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Perspectives

Preparing for the future of precision medicine: synthetic cell drug regulation

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Abstract

Synthetic cells are a novel class of cell-like bioreactors, offering the potential for unique advancements in synthetic biology and biomedicine. To realize the potential of those technologies, synthetic cell-based drugs need to go through the drug approval pipeline. Here, we discussed several regulatory challenges, both unique to synthetic cells, as well as challenges typical for any new biomedical technology. Overcoming those difficulties could bring transformative therapies to the market and will create a path to the development and approval of cutting-edge synthetic biology therapies.

Key words: synthetic cells; artificial cells; personalized medicine; liposomal bioreactors; cell-free protein expression

Graphical Abstract

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1. Introduction

In 2017, researchers estimated that it would take 5000 expert years to engineer the first synthetic living cell: an organism capable of growth and replication, consisting entirely of artificial components (1, 2). While there is still ongoing discussion on the exact definition of 'synthetic' and 'living' in this field, there is general consensus on the hallmarks of living systems: compartmentalization, growth and development, information processing, energy transduction and adaptability (3). If we can address these principles, we may be able to start building cells from entirely non-living parts (4). Taking on this enormous engineering challenge requires the participation and collaboration from researchers from a wide range of disciplines worldwide (5).

Synthetic cells are bioreactors that metabolize and reproduce, just as living cells do, but that are constructed entirely from non-living organelles and cell membranes, synthetically derived chemicals and a synthetically engineered genome, all constructed in a lab. These cell-like molecules are created from artificial parts and, when put together to form a 'cell', are identifiable and comprehensible from the inside out. Synthetic cells have artificial genomes (this could be both extensively modified natural genomes and genomes designed and synthesized entirely from scratch), similar to existing chimeric antigen receptor T (CAR-T) cell therapies. They can express genes into proteins, just as natural cells do. While as of now, synthetic cells cannot self-replicate, scientists can replicate them artificially in the lab (3). We do, however, envision a future where these cells may evolve to be able to do this on their own. This differs from what are often referred to as synthetic drug delivery systems, known as lipid nanoparticle-based drug delivery systems, which are isolated lipid compartments that often have an engineered genome, which some may refer to as synthetic (6).What sets these systems apart is that one is derived from a living cell, while the other is constructed from artificial components from the bottom up. The bottom-up assembled systems include lipid vesicle and nanoparticle-based delivery vehicles, while the top-down approach yielded live-cell-derived CAR-T type of therapeutics. The Food and Drug Administration (FDA) approval process focuses on the end product, not the research route that led to it; therefore, the exact mechanisms that led to the development of specific formulations might not be critical in the process of reaching the market.

Synthetic cells hold the potential to advance precision medicine, increase access to pharmaceuticals in underserved communities, and transform therapeutic production processes globally (7, 8). However, because artificial cells are an emerging technology, they still await lengthy scale up of the manufacturing and testing protocols. Like with all technologies, their novelty raises many concerns regarding efficacy, safety and biosecurity. Because regulatory agencies like the FDA have never seen a therapeutic application of synthetic cells, regulators have yet to fully evaluate whether current review processes align with artificial cell anatomy, functionality and contemporary bioethical dilemmas (9).

2. Why use synthetic cells

While natural living cells and liposomal drug delivery systems exist, synthetic cells may offer several unique advantages to those technologies (Table 1, Figure 1).

Specially engineered synthetic cells may provide researchers and caregivers the benefit of easily identifiable signals, known chemical makeup and full programmability, in addition to lowering the costs of drug development and testing. This allows advancing novel fields of health care, such as precision medicine and point-of-care biomanufacturing.

Precision medicine includes personalized therapeutics, engineered to fit the genetic makeup of individual patients. The promise of precision medicine is a future where practitioners can use synthetic cells' adaptable makeup to design drug delivery systems that target the specific cells of the body. In the example of cancer treatments, this means targeting tumor cell while preserving cells with healthy DNA—in a small scale, agile manufacturing platform (10).

Another asset of synthetic cells is controllability. A lot of research effort was and is being spent to increase the controllability and programmability of synthetic cell bioreactors, mainly using genetic circuits, logic gates and small-molecule transcription and translation modulation tools (11–13). The programmability of artificial cells allows us to control the amount of product a cell-based treatment produces and how long production continues.

Finally, synthetic cells enable efficient therapeutic development, because they do not require the traditional cloning steps, and reactions could be more easily automated (14). Cell-free protein synthesis (CFPS) enables transcription and translation with crude cellular extracts instead of intact cells. In contrast to traditional cells, CFPS and synthetic cells do not require life to be sustained, allowing for faster and less costly reactions, with less byproducts and side processes (15).

3. Regulatory challenges

Synthetic cells offer opportunities to treat rare diseases, improve treatment efficacy and engineer life-saving therapeutics, much like vaccines (7, 8, 16). At the moment, however, they lack regulatory guidelines (9). Among synthetic biologists, it is thought that because synthetic cells are anticipated to be built from the bottom up, allowing for more precision and less complexity in their composition, they will be more easily controlled and possess less risk than top-down synthetically engineered microorganisms.

FDA guidelines for regulating synthetic cell drug delivery systems do not yet exist. If synthetic biologists were to follow existing guidelines for CAR-T cells, which the FDA currently regulates as gene therapies, there remain several gaps in the investigative new drug (IND) application that synthetic cells could not fulfill, mainly because there is lack of data—no synthetic cell-based drug has yet reached the clinical trial stage. See Figure 2 for an overview of this process. The specific major gaps that will need to be filled before the first synthetic cell therapeutic product enters the clinical pipeline are related to the reproducibility of the formulation, the need for safety assessment of individual components included in making of a complex synthetic cell and the need to investigate clearing pathways and metabolites.

CAR-T drug developers first encountered challenges in evaluating the complex functional elements these cells are composed of (17). Similar to CAR-T therapies, synthetic cell drug delivery will likely contain antigen recognition and signaling domains, both of which must be assessed for their abilities to bind to and activate target molecules. Similarly, the means by which synthetic cell drug delivery systems actually deliver a drug to cells, likely via a vector complex, will need to be thoroughly outlined and accounted for in an IND application.

For CAR-T cells, the FDA also recommends that drug developers account for all risks associated with cellular starting materials for these cell therapies (18). Here begins a major gap in regulatory

Table 1. Comparison of advantages of natural living cells, synthetic cells, liposome drug delivery systems and cell-free-based therapeutics

	Live cell therapeutics	Synthetic cells	Liposome drug delivery	Cell-free systems
Ability to use unnatural building blocks (26, 27)	Limited	High	High	High
Responsiveness to changes in the environment and patient condition (28)	High	High	Low	High
Speed of design iteration for new variants (15)	Low	Highest	High	High
Controllability of formulation and programmed behavior (29)	Low	Low	High	High
Reproducibility of formulation (30)	Low	Low	High	Lowest

This table is a very approximate comparison based on current state of the art, with the possibility of future work bringing in new advantages or development of new technologies negating some of the benefits of other methods.

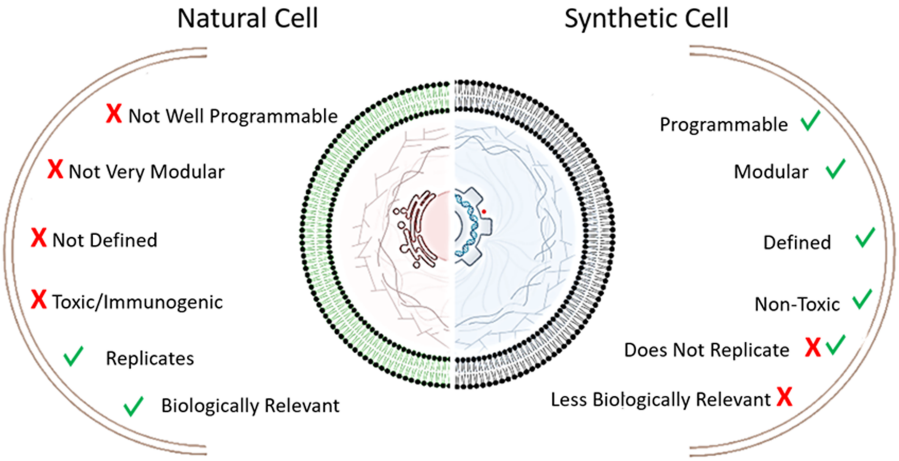

Figure 1. General comparison of natural versus synthetic cells.

guidelines for synthetic cells, as they will be the first of their kind to not originate from cellular starting materials.

Following the regulatory process for CAR-T cell-based therapies provides a good blueprint for potential challenges of approving complex synthetic cell formulations. Both technologies can be similarly undefined in their chemical makeup, and there is expected variability between each cell batch or synthetic cell preparation. Additionally, the most clinically advanced synthetic cell indications are in the area of cancer therapies (10), drawing additional similarities with CAR-T indications.

A second challenge for synthetic cell manufactures is abiding by central good manufacturing processes (cGMPs), a step required by all drug developers after gaining initial FDA authorization. According to the guidance issued by the FDA in 2008, cGMPs for Phase 1 of production must include written procedures, equipment, facility and manufacturing controls and accurate record-keeping. The FDA also, however, has outlined the added caveat that gene and cell therapies require novel means of production and thus are exempted from abiding by Phase 1 cGMP requirements. It is reasonable to assume that if synthetic cells are classified as 'cell therapies' for the purpose of regulatory process, this exemption will apply to most synthetic cell technologies as well. If the synthetic cell is used merely as a drug delivery vehicle, the exemption might not apply.

Because synthetic cell drug delivery systems are in the early stages of development, the cGMPs for these technologies do not yet exist. Drafting sufficient cGMPs proves especially difficult for synthetic cells, as they combine individual artificial components that have not been necessarily approved by themselves. In some cases, depending on the synthetic cell anatomy, different cGMPs may need to be approved to account for each novel piece of technology. In addition, systems containing engineered proteins may require their own biological or chemical approval process. Adherence to cGMP is required for FDA licensing of genetically engineered T cells and will likely be required for synthetic cells as well. Once synthetic cells are successfully built for the first time, it is likely that some aspects of this process will be standardized, making determining cGMP regulations easier.

A third area of concern is classifying biosafety levels (BSLs) of synthetic cell laboratories. When laboratories work with infectious agents, they perform a risk assessment to determine the level of threat various agents present to lab and health care workers and determine guidelines for appropriate laboratory safety equipment. BSLs range from BSL-1 to BSL-4, with 4 defining the maximum level of containment required in a lab space. BSL ratings are, in part, determined by the pathogen type. Because synthetic cells do not fit in with current definitions of pathogens, it may be difficult to employ this section of the rating scale. Therefore, the BSL rubric must be reevaluated upon the launch of synthetic cell therapeutic systems to mitigate potential safety concerns.

A fourth area that might prove challenging is the potential for synthetic cell therapeutics to fall under different FDA classification areas. While each area might have its own, unique, regulatory requirements, approval of a synthetic cell therapeutic might require satisfying diverse set of rules and provisions.

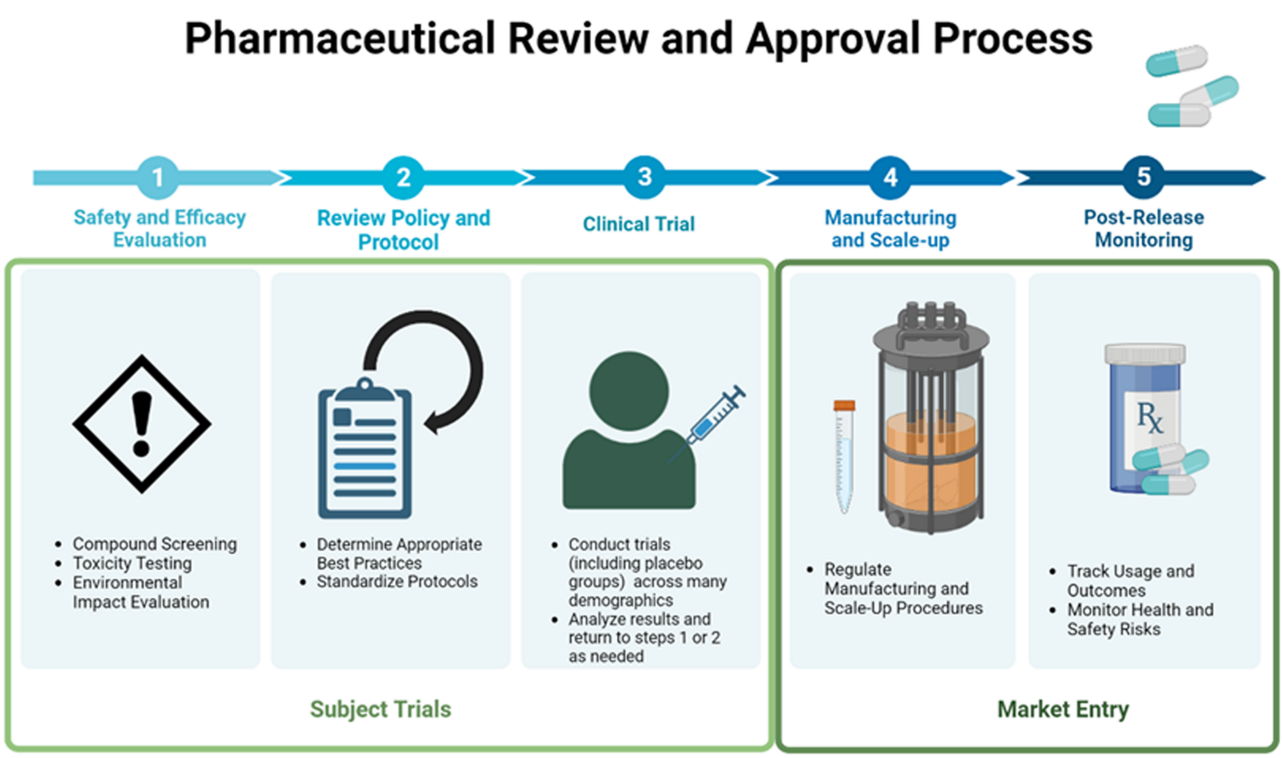

Figure 2. The schematic of the process of developing new FDA approved drug during and after trial. Synthetic cell engineering challenges will need to be met at each of those steps. This process is likely to differ in details and length, depending on the indication and technology the drug is based on.

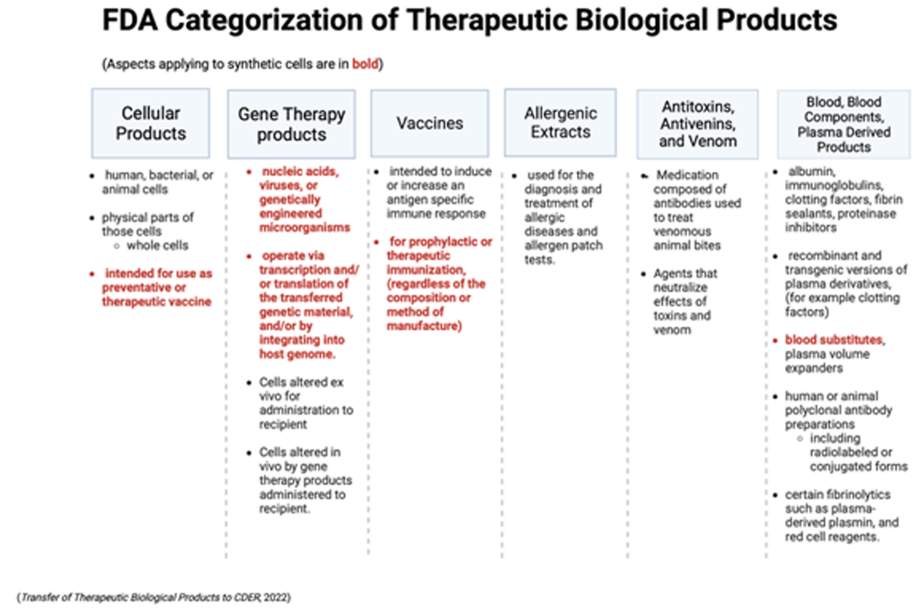

Figure 3. Different categories of therapeutic biologicals, with the main synthetic cell application possibilities highlighted.

Figure 3 summarizes the main categories of biological therapeutics and highlights the potential areas matching synthetic cell therapeutics likely to enter the pipeline in the near future.

The evaluation challenges for synthetic cell therapeutics in different areas will depend mainly on the composition of the formulation. Most synthetic cells might be possible to formulate using completely known chemical composition. However, in cases where whole-cell translation system or other less strictly defined components will be needed, the regulatory challenges will include reproducibility of the formulation and sourcing of the materials.

Finally, the cost of research and development remains a prominent barrier to advancements toward future synthetic cell drug delivery systems (19). Lacking a viable pipeline toward application hinders interest in early support and funding. There are also examples of recent gene therapy products, such as Hemgenix, recently approved to treat hemophilia B, that end in a product that

imposes exorbitant costs to the consumer. Such trials and treatments can be learned from and potentially better adapted in the form of synthetic cells (20).

Overall, the regulatory challenges expected to arise in the process of approval of the first synthetic cell therapeutics can be divided into two groups: the uncertainty about the approval path and the need for specific data for new systems.

In some cases, it is still even unclear what category and criteria will be used. This uncertainty of which approval path to pursue includes, for example, a complex synthetic cell capable of expressing proteins using a whole-cell lysate *in vitro* translation system. Would this formulation be evaluated following in the footsteps of CAR-T and other live cell technologies or would regulators insist on performing detailed characterization of a complete chemical composition?

The other group includes technologies where more clarity is needed in characterization of the specific features of the system. For example, for drugs made using cell-free translation systems (like small-molecule therapeutics or vaccines), it will be necessary to characterize the entirely new purification process or assess the acceptable carryover of enzymes and other components of the synthesis machinery into the final product. In another example, preparing liposomal formulations of synthetic cells, the necessary membrane modifications and size of the liposomes can be inferred from existing liposomal drugs but still needs to be characterized in detail for each formulation.

Perhaps all these challenges lie under a larger dilemma that scientists still lack a clear definition of what a synthetic cell is. Does a synthetic cell need to both replicate and evolve to be considered a cell? While clarity is abundantly needed in this regard, this conflict further stresses why regulators and scientists should begin an open dialogue now on how this biotechnology will be regulated once it comes into existence (21).

4. The FDA regulatory environment

Ultimately, gaining FDA approval requires demonstrating development feasibility and a need for the product under consideration.

The coronavirus disease pandemic posed unique regulatory challenges that demanded innovative solutions from regulatory agencies. Specifically, the FDA's emergency use approval of vaccines utilizing lipid nanoparticles to enclose mRNA and employ *in-vivo* gene delivery technology required a reevaluation of certain aspects of the regulatory process (22). Similarly, the evaluation and approval of synthetic cell drug delivery systems may also necessitate adaptability.

While certain stages of evaluating the first mRNA vaccines, including pre-clinical trials, clinical trials and post-market surveillance, followed established protocols used for previous vaccines, these vaccines introduced unprecedented components that warranted their own evaluation and the formulation of new guidelines. Consequently, regulators must be prepared to navigate the forthcoming generation of synthetic cell drug delivery systems by independently assessing each distinct artificial component.

To effectively address these evolving technologies, regulators need to possess the knowledge and expertise required to evaluate the safety and efficacy of each synthetic cell component. Collaboration among researchers, industry experts and regulatory bodies may be vital in establishing comprehensive evaluation protocols that accurately assess the potential risks and benefits associated with these innovative therapies.

By proactively adapting regulatory frameworks and developing specific guidelines for evaluating synthetic cell drug delivery systems, regulators could ensure public safety while promoting scientific advancements. This adaptability would pave the way for successful integration of synthetic cell therapeutics into mainstream medical practices, benefiting both patients and the health care community. Beyond mRNA vaccines, regulators have had to carry out novel evaluation approaches with the many emerging gene therapies now coming to market (23). While it would speed up approval of future pharmaceuticals based on novel technologies, it is the current reality that regulatory agencies only evaluate each specific drug presented to them rather than performing proactive horizon scanning.

Market competition remains a significant barrier to FDA authorization. Researchers must demonstrate that their technology is advantageous over existing products. Pharmaceuticals represent a very competitive market, in which many factors must be weighed: cost, availability, effectiveness, side effects, etc. It remains to be seen how synthetic cells will prove competitive with existing options.

One mechanism to increase competitiveness is lowering production costs. While currently, high initial manufacturing costs for synthetic cell drug delivery systems are likely, in the long term, synthetic cell therapeutics may be less expensive to produce than those of living cell systems (16).

One way to identify a need for synthetic cell therapeutic systems is identifying ways they can treat diseases that lack adequate therapeutic or personalized solutions, such as rare diseases. In 1982, the FDA passed the Orphan Drug Act to incentivize research toward treatments for rare diseases. The FDA defines orphan drugs as those targeting diseases affecting 200 000 people or less or those unlikely to be profitable for seven years after FDA approval (24). Cystic fibrosis, multiple sclerosis and muscular dystrophy are prevalent orphan diseases (19). This program enables the FDA to expedite the drug approval process when a promising therapy for a rare disease appears in the pipeline.

Novel gene therapies such as Beti-Cel, a drug recently approved to treat beta-thalassemia, continue to emerge and gain approval for their abilities to treat rare diseases. The question then arises, how could fully synthetic cells both follow in these existing therapeutics footsteps but also potentially treat rare diseases better than existing medications. If a synthetic cell therapeutic targeting an orphan disease emerges, it is likely to follow an expedited approval process. This might help circumvent some of the shortcomings of the current regulatory pipeline, mainly lack of precedent for those types of technologies (Figure 2).

Since the FDA's primary goal is to protect public health, the agency cannot compromise on safety and effectiveness to speed up the approval process. However, once the first synthetic cell-based therapeutic formulation goes through the approval pipeline, the subsequent instances of this technology will have an established path to follow.

While the FDA plays a pivotal role in controlling the US drug market, institutions abroad face diverse challenges posed by their regulatory bodies. For example, while the FDA is a centralized agency that oversees drug development processes in a single country, the European Medicines Agency (EMA) is a reviewing body that manages operations in many European nations. Individual European nations also possess their own regulatory bodies that look to the EMA for oversight. Countries with universal health care also factor cost into approval decisions differently than countries with highly profitable pharmaceutical industries like the USA. In addition, organizations

like the Asian Synthetic Biology Association, created to promote scholarly communications and commercialization in synthetic biology, are actively promoting government and private engagement in synthetic cell therapeutic development (25). In order to maximize the potential for synthetic cells' positive public health impacts and minimize safety threats, it is important that international collaborations continue to practice open communication and that regulatory bodies look to one another as resources in drafting guidance and making decisions on approvals.

5. Path forward

The emergence of synthetic cell therapeutics is an exciting development that holds promise for biomedical research and the advancement of drug development. However, this innovative field requires new strategies to regulate, oversee and ensure public awareness of the associated risks and benefits. Engaging in discussions about this technology is of utmost importance among various stakeholders, including researchers, policymakers, regulators, media representatives, patient advocates and investors, well in advance of the introduction of the first synthetic cell product into the FDA approval process. Synthetic cells offer an interesting avenue of research and greater understanding of many biological processes and biotechnologies. They may also represent an incredible turning point in the field of precision medicine. Such advancements must also come with regulation and guiding policy. Practical application in medicine is still a faraway dream for synthetic cells. What is most needed now is for invested parties to be informed and engaged to best support policy and practices that will govern a safe and controlled shift into applied medical technology. This is no easy task.

There are several steps that can be taken at this early stage that will benefit this long-term goal. Many groups and organizations of synthetic cell researchers are striving to maintain open-source fora to exchange knowledge and to share resources, to establish standard practices early. Recently, the international synthetic cell engineering community is beginning to develop common information exchange, including unpublished data and procedures, through annual SynCell meetings. Early engagement in conversations with the public and with regulatory officials on ongoing research and development phases will help bolster support for synthetic cell development, and guide safe and effective policy for future applications. Building and fostering opportunities for funding and investment will help support development of foundational synthetic cell technologies, strengthen manufacturing systems and ultimately lower at-scale cost of production.

First and foremost, safety and security of synthetic cell therapeutics must be a top priority. This entails establishing robust protocols for quality control, rigorous testing procedures and thorough risk assessments. By setting stringent standards and monitoring mechanisms, we can minimize potential adverse effects and guarantee the well-being of patients receiving these innovative treatments. Fostering public engagement is also essential, to build trust and generate informed discussions around synthetic cell therapeutics. As this technology becomes more prevalent, open and transparent communication between all stakeholders is key. Gaining a clearer understanding of the pathway toward market and application is crucial. Collaborative efforts between researchers, policymakers, regulators, media representatives, patient advocates and investors are necessary to reach successful approval of the first synthetic cell therapeutic on the market.

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