polymer was synthesized through the coupling activity of photoinduced phosphorylation of MR and ATPase F domain. ATPase maintains its rotational activity during the synthesis of polymers, utilizing the photoinduced proton gradient generated by MR activity

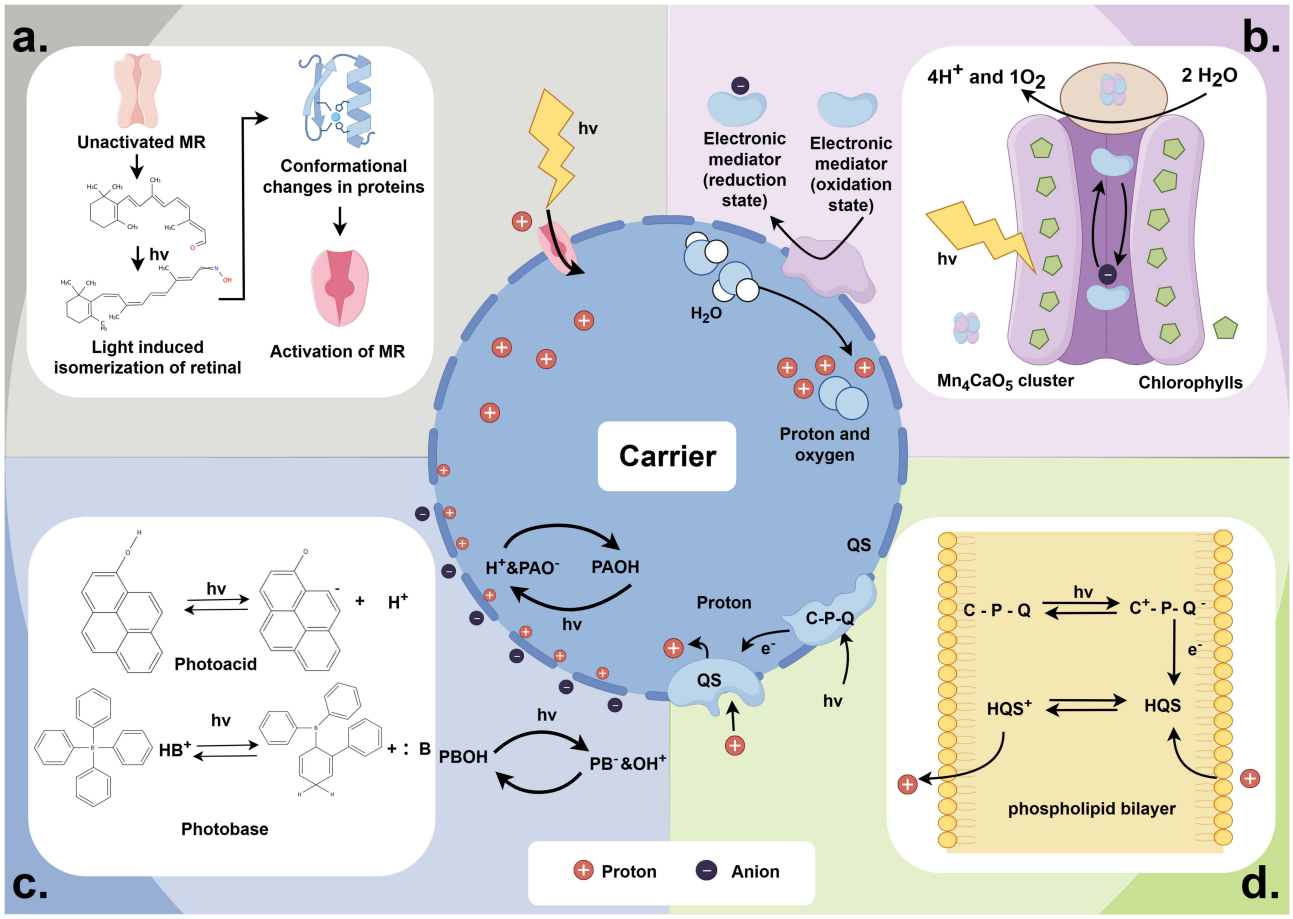

Figure 1 Different types of photooxidation devices. (**a**) Microbial rhodopsin: microbial rhodopsin is a bacterial pigment protein that function as a pump to transport hydrogen ions in the presence of light; (**b**) Photosystem II complex: photosystem II complex is capable of decomposing water into electrons, protons and oxygen through its photosynthetic reaction center, thereby forming an electrochemical gradient; (**c**) Photoacid generators and photobase generators: photoacid generators and photobase generators dissociate under light and automatically recover under dark conditions, resulting in an electrochemical gradient under light; (**d**) Artificial photosynthesis system: artificial photosynthesis system transfers electrons to redox pairs through the dissociation of C-P-Q complexes under light, thereby achieving active transport of hydrogen ions.

to produce ATP. In a recent study, Samuel et al have achieved the construction of intracellular ATP batteries using MR.[23] In this approach, a small protein liposome composed of purified ATPase and MR is placed in a large monolayer vesicle. This artificially synthesized ATP cell is capable of detecting ATP production under light.[23] In another study, researchers also reconstructed ATPase and MR in hybrid vesicles based on graft polymers and deblock polymers, observing over 90% activity and ATP production in lipid/polymer hybrid vesicles, demonstrating excellent biocompatibility and biological activity of MR-based batteries.[32]

Fundamentally, MR is a highly streamlined and efficient single-component proton pump. The MR protein itself exhibits extraordinary structural and functional stability. It is capable of tolerating a wide range of pH, temperature, and environmental conditions which is attributable to its provenance from archaea. The core function of the subject is characterized by its simplicity and specificity: namely, the absorption of a photon and the subsequent expulsion of a proton. As a membrane protein, it can be directly and functionally reconstructed into various artificial liposomes or polymer membranes. This makes it an ideal choice for building embedded bioenergy units, such as intracellular ATP synthesis system. Unlike artificial materials, however, the absorption spectrum of this material is fixed by its chromophore and cannot be easily shifted through chemical modification to cover a wider solar spectrum. Despite the stability of the process, large-scale production, purification, and reconstruction of the correct orientation into artificial membranes remains a complex and costly biological process (Figure 1a).

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Photosystem II Complex

Photosynthesis converts solar energy into chemical energy, providing the foundation of life on Earth by generating oxygen and organic compounds while regulating atmospheric CO2 levels. In this process, PSII catalyzes water oxidation and oxygen evolution, whereas Photosystem I (PSI) supplies reducing power for the reduction of NADPH.[33,34] Uniquely, PSII drives photophosphorylation by using its Mn4CaO5 cluster to split water into protons, electrons, and oxygen under visible to near-infrared light.[35,36]

Light absorption by PSII triggers energy transfer to the reaction center, exciting a central chlorophyll pigment (P680) to release a high-energy electron to the primary electron acceptor, pheophytin (Pheo). The strongly oxidizing P680 (+) extracts electrons from water, while Pheo (-) donates electrons to plastoquinone, initiating electron flow.[36,37] Protons released during water splitting are translocated across the membrane via the coupled electron transport chain. A notable advantage of PSII is its compatibility with various immobilization strategies, such as attachment to functionalized surfaces via covalent or non-covalent interactions and encapsulation within sol-gel matrices, which facilitates its modification and integration into artificial systems.[38,39]

PSII has been successfully applied in artificial photosynthesis.[35,40] For example, 1) Lee et al purified PSII from Spinacia oleracea, subsequently reconstructing the purified proteins into vesicles. The subsequent objective is to reconstruct ATPase from Bacillus subtilis into PSII protein liposomes for the purpose of constructing an artificial photosynthesis system based on PSII. The researchers then measured the production capacity of artificial photosynthesis system under illumination and applied artificial organelles to simulate a common process in cells, namely the formation of the cytoskeleton through ATP-dependent actin polymerization.[40] The experimental results demonstrate that ATP batteries exhibit a high production rate under illumination, and that the rate of ATP generation is proportional to the synthesis rate of the cytoskeleton. The present study demonstrates that photosynthetic organelles, which can be switched on and off, can control the formation of ATP-dependent cytoskeleton, thereby regulating the morphology of native cellular systems and supporting the possibility of developing artificial cell-like systems that replicate stable and complex cellular behaviors in vitro.[40] These findings may provide new treatment ideas for some neurodegenerative diseases caused by damage to the cytoskeleton. 2) Feng et al constructed a novel type of PSII-based microsphere coated with ATPase protein liposomes with a special structure through molecular assembly to simulate the light-to-ATP conversion process occurring in thylakoid membranes.[35] This construction was inspired by the natural photosynthetic chain in chloroplasts. In summary, the microspheres containing PSII were initially prepared by means of a coprecipitation method, resulting in a hydrogel-like structure. Subsequently, the encapsulation of ATPase protein liposomes on the surface of the aforementioned microspheres was undertaken to establish a simple chloroplast-like photoinduced artificial photosynthetic phosphorylation system. Under red light irradiation, PSII embedded in the hydrogel-like solid microspheres decomposes water into protons, which in turn promotes the rotational catalysis of ATPase protein liposomes on the shell. The decoupling of the natural photosynthetic phosphorylation pathway is a key feature of this smallest form of organelle-sized bioreactor, which enables it to bypass PSI and achieve independent ATP synthesis.[35] This strategy of partitioning and integration has the potential to create new opportunities for the assembly and simulation of complex biochemical processes in multifunctional units. 3) Tang et al engineered a hybrid Escherichia coli strain incorporating an integrated dual-channel energy pathway by implanting thylakoids into the bacteria. This system enables direct utilization of photogenerated electrons for the synthesis of ATP and NADPH under light illumination. In one mechanism, the photoelectrons generated within thylakoids are directly harnessed to produce ATP and NADPH, which are subsequently delivered to the host bacterium. Alternatively, these photoelectrons can be transferred and captured by redox mediators, enhancing cellular levels of ATP and NADPH by promoting the electron transport chain and supporting the glycolytic pathway in E. coli.[41]

Beyond full PSII complexes, the photosynthetic reaction center (RC), a transmembrane protein within PSII, can be purified and used separately as a photo-driven oxidoreductase.[42] In purple bacteria, a simplified RC binds cytochrome c2 and ubiquinone to establish a proton motive force across the membrane upon illumination.[43,44] However, if extracted from living systems and reconstructed in suitable lipid compartments, it can also function independently of auxiliary proteins. For instance, Altamura et al extracted photosynthetic reaction centers and reconstructed the electrochemical

gradient generator on giant vesicles in a highly oriented manner, which has been demonstrated to generate transmembrane proton gradients under illumination. Further experiments have demonstrated that this reconstructed RC exhibits markedly elevated biological activity and is readily synthesized and isolated. Additionally, under illumination, the researchers observed pronounced electrochemical gradients in the lipid membranes on either side of the RC. Consequently, RC reconstruction exhibits the characteristics of facile synthesis and high biological activity, rendering it an optimal photooxidant.

PSII is a key component of the natural photosynthetic apparatus, capable of catalyzing water splitting under illumination. Unlike some artificial molecular systems, it simultaneously generates both a proton gradient and oxygen, thereby supplying essential proton dynamics and an aerobic environment for the overall photosynthetic process. This unique functionality offers a biological rationale for its potential application in treating diseases associated with local hypoxia. The practical utilization of PSII is primarily limited by its stability: the complex is structurally fragile and prone to photoinhibition, where excessive light irreversibly damages its core proteins. This vulnerability represents the major constraint for its real-world applications (Figure 1b).

Photoacid Generators and Photobase Generators

PAGs are unstable compounds that dissociate under light to produce hydrogen ions. In a similar manner, PBGs yield hydroxide ions when exposed to light.[45] These compounds have been the focus of extensive research in the context of light-induced polymerization and degradation. In recent years, however, attention has shifted towards the biomedical field, where PAGs have been shown to possess significant clinical value. Consequently, there has been a notable increase in the number of novel PAGs that have been reported in recent years.[46,47]

The process of hydrogen production by PAG under illumination comprises both irreversible and reversible processes. Reversible PAG demonstrates significant potential in the manufacture of artificial photooxidation devices. The following example will be given in order to briefly describe the mechanism of reversible PAG hydrogen ion production. In 2022, Zhao et al reported a novel reversible PAG mechanism termed W-RPA. This novel PAG mechanism is distinct from previous PAGs in that it lacks the capacity to dissociate hydrogen ions independently due to the absence of active hydrogen in its molecular structure. However, it has been demonstrated to reversibly generate hydrogen ions under irradiation. The mechanism of W-RPA is as follows: under 660 nm laser irradiation, two hydrogen bonds are formed between water and photoacid molecules, forming a metastable six membered ring, and then the dissociated hydrogen atoms in water dissociate in the form of hydrogen ion. Subsequent to this process, the six-membered ring undergoes dissociation in the absence of light, resulting in the restoration of the hydrogen ions that were previously produced.[46,48–50] Notably, this process does not involve the consumption of oxygen. It is noteworthy that this PAG and its derivatives have been employed in photodynamic therapy (PDT) for the treatment of tumors, with encouraging clinical outcomes.

The construction of a closed membrane structure, with PAG embedded on the inner side, or with PBG added to the outer environment, allows for the formation of an electrochemical gradient on the inner and outer sides of the membrane under light conditions. This is achieved through the decomposition of PAG and PBG. The reversible nature of PAG within the device ensures its continuous operational capacity. In the current research, reversible PAGs and ATPase have been loaded onto silica nanoparticles, thereby achieving in vitro synthesis of ATP.[51–53] It is noteworthy that the photophosphorylation activity of this process is comparable to that of traditional photoinduced proton generation or pumping systems.[52]

The primary challenge confronting PAG & PBG in its role as an electrochemical gradient generator pertains to the limited lifetime of the proton dissociation state, which is constrained by the lifetime of the photo acid conjugated base in the ground state.[45] The brief lifetime of proton dissociation states is advantageous for the study of certain rapid processes; nevertheless, the released protons lack the necessary time to diffuse out of their counterions, thus hindering the catalysis of chemical processes or the substantial alteration of macroscopic properties, despite the theoretical excited state being capable of achieving a low level.[52] A recent study reported a PAG with a proton dissociation state relaxation time close to 1 second. This protracted dissociation state PAG affords protons sufficient time to diffuse out of their antiparticles and engage in the subsequent phase of ATP synthesis.[45]

Unlike their biological counterparts, PAGs systems do not require the handling of complex biological proteins, offer more flexible storage and operating conditions. However, the protons released by conventional PAGs typically have a very short lifespan, often recombining with their conjugated bases before they can be effectively utilized. This severely limits their capacity to drive biochemical processes, such as ATP synthesis. Furthermore, the technical challenge of effectively confining PAGs to one side of a membrane to establish a directional proton gradient is significantly greater than that of integrating a single membrane protein (Figure 1c).

Artificial Photooxidation Device

Conventional photooxidation devices have primarily relied on natural components such as MR and PSII. However, recent advances have enabled the development of fully synthetic photosynthetic membranes for photooxidation. Although biological building blocks remain prevalent in photocatalytic systems, synthetic chemical units are increasingly being incorporated.

The maturity of artificial photooxidation systems varies significantly. The most advanced is the Janus MOLs system, which is capable of establishing proton gradients and facilitating ATP synthesis. Second are the other light-driven proton transport systems such as the carotenoid-porphyrin-naphthoquinone (C-P-Q) system. They can generate proton gradients but their role in promoting ATP synthesis has not yet been demonstrated. The least mature in this specific context are photo enzyme catalytic systems, which perform redox reactions under light but cannot generate a proton gradient to power ATP synthesis.

The most comprehensive investigation in this field was undertaken by Wang et al. They reported a light-driven proton transport system based on two-dimensional porphyrin-based asymmetric metal-organic layers. This study utilized a microemulsion method to asymmetrically functionalize the two sides of a MOL, attaching carboxyquinone as an electron acceptor on one side and Acitretin as a hole donor on the other, thus constructing the Janus-MOL. Attaching the Janus-MOL to the liposome surface formed an LP-Janus-MOL composite system, successfully mimicking the directional transmembrane proton transport based on membrane asymmetry found in photosynthetic bacteria. The working mechanism is as follows: upon light irradiation, the porphyrin units in the MOL absorb light energy and undergo charge separation, with the resulting electrons and holes transferring to carboxyquinone and acitretin, respectively; these then undergo redox reactions with freely diffusing quinone/hydro semiquinone within the lipid bilayer. Through the protonation/deprotonation cycle of hydro semiquinone at the inner and outer membrane interfaces, directional transmembrane transport of protons from the outside to the inside is achieved, thereby establishing a proton gradient. To experimentally validate the bioenergetic function of this gradient, ATPase was then incorporated into the LP-Janus MOL system. The result was a clear observation of ATP production, confirming that the photochemically generated proton gradient is sufficient to drive the co-loaded ATPase to catalyze ATP synthesis.[54]

Other light-driven proton transport systems include the C-P-Q molecular triad, spiropyran-based artificial light-harvesting membranes, graphene oxide nanofluidic films, and covalent organic frameworks. A classic example in this field is the C-P-Q molecular triad. In this system, the proton gradient is generated through a photochemical process initiated by light absorption of lipophilic quinones, which undergo transitions between their reduced and oxidized states. This leads to the formation of carotenoid radical cations and naphthoquinone radical anions. Subsequent reduction near the outer bilayer interface enables quinones to accept electrons and form anions. The cyclic oxidation and reduction of quinones ultimately establishes a transmembrane proton gradient.[55–57] Another representative system was developed by Xie et al, who constructed an artificial light-harvesting membrane by incorporating spiropyran, a cation exchanger, and the lipophilic salt tetradodecylammonium tetrakis borate into a supported liquid membrane. Under illumination, the reversible structural transformation between spiropyran and merocyanine enables directional proton binding and release, thereby generating a proton gradient.[58] In addition, Di et al fabricated a laterally heterogeneous two-dimensional nanofluidic film composed of horizontally connected layers of positively and negatively charged graphene oxide. Light irradiation triggers asymmetric changes in the surface potential of these regions, altering their proton affinity. This change initiates directional proton transport from the positively to the negatively charged portion, and continuous lateral proton flow establishes a pronounced proton concentration gradient across the membrane at a remarkably high pumping rate.[59] Furthermore, Sun et al successfully developed COF membranes featuring intra- and interlayer heterojunction structures.

Under light exposure, porphyrin units within the membrane absorb photons and generate electron-hole pairs. Owing to the vertically gradient protonation structure introduced during synthesis, photogenerated charges separate efficiently, creating a strong built-in electric field. This field enables directional proton transport against concentration gradients of up to 2000-fold, as experimentally demonstrated.[60] It should be noted, however, that current studies on these systems focus primarily on proton gradient generation, and no reports have yet demonstrated their use in driving ATP synthesis.

Of particular note is the emerging frontier of photo enzyme-coupled catalysis. A representative example is the system based on artificial thylakoid membrane-assisted NiMn2O4@PoPDA hierarchical hollow nanospheres. Under illumination, this artificial thylakoid membrane system enables efficient separation and transport of photogenerated electron-hole pairs, thereby driving redox reactions.[41] Another type of photocatalyst is created using ZrOCoII as photo absorbers combined with metal oxide cluster catalysts. This type of light-absorbing agent has the capacity to convert CO2 to CO during the oxidation of H2O to O2 under light in the presence of a carbon dioxide water gas mixture.[61] This photo enzyme coupled catalytic method can catalyze redox reactions by absorbing light energy and is a potential photo oxidation device.

The artificial photooxidation system is designed to build a photosynthetic process from the ground up using fully synthetic components. Inorganic materials typically have a smaller footprint than biological proteins and exhibit greater resistance to heat, light, and chemical degradation, enabling operation in more extreme conditions. These designs also allow precise artificial control over properties like light absorption, energy levels, and redox potentials. However, the technical barriers and costs associated with fabricating artificial nanostructures with precise morphology and uniform performance are generally much higher than those for cultivating bacteria or extracting proteins. Moreover, electron and proton transfer across interfaces between synthetic materials and biological enzymes tends to be significantly less efficient than the interprotein transfer occurring in natural systems. Another key limitation is that many high-performance inorganic nanomaterials may exhibit cellular toxicity, which restricts their direct use in biomedical applications (Figure 1d).

Calculation of ATP Production Efficiency in Different Photooxidation Systems

Experimentally confirmed photooxidation systems capable of ATP synthesis include PSII system, MR system, and artificial photosynthesis system. It is important to calculate and compare the ATP production efficiencies of these three systems.

First, the ATP synthesis rate of thylakoid vesicle systems based on PSII is calculated. In nature, a typical chloroplast can fix approximately 10^6 CO2 molecules per second. Fixing one CO2 molecule into carbohydrates requires the consumption of about 3 ATP. Thus, the ATP generation rate of a typical chloroplast is 3×10^6 per second. A single chloroplast contains approximately 5000 thylakoid vesicular structures. It can be calculated that the ATP production rate per thylakoid is 36,000 molecules per minute.[62,63] However, in artificial synthesis processes actual ATP production rate that is lower than that of natural thylakoids. For example, in the study by Chen et al, these nano-thylakoids (130 nm) were capable of catalyzing ATP production from ADP at a rate of 6.4 ± 0.1 μM min^{-1} μg^{-1} (based on total chlorophyll).[64] According to other studies, nano-thylakoids contain about 9.1% chlorophyll.[65,66] Using a typical density ρ of biological materials of approximately 1 g/cm,[3] the ATP production rate per nano-thylakoid can be calculated to be about 20,000 ATP molecules per minute. Additionally, in a study by Lee et al, the artificially assembled cell membrane–PSII constructs (100–200nm) produced 300 times the number of ATP molecules relative to the chromophore groups over 50 minutes.[67] A single nano-thylakoid contains approximately 3200 chromophore groups. Based on this, the ATP production rate of these artificially assembled nano-thylakoids is calculated to be approximately 19,200 ATP molecules per minute. The ATP production rates of nano-thylakoids in these two experiments are both around 20,000 ATP molecules per minute, which is relatively close to the ATP production rate of natural thylakoids. Therefore, we have reasonable grounds to believe that these calculated results are close to the actual values.

Next, the ATP synthesis rate of MR-based vesicles is calculated. Choi et al constructed polymer composed of reconstituted MR and ATPase (about 37 nm), with a maximum ATP synthesis rate of 116 nmol/min/mg and a saturation rate of 4.2 mol/min/mg.[64] The maximum ATP synthesis rate for these vesicles is calculated to be approximately 1850 molecules per minute, with a saturation rate of 67 molecules per minute. In a more recent study, Samuel et al construct larger bacteriorhodopsin vesicles (100–200 nm), called bRFoF1-PL. A single bRFoF1-PL produced approximately 0.6×10^6 ATP molecules over 4 hours of illumination, equivalent to 2500 molecules per minute, with a maximum ATP production rate of 9000 molecules per minute.[23]

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Finally, we calculate the ATP synthesis rate of photooxidation system. The LP-Janus-MOL (2.5 ± 0.5 μm) constructed by Wang et al exhibits an average ATP production rate of approximately 42 molecules per minute per ATPase.[54] However, since the conformation and quantity of ATPase installed on a single vesicle remain unclear, it is not possible to accurately calculate the ATP synthesis rate per vesicle. Although the precise ATP synthesis rate for each artificial photooxidation system vesicle cannot be determined, given its relatively large volume and extremely low ATP production efficiency compared to the normal chloroplast ATPase working rate of 18,000–30,000 ATP/min, which far exceeds the 42 ATP/min observed in this experiment. We can reasonably conclude that the loading efficiency of this type of photooxidation system is very low.

In summary, the calculations indicate significant differences in energy production efficiency among different types of photooxidation systems. Various experiments have demonstrated that thylakoids can achieve high-efficiency energy production (approximately 20,000 ATP per minute per unit) within a relatively small volume (100–200 nm). In contrast, the MR system, even at its maximum, only reaches about half the efficiency of thylakoids (approximately 9000 ATP per minute per unit) within the same 100–200 nm scale. We have also performed a rough estimation of the ATP synthesis rate for artificial photooxidation-based photosynthetic devices and concluded that their ATP production efficiency is exceedingly low. This conclusion aligns well with biological evolutionary maturity: thylakoids, as highly evolved photooxidation apparatuses, exhibit higher efficiency than the relatively primitive MR systems, while artificial photooxidation systems are the least mature. Human efforts to mimic nature still have a considerable distance to cover.

Comparison of Different Photooxidation Module in Artificial Photosynthesis System

In summary, the evolution of light-driven systems reflects a dynamic interplay between natural and synthetic design paradigms. Natural systems, such as MR and PSII, leverage inherent biocompatibility and high catalytic efficiency, making them indispensable in bio-inspired energy harvesting and therapeutic applications. However, their reliance on fragile biological components and complex extraction protocols limits scalability. In contrast, artificial photosynthetic membranes-transcend biological constraints through modular architectures, enabling programmable light-to-energy conversion and environmental adaptability. Yet, challenges persist in quantum yield optimization and cost-effective large-scale deployment (Table 1).

Structural factors exert a profound influence on the practical deployment of photooxidation systems. 1) Biological Function: At the biological functional level, PSII surpasses other systems due to its high efficiency in generating proton gradients and creating an oxygenated environment. As a biologically evolved photosynthetic system, its maturity in proton transfer structure far exceeds that of artificial devices, which remain largely in the experimental exploration stage. In comparison, the use of PAGs as energy-producing units remains largely conceptual. The protons they release have an extremely short lifetime, often recombining with their conjugate bases before being effectively utilized. Currently, no structural design has been developed to effectively prolong their proton lifetime, limiting their application to auxiliary

Table 1 Comprehensive Comparison of Different Photooxidation Systems

	MR System	**PSII System**	**PAGs & PBGs System**	**Artificial Photooxidation System**
Naturalness	Natural protein	Natural protein	Fully synthetic	Fully synthetic
Efficiency	Medium	High	NA	Low
Stability	Medium	Low	Very low	High
Size	100-200 nm	40-200 nm	-	2-3 μm
Clinical risk	Endotoxin contamination	ROS accumulation	Metabolic toxicity	Organ accumulation, chronic inflammation
Applications	PDT adjunct therapy, ATP battery	Oxygen producer, PDT adjunct therapy, ATP battery	PDT adjunct therapy	CO2 conversion
Maturity	Mature	Mature	Conceptual	Immature

Abbreviations: MR, microbial rhodopsin; PSII, photosystem II complex; PAGs & PBGs, photoacid generators and photobase generators; NA, not applicable; ROS, reactive oxygen species; PDT, photodynamic therapy.

roles in modalities such as PDT. 2) Load capacity: The load capacity of the photocatalytic oxidation system is influenced by both its production efficiency and size. An excellent production system should have the highest ATP production efficiency on the smallest possible scale. In this regard, the PSII system is the best, as it can achieve the highest ATP synthesis rate (20,000 ATP/min) on a small scale (100–200 nm). On the contrary, restricted by immature fully artificial structures, artificial photooxidation systems have a large volume and extremely low production efficiency. 3) Stability and Environmental Resilience: In terms of stability and environmental resilience, MR and artificial photooxidation systems outperform PSII and PAGs. MR exhibits remarkable resilience owing to its compact seven-transmembrane helical bundle and extremophile-derived protective protein shell. Similarly, artificial systems achieve durability through non-proteinaceous photosensitive cores engineered for structural integrity. In contrast, PSII exhibits high instability; its central D1 protein is prone to denaturation under strong light (a phenomenon known as photoinhibition), which represents a major bottleneck for its practical application.[68] The instability of PBGs lies in their inability to provide sustained conditions required for ATP synthesis. Protons released by conventional PAGs also have an extremely short lifespan, which severely limits their clinical applicability.

Beyond these structural factors, different photooxidation systems present distinct safety profiles. As a bacterial-derived protein complex, MR may carry risks of endotoxin contamination introduced during extraction and purification. Similarly, PAGs can also generate potential metabolic toxicity, directly interfering with intracellular acid-base balance. PSII, on the other hand, poses safety concerns due to its byproduct, oxygen, which can under certain conditions be converted into reactive oxygen species (ROS). In closed or implantable systems, the accumulation of ROS may lead to tissue damage and oxidative stress in surrounding areas. Although artificial photooxidation devices exhibit high stability and lack immunogenicity, nanomaterials are often resistant to biodegradation. This raises concerns regarding their potential accumulation in biological systems, which could result in organ dysfunction and chronic inflammation.[69,70]

Based on comparative analyses of various photooxidation systems in terms of energy production efficiency, safety, and stability, distinct application scenarios have been identified for each system. For instance, the PSII system is characterized by high energy production efficiency and the ability to generate oxygen while producing ATP, highlighting its potential for ameliorating tumor hypoxia in therapeutic contexts. In contrast, the MR system functions as a light-driven proton pump, enabling not only energy generation but also precise cellular signaling modulation. By applying light stimuli of varying intensities in vitro, the MR proton pump can be activated, triggering a range of cellular responses including alterations in acid-base homeostasis. Similarly, regulating the synthesis and hydrolysis of PAGs via optical signals can induce analogous cellular changes. Several studies have already demonstrated fine-tuned cellular manipulation leveraging the unique photo switching properties of MR and PAGs.[71–73] As for artificial photosynthesis systems, although still at a nascent stage, advances in synthetic biology are expected to enhance their conversion efficiency and reduce production costs, thereby offering new avenues for large-scale solar energy utilization.

Photophosphorylation Module in Artificial Photosynthesis System

Following the photooxidation system, a concise exposition will be provided on the composition and operational mechanism of the photophosphorylation system. The energy transfer process of a complete artificial photosynthesis system can be described as "from light energy to electrochemical gradient, then to chemical energy in ATP". The photooxidation module is responsible for the conversion of light energy into electrochemical gradients, while the photophosphorylation module employs these electrochemical gradients to facilitate ATP synthesis.

The chemical permeation hypothesis provides the foundational framework for the working mechanism of ATPase. This hypothesis posits that during oxidative phosphorylation, electrons traverse a series of membrane proteins and electron shuttles with progressively increasing positive redox potentials, transferring from electron donors with more negative redox potentials to electron acceptors with corrected redox potentials. The transfer of electrons from one respiratory enzyme to other results in the translocation of protons across the membrane by at least one of the enzymes, thereby establishing proton dynamics. The chemical osmotic gradient is posited to act as the driving force behind the synthesis of ATP from ADP and inorganic phosphates, a process catalyzed by ATP and ATPase. In eukaryotes, this process occurs in highly specialized organelles, namely mitochondria. A similar principle underlies the process of chloroplast ATP synthesis. In contrast, oxidative phosphorylation in prokaryotes is characterized by a branched, flexibly

inducible and modular structure. Bacteria and archaea express a multitude of respiratory enzymes and produce disparate respiratory chains, thereby enabling them to process a variety of electron donors and acceptors in accordance with their surrounding environment. In addition, there is a substantial body of evidence that suggests the bioenergy efficiency of prokaryotes is comparable to that of eukaryotes. This finding suggests that bacterial ATPase may represent a novel and efficient photophosphorylation module.[74–77]

The core engine of this module is the ATPase, a remarkable enzymatic nanomotor that is among the smallest and most efficient molecular machines in nature. This protein complex consists of two primary functional domains: a membrane-embedded F_0 unit, which forms a proton channel, and a soluble F_1 unit, which catalyzes the synthesis of ATP from ADP and inorganic phosphate (Pi). The operational principle is governed by the binding change mechanism and rotational catalysis. The flow of protons down their electrochemical gradient, through the F_0 channel, drives the rotation of a central rotor stalk (the γ-subunit). This mechanical rotation induces cyclical conformational changes in the three catalytic β-subunits of the F_1 unit, sequentially promoting ADP and Pi binding, ATP formation, and finally ATP release.[31,39] This process essentially converts the potential energy of the proton gradient into the chemical energy of the phosphoanhydride bond in ATP with astonishingly high efficiency.

The ATPases employed in these systems are typically extracted from various biological sources, each with distinct advantages. Those derived from mitochondria[78,79] and chloroplasts[35,79,80] are highly optimized for their native environments and exhibit exceptional catalytic proficiency. However, bacterial ATPase offer significant practical benefits for synthetic biology applications.[31,40,74–77] Their relative simplicity, ease of production through microbial fermentation, and robust nature often make them more amenable to purification, reconstruction, and functional integration into hybrid artificial systems. Furthermore, the bioenergetic efficiency of prokaryotes is comparable to that of eukaryotes, validating the use of bacterial ATPase as a potent photophosphorylation module.

The central challenge in building a functional photophosphorylation module is the maintenance of its structural integrity and functional stability within the complex physiological environment of a human cell. The enzyme may be vulnerable to proteolytic degradation, oxidative damage from ROS, or denaturation due to shifts in pH or temperature. Furthermore, the potential immunogenicity of non-human ATPase, particularly bacterial variants, poses a significant hurdle. The introduction of these foreign proteins could trigger host immune responses, leading to rapid clearance of the therapeutic complexes, neutralizing antibody production, or even adverse inflammatory reactions, thereby compromising both safety and efficacy. Another critical challenge is the efficient coupling between the photooxidation and photophosphorylation modules in vivo. The proton gradient generated by the photooxidation module must be precisely channeled to the F_0 unit of ATPase without significant dissipation. In the crowded and buffered intracellular milieu, maintaining a sufficiently localized and strong proton motive force across the artificial membrane is considerably more difficult than in controlled in vitro systems. Finally, achieving targeted and functional delivery of the fully assembled and oriented module to specific diseased cells or tissues remains an unsolved problem. The module must not only evade immune surveillance during transit but also successfully internalize into target cells and localize to an appropriate intracellular compartment where it can access light and substrates without disrupting native cellular processes.

Addressing the biocompatibility, stability, coupling efficiency, and delivery challenges is paramount for realizing the therapeutic potential of artificial photophosphorylation in human diseases. Recent research advances are paving the way for more efficient photophosphorylation systems. A case in point is the development of protein-directed control and reassembly techniques. A fundamental challenge has been that ATPase, when randomly assembled on biological membranes, often have randomized orientations which cause their proton gradients to cancel each other out, thereby hindering overall efficiency. To overcome this, Andrea et al devised a novel strategy for the unidirectional incorporation of light-driven proton pumps into liposomes. This approach enables a more precise synthetic biology construction for functional optimization.[81]

Encapsulation Systems in Artificial Photosynthesis System

Sea slugs are a rare species of marine animal that are capable of performing photosynthesis. The ingestion of seaweed enables the absorption of chlorophyll by the organism. This process enables them to transform the ingested chlorophyll into a photosynthetic organelle within their body. It is our hope that humans will also be able to achieve cross-species drug delivery, whereby chloroplasts are transported into human cells to play a role.

The objective of the encapsulation system is to provide a physical separation between the photooxidation and photophosphorylation modules. As is the case with natural chloroplasts, the photooxidation module and the photophosphorylation module are unable to coexist in the same space. This incompatibility can be attributed to the inability of the photophosphorylation module to utilize the electrochemical gradient generated by the photooxidation module for oxidative phosphorylation. Concurrently, the encapsulation system must guarantee the successful transportation of the photooxidation module and photophosphorylation module into the cell and their stable existence therein. This necessitates evading recognition by the immune system outside the cell and avoiding degradation by lysosomes inside the cell. Given that the initial objective of artificial photosynthesis system was to provide a source of ATP for the treatment of disease, it is necessary that the encapsulation system be modifiable in order to facilitate targeted drug delivery.

The development of ATP batteries has been informed by the utilization of simple structures such as soybean phospholipids, blue-green algae phospholipid coatings, nylon and polycarbonate encapsulation device. However, the targeted transport of ATP batteries has yet to be achieved. In light of these challenges, concerted efforts are underway to integrate the latest findings, with the aim of proposing novel encapsulation devices that meet the criteria for conventional artificial photosynthesis system and demonstrate targeted transport capabilities. The transport encapsulation systems that are currently feasible include multifunctional nanoparticles (NPs), cells and bacteria. Furthermore, genetic engineering has been identified as a promising avenue despite the numerous challenges that must be overcome to realize its full potential (Figure 2).

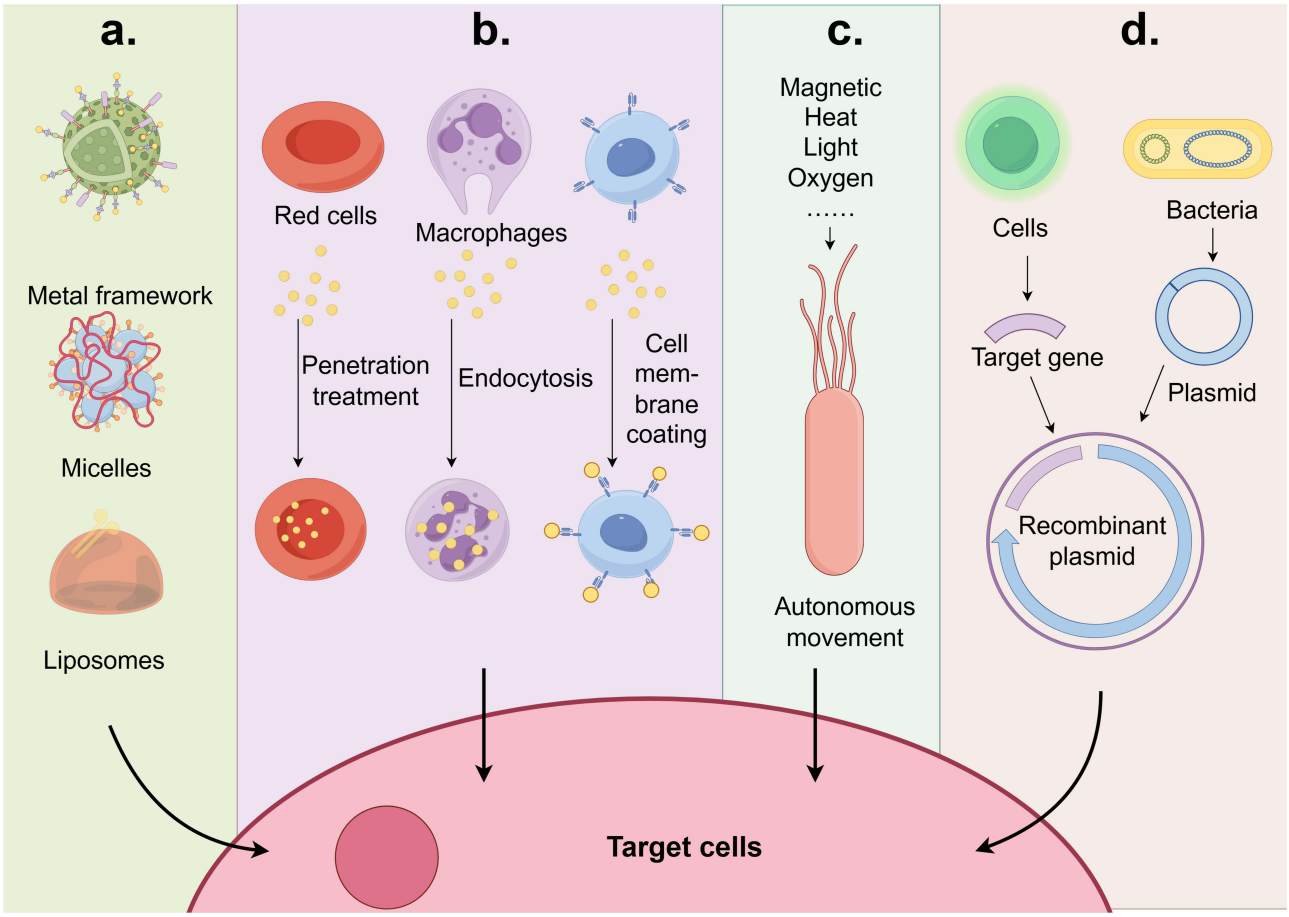

Figure 2 Different types of encapsulation systems. (**a**) Nanoparticles: nanoparticles synthesized from organic/inorganic materials enable programmable modifications for enhanced targeting and biocompatibility, with dual functionality in drug delivery and imaging; (**b**) Cell: cell encapsulation systems possess natural biocompatibility, high biological safety, and immune clearance avoidance, and there are various loading methods: diffusion, endocytosis, electroporation, and "Trojan horse" method; (**c**) Bacteria: bacteria possess the capacity for autonomous movement, relying on flagella/pili for propulsion. In addition, bacteria have the capacity to respond to environmental signals such as light, heat, and magnetic fields, exhibiting good targeting properties; (**d**) Genetic engineering: genetic engineering vectors utilize CRISPR/Cas9 technology to achieve efficient and cost-effective gene modification, utilizing various delivery methods, including viral vectors, synthetic materials, and physical methods.

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Multifunctional Nanoparticles

The advent of advanced nanotechnology has facilitated the development of precise treatment modalities, enabling the selective delivery of therapeutic and/or diagnostic drugs to specific targets through the use of multifunctional NPs.[10,82] The objective of these synthetic nanomedicines is to address the physical and chemical issues associated with free drugs, such as low stability and non-selectivity, while also addressing biological barriers during transportation (such as immune clearance, off-target deposition, continuous blood circulation, and cell entry).[83] To date, the most commonly utilized NPs comprise a range of organic and inorganic nanomaterials, including liposomes, micelles, polymers, metal oxides and MOFs.[84–87]

A significant benefit of NPs is its capacity for chemical modification, which enhances its biocompatibility and targeting capabilities.[88,89] The outer surface of cells is composed of complex biological substances, including polysaccharides, proteins, and lipids. These substances provide a range of surface properties and functional groups that allow for the modification of various synthetic materials on the cell surface. Consequently, chemical and physical techniques have been employed to synthesize hybrid materials comprising biological and non-biological components. For instance, the presence of substantial quantities of reactive groups on the cell surface including reduced thiol and amino groups enables the formation of covalent bonds at the surface through the reaction of carboxylated or thiol-reactive maleimide-modified NPs with biological units.[85,90]

In contrast, physical modification represents a non-covalent strategy in the context of live cell engineering, whereby the forces of electrostatic and hydrophobic interactions are typically the driving forces. Due to the lipid bilayer and the negatively charged characteristics of the cell membrane, therapeutic molecules or NPs with positively charged electronic characteristics and hydrophobic parts can attach to the cell surface with high stability. To illustrate, the electrostatic interaction between anionic bacteria and cationic gene nano encapsulation systems facilitates the formation of DNA vaccines, which are employed as an oral immunotherapy for tumor.[85,91] Through chemical or physical modifications, these NPs can be tailored to enhance targeting and biocompatibility. These particles possess the dual capabilities of drug loading and imaging.

NP synthesized from organic/inorganic materials can be programmable to enhance targeting and biocompatibility, with dual functions in drug delivery and imaging. While these nanoparticles hold considerable promise for precision oncology, several inherent limitations impede their clinical translation. The most critical challenges include the intrinsic biological toxicity of the constituent materials and the difficulties in scaling up production. Many organic and inorganic components used in nanoparticle formulations may induce unforeseen long-term toxicological responses, and laboratory-scale synthesis methods encounter substantial technical and economic barriers when transitioning to large-scale manufacturing that meets requirements for uniformity and stability. Furthermore, the formation of a protein corona in complex physiological environments compromises nanoparticle targeting and, consequently, their theoretical advantages in practice. Thus, future advancements will rely not only on continued innovation in physicochemical design, but also on achieving fundamental progress in biosafety validation and scalable production processes[92,93] (Figure 2a).

Cell-Based Encapsulation System

Hollow cells exhibit high biocompatibility and are not readily recognized or eliminated by the immune system. The transportation of ATP batteries can be achieved safely through the combination of hollow batteries and nanoparticles.[94]

The initial step in this process is the safe loading of NPs into cells. The encapsulation of NPs within cells can be accomplished through various established methodologies, including diffusion, endocytosis, and electroporation, depending on the specific cell type under consideration.[94,95] It has been documented that the low permeability treatment of red blood cells (RBCs) generates pores on the cell membrane, thereby enabling the diffusion of substances from the surrounding solution into the cell's internal space.[96,97] The restoration of the cell membrane can then be achieved by restoring osmotic pressure, a process which allows a significant quantity of drugs and NPs to be encapsulated into RBCs for long-term release in the blood.

Additionally, certain cell types, including macrophages and monocytes, have been shown to have the ability to engulf foreign substances. In view of this characteristic, a distinct technique was proposed for loading NPs into cells for targeted therapy by incubating them with these cells, a strategy referred to as the "Trojan Horse" approach.[97–99] This method has

been employed to incorporate a variety of therapeutic NPs, including gold NPs, nanoenzymes, and drug, into cells, thereby constructing cell-based delivery systems.[100] The modification of ligands has been shown to enhance the selectivity and efficiency of endocytosis.[101] Furthermore, the coating of cell membranes represents an emerging technology that is being employed in the design of nanomaterials with biofilms. These materials are capable of directly encapsulating and synthesizing NPs through the outermost layer of cells.[102] This method facilitates the transfer of cell surface molecules to the resulting membrane-based nano platform. A variety of techniques have been employed to prepare this biomimetic nanoparticle, including membrane extrusion, ultrasonic treatment, and microfluidic electroporation. The artificial photosynthesis system formed by cell membrane coating technology in conjunction with thylakoids has been demonstrated to successfully enter host cells and exert its effects, markedly improving the inflammatory microenvironment in patients with osteoarthritis, tumor, and Alzheimer's disease.[94,103–105]

Hollow cells offer a promising platform for drug delivery in nanomedicine, leveraging their inherent biocompatibility and low immunogenicity to avoid immune detection and extend circulation time. A range of techniques including diffusion, endocytosis, electroporation, and the "Trojan Horse" strategy have been developed to load therapeutic NPs into these cellular vehicles, enabling advanced drug delivery systems. However, clinical translation of cell-based encapsulation is limited by key challenges. Loading efficiency varies significantly by cell type, and a persistent trade-off exists between maintaining cell viability and achieving sufficient drug payload. Additionally, large-scale, standardized production remains technically difficult, hampering reproducible manufacturing. While these systems excel in sustained drug release and compatibility with advanced therapies like CAR-T, issues such as variable loading, scalability, and the balance between cell health and cargo capacity continue to pose hurdles (Figure 2b).

Bacterial Encapsulation System

Bacteria are a fascinating field of study, and some pathogens have been linked to a variety of tumors. Conversely, certain probiotics have been shown to treat and prevent some of the most lethal tumors, suggesting that specific bacteria may represent a novel avenue for the development of encapsulation systems.

One of the most significant attributes of bacteria is their capacity for self-propulsion.[106] The ability of living bacteria to move is powered by their chemical energy and supported by their surface flagella and pili, enabling them to actively move forward in liquid/semi-solid environments through swimming or gliding.[107] Moreover, this type of exercise exhibits a number of well-documented tendencies, including chemotaxis, phototaxis, heat resistance, pH orientation, and oxygen demand.[108–110] The distinctive mobility of bacteria allows for their targeted delivery to specific regions of the body. For instance, certain obligate or facultative anaerobic bacteria have been shown to possess intrinsic tumor-targeting capabilities, enabling them to migrate from distant vascular systems, selectively colonize tumors and even penetrate inaccessible tumor areas along oxygen gradients.[111] In addition, bacteria are capable of perceiving and responding to external environmental cues, thereby enabling the precise control of their therapeutic effects. In summary, bacteria have the capacity to produce highly efficacious therapeutic effects in localized areas through their biological sensing and propulsive abilities.[112,113]

In contradistinction to passive and conventional active targeting strategies, live bacteria proffer a distinctive approach to lesion targeting in view of their intrinsic capabilities, including mobility, self-propulsion, biological drive, sensing, and the execution of predefined tasks.[114,115] In this regard, bacteria may be regarded as a biological agent, akin to a missile or engine, capable of delivering nano encapsulation systems to specific locations within a cell, thereby circumventing the constraints imposed by conventional targeted delivery methods. Furthermore, due to its low immunogenicity, high flexibility, controlled release kinetics, and capacity to encapsulate a range of hydrophilic and hydrophobic drugs, NP has been extensively investigated as a synthetic drug encapsulation system. It can be deduced that the combination of drug-loaded synthetic encapsulation systems and bacteria will result in a delivery system that is more effective and controllable.[116] Significant progress has been made by researchers in the field of biological hybrid systems, with the employment of a range of nanomaterials and diverse binding techniques, including hydrophobic, electrostatic, and antigen-antibody interactions.

In a study combining clever methodology, the Magneto coccus marinus strain MC-1 was used as a self-propelling agent to transport drug-loaded nanoliposomes to hypoxic tumor regions.[117,118] The selection of MC-1 magneto tactic

bacteria is based on their magneto aerodynamic migration behavior, which enables the guidance of bacterial movement along external magnetic lines to hypoxic regions.[119] In their study, the drug-containing nanoliposomes were chemically linked to the surface of MC-1 bacteria via carbodiimide. This process entailed the crosslinking of the terminal amine groups present on the bacterial outer surface with carboxyl groups on the nanoliposomes, utilizing carbodiimide dehydrating agents. It is hypothesized that the resulting biological conjugate will actively migrate and penetrate deeply into the tumor area, which is depleted by external magnetic sources and oxygen gradients. The use of tumor xenograft mouse models for systematic evaluation has demonstrated that a number of therapeutic agents accumulate in difficult-to-treat solid tumors, including those with a high level of hypoxia and necrotic areas. The results also indicate that this strategy has significant advantages in overcoming the difficulties associated with tumor targeting and drug diffusion, which cannot be achieved for independent NP encapsulation systems and conventional drug molecules.

Bacteria possess the capacity for autonomous movement, relying on flagella/pili for propulsion. In addition, bacteria have the capacity to respond to environmental signals such as light, heat, and magnetic fields, exhibiting good targeting properties. However, it is important to note that bacteria also possess potential pathogenic risks, as internal reproduction may be uncontrolled, necessitating the incorporation of safety switch design. The dynamic targeting ability of bacteria far exceeds that of passively diffused NPs, however, a balance must be struck between biosafety and efficacy. For instance, temperature-sensitive plasmids of engineered bacteria can limit their overgrowth. The technology is considered to be suitable for high-precision targeted drug delivery and local treatment of the intestine. Although genetic engineering approaches, such as the incorporation of temperature-sensitive plasmids, can mitigate the risk of bacterial overgrowth, these modifications often come at the expense of treatment persistence. Additional challenges include the potential pathogenicity of live bacteria, unpredictable in vivo behavior, and the complexity of scalable manufacturing. Therefore, while bacterial delivery systems represent a paradigm shift in dynamic targeting, their clinical translation hinges on our ability to ensure their precise control and safety (Figure 2c).

Genetic Engineering Encapsulation System

Genetic engineering is a technology that has the capacity to alter cell phenotypes through the implementation of precise gene editing. The transfer of exogenous genes to target cells can be achieved through the use of viral vectors such as adenovirus, synthetic materials such as cationic polymers or lipids, or physical treatment such as microinjection, electroporation, gene gun, and laser irradiation.[120,121] This enables the alteration of almost all genetic information of living cells, resulting in significant changes in cellular biosynthetic characteristics. Consequently, this technology facilitates the production of a variety of essential proteins, antibiotics, enzymes, and peptides, thereby enabling the development of sophisticated materials with advantageous novel properties. The integration of gene modification methodologies with CRISPR/Cas9 technology has recently led to the emergence of more cost-effective and rapid gene editing capabilities.[122] A proposal is currently under consideration that involves the introduction of the complete chloroplast genome into human cells through genetic engineering, with the objective of achieving the expression of chloroplasts in human cells. It is anticipated that this will prove an efficacious method for introducing the substantial exogenous cell structure of thylakoids into human cells. However, translating plant genes into animal cells is a complex process that involves several challenges. One such challenge is the process of mRNA expression, which involves the transcription of hnRNA followed by intron splicing. However, it should be noted that the process of intron splicing varies between different species.[123,124] Consequently, issues with intron splicing can result in the target gene not being correctly spliced in the receptor. It should be noted that the absence of pertinent experiments has thus far hindered the advancement of this concept.

Gene engineering vectors utilize CRISPR/Cas9 technology to achieve efficient and cost-effective gene modification, utilizing various delivery methods, including viral vectors, synthetic materials, and physical methods. However, obstacles remain in the way of cross-species gene expression. It is imperative for genetic encapsulation systems to deliberate on species barriers and ethical boundaries. The exploration of genetic engineering for cross-species drug delivery is an area of ongoing research (Figure 2d).

Calculation of Load Capacity for Different Encapsulation Systems

Currently, experimentally confirmed encapsulation system capable of transporting ATP batteries include NPs, cell-based carriers, and bacterial carriers. The objective of this study is to calculate and compare the loading capacity and loading efficiency of these three types of encapsulation systems, and to analyze them in the context of DNA repair.

First, an approximate estimate of the quantity of ATP batteries that can be accommodated within different encapsulation systems will be made. As mentioned earlier, a typical ATP battery has a diameter of 100–200 nm, and our calculations will be based on this. 1) NPs encompass a wide variety of types. For simplicity, the present study will make direct use of experimental data from previous studies. It has been reported that researchers encapsulated ATP batteries into giant unilamellar vesicles (GUVs) with a volume of 1000 μm^3, each containing approximately 11,000 ATP batteries.[23] 2) Cell-based carriers, using RBCs as an example. RBCs have a volume of about 90 μm^3, with a maximum drug-loading capacity of 4.5 mg/mL. Calculations show that the drug-loading volume per RBC is approximately 0.41 μm^3, which can accommodate about 230 ATP batteries.[125–127] 3) Bacterial carriers, using E. coli as an example: A typical E. coli cell has a volume of about 0.5–1 μm^3, with a loading efficiency of approximately 37%. Thus, a single E. coli cell can carry 105–209 ATP batteries.[128,129] In terms of loading efficiency (spatial utilization), the values are as follows: GUVs: 11 ATP batteries/μm^3, RBCs: 2.6 ATP batteries/μm^3, E. coli: 210 ATP batteries/μm^3. It is evident that E. coli exhibits significantly higher loading efficiency compared to GUVs or RBCs.

As previously mentioned, a relatively well-established ATP battery has a production rate of approximately 20,000 ATP molecules per minute, and the calculations will be based on this. A mammalian cell requires the repair of about 20,000 DNA lesions per day, averaging 14 lesions per minute. Conservatively, the energy required to repair a single double-strand break is estimated to be at most 5000 ATP molecules.[130–132] To address 14 lesions simultaneously, the total ATP requirement would be 140,000 molecules. The time required for DNA repair ranges from several minutes to several tens of minutes.[133–135] Assuming a conservative repair time window of 1 minute, the ATP production rate needed to repair 14 DNA lesions simultaneously would be 140,000 ATP molecules per minute. This means that, even under the most conservative estimates, introducing just 7 ATP batteries into a cell would be sufficient to meet its DNA repair needs. Based on the earlier calculations, one GUV loaded with ATP batteries can meet the DNA repair demands of 1500 cells, one RBC can support 33 cells, and one E. coli cell can support 12–23 cells.

The above calculations indicate that, in terms of loading capacity, GUVs outperform RBCs, which in turn outperform E. coli. However, in terms of loading efficiency, the order is reversed. Moreover, even under the most conservative estimates, only a minimal number of ATP batteries and carriers are required to meet a cell's daily DNA repair demands. This indirectly demonstrates the powerful functionality and promising potential of artificial photosynthesis systems.

Comparison of Different Encapsulation Systems in Artificial Photosynthesis System

In the context of artificial photosynthesis systems, the selection of encapsulation system is of paramount importance in determining the success or failure of biomedical applications. This selection directly impacts the delivery efficiency, duration of action, and ultimate therapeutic safety of ATP batteries. In order to make reasonable choices in practice, it is necessary to compare the main strategies of NPs, cell encapsulation system, bacterial encapsulation system, and genetic engineering encapsulation system horizontally.

In terms of loading capacity and loading efficiency, significant differences exist among different encapsulation systems. Multifunctional NPs exhibit exceptional chemical programmability and high loading capacity. Furthermore, their drug loading can be precisely modulated by adjusting their size and structure. Cell encapsulation systems, including engineered red blood cells and macrophages, demonstrate moderate loading capacity and efficiency, which can be attributed to their inherent biological characteristics. In contrast, while bacterial encapsulation systems possess a relatively weak loading capacity, they show the highest loading efficiency. This is likely associated with the "bacterial ghost" strategy, which involves the complete removal of internal nucleic acids and protoplasm from the bacteria.

Regarding safety, cell encapsulation systems hold distinct advantages due to their natural biocompatibility and low immunogenicity. NPs, however, carry inherent risks of biotoxicity, and the use of poorly metabolizable organic/inorganic materials may lead to organ accumulation and chronic inflammatory responses. Bacterial systems pose the most

significant safety concerns. During their production, incomplete separation and purification may leave residual endotoxins, which can cause harm to the human body. Additionally, introduced bacteria still carry the potential risk of uncontrolled proliferation within the body, potentially leading to infections or more severe consequences.

And concerning stability, cell encapsulation systems benefit from the high stability of cell membranes and their immune evasion capabilities, making them the most stable option. Both NPs and bacterial systems face risks of being recognized and cleared by the human immune system. Moreover, NPs are prone to adsorbing proteins in complex physiological environments, which can lead to the loss of their intended biological functions. It is noteworthy that genetically engineered encapsulation systems theoretically possess extremely high stability, as once the target gene is successfully integrated into the genome, the effect can be sustained and stable.

Different encapsulation systems possess distinct advantages and disadvantages, which consequently determines their respective suitable application scopes. The size and material of NPs offer great flexibility for selection, and they can integrate both drug delivery and imaging functions. However, their instability in vivo and susceptibility to environmental interference can compromise their targeting ability. They are thus suitable for theranostic (integrated diagnosis and therapy) applications and treatments targeting relatively superficial sites. Bacterial systems exhibit autonomous motility and chemotaxis, enabling them to sense and respond to external signals such as temperature, pH, and magnetic fields. Nonetheless, their associated safety risks are higher. Therefore, they are applicable for drug delivery to deep-seated tumor regions that are difficult to reach with conventional drugs. Cell-based systems offer excellent biocompatibility and stability, presenting a relatively balanced profile across various aspects. Consequently, they have the broadest application range, particularly in the treatment of systemic chronic diseases.

In summary, the encapsulation system types constitute a complete technological spectrum, ranging from chemical design to biological utilisation. The field of drug delivery has seen significant advancements in recent years, it is inevitable that future development will move towards the intelligent integration of multiple strategies. One such strategy is the construction of a bacteria-nano hybrid system, which will simultaneously balance the advantages of active targeting and high load.[136,137] This will ultimately realize the enormous potential of artificial photosynthesis systems in precision medicine (Table 2).

Clinical Application of ATP Batteries in Human Diseases

Tumor

The efficacy of tumor drug delivery is fundamentally limited by complex physiological barriers and a dynamic tumor microenvironment (TME).[138] The efficacy of passive drug targeting via the enhanced permeability and retention effect is compromised not only by the dysfunctional and inefficient tumor vasculature but also by the dense extracellular matrix (ECM), which acts as a physical barrier to deep penetration.[139] The efficacy of anticancer therapies is severely hampered

Table 2 Comprehensive Comparison of Different Encapsulation Systems

	Multifunctional Nanoparticles	**Cell-based Encapsulation Systems**	**Bacterial Encapsulation Systems**	**Genetic Engineering Systems**
Precision	Low	Moderate	High	Very high
Safety	Medium	High	Low	Under investigation
Durability	Low	High	Moderate	Very high
Load capacity	Variable	Moderate	Low	-
Load efficiency	Moderate	Low	High	-
Advantages	Variable load capacity	Biocompatibility, sustained release	Self-propulsion, deep penetration	Precision, durability
Limitations	Low precision, low durability	Low efficiency	Low safety	Technical and ethical barriers
Applications	Treatment of superficial conditions	Drug sustained release, cell therapy	Targeted delivery, deep-tissue delivery	-
Maturity	Mature	Mature	Mature	Conceptual

by the TME. Key obstacles include elevated interstitial fluid pressure and a hypoxic, acidic milieu, which jointly hinder drug perfusion and efficacy, while immunosuppressive elements limit immunotherapy responses. Furthermore, pharmacological hurdles such as nonspecific biodistribution causing systemic toxicity, intrinsic tumor heterogeneity, and multidrug resistance mechanisms further undermine treatment success.[140]

Emerging ATP-driven therapeutic platforms represent a promising potential to overcome these challenges. These systems are designed to enhance anti-tumor responses through multiple mechanisms, including alleviating the immunosuppressive TME, potentiating immunotherapy via metabolic reprogramming, and synergistically augmenting PDT through ATP-mediated energy modulation (Figure 3a).

Microenvironment-Modifying Capability

Tumor cells consume oxygen through a variety of mechanisms, including a high metabolic rate and the disruption of oxygen delivery by affecting blood vessels, which results in limited oxygen diffusion.[141,142] The elevation in H2O2 levels resulting from tumor hypoxia can function as a secondary messenger in cellular signaling, thereby facilitating malignant progression and drug resistance in tumors.[143,144] The 2019 Nobel Prize in Physiology or Medicine was awarded to three scientists who discovered hypoxia-inducible factor (HIF) and elucidated the mechanisms by which cells perceive and adapt to changes in oxygen supply.[145,146] Tumor cells induce hypoxia through various mechanisms, including the induction of endothelial dysfunction and disruption of oxygen delivery due to their effects on blood vessels. This results in the creation of a chronic hypoxic environment, which in turn activates the HIF signaling pathway,

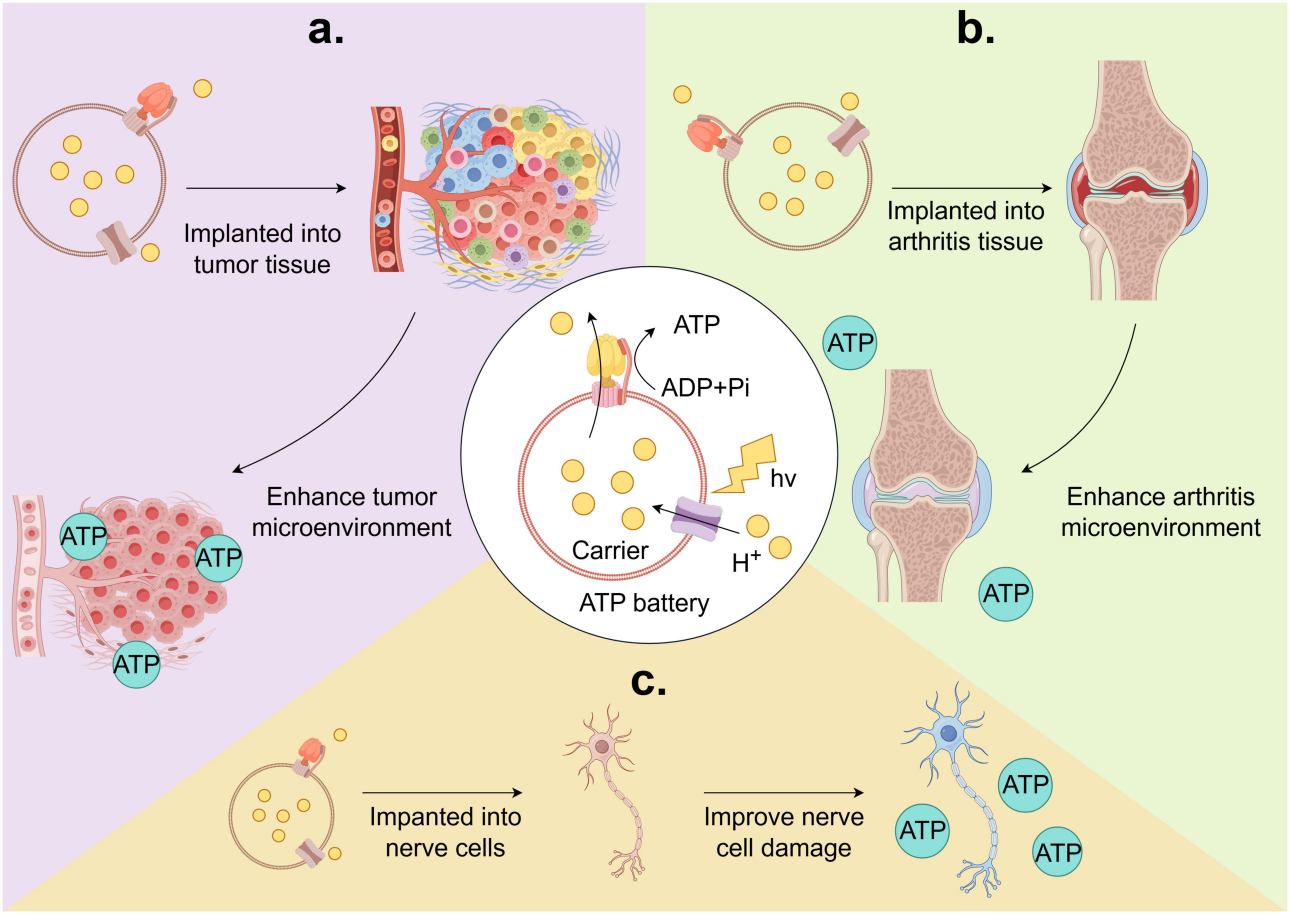

Figure 3 The clinical application in human diseases of the cross-species implantable ATP batteries. (**a**) Tumor: ATP batteries reverse hypoxia by producing oxygen through photosynthesis, reduce HIF/H2O2 levels, inhibit tumor invasion, and optimize TME; (**b**) Osteoarthritis: the restoration of ATP batteries through targeted delivery can restore ATP/NADPH levels under light, reduce ROS and synovial hyperplasia, promote collagen II/proteoglycan synthesis, and improve joint degeneration; (**c**) Neurodegenerative diseases: ATP cells can enhance ATP/NADPH in target cells after exposure to light, repair muscle satellite cells, neural progenitor cells, and endothelial cells, providing a new metabolic regulation strategy for Alzheimer's disease and other diseases.

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thereby accelerating tumor growth, increasing tumor invasiveness and promoting tumor metastasis. In an experimental setup, lung tumor cells were cultured in environments with normal oxygen content, low oxygen content, and hypoxia. The results demonstrated that the proliferation, invasion, and metastasis activity of lung tumor cells were significantly higher in low oxygen or hypoxic environments than in the normal oxygen content culture group.[147,148]

It is evident that the alleviation of tumor hypoxia is importance for the effective treatment of tumors. The introduction of ATP batteries into tumorous tissues has the potential to reverse the hypoxic state that characterizes such tissues (Figure 3a).

Immunotherapy-Enhancing Capability

The hypoxic conditions present within the TME have the capacity to induce the production of immune suppressive cells, including regulatory T cells and myeloid-derived suppressor cells.[149] Furthermore, they have the ability to inhibit the normal and activated immune cells, thereby regulating immune escape and tumor metastasis in the context of tumor immunotherapy.[150] The immunosuppressive M2 phenotype tumor-associated macrophages within the TME significantly impede the anti-tumor efficacy of tumor immunotherapy.[151] Moreover, the HIF previously discussed are also associated with tumor immune resistance. Immune checkpoints represent a key target for immunotherapy. Currently, a range of nanomaterials, including metal-based NPs, mesoporous silica NPs, polymer NPs, liposomes and hydrogels, have been employed to regulate TME hypoxia with the objective of enhancing immunotherapy.[101,152,153] Given the outstanding oxygen and energy production capacity of ATP batteries based on PSII system, it may provide a promising pathway for overcoming hypoxia related immune suppression.

Photodynamic Therapy-Enhancing Capability

PDT has emerged as a highly efficacious modality for tumor treatment, largely due to its non-invasive nature, minimal incidence of adverse effects, negligible propensity for drug resistance, and low systemic toxicity.[154,155] PDT primarily results in the irreversible destruction of tumor cells due to the generation of toxic ROS under light irradiation. However, tumor hypoxia severely hinders the therapeutic effect of PDT, mainly because the production of toxic ROS in PDT heavily relies on oxygen.[156] Type I photosensitizers, also known as electron transfer sensitizers, represent a promising avenue for advancement in the field of PDT, as they facilitate relatively low oxygen concentration-dependent ROS production, even in hypoxic TME. Although the generation of ROS through energy transfer mechanisms remain the dominant process in most PDT procedures, the excitation energy required for the conversion of molecular oxygen to singlet oxygen is relatively low. Conventional nano systems have been devised to facilitate the delivery of oxygen generators or catalyze the decomposition of hydrogen peroxide into oxygen within tumors. Nevertheless, the efficacy of PDT remains constrained by the spatiotemporal discrepancies between the generation and distribution of oxygen and the formation of ROS.[157,158] Therefore, ATP batteries based on the PSII system have significant advantages in this regard. The PSII based ATP batteries not only produce ATP under light, but also produce oxygen, thus supplementing the rapidly consumed ROS in PDT.

Osteoarthritis

Osteoarthritis is a common degenerative disease characterized by the depletion of ATP and NADPH in pathological chondrocytes, along with an increased production of ROS and matrix metalloproteinases.[159] Chondrocytes with insufficient energy exhibit a reduction in the synthesis of extracellular ECM proteins, including collagenases and proteoglycans. The depletion of energy reserves in chondrocytes triggers a metabolic shift toward glycolysis, a change that ultimately impairs ECM synthesis and metabolism in pathological states.[160] The current treatment methods are unable to correct the metabolic imbalances occurring in degenerated chondrocytes in a systematic manner and are associated with adverse clinical outcomes.

There have been some successful cases of ATP batteries being used to improve chondrocyte metabolism. For instance, researchers have developed a device based on nanocapsules named NTU and kondrocyte cell membrane (CM) for the treatment of osteoarthritis.[161] The NTU particle size is approximately 130 nm, and the surface retains intact thylakoid membrane photosynthesis-related proteins. The composition of CM protein is related to the structure of

cell membrane. The combination of NTU and CM has been shown to yield a stable particle size and to be non-toxic tochondrocytes. Experimental evidence has demonstrated that CM-NTU significantly enhances selective uptake bychondrocytes through membrane-specific targeting compared to reduced fluorescence intensity in other cells, such as macrophages. In the IL-1β-induced chondrocyte metabolic injury model, CM-NTU has been shown to restore ATP and NADPH levels to normal in damaged cells and enhance energy metabolism in undamaged cells under red light (80 μmol photon /m^2s^1) irradiation. In vitro experiments have confirmed that CM-NTU combined with light therapy significantly reduces the incidence and severity of knee osteoarthritis. Histological analysis of joint sections reveals an augmentation in type II collagen and aggrecan content, a diminution in ROS generation, and a reduction in synovial hyperplasia. This device combines stability, targeting, and metabolic regulation functions, providing a new strategy for the treatment of osteoarthritis (Figure 3b).

Neurodegenerative Diseases

Neurodegenerative diseases involve the progressive loss of neurons and myelin sheaths, a process often linked to insufficient energy supply in the nervous system. This energy deficit contributes to mitochondrial dysfunction, oxidative stress, and accumulation of metabolic waste, ultimately disrupting cellular integrity.[162–165] The prevalence of neurodegenerative diseases is significant, and currently, there is no effective treatment option available.

Implantable ATP batteries are a promising approach. In the previous research on CM-NTU, researchers successfully applied this battery technology to a series of damaged cell models. When exposed to light, the system increased intracellular ATP and NADPH levels. 1) In stressed muscle satellite cells (SCs), the ATP batteries enhanced protein levels of myogenic markers (MyoD, MyoG). 2) In stressed neural progenitor cells (NPCs), it increased collagen II and decreased matrix metalloproteinase MMP-13. 3) In oxidatively damaged human umbilical vein endothelial cells (HUVECs), it elevated the antioxidant marker NRF2.[64] These findings indicate that the implantable ATP batteries can enhance cellular synthesis and metabolism, including in nerve cells. These findings indicate that the light-activated system can enhance cellular synthesis and metabolism. Furthermore, evidence suggests that such ATP platforms can regulate the ATP-dependent cytoskeleton, influencing cell morphology. This not only offers a potential treatment strategy for cytoskeleton-related neurodegenerative diseases but also opens avenues for creating artificial cell-like systems to replicate complex cellular behaviors in vitro. Furthermore, Lee et al conducted a cytoskeleton synthesis experiment in their study on constructing photosynthetic artificial organelles using thylakoids. The results demonstrated that optical stimulation triggered ATP synthesis, which subsequently induced ATP-dependent actin polymerization, thereby promoting cytoskeletal assembly.[40] Given that cytoskeleton formation is a critical component of neuronal axon regeneration, this experiment indirectly suggests the potential of such an ATP-generating system in facilitating neuronal repair (Figure 3c).

The Therapeutic Potential in Different Diseases

As evidenced by prior research, the application of ATP batteries in oncology, osteoarthritis, and neurodegenerative diseases reveals distinct clinical application potential. By evaluating technical feasibility, biological barriers, and preclinical evidence, the sequence and trajectory of clinical deployment can be projected.

In the realm of contemporary medical research, osteoarthritis stands as a particularly promising candidate for clinical breakthroughs, owing to its distinct anatomical and physiological characteristics. The basis of this judgment is primarily the convenience of local administration, the controllability of external light activation, and the relatively simple joint microenvironment. The nano thylakoids coated with chondrocyte membrane have demonstrated clear targeting and therapeutic effects in experimental models, which can restore the energy level of damaged chondrocytes and promote ECM synthesis. These solid preclinical data provide a robust foundation for their subsequent transformation. Nevertheless, further clinical translation is required to address significant challenges, including long-term safety concerns, the optimization of lighting schemes, and the scale-up of production.

Conversely, the application prospects of ATP batteries in tumor therapy are more intricate and challenging. The heterogeneity, multiple physiological barriers, and dynamic evolution characteristics of TME determine that ATP batteries are unlikely to be used as independent treatment methods in this field, but rather as synergistic modules with existing therapies. Specifically, it has been demonstrated that ATP batteries have the capacity to enhance the response

efficiency of immunotherapy and improve the efficacy of PDT by addressing the fundamental limitation of tumor hypoxia. This assertion has been substantiated through various nano encapsulation system combination therapy strategies. However, the limitations of system delivery efficiency, the challenge of spatiotemporal matching between oxygen production and reactive oxygen species generation, as well as the heterogeneity and adaptive resistance of tumor cells, constitute the main obstacles to its clinical translation. The solution to these challenges necessitates interdisciplinary innovation, particularly in the domain of intelligent encapsulation systems and controllable release technologies.

The application of ATP batteries in the treatment of neurodegenerative diseases represents the most audacious and transformative concept; however, its clinical implementation pathway is also the most protracted. The fundamental challenges in this direction stem from the strict barrier of the blood-brain barrier, the enormous energy required for neuronal cell repair, and the chronic progression characteristics of the disease. In the foreseeable future, the primary focus of relevant research will be on the validation of in vitro models and the in-depth exploration of mechanisms of action, rather than direct clinical interventions. The development of intelligent encapsulation systems capable of crossing the blood-brain barrier, ensuring precise delivery of ATP batteries in large quantities, and evaluating the long-term safety of exogenous plant organelles in the central nervous system are all major scientific issues that must be addressed.

Discussion

This article elaborates on the process of utilizing light energy to synthesize ATP, beginning with its most fundamental components: the photooxidation module, the photophosphorylation module, and the encapsulation system. 1) The construction of the photooxidation module is the core and most challenging aspect of the entire artificial photosynthesis system. A common mechanistic principle unites these diverse modules, from simple proton pumps and membrane structures to complex assemblies: light-induced conformational changes propel protons to generate an electrochemical gradient. For instance, in MR, the core retinal chromophore isomerizes from all-trans to 13-cis; in PSII, the excited chlorophyll P680 in the reaction center releases a high-energy electron to its primary acceptor and subsequently extracts electrons from water; and in the Janus MOLs membrane, light energy absorbed on the outer surface generates excited-state electrons that rapidly transfer to the inner surface. These photochemical events initiate the entire process of proton gradient formation. Following these changes, protons are either actively transported across the membrane or are directionally generated/consumed on opposite sides of the membrane (Janus MOLs), thereby establishing the proton gradient. 2) The photophosphorylation module utilizes this proton gradient to synthesize ATP. To the best of our current knowledge, ATPase is the only entity in nature confirmed to harness an electrochemical gradient for ATP synthesis. 3) Finally, the encapsulation system co-localizes these two modules, ensuring their orderly operation and precise delivery. We discussed four types of encapsulation systems: NP systems, cell-based systems, bacterial systems, and the still-theoretical genetic engineering approach. Each system presents distinct advantages and disadvantages. For example, NP systems exhibit exceptionally high loading capacity but suffer from lower stability; bacterial systems possess autonomous chemotaxis and motility but carry higher safety risks. Consequently, we have proposed suitable application scenarios for these different encapsulation systems.

We have detailed four types of photooxidation modules. Among them, the MR and PSII systems are relatively mature, boasting a solid foundation of in vitro experimental validation and high energy production efficiency.[23,32,35,40,41] In contrast, the PAGs system remains largely theoretical, limited by its inability to generate a stable proton gradient (only a pulsed gradient).[45,52] The maturity of various artificial photooxidation modules varies significantly. The most advanced is the Janus MOLs system, which can establish a proton gradient and facilitate ATP synthesis.[54] Next are other systems capable of generating proton gradients, though their role in promoting ATP synthesis has not yet been demonstrated.[55–60] The least mature are photo-enzyme catalytic systems, which perform redox reactions under light but cannot generate a proton gradient to power ATP synthesis.[41,61] Notably, our calculations indicate that the efficiency of different photooxidation systems aligns remarkably well with their biological evolutionary maturity: thylakoids, as highly evolved photooxidation apparatuses, exhibit higher efficiency than the relatively primitive MR systems, while artificial photooxidation systems are the least efficient.

The primary unresolved challenges primarily involve biocompatibility, immune response, light penetration, stability and efficiency. 1) Components of non-human origin may possess inherent toxicity. For natural materials, such as MR and

bacterial carriers, risks of endotoxin contamination during extraction and purification processes exist. For synthetic materials used in constructing artificial photooxidation systems, the constituents are often non-biodegradable, raising concerns about organ accumulation and the potential to trigger chronic inflammation. Despite the encouraging results of studies conducted in zebrafish and mice shows great biocompatibility of injected thylakoid-based photosynthetic nanostructures,[166,167] these experiments did not involve research on biocompatibility in the human body. 2) Whether they are bacterial-derived proteins, plant-derived protein complexes, or artificial nanomaterials, these components can be recognized as foreign and rapidly cleared by the immune system, preventing them from reaching their target sites or persisting long-term. Current research focuses on employing encapsulation systems to evade this immune recognition. Strategies such as coating with human cell membranes can effectively confer self-camouflage, enabling the systems to evade immune surveillance. 3) Skin and tissues absorb and scatter light, severely limiting the intensity and effective wavelength of light that can reach deeper tissues. This constraint currently directs applications toward superficial or accessible diseases. However, some systems (like PSII and certain artificial systems) can utilize red or even near-infrared light, which has slightly better tissue penetration, though efficiency issues still require optimization. 4) Natural components, particularly PSII, are susceptible to photoinhibition under strong light, where their core proteins denature, leading to rapid functional decline. Furthermore, encapsulation systems themselves can be deactivated in vivo or metabolically degraded. Currently, this issue can only be partially mitigated by employing more stable cell-based encapsulation systems. A true breakthrough hinges on the development of more stable and efficient photooxidation systems alongside more robust encapsulation technologies. 5) The low energy conversion efficiency of the photooxidation module itself is the fundamental efficiency bottleneck. Whether it is the PSII system, MR system, or artificial photosynthesis system, their efficiency is lower than that of natural photosynthesis systems. Especially for artificial photooxidation systems, their efficiency is much lower than other systems.

Currently, emerging research offers promising avenues to address these challenges. A representative example is the development of protein orientation-controlled reconstitution techniques. In the construction of artificial cell-like systems, a long-standing obstacle has been the random incorporation of light-driven proton pumps, such as MR into liposomal membranes. Statistically, approximately half of these proteins orient themselves to pump protons inward, while the other half pump outward, resulting in the mutual cancellation of the generated proton gradients and consequently very low net efficiency. To overcome this limitation, Andrea et al developed a novel strategy that enables the unidirectional incorporation of light-driven proton pumps into liposomes. This is achieved through post-translational conjugation of the proton pump to a membrane-impermeable protein domain. By integrating these unidirectionally oriented proteorhodopsin-liposomes with ATPase, highly efficient ATP production was achieved. The system reached its maximum ATP synthesis rate at economically feasible protein concentrations, demonstrating performance that significantly outperforms conventional systems with random protein orientation.[81] Furthermore, the research by Jiang et al offers novel perspectives for precisely analyzing the cell-type-specific effects of ATP batteries and guiding the intelligent design of encapsulation systems. Its core contribution lies in leveraging single-cell technologies to uncover, with unprecedented resolution, the cellular heterogeneity underlying the multi-component, multi-target, and systemic regulatory mechanisms of traditional Chinese medicines, thereby providing new pathways for related research.[168] Similarly, after applying ATP batteries to complex tissue samples, single-cell RNA sequencing (scRNA-seq) can simultaneously identify which cells have successfully internalized the ATP batteries and elucidate the subsequent effects on the metabolic pathways of these cells. Moving a step further, scRNA-seq can be employed in post-treatment tissues to evaluate the impact of ATP batteries on the entire cellular community. By integrating multi-omics approaches with synthetic biology, this strategy collectively advances the development of bioinspired therapeutic strategies.

The prospective avenues of inquiry for ATP batteries based on photosynthetic systems can be delineated as follows: 1) The utilisation of rapidly developing chemical synthesis technologies to synthesize photooxidants with higher energy conversion efficiency and stronger operability. 2) The development of new integration strategies to facilitate the more accurate transfer of ATP batteries into specific organelles. For instance, the functional co-assembly of the entire mitochondria could be employed to enhance cellular metabolism from a more detailed organelle structure, thereby facilitating precise disease treatment. 3) The development of more targeted encapsulation systems, such as ones that specifically target tumor tissue or neural tissue, while enhancing the observability, is a promising avenue of research. This

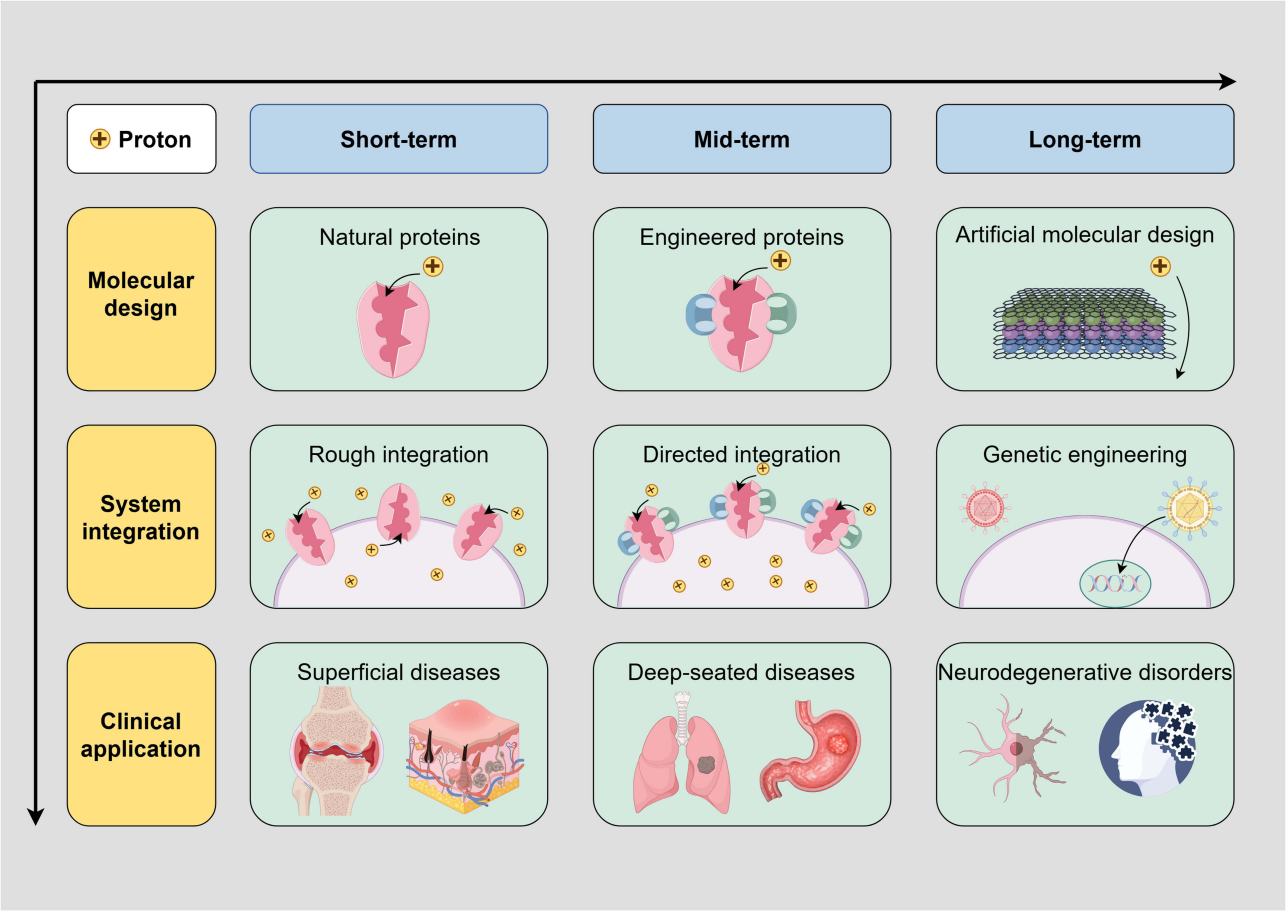

Figure 4 Roadmap for the development of implantable cross-species ATP batteries. This schematic outlines the projected evolution from foundational research to clinical translation across three progressive tracks: Molecular Design, System Integration, and Clinical Application. Near-Term focuses on natural biological components (eg, MR, PSII proteins) with crude integration for treating superficial diseases. Mid-Term advances to engineered proteins and efficient, directed assembly for application in deep-tissue conditions. Long-Term envisions fully synthetic systems and artificial synthesis pathways, and address complex systemic and neurodegenerative diseases.

could be achieved by making the encapsulation systems detectable by photothermal imaging and magnetic resonance imaging. This will facilitate the precise delivery of ATP batteries in vivo. 4) There is scope to extend the function of ATP batteries in the photosynthetic system. Currently, ATP batteries are primarily concerned with ATP synthesis. The incorporation of a specific protein synthesis system, in addition to the electrochemical gradient generator and ATP synthesis system, has the potential to specifically supplement specific proteins in certain cells, thereby improving diseases caused by protein errors, such as neurodegenerative diseases and Huntington's disease (Figure 4).

Conclusion

Artificial photosynthetic systems for intracellular ATP synthesis represent an emerging frontier in synthetic biology, designed to overcome inherent metabolic constraints in human cells. These systems integrate three core components: a photooxidation module that converts light into an electrochemical gradient, a photophosphorylation module that harnesses this proton-motive force for ATP synthesis, and an encapsulation system matrix enabling spatial organization, functional maintenance, and targeted delivery. Clinically, they have shown promise in multiple domains: rescuing metabolic function in osteoarthritic chondrocytes and promoting ECM synthesis; remodeling TME by alleviating hypoxia to augment immunotherapy and PDT; and providing sustained energy support to compromised neurons in neurodegenerative diseases. By introducing an exogenous light-driven energy mechanism, this technology challenges conventional paradigms of cellular metabolism and expands the functional possibilities of human cells, opening new avenues for therapeutic intervention.

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Authors declare that they do not use any Artificial Intelligence Generated Content (AIGC) tools such as ChatGPT and others based on large language models (LLMs) in developing any portion of their manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Authors declare that they have no competing interests.

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