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Programmable Cells Are Emerging as Drug Factories with Context-Dependent Pharmacology

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ABSTRACT

Programmable therapeutic cells challenge a central assumption of conventional pharmacology: that dose is administered as a chemically defined quantity whose subsequent exposure can be separated from the machinery that produced it. Engineered mammalian cells and microorganisms instead remain biologically active after administration. They may sense endogenous or environmental signals, change state, execute genetic logic, migrate or persist in selected compartments, and generate therapeutic molecules only under particular conditions. Consequently, the pharmacologically relevant “dose” may evolve after treatment begins. This Perspective argues that living drug factories should be interpreted through two linked but separable processes: the disposition of the producer cells and the production, disposition, and action of their therapeutic outputs. Evidence from engineered bacteria, programmable immune cells, synthetic gene circuits, local protein secretion, and closed-loop metabolic control demonstrates components of this behavior, but no universal living-cell pharmacokinetic or pharmacodynamic model has been established. We therefore develop a proposed living-pharmacology framework in which therapeutic response emerges from the interaction among viable-cell exposure, sensing performance, circuit state, spatial context, production state, payload disposition, host physiology, and safety constraints. This framing explains why equivalent administered cell numbers need not generate equivalent therapeutic exposure and why apparently identical circuits may behave differently across tissues, hosts, or disease states. Translation will require qualification of these state transitions rather than reliance on administered-cell dose or release testing alone.

Keywords: Programmable cell therapy, Living therapeutics, Synthetic gene circuits, Cellular drug factories, Context-dependent pharmacodynamics, Living-cell pharmacokinetics

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INTRODUCTION

Programmable cell therapies are moving beyond the idea of cells as passive replacement units or constitutively active effectors. Contemporary platforms can be engineered to detect endogenous disease signals or externally supplied inputs and, conditional on that information, secrete proteins, alter metabolism, execute cytotoxic programs, or change other therapeutic functions [1]. This capability creates a pharmaceutical problem that is only partly captured by conventional discussions of cell engineering. The therapeutic entity is not simply a manufactured cell product administered at time zero. It is a living system whose state can change after administration.

Synthetic-biology approaches already provide the basic architecture for this change: sensing, information processing, and therapeutic action can be coupled inside mammalian or microbial cells [2]. Yet programmability should not be mistaken for predictability. The same broad category of “living therapeutic” includes immune cells, engineered stem or somatic cells, probiotics, and other microbial platforms with fundamentally different persistence, replication, trafficking, immune interactions, and manufacturing constraints. Cell chassis therefore defines an important boundary on any pharmacological interpretation [3].

The distinction becomes more important when exposure is considered. Delivery technologies can modify therapeutic-cell survival, retention, trafficking, tissue access, and functional state [4]. For a conventional soluble drug, pharmacokinetics usually follows the administered molecular entity. For a living factory, at least two objects may require separate interpretation: the producer cell and the molecular or cellular output it generates. The producer may persist while production stops, produce different amounts at different times, change phenotype, or disappear while a previously produced payload remains pharmacologically active.

Computational design adds another layer but does not remove these biological contingencies. Artificial intelligence may assist the design of receptors, regulatory sequences, gene circuits, or other components of living delivery systems, but present evidence supports such methods primarily as design-enabling tools rather than validated autonomous controllers of therapeutic pharmacology [5]. The central argument of this Perspective is therefore narrower and more testable: programmable cells should be treated as context-dependent drug factories whose pharmacology emerges from linked cellular, circuit, spatial, and host states. The framework developed below is proposed as an organizing model, not as an empirically validated universal law.

Cells as therapeutic production systems

A programmable therapeutic cell occupies two identities that pharmaceutical development often evaluates separately. Before administration, it is a manufactured product whose viability, phenotype, genetic construct, expression state, and other quality attributes must be controlled. After administration, it becomes a potentially dynamic production system operating inside an environment that was absent during release testing. Mammalian synthetic circuits can regulate expression, feedback, feedforward control, and other production-relevant functions, demonstrating that cellular manufacturing behavior itself is engineerable [6]. What cannot be assumed is that a pre-administration production phenotype transfers unchanged into a patient.

This limitation is especially clear for engineered bacteria. Bacterial therapeutics can combine localization, environmental sensing, metabolic activity, payload production, and immune interactions within the same chassis, but their behavior remains strain-, niche-, and host-dependent [7]. Replication or persistence can prolong function, yet those same properties can amplify uncertainty. A living factory therefore cannot be described adequately by whether the genetic program is present; it must also be in the physiological state required for that program to function.

SYNB1618 illustrates this distinction. The engineered *Escherichia coli* Nissle platform was designed to metabolize phenylalanine under gut-relevant conditions, and animal studies demonstrated biochemical activity and an associated activity biomarker [8]. The therapeutic mechanism consequently depended on more than administered cell number: the bacteria had to reach an appropriate environment, remain metabolically competent, and express the engineered pathway sufficiently to alter substrate handling. These findings establish environmental gating of a therapeutic metabolic program, but they do not establish human clinical efficacy.

Human data reinforce the need to separate administered dose from active living exposure. In a phase I study of the engineered *E. coli* Nissle strain SYNB1020, escalating oral administration produced measurable, dose-related bacterial exposure and biochemical activity in healthy volunteers [9]. The study provides direct evidence that living therapeutic exposure can be observed pharmacologically in humans, while also showing why exposure cannot simply be equated with clinical response: the participants did not establish efficacy in the intended disease population.

Physical architecture can further redefine the production system. Engineered bacteria confined within an implantable hydrogel have been shown preclinically to remain contained while sensing local conditions and producing therapeutic outputs [10]. In such a system, the material boundary is part of the pharmacology because it changes where viable producers can exist without necessarily abolishing their engineered function. Containment is therefore not merely a safety accessory; it may alter exposure geometry.

Programmable probiotics extend the same reasoning to naturally compartmentalized biological niches. Their appeal lies partly in the possibility of sustained, locally responsive therapeutic activity [11]. However, persistence alone is not equivalent to continuous productive activity. Spatial and temporal activation must be controlled

because bacterial replication, immunostimulation, and therapeutic output may produce different benefit-risk relationships in different tissues or host states [12]. The relevant production variable is thus not simply “cells present,” but cells that are viable, accessible to the intended signal, functionally in the intended circuit state, and capable of generating the required therapeutic output.

Sensing disease signals

Context-dependent pharmacology begins with the ability to discriminate biologically meaningful inputs. A sensor that performs well before administration may lose function through mutation, altered physiology, changing receptor abundance, signal saturation, or host-environment effects. Longitudinal studies with engineered gut bacteria provide proof that durable in-vivo sensing is possible: an inflammation-responsive memory circuit retained function during prolonged residence in defined mouse-gut conditions [13]. The appropriate conclusion is not that engineered sensors are intrinsically stable, but that sensor stability is measurable and should be qualified over the intended therapeutic residence period.

Sensor performance also requires more resolution than a binary distinction between “responsive” and “nonresponsive.” Synthetic macromolecular switches differ in sensitivity, detection range, specificity, reversibility, and input modality [14]. These properties determine which biological states are translated into circuit activation. A disease-associated signal below the effective sensing range may be pharmacologically invisible, whereas a signal shared by healthy tissue may compromise specificity. Consequently, the input-output transfer function of the sensor is part of therapeutic pharmacology.

Combinatorial logic offers a means to improve discrimination. Synthetic DNA circuits can process multiple molecular inputs and interface with endogenous cellular pathways [15]. AND-like, OR-like, sequential, or inhibitory logic can therefore restrict output to particular combinations of cues rather than a single marker. Yet molecular logic should not be confused with clinical decision accuracy. A truth table can behave correctly at the circuit level while tissue heterogeneity, fluctuating signal abundance, incomplete target accessibility, or cell-state variation still produces an unintended therapeutic response.

Genetic logic and therapeutic output

Once a disease signal is detected, genetic or protein-level logic determines what the cell does with that information. This creates an important distinction between open-loop and closed-loop therapeutic control. Externally activated systems generally depend on a clinician- or device-supplied trigger, whereas circuits responsive to endogenous physiological variables can, in principle, connect the measured disturbance directly to therapeutic output [16]. These architectures differ pharmacologically because the timing and magnitude of output are governed by different control relationships.

Therapeutic output should also not be reduced to secretion rate. Synthetic protein circuits demonstrate that circuit state can determine qualitatively different cell-fate outcomes, including distinct programmed cell-death modalities, in response to combinations of protease inputs [17]. This establishes a broader principle: identical cellular chassis can generate different pharmacological actions according to internal computational state. For secretory therapies the relevant difference may be payload identity or amount; for engineered immune cells it may be activation, migration, proliferation, cytokine production, or self-elimination.

Safety controls add another layer to this logic. Synthetic genetic switches developed for CAR-T cells include mechanisms intended to regulate temporal activation, terminate activity, redirect targeting, or restrict function spatially [18]. These mechanisms should not be collapsed into a generic “safety switch” category because they address different failure modes. A rapid kill switch does not solve poor spatial discrimination, and spatially restricted activation does not necessarily protect against prolonged activity within the correct tissue.

The central analytical problem is therefore not whether a circuit activates, but under which cellular and biological states its output remains interpretable. The comparison becomes clearest when the boundary condition is kept beside the inferred therapeutic consequence rather than discussed separately.

Table 1 is placed here because genetic logic becomes pharmacologically interpretable only when the observable output is considered together with the hidden cellular state and the condition under which that interpretation ceases to hold.

Table 1. Boundary conditions that determine when programmable-cell output can be interpreted as intended therapeutic action

Source state and scale	Transfer conditions	Qualification endpoint
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Process or cellular state / Measured variable	Boundary on the supported interpretation	Genetic-logic qualification case / Hidden biological state qualification / Therapeutic and regulatory consequence
Process or cellular state: Viable producer responds to supplied inducer Measured variable: Reporter or therapeutic-output signal	Output supports trigger responsiveness only while the producer remains accessible and competent	Genetic-logic qualification case: Externally triggered production Hidden biological state requiring qualification: Inducer access, receptor or switch competence, cellular metabolic capacity Therapeutic and regulatory consequence: Administration of an inducer cannot substitute for verification of in-vivo cell state
Process or cellular state: Disease-associated cue activates the circuit Measured variable: Secreted or intracellular therapeutic output	Output is interpretable as disease-responsive only within a qualified sensing range and specificity context	Genetic-logic qualification case: Endogenous disease- responsive production Hidden biological state requiring qualification: Actual cue concentration at the producer cell and sensor transfer state Therapeutic and regulatory consequence: Sensor performance becomes part of product-function qualification
Process or cellular state: Required combination of signals is processed Measured variable: Logic- dependent output state	Correct circuit logic does not establish correct tissue-level classification when inputs are heterogeneous	Genetic-logic qualification case: Multi-input logic gating Hidden biological state requiring qualification: Spatial and temporal co-occurrence of inputs Therapeutic and regulatory consequence: Validation must challenge clinically relevant combinations and near- miss states
Process or cellular state: Circuit changes cell fate or effector program Measured variable: Output identity rather than only magnitude	A change in measured output may reflect a different cell program rather than a stronger version of the same response	Genetic-logic qualification case: Qualitative output switching Hidden biological state requiring qualification: Protease, transcriptional, signaling, or stress state Therapeutic and regulatory consequence: Potency interpretation must distinguish output identity from output quantity
Process or cellular state: Engineered control suppresses or eliminates therapeutic cells Measured variable: Decline in activity, viability, or effector output	Demonstrated switch responsiveness does not prove elimination of every hazardous state	Genetic-logic qualification case: Safety-gated shutdown Hidden biological state requiring qualification: Completeness and kinetics of switch engagement Therapeutic and regulatory consequence: Safety claims require failure-mode-specific rather than generic switch qualification
Process or cellular state: Sensor, logic, cell physiology, and output are jointly assessed Measured variable: Linked input-state-output evidence	Interpretation becomes indeterminate when the measured output cannot be traced to the expected internal state	Genetic-logic qualification case: Proposed integrated qualification state Hidden biological state requiring qualification: Unmeasured state between genetic instruction and pharmacological consequence Therapeutic and regulatory consequence: The proposed living-pharmacology framework treats circuit state as a required bridge between product identity and therapeutic action

Spatially restricted production

Programmable cells can alter not only when a therapeutic is produced but where production occurs. CAR-T cells engineered to secrete a PD-1-blocking single-chain antibody fragment demonstrated that therapeutic cells can act as local sources of a biologic within tumor models [19]. The pharmacological significance is greater than simple co-delivery: the distribution of the producer cell can help determine the spatial origin of the payload.

A related strategy used CAR-T cells that secreted bispecific T-cell engagers to address heterogeneous antigen expression in glioblastoma models [20]. Here, the producer cell and the therapeutic payload had different effective target repertoires. CAR recognition directed the engineered cell, while the secreted engager recruited additional T cells against a broader antigen target. Local production therefore created a pharmacological radius of action that extended beyond direct producer-cell contact. That radius should not be assumed to be fixed or exclusively local in other settings; it depends on payload diffusion, stability, tissue architecture, clearance, and producer localization.

Spatial control can also operate upstream of production. SynNotch-based CAR-T designs have been used to require recognition of a local priming antigen before CAR expression, producing a form of tissue-context-dependent therapeutic activation in preclinical glioblastoma models [21]. This illustrates a critical distinction: spatial restriction is not synonymous with biodistribution. A producer cell may physically reach multiple tissues but generate its principal therapeutic program only where an appropriate input configuration is present.

Living drug factories can therefore achieve spatial selectivity through at least three non-equivalent mechanisms: confinement of the producer, preferential localization of the producer, or context-gated activation of production. Each mechanism creates different failure modes. Physical presence outside the target tissue is most concerning when the circuit remains active there; conversely, apparently favorable localization is insufficient when cells at the target site are not in a productive state.

Feedback and self-regulation

The strongest departure from conventional fixed-dose pharmacology occurs when therapeutic output feeds back on the variable that controls its own production. In a preclinical metabolic example, engineered human cells incorporating a cholesterol-responsive circuit were implanted in mice and used to couple an endogenous lipid signal to compensatory therapeutic output [22]. Such systems demonstrate that cell-based therapy can be engineered to operate as a closed loop in vivo, but the observation should remain system-specific: a closed-loop architecture is not automatically stable, safe, or homeostatic.

Feedback can also serve a different purpose. Tumor-responsive synthetic circuits have triggered local interleukin-2 production in engineered T cells, supporting expansion and function in otherwise immune-excluded tumors [23]. This is not equivalent to negative homeostatic feedback. Instead, local sensing can create an amplifying response in which the tissue context initiates a therapeutic program that changes the cellular population and microenvironment. Feedback must therefore be classified by its biological role rather than by the mere presence of a return arrow.

For living drug factories, at least four elements determine whether self-regulation performs as intended: the fidelity of the sensed variable, the circuit transfer function, the delay between sensing and output, and the effect of the output on the biological variable that generated the signal. Host physiology can add additional feedback because therapeutic-cell activity may alter nutrient availability, inflammatory state, immune recognition, tissue accessibility, or cell survival. The resulting control structure is therefore distributed across the engineered circuit and the host.

Artificial intelligence could eventually assist the design or adaptive interpretation of such systems, but current evidence does not justify placing an AI controller above the biology as an independently validated decision-maker. A quality-first view instead treats computational design as one lane within a larger qualification architecture: sensor performance, circuit state, cell state, therapeutic output, host response, and safety boundaries must each remain observable enough to falsify an incorrect mechanistic interpretation.

The relationships become clearer when feedback is shown as a set of parallel evidence states rather than a single circular loop; **Figure 1** therefore separates what is measured from what is inferred and places computational design outside the biological feedback path unless empirically validated.

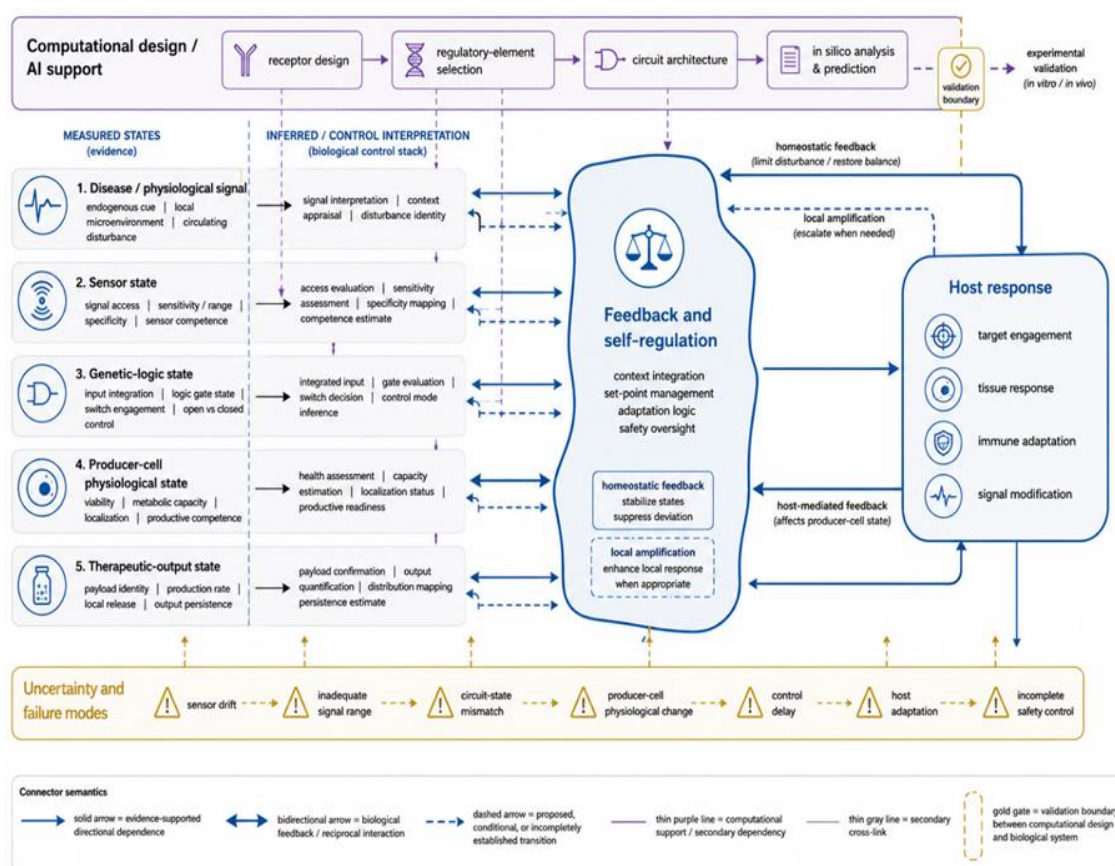


Figure 1. Feedback control in living drug factories depends on separable sensor, circuit, cellular, and host states

Pharmacokinetics of living drug factories

Pharmacokinetics becomes conceptually different when the administered entity can remain alive and generate a second pharmacologically active entity. Delivery research in cell therapy already shows that cell survival, trafficking, retention, and tissue environment affect therapeutic-cell exposure [4]. The additional step for a living drug factory is production. Producer-cell disposition and payload disposition should therefore be analyzed separately even when they ultimately contribute to the same therapeutic outcome.

The first object is the administered cell population. Its relevant states may include administered cells, viable cells, tissue-accessible cells, persistent cells, and cells occupying a physiologically competent state. Human experience with SYNB1020 demonstrates that administered microbial dose can produce dose-related patterns of fecal exposure and biochemical activity [9], but this does not imply a fixed conversion between administered cell number and therapeutic production. Cell death, growth, transit, nutrient availability, local oxygenation, circuit state, and host clearance can all intervene before production is measured.

The second object is the therapeutic output. Once generated, a secreted protein, metabolite, cytokine, engager, or other effector can acquire pharmacokinetics partly independent of the cell that produced it. A localized producer can create a locally concentrated output, as demonstrated with engineered CAR-T secretion strategies [19], whereas an output with sufficient diffusion or systemic access may extend beyond the producer compartment. Consequently, measuring cell abundance alone may fail to predict payload exposure, and measuring payload concentration alone may conceal changes in the size or state of the producer population.

Containment and anatomical restriction introduce further divergence. Implantable confinement of engineered bacteria can sharply limit producer-cell distribution while preserving local sensing and production [10]. Programmable probiotics illustrate a different boundary: producer cells may remain within a gastrointestinal niche, but their productive state can vary with local ecology and physiology [11]. In both cases, “persistence” is pharmacologically incomplete unless it is linked to functional production.

Feedback makes the system still more dynamic. A biomarker-responsive factory may reduce the signal that originally activated it, thereby changing its own production rate [22]. Thus, therapeutic exposure can be history-dependent: identical cell numbers observed at two time points need not imply identical output because the

upstream biological signal, circuit state, or host response may differ. This is one reason conventional proportionality assumptions should not be transferred automatically to living therapeutics.

We therefore propose a two-object pharmacokinetic interpretation. Producer-cell PK describes the time-varying availability and state of cells capable of production. Payload PK describes the generation, distribution, persistence, and clearance of the therapeutic output. These are linked by a productive-state boundary: only the subset of cells that is viable, appropriately localized, sensor-competent, circuit-competent, and physiologically capable of executing the program contributes to contemporaneous payload generation. The productive-state boundary is a proposed analytical construct; current literature supports its individual components but has not validated a universal quantitative model connecting them.

This distinction changes what should be measured experimentally. Administered-cell dose should be complemented, where technically feasible, by longitudinal evidence of viable-cell burden or localization, circuit activity, production biomarkers, payload exposure, and relevant host-response variables. Different platforms will require different measurements, and no universal assay set follows from the framework. The purpose is instead to prevent one measurable state—such as cell presence—from being mistaken for another—such as active therapeutic production.

Figure 2 is used here because living-cell pharmacokinetics is not a single disposition curve: it is a propagation problem in which upstream changes in producer-cell state can alter both whether a payload is generated and how its subsequent exposure should be interpreted.

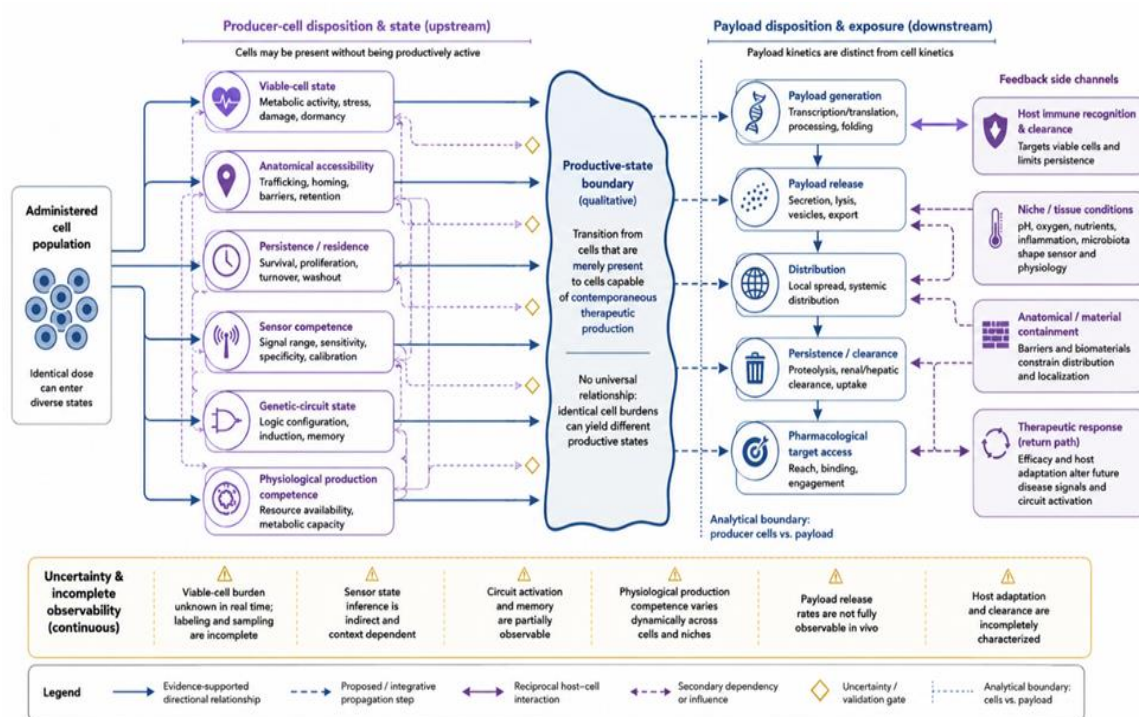


Figure 2. Producer-cell disposition and payload exposure diverge across living-factory pharmacokinetics

Context-dependent pharmacodynamics

A programmable cell can carry an unchanged genetic construct yet produce a different pharmacological response when its physiological environment changes. Synthetic circuits interact with host resources, growth state, stress responses, endogenous regulatory networks, and metabolic capacity; these interactions can change both deterministic output and variability [24]. Context dependence is therefore not an experimental nuisance surrounding an otherwise fixed dose-response relationship. For living drug factories, it can be part of the mechanism that generates the response.

Pharmacodynamics must consequently be resolved across several states. A disease signal must first reach the relevant sensor, the sensor must operate within its useful transfer range, genetic logic must enter the intended state, the producer cell must remain physiologically competent, the therapeutic output must reach an appropriate target, and the host must remain responsive to that output. Failure at one stage can produce an apparently weak therapeutic response even when upstream engineering remains functional. Conversely, a strong measured output does not prove that the intended disease-selective mechanism produced it.

This interpretation also clarifies discordant observations. Local therapeutic secretion may coexist with weak tissue response because the target is insensitive; correct circuit activation may coexist with inappropriate pharmacology because spatial inputs are misclassified; and apparently adequate producer-cell abundance may coexist with declining output because cellular physiology has changed. Rather than averaging such observations into a single efficacy judgment, we propose treating discordance as evidence that identifies which living-pharmacology boundary requires discrimination.

The inference problem is most transparent when concordant and discordant patterns are placed beside both the interpretation they permit and the evidence needed to resolve remaining ambiguity.

Table 2. Evidence patterns that determine how context-dependent output should be interpreted in programmable-cell pharmacology

Evidence configuration		Interpretive alternatives	Adjudication requirement
Inference scenario / Process or cellular state	Measured variable / Hidden biological state / Disturbance source and propagation path	Inference not justified	Inference justified / Discriminating evidence
Inference scenario: Input detected, expected output absent Process or cellular state: Sensor-positive producer	Measured variable: Disease signal present; therapeutic output low Hidden biological state: Circuit competence or cellular production capacity uncertain Disturbance source and propagation path: Host or metabolic disturbance acts downstream of sensing	The genetic program is intrinsically ineffective	Inference justified: The relevant input reached the sensor Discriminating evidence required: Direct circuit-state and production-competence measurements
Inference scenario: Output present, therapeutic response weak Process or cellular state: Productive producer	Measured variable: Payload detectable; target response limited Hidden biological state: Target accessibility or host susceptibility uncertain Disturbance source and propagation path: Payload generation succeeds but downstream pharmacology is constrained	Higher production would necessarily restore efficacy	Inference justified: Production occurred Discriminating evidence required: Local target engagement and response-state evidence
Inference scenario: Producer cells persist while output declines Process or cellular state: Viable persistent population	Measured variable: Cell burden stable; payload decreases Hidden biological state: Productive state changing over time Disturbance source and propagation path: Niche, resource, inflammatory, or circuit-state change reduces production	Persistent cells remain pharmacologically equivalent	Inference justified: Persistence is maintained Discriminating evidence required: Longitudinal viability, circuit-state, and production biomarkers
Inference scenario: Local activation with heterogeneous tissue response Process or cellular state: Spatially gated producer	Measured variable: Regional output or cellular activation Hidden biological state: Microenvironment and target state vary spatially Disturbance source and propagation path: Tissue heterogeneity modifies propagation from output to response	Spatial restriction guarantees uniform therapeutic effect	Inference justified: Activation is context restricted in the studied setting Discriminating evidence required: Matched spatial measurements of producer, payload, target, and response
Inference scenario: Proposed integrated living-pharmacology state Process or cellular state: Multiple linked states qualified	Measured variable: Producer, circuit, payload, and response evidence concordant Hidden biological state: Residual unmeasured host state remains possible Disturbance source and propagation path: Disturbances may arise at several coupled boundaries	The full causal chain is proven or universally transferable	Inference justified: The observed response is consistent with the proposed mechanism Discriminating evidence required: Prospective perturbation and boundary-specific validation

Containment and safety

For living drug factories, persistence is simultaneously a therapeutic asset and a safety liability. Long-lived cells may sustain production and reduce repeated administration, but persistence also prolongs exposure to unintended cellular states. Host immune recognition is therefore part of pharmacology as well as safety. Hypoimmunogenic engineering may reduce rejection of allogeneic therapeutic cells, yet residual immune, tumorigenic, and manufacturing concerns remain [25]. Reduced immune clearance cannot be interpreted as automatically desirable unless the resulting persistence remains controllable.

Engineered microorganisms introduce an additional containment problem. Genetic safeguards, auxotrophic dependencies, or kill mechanisms can reduce persistence or environmental spread, but their performance depends on organismal fitness, evolutionary pressure, and surrounding conditions [26]. Biocontainment should therefore be treated as a behavior requiring validation rather than as a property established by the presence of a safeguard. Physical and genetic containment are complementary rather than interchangeable. Physical confinement restricts where producer cells can travel, whereas genetic control attempts to constrain viability or activity when specified conditions are lost. The proposed framework therefore treats containment failure as a pharmacological escape state: producer cells, productive activity, or both have crossed a boundary assumed by the intended exposure model.

A living-pharmacology framework

The evidence assembled here supports individual capabilities—sensing, logic processing, localized production, feedback control, persistence, and containment—but it does not establish one universal pharmacokinetic or pharmacodynamic model. We therefore propose living pharmacology as an organizing framework rather than a validated quantitative theory.

The framework separates five coupled states. First is producer exposure: where viable therapeutic cells are and how long they remain accessible. Second is context sensing: which biological inputs actually reach and activate the engineered sensor. Third is productive state: whether the cell and circuit can execute the intended program. Fourth is payload exposure: where the generated therapeutic product distributes and persists. Fifth is response context: whether the target tissue and host remain susceptible to that output.

These states are connected but should not be substituted for one another. A detectable producer does not prove production; production does not prove adequate target exposure; target exposure does not prove response; and response does not by itself prove that the intended sensing-and-logic pathway caused it. Sensor characteristics therefore remain mechanistically relevant [14], while direct closed-loop examples demonstrate that host variables can also feed back onto future production [22].

The principal contribution of the framework is a falsification structure. When response is inadequate or unexpected, development should ask which boundary failed rather than classify the entire platform as simply active or inactive. The same logic applies to apparently successful responses: concordant evidence across producer, circuit, payload, target, and host states provides stronger mechanistic confidence than any single output measurement.

Translational requirements

Translation should therefore qualify a sequence of linked pharmaceutical functions rather than only the manufactured cell at release. Product identity and critical quality attributes remain essential, but they should be complemented by evidence that the clinically relevant sensor, circuit, and productive states remain interpretable after administration. Synthetic-circuit performance in manufacturing systems supports the feasibility of controlled cellular functions, but productivity cannot be assumed to predict in-vivo therapeutic quality [6].

Early clinical development should distinguish administered-cell dose from viable-cell exposure and pharmacodynamic activity wherever technically possible. The SYN1020 experience demonstrates that living-cell exposure and biochemical activity can be measured separately in humans [9]. Other platforms will require different biomarkers, imaging methods, molecular readouts, or sampling strategies; no universal assay panel is implied.

Spatial restriction, persistence, immune compatibility, and containment also require longitudinal challenge testing. Demonstrating appropriate localization at one time point cannot establish future productive state, and demonstrating an engineered safeguard cannot establish indefinite control. Failure conditions should therefore be specified prospectively for loss of sensing, altered circuit behavior, uncontrolled persistence, unintended output, or escape from spatial or biological containment.

Computational and AI-assisted design should follow the same evidence hierarchy. Design predictions may narrow the search space, but biological qualification remains necessary because circuit performance changes with host context [24]. Translation ultimately depends on demonstrating that the clinically relevant chain from producer exposure to therapeutic response remains observable, controllable, and falsifiable within the intended patient, tissue, and temporal context.

CONCLUSION

Programmable therapeutic cells are not simply conventional drugs manufactured inside the patient. Their pharmacology can change as producer cells survive, move, sense, compute, produce, respond to feedback, and interact with host physiology. The proposed living-pharmacology framework therefore separates producer exposure, sensing, productive state, payload exposure, and response context while treating containment and failure states as part of the same pharmaceutical system. This framework does not establish a universal quantitative model. Its value is instead analytical: it identifies which state must be measured or challenged before a context-dependent cellular response can be interpreted as controlled therapeutic action.

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REFERENCES

1. Teixeira AP, Aubel D, Fussenegger M. Next-generation programmable cell therapies for precision medicine. *Nat Rev Genet.* 2026;27(8):585-602. doi:10.1038/s41576-026-00945-3
2. Cubillos-Ruiz A, Guo T, Sokolovska A, Miller PF, Collins JJ, Lu TK, et al. Engineering living therapeutics with synthetic biology. *Nat Rev Drug Discov.* 2021;20(12):941-60. doi:10.1038/s41573-021-00285-3
3. Li Z, Wang Y, Gu Z, Hu Q. Engineering cells for therapy and diagnosis. *Nat Rev Bioeng.* 2024;2(9):770-84. doi:10.1038/s44222-024-00198-x
4. Wang LLW, Gao Y, Feng Z, Mooney DJ, Mitragotri S. Designing drug delivery systems for cell therapy. *Nat Rev Bioeng.* 2024;2(11):944-59. doi:10.1038/s44222-024-00214-0
5. Yang JH, Bashor CJ. Opportunities for artificial intelligence and synthetic biology in designing living drug delivery systems. *Adv Drug Deliv Rev.* 2026;235:115883. doi:10.1016/j.addr.2026.115883
6. Lim SLY, Gialamoidou S, Kaur R, Jimenez del Val I. Mammalian synthetic gene circuits for biopharmaceutical development & manufacture. *NPJ Syst Biol Appl.* 2026;12(1):1. doi:10.1038/s41540-025-00621-y
7. Xie R, Fan D, Cheng X, Yin Y, Li H, Wegner SV, et al. Living therapeutics: Precision diagnosis and therapy with engineered bacteria. *Biomaterials.* 2025;321:123342. doi:10.1016/j.biomaterials.2025.123342
8. Isabella VM, Ha BN, Castillo MJ, Lubkowitz DJ, Rowe SE, Millet YA, et al. Development of a synthetic live bacterial therapeutic for the human metabolic disease phenylketonuria. *Nat Biotechnol.* 2018;36(9):857-64. doi:10.1038/nbt.4222
9. Kurtz CB, Millet YA, Puurunen MK, Perreault M, Charbonneau MR, Isabella VM, et al. An engineered *E. coli* Nissle improves hyperammonemia and survival in mice and shows dose-dependent exposure in healthy humans. *Sci Transl Med.* 2019;11(475):eaau7975. doi:10.1126/scitranslmed.aau7975
10. Harimoto T, Herrero Quevedo F, Zillig J, Schreiber S, Wu Y, Ahn CH, et al. Implantable living materials autonomously deliver therapeutics using contained engineered bacteria. *Science.* 2026;392(6799):729-34. doi:10.1126/science.aec2071
11. Li N, Yin L, Wang J, Zhang J, Tong Y. Programmable probiotics as next-generation living therapeutics: Bridging synthetic biology and precision medicine. *Curr Opin Biotechnol.* 2025;96:103375. doi:10.1016/j.copbio.2025.103375
12. Hahn J, Ding S, Im J, Harimoto T, Leong KW, Danino T. Bacterial therapies at the interface of synthetic biology and nanomedicine. *Nat Rev Bioeng.* 2024;2(2):120-35. doi:10.1038/s44222-023-00119-4

13. Riglar DT, Giessen TW, Baym M, Kerns SJ, Niederhuber MJ, Bronson RT, et al. Engineered bacteria can function in the mammalian gut long-term as live diagnostics of inflammation. *Nat Biotechnol.* 2017;35(7):653-8. doi:10.1038/nbt.3879
14. Teixeira AP, Fussenegger M. Synthetic macromolecular switches for precision control of therapeutic cell functions. *Nat Rev Bioeng.* 2024;2(12):1005-22. doi:10.1038/s44222-024-00235-9
15. Wang M, Tang W, Jiang S, Wei P. Synthetic DNA circuits for programming cell functions. *Curr Opin Chem Biol.* 2026;93:102701. doi:10.1016/j.cbpa.2026.102701
16. Teixeira AP, Fussenegger M. Synthetic gene circuits for regulation of next-generation cell-based therapeutics. *Adv Sci (Weinh).* 2024;11(8):e2309088. doi:10.1002/advs.202309088
17. Xia S, Lu AC, Tobin V, Luo K, Moeller L, Shon DJ, et al. Synthetic protein circuits for programmable control of mammalian cell death. *Cell.* 2024;187(11):2785-2800.e16. doi:10.1016/j.cell.2024.03.031
18. Lu L, Xie M, Yang B, Zhao WB, Cao J. Enhancing the safety of CAR-T cell therapy: Synthetic genetic switch for spatiotemporal control. *Sci Adv.* 2024;10(8):eadj6251. doi:10.1126/sciadv.adj6251
19. Rafiq S, Yeku OO, Jackson HJ, Purdon TJ, van Leeuwen DG, Drakes DJ, et al. Targeted delivery of a PD-1-blocking scFv by CAR-T cells enhances anti-tumor efficacy in vivo. *Nat Biotechnol.* 2018;36(9):847-56. doi:10.1038/nbt.4195
20. Choi BD, Yu X, Castano AP, Bouffard AA, Schmidts A, Larson RC, et al. CAR-T cells secreting BiTEs circumvent antigen escape without detectable toxicity. *Nat Biotechnol.* 2019;37(9):1049-58. doi:10.1038/s41587-019-0192-1
21. Choe JH, Watchmaker PB, Simic MS, Gilbert RD, Li AW, Krasnow NA, et al. SynNotch-CAR T cells overcome challenges of specificity, heterogeneity, and persistence in treating glioblastoma. *Sci Transl Med.* 2021;13(591):eabe7378. doi:10.1126/scitranslmed.abe7378
22. Unal G, Xie YQ, Fussenegger M. A closed-loop cholesterol shunt controlling experimental dyslipidemia. *Cell Metab.* 2025;37(10):2066-75.e3. doi:10.1016/j.cmet.2025.08.011
23. Allen GM, Frankel NW, Reddy NR, Bhargava HK, Yoshida MA, Stark SR, et al. Synthetic cytokine circuits that drive T cells into immune-excluded tumors. *Science.* 2022;378(6625):eaba1624. doi:10.1126/science.aba1624
24. Stone A, Youssef A, Rijal S, Zhang R, Tian XJ. Context-dependent redesign of robust synthetic gene circuits. *Trends Biotechnol.* 2024;42(7):895-909. doi:10.1016/j.tibtech.2024.01.003
25. Hotta A, Schrepfer S, Nagy A. Genetically engineered hypoinmunogenic cell therapy. *Nat Rev Bioeng.* 2024;2(11):960-79. doi:10.1038/s44222-024-00219-9
26. Moon TS. Be a GEM: Biocontained, environmentally applied, genetically engineered microbes. *Adv Drug Deliv Rev.* 2025;221:115578. doi:10.1016/j.addr.2025.115578