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Bioinspired and Biomimetic Nanomedicines

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CONSPECTUS:

Nanomedicine development aims to enhance the efficacy, accuracy, safety, and/or compliance of diagnosis and treatment of diseases by leveraging the unique properties of engineered nanomaterials. To this end, a multitude of organic and inorganic nanoparticles have been designed to facilitate drug delivery, sensing, and imaging, some of which are currently in clinical trials or have been approved by the Food and Drug Administration (FDA). In the process, the increasing knowledge in understanding how natural particulates, including cells, pathogens, and organelles, interact with body and cellular systems has spurred efforts to mimic their morphology and functions for developing new generations of nanomedicine formulations. In addition, the advances in bioengineering tools, bioconjugation chemistries, and bio-nanotechnologies have further enabled researchers to exploit these natural particulates for theranostic purposes.

In this Account, we will discuss the recent progress in our lab on engineering bioinspired and biomimetic synthetic and cellular systems toward rational design of nanomedicine platforms for treating diabetes and cancer. Inspired by the structure and response mechanism of pancreatic β-cells, we synthesized a series of insulin granule-like vesicles that can respond to high blood or intestinal glucose levels for aiding in transdermal or oral insulin delivery, respectively. Then, to more closely mimic the multicompartmental architecture of β-cells, we further developed synthetic artificial cells with vesicle-in-vesicle superstructures which can sense blood glucose levels and dynamically release insulin via a membrane fusion process. Meanwhile, clues drawn from the traits of anaerobic bacteria that selectively invade and proliferate in solid tumors inspired the synthesis of a light-tuned hypoxia-responsive nanovesicle for implementing synergistic cancer therapy. In parallel, we also studied how autologous particulates could be recruited for developing advanced drug delivery systems. Through combination of genetic engineering and top-down cell engineering technologies, biomimetic nanomedicines derived from cytoplasmic membrane with programmed death 1 (PD1) receptors expressed on surfaces were generated and employed for

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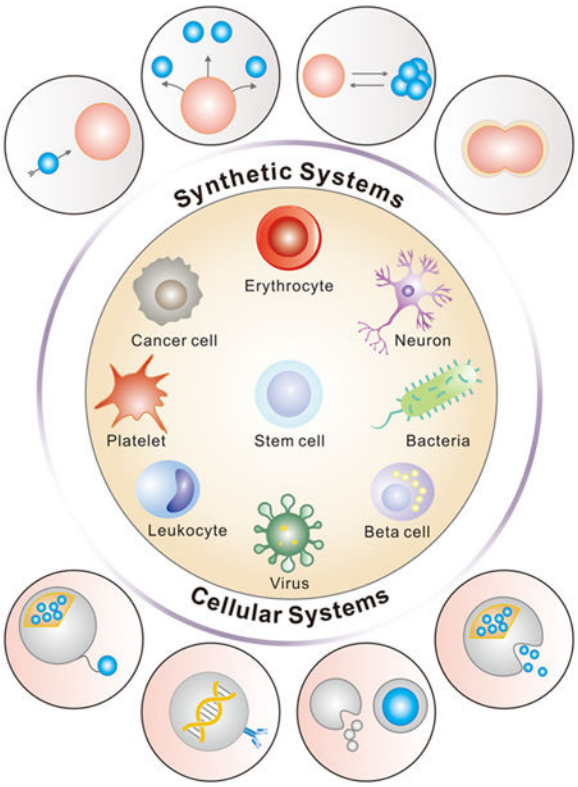
cancer immunotherapy. Based on our earlier study where aPD-L1 (antibodies against PD ligand 1)-conjugated platelets could release aPD-L1-bearing particles *in situ* and inhibit postsurgical tumor recurrence, we further genetically engineered megakaryocytes, the precursor cells of platelets, to express PD1 receptors. In this way, platelets born with checkpoint blocking activity could be produced directly *in vitro*, avoiding post chemical modification processes while exerting similar therapeutic impact. As a further extension, by virtue of the bone marrow-homing ability of hematopoietic stem cells (HSCs), we recently conceived a cell-combination strategy by conjugating HSCs with platelets decorated with antibodies against PD1 (aPD-1) to suppress the growth and recurrence of leukemia. While we are still on the way of digging deep to understand and optimize bioinspired and biomimetic drug carriers, we expect that the strategies summarized in this Account would contribute to the development of advanced nanomedicines.

Graphical Abstract



1. INTRODUCTION

Many diseases arise from abnormalities in biological processes at molecular and nanoscale levels, such as gene mutations, protein misfolding, and infections induced by pathogens.[1] In addition, nanometer-scale topologies exist at the sites of diseased lesions as well.[2] In light of these facts, nanomaterials are considered to be able to gain more access to cellular and tissue compartments since they possess similar size scale as the biological molecules or structures.[3] Along this line, nano-medicine is proposed as a field leveraging sub-micrometer sized materials (1−1000 nm) for treating and diagnosing diseases.[2] Importantly, the properties of

nanomaterials can be readily programmed by tuning their physiochemical parameters, including size, shape, and surface chemistry, which could contribute to maximization of the potency of nanomedicines.[1] To date, a range of nanoparticles including liposomes, polymers, antibodies, metals, metal oxides, and hybrids have been developed and proposed for the management of disorders such as cancer, diabetes, infections, and cardiovascular diseases.[4–7] However, only a small number of the proposed nanomedicines are currently in clinical use for patients or under clinical trials. Most nanomedicines are typical “foreign objects” and are subject to biological barriers such as opsonization, immune clearance, and negotiation with vascular systems.[9]

To tackle these hurdles, different approaches are being adopted via manipulating the physicochemical properties of nanomaterial themselves or functionalizing the surface with stealth or targeting ligands.[8] Particularly, the growing insights into how natural cellular particles interact with the body, such as pathogen invasion, platelet functions in hemostasis, and β-cells for maintaining glycemic homeostasis, to name a few, provide researchers clues to find alternative solutions by learning and mimicking the tricks that biology has evolved.[9,10] In these biological processes, an important basis is intercellular information exchange through secreting soluble factors or presenting surface ligands, and also, the size, structure, and mechanical properties of natural particulates play essential roles in orchestrating cell-to-cell communications.[10,11] As a first step toward recreating such scenarios in the context of nanomedicines, bioinspired synthetic nanocarriers built from bottom-up have been designed to resemble the structure and recapitulate one or more functional modules of their native counterparts, intending to deliver cargoes in a manner that mimics how the signals are transduced in natural systems.[9,10] Given that synthetic systems are still inadequate in completely reproducing the complexity of cellular systems, biomimetic nanomedicines have recently been developed via top-down engineering of biological membranes into delivery systems, which maintain some of the key membrane protein functionalities of the origin cells.[12–14] Moreover, encouraged by the remarkable mechanisms by which natural particulates communicate with biological entities, various cells have been utilized as carriers (called “chaperones”) for nanoparticles and drug cargos, which facilitates evading host immune response, prolonging circulation time, and allowing for actively delivering theranostic agents to specific sites.[14–17] This Account will introduce our recent efforts on rational design of bioinspired and biomimetic nanomedicines, focusing on synthetic and cellular engineering strategies (Figure 1).

2. SYNTHETIC SYSTEMS

Vesicles built from scratch with lipids or synthetic polymers have been widely employed to recreate the compartmentalized scenario of cellular or subcellular structures. Therein, the three topological regions of vesicles, namely, the inner space, the membrane barrier, and the exterior surface, all provide niches for loading, embedding, and conjugating functional handles, including theranostic agents and targeting ligands. Specially, the versatility of chemical engineering enables further incorporation of responsive units into the material matrices that are used to construct synthetic vesicles. These characteristics support the manufacture of smart delivery systems that can release cargoes “on demand” upon

responding to pathological or external stimulus, in a way that mimics natural particulates interacting with body systems.[18]

2.1. Diabetes Treatment

Diabetes mellitus refers to a group of chronic diseases that are associated with elevated blood glucose levels (BGLs). To overcome the key shortcomings in the two currently common treatment methods, hard to control of doses in periodic injection as well as inconvenience and biofouling risk in electronic insulin pump, glucose responsive synthetic systems including nanomedicines have been widely developed to mimic the function of pancreatic β-cells for tuning insulin release under hyperglycemic conditions.[19–21] In this context, by drawing inspiration from how natural β-cells regulate BGLs, we have engineered several insulin delivery vesicles whose conformation and morphology could be changed in response to chemical gradients provoked by glucose oxidase (GOx)-catalyzed reaction (eq 1), with the goal of achieving (1) fast responsiveness, (2) good biocompatibility, and (3) easy administration.

$$\text{glucose} + O_2 + H_2O \xrightarrow{\text{GOx}} \text{gluconic acid} + H_2O_2 \quad (1)$$

2.1.1. Single-Compartmental Vesicles.—In mature β-cells, insulin is stored in dense core granules, which will fuse with the plasma membrane to trigger secretion in response to increases in extracellular glucose levels.[22] To mimic such biological processes, our early work involved the synthesis of a pH responsive nanovesicle loaded with insulin, GOx, and catalase (CAT) as an insulin granule mimic while enabling glucose-regulated insulin delivery (Figure 2A).[23] CAT was coloaded because it could decompose the byproduct H_2O_2 (see eq 1) into O_2 which further promoted GOx-catalyzed oxidation.[24] The nanovesicles were self-assembled from diblock copolymer poly(ethylene glycol)-*b*-poly(*O*-acetyl-L-serine) (designated PEG-Poly(Ser-Ketal), Figure 2B), which consists of a hydrophilic segment and a mildly acid-sensitive tail. The polymeric bilayer in the membrane conferred the nanovesicles with enough mechanical stability to prevent the premature loss of the encapsulated insulin, whereas the allowance of passive diffusion of glucose into the inner cavity[25] enabled the catalytic conversion of glucose into gluconic acid, leading to a decrease of local pH. The inner pool of protons would trigger the acidic hydrolysis of the ketals on the hydrophobic segment and generate a water-soluble diblock polymer, PEG-polyserine. As such, the nanovesicles disassembled and released the loaded insulin. However, in biological buffering environment, the internal pH change strongly depends on the external glucose concentrations since substrate passive diffusion kinetics is defined by concentration gradient.[26] This study showed that the pH change in the solution of the nanovesicles was much faster and more remarkable under hyperglycemic (400 mg/dL) conditions than that at normal glucose (100 mg/dL) levels. As the hydrolysis rate of acetals was determined by the local proton concentration, rapid insulin release was observed at high glucose levels while flat release was detected for groups at normal glucose concentration. Moreover, the nanovesicles displayed pulsatile insulin release patterns when alternatively exposed to hyperglycemic solutions and normoglycemic conditions. By subcutaneously injecting the nanovesicles,

which were predispersed in a thermoresponsive hydrogel (30% Pluronic-127, PF127), into the dorsum of mice, tight BGL control was observed over 5 days.

To overcome the relatively slow responsiveness of pH decrease-dependent systems,[19] we shifted our focus on developing a new type of insulin delivery nanovesicles made of hypoxia-sensitive components, since the consumption of oxygen by GOx also produces a local hypoxic microenvironment (Figure 3A).[27] To accomplish this, we first synthesized an amphiphilic polymer by conjugating hyaluronic acid with 2-nitroimidazole (HA-NI). Then, HA-NI self-assembled into nanovesicles, in which insulin and GOx were encapsulated. NI itself is hydrophobic but can be reduced into hydrophilic 2-aminoimidazole under hypoxic conditions by nitroreductases and NADPH, both of which are common in tissues.[28] As a result, the amphiphilic HA derivative returned to its original hydrophilic state and thus the nanovesicles dissociated. An in vitro insulin release study demonstrated that much faster oxygen consumption was observed at 400 mg/dL glucose level than that at 100 mg/dL. Correspondingly, the reduction of NI, the disassembly of the nanovesicles, and the kinetics of insulin release were faster under hyperglycemic conditions. Notably, about 6.6-fold difference in insulin release rate was detected when the glucose concentration was altered from 100 to 400 mg/dL at an interval of 20 min, which was much faster than our first work relying on the pH-responsive process.[23] The introduction of hypoxia responsive elements into nanovesicles provided a new approach for tuning BGLs in a biomimetic way.

Although GOx-based reaction is the most prevalent mechanism for various glucose-sensing and insulin delivery systems, the undesired H_2O_2 raises issues of inactivating GOx, as well as long-term biosafety concerns.[24] Further incorporation of CAT or enzyme-mimicking nanomaterials has been shown to mitigate these side effects, yet it increases the complexity of the system and requires additional labor to optimize the ratio of each component.[29,30] To this end, we engineered a nanovesicle that could directly respond to H_2O_2 (Figure 4A).[31] This nanovesicle was self-assembled from block copolymer consisting of PEG and phenylboronic ester-conjugated polyserine (designated mPEG-*b*-P(Ser-PBE), Figure 4B). Once the glucose level in external solution was elevated, the inwardly diffused glucose would increase as well, which led to the generation of H_2O_2. Since phenylboronic ester is known for its quick degradation by H_2O_2 under mild conditions,[32] the removal the hydrophobic phenylboronic ester turned the block polymer from amphiphilic to hydrophilic, and finally, the nanovesicles disassembled, thereby inducing fast insulin release under the physiological conditions.

To fully explore the products generated by glucose oxidation, we then synthesized a nanovesicle that could simultaneously respond to both hypoxia and H_2O_2. The nanovesicle was made from diblock copolymer composed of PEG and polyserine conjugated with 2-nitroimidazole via a thioether bond, designated PEG-poly(Ser-S-NI).[33] As discussed above, NI could be readily bioreduced into hydrophilic 2-aminoimidazole upon oxygen consumption; meanwhile, the thioether part could be oxidized by H_2O_2 into hydrophilic sulfone.[34] Through such a dual-responsive process, the hydrophobic segment could be turned to hydrophilic when both gradients were generated under hyperglycemic conditions, thus leading to quick nanovesicle structural change with concurrent insulin release.

Moreover, elimination of H_2O_2 by the nanovesicle matrix could help to ameliorate the correlated side effects even at high GOx dose.

To make them easy to administer, the glucose-responsive nanovesicles discussed in refs 25, 29, and 31 were further incorporated into the tips of HA-derived microneedle arrays to form "smart insulin patches", conferring a convenient and painless closed-loop transdermal delivery device (Figure 3B). All of such nanovesicle-integrated microneedle patches facilitated tight glycemic control while reducing the risk of hypoglycemia *in vivo*, replicating the physiological response to changes in glucose levels. Moreover, the skin could recover quickly after removal of the patches without causing apparent inflammation or other pathophysiological responses.

Given that oral delivery is the most common route for drug administration,[35] our group also prepared insulin-loaded liposomal vesicles for postprandial glucose-responsive oral insulin delivery (Figure 5A).[36] To confer glucose-responsive capacity on the system, lipids modified with dopamine were incorporated into the liposomes, which enabled the subsequent coating of a layer of phenylboronic acid (PBA)-modified HA by forming boronate ester bonds between the catechol and PBA groups (Figure 5B). The liposome surfaces were also functionalized with Fc fragment (designed HA-FC-liposome) for targeting the neonatal Fc receptors on the apical region of epithelial cells in the small intestine, which could improve the transport of vesicles across the intestinal epithelium into circulation.[20] Insulin release kinetics at different pH values suggested that the shell of HA could effectively protect insulins from leakage and digestion in the upper gastrointestinal tract. At elevated glucose levels mimicking postprandial conditions, the HA shell gradually detached from the surface due to the competitive binding of glucose with PBA, accompanied by the exposure of Fc. Such responsive mechanism enabled improved intestinal absorption of the insulin-loaded vesicles.

2.1.2. Multicompartmental Vesicles.—Inspired by the biochemical processes of living β-cells, which are well-organized within spatially defined compartments, we then utilized multicompartmental vesicle-in-vesicle superstructures to build a synthetic artificial β-cell (AβC) for tuning insulin delivery via a membrane fusion-mediated process (Figure 6A,B).[37] The inner lipid nanovesicles were loaded with insulin and mimicked the granules in natural β-cells, while the outer large liposome vesicle acted like the cytoplasmic membrane. Also, we equipped this superstructure with a glucose metabolism system (glucose transporter 2 (GLUT2), GOx/CAT, and proton channel gramicidin A) and a membrane fusion machinery (complementary peptides that can form coiled coils and pH-controlled reversible shielding polymers). In this way, the AβC could distinguish different glucose levels by changing the pH inside the large vesicles to different degrees, which in turn could trigger the fusion of inner nanovesicles with the outer large vesicle and thereby triggering insulin "excretion" under hyperglycemic conditions while maintaining basal low insulin release at normal BGLs. By confinement of all the biochemical processes inside the large vesicles, interference from the buffered biological environment was avoided, which enabled fast response to the dynamic fluctuations in BGLs. These bioinspired AβCs could be directly "transplanted" subcutaneously with the assistance of F127 thermogel and

maintain normal BGL for many days (Figure 6C), without needing immunosuppressive drugs required in the conventional cell transplantation therapy.

To accelerate the potential translation of the above insulin delivery formulations and devices in which enzymes were used as the glucose sensing machinery, we should point out that issues regarding the source and immunogenicity of enzymes should be considered for long-term applications. Also, attention should be paid to the stability of these formulations and devices during manufacturing and storage processes, as there are sensitive and labile chemistries, such as ketals and aryl boronate, involved.

2.2. Cancer Therapy

Besides mimicking β-cell's function for treating diabetes, the interactions between other bioparticulates with body systems have also stimulated the development of anticancer drug delivery systems. For example, the ability of pathogens to escape immune responses and preferentially accumulate in specific host environments, such as tumors, makes them promising for targeted therapeutic delivery applications.[38] Moreover, to overcome the safety concerns associated with their pathogenic nature and potential immunogenicity, alternative strategies by developing pathogen-mimicking synthetic particles provide inspiring means for improving drug delivery specificity and therapeutic outcomes.[39]

Inspired by the tumor hypoxia-tropism of anaerobic bacteria and their capacity in metabolizing oxygen, we designed a nanovesicle system that could respond to hypoxia induced by external light irradiation and deliver cargoes into the tumor microenvironment (Figure 7).[40] The nanovesicles were assembled from two diblock copolymers: one was chlorine e6 (Ce6)-modified PEG-polyserine, and the other one was PEG-poly(Ser-S-NI). Upon light irradiation, the photosensitizer Ce6 could convert oxygen into singlet oxygen, which was further consumed through oxidizing the thioether on PEGpoly(Ser-S-NI) into a hydrophilic oxidized state,[41] accompanied by the generation of a hypoxic niche. The hypoxia could facilitate the bioreduction of NI pendants into hydrophilic units and finally lead to the disassociation of the nanovesicles. Moreover, by loading a hypoxia-activated prodrug, tirapazamine, inside the compartment of nanovesicles, self-regulated site-specific drug delivery as well as synergistic therapeutic effect between photodynamic therapy and chemotherapy could thus be accessed.

3. CELLULAR ENGINEERING SYSTEMS

The key features of cells in communication with biological entities, namely, self-recognition, avoidance of immune response, tropism, and migration in response to special biological signals, have motivated broad research to engineer parts of cells or whole cells as chaperones for organ-specific drug delivery.[9,14] Moreover, advances at cell−nanoparticle interfaces, such as internalization and surface conjugation, have enabled natural particulates to be used as carriers, promising for overcoming the biological barriers frustrating traditional nanomedicines.[9,14]

3.1. Semibiological Biomimetic Systems

For biomimetic particulates, they are often semibiological (or semiartificial) assemblies that incorporate at least one natural component, which correspondingly enables them to resemble their parent particulates from one or more aspects. A prominent biomimetic paradigm recently reported by several groups including us was to utilize cellular membranes to derive nanovectors.[12] Biomimetic nanomedicines developed with this top-down cell-engineering approach facially replicate the complexity of their source cells, which allows efficient interfacing with the biological entities and hence facilitates augmentation of therapeutic efficacy. For instance, by binding glucose-modified insulin with the glucose transporters on an erythrocyte membrane that was wrapped around nanoparticles, our group developed an biomimetic insulin delivery system with long-term stability in blood circulation.[42] Similarly, the intrinsic interactions between platelets and cancer cells enabled us to develop biomimetic nanovehicles by coating platelet membranes onto drug-loaded nanogels, which could effectively accumulate in tumor regions.[43]

Without further translocating onto the surface of manmade nanomaterials, cellular membrane-derived nanovesicles can also be directly leveraged as biomimetic nanomedicines. Biomimetic nanovectors of this kind are also called nanoghosts and have been utilized for targeted drug and gene delivery studies.[44,45] In conjunction with genetic engineering technology, our group recently developed a biomimetic nanovesicle with PD-1 receptors presenting on the surface for cancer immunotherapy (Figure 8).[46] HEK 293T cells were first transfected with plasmid to stably express PD-1 on the extracellular leaflet of membrane and then nanovesicles were prepared via cell dialysis and repeated extrusion processes (Figure 8A). Like that in source cells, PD-1 preserved right-side out orientation in most nanovesicles. Since PD-1/PD-L1 engagement is one of mechanisms that suppress host antitumor immune response (Figure 8B), effective blockade of PD-1 or PD-L1 is crucial for boosting immunotherapeutic outcomes.[47] *In vitro* experiments demonstrated that the PD-l bearing nanovesicles could effectively bind cancer cell membranes via interacting with the PD-L1 ligands (Figure 8C). *In vivo* studies showed that nanovesicles intensively accumulated in the tumor sections and significantly delayed tumor growth by increasing the filtration of $CD8^+$ T cells. Moreover, the interior space of the nanovesicles could be readily loaded with drugs such as 1-methyl-tryptophan (1MT), an inhibitor of the immunosuppressive enzyme indoleamine 2,3-dioxygenase (IDO),[47] allowing for gaining synergistic immunotherapeutic effect by blocking two tolerance pathways (Figure 8D).

3.2. Whole-Cell-Based Systems

In addition to deriving biomimetic nanovectors from cells *ex vivo*, we also looked to leverage the capacity of cells *in situ* to release particles with size in sub-micrometer scale to develop alternative types of advanced nanomedicines. Relevant research mainly involved the utilization of platelets for immune checkpoint inhibitor delivery. The first immunoplatelet complex of this class was prepared by chemical conjugation of aPD-L1 onto platelet surface.[48] After homing to the surgical wound site, platelets could be activated *in situ* and release antibody-bearing particles with size around 200 nm. Together with platelet's abilities of mediating inflammation, a checkpoint blockade system with limited off-target effect was

built for eliciting immunotherapeutic response and thereby inhibiting postsurgical tumor recurrence.

Considering the difficulties in platelet harvesting and scale-up production, we recently developed an alternative immunoplatelet complex by genetically engineering megakaryocyte progenitor cells to express PD-1 on the membrane and further release PD-1-presenting platelets upon maturation (Figure 9A).[49] Notably, this strategy allowed the production PD-1-bearing platelets with large resources (Figure 9B), and moreover, it did not require a complicated chemical modification process, which might affect the orientation of checkpoint inhibitors or the integration of platelets. This PD-lpresenting platelet could not only execute the common biological functions of the platelet in isolation (Figure 9C) but also bind to B16F10 melanoma cells through the PD-1/PD-L1 interaction. Although the detailed mechanisms of antiPDL1- and PD-1-bearing platelets in eliciting immune response were more or less different, the PD-1-bearing platelets also showed high efficiency in reverting T cell exhaustion and inhibiting tumor relapse after surgery. Moreover, cyclophosphamide, an immunosuppressive drug, could be internalized by the PD-1 platelets and then released to the outside, which helped to further improve anticancer immune response by depleting regulatory T cells (Tregs) within the tumor microenvironment. From a broad perspective, this strategy of bioengineering natural particulates could be extended to express more than one kind of checkpoint inhibitor for generating systems with combination immunotherapy potency.

The flexibility of bioparticulate engineering enabled us to develop a cell combination strategy, in which one cell could home to specific tissues while the other one acted as a drug carrier.[50] Acute myeloid leukemia (AML), a heterogeneous clonal disorder of blood-forming cells starting in the bone marrow, carries a risk of relapse after traditional chemotherapy, one reason for which is the retention of residual leukemia cells in the bone marrow.[51] Based on the preclinical studies disclosing the potency of checkpoint immunotherapy in treating AML,[52] we coupled aPD-1-modified platelets to hematopoietic stem cells (HSCs) to develop a cell combination formulation that could migrate to bone marrow and locally release aPD-1-conjugated particles for promoting antileukemia immune response (Figure 10A).[50] aPD-l-decorated platelets were prepared similar to our previous work[48] and then connected with HSCs using click chemistry, and the ratio of HSC to platelet was optimized to 1:1 (Figure 10B). In the complex, both the platelets' biological functions, including release of particles after activation (Figure 10C), and the bone marrow-homing property of HSCs (Figure 10D) were well preserved. Moreover, detailed *in vivo* study demonstrated that the cell−cell complex effectively decreased the AML burden in the blood, marrow, and other main organs via activating the antitumor immune response, which was confirmed by the higher number of T cells, increased percentage of $CD8^+$ T cells, and elevated pro-inflammatory factors. Such cell−cell combination construct could be extended for treating other diseases by incorporating different cell types.

4. SUMMARY AND OUTLOOK

In this Account, we have briefly summarized our recent studies of utilizing natural particulate-inspired synthetic and cellular nanoformulations for treating diabetes and cancer,

with which we expect to augment the therapeutic efficiency and minimize undesired side effects by mimicking or directly taking advantage of the ways that cells interact and communicate with living entities. In the meantime, the advances of bioconjugation chemistry, bionanotechnologies, and genetic engineering tools further broaden the choice scope and design flexibility of nanomedicines within these categories. In some sense, such designs fuse “life” to nanomedicines and enable them to “communicate” with the biological environment and release feedback in response to specific biological factors. It is worth mentioning that these strategies are not independent and can be combined together to develop more potent nanomedicines.

Although considerable progress has been made in the field of natural particulate-inspired or -based drug delivery, there are still several challenges that need to be overcome before translation from the bench to the bedside. First, for bioinspired and biomimetic systems, their architecture is complicated to some degree but still far from that of natural systems; for instance, most synthetic cell-mimicking systems lack the capacity for self-cloning and self-replenishing possessed by natural cells, which means that they only provide therapeutics temporarily and are inadequate in treating diseases that need sustainable drug delivery. Moreover, for many bioresponsive drug delivery systems, it is still hard to replicate the fast dynamics of natural processes, meaning that there is lag time between sensing and drug release. Second, different from well-defined synthetic systems, for biological membrane-derived biomimetic nanomedicines, concerns regarding reproducibility of the quantities of membrane proteins, and their scale-up manufacturing have to be addressed. Third, for genetically or chemically engineered natural particulates, although their viability and desired biological functions could be well preserved, the undesired effects on their other functions and long-term behaviors in biological systems should be thoroughly assessed as well. The overall biodistribution of the administered engineered bioparticulates and their effect on nontargeted tissues also remain to be revealed before clinical studies. As this field is still expanding, future advances rely on deep understanding of natural particulates and advanced synthesis techniques, as well as collaborative efforts from different fields. Exciting applications of bioinspired and biomimetic nanomedicines for treating numerous diseases associated with different indications are foreseen through unique designs of structure and function as well as different delivery routes, learning from nature to improve our life.

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Biographies

Zhaowei Chen received his B.Sc. degree at Northwestern Polytechnical University in 2010 and Ph.D. in Inorganic Chemistry and Chemical Biology at Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, in 2016. After finishing the first-term postdoctoral training in the Joint Department of Biomedical Engineering at the University of

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Zejun Wang obtained her B.Sc. in Chemistry in 2013 from Hunan University and her Ph.D. degree in Inorganic Chemistry at Shanghai Institute of Applied Physics, Chinese Academy of Sciences, in 2018. In the same year, she joined Prof. Zhen Gu's research group at University of California, Los Angeles, as a postdoctoral research fellow. Her research interests mainly focus on the design and synthesis of analytical probes, biomedical devices, and biomimetic materials.

Zhen Gu is a Professor in the Department of Bioengineering and Director of NIH Biotechnology Training in Biomedical Sciences and Engineering Program at University of California, Los Angeles (UCLA). Dr. Gu received his B.S. degree in Chemistry and M.S. degree in Polymer Chemistry and Physics from Nanjing University. In 2010, he obtained Ph.D. at UCLA, under the guidance of Dr. Yi Tang in the Department of Chemical and Biomolecular Engineering. He was a Postdoctoral Associate working with Dr. Robert Langer at MIT and Harvard Medical School during 2010 to 2012. Before he moved to UCLA in 2018, he had been appointed as a Jackson Family Distinguished Professor in the Joint Department of Biomedical Engineering at the University of North Carolina at Chapel Hill and North Carolina State University. His group studies controlled drug delivery, bioinspired materials, and nano-biotechnology, especially for cancer and diabetes treatment.

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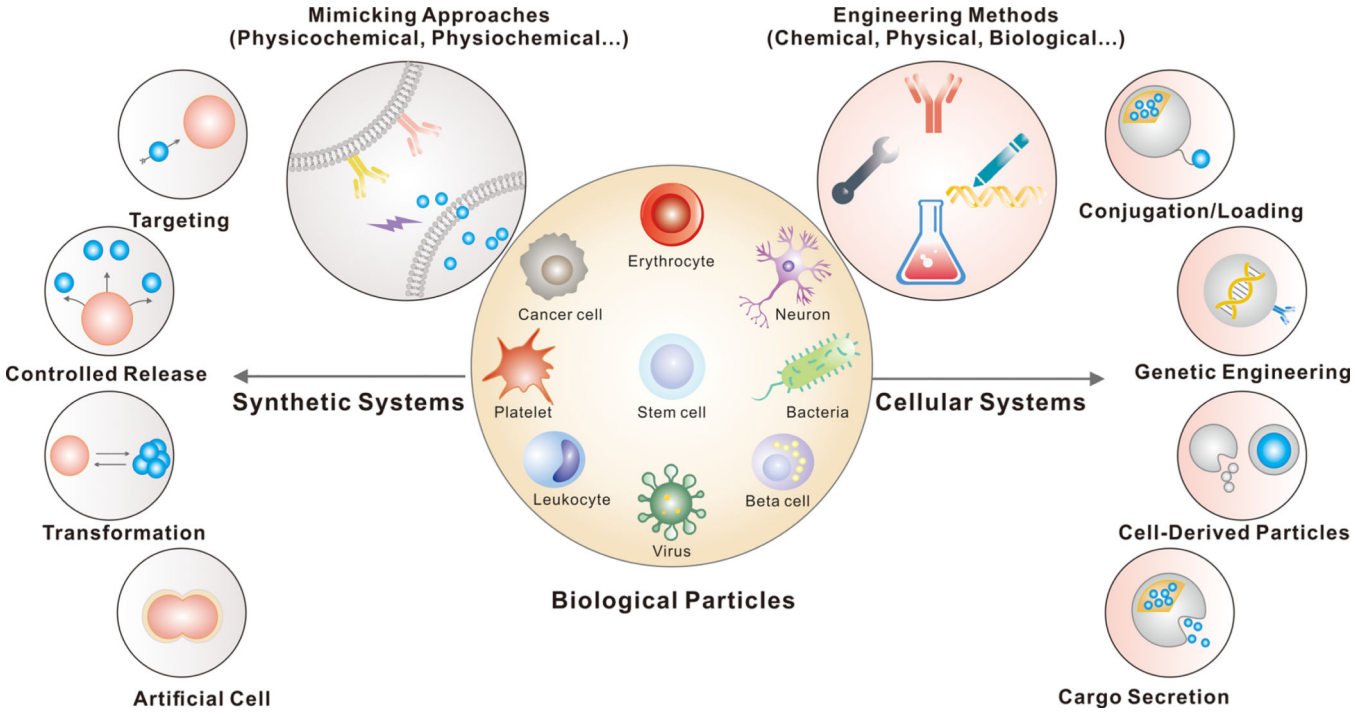

Figure 1.

Schematic illustration of different approaches of engineering bioinspired and biomimetic nanomedicines based on synthetic and cellular systems, respectively.

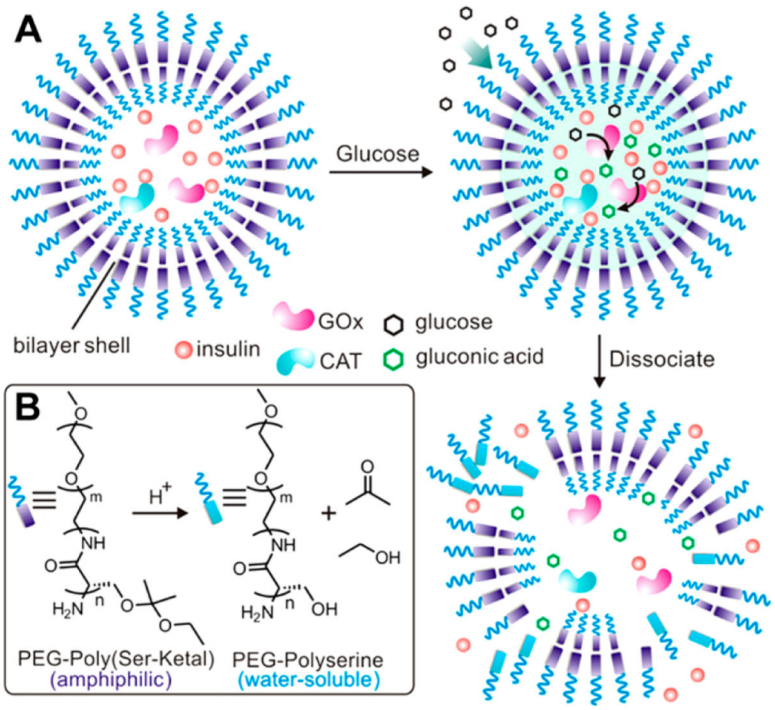

Figure 2.

(A) Schematic illustration of the pH responsive nanovesicle packed with insulin, GOx, and CAT for glucose-tuned insulin release. (B) The chemical structure of the acid-sensitive diblock copolymer PEG−poly(Ser-Ketal). Reprinted and modified with permission from ref 23. Copyright 2014 American Chemical Society.

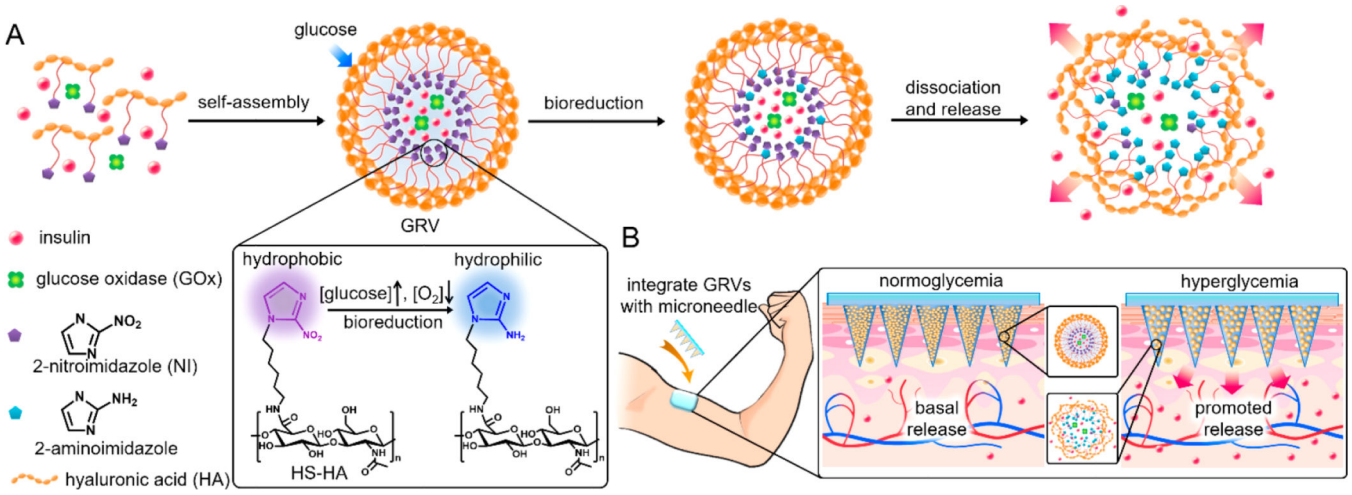

Figure 3.

(A) Schematic illustration of the fabrication of insulin-loaded nanovesicles that could respond to the hypoxia induced by glucose oxidation. (B) Integration of the glucose responsive vesicles (GRVs) into a microneedle-array patch, the first prototype of a “smart insulin patch”, for transdermal insulin delivery. Reprinted with permission from ref 27. Copyright 2015 National Academy of Sciences.

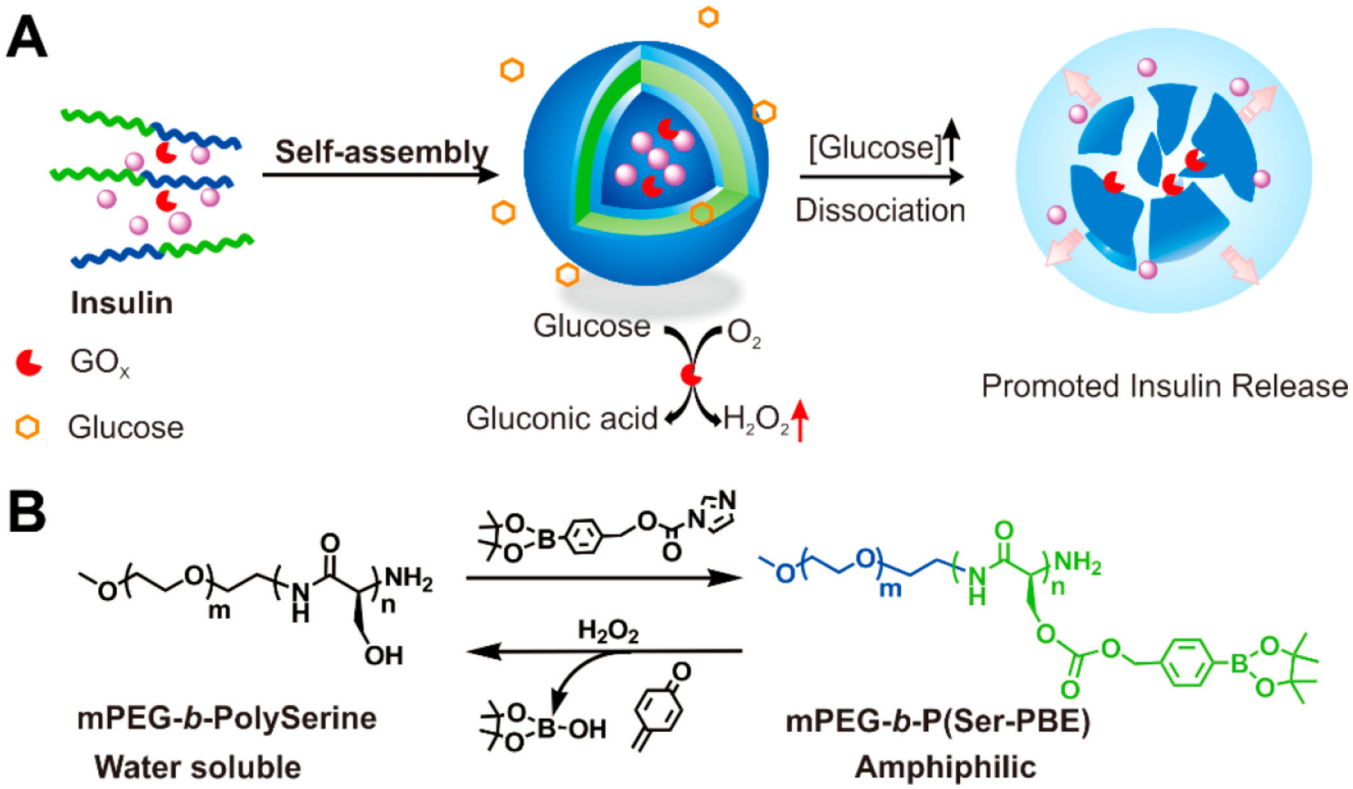

Figure 4.

(A) Schematic illustration of the H_2O_2-responsive nanovesicles for glucose-mediated insulin delivery. (B) Chemical structure of mPEG-bP(Ser-PBE) and its degradation mediated by H_2O_2. Reprinted and modified with permission from ref 31. Copyright 2017 American Chemical Society.

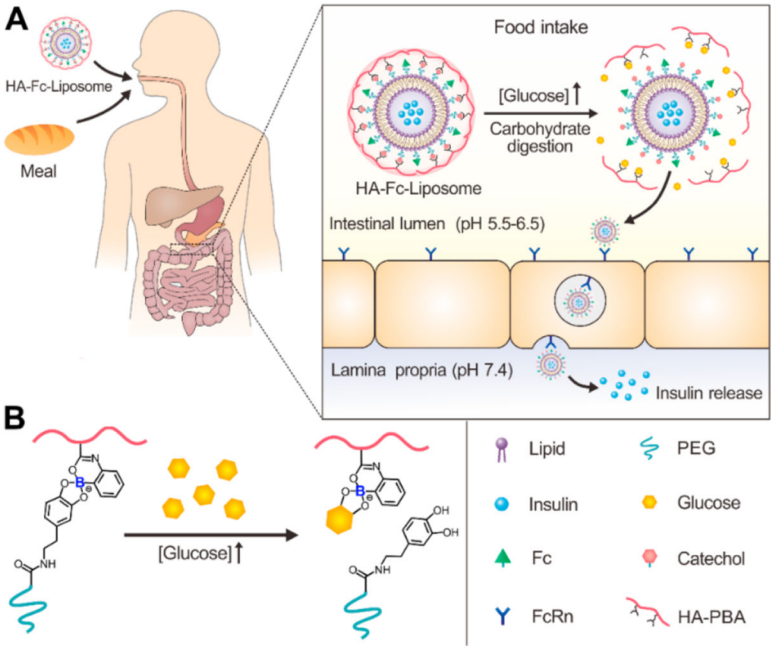

Figure 5.

(A) Schematic illustration of oral-insulin delivery with engineered liposome vesicles that could respond to postprandial evaluated glucose concentration. (b) Competitive binding of PBA with catechol groups and glucose. Reprinted and modified with permission from ref 36. Copyright 2018 Tsinghua University Press and Springer-Verlag GmbH Germany, part of Springer Nature.

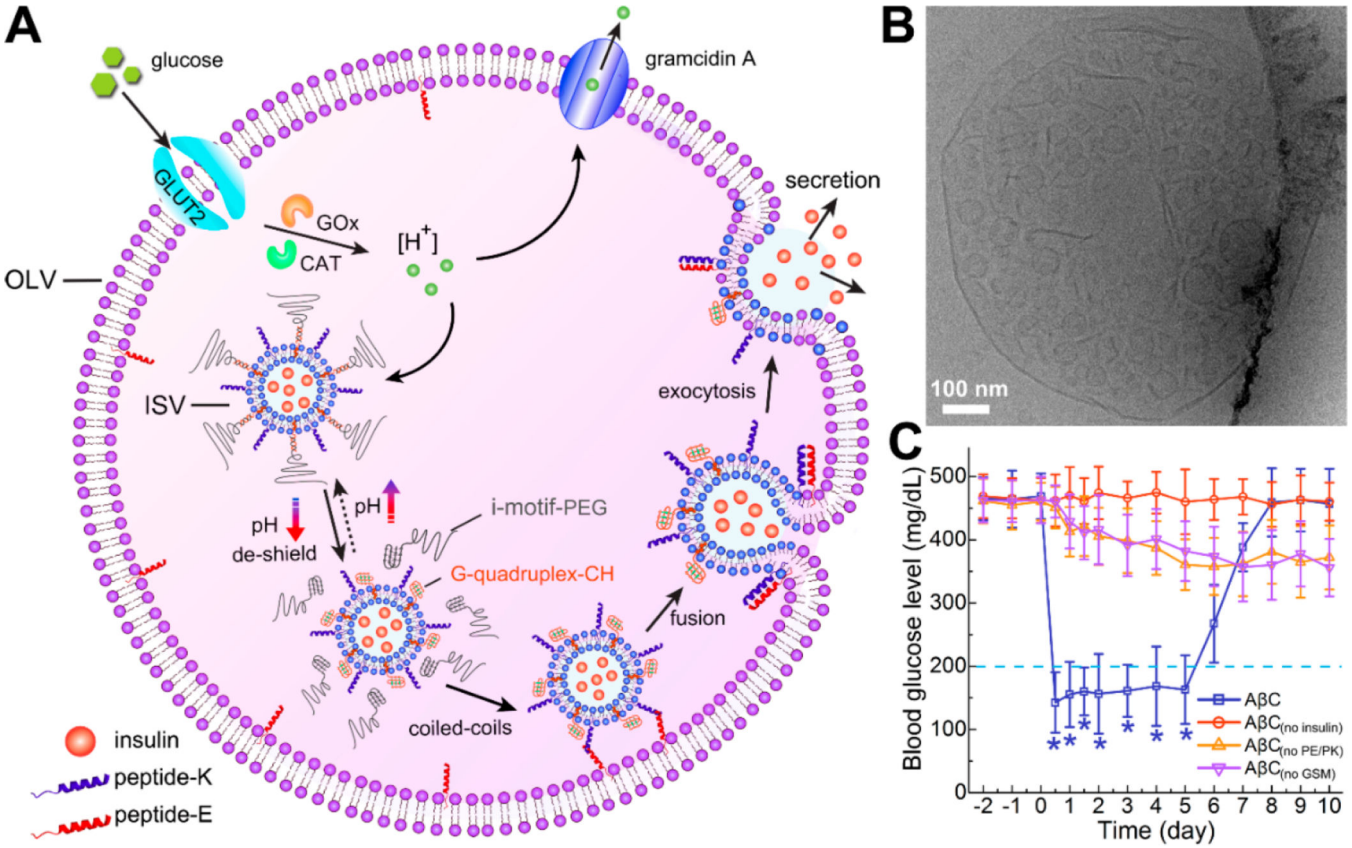

Figure 6.

(A) Schematic illustration of a synthetic AβC that can sense external glucose levels and release insulin through fusion of the inner small vesicles (ISVs) with the outer large vesicle (OLV). (B) Cryogenic transmission electron microscopy (TEM) image showing the vesicle-in-vesicle structure. (C) BGLs of diabetic mice after injecting hydrogels containing AβCs or control AβCs that lacked insulin (AβC$_{(no-insulin)}$), membranefusion peptides E/K (AβC$_{(no-PE/PK)}$), or glucose-sensing machinery (AβC$_{(no-GSM)}$); $^{*}P < 0.001$. Reprinted with permission from ref 37. Copyright 2018 Nature Publishing Group.

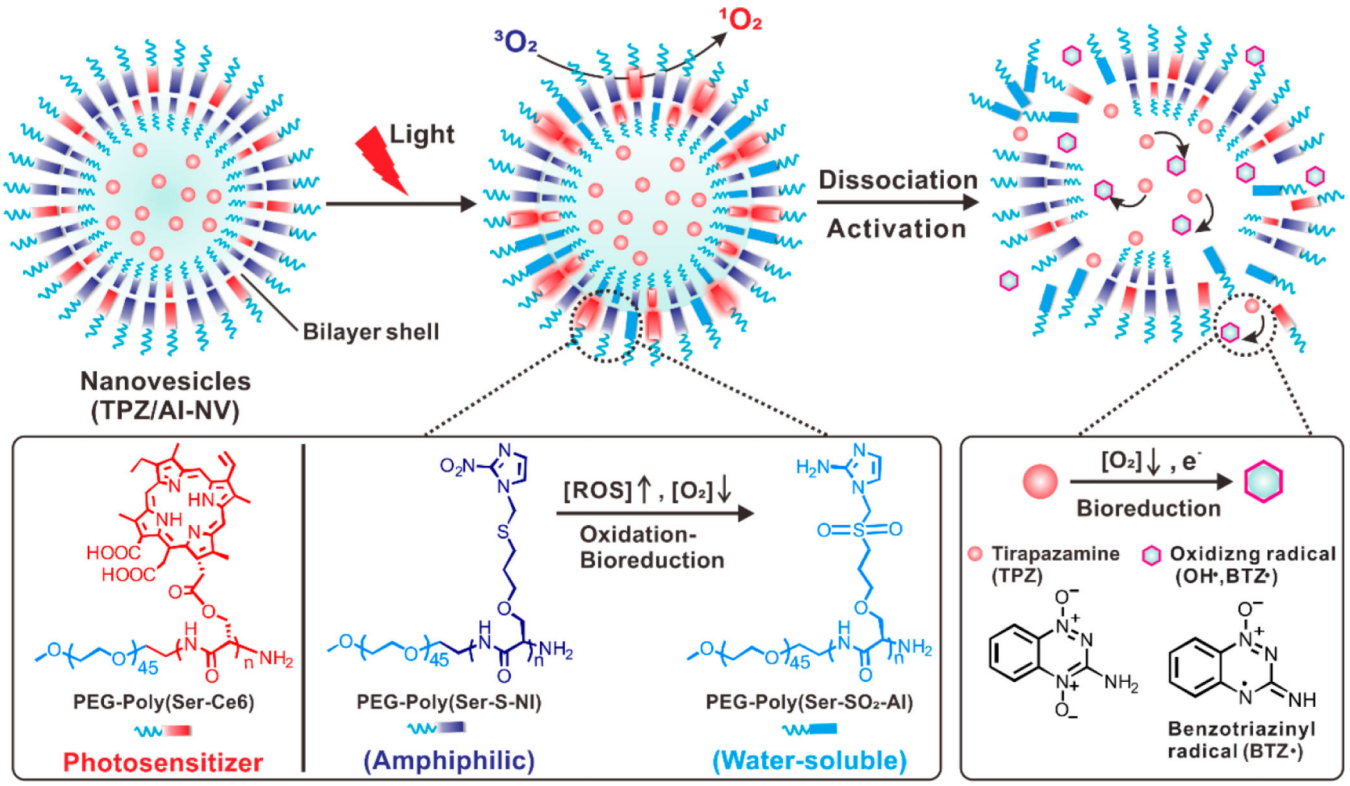

Figure 7.

Schematic illustration of the anaerobic bacteria-inspired nanovesicle system that could respond to hypoxia induced by external light irradiation for anticancer drug delivery and prodrug activation. Reprinted with permission from ref 40. Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

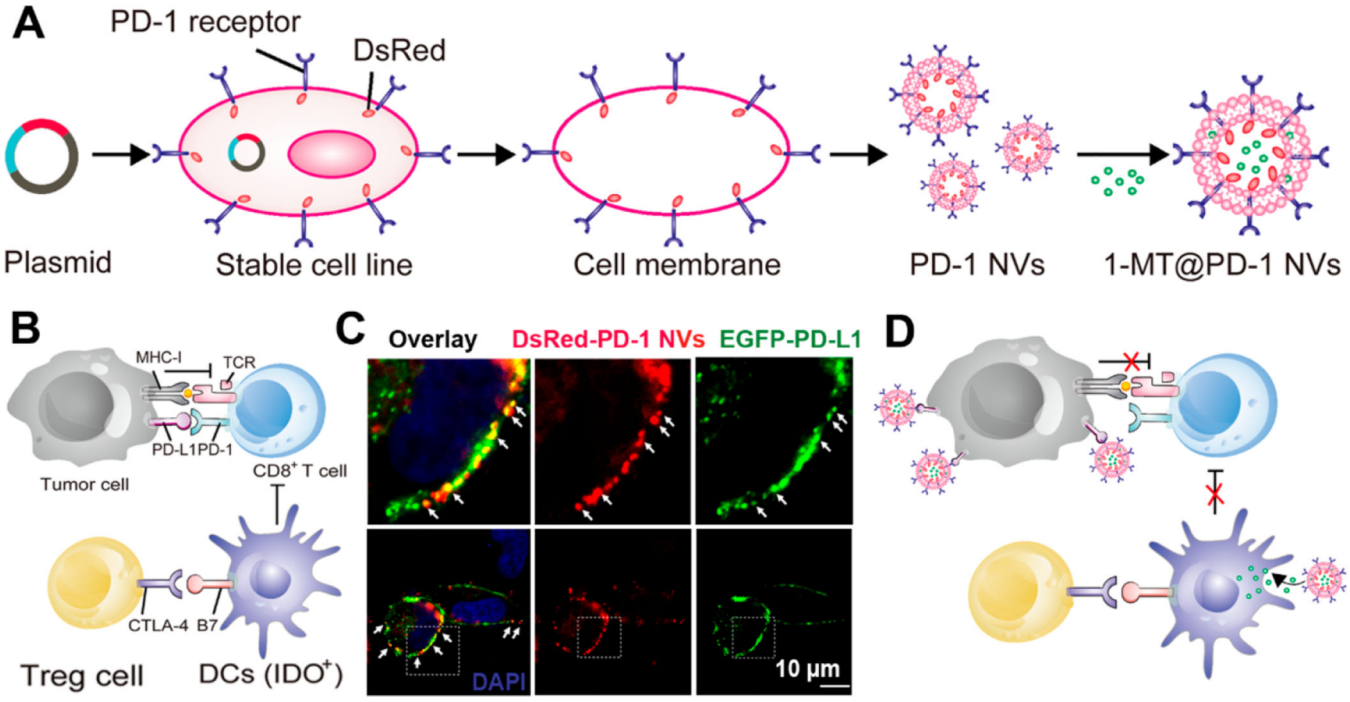

Figure 8.

(A) Schematic illustration of fashioning genetically engineered HEK 293T cells into nanovesicles with PD-1 presenting on the surface and 1-MT loading in the inner cavity; the C-terminal of PD-1 was tagged with DsRed protein. (B) Suppression of $CD8^+$ T cell activity via PD-1 and IDO pathways. (C) Confocal microscopy image showing the colocalization of PD-1 nanovesicles and PD-L1 (green) on B16F10 melanoma cell membrane. (D) Synergistic reversion of $CD8^+$ T cells with the biomimetic nanovesicles by blocking dual tolerance pathways. Reprinted with permission from ref 46. Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

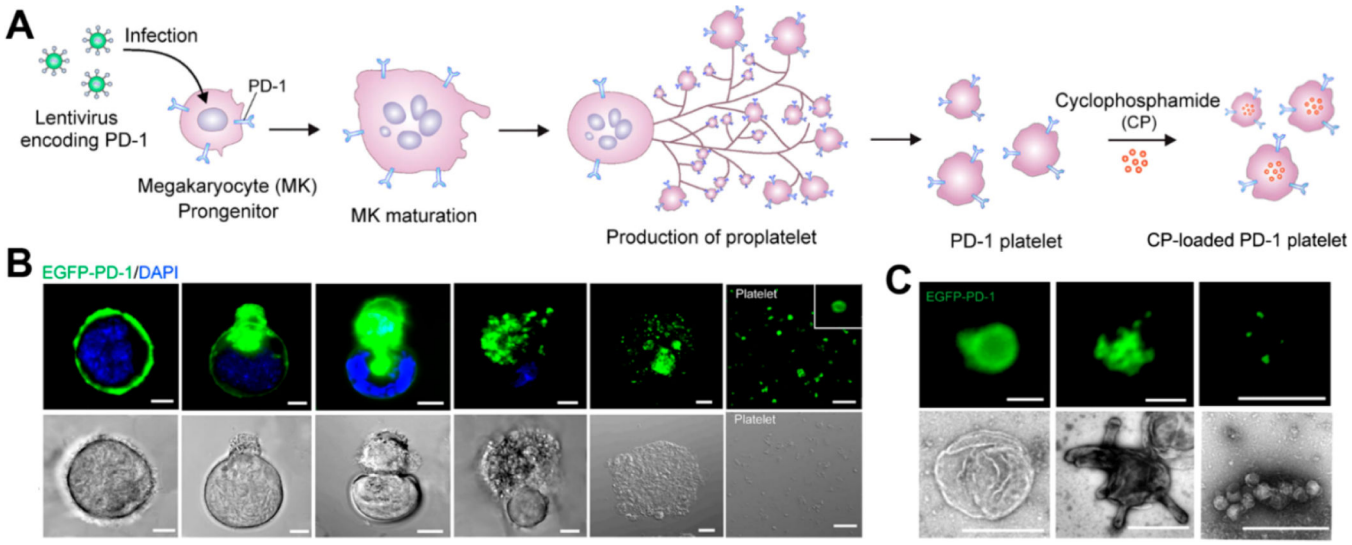

Figure 9.

(A) Schematic illustration of producing PD-1 platelets *in vitro* with genetically engineered megakaryocyte progenitor cells and the obtained platelets being further loaded with cyclophosphamide. (B) Confocal microscopy images of the evolution process (from left to right) of releasing enhanced green fluorescent protein (EGFP)-tagged PD-1-bearing platelets from megakaryocytes upon stimulation. Scale bar: 10 μm. (C) Confocal microscopy (top) and TEM (bottom) images of platelets, activated platelets, and released particles (from left to right). Scale bar: 1 μm. Reprinted and modified with permission from ref 49. Copyright 2018, American Chemical Society.

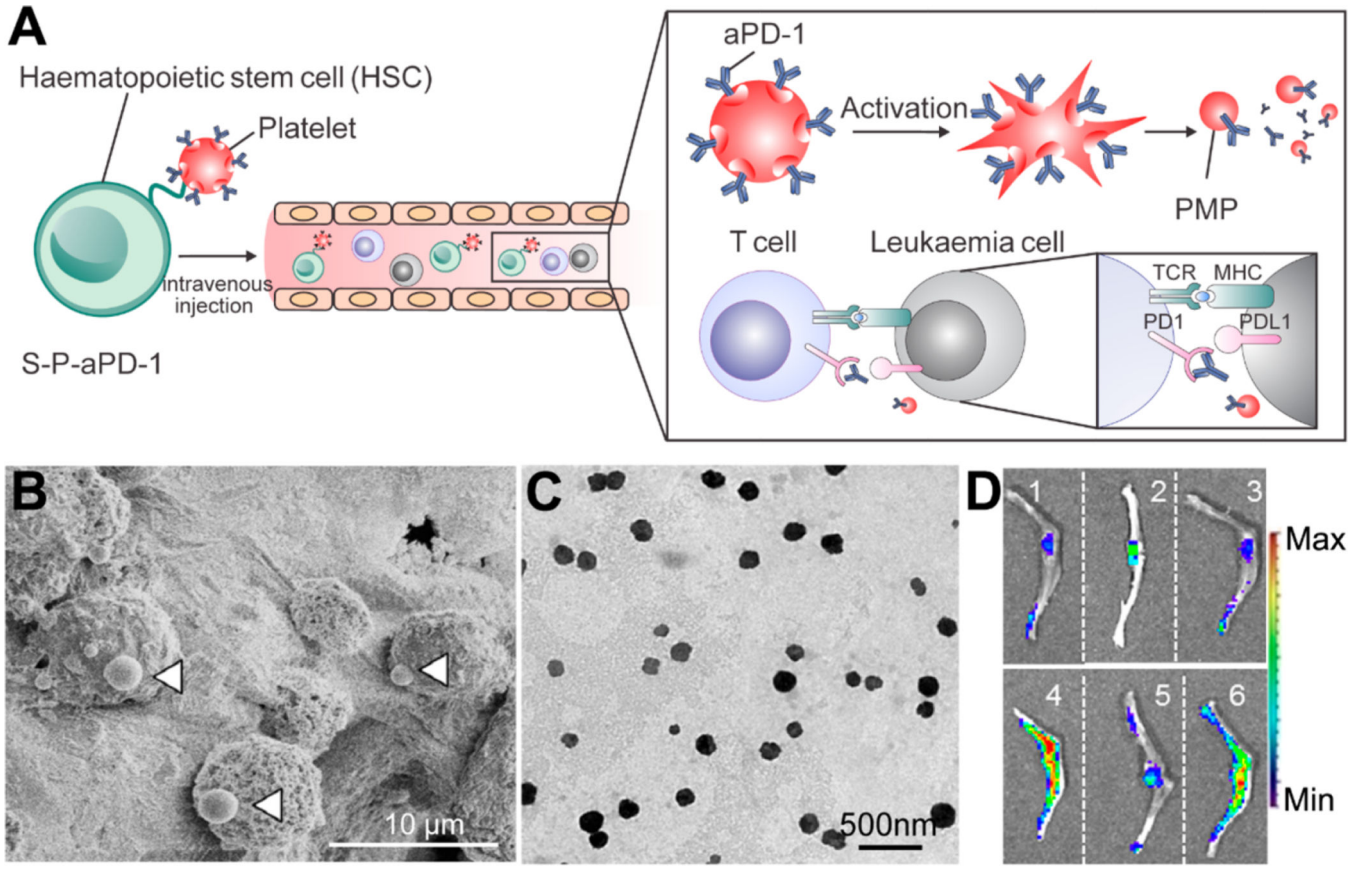

Figure 10.

(A) Schematic illustration of the HSC-platelet assembly for aPD-1 delivery. (B) Cryogenic electron microscopy image of the HSC-platelet−aPD-1 complex (designated S-P-aPD-1). (C) TEM image of the particles released from the S-P-aPD-1 after activation. (D) Ex vivo fluorescence imaging of the bone tissues from mice treated with silane (1), Cy5.5-tagged aPD-1 (2), aPD-1-conjugated platelet (3), aPD-1conjugated HSC (4), HSC + aPD-1-conjugated platelet (5), and S-P-aPD-1 (6). Reprinted with permission from ref 50. Copyright 2018 Nature Publishing Group.