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Cell-in-Shell Metacells in Single-Cell Nanoencapsulation

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ABSTRACT

Single-cell nanoencapsulation (SCNE) enables the direct integration of synthetic materials with living cells, forming cell-in-shell structures that augment native cellular functions without genetic modification. While SCNE has advanced applications in cytoprotection and cell-surface engineering, its full potential remains constrained by the absence of a unifying conceptual framework. In this Concept report, we introduce the term "metacells" to define a new class of engineered, living cell-in-shell systems endowed with dynamic functionality, environmental responsiveness, and programmable behavior. We propose that metacells are characterized by three core functional hallmarks—reconfigurability, loadability, and motility—which collectively distinguish them from conventional SCNE platforms. Through selected examples, we illustrate how these features enable metacells to sense and respond to external stimuli, carry and release functional payloads, and exhibit guided or autonomous motion. By establishing a foundational definition and organizing framework for metacells, this report provides a roadmap for future research at the intersection of materials science, synthetic biology, and cellular engineering, with implications for advanced therapeutics, microscale robotics, and interactive biohybrid systems.

1 | Introduction

A cell is the smallest structural and functional unit of life, capable of performing essential biological processes such as metabolism, growth, reproduction, and interaction with the environment. The engineering of single-cell units to harness these intrinsic capabilities has driven key advancements in modern medicine and bioproduction. Distinct from genetically modified organisms (GMOs) produced through genetic alteration, the field of single-cell nanoencapsulation (SCNE) has introduced the direct integration of synthetic materials with living cells in the form of cell-in-shell structures [1, 2]. SCNE represents a transformative platform for the development of functional nanobiohybrid systems, offering a versatile, rapid, and efficient method to augment innate cellular functions with exogenous capabilities—without altering genetic material.

While advances in SCNE have enabled notable progress in cytoprotection and cell-surface engineering, these approaches have largely focused on passive protection and structural reinforcement of individual cells. A critical gap, therefore, remains in the conceptual framework needed to guide the development of next-generation cell-in-shell systems designed for higher-order functional integration beyond cytoprotection alone.

In this Concept report, we introduce the term "metacells" to define a distinct class of engineered, living cell-in-shell systems that extend beyond the scope of current SCNE. Specifically, metacells exhibit: (1) dynamic functionality through environmental sensing and responsiveness, (2) programmable behaviors not achievable with existing SCNE architectures, and (3) preservation of the core biological operations of the SCNEd cells.

The introduction of metacells represents a necessary conceptual advancement rather than a semantic extension. Whereas traditional SCNE primarily aims at cytoprotection and structural reinforcement [3, 4], metacells are conceived as active, information-processing cellular systems capable of adaptive interaction with their environment and execution of predefined or emergent functions. This Concept report presents the first formal

conceptualization of the metacell framework, establishing a foundation for the rational design of programmable cell-based systems.

We propose that metacells can be characterized, at this stage, by three core functional hallmarks—reconfigurability, loadability, and motility—which distinguish the metacell concept from previous SCNE strategies. These hallmarks represent distinct conceptual and functional axes rather than mutually exclusive categories; advanced metacell systems may exhibit multiple hallmarks simultaneously. The framework is intended to identify the key dimensions along which metacells can be designed and evaluated, and examples presented in this report demonstrate various degrees of integration among these hallmarks.

- Reconfigurability refers to the ability of metacells to undergo structural or functional transformation—including shell degradation, remodeling, or biochemical reprogramming—in response to environmental stimuli or programmed cues. This hallmark is defined by stimulus-responsive alterations in shell structure, composition, or function, enabling metacells to adapt in real time to fluctuating conditions and making them suitable for applications that demand dynamic responsiveness.
- Loadability defines the capacity of metacells to encapsulate, integrate, or transport functional components such as therapeutic agents, enzymes, imaging probes, or signaling molecules. This hallmark is characterized by the deliberate incorporation of exogenous cargo—whether embedded within the shell matrix, displayed on its surface, or compartmentalized within the construct—to confer new or enhanced functionalities. This feature allows metacells to serve as targeted delivery vehicles or localized functional reactors capable of processing biochemical signals or mediating site-specific reactions.
- Motility imparts the capacity for directional movement in response to enzymatic, chemotactic, optical, magnetic, or other programmable inputs. This hallmark is characterized by autonomous or externally guided locomotion that enables spatial repositioning and dynamic navigation within complex environments. This capability expands metacell functionality in targeted therapeutic delivery, spatially resolved sensing, microrobotic cell systems, and intelligent biointerface design.

Together, these hallmarks provide a functional framework for classifying and designing metacell systems based on their engineered capabilities. These properties collectively imbue metacells with dynamic functionality, stimulus-responsiveness, and autonomous behaviors, positioning them as a new platform at the intersection of chemistry, biology, materials science, and synthetic biology.

This Concept report highlights emerging yet still fragmented research efforts toward the realization of metacells, with particular emphasis on the shell materials and synthetic strategies enabling reconfigurability, loadability, and motility (Figure 1). Our aim is to establish a unified conceptual foundation for metacells by contextualizing early-stage developments in this nascent field. The report concludes by identifying current challenges and proposing future directions for metacell development and application.

Table 1 summarizes the representative metacell examples discussed in this report. Examples that exhibit multiple hallmarks simultaneously are presented in multiple subsections, ordered by reconfigurability, loadability, and motility.

2 | Reconfigurability

In nature, living organisms have evolved self-defense strategies to enhance adaptive survival. For instance, certain bacteria and fungi utilize a mechanism known as sporulation, whereby a resilient shell encapsulates the cellular core to protect DNA and essential components from external stresses, such as extreme heat, desiccation, nutrient deprivation, radiation, and others [49, 50]. Although metabolically inactive in their dormant state, spores remain viable and can readily germinate into functional vegetative cells when favorable conditions return. Inspired by natural spores, researchers have developed artificial spores—chemically synthesized cell-in-shell structures characterized by durable synthetic nanoshells composed of external materials [3, 4]. The nanoshells safeguard the SCNEd cells, while preserving their intrinsic biological functions.

As previously noted, early SCNE research primarily focused on the chemical mimicry of the remarkable resilience of natural spores by forming ultrathin (<100 nm), yet robust, nanoshells [1–4]. A wide range of nanoshell materials—including inorganic compounds such as silica (SiO_2) [51–54] and titanium dioxide

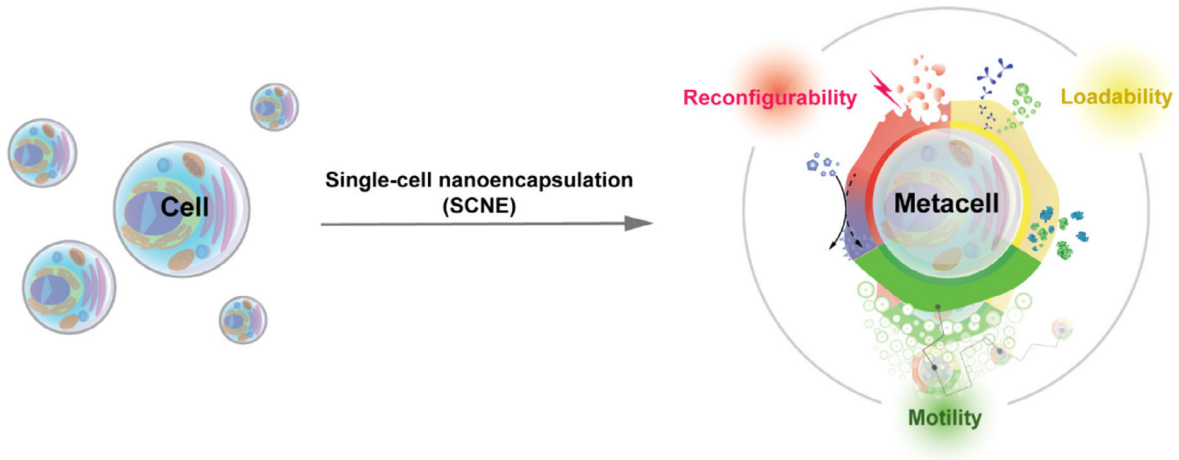

FIGURE 1 | Schematic for SCNE-based construction of cell-in-shell metacells characterized by reconfigurability, loadability, and motility.

TABLE 1 | A summary of metacells discussed in this report.

Shell materials	Functional hallmarks			Features	References
	Recon-figurability	Loadability	Motility		
$CaCO_3$	•			Gastric acid–triggered degradation of $CaCO_3$ shells; simultaneous neutralization of gastric acid and sequestration of bile acids	Liu (2023) [5]
$CaCO_3$/Polymer	•			EDTA-mediated removal of $CaCO_3$ inner shells, enabling yolk–shell structures	Yang (2023) [6]
MOCs (Fe^{3+}-TA, Ca^{2+}-TA, Fe^{3+}-luteolin, etc.)	•			HCl, EDTA, L-ascorbic acid, and H_2O_2-triggered shell disassembly; manipulation of cellular metabolism, activity, and fate (e.g., lag-phase elongation, germination, and proliferation)	Choi (2014, 2015, 2022, 2024, 2025) [7–12], Qu (2015) [13], Furst (2022) [14, 15], Ejima (2022, 2024) [16, 17], Liu (2024) [18], Shi (2022) [19], Liu (2024) [20], Zan (2024) [21]
ZIF-8; MOF NP	•			EDTA-triggered disassembly and controlled degradation of MOF shells	Falcaro (2016) [22], Brinker (2019) [23]
MnO_2; S–S bond-bearing polymer	•			Glutathione-mediated shell degradation	Qu (2017) [24], Ryu (2015) [25]
Polyelectrolyte	•			On-demand cell release via enzyme-mediated shell degradation	Choi (2020) [26], Wurm (2020) [27], Yang (2016) [28], Chen (2019) [29]
DNA	•			Selective shell degradation by specific restriction endonucleases	Li (2019) [30]
ZIF-8; ZIF-8/ZIF-C	•	•		Incorporation of β-galactosidase into ZIF-8 shells, enhancing cell survival in lactose-containing media; EDTA-triggered degradation of ZIF-8/ZIF-C shells, enabling controlled release of encapsulated α-1-antitrypsin	Falcaro (2017) [31], Falcaro (2022) [32]
Fe^{3+}-TA	•	•		Acid-triggered disassembly of Fe^{3+}-TA shells, enabling controlled release of preloaded small molecules, proteins, and antibodies	Choi (2021) [33], Liu (2023) [34]
Fe^{3+}-BTC	•	•		Concomitant encapsulation of multiple enzymes during shell formation, preserving enzymatic activity and enabling cascade reactions	Choi (2022) [35]
Fe^{3+}-BTC to Fe^{3+}-P	•	•		Phosphate-induced shell transformation from Fe^{3+}-BTC	Choi (2024) [36]

(Continues)

TABLE 1 | (Continued)

Shell materials	Functional hallmarks			Features	References
	Recon-figurability	Loadability	Motility		
				to Fe-P, triggering release of encapsulated proteins and antibodies	
pDA		•		Cargo incorporation (e.g., ICG, antigens, antibodies, enzymes, and small molecules) via co-deposition or post-functionalization	Liu (2023, 2021, 2022) [37–39, 40], Huang (2019) [41]
Liposome		•		Liposome-based shells loaded with enzymes, magnetic nanoparticles, or fluorescent dyes	Choi (2025) [42]
SiO_2		•	•	Layer-by-layer construction of MNP/SiO_2 shells, enabling magnetic responses and movement	Choi (2016) [43]
Liposome		•	•	Glucose oxidase-tethered liposomes serving as shell building blocks, enabling chemotactic movement in response to D-glucose gradients	Choi (2023) [44]
Polymer		•	•	Urease immobilized on cells via chemical conjugation; urease-driven self-propulsion through catalytic decomposition of urea into CO_2 and NH_3	Yang (2021) [45]
SiO_2 NP		•	•	Urease immobilized on aldehyde-functionalized SiO_2 NPs via Shiff base reactions; urease-driven self-propulsion through catalytic urea decomposition	Huang (2023) [46]
pDA		•	•	Urease immobilized on pDA shells via Schiff base reactions; urease-driven self-propulsion through catalytic urea decomposition	Choi (2025) [47]
TiO_2 NP			•	UV-induced phototactic behavior and collective swarming of cells	Huang (2023) [48]

(TiO_2) [55, 56], as well as polymers such as polydopamine (pDA) [57–59] and polypyrrole (PPy) [48, 60, 61]—have demonstrated the capacity to enhance cell survival under harsh conditions, including ultraviolet (UV) irradiation, thermal stress, freeze–thaw cycling, exposure to toxic chemicals, and nutrient deprivation. However, first-generation artificial spores exhibit static shell configurations and lack dynamic reconfigurability. This limitation primarily stems from a chemical challenge: the disassembly or modification of the physicochemically durable shell often demands harsh reaction conditions that are incompatible with cell viability and detrimental to the SCNEd cells.

2.1 | Micrometric Iron Men

A foundational demonstration of reconfigurable metacells involves stimulus-responsive shell degradation under cytocompatible conditions, enabling the construction of the so-called

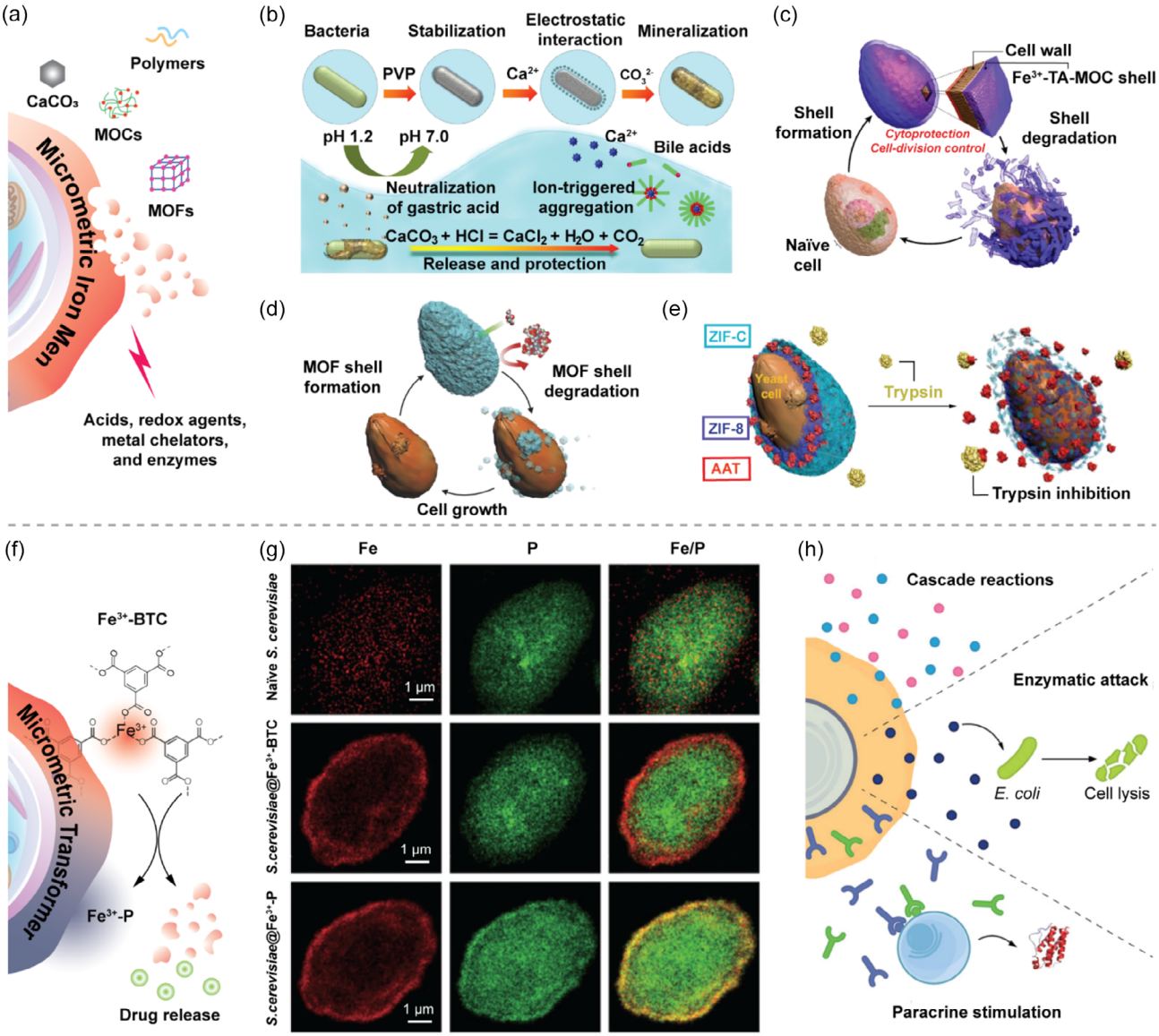

FIGURE 2 | (a–e) Micrometric Iron Men: (a) Schematic for Micrometric Iron Men with shell degradability; (b) Construction of $CaCO_3$-SCNEd bacteria and $CaCO_3$-shell degradation in gastric acid. PVP: polyvinylpyrrolidone. Reproduced from Ref [5]. Copyright (2023) with permission from American Association for the Advancement of Science; (c) Controlled formation and degradation of Fe^{3+}-TA-MOC shells on individual *S. cerevisiae*. Reproduced from Ref [7]. Copyright (2014) with permission from Wiley-VCH; (d) Controlled MOF shell formation and degradation on individual *S. cerevisiae*. Reproduced from Ref [22]. Copyright (2016) with permission from Wiley-VCH; (e) Shell-degradation-triggered release of AAT proteins embedded within multilayered ZIF shells on *S. cerevisiae*. Reproduced from Ref [32]. Copyright (2022) with permission from Royal Society of Chemistry. (f–h) Micrometric Transformers: (f) Schematic for Micrometric Transformers with compositional transformation to Fe^{3+}-P as an example; (g) Energy-dispersive spectroscopy elemental mapping images of (top) naïve *S. cerevisiae*, (middle) Fe^{3+}-BTC-SCNEd *S. cerevisiae*, and (bottom) Fe^{3+}-P-SCNEd *S. cerevisiae*; (h) Shell transformation-coupled release of embedded biomolecules. (g and h) Reproduced from Ref [36]. Copyright (2024) with permission from Wiley-VCH.

"Micrometric Iron Men" (Figure 2a) [62]. Micrometric Iron Men are designed to protect or enhance cellular functionality before or during targeted tasks over a defined period, after which the nanoshells are removed to restore the cell's native state and functions. Examples include the SCNE of *Bacteroides fragilis*, an obligate anaerobic probiotic, within calcium carbonate ($CaCO_3$) shells (Figure 2b) [5]. $CaCO_3$ nanoshells effectively protected *B. fragilis* from manufacturing-associated stressors—such as air exposure, UV irradiation, and 75% ethanol—in vitro. Upon oral administration in a dextran sulfate sodium-induced murine model of colitis, the $CaCO_3$ shells disassembled in the stomach, neutralizing intragastric acidity and inducing Ca^{2+}-mediated micellar aggregation of bile acids to support cytoprotection, while the disassembly itself led to cellular restoration. The synergy between the shell formation and degradation enhanced the intestinal delivery and therapeutic efficacy of *B.fragilis*@$CaCO_3$ compared with naïve cells. In another study, $CaCO_3$ in double-layered $CaCO_3$/polymer shells was selectively removed using ethylenediaminetetraacetic acid (EDTA), generating a hollow void between the cell core and the surrounding polymeric shell and resulting in the formation of yolk-shell structures [6]. This transformation of reconfigurable metacells from a

core–shell to a yolk-shell architecture offers an additional SCNE platform for chemically manipulating the cytospace and the pericellular microenvironment in a controlled manner.

Since the initial introduction of the Micrometric Iron Men concept, a broad range of materials and protocols for controlled shell formation and degradation have been developed. Among these, metal-ligand coordination systems—such as metal-organic complexes (MOCs) and metal-organic frameworks (MOFs)—have emerged as particularly promising shell components due to their capacity for disassembly under cytocompatible conditions.

Notably, the MOC of Fe^{3+} and tannic acid (TA) was among the earliest systems employed in the construction of Micrometric Iron Men, in which shell degradation using 20 mM HCl was demonstrated in both agar plates and suspension cultures of *Saccharomyces cerevisiae* (Figure 2c) [7]. The cytocompatible formation and degradation of Fe^{3+}-TA MOC shells were further validated in various microbial and mammalian cell types—including *Bacillus subtilis*, *Bacteroides thetaiotaomicron*, *Chlamydomonas reinhardtii*, *Escherichia coli*, PC-12, Jurkat, NIH 3T3, and HeLa cells—using HCl, EDTA, L-ascorbic acid, or even H_2O_2 as degradation cues, thereby demonstrating the chemical mimicry of natural sporulation and germination processes [8, 9, 13–18].

Noticeably, the SCNE of *Euglena gracilis* induced a transformation into an ellipsoidal, immotile state, and the Fe^{3+}-TA MOC shell degradation with 10 mM HCl restored a spindle-shaped, motile phenotype, highlighting the capacity of Micrometric Iron Men in the chemical manipulation of cellular metabolism, activities, and fate [18].

In addition to the Fe^{3+}-TA MOC system, other MOC types also showed controlled shell degradability, including MOC nanoshells composed of Fe^{3+}/gallic acid, Fe^{3+}/phytic acid, Fe^{3+}/benzene-1,3,5-tricarboxylic acid (BTC, trimesic acid), Fe^{3+}/benzenehexacarboxylic acid, Fe^{3+}/luteolin, Fe^{3+}/procyanidine, and Ca^{2+}/TA pairs [10–12, 15, 19–21, 35].

Moreover, post-functionalization of MOC shells—such as the incorporation of functional adlayers—has enabled programmable, target-specific in vivo degradation [19–21]. For instance, high-molecular-weight hyaluronan, which specifically binds to CD44 receptors overexpressed in inflammatory bowel disease lesions, was adsorbed onto the Fe^{3+}-procyanidine MOC shells nanoencapsulating probiotic *E. coli* Nissle 1917 (EcN). In addition to providing cytoprotection and enhancing targeted delivery, on-site shell degradation at the inflammation site—mediated by transferrin, which is highly accumulated in the inflammation site—further improved therapeutic efficacy, as demonstrated in a murine model of dextran sulfate sodium-induced acute colitis [21].

On the other hand, MOFs have attracted attention as crystalline, porous materials with functionalizable sites and large surface areas. In SCNE, the cytocompatible degradability of MOF-based nanoshells—particularly those constructed from zeolitic imidazolate frameworks (ZIFs)—has enabled the development of Micrometric Iron Men (Figure 2d). The earliest study demonstrated the formation of ZIF-8 nanoshells by simply mixing *S. cerevisiae* or *Micrococcus luteus* with zinc acetate and 2-methylimidazole in water, followed by EDTA-mediated shell degradation [22]. The same SCNE protocol was subsequently applied to β-galactosidase-adsorbed *S. cerevisiae* to enhance cell survivability in extreme oligotrophic cell media containing lactose along with lyticase or protease [31]. Through a combination of cytoprotection and lactose metabolism into D-glucose and D-galactose, the β-galactosidase/ZIF-8 shell increased the viability of Micrometric Iron Men to 89% after 48 h of incubation in the aforementioned oligotrophic medium, followed by 30 sec of UV-C exposure, compared with 5% survivability observed in naïve cells.

Controlled degradation of ZIF-based shells was also demonstrated for double-layered ZIF-8/ZIF-C shells encapsulating *S. cerevisiae*, with α-1-antitrypsin (AAT) embedded between the ZIF layers (Figure 2e) [32]. Upon EDTA treatment, the faster degradation of the outer ZIF-C layer enabled the controlled release of AAT, which protected the SCNEd cells from trypsin-induced lysis, while the inner ZIF-8 layer maintained cytoprotective integrity.

Furthermore, pre-synthesized MOF nanoparticles (NPs)—including ZIF-8 NPs (50 nm) and MIL-100(Fe) NPs (100 nm)—were employed to construct MOF shells via TA cross-linking in the SCNE of HeLa cells, with the shells degraded using EDTA. These Micrometric Iron Men were also referred to as SupraCells [23].

With respect to degradation cues, biological triggers—particularly endogenous enzymes localized at disease sites—offer a highly specific, site-responsive, and on-demand strategy for initiating the disassembly of Micrometric Iron Men shells. Most reported examples of enzyme-induced shell degradation involve polymeric shells, which are typically constructed through layer-by-layer (LbL) self-assembly [63, 64]. LbL shell pairs such as starch/alginate [26], lignosulfonate/cationic lignin [27], and chitosan/poly-L-glutamic acid [28] were selectively degraded by α-amylase, laccase, and chitosanase, respectively. In addition, gelatin-based LbL shells were assembled around HeLa cells and human mesenchymal stem cells, and crosslinked using a peptide cleavable by human matrix metalloproteinase-7, an enzyme overexpressed in tumor microenvironments, demonstrating the potential of Micrometric Iron Men for targeted cell therapy applications [29]. Furthermore, DNA-based shells—also referred to as DNA polymer cocoons—were employed in the construction of Micrometric Iron Men and selectively degraded by specific restriction endonucleases (*Eco*RI-HF, *Hin*dIII-HF, or *Pst*I-HF), depending on the encoded DNA sequences, for applications in cell encoding and decoding [30].

As another strategy for shell degradation, glutathione has also been utilized. For example, MnO_2 shells were constructed around *S. cerevisiae* via in situ formation of MnO_2 from $MnCl_2$ [24]. These robust shells exhibited superoxide dismutase- and catalase-like nanozyme activities, providing cytoprotection against reactive oxygen species, and underwent degradation upon exposure to glutathione. In another example, polymeric nanoshells crosslinked via disulfide bonds (S-S) demonstrated glutathione-mediated degradation in the construction of Micrometric Iron Men [25].

2.2 | Micrometric Transformers

"Micrometric Transformers" are a class of reconfigurable metacells equipped with adaptive shell architectures that are capable of undergoing structural or compositional transformations in response to environmental stimuli, offering enhanced versatility

in dynamic external environments (Figure 2f). This transformative behavior enables real-time modulation of shell properties such as permeability, composition, or functionality without requiring complete disassembly. Such adaptability allows for more precise control over cell-environment interactions, expanding the potential applications of metacells in biosensing, responsive therapeutics, and programmable cellular systems. However, it is also envisaged that a given reconfigurable metacell may function as either a Micrometric Iron Man or a Transformer, depending on the nature of the external stimulus.

Research on Micrometric Transformers is in its infancy. To date, a single proof-of-concept study has demonstrated the adaptive behavior of reconfigurable metacells [36]. Specifically, nanoshells composed of the Fe^{3+}-BTC MOC (described in Section 2.1) underwent a compositional transformation into Fe^{3+}-phosphate (Fe^{3+}-P) shells upon exposure to phosphate-containing media (Figure 2g). This transformation enabled the controlled release of biomolecules embedded within the shells, such as enzymes and antibodies, without compromising the viability of the SCNEd cells (Figure 2h). Importantly, the cytoprotective function of the shells was preserved, as demonstrated by their continued protection against external stressors such as lysticase and heavy metal ions (Cd^{2+} and Zn^{2+}).

3 | Loadability

Loadability is pivotal in the advancement from purely cytoprotective artificial spores to bioaugmented metacells endowed with diverse exogenous functions. For instance, it allows metacells to serve as living vehicles for targeted drug delivery, as bioreactors for localized chemical reactions within individual cells, or as biochemical signaling units that release bioactive compounds with precise spatiotemporal control. The incorporation of functional entities into nanoshells is facilitated by semipermeability-driven retention, surface anchoring sites, and covalent/noncovalent interactions (e.g., hydrogen bonding, electrostatic interactions, and hydrophobic effects) (Figure 3a). The loaded entities may function autonomously, integrate with cellular metabolic pathways, or be released in response to defined environmental cues.

pDA nanoshells have been extensively used for the incorporation of functional entities [59]. For example, photoactive indocyanine green (ICG) was co-deposited with pDA on genetically engineered *E. coli* BL21 cells that expressed melanin on their surfaces (Figure 3b) [37]. The combination of melanin, pDA, and ICG—all biocompatible photosensitizers—exhibited strong near-infrared (NIR) absorption at 808 nm, along with a significant synergistic enhancement in photoacoustic and photothermal conversion compared with shells composed of melanin alone or melanin/pDA. The natural propensity of *E. coli* BL21 to colonize the hypoxic and immunosuppressive tumor microenvironment enabled both photoacoustic imaging and photothermal therapy under monochromatic NIR irradiation.

In addition to co-deposition, functional entities—particularly amine-bearing molecules such as enzymes, antigens, antibodies, fluorescent dyes, and chitosan—have been loaded into pDA shells via post-functionalization strategies involving hydrogen bonding, π-π stacking, Michael addition, and Schiff base formation [38, 39, 41]. For instance, laccase was immobilized onto the pDA nanoshells of *Chlorella pyrenoidosa* and sandwiched with a TA layer (Figure 3c) [41]. Laccase embedded in the shell consumed oxygen (O_2), employing TA as a reductant, which generated a localized anaerobic environment and shifted cellular metabolism from O_2 to H_2 production. In another study, anti-programmed death-1 antibody and ovalbumin antigen were loaded onto the pDA nanoshells on EcN through co-deposition and post-functionalization, respectively (Figure 3d) [40].

The loadability of metacells can be coupled with their reconfigurability to enable on-demand payload release, as exemplified by the ZIF-8/ZIF-C system discussed in the previous section, in which AAT was loaded between the two ZIF layers via physisorption, followed by the controlled release upon EDTA treatment [32]. In other studies, Micrometric Iron Men were loaded with enzymes for catalytic activities or small-molecule drugs for probiotic therapy [33, 34]. For example, cytotoxic drugs, berberine and doxorubicin (DOX), were loaded into EcN@Fe^{3+}-TA by adsorption onto the shell without compromising the cell viability, and released in the intestine through acid-triggered shell disassembly, leading to enhanced alleviation of colonic inflammation and suppression of *Salmonella* infection (Figure 3e) [34]. The Fe^{3+}-BTC shell also possessed both reconfigurability and loadability by concomitantly encapsulating functional cargos during its formation and releasing them during its compositional transformation, exemplified by the loading and release of lysozyme and anti-CD3/anti-CD28 antibodies, which, respectively, killed co-cultured *E. coli* and stimulated Jurkat cells for interleukin-2 secretion [36].

Furthermore, the concept of extracellular artificial organelles (exorganelles) was introduced in the context of loadability (Figure 3f) [42]. Multilayers of liposomes, loaded with enzymes, magnetic NPs (MNPs), or fluorescent dyes, were assembled on the cell surface, serving as functional add-ons to expand cellular capabilities.

4 | Motility

Motility in metacells refers to the capacity of shell-powered, autonomous or guided movement that surpasses Brownian motion and normal diffusion, characterized by directional locomotion in response to environmental cues. In most motility examples, loadability was also featured through the integration of operational entities, such as NPs and enzymes, as a primary approach to impart motility to cells, although the shell itself (e.g., TiO_2 NP shell), in principle, can serve as a movement-inducing component. Driven by external fields, light, or (bio) chemical reactions, motile metacells have demonstrated their potential in biomedical applications, including targeted drug delivery and active biotherapy.

Motile metacells are classified into symmetric and asymmetric (i.e., Janus) types, corresponding to full and partial shells, respectively (Figure 4a). Directional movement generally requires at least one source of asymmetry, such as anisotropic environmental cues (e.g., magnetic field, light irradiation, or chemical gradients), an uneven shell distribution, or a combination of both, to generate an asymmetric force distribution acting on the metacells.

Earliest examples in motility include the use of MNPs to direct cell migration via external magnetic fields.

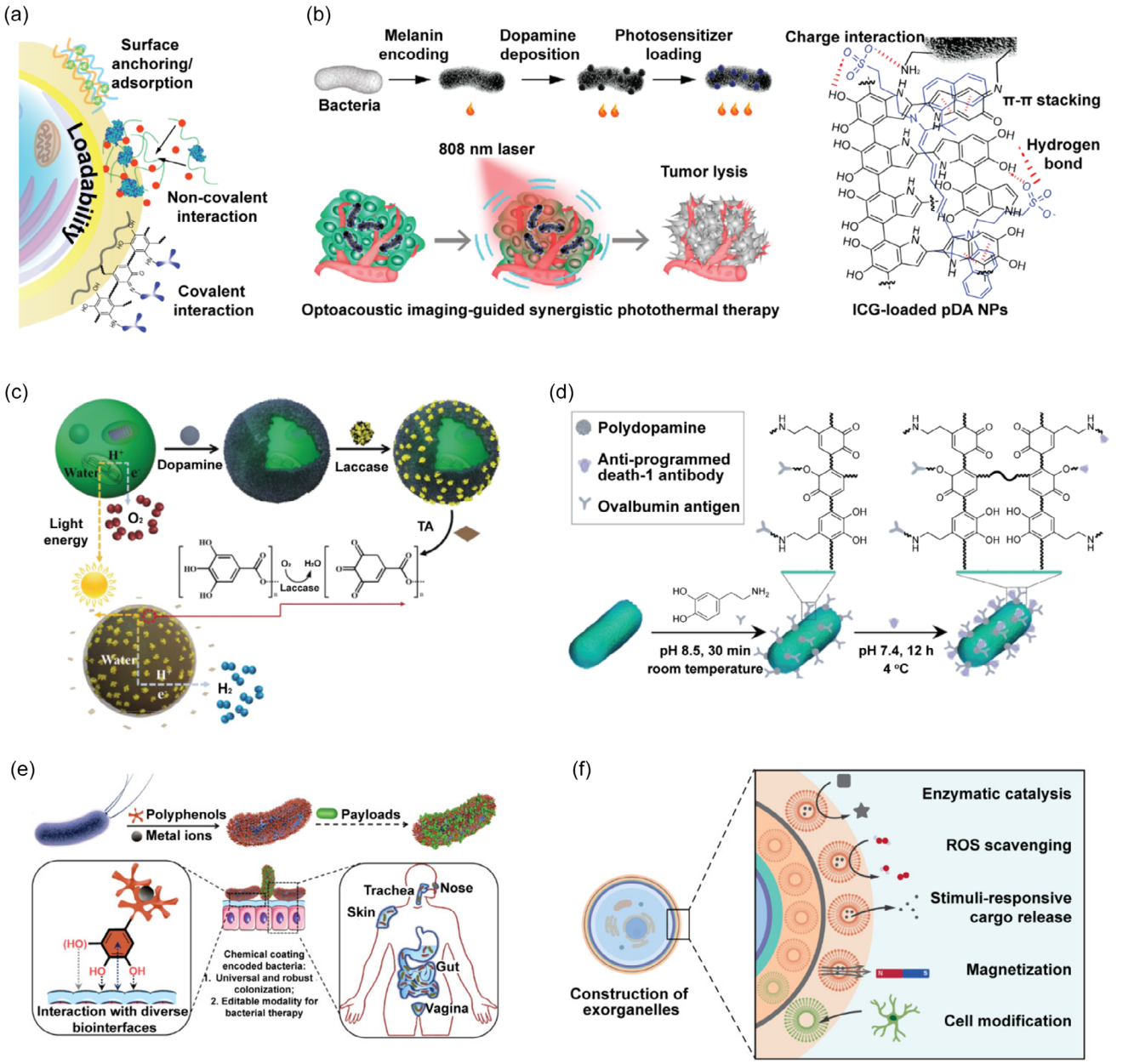

FIGURE 3 | (a) Strategic examples of metacell loadability. (b) SCNE of genetically engineered, melanin-expressing *E. coli* BL21 via co-deposition of pDA NPs and ICG for construction of photosensitive bacteria with enhanced optoacoustic imaging and photothermal therapy. Reproduced from Ref [37]. Copyright (2023) with permission from American Chemical Society. (c) Formation of laccase-loaded pDA nanoshells on *C. pyrenoidosa* for H_2 production under aerobic conditions. Reproduced from Ref [41]. Copyright (2019) with permission from Wiley-VCH. (d) Schematic for the formation of pDA-SCNEd EcN cells loaded with antigens and antibodies for immunotherapy. Reproduced from Ref [40]. Copyright (2022) with permission from Wiley-VCH. (e) Construction of loadable Fe^{3+}-TA-MOC-SCNEd EcN for probiotic therapy. Reproduced from Ref [34]. Copyright (2023) with permission from Elsevier. (f) Exorganelle formation on cell surfaces for incorporation of functional entities. Reproduced from Ref [42]. Copyright (2025) with permission from Wiley-VCH.

Poly(diallyldimethylammonium chloride)-functionalized MNPs were deposited onto *S. cerevisiae*, followed by bioinspired SiO_2 formation to form MNP-incorporated SiO_2 shells (Figure 4b) [43]. The SCNEd cells migrated toward a permanent magnet in response to a magnetic field gradient. Their migration velocity could be modulated by adjusting either the number of deposited MNP/SiO_2 layers or the strength of the external magnetic field. In pseudo-uniform magnetic fields, the magnetized cells functioned as biohybrid magnets and self-assembled into one-dimensional linear structures, which hold potential in cell patterning and tissue engineering.

In another study, light-responsive mobile metacells were constructed by incorporating photocatalytic TiO_2 NPs into the nanoshells, enabling control over the cell's swarming and phototactic behaviors under UV irradiation (Figure 4c) [48]. Aldehyde-functionalized TiO_2 NPs (TiO_2-CHO) were conjugated to the *S. cerevisiae* surface via Schiff base reactions, and subsequent Fe^{3+} adsorption facilitated the formation of a conductive

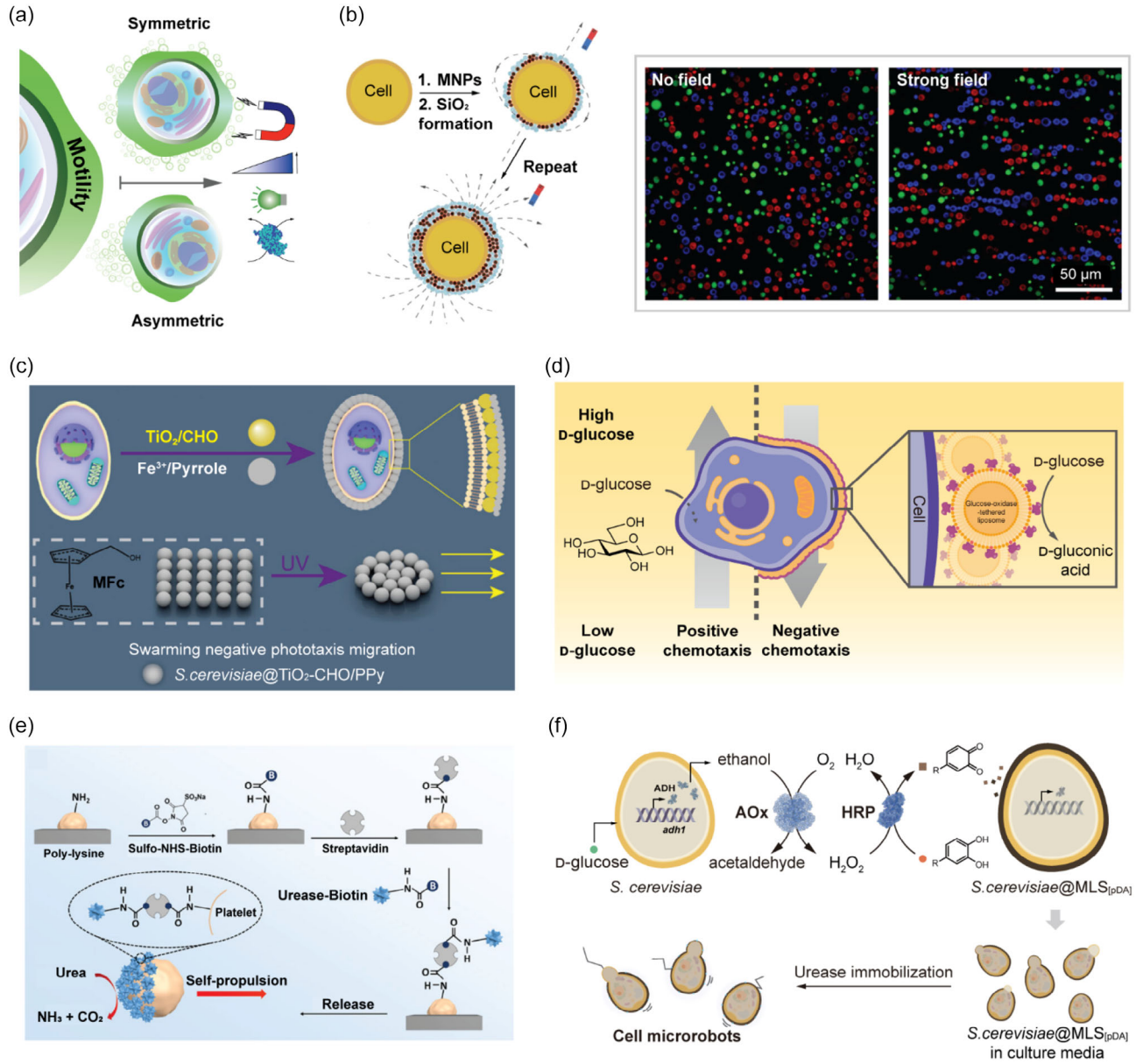

FIGURE 4 | (a) Symmetric or asymmetric structures of motile cell-in-shell metacells. (b) (left) Schematic for SCNE of *S. cerevisiae* within MNP/SiO_2 nanoshells and (right) confocal laser-scanning microscope images of (green) naïve *S. cerevisiae* and (red and blue) MNP/SiO_2-SCNEd *S. cerevisiae* without and with a magnetic field. Reproduced from Ref [43]. Copyright (2016) with permission from Springer Nature. (c) Illustration of *S.cerevisiae*@TiO_2-CHO/PPy formation and movement behavior under UV irradiation. Reproduced from Ref [48]. Copyright (2023) with permission from American Chemical Society. (d) Chemotactic behavior of Jurkat cells SCNEd with glucose-oxidase-tethered liposomes in D-glucose gradients. Reproduced from Ref [44]. Copyright (2023) with permission from Wiley-VCH. (e) Construction of Janus-type platelets, functionalized with urease for active, self-propelled cell movements. Reproduced from Ref [65]. Copyright (2020) with permission from American Association for the Advancement of Science. (f) Chemo-metabolically coupled SCNE for pDA shell formation and construction of cell microrobots with asymmetric urease immobilization. melanin-like species (MLS). Reproduced from Ref [47]. Copyright (2025) with permission from American Association for the Advancement of Science.

PPy layer, yielding *S.cerevisiae*@TiO_2-CHO/PPy. The PPy layer improved the photocatalytic activity of TiO_2 NPs by suppressing the recombination of photogenerated electron–hole pairs. Upon UV irradiation of SCNEd cells suspended in a ferrocene methanol (MFc) solution, TiO_2-mediated photocatalytic reactions generated MFc^+ and MFc species on the illuminated and unilluminated sides of the cells, respectively. This process induced a local electric field across the cell surface, driving negative phototactic movement accompanied by cellular aggregation.

In addition to external field actuation and light-driven motility, motile metacells have also been constructed to achieve self-propulsion through enzymatic reactions. Jurkat cells encapsulated with glucose oxidase-tethered liposomes exhibited reversed migratory behavior, shifting from innate positive to negative chemotaxis in D-glucose gradients (Figure 4d) [44]. Despite the symmetric shell architecture, the enzymatic reaction likely generated a locally asymmetric ionic distribution, inducing an electric field near the cell surface that guided cell movement.

On the other hand, the construction of anisotropic (i.e., asymmetric) nanoshells with spatially localized enzymes enables efficient directional propulsion of cells by introducing intrinsic asymmetry in the driving forces. To this end, a few strategies have been developed to fabricate anisotropic nanoshells, most commonly involving partial masking of the cells followed by selective functionalization of the exposed surfaces. For example, Janus-type nanoshells were formed on *S. cerevisiae* by immobilizing the cells on a glass slide, followed by visible light-induced polymerization of poly(ethylene glycol) diacrylate on the unbound side [45]. After cell detachment, the resulting polymeric shells were functionalized with urease, yielding asymmetric urease distribution. In this system, urease catalyzed the decomposition of urea into carbon dioxide (CO_2) and ammonia (NH_3), generating a chemical gradient that drove directional metacell movement. A similar approach was applied to platelets adsorbed onto a poly-L-lysine-modified substrate, where urease was conjugated to the exposed side via sequential treatment of sulfo-*N*-hydroxysuccinimide (NHS)-biotin, streptavidin, and biotinylated urease (Figure 4e) [65]. Noticeably, Janus-typed platelets loaded with DOX showed accelerated binding to breast cancer cells (MDA-MB-231) due to their endowed motility, resulting in the increased local DOX concentration and improved therapeutic efficacy. The same synthetic protocol was extended to neutrophils for targeted thrombolytic drug delivery [66]. Urokinase-coupled silver NPs—inducing thrombolysis—were internalized into asymmetrically urease-functionalized neutrophils, where urease-driven self-propulsion enhanced inflammatory site targeting.

Alternative strategies for constructing anisotropic metacells have leveraged cell-intrinsic anisotropy generated during proliferation. *S. cerevisiae* or *Schizosaccharomyces pombe* cells were coated with aldehyde-functionalized mesoporous SiO_2 NPs onto which urease was immobilized, and subsequent incubation in growth media led to the asymmetric distribution of the SiO_2 shells and associated urease [46]. In a distinct approach, chemo-metabolic coupling was employed to fabricate asymmetric shells (Figure 4f) [47]. Specifically, alcohol fermentation by *S. cerevisiae* was coupled with enzymatic reactions of alcohol oxidase (AOx) and horseradish peroxidase (HRP) to drive the in situ formation of pDA shells. Concurrent cell growth and shell formation under culture conditions produced anisotropic pDA nanoshell structures, which were subsequently functionalized with urease.

5 | Summary and Outlook

This Concept report defines metacells as next-generation artificial cell-in-shell constructs within the field of SCNE, distinguished by three fundamental and essential features: reconfigurability, loadability, and motility. These attributes endow metacells with adaptive, interactive, and dynamic responses to a wide range of environmental stimuli. As demonstrated in previous studies, these functional hallmarks are not mutually exclusive but can be integrated synergistically to enhance the functionality of individual living cells in both in vitro and in vivo settings. Accordingly, several metacell examples discussed in this report span the domains of reconfigurability, loadability, and motility. In many instances, reconfigurability serves as a foundational feature, with loadability enabling motility to facilitate multifunctional behavior. Looking ahead, it is also anticipated that additional functional traits of metacells will emerge, driven by ongoing scientific innovation and creative exploration.

Despite early progress, the field has substantial room for advancement. In the context of reconfigurability, systems such as Micrometric Iron Men and Transformers are expected to evolve beyond single or irreversible transformations—including shell degradation—toward reversible or multi-configurational switching. Such developments would enable metacells to dynamically modulate shell composition and properties in response to periodic, fluctuating, or simultaneous stimuli over time, functioning as "Micrometric Morphonauts"—a term we introduce to describe metacells capable of reversible, stimulus-responsive transformations and active environmental adaptation. The multi-configurational adaptability would allow metacells to toggle between distinct functional states—such as protective, communicative, or motile modes—based on environmental context, thereby enhancing both cellular survivability and functional versatility. Loadability could be further improved through advances in materials and SCNE strategies, enabling the compartmentalization of diverse functional entities across multiple layers of the nanoshell. In terms of motility, current strategies for constructing Janus-type metacells remain limited to a narrow range of cell types—such as adherent mammalian cells and yeast—and rely on a restricted set of catalytic systems for generating propulsion forces. To broaden applicability, future approaches should aim to accommodate a wider spectrum of cell types and harness diverse self-propulsion mechanisms that are compatible with various biochemical fuels and environmental conditions.

Another major leap in metacell research centers on the concept of "autonomy", wherein individual cells sense and respond to external conditions from the point of shell formation, even when incorporating externally introduced materials. The creation of autonomous, self-regulating metacells represents a paradigm shift—from passive recipients of researcher-directed materials to active, self-driven units capable of assembling and disassembling their own nanoshells, determining shell configurations, and fueling their own movements using self-produced signals. A key starting point for this direction involves the chemical coupling of cellular metabolism with externally provided reactions during in vitro shell formation, enabling the integration of shell assembly with loadability and reconfigurability of the shell materials. This advancement holds considerable promise not only for practical applications, as outlined in this report, but also for fundamental scientific inquiry. For instance, beyond contributing to single-cell biology, studies of the collective and interactive behaviors of homogeneous or heterogeneous metacell populations are expected to yield critical insights into the spatial and temporal transmission of information between cells, including phenomena such as quorum sensing.

On the other hand, comprehensive biosafety evaluation remains essential for the safe clinical and environmental deployment of metacells across biomedical, environmental, and biotechnological applications. The shell materials used in metacells—including MOCs, polymers, and nanomaterials—must be carefully selected to minimize immunogenicity and inflammatory responses. Although many metacell components have demonstrated low intrinsic toxicity in preclinical studies, factors

such as material composition, shell thickness, surface chemistry, and degradation products can influence immune recognition and clearance. Long-term studies examining biodistribution, circulation kinetics, immunological responses, and potential accumulation in organs and tissues are necessary to fully assess the safety profile of metacells for clinical applications. From an environmental perspective, metacells may offer potential safety advantages over GMOs, which can pose risks associated with genetic material leakage, horizontal gene transfer, unintended mutations, and ecological disruption. In contrast, metacells are produced through chemical or materials-based SCNE processes without direct genetic modification, thereby avoiding concerns related to genetic instability. However, containment strategies remain necessary, particularly when metacells carry functional cells with biological activity. Appropriate safeguards—including controlled degradation mechanisms, biocontainment shells, and environmental monitoring—should be developed to prevent unintended release and mitigate ecological risks.

Overall, as the SCNE field continues to develop, metacells have the potential to become a versatile platform at the intersection of materials science, synthetic biology, and cellular engineering. Their capacity to integrate dynamic functionality, programmable behavior, and environmental responsiveness presents promising opportunities for both fundamental studies and prospective applications. Continued progress in metacell research will likely depend on interdisciplinary efforts that merge molecular design, system-level control, biochemical logic, and biosafety assessment. With further advancements, metacells may eventually be engineered to perform autonomous functions such as sensing, decision-making, and self-actuation, contributing to future developments in therapeutic delivery, synthetic multicellularity, and nanobiohybrid technologies.

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Conflicts of Interest

The authors declare no conflicts of interest.

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