INNOVATION

Cell-Based Therapeutics: The Next Pillar of Medicine

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Two decades ago, the pharmaceutical industry—long dominated by small-molecule drugs—was revolutionized by the the advent of biologics. Today, biomedicine sits on the cusp of a new revolution: the use of microbial and human cells as versatile therapeutic engines. Here, we discuss the promise of this "third pillar" of therapeutics in the context of current scientific, regulatory, economic, and perceptual challenges. History suggests that the advent of cellular medicines will require the development of a foundational cellular engineering science that provides a systematic framework for safely and predictably altering and regulating cellular behaviors.

The advent of biologics—recombinant hormones, soluble receptors, and antibody-based drugs—transformed the pharmaceutical industry. Once supported largely by a single pillar—small-molecule drug discovery—the industry now had a second foundational structure. Biologics paved the way to a broad range of new targets, functional capabilities, and disease applications and now represent a large fraction of new medicines brought to market. Today, biomedical science stands poised at the threshold of another pharmaceutical frontier: cell-based therapies. In this Perspective, we discuss the potential power of this new pillar of human therapeutics.

BUILDING A THIRD PILLAR

Historically, the establishment of a new pillar in the drug industry has been preceded by the emergence of a foundational engineering science. The shift from the use of natural products in drug screens to the small-molecule industry of today required the development of synthetic organic chemistry as a foundational science. In this realm, the singular innovation of Big Pharma was their definition and mastery of the science of turning small molecules into drugs: discovering or designing and synthesizing lead compounds that bind biological targets of interest; optimizing a drug's target-binding properties, pharmacokinetics (PK), and pharmacodynamics (PD); and mitigating toxicity.

The first biological therapeutics were natural proteins, such as purified porcine insulin and largely uncharacterized polyclonal antibodies. The modern biologics industry (which began in the early 1980s) was built on the molecular biology revolution, the creation of monoclonal antibody technology, and the foundational science of protein engineering. But the development of biologics exploded only after key start-up companies such as Genentech, Genzyme, and Amgen developed world-class expertise in an area that was entirely distinct from that of Big Pharma: designing and producing highly functionally optimized recombinant proteins.

Today, biomedical science sits on the cusp of another revolution: the use of human and microbial cells as therapeutic entities (*1*). In principle, cells have therapeutic capabilities that are distinct from those of small molecules and biologics and that extend beyond the regenerative-medicine arena. Part drug and part device, cells can sense diverse signals, move to specific sites in the body, integrate inputs to make decisions, and execute complex response behaviors—all in the context of a specific tissue environment. These attributes could potentially be harnessed to treat infections, autoimmunity, cancers, metabolic diseases, and tissue degeneration as well as realizing tissue repair and regeneration. Indeed, pioneering clinical trials have highlighted the benefits of using cells as therapeutic agents (*2*–*7*). However, the complexity of cells and the challenge of controlling their actions in a therapeutic setting provide daunting scientific, regulatory, economic, and cultural obstacles to the establishment of cells as a widespread and viable pharmaceutical platform.

With our deep mechanistic understanding of cellular systems biology, researchers are poised to harness these intricate behaviors in new ways to generate an array of precisely regulated weapons against a broad range of diseases. However, a critical step that will enable the emergence of cells as the next therapeutic pillar is the development of cellular engineering as a foundational science. This will include mechanisms for editing and recoding genomes, the assembly of a toolkit of molecular parts and regulatory modules that behave predictably, and a systems-based theoretical framework that can provide strategies for tuning and optimizing cellular behaviors.

HOW WHOLE CELLS TRUMP THEIR PARTS

If small molecules and biologics are tools, then cells are carpenters—and architects and engineers as well. Of the three pillars, only cells sense their surroundings, make decisions, and exhibit varied and regulable behaviors (Table 1). Devices share some

Table 1. Therapy's cast of characters. Cell-based therapeutics are compared to small molecules and biologics.

Comparisons	Small molecules and Biologics	Cells
Selectivity	Molecular recognition	Complex sensing and response systems
Distribution	Diffusion and transport Controlled PK/PD	Directed cell migration
Dose	Controlled at time of administration	Cell decision-making: • Proliferation/activation/death • Closed-loop autoregulation
Therapeutic niche	Conditions for which distribution and duration of action do not need fine control	Conditions that require precise dynamic control over distribution, level, and duration of action

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of these advantages; indeed, some abiotic therapeutic nanodevices mimic cellular behaviors, although these equally fascinating new therapeutic candidates will not be discussed here.

Cells naturally perform therapeutic tasks. The human body has three kinds of natural agents that perform the tasks we demand of therapeutics. The first two are small molecules (for example, neurotransmitters) and biologics (such as antibodies, growth factors, cytokines, and peptide hormones). Cells are the third—and the only ones that can perform complex biological functions. For example, macrophages engulf pathogens and recruit adaptive immune cells; hematopoietic stem cells give rise to myeloid and lymphoid lineages; chondrocytes produce a cartilaginous extracellular matrix; pancreatic β cells sense glucose and respond by producing insulin; and gut bacteria convert indigestible fibers into short-chain fatty acids that fuel intestinal epithelial cells.

Cell behavior is exquisitely selective. Most small molecules and biologics are always active; they do not have ON or OFF switches, and if they reach their target, they will bind it and exert a biological effect. In contrast, cells sense their environment and respond with an action only when in the presence of a specific array of molecular inputs. Thus, cells can have exquisite sensitivity and specificity, which impart a greater ability to limit off-target action. Engineering and controlling key cellular receptors and how their signals are processed could, in principle, allow customization of responses such that only therapeutically relevant signals trigger activation of a selected cellular behavior (*8*).

Cells are special delivery agents. PK and PD properties and metabolism determine where in the body small molecules and biologics distribute. The inability to limit their distribution to a single tissue or cell type often results in off-target effects, which can be serious enough to end a drug-development program, even at a costly late stage. For example, the insulin sensitization activity of rosiglitazone, a peroxisome proliferator-activated receptor (PPAR)–γ ligand, results from its activity in adipocytes, but the increased risk of myocardial infarction observed in some patients arises from the drug's action in cardiac cells. Although rare, this outcome has had a chilling effect on drug sales and on the development of other PPAR-γ–targeted drugs. Cells are less likely to have off-target effects because they can selectively recognize and actively migrate toward specific signals and exert their effects in a highly targeted manner. One can imagine an ideal cellular agent that is engineered to produce a PPAR-γ ligand, but only in the local environment of adipocytes.

Cells can handle human genetic variability. Determining the right dose of a drug for a diverse patient population can be challenging. Common polymorphisms in genes that encode drug transporters or drug-metabolizing cytochromes P450 can tweak the transport of a small molecule in and out of cells or alter drug metabolism, respectively; as a result, the same dose of a small molecule can, in different individuals, result in widely varying amounts of the active metabolite reaching its target. For example, common polymorphisms in the gene that encodes organic cation transporter 1 (OCT1) lead to reduced uptake of the type 2 diabetes drug metformin, resulting in differences in the efficacy of metformin among individuals (*9*). In contrast, cells could potentially be engineered to automatically adjust to differences in host metabolism and transport by harboring a rheostat-like circuit that produces more of a molecule when needed and degrades the excess when a threshold concentration is exceeded. Thus, in principle, cells could yield therapeutic responses that are less variable in different individuals.

Cell behaviors can be engineered. To manage their disease, patients with autoimmune (type 1) diabetes (T1D) have to monitor their blood sugar, inject insulin, and limit their diets. Failure to control T1D can have grave consequences, including blindness, limb amputation, and death. Because T1D results from the autoimmune destruction of insulin-synthesizing pancreatic β cells, simply replacing these cells is not a viable therapeutic strategy. Instead, introducing a cell that has been engineered to perform an unnatural yet important task—for example, a T lymphocyte that has been modified to sense glucose and produce insulin—is a provocative alternative. Such a cell is potentially within the reach of synthetic biology and, if it relieved the insulin dependency of T1D patients, would represent a major therapeutic breakthrough. For the subset of T1D cases characterized by the presence of autoantibodies that recognize and destroy insulin, this cell might be engineered to produce an insulin derivative that recognizes and modulates the activity of insulin receptors but evades binding by insulin autoantibodies.

KILLER APPS FOR CELL THERAPY

Although small molecules and biologics will always have important therapeutic niches, there are applications for which cells are better equipped. This section explores critical unmet needs in human disease that cell-based therapeutics are uniquely well suited to address (Fig. 1). We focus on three specific cases, although there are arrays of other promising applications that are not discussed here, including stem cell and dendritic-cell therapeutics, which have been the subjects of numerous reviews (*10*–*13*). Two of these cases are built on recent pioneering examples of cell-based therapies that have demonstrated clinical efficacy: chimeric antigen receptor (CAR)–modified T cells and fecal transplantations.

Immune cells that seek and destroy cancer. The most effective new small-molecule (kinase inhibitors) and biologic (antibody) cancer therapies offer as little as 6 to 36 months of disease-free survival before cancer progression (*14*, *15*). Therefore, one of the major challenges for cancer therapy is to block the growth of drug-tolerant or resistant cancer cells that underlie progression and to kill metastatic cells that have broken free of the primary tumor mass and intravasated into a blood or lymphatic vessel.

Combination therapies that prevent the outgrowth of resistant cells are one possible therapeutic avenue, but small molecules and biologics have a difficult time being sentinels. They cannot turn themselves on and off, and so they rely entirely on specific molecular recognition to determine whether or not they act. And because the target cell can evolve resistance mechanisms (*14*), the therapeutically useful lifetime of a small molecule or biologic is limited.

The job of detecting and destroying a shape-shifting cellular target may be better suited to a cell-based therapeutic. Recent clinical studies have shown the efficacy of using engineered T lymphocytes in treating chronic lymphoid leukemia (*3*, *4*). The ex vivo–transformed T cells were modified to express a CAR in which the receptor extracellular targeting domain has been replaced by an single-chain antibody that recognizes a tumor-specific molecule. These and related studies: (*7*) (i) prove that it is possible to retarget immune cells to detect and respond to new, non-natural signals and (ii) establish T cells as a favorable chassis for engineering. Future versions of CAR-modified T cells may encode control circuits that enable them to be activated or deactivated in

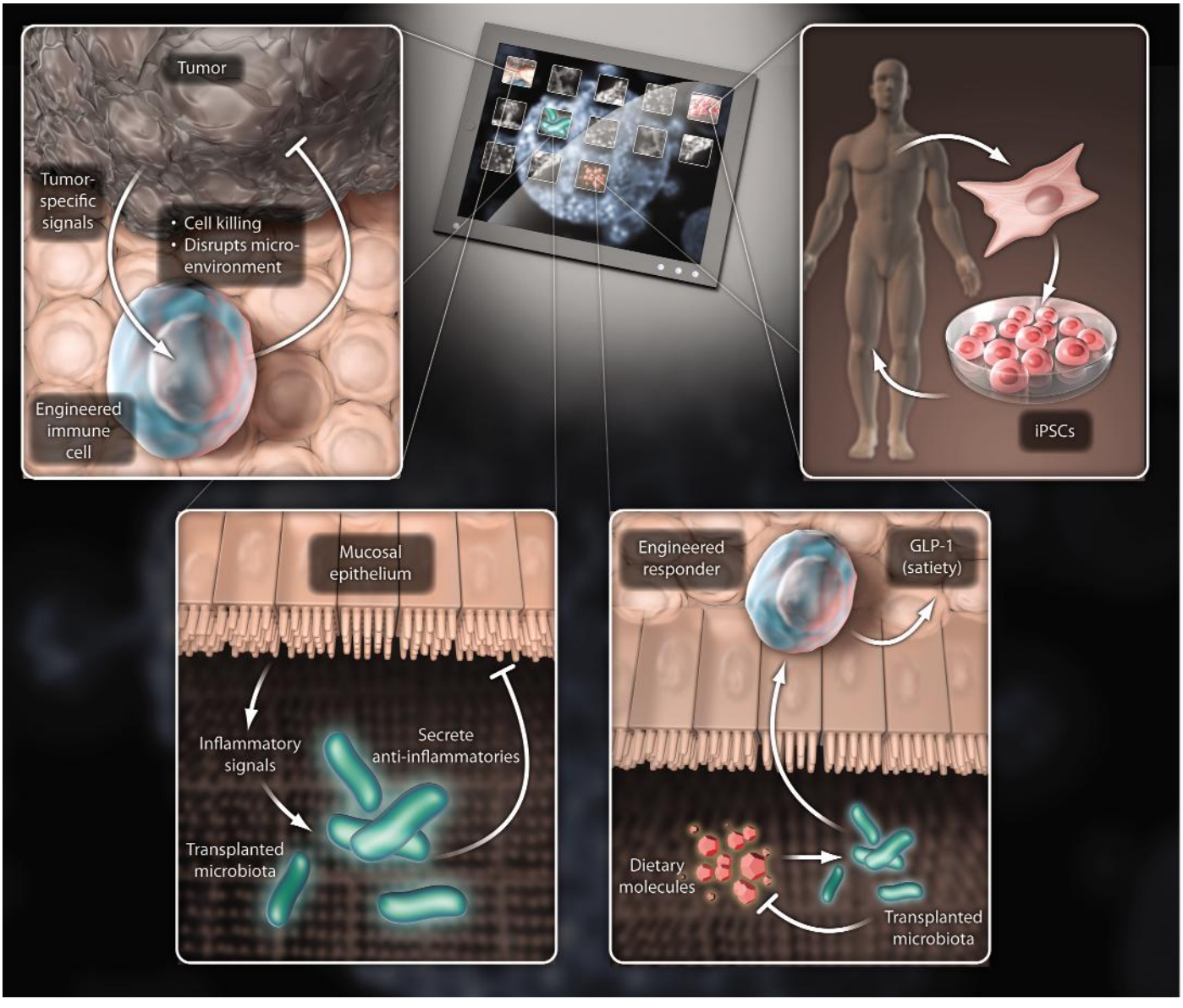

Fig. 1. Killer apps. Although small molecules and biologics will always have important therapeutic niches, there are numerous applications for which cells are better equipped. Four killer applications for cell-based therapeutics are shown: immune cells engineered to recognize and kill tumor cells, transplanted microbiota that detect and treat intestinal inflammation (e.g., Crohn's disease) by producing an anti-inflammatory small molecule or biologic, a combination bacterial/mammalian cell therapeutic in which the bacterial cell converts dietary sugars into a nonabsorbed fermentation product and activates the production of a satiety-inducing hormone by the companion human cell therapeutic, and patient-specific stem cells for regenerative medicine [not discussed herein, but see (*13*)]. iPSCs, induced pluripotent stem cells.

a small-molecule–dependent fashion and to produce a biologic that counteracts adverse side effects, such as cytokine storm (for example, an anti–IL-6 antibody).

Establishment of drug resistance is less likely to be a problem for a sentinel cell therapeutic than for small molecules and biologics. A therapeutic cell could be engineered to recognize multiple features of a target cell so that changing any one of them would not be enough to evade detection (in effect, a combination therapy). Given the ability of a cell-based therapeutic to adapt to an evolving pathogen, cells may be a natural choice for other surveillance jobs as well, including seeking and destroying activated cells from chronic infections, such as a latent *Mycobacterium tuberculosis* population.

Bacterial treatment for Crohn's disease. Gastrointestinal diseases are a promising target for microbiota-based therapies (*16*–*18*). Recent clinical studies have demonstrated that fecal transplants—a group of procedures in which an intact bacterial community is transplanted into the GI tract of a patient, replacing his or her endogenous microbial community—are effective treatments for recurrent *Clostridium difficile* infection (*5*). Could similar therapies be effective against much more prevalent maladies?

The inflammatory bowel disorder Crohn's disease can be difficult to manage, and treatment sometimes involves potent

immunosuppressive drugs with serious side effects or surgical resection of inflamed segments of the intestine. Two lines of evidence indicate that altering the composition of the gut microbial community could be a viable treatment for Crohn's. First, enumeration studies show major perturbations to the gut community in Crohn's patients. Even if these are a consequence of gut inflammation rather than the primary cause of disease, the symptoms of Crohn's could be downstream of the population shift, creating a vicious cycle that leads to more inflammation. Thus, adjusting the community composition could be enough to interrupt the cycle and return the patient to an asymptomatic state. Second, antibiotic treatment is often effective for treating Crohn's flares. In contrast to a broad-spectrum antibiotic, a therapeutic fecal transplantation into the gut could shift the community to a disease-free state without the risk of a secondary *C. difficile* infection.

In the future, the microbial community to be transplanted is likely to be an artificial, well-characterized mixture of strains (*19*) with the properties of a natural community (for example, resilience) and may include species that have been engineered to sense inflammation and respond by producing anti-inflammatory small molecules or biologics. The advantages of a fecal transplant or its equivalent are manifold: A single treatment could have a long duration, it would not be nearly as invasive or costly as surgery, it would not carry the risk of a secondary infection, and it would avoid the consequences of immunosuppressive therapy.

Combining bacterial and mammalian cell therapeutics. Some diseases might benefit from the combination of a bacterial cell therapeutic and a mammalian cell therapeutic. One example is metabolic syndrome, for which a combination cell therapy that simultaneously decreases caloric harvest from the diet and appetite would be a powerful solution. A therapeutic bacterium in the gut lumen could sense the presence of carbohydrate intake and convert it into a nonabsorbed fermentation end product that is consumed by a secondary fermenter. At the same time, it could signal to a human cell–therapeutic situated adjacent to the basolateral surface of the intestinal epithelium to activate its satiety program, including the production of satiety-inducing peptide hormones such as GLP-1. A combined bacterial-mammalian cell therapeutic would likely require engineered interkingdom communication systems that are orthogonal to natural signaling pathways.

MAKING CELL THERAPEUTICS SAFE

The two major challenges in developing any new therapy are safety and efficacy. As the examples above examine the potential efficacy of cell-based therapeutics, we focus here on safety and cost concerns that lie at the core of much of the skepticism about cell-based therapeutics. The development pipeline of cell-based therapeutics likely will be considerably different from that of small molecules. More effort may be required to engineer these agents and to optimize their activity profiles, but we predict that cell therapies are less likely to yield the kinds of unanticipated, late-stage problems that so often kill promising small molecules.

The lifetime of a cell can be carefully controlled. An important limitation of small molecules and biologics is that their half-lives are often difficult to tune. Too short a half-life can necessitate an onerous dosing schedule or render a drug candidate unviable, while too long a half-life can carry safety risks.

The lifetime of a cell-based therapeutic represents both a liability and an opportunity. On one hand, a primary safety concern for mammalian cell-based therapeutics is that the cells will become transformed and divide uncontrollably, forming a circulating cancer or a solid tumor (*20*). Likewise, a bacterial cell therapeutic could breach an epithelium or enter an open wound and cause a deadly infection.

On the other hand, the lifetime of a cell can be controlled by natural and unnatural (engineered) circuits. Most mammalian cell types can only undergo ~40 cell divisions before their telomeres grow too short for continued viability. In addition, two types of synthetic lifetime controls hold great promise. First, a signaling pathway could be introduced that causes a cell to destroy itself after a defined number of cell divisions (*21*) or in response to a diffusible signal (*22*). Second, multiple auxotrophies (that is, metabolic dependencies) or drug susceptibilities can be engineered into cells so that they require an external nutrient in order to divide or can be killed easily by drugs that do not harm other cells, respectively.

If reliable mechanisms to control cell division can be introduced, there would be great advantages to a therapeutic that can make more of itself—in principle, one treatment could last indefinitely (for example, memory T cells that expand only when disease reappears). In the end, the safety concern will be that one in a billion cells evades the control mechanism, but even those odds can be overcome by using redundant mechanisms.

The U.S. Food and Drug Administration (FDA) has well-defined safety and efficacy criteria for small molecules and biologics (www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm). If regulatory agencies develop similar criteria for cell-based therapeutics (*23*) so that prospective developers know what standards have to be met, it might encourage early movers to invest in new companies focused on developing creative cell-based therapeutics.

Better odds in the therapeutic development pipeline? Clinical outcomes for small molecules and biologics are notoriously unpredictable, even when the preclinical data appear promising; the average length of time from target discovery to approval of a new drug averages ~14 years, the failure rate exceeds 95%, and the cost per successful new medical entity is >$2 billion (after adjusting for failures) (www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs). Because cell-based therapeutics are more complicated, the argument goes, their clinical performance will be even less predictable. Will therapeutic cells be reliable and predictable with respect to their proliferative capacities, localization, behaviors, and mechanisms of action (for example, how much cytokine will an engineered therapeutic immune cell produce and under what physiological cues)? Will engineered regulatory circuits be robust enough to remain in control of a cell even if it mutates in the host? What are the long-term effects of cell therapies?

However, the very trait that makes researchers, investors, and regulatory agencies leery of cell therapies—their complexity—might actually make these agents more predictable in the clinic than small molecules or biologics. Many of the complicated circuits in a cell exist to *restrict* its activity, both spatially and temporally (*24*, *25*). An unintended toxicity that results from the action of a drug in an off-target tissue could be overcome by using a cell-based therapy specifically designed to attack one cell type. Likewise, using a cell that automatically modulates its activity on the basis of a measured response could surmount toxicity that occurs, for example, because of a rare polymorphism that alters the concentration of active drug in circulation.

Cell-based therapeutics may suffer from their own kinds of unintended side effects, such as an inability to easily eliminate the cells, stability of the cells in different tissue ecosystems, and targeting the cells to the right place and only the right place. But these problems may eventually prove to be easier to fix with a designer cell–therapeutic than with small molecules or biologics, because with cells, one has the option of adding or modifying a regulatory control circuit.

BUILDING A FOUNDATION

With the many challenges outlined above, how does the field of cell-based therapeutics move forward so that the potential of the third pillar is transformed into opportunities that display advantages over other therapeutic platforms? Here, it is useful to consider historical precedent: How was skepticism overcome for earlier therapeutic pillars, allowing them to become the basis of viable industries?

At the beginning of both the small-molecule and biologics eras, the fields were composed mainly of naturally occurring entities, such as natural-product drugs and hormones purified from mammalian tissues. But after a couple of decades, these industries became dominated by engineered entities. Fully synthetic small molecules designed by skilled synthetic chemists allowed the freedom to achieve more specific targeting, control over PK and PD, and minimization of toxicity. The realm of biologics has become, to a large extent, dominated by molecules designed by protein engineers—for example, insulin derivatives with customized PK or humanized antibodies optimized for specific target recognition and minimal immunogenicity.

These precedents strongly suggest that the sustainable growth of a cell-based therapeutics industry will require the development of a foundational science of cellular engineering (Fig. 2). How could it not? Imagine trying to develop new small-molecule drugs without the ability to make or break specific carbon-carbon bonds or without theories that predict how the changes will affect drug properties such as PK, PD, and target binding affinity. Imagine trying to develop a new biologic without ways to reliably and efficiently make site-specific mutations or without a knowledge base that predicts how these changes will affect target recognition and immunogenicity. Without a parallel cellular engineering science, cell-based therapeutics will likely continue to rely on ad hoc solutions that we happen to stumble upon, with no systematic way to design or optimize cells in a strategic, reproducible way.

We believe that the nascent fields of systems biology and synthetic biology can be steered, by funding mechanisms and interdisciplinary education programs, to grow into a predictive engineering science that will allow researchers to control and tune the behaviors of cells in a reliable and flexible manner. To this end, the fundamental capabilities required for a foundational cell engineering science must be defined. Below we list some of the key control modules needed in a nascent cellular engineer's toolbox:

- Control over cell proliferation in order to ensure their survival upon implantation.
- Control over cell death, both by self-regulated mechanisms and by externally regulable "safety-switch" mechanisms.
- The ability to redirect cellular migration and movement toward specific signals and sites in the body where the cells should execute their action (for example, cell killing, differentiation, and repair).
- Quantitative control of therapeutic cellular responses, including the ability to independently tune activation thresholds and response amplitudes. In addition, the ability to specifically control the type of response a cell elicits (for example, independent control of different classes of T-cell responses, such as activation, cytotoxicity, and memory cell establishment).
- The ability to reprogram cell communication, including cell-cell, small-molecule–cell, and biologic-cell communication. We will also require the development of orthogonal communication systems that provide the physician with the ability to directly instruct cells using modalities such as drugs or light (*26*).
- On-demand production and secretion

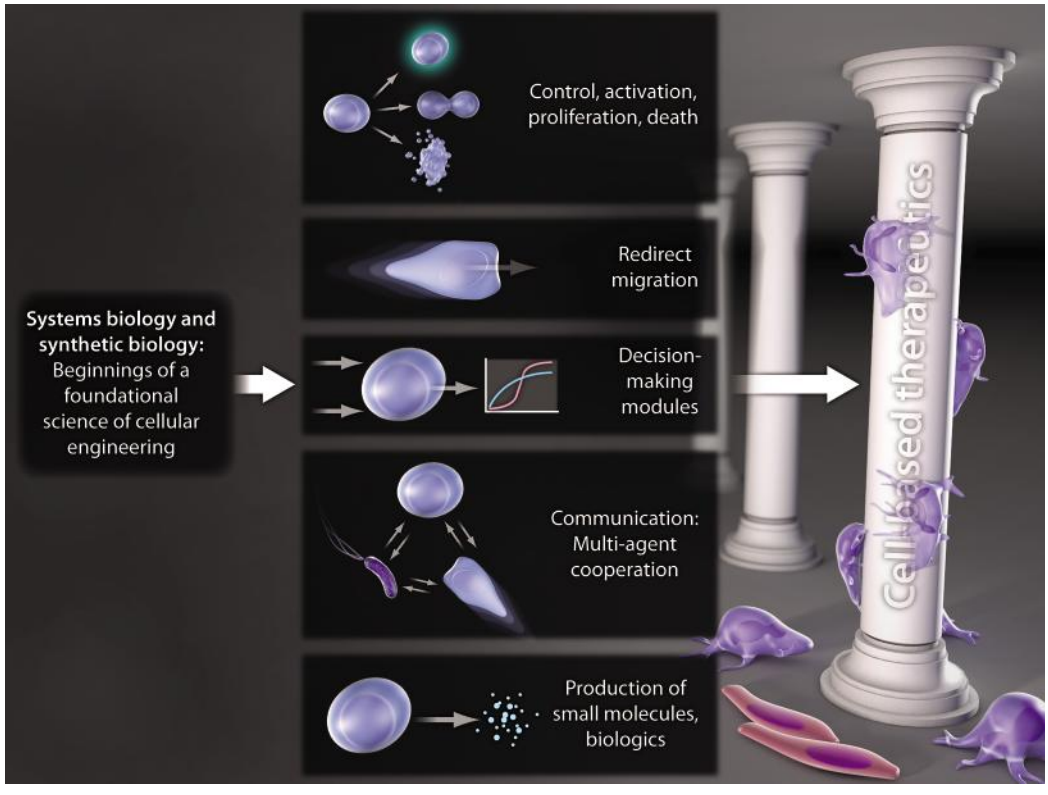

Fig. 2. Evolution and (beyond) tinkering. The sustainable growth of a cell-based–therapeutic industry requires the evolution of a foundational science of cellular engineering. Fundamental knowledge and capabilities developed by cellular engineering scientists will allow us to move beyond tinkering toward systematic mechanisms for predictable modulation of cell proliferation, migration, communication, and the production of small molecules and biologics.

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of small molecules and biologics by engineered cells, extending beyond those molecules that a cell naturally makes.

• Development of systematic strategies and intuition for how to tune and reshape cellular behaviors, rather than relying on ad hoc tinkering of cells. One precedent is the sophisticated engineering science of control theory, which is currently used to design myriad autoregulated devices, including thermostats, cruise control systems, and autopilot systems. Control theory is founded on the basic idea that there are defined control circuits that are optimal for particular situations. Can we develop analogous theories that guide our choice of cellular control modules?

As we look forward, the idea of developing such tools for the rational engineering of therapeutic cells is tremendously exciting, yet also daunting. But it is important to remember that cells have the ability to use molecular circuits to achieve remarkably precise and controlled behaviors and, thus, that these goals are physically possible. The challenge of genetically engineering cells at this level of complexity is also daunting, but it would be a mistake to let this limit what we try to do. Our capability to genomically edit even human cells is growing rapidly (*27*), and it is important that we be prepared with ideas about the types of genetic changes we will want to make using advanced genetic engineering technologies that will be available in 5 to 10 years. Now is the time to begin taking these simple and systematic steps forward, much as early practitioners of synthetic chemistry and protein engineering began to tinker and expand their toolboxes to lay the solid foundation for future therapeutic industries.

REFERENCES AND NOTES

1. C. Mason, D. A. Brindley, E. J. Culme-Seymour, N. L. Davie, Cell therapy industry: Billion dollar global business with unlimited potential. *Regen. Med.* **6**, 265–272 (2011).
2. C. G. Brunstein, J. S. Miller, Q. Cao, D. H. McKenna, K. L. Hippen, J. Curtsinger, T. Defor, B. L. Levine, C. H. June, P. Rubinstein, P. B. McGlave, B. R. Blazar, J. E. Wagner, Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: Safety profile and detection kinetics. *Blood* **117**, 1061–1070 (2011).
3. D. L. Porter, B. L. Levine, M. Kalos, A. Bagg, C. H. June, Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N. Engl. J. Med.* **365**, 725–733 (2011).
4. N. P. Restifo, M. E. Dudley, S. A. Rosenberg, Adoptive immunotherapy for cancer: Harnessing the T cell response. *Nat. Rev. Immunol.* **12**, 269–281 (2012).
5. E. van Nood, A. Vrieze, M. Nieuwdorp, S. Fuentes, E. G. Zoetendal, W. M. de Vos, C. E. Visser, E. J. Kuijper, J. F. Bartelsman, J. G. Tijssen, P. Speelman, M. G. Dijkgraaf, J. J. Keller, Duodenal infusion of donor feces for recurrent Clostridium difficile. *N. Engl. J. Med.* **368**, 407–415 (2013).
6. E. J. Culme-Seymour, N. L. Davie, D. A. Brindley, S. Edwards-Parton, C. Mason, A decade of cell therapy clinical trials (2000-2010). *Regen. Med.* **7**, 455–462 (2012).
7. M. Kalos, B. L. Levine, D. L. Porter, S. Katz, S. A. Grupp, A. Bagg, C. H. June, T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. *Sci. Transl. Med.* **3**, 95ra73 (2011).
8. W. A. Lim, Designing customized cell signalling circuits. *Nat. Rev. Mol. Cell Biol.* **11**, 393–403 (2010).
9. Y. Shu, S. A. Sheardown, C. Brown, R. P. Owen, S. Zhang, R. A. Castro, A. G. Ianculescu, L. Yue, J. C. Lo, E. G. Burchard, C. M. Brett, K. M. Giacomini, Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *J. Clin. Invest.* **117**, 1422–1431 (2007).
10. S. J. Sharkis, R. J. Jones, C. Civin, Y.-Y. Jang, Pluripotent stem cell–based cancer therapy: Promise and challenges. *Sci. Transl. Med.* **4**, 127ps9 (2012).
11. N. Uchida, K. Chen, M. Dohse, K. D. Hansen, J. Dean, J. R. Buser, A. Riddle, D. J. Beardsley, Y. Wan, X. Gong, T. Nguyen, B. J. Cummings, A. J. Anderson, S. J. Tamaki, A. Tsukamoto, I. L. Weissman, S. G. Matsumoto, L. S. Sherman, C. D. Kroenke, S. A. Back, Human neural stem cells induce functional myelination in mice with severe dysmyelination. *Sci. Transl. Med.* **4**, 155ra136 (2012).
12. D. Scadden, A. Srivastava, Advancing stem cell biology toward stem cell therapeutics. *Cell Stem Cell* **10**, 149–150 (2012).
13. I. Weissman, Stem cell therapies could change medicine... If they get the chance. *Cell Stem Cell* **10**, 663–665 (2012).
14. P. B. Chapman, A. Hauschild, C. Robert, J. B. Haanen, P. Ascierto, J. Larkin, R. Dummer, C. Garbe, A. Testori, M. Maio, D. Hogg, P. Lorigan, C. Lebbe, T. Jouary, D. Schadendorf, A. Ribas, S. J. O'Day, J. A. Sosman, J. M. Kirkwood, A. M. Eggermont, B. Dreno, K. Nolop, J. Li, B. Nelson, J. Hou, R. J. Lee, K. T. Flaherty, G. A. McArthur, BRIM-3 Study Group, Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N. Engl. J. Med.* **364**, 2507–2516 (2011).
15. A. Sandler, R. Gray, M. C. Perry, J. Brahmer, J. H. Schiller, A. Dowlati, R. Lilenbaum, D. H. Johnson, Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* **355**, 2542–2550 (2006).
16. K. P. Lemon, G. C. Armitage, D. A. Relman, M. A. Fischbach, Microbiota-targeted therapies: An ecological perspective. *Sci. Transl. Med.* **4**, 137rv5 (2012).
17. J. L. Sonnenburg, M. A. Fischbach, Community health care: Therapeutic opportunities in the human microbiome. *Sci. Transl. Med.* **3**, 78ps12 (2011).
18. E. Holmes, J. Kinross, G. R. Gibson, R. Burcelin, W. Jia, S. Pettersson, J. K. Nicholson, Therapeutic modulation of microbiota-host metabolic interactions. *Sci. Transl. Med.* **4**, 137rv6 (2012).
19. E. O. Petrof, G. B. Gloor, S. J. Vanner, S. J. Weese, D. Carter, M. C. Daigneault, E. M. Brown, K. Schroeter, E. Allen-Vercoe, Stool substitute transplant therapy for the eradication of Clostridium difficile infection: 'RePOOPulating' the gut. *Microbiome* **1**, 3 (2013).
20. S. Hacein-Bey-Abina, C. von Kalle, M. Schmidt, F. Le Deist, N. Wulffraat, E. McIntyre, I. Radford, J. L. Villeval, C. C. Fraser, M. Cavazzana-Calvo, A. Fischer, A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. *N. Engl. J. Med.* **348**, 255–256 (2003).
21. A. E. Friedland, T. K. Lu, X. Wang, D. Shi, G. Church, J. J. Collins, Synthetic gene networks that count. *Science* **324**, 1199–1202 (2009).
22. A. Di Stasi, S. K. Tey, G. Dotti, Y. Fujita, A. Kennedy-Nasser, C. Martinez, K. Straathof, E. Liu, A. G. Durett, B. Grilley, H. Liu, C. R. Cruz, B. Savoldo, A. P. Gee, J. Schindler, R. A. Krance, H. E. Heslop, D. M. Spencer, C. M. Rooney, M. K. Brenner, Inducible apoptosis as a safety switch for adoptive cell therapy. *N. Engl. J. Med.* **365**, 1673–1683 (2011).
23. P. Au, D. A. Hursh, A. Lim, M. C. Moos Jr., S. S. Oh, B. S. Schneider, C. M. Witten, FDA oversight of cell therapy clinical trials. *Sci. Transl. Med.* **4**, 49fs31 (2012).
24. T. Cheng, N. Rodrigues, H. Shen, Y. Yang, D. Dombkowski, M. Sykes, D. T. Scadden, Hematopoietic stem cell quiescence maintained by $p21^{cip1/waf1}$. *Science* **287**, 1804–1808 (2000).
25. R. H. Schwartz, T cell anergy. *Annu. Rev. Immunol.* **21**, 305–334 (2003).
26. A. Levskaya, O. D. Weiner, W. A. Lim, C. A. Voigt, Spatiotemporal control of cell signalling using a light-switchable protein interaction. *Nature* **461**, 997–1001 (2009).
27. P. Mali, L. Yang, K. M. Esvelt, J. Aach, M. Guell, J. E. DiCarlo, J. E. Norville, G. M. Church, RNA-guided human genome engineering via Cas9. *Science* **339**, 823–826 (2013).

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