CELL & GENE THERAPY INSIGHTS

INDUSTRIALIZING IMMUNO-ONCOLOGY MANUFACTURE & SUPPLY CHAIN

SPOTLIGHT

COMMENTARY

Why we need a revolution for personalized cell therapies

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The dawn of cell and gene therapies has revolutionized the treatment of several debilitating or deadly diseases. However, the current paradigm in the development of cell therapies needs a profound remodeling as the ecosystem that supports new innovative treatments is not fit for the future in terms of patient access, costs, speed, and ecological footprint. In addition, the gap between academia and industry is widely recognized by all but not addressed. Ignoring this elephant in the room is no longer an option as the industry strives to maintain a steady flow of life-saving innovative medicine reaching patients in need. One major improvement would be the use of closed manufacturing platforms, in a distributed setup but supported by standardized control, that could accelerate the translation of innovative treatments from bench to bedside. Reshaping the cell and gene therapy landscape needs a joint commitment of all stakeholders to ultimately offer the best possible personalized care to patients.

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WITH THE CELL & GENE THERAPY FIELD COMING OUT OF INFANCY, THE HEALTHCARE SYSTEM WILL BE OVERSTRAINED, & THE PATIENTS NOT WELL SERVED

The dawn of cell and gene therapies has revolutionized the treatment of several debilitating or deadly diseases. While CAR-Ts have shown transformative efficacy in hematological cancers, solid tumors remain a large

challenge. Innovation in other cell therapies has bloomed, building on the development of dendritic cell and T-cell culture breakthroughs during the last decade. With the rise of personalized immunocellular therapies, such as tumor-infiltrating lymphocytes directed at tumor-specific antigens and genetically modified T cell therapies, the potential to achieve the eradication of solid cancers is on the horizon.

More than 1300 cell therapy trials were active in April 2021, representing an increase of 43% compared to 2020 [1]. While already an annual cost rise in the health care systems of 2–3% leads to fierce social and political debates, a global annual growth of 20–30% in approved cell and gene therapies will likely drive us on the road of a system collapse or glaring inequalities in patient access. It is also clear that the costs of research and development together with the manufacturing costs are the frontline factors driving the high prices that will overstrain the healthcare system. Moreover, these prices lead to many therapies only being available in a small number of countries, thus limiting access of patients to the best possible personalized care.

The current paradigm in the development of cell therapies needs a profound remodeling as the ecosystem that supports new innovative treatments is not fit for the future in terms of patient access, costs, speed, and ecological footprint as discussed below (Figure 1).

A fundamental shift in the way the main stakeholders in this ecosystem interact is required to accelerate the transformation of the cell therapy industry and guarantee fair access of patients to novel treatments (Figure 2). Such change can only arise through close collaboration between academia and industry, but also between payers and hospitals, without forgetting the patient's voice.

The dialogue between academia, clinicians and industry should occur early when generating novel therapeutic ideas to ensure an effortless continuum during clinical development, especially at the manufacturing level. One major improvement would be the use of dedicated manufacturing platforms that could facilitate the transition from a creativity-driven approach to an industrialized production. In this context, a patient-centric production model that allows for on-time production guided by the treating physician, with the necessary quality controls, would complement and benefit the entire cell therapy ecosystem.

TAMING THE ELEPHANT IN THE ROOM: CATALYZING THE COLLABORATION BETWEEN ACADEMIA & INDUSTRY

The gap between academia, clinicians and industry is widely recognized by all but not

FIGURE 1

The current growth pharma model is not fit for purpose for the growth in approved cell and gene therapies.

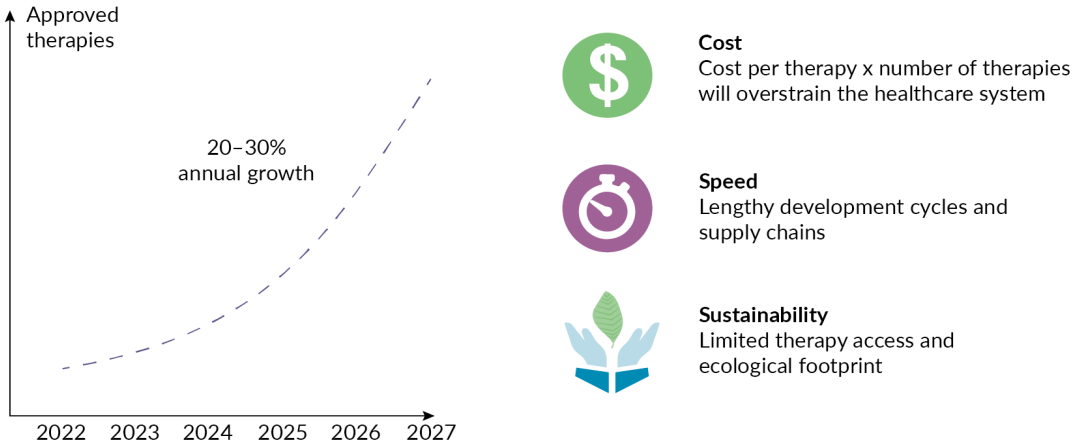

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FIGURE 2

Key drivers for an accelerated industry transformation are people, technology, data and regulations.

Early collaboration
Mutual understanding and co-development

Closed platforms
Integrated data, process development and new technologies

Patient centricity
On-time, guided by physician, standardized quality control

addressed properly. Ignoring this elephant in the room is no longer an option as the industry strives to maintain a steady flow of life-saving innovative medicine reaching patients in need.

Cell therapy treatments are usually developed in sequence by both the academia and the industry, and approved products are distributed worldwide by the industry [1]. Hospitals and academic institutions are paving the way for scientific innovation through proof-of-concept studies and early-stage clinical trials aimed at evaluating the safety and early clinical activity of new cell therapies. These studies are of utmost importance in the discovery of innovative treatments for patients, where many would otherwise remain without any available therapeutic option. Many leading academic hospitals are routinely manufacturing cellular therapies, mainly for autologous and allogenic stem cell transplantation, or for CAR-T therapies in the frame of clinical trials or single-patient use. The complexity of the production and associated costs of cell therapies in academic settings has been described elsewhere [2–6]. Late-phase clinical studies are usually carried out by the industry due to the costs, required infrastructure, operational complexity, and personnel needed to conduct large international studies.

The highly manual and adaptable manufacturing processes originated in academia are well suited for the early phase of cell therapy development because they provide enough freedom to explore different modalities via in-house manufacturing in a single center. However, albeit compliant with Good Manufacturing Practice, they represent a challenge for later stages of clinical development and post-approval, as highly standardized and consistent systems are required to ensure product quality in commercial production. The transition from an academic to an industrial manufacturing process requires substantial process optimization steps that usually need to be validated by additional clinical studies. As a consequence, the development and time to market availability of life-saving cell therapies can be delayed by two to three years. Such delays increase the risk for biotech and pharmaceutical companies, raises costs significantly, and affects economic benefits if not compensated by high list prices. For instance, prior to a new cell therapy Phase 2–3 clinical trial, at least 10–15 million USD need to be allocated only for process development and technology transfer to large facilities to increase manufacturing capacity. Ensuring a smooth transition of manufacturing processes between academia and industry could not only halve the manufacturing costs and subsequently decrease the overall therapy cost by 25%, but also would allow for a rapid diffusion of new science to physicians and their patients across the world.

In a word, throwing innovative therapies over the fence that separates academia from industry and hope for an optimized and sustainable collaboration has not proven favorable so far. Finding the sweet spot between exploratory freedom and standardized scale-out is crucial to increase the speed with which

cell therapies reach the right patients (Figure 3). Certainly, this is an area where regulators need to be involved in order to assess risk factors.

Supporting academia with experienced teams for setting up a scalable system at the early stage of the development would enable academic institutions to translate effortlessly their creative proof-of-concept into viable cell therapies without the burden of additional process development.

STANDARDIZED MANUFACTURING PLATFORMS REPRESENT THE ONLY SUSTAINABLE OPTION FOR TIMELY AND AFFORDABLE ACCESS TO NOVEL THERAPIES

One of the biggest challenges perceived by academic manufacturing facilities in building up their capacity for cell therapy production is the limited understanding of logistics and regulatory requirements. The definition and implementation of suitable quality policies according to the phase of the product development and their enforcement was reported to be another challenge; additionally, quality systems staffing was considered under-resourced [4].

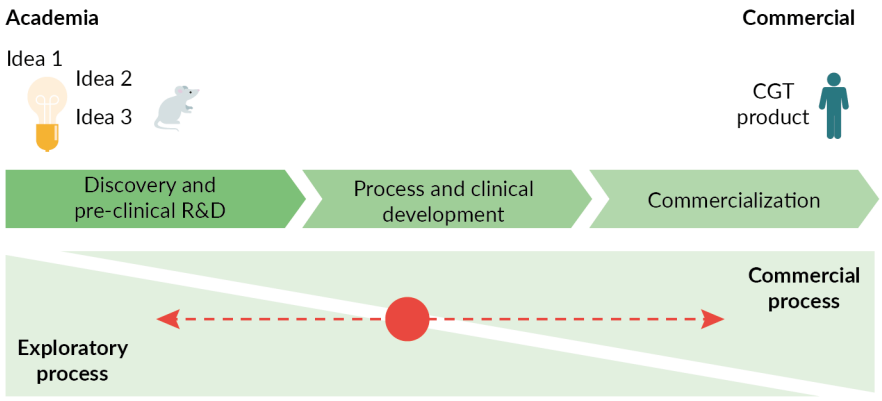
A versatile platform composed of a set of qualified equipment in an automated, fully aseptically closed setting, backed by a robust technical process, would have the potential to reshape the cell therapy landscape. It will allow the manufacturing of new modalities in a system supporting late-stage clinical studies with minimal process development. Additionally, by closing and automating the process, it will become possible to carry out manufacturing of T-cell-based therapies in D-level clean rooms instead of expensive B-level rooms. These features could dramatically increase the global manufacturing capacity and radically improve a broad patient access to such therapies. Standardized equipment that could be adapted to fit different manufacturing platform designs could provide enough flexibility throughout all stages of clinical development.

DISTRIBUTED, CLOSE-TO-BEDSIDE MANUFACTURING IS A MUCH-NEEDED ALTERNATIVE TO CENTRAL MANUFACTURING

Currently, the late-stage and commercial manufacturing mainly follows the traditional standards of the pharmaceutical industry that were built on large-volume products: the production is centralized or limited to a few production sites scattered across the globe to supply certain regions. Despite numerous efforts to build new production facilities, the currently available global manufacturing

FIGURE 3

Finding the right balance between exploratory freedom and standardized scale out is crucial for collaboration.



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capacity does not allow for the timely production of the right products to treat cancer patients in urgent need. Time is crucial for the survival of the patients as several cancers show aggressive and fast progression. Cell logistics require a very precise timing complicated by cross-border transportation. The waiting time from diagnosis to treatment is often too long, and the slightest disturbance (e.g., a patient leukapheresis appointment delayed) can break the entire flow.

There is an increasing demand of society towards the pharmaceutical industry to purposefully adhere to their pledge of sustainability. The environmental footprint of central manufacturing sites is substantial: patient's cells are shipped deep frozen with special courier from hospitals all around the world to a central manufacturing site and sent back again to the patient, leaving a major CO_2 footprint. For instance, to treat 100,000 patients worldwide, 200,000 van journeys and airfreight shipments (with at least half of them in liquid nitrogen tanks) are needed.

The availability of personalized cell-based treatments manufactured closer to the patient's bedside, in a distributed setup and cancer centers, would reduce the turnaround time significantly. In such a setting, a standardized quality management system and real-time quality control is imperative to ensure highest quality standards and compliance to current Good Manufacturing Practice requirements. The combination of the closed, automated platform described above, and a standardized quality system could make cell therapies also available in underserved regions of the world – more specifically, in regions where the logistics and cold chain may be problematic, and in regions where no B-level clean rooms and highly trained workforce are available.

New technologies, AI, machine learning, fast internet connections, full data integration, and equipment will be of paramount importance to ensure a distributed manufacturing compliant with Good Manufacturing Practice. A standardized quality management system is mandatory to support understaffed academic teams to meet regulatory requirements and ensure the safety of patients.

Finally, the price of cell therapies also circumscribes the availability of this type of treatment to the richest countries. To date, no considerable progress has brought the manufacturing capacity to bearable costs for society in developing countries. A fully closed and serviced equipment platform set up close to the patient's bedside in a distributed setup could contribute to broaden the reach of cell therapy to developing countries, by limiting the costs of logistics, qualified personnel, and cleanroom maintenance.

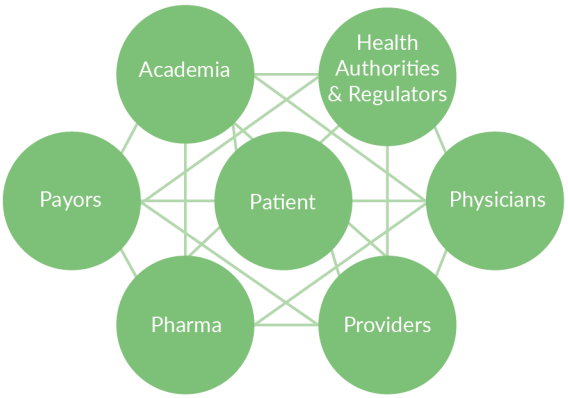
A REVOLUTION IN THE WAY THE ACTORS OF THE CELL & GENE THERAPY ECOSYSTEM INTERACT IS WARRANTED

A distributed setup for cell therapy manufacturing supported by expert service has the potential to accelerate the translation of innovative treatments from bench to bedside. However, this transformation needs a deep commitment by all stakeholders to shape the cell and gene therapy landscape together (Figure 4):

- Insurance companies, payors, and policy makers: these major players need to be involved in the development process to substantiate their assumptions and calculations with hands-on data and insights;
- Regulatory authorities: regulators must be consulted prior to starting and throughout product development to discuss plans, quality systems, potential findings, and to assess risk evaluation criteria;
- Patients: the distributed manufacturing facilities will offer new therapeutic options to patients in need but may require them to get treatment in regional specialized centers;

FIGURE 4

The stakeholders in the cell and gene ecosystem adapt at different pace – with individual drivers for change.



- Academia: new collaborative approaches to integrate experiences and analogies from commercial partners will have the potential to boost the development pipeline;
- Pharmaceutical companies: a mind shift from a blockbuster approach to a more agile therapy portfolio approach will be required from pharmaceutical companies. Their strength in market access and distribution will be a key driver for distributed manufacturing. The industrial partners will also need to actively support academia in their strive for creativity and innovation;
- Physician and health care providers: the platform approach will enable specialized hospitals to get back into the driver seat of cell therapy use. It will allow for an accelerated access to patients, including in rare indications and underserved geographical regions. Furthermore, it will support personalized care by allowing the right therapy to be tailored specifically for each patient at the right time.

All these actions would result in a situation that all stakeholders have been aspiring to for years: putting the patient at the center and give them the best possible personalized care.

TRANSLATION INSIGHT

A distributed setup for cell therapy manufacturing supported by standardized control has the potential to accelerate the translation of innovative treatments from bench to patient's bedside and reshape the cell therapy landscape.

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