

PERSPECTIVE ARTICLE

Synthetic cells: Potential benefits and risks of interactions with commensal and pathogenic microorganisms

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Abstract

Synthetic cells are shifting biology from the observation and modification of existing life toward the deliberate construction of cell-like systems. The term, however, includes two biologically different entities: bottom-up protocells assembled from nonliving molecular components and top-down cells whose natural genomes have been minimized, rewritten, or replaced. These two classes occupy the extremes of a much broader landscape of engineered living systems, one that also includes conventional bacteria, yeasts, and mammalian and immune cells carrying synthetic gene circuits, logic programs, and redesigned metabolic pathways. This Perspective is deliberately centered on the two extremes, because they bracket the range of biological autonomy and pose the sharpest contrast between a programmable chemical package and a self-replicating organism; the wider landscape is noted and is drawn upon throughout wherever it bears directly on interaction with microbial communities. Both approaches can clarify the minimum requirements for cellular organization, test hypotheses about the origin and evolution of life, expand biological chemistry, and support programmable sensing or therapy. Their most consequential future setting may not be an isolated laboratory vessel but a microbial ecosystem. Synthetic cells could detect pathogens, intercept virulence signals, deliver antimicrobials locally, support commensal organisms, or restore metabolic functions lost from a disturbed microbiome. The same capacity for molecular communication could also disrupt commensal networks, impose new selective pressures, transfer genetic information, provide exploitable metabolites, or behave unpredictably in complex communities. Because the deep architecture of life—an informational core, a bioenergetic engine, and a membrane-bounded interface under selection—is broadly conserved and governed by conformational matching, engineered constructs will be interpreted through the same molecular languages that natural organisms use to recognize nutrients, competitors, hosts, and threats. It is proposed that synthetic-cell safety should therefore be evaluated relationally: not only by what an engineered cell does alone, but by how natural microorganisms recognize, use, resist, modify, or reorganize around it. Throughout this Perspective, interactions are described as desired or unwanted relative to an explicitly stated design intention, rather than as beneficial or negative, because the same molecular event may be desirable in one ecological and clinical context and unwanted in another. The central

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challenge is to engineer compatibility where benefit is intended while preserving strong limits on persistence, evolution, and ecological reach.

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1. Introduction: Constructing rather than merely observing life

Synthetic cells represent a conceptual transition in biology. Instead of asking only how natural cells work, investigators can now ask which components are sufficient to produce selected cellular properties and whether those properties can be assembled in a controlled sequence. In the bottom-up approach, membranes, nucleic acids, proteins, metabolites, and cell-free expression systems are combined to create cell-like compartments. In the top-down approach, an existing organism is simplified or supplied with a chemically synthesized genome. These approaches overlap in purpose but not in biological status, autonomy, or risk.^{1,2}

These two categories, however, do not exhaust what the field calls a synthetic cell. Over the past two decades, the dominant paradigm in synthetic biology has arguably been neither protocell assembly nor genome minimization, but the construction of synthetic gene circuits within otherwise conventional cells. The genetic toggle switch³ and the repressilator⁴ established that natural transcriptional regulators could be composed into bistable and oscillatory devices with designed behavior, and that cellular engineering could proceed by circuit design rather than by reconstruction of the chassis. From that foundation have come bacteria carrying diagnostic and therapeutic circuits,⁵ including engineered *Escherichia coli* Nissle strains developed as live biotherapeutics for inherited metabolic disease,⁶ mammalian cells carrying logic circuits and metabolite-responsive controllers,⁷ synthetic receptors such as synNotch that equip a cell with a designed sensing-and-response program,⁸ CAR-T and related immune cells incorporating combinatorial antigen-sensing circuits,⁹ and yeast chassis carrying redesigned metabolic pathways.¹⁰ None of these systems has a minimized or chemically synthesized genome, yet all are unambiguously engineered cells, and many are already deployed within or alongside living microbial communities.

The scope of this article is therefore stated explicitly at the outset. The analysis that follows is centered on bottom-up protocells and on top-down minimal-genome

or genome-synthesized bacteria. Circuit-carrying bacterial, fungal, and mammalian cells are treated not as a separate subject but as the intermediate and, at present, most clinically advanced region of the same landscape (Table 1), and they are brought into the argument wherever they supply evidence about communication with microbes, containment, or ecological consequence. The relational argument developed here is intended to apply across that entire landscape, and the framework proposed in the penultimate section is formulated accordingly.

The distinction matters. Most present-day bottom-up synthetic cells do not reproduce indefinitely and are better understood as programmable biochemical systems enclosed by a boundary. In contrast, a genome-designed bacterium is alive, self-replicating, mutable, and capable—at least in principle—of ecological and evolutionary participation. The first cell controlled by a chemically synthesized genome demonstrated that a designed chromosome could direct cellular reproduction.¹¹ Subsequent construction of JCVI-syn3.0 produced a self-replicating cell with 473 genes, yet 149 of those genes initially lacked a defined function. The result simultaneously advanced minimal-cell science and exposed the depth of our remaining uncertainty.¹²

This uncertainty should not diminish the field; it should define its intellectual discipline. A synthetic cell is not simply a miniature machine placed into an inert environment.¹³ If introduced into the body, soil, water, or a bioreactor, it enters a living community whose members exchange metabolites, signals, toxins, vesicles, and genetic material. The behavior that matters will emerge from these relationships.

2. What synthetic cells may reveal

Minimal genomes provide an experimental route toward identifying functions required for cellular continuity. Yet there is unlikely to be one universal minimum genome: essentiality depends on nutrients, physical conditions, neighboring organisms, and the functions supplied by the environment. A gene dispensable in a nutrient-rich monoculture may become essential during competition, stress, or colonization. Synthetic cells therefore reveal not only a core of life but also the dependence of life on context.

Table 1. The landscape of synthetic and engineered cells, and the relational question each class raises

Class of engineered cell	Biological status	Representative examples	Principal relational question
Bottom-up protocells and artificial cells	Assembled from nonliving components; no genome of its own beyond supplied templates; does not reproduce indefinitely	Vesicle bioreactors; two-way chemical communication with bacteria; chemically defined replicating synthetic cell	What does a transient chemical influence do to community signaling, and what do its degradation products feed?
Bacteria carrying synthetic gene circuits	Conventional genome plus engineered regulatory modules; fully self-replicating	Toggle switch; repressilator; engineered <i>E. coli</i> Nissle live biotherapeutics	Can it colonize and compete, and can the circuit move horizontally into resident organisms?
Engineered eukaryotic cells (yeast, mammalian, immune)	Conventional genome plus engineered receptors, logic, or metabolic pathways; self-replicating within host constraints	synNotch; CAR-T with combinatorial antigen sensing; quorum-quenching designer cells; artemisinic acid yeast	How is its behaviour conditioned by the microbiota and immune tone around it, and what contains it?
Minimal-genome cells	Natural genome reduced toward a near-essential set; self-replicating	JCVI-syn3.0	Which of its dispensable genes become essential in a community, and which lost functions can be re-acquired?
Synthetic- and recoded-genome organisms	Chemically synthesized or codon-recoded genome; self-replicating	Synthetic <i>Mycoplasma</i> ; recoded <i>E. coli</i>	How far does reduced genetic compatibility actually restrict exchange, given that recoding is a partial firewall?

Notes: Classes of engineered cellular system are arranged by increasing biological autonomy, from a nonreplicating protocell to a self-replicating organism carrying a synthesized or recoded genome. The two classes on which this Perspective is centered are the first and the last two; the intermediate classes, which carry most present clinical experience, are drawn upon throughout. The rightmost column states the question this article argues should be asked first in each case. Risk is not a property of a row on its own: it emerges from the pairing of a row with the community the construct enters, which is why two constructs that are identical by conventional classification may differ in relational risk.

Bottom-up systems complement this work by reducing biological complexity without requiring a self-replicating organism. Encapsulated cell-free transcription and translation can generate proteins within lipid vesicles, allowing investigators to isolate relationships among information, metabolism, membrane transport, and spatial organization.¹⁴ Such systems can model possible steps in early cellular evolution while permitting quantitative control that is difficult to achieve in a natural cell. The same reductionist logic underlies circuit engineering in a living chassis, where a defined regulatory module is placed within a complex cellular background. In both cases the module's measured behavior proves to depend on the context surrounding it, and that dependence becomes decisive once the surrounding context is a microbial community rather than a culture vessel.

Genome synthesis also enables recoding. A four-million-base-pair *Escherichia coli* genome has been rewritten to use a reduced set of synonymous codons, demonstrating that large-scale changes to the genetic code can remain compatible with cellular life.¹⁵ Recoding may create space for noncanonical amino acids and proteins with new chemical properties. It may also support biological containment by reducing compatibility with natural gene exchange, although no recoding strategy should be assumed to provide an absolute firewall. Together, these approaches make biology more

experimentally constructive. They allow hypotheses about life's requirements, evolutionary transitions, biochemical communication, and organizational stability to be tested by assembly. Importantly, however, a system that is predictable in isolation may cease to be predictable when surrounded by evolving microorganisms.

3. Organizational continuity, chirality, and immune recognition

Two recent developments further illuminate synthetic cells as organized biological systems rather than isolated engineered objects. Gaut and colleagues¹⁶ described a chemically defined synthetic cell, assembled from nonliving components, that completes a cell cycle involving genome replication, growth, resource acquisition, division, and selection. This result suggests that the coupling of organizational continuity with heritable variation is a general property of self-replicating, selectable systems, rather than a feature unique to naturally evolved cells.¹³ This principle can be considered alongside the near-universal biological use of L-amino acids and D-sugars as a shared stereochemical framework for molecular recognition and compatibility. Ozturk and Sassellov¹⁷ proposed that homochirality propagated outward from nucleic acids through a coupled prebiotic chemical network, linking the handedness of informational polymers to the broader chemistry of life.

Chirality should not, however, be read as existing to permit recognition. The near-universal use of a single enantiomeric series is better understood as a contingency fixed early in the history of life and maintained since, with stereospecific recognition following as a consequence rather than as a purpose: because enzymes, receptors, and immune molecules are themselves built from chiral monomers and act upon chiral substrates, molecular discrimination in extant organisms is stereochemically constrained whether or not that constraint confers any advantage. What matters for synthetic-cell design is the empirical constraint itself, not a function attributed to it.

The risks anticipated for hypothetical mirror life underscore how functionally consequential this shared framework may be. Adamala and colleagues¹⁸ warned that self-replicating organisms constructed from opposite-handed biomolecules could evade many established mechanisms of immune recognition and ecological control. Although this assessment is prospective rather than experimental evidence that mirrors organisms evading immunity, it supports a broader organizational interpretation: chirality supplies a conserved molecular substrate for compatibility, immunity monitors and regulates compatible relationships across biological levels, and synthetic minimal cells demonstrate how continuity and adaptive change can emerge together. Synthetic-cell design should therefore consider not only engineered function, but also whether its molecular language remains recognizable to host defenses and microbial communities.

4. Synthetic cells as participants in microbial communication

Microorganisms sharing an environment do not merely coexist; they sense and modify one another. Quorum-sensing molecules coordinate population-dependent behaviors that can include biofilm formation, secretion, motility, competition, and virulence.¹⁹ Metabolic cross-feeding allows one species to survive on another's products. Bacteriocins, acids, reactive molecules, extracellular vesicles, and phages alter community structure. A synthetic cell placed in this environment may become a sender, receiver, competitor, substrate, decoy, or refuge. This possibility has already moved beyond theory. Artificial cells have been engineered to translate chemical messages and direct *E. coli* behavior, demonstrating functional communication between a nonliving cell-like system and living bacteria.²⁰ Other liposome-based artificial cells have sensed a bacterial signal and produced a bactericidal response against *E. coli*.²¹ These studies establish a central principle: synthetic and natural cells can share enough of a biochemical language to influence one another.

That common language creates therapeutic opportunity, but it also removes the comforting assumption that nonreplicating means biologically irrelevant. Even a short-lived vesicle can alter microbial decisions if it releases the right signal at the right concentration and time. Conversely, a living microbe may degrade, sequester, activate, or repurpose material released by a synthetic cell. Interaction, rather than replication alone, is therefore the correct starting point for assessing consequence.

5. Engineered living cells as partners and antagonists of microbial communities

The claim that safety is relational is not confined to protocells and minimal-genome bacteria, and the strongest present evidence for it comes from engineered cells lying between those extremes. Human designer cells carrying synthetic gene circuits have been built to eavesdrop on bacterial quorum-sensing signals and to answer them. A mammalian cell equipped with a bacterial autoinducer receptor, coupled through a synthetic signaling cascade to an output module, can detect *Pseudomonas aeruginosa* communication and release a quorum-quenching lactonase or an antimicrobial peptide in closed loop, reducing biofilm formation in animal models.^{22,23} Such systems are neither minimal nor synthetic in genome, yet they perform precisely the sense-and-correct function proposed below for bottom-up synthetic cells, and they perform it while embedded in host tissue alongside a microbial community.

Engineered eukaryotic cells raise the same relational questions in a different register. A CAR-T or synNotch-equipped immune cell is deployed into a body that contains a microbiome, an immune system shaped by that microbiome, and frequently an active infection; its behavior is conditioned by microbial metabolites, inflammatory tone, and antibiotic exposure in ways that characterization in culture does not capture.⁷⁻⁹ Engineered bacteria intended as live biotherapeutics face the mirror-image problem, since they must colonize, compete, and persist for a defined interval within an existing community before being cleared.^{5,6} Across all of these platforms, the operative questions are the same ones this Perspective puts to protocells and minimal cells: which organisms can recognize or modify the engineered function, what resources does the construct consume or release, and what community state remains once it is gone.

6. Potentially desired interactions with commensal microbes

Importantly, a healthy microbiome is not a fixed list of commensal species. It is a dynamic community whose functions depend on location, diet, host physiology,

immune state, and relationships among organisms. Here too I speculate that synthetic cells could support this community without attempting to replace it.

First, nonreplicating synthetic cells could provide missing metabolites or enzymes locally. In a dysbiotic intestine, for example, they might release a defined nutrient, consume an inflammatory metabolite, or restore a biochemical conversion normally supplied by diminished commensals. Because the platform can be designed to decay, it may offer more temporal control than permanent colonization by a living engineered strain. Engineered living bacteria pursue the same objective by a different route, and the comparison is instructive: a live biotherapeutic colonizes and produces continuously, whereas a nonreplicating synthetic cell delivers a bounded dose and then decays, trading potency and duration for predictability of exit.^{5,6}

Second, synthetic cells could act as communication buffers. They might absorb excessive quorum signals, inflammatory microbial products, or toxins while leaving the producing organism intact. Alternatively, they could deliver signals that favor colonization resistance, mucosal repair, or cooperative metabolism among commensal organisms. Such interventions would aim to restore community function rather than indiscriminately eliminate microbes.

Third, synthetic cells could serve as protected microreactors. Encapsulation may separate a potent enzymatic reaction from host tissue while allowing selected substrates and products to cross the membrane. This could support commensal microbes indirectly by reshaping the local chemical environment.

Finally, synthetic cells could become diagnostic partners. Systems that detect combinations of microbial metabolites rather than a single species may report the functional state of a community. A synthetic-cell sensor could theoretically couple detection to a restrained local response, creating a sense-and-correct platform. The advantage would be specificity; the danger would be overconfidence in a circuit tested outside the full ecosystem.

7. Potentially desired interactions with pathogens

The most immediate antimicrobial application is targeted detection and response. Synthetic cells can be programmed to recognize pathogen-associated signals and release an antimicrobial peptide, enzyme, small molecule, or phage-derived component at the site where the signal is detected. The work of Ding and colleagues provides proof of principle that artificial cells can sense and kill bacteria under laboratory conditions.²¹

A second strategy is signal interception. Many pathogens coordinate virulence and biofilm formation through quorum sensing. Synthetic cells could function as decoys that bind autoinducers, enzymatically destroy them, or emit misleading signals. This could reduce pathogenic organization without imposing the same direct lethal pressure as a conventional antibiotic. It may therefore be particularly valuable against biofilms or antibiotic-resistant infections, although resistance to signal interference can also evolve. This strategy has already been realized in a living engineered chassis: mammalian designer cells that intercept *P. aeruginosa* autoinducers and answer them with quorum-quenching enzymes suppress biofilm formation *in vivo*,^{22,23} which establishes the principle independently of the platform used to implement it and provides a benchmark against which a protocell-based decoy should be judged.

A third possibility is ecological reinforcement. Instead of attacking a pathogen directly, synthetic cells could strengthen commensal competitors by providing a selective nutrient, enhancing production of protective metabolites, or removing a resource disproportionately required by the pathogen. This approach treats infection as a disturbed relationship within an ecosystem rather than solely as the presence of an unwanted organism.

Synthetic cells may also improve drug delivery by concentrating treatment where microbial signals are present. Local activation could lower systemic exposure and preserve organisms outside the diseased niche. The therapeutic ideal is not maximal antimicrobial force, but sufficient, spatially restricted correction followed by disappearance of the engineered system.

8. Unwanted interactions and unintended consequences

The same properties that enable desired communication can produce harm. A synthetic cell designed to suppress a pathogen's quorum signal might also disrupt signaling used by commensal organisms. Because chemically related signals can cross species boundaries, apparent specificity in a simplified assay may not persist in a polymicrobial community. Synthetic cells may also alter nutrient competition. Consumption of oxygen, iron, carbon sources, or vitamins could suppress commensal organisms or open a niche for an opportunistic pathogen. Conversely, breakdown products from the synthetic system could become nutrients for organisms that were not intended targets. A therapeutic platform might therefore select for a new community state even after the platform itself disappears.

Direct antimicrobial action creates selective pressure. Repeated or incomplete exposure could enrich resistant

variants, favor biofilm phenotypes, or shift the community toward organisms intrinsically insensitive to the released agent. Signal-disruption strategies may reduce but do not eliminate evolutionary selection. Additionally, for genome-designed, replicating cells, the concerns are broader. Mutation can change sensing thresholds, production rates, host range, or containment functions. Horizontal gene transfer could move engineered DNA into natural microorganisms, while natural mobile elements could enter the synthetic cell and restore functions intentionally removed. Genomic recoding and synthetic auxotrophy can reduce compatibility or environmental independence, but biological containment should be layered rather than entrusted to one genetic mechanism.^{24,25}

Containment should not, however, be discussed as though it were a property peculiar to minimized or recoded genomes. Most tested biocontainment strategies have in fact been built into ordinary engineered cells. Synthetic auxotrophy for a nonstandard amino acid, engineered dependence of essential proteins on that amino acid, and circuit-based kill switches such as the Deadman and Passcode designs, which couple survival to the continuous presence of an external signal or to a defined environmental password, all operate in conventional chassis.^{24–26} Measured escape frequencies in these systems are low but finite, and each mechanism fails in a characteristic way—by mutation of the switch, by environmental cross-feeding of the required metabolite, or by loss of the construct. That pattern of failure, rather than genome size, is the practical argument for layering independent containment mechanisms.

Evolution acts on the community as well as on the construct. Directed-evolution experiments performed on whole microbial consortia show that community-level function can be selected and shifted over comparatively few generations, and that the states reached depend on how and when selection is applied.²⁷ A synthetic cell introduced repeatedly into a microbiome constitutes a recurring selective event of precisely this kind, whether or not it replicates. Its evolutionary footprint should therefore be assessed at the level of the community it perturbs and not only at the level of its own genome, and the informative measurement is whether community composition and function return to baseline after withdrawal.

Host biology introduces another level of uncertainty. Lipids, nucleic acids, and proteins from synthetic cells may activate complement, innate immune receptors, coagulation, or inflammatory pathways. Microbial modification of the synthetic membrane could expose new molecular patterns. Equally, a system intended to reduce

microbial inflammation might remove signals required for immune education or barrier maintenance.¹³ Finally, ecosystem effects may be delayed. A synthetic cell need not persist to leave a persistent consequence; a transient change in resource availability, signaling, or selective pressure may reorganize a community into a new stable state. Safety assessment must therefore extend beyond immediate toxicity and short-term recovery.

9. The biological architecture and why it bears on safety

This section states the organizational premise on which the relational framework rests. If engineered constructs are to be interpreted by natural organisms through a shared molecular language, that language must itself be conserved. What follows sets out the basis for that conservation and, more importantly for the present argument, the three safety consequences that follow from it; the wider theoretical development is given elsewhere and is not repeated here.^{28,29}

The biological architecture of life appears intrinsically stable across evolutionary time. From prokaryotes to eukaryotic cells and multicellular organisms, the same scaffolding—nucleic acid information storage, a shared biochemical repertoire, and stereospecific protein interaction—is retained rather than replaced, so that vertical evolution stabilizes long-lasting configurations along a thermodynamic flow rather than inventing successive, unrelated designs (Table 2).²⁸ The evidence lies in the demonstrable shareability of biological informational components across levels of complexity: horizontal gene transfer, viral integration and molecular mimicry, extracellular-vesicle and tunneling-nanotube trafficking of nucleic acids, and intercellular mitochondrial transfer all show genetic material moving routinely between viruses, bacteria, and eukaryotes, retained wherever conformational matching permits energetic and morphological compatibility with the recipient system.^{28,29}

Synthetic biology supplies some of the clearest experimental demonstrations of this shareability. The bacterial tetracycline repressor, an element whose native role is the regulation of antibiotic resistance in bacteria, has become one of the standard tools of eukaryotic gene control, functioning in yeast, in mammalian cells, and in whole animals once fused to eukaryotic effector domains³⁰; negative autoregulation constructed from that same bacterial component linearizes the dose–response and suppresses expression noise in yeast.³¹ A regulatory part thus carries its function across a domain boundary essentially intact. This is at once the practical basis

of chassis-independent circuit design and the reason engineered parts cannot be assumed to remain confined to the organism for which they were designed.

This conservation extends into infectious processes, which are expressions of the architecture rather than breaches of it: mitochondria—prokaryotic endosymbionts retained within their host cells—raised the energetic ceiling of eukaryotic life while preserving the genomic, bioenergetic, immune (MAVS, cGAS–STING), and signaling traits of their free-living ancestry. Pathology, on this view, is a variation of the same principles under dysregulation.^{28,29}

Three consequences bear directly on synthetic-cell safety. First, the portability of parts across chassis is not an engineering convenience but a consequence of the very architecture that made gene transfer and endosymbiosis possible; a designer should therefore expect engineered modules to be transferable in both directions, out of the construct as well as into it. Second, the claim is not that this architecture is thermodynamically obligatory. Expanded genetic alphabets, XNA backbones, noncanonical amino acids, and reduced minimal genomes all show that alternative chemistries can be made to function under laboratory support; the distinction that matters is between what can be constructed and what can be retained, since

conformational matching constrains persistence within a lineage and its metabolic and ecological context rather than the space of what a chemist can assemble. Recoding and synthetic auxotrophy function as containment for exactly this reason, degrading retention rather than construction. Third, the model is framed so that it can fail. Constructs preserving the conserved triad of an informational core, a bioenergetic engine, and a membrane-bounded interface under selection should show greater stability, lower metabolic burden, and superior persistence upon transfer and serial passage than those departing from it, and genetic exchange should be most permissive where compatibility constraints are loosest, becoming progressively restricted as nuclear compartmentalization, germline sequestration, and immune surveillance raise the threshold for integration. Should engineered systems that abandon the conserved architecture prove equally persistent, the continuity argued for here is weaker than proposed.

10. A relational framework for safe development

What is proposed here is not the general observation that context matters, which is well established, but a specific reordering of the evaluation itself. Existing frameworks classify a construct by its method of construction—

Table 2. Functional comparison of microbes, synthetic cells, and mitochondria

Property	Microbes	Synthetic cells	Mitochondria
Genetic material	Complete genome, chromosomal and often plasmid-borne	Selected nucleic acid modules, or a minimized or chemically synthesized genome, by design	Own reduced genome (mtDNA); most ancestral genes transferred to the nucleus
Protein synthesis	Full ribosomal machinery	Encapsulated cell-free transcription and translation, or the machinery of the host chassis	Own mitochondrial ribosomes; most proteins imported from the cytosol
Energy conversion	Complete metabolic pathways; independent energy capture	Supplied or partially reconstituted energy regeneration	Oxidative phosphorylation; principal ATP source of the cell
Boundary	Cell membrane, often with a wall	Engineered lipid or polymer membrane with selected transport	Double membrane inherited from the endosymbiotic ancestor
Autonomy	Independently living	Dependent on a designed environment; not autonomous	Host-dependent organelle
Replication	Autonomous division	Division-like behavior under defined conditions, or none	Fission coordinated with the host cell cycle
Immune and signaling role	Recognized through conserved microbial patterns; signals via quorum sensing	Interpreted through whatever molecular patterns its components present	Retains innate immune signaling of free-living ancestry (MAVS, cGAS–STING)

Notes: Microbes are independently living cellular systems equipped with complete cellular machinery, genetic material, ribosomes, metabolic pathways, and mechanisms for environmental adaptation. Synthetic cells are engineered, membrane-bound systems containing selected biochemical or genetic modules designed to reproduce specific cellular functions under controlled conditions. Mitochondria are host-dependent organelles that retain their own DNA and ribosomes but specialize primarily in oxidative phosphorylation and ATP production. Despite these differences, all three exhibit compartmentalization, energy conversion, information processing, and, depending on biological context or design, growth- or division-like behavior. The comparison is presented here as a table rather than as a rendered illustration so that each point of correspondence can be read directly.

bottom-up or top-down, replicating or not, contained or free—and then ask what the classified object does. The relational ordering reverses this. It asks first which organisms in the intended setting can recognize, metabolize, resist, or acquire the engineered function, and treats the method of construction as one determinant of that answer among several. The difference is testable rather than rhetorical: two constructs identical under conventional classification can carry substantially different relational risk if the communities they enter differ in signal repertoire, mobile-element load, or resource limitation, and the same construct can carry different risk in the gut, the airway, and soil.

I propose that synthetic-cell evaluation should be organized around biological relationships. The primary question is not simply, what function was engineered? It is, which organisms can recognize or modify that function, and what new relationships become possible? Thus, five potential principles follow. First, classify the platform accurately along the full landscape of **Table 1**, as nonreplicating bottom-up, circuit-carrying but genomically conventional, minimized or recoded, or autonomously replicating; these categories should not share a single risk label, and the intermediate classes carry most of the current clinical experience. Second, test function in progressively realistic communities, moving from single species to defined consortia, organoid-associated microbiota, and spatially structured models. Third, measure community function as well as taxonomic abundance, including metabolite flow, resistance, virulence, and recovery after withdrawal. Fourth, build layered containment through physical localization, limited lifetime, nutrient dependence, genetic safeguards, and monitoring. Fifth, design an off-state and an exit route from the beginning: therapeutic performance should include predictable termination. This relational view also clarifies the meaning of compatibility. A successful synthetic cell should be compatible with the host and intended commensal functions while remaining incompatible with uncontrolled persistence, genetic exchange, or exploitation by pathogens. Compatibility is therefore selective and conditional, not universally benign.

11. Conclusion

Synthetic cells are becoming experimental bridges between chemistry and life. They can reveal minimal cellular requirements, reconstruct evolutionary possibilities, expand biological chemistry, and create programmable systems that are able to communicate with microorganisms. Their medical promise is substantial: they may support commensal functions, detect pathogens, intercept virulence, deliver localized therapy, and reshape microbial ecosystems with greater precision than broad antimicrobial

treatment. Yet they will not enter an empty biological space. Commensal and pathogenic microorganisms may interpret them through the same ancient molecular languages used to recognize nutrients, competitors, hosts, and threats. Desired and unwanted outcomes are therefore likely to arise from interaction rather than from design alone. The next phase of the field potentially should treat synthetic cells not only as engineered objects but as prospective members—however temporary—of evolving biological communities. This holds with equal force across the landscape mapped in **Table 1**, from a protocell that persists for hours to a circuit-carrying bacterium intended to colonize for weeks, and the relational questions posed here are the ones that landscape has in common. Their success will depend on whether we can engineer useful relationships without creating uncontrolled ones.

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