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What we are learning from CAR-T implementation: development, regulatory and clinical practices

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Summary

The last decade has witnessed a significant advancement in medical science and technologies. The cell and gene therapies represent remarkable outcomes of such progress achieved in a very short timeframe. The COVID-19 pandemic has created roadblocks for patients to access hospitals for diagnosis and treatments since the onset of its first-wave. On the contrary, this one-year leap has witnessed unprecedented technological advances, especially in terms of mRNA-based therapies and their regulations. The present review focuses on CAR-T as a model with all key attributes and implications in complicated chains from early science to a variety of models and trends in clinical practice.

Keywords

Cell and gene therapy, CAR-T therapy, risk management plan, agile development approach.

Introduction

Cell and gene therapy comprise a booming avenue in devising novel, emerging healthcare products during the last decade. One such approach with a variety of applications includes CAR-T therapy, which, owing to its innovative and effective approach, has leaped outstandingly fast from idea to clinical practice. Contrary to the prolonged procedure of FDA approval, as observed in case of conventional drugs, the anti-CD-19 CAR-T, KYMRIAH was approved by the FDA within a short span of 4 years in 2017 [1, 2]. This therapeutic was imminently bestowed with the title of the ASCO breakthrough of the year in January 2018 [3]. However, cell and gene therapies such as KYMRIAH are distinct from the "ordinary" drugs in most aspects, and such differences are commonly shared between most cell and gene therapies. In this review, we will focus on some distinct features of such therapies throughout their development, from the R&D bench to the patient bedside, including the regulatory and business aspects of such new therapies which are often overlooked in the reviews on this topic.

The journey of a new drug from labs to shelves is divided into five main areas: R&D, production, regulatory approval, business, and funding. If one of these aspects is missing or is defunct, the drug, irrespective of its efficacy or safety, fails to reach the clinic. The new cell and gene therapies are different from the common drugs in all these areas, as CAR-Ts vividly demonstrate or highlight such differences as well as features that are common to the cell and gene therapies, it is the focus of this review which emphasizes on each of these areas.

Area #1. R&D and emerging technologies

The most distinct feature of CAR-T is that it is based on the concept of personalized medicine which has completely

shifted the healthcare ecosystem paradigm from the "one pill fits all" to "every pill made for one patient". The most fascinating aspect of this approach is that it can be effective, not only from a therapeutic but from a business perspective as well. Moreover, these personalized drugs do not disrupt the previous approach, since they can fit well together.

Although the CD-19 CAR-T therapies usher the prospect of long-lasting recovery from advanced stages of cancer which were previously thought incurable [4], its road to approval is fraught with the reports of patient deaths due to cytokine storm [5]. At present, researchers are exposed to new challenges to enable widespread application of this therapy in new areas like infectious diseases, to cure solid tumors, and to enhance its safety, efficacy as well as affordability. To accomplish these goals, the key role is being played by the R&D sector and academic research, which are advancing towards clinical trials with new technology (Table 1).

Firstly, the process of development of personalized drugs shares numerous features with those of the new product development strategies from information technology (IT), or agile processes [6], involving 3 three-step cycle testing ideas like:

–Producing minimal viable product (MVP) as fast as possible.

–Measuring the performance with real-life patients (customers) and gaining knowledge about the improvements needed.

– Repeating [7], and application of agile development methodology.

In this process, every iteration adds some additional features, and fast testing with real-life data shows whether the ideas are right or wrong. One important feature of such products is that they must be very flexible, allowing changes in parts, but maintain the basic functional concept. The software-based products are the best fit for this since they usually utilize the same platform which is used to design the product. This is the case with platforms in biologics, cell, and gene therapies; it allows the use of a platform-based approach for development. Every drug that is based on introducing changes in the DNA or RNA is a kind of "reprogramming" or "genetic software development" suggesting that some effective approaches from IT can be transferred to drug development. This includes all gene and cell-based therapies such as CAR-Ts, or plasmid DNA, or several mRNA-based COVID vaccines, CRISPR-based therapies, etc.

Although there are differences in time frames and regulatory pathways, the approach utilized for personalized drug-development appears to be more similar to this iteration-based development strategy than the standard one-at-a-time perfect drug development strategy used in pharmaceutical industry in the previous as well as present times. Indeed, if we look at the most splendid example- how CAR-T technology developed into its present and future, we can see many similarities.

The first-generation CAR-T therapies were a breakthrough technology in the 1980s [9]; however, despite big hopes, its design was too simple to generate reliable outcomes in clinical trials [8, 10]. Technologically, the first generation of CARs included only the CD3ζ signaling endodomain fused to the extracellular scFv to act as an activator of the T cells. In terms of IT development, it fell exactly in the "minimal viable product" (MVP) category, the product that has the absolute minimum set of features to function. However, despite promising preclinical results, the clinical trials demonstrated caveats such as poor anti-tumor efficacy in patients, caused by low-level CAR-T cell activation. Therefore, the next 2nd generation was introduced, which included co-stimulatory domains for additional activation. This design was highly successful in the clinical trials in treating hematological malignancies, such as acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL). This success was confirmed by

Table 1. Cell therapy production. Emerging models

Approach	Investments needed	External conditions	Production volume	Examples
Big plant (good old big pharma approach)	100 MUSD *per* facility	Fast and safe all-country delivery, no borders to cross (US, EU) for distribution	Big production volume (100-s mln of people population)	CAR-T: Novartis – 97MUSD in one facility in Europe for KYMRACH – 150 MUSD cell therapies
Small-scale facility very close or inside a hospital research	1-10 MUSD *per* facility	Mostly therapy for patients of clinic, or clinics in one town. No problems with delivery	Limited production volume (town with millions of people)	Stem cell products, fibroblasts etc. that use to fall into minimal manipulated products, CAR-T based on university/clinic concortia
Medium scale facility based on existing life-science production	From 0,5 to 10 MUSD depending on existed equipment	Fast and safe within-country delivery	Medium production volume (small country)	New idea for CAR-T or other complex cell products

the FDA approval of two CD-19 CAR-T drugs, KYMRIAH (Tisagenlecleucel) for r/r ALL and r/r large B cell lymphoma and YESCARTA (Axicabtagene ciloleucel) for r/r extent CLL.

In the process of successful clinical trials for both of these drugs, the core of the "agile development approach" was used to adapt for its clinical features and limitations. Additionally, various CAR-T cell-mediated toxicities were reported, such as tumor lysis syndrome [11], cytokine release syndrome (CRS), neurotoxicity [12], and on-target off-tumor toxicity [13], leading to a few patient deaths during the clinical trials.

The most frequent and dangerous feature of CAR-T therapy is cytokine release syndrome (CRS) [14], which leads to some lethal cases during the trials. The iteration product development cycle, which was at this point enabled by the FDA regulations for adaptive clinical trial design, allowed the identification of strategies to avert this risk by introducing several therapeutic options for CRS, such as anti-IL-6 therapy in case of CRS development, and tools to observe the patient, such as hospitalization for a week after CAR-T infusion to closely monitor for adverse reactions [12, 15].

However, the second CAR-T generation failed to show promising results in the case of solid tumors and had several limitations in treating hematological malignancies, such as antigen loss and consequent tumor escape. Such peculiarities of the second generation CAR-T limited the long-term success of CAR-T cell therapy for a quite large group of patients, leading to relapses or lack of tumor response [15, 16]. With further studies, new ideas emerged, leading to the third and fourth generation of CAR-T cells, comprising more receptor domains with different functions added to the chimeric receptor (Fig. 1).

The third-generation CAR-T cells combined the signaling potential of two costimulatory domains (CD28 and 4-1BB). To overcome the limitations of the third generation, the fourth generation of CAR-T assimilated various improvements in different parts of the chimeric construct, mostly linked with solid tumor therapies. The antitumor activity of the fourth-generation CAR-T cells was enhanced by features such as additional transgenes for cytokine secretion (e.g., IL-12) or additional costimulatory ligands. Based on the same principle, armored CAR-T cells and TRUCKs (T cells redirected for universal cytokine killing) are constructed i.e., they were modified to express not only CAR but also the inducible cytokine genes. The cytokine expression occurs only when antigen-binding activates the CAR-T cells [17, 18]. Other CAR-T approaches include the dual-receptor CAR-T cells, which are activated only in the presence of dual antigen tumor cells [19], and bi-epitope CARs [20], which fight antigen escape and loss.

With the increasing potency of CAR-T cells, more caution must be taken to ensure their safety. For solid tumors, the off-target activity becomes a limiting factor, since the target antigens are still expressed on some normal cells, and the cytotoxic activity toward these is not desirable. The first potential action is to adjust antibody affinity, thus mitigating on-target off-tumor toxicities related to low-level antigen expression in the normal tissues. The chimeric antibodies with middle or even low affinity to target can have sufficient potential to eradicate the antigen-overexpressing malignant cells, but not to damage normal tissues with low-level antigen expression [21]. Such situation is possible in case of solid tumors, which can even cause death during CAR-T therapy [22].

Another approach for reducing off-target activity is to fabricate short-lived CAR-T cells. This can be achieved via mRNA delivery with a chimeric construct instead of DNA incorporation into the T-cells. In this case, the T-cells express a CAR for up to several days at high efficiencies; however, the drawback of this approach is rapid loss of the transgenic construct and the T-cell activity associated with it, and a need for several dosages to obtain clinically relevant results [23]. This approach not only allows temporal control over the CAR-T

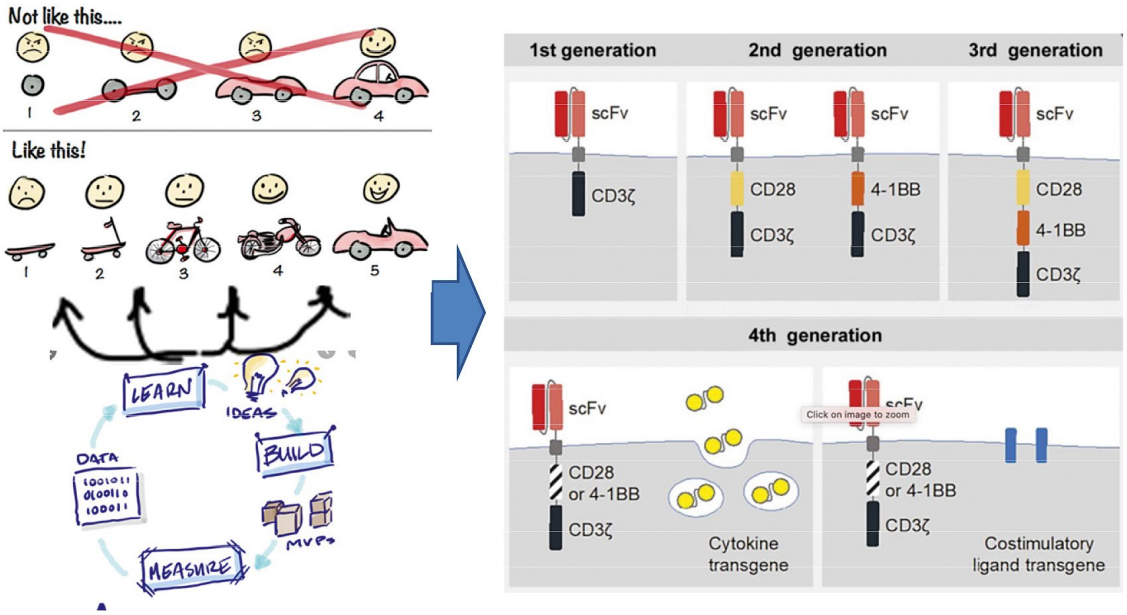

Figure 1. Agile Development process and CAR-T (adapted from [7, 8])

pharmacokinetics but can also be applied with gene-editing tools such as TALEN, disrupting TCR and CD52 expression in the CAR-T cells, thus creating off-the-shelf CAR-Ts. In addition, this approach can expand the scope of therapy to treat hematological tumors. In this context, previous studies reported that by using mRNA-transduced anti-CD19 CAR-T cells targeted against the tumor microenvironment, promising results were obtained in the treatment of Hodgkin's lymphoma [24]. The transient CAR-T production with mRNA delivery can be a potential option for future *in vivo* CAR-T therapy wherein, mRNA-loaded particles can be injected into specific T-cells within the patients [25].

Yet another approach to increase safety is via the on-off control of CAR-T cells. The most clinically advanced technology is the inducible suicide caspase-9 gene based on a modified human caspase-9 fused to the human FK506 binding protein (FKBP). This fusion protein, expressed in the T-cells, can form dimers when a chemical inducer of dimerization (AP1903 or Rimiducid) is administered to the patient. A single dose of the inducer drug causes rapid elimination of 85-90% of iC9-transduced T cells [26, 27]. Caspase-9-transduced T cells were used in the clinic as a tool to control graft-versus-host-disease (GVHD) after haploidentical stem cell transplantation, and the GVHD-associated symptoms could be also quickly eliminated following the caspase switch activation [28].

With more than 600 ongoing clinical trials [29], there are a lot of features emerging continuously in the CAR-T field, similar to the software "add-ons", aimed to solve particular tasks within a particular setting (or overcome particular difficulties) with a combination of different targets and approaches to improve safety and efficacy, some of which were discussed above. Another important limitation concerns the costs and timing of production. Being completely personalized, the currently approved CAR-T relies solely on the patient's T-cells for the CAR-T production. Therefore, apart from difficulties in logistics and lead times for therapy, the cost of such therapies becomes a huge burden to the patient and acts as a barrier to the widespread use of CAR-T therapies [30].

This issue has been addressed by off-the-shelf CAR-T and CAR-NK products in development. There are several approaches to treat GVHD which is the main challenge for off-the-shelf CAR–based therapies. One approach to solve this problem is to use other cells with the cytotoxic ability and not αβ T-cells. The NK cells fit this approach and have been used in phase 2 clinical trials. However, such off-the-shelf therapy seems to require fourth-generation CAR constructs including death switches and expression of stimulatory molecules to generate stable CAR-NK cell populations [31]. Gene-editing methods such as CRISPR/Cas9 and TALENs are used to disrupt genes encoding the endogenous TCR as well as human leukocyte antigen (HLA), thus creating universal CAR-T therapy. Apart from deleting human histocompatibility loci in CAR-introduced T-lymphocytes, gene editing and CRISPR-like technologies can be used to insert CAR constructs precisely into particular genome regions, instead of just delivering CAR-programming viral plasmids, which can improve the survival of modified T-cells [32, 33, 34]. Yet another promising option is that gene editing allows the deletion of T-cell suppressive receptors, thereby rendering the T-cells less susceptible to tumor-mediated immunosuppression [35].

The efficacy and safety of CAR-T cell therapy still have broad space for improvement, since not only increased safety but also higher efficacy is required. Notably, disease relapse can occur in up to 50% of patients within a year of therapy. Specific tumor biomarkers are widely used to choose and direct therapy with a growing variety of anti-cancer drugs [36]; therefore, the same approach is expected to benefit more complex CAR-T treatments, introducing the idea of individualized disease management as well as personalized therapy [37]. Safety is the first concern that can be managed with the help of biomarkers as cytokine release syndrome (CRS) and CAR-related encephalopathy syndrome (CRES) which cause up to 60% of life-threatening toxicities [38]. Response rate is also an important aspect that can be determined by biomarkers, especially the primary indications: if up to 90% response can be seen in ALL, according to a meta-analysis by Hou et al. [39], this figure drops to 9% (10-fold lower) in solid tumors.

CRS is caused by activation of T-cells after engagement of their CAR targets. Activated T-cells release various cytokines and chemokines, including interleukin (IL)-6, interferon (IFN)-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), and soluble IL-2Rα [40]. These cytokines activate monocytes, macrophages, and other immune cells, which in turn release inflammatory cytokines. However, only a few biomarkers have been identified as predictors in clinical trials: serum levels of IL-6 and IFN-γ in the first 24 h after CAR-T-cell infusion in B-ALL patients have been reported as robust biomarkers of severe CRS and CRES [41]. In NHL patients, increased serum IL-8, IL-10, and IL-15 levels, as well as decrease of transforming growth factor (TGF)-β could also predict severe CRS and potential neurotoxicity [42].

CAR-T efficacy prediction is still a challenging issue [43, 44]. Hence, there is a need to identify new biomarkers, especially with growing insights from the new genomic and transcriptomic analysis methods powered by next-generation sequencing, enabling TCR repertoire and lentiviral integration site analysis that allows for clone evolution of the CAR-T cells in the patient and its interaction with immune system [45].

We can see from the above discussion that the technical part of CAR-T development is open to a huge number of options and features, which can be combined into an optimal product to deliver the best possible combination of safety and efficacy for a wide variety of cancers in a personalized therapeutic manner. It is also clear that the diversity of combinations that is possible with CAR-T cells is huge and growing, along with the complexity and uncertainty of the result. This is similar to the current state of software development; thus, the transfer of effective approaches from this field into CAR-T's development may benefit research and clinical development.

Area #2 Regulatory

As noted in the Harvard Business Review publication "Embracing Agile" [6], the type of innovation that will favor agile

methodology is when "Problems are complex, solutions are unknown, and the scope is not clearly defined. Product specifications may change. Creative breakthroughs and the time to market are important. Cross-functional collaboration is vital".

The experience of drug regulation was just about the opposite: regulatory agencies and financial reimbursement bodies that set bottlenecks for fast drug development processes [46]. However, in recent decades, the most influential regulatory agencies, such as the FDA and EMA, have made huge steps toward flexibility, dialog, and increasing speed for innovations, especially in the field of gene and cell therapies. If we look at the history of changes in FDA regulations, the Orphan Drug Act, which loosens regulations for drugs aimed at conditions affecting less than 200,000 people in the USA (and personalized medicines can fit very well in that) was followed by the Accelerated Approval program that allows approval based on surrogate endpoints (with completion of post-approval Phase 4 trials to maintain approval) [47]. Next, the Fast Track designation allowed more frequent reviews with the FDA and expedited rolling reviews, allowing tighter contact between the regulator and developer [48]. The breakthrough therapy program added on top of it by the FDA allows drugs that fall within it to be approved based on clinical studies with alternative clinical designs that could be smaller in the number of subjects and use surrogate endpoints or biomarkers to determine efficacy [49]. The 21st Century Cures Act [50] has driven the FDA to maximize the use of these programs and supports the use of biomarkers as determinants of therapeutic efficacy rather than clinical outcomes alone. And most importantly for Gene and Cell therapies this act set a new Regenerative Medicine Advanced Therapies (RMAT) designation, that includes cell therapies, therapeutic tissue engineering products, human cell, and tissue products as well as certain human gene therapies and xenogeneic cell products aimed to treat serious disease.

It is important to note that drugs carrying an "orphan drug" designation can access the accelerated pathways mentioned above, requiring smaller trials (on average 3 times smaller *vs* common diseases), avoiding the need for randomization or double-blinding, and obtaining approval based on surrogate endpoints rather than stricter mortality or survival clinical endpoints.

Similar approaches are used by the European Medicinal Agency (EMA) and set in the number of directives [51, 52], which defines the special types of products-advanced therapy medicinal products. Such ATMPs can also be subject to orphan designation, which is different in the EU *vs* the USA-prevalence is not more than 5 in 10,000 [53]. Most of the activities and benefits that the developer obtains under ATMP, PRIME, and other expedited regimes are based first on extensive communication and obtaining advice and guidance from regulator experts on the development plans and regulatory strategies, including preclinical and clinical aspects. Again, the conditional approval option on the limited data of safety and efficacy (Phase II) is also possible.

The expedited reviews of new product development, readily available for gene and cell therapies, now provide unique opportunities for implementing the agile approach and increasing the efficiency of development for new therapeutics in this very demanding field. This is especially true when combined with therapy personalization, based not only on clinical diagnosis but also on specific biomarkers that enable particular therapeutic interventions. Since this itself opens the orphan pathway to approval, which is more frequently used, up to 25% of new approvals got an orphan designation [46].

New drugs are not only products to be developed for patients but are also products to be developed as regulators. The fate of the same drug candidate can differ dramatically with differences in clinical and pre-clinical data generation and presentation, in manufacturing and quality control processes and documentation [54], as well as the financial, organizational, and even behavioral characteristics of patients in clinical trials [55]. In this case, the ability to create a set of documents and approaches for approval as an "MVP for regulator" and test it during a face-to-face discussion in the iteration process can provide substantial benefits for the developer to make things faster and cheaper. Importantly, most advanced regulators such as FDA understand the uncertainty in development, which is reflected in recent and important for cell and gene therapy products CMC guidance [56] that of states about critical quality attributes (CQA). "We further acknowledge that understanding and defining product characteristics that are relevant to the clinical performance of the gene therapy may be challenging during early stages of product development, when product safety and quality may not be sufficiently understood".

Accelerated approval options (which not only allow approval of the drug based on the Phase II data but also requires tight communication with the regulator) according to some analysis may decrease R&D costs by up to 500 M$ and shorten the time to market for two years on average [57].

However, accelerated approval or conditioned approval in EMA forces developers to follow additional risk mitigation strategies, such as risk evaluation and mitigation strategies (REMS). The REMS program empowers the FDA to regulate post-market activities in exchange for pre-market approval. Under REMS, providers must continue to monitor and report patients with side effects. The CAR-T treatment sites needed to comply with REMS, approved by the FDA, for 15 years.

REMS for CAR-T includes a set of requirements before the site can start CAR-T treatments (such as having two doses of tocilizumab to prevent CRS and neurological toxicities per patient, requirements for medical staff training, and a system to report adverse effects). Fulfillment of the REMS (FDA) or risk management plan (EMA) requirements should be covered and controlled by the pharmaceutical company in partnership with the practicing clinicians.

Since the regulators understand well that cell and gene therapies are much different even from biologics, they are working intensively to create guidelines for this area. Currently, some guidelines cover areas from preclinical, manufacturing, clinical development, and follow-up [56, 58-65]. It is important to highlight new guidance for devices used in regenerative medicine advanced therapies in which CAR-T therapies are

commonly included since it clearly defines the requirements for auxiliary devices used in the CAR-T production process [66].

CAR-T regulatory landscape in Russia

CAR-T in Russia falls into the category of biomedical cell products, which are regulated by the federal law # 180-FZ and all linked documents [67]. A full set of regulatory documents was completed in 2020, and real-life application for this law is in the early stage, there are no approved products and only one completely certified production site for cell therapy. Importantly, this law allows for written and even face-to-face consultations directly with experts of the regulator (Federal State Budgetary Institution "SCEEMP"), which is an important step to support the development of complex cell therapies.

Area #3. Production

The next step involved in making the therapy available to the patient is production. Since we are transitioning from the one-pill-fits-all to the one-pill-for-one patient model, the industry understands that big plants are not of much use in this new reality. CAR-T development not only opens issues that are specific to this field, but also provides some solutions to it [68]. New models of production start to emerge (see Table 1 "Cell therapy production. Emerging models", [69-71]). One of the most common strategies to produce in-house CAR-T cells is small-scale production volume, which is just fit to the number of patients in the clinic using cell-modifying equipment such as the CliniMACS Prodigy® system [67], which allows for the small-scale process of cell transformation and sorting for clinical applications.

The overall "agile-like" approach we have discussed above is used in personalized therapies like CAR-Ts such that the therapies are more effective and shorten the development cycle. If we can reduce the production duration and bring the product closer to the patient, it will bring several benefits to the entire system:

1. Benefits to the patient by shortening the duration of manufacturing and transportation. Better adjustment of therapy options due to faster response if the production site is in the clinics, enabling flexibility of regimes and targets.
2. The benefit to pharma companies – big investments in large production facilities are not needed.
3. The benefit to the regulator-better control of safety.

Such close-to-patient therapy production opens new possibilities for treatment adjustments, such as biomarker-assistant cell dosage, relapse, and tumor escape treatment with CARs aimed at different targets.

Academia in business

One feature of the agile approach towards product development is the non-hierarchical horizontal structure of teams of interdisciplinary experts. CAR-T is a product which requires tight collaboration between the pharmaceutical industry and clinics, that are most frequently vertically oriented; however, there are several examples of academia being an active part of the business. Some examples are:

Joint ventures | Startups

In 2013, the Fred Hutchinson Cancer Research Center (FHCRC), Memorial Sloan Kettering Cancer Center (MSKCC), and Seattle Children's Research initiated Juno Therapeutics company as a result of previous long collaboration in CAR-T development, and further started joint ventures with Juno Therapeutics for more than four clinical trials [73].

Academic institution networks, that unite researchers, developers, clinical centers, and companies for developing new therapy

The BioCanRx network (Canada immunotherapy network) is a pan-Canadian network of expertise and infrastructure for the development, manufacturing, and clinical testing of new immunotherapies. It was established in 2016 to boost infrastructure and manufacturing capacity to support bench-to-bedside research and to ultimately increase the access to CAR-T by increasing the number of clinical trials available to Canadian patients, as well as to empower innovations in the engineered T-cell area. It survived government financing cuts and delivered two CAR-T candidates in several clinical trials, including closed-cycle point-of-care CAR-T devices [74].

Multi-country consortia between the academic institutions and small companies allow bypassing big pharmaceutical companies or large investments in CAR-T development

The EURE-CART Alliance involved six academic centers from five countries, and three small and one medium-sized enterprise to conduct clinical trials of CAR-T candidates and to clinically develop CAR-T platforms. In 2020, the alliance started the first clinical trial of a CAR-T, CD44v6 candidate [75].

Crowdfunding consortia

The rare disease consortia started in 2008, uniting patients, charity, and academic research to develop a treatment for the Rett syndrome. In total, more than 60 M$ were collected to finance research or attract research teams in gene therapy and cell therapy dedicated towards curing this syndrome. Multiple collaborations of scientists covered different steps in therapy development. Enabling collaboration with AveXis made this company focus on Rett syndrome, develop AVXS-201 gene replacement therapy up to the preclinical phase, and even managed to keep it in the Novartis pipeline with a fixed date for IND application in 2021 [76]. The same community advanced other gene therapy candidates TSHA-102 with Taysha Therapeutics [77].

As we can see from these examples, forming [6] consortia can indeed deliver therapeutic products in this very complex and challenging field of gene and cell therapy due to advancements in collaboration and working in cross-functional teams, even though it lacks the power and experience of big pharmaceutical companies. However, this can be addressed by skillful application of agile processes technology giants.

Gene and cell technologies and new technology giants

An important point for the future of the healthcare sector, which was boosted in recent years, is the increased support

from regulators, such as the US FDA, emerging and more effective technologies, decreasing time to market for them. Big data, genome-based personalization of treatments, and gene-editing are all included in the new focus of attention of regulators, which can possibly reduce the costs of treatment and drugs, and overall decrease the healthcare expenses [78, 79].

Since IT-born agile ideology can be applied to the development of personal therapeutics, they are sweet points of entry into the pharmaceutical market for tech giants who are experts in this development methodology.

One interesting example is the story of Jeff Bezos, Amazon, and Juno Therapeutics, which initiated a possible entry of Amazon into the CAR-T business with 7 years of approval, and possible changes in the US healthcare industry [80].

- 2013 – Juno Therapeutics spin-off from the Fred Hutchinson Cancer Research Center.
- 2014 – Bezos invests Juno 20M$ in 140M$ round.
- 2014 – Bezos family gifted the Fred Hutchinson Cancer Research Center 30M$ to create 1 in the USA clinic for immunotherapy treatment (Bezos Family immunotherapy clinic).
- 2018 – Celgene Juno was sold to Celgene, later to BMS.
- 2018 – Bezos (Amazon) enter the US drug market.
- 2019 – Juno ex-executives started company Sana, dedicated to the development of cell-based treatments ("ultimate next-gen cell engineering company with gene therapy and cell therapy").
- 2019 – Bezos (Amazon) enter the telemedicine and medical insurance markets.
- 2020 – Bezos and other VC invest 700M$ in Sana.
- 2020 – Seattle Cancer Care Alliance, including Bezos Family immunotherapy clinic, hosts 33 clinical trials of immunotherapies.
- 02.2021 – Approval of Juno CAR-T JCAR017 (BMS' Liso-cel).

One interesting story to tell is Jeff Bezos's investments in the gene and cell therapies company, Juno back in 2014. From that time, Juno went through a series of M&As, starting from $6 billion ended up with $67 billion to BMS. Last year, Bezos again invested in the same Juno team, now gathered under the name Sana, to develop next-generation gene and cell therapies [81]. During these times, Amazon entered the drug delivery and medical insurance markets [82]. Some might infer that it was just smart investments, and it can be seen that Amazon now understands and is building a technology-oriented healthcare infrastructure, opening the existing bottlenecks for new, high-tech, and more efficient healthcare solutions. When the technology giants enter the field of healthcare, the market is destined to change dramatically.

Conclusion

When we look at the gene and cellular therapies, and, in particular, the CAR-T therapies as its most developed and effective segment, it vividly shows general approaches and challenges of this field, as well as features that are particular to the personal therapeutics. We can see that on the technological side, despite the common CAR-T platform, a variety of diseases and corresponding molecular targets, combined with the particularities of patient population groups, will require a diverse set of properties for such drugs, possibly with some features of opposite functions. In turn, to make the most of such flexible and programmable therapeutic platforms as CAR-T, an agile, iteration-based approach of product development can be used, and in fact, has already been used to bring the current flagship therapeutics like KYMRIAH to the market. Moreover, the current regulation for the cell- and gene-based therapeutics, new production technologies, methods of research, development, and clinical collaboration for such products can empower the agile approach, decreasing the costs and time to market such therapies, as well as bringing in new players from the IT and high technology industries to the pharmaceutical market.

Conflict of interest

No potential conflict of interest is reported.

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Наши уроки внедрения CAR-T клеток: разработка, законодательная и клиническая практика

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Резюме

За последнее десятилетие достигнуты значительные успехи в медицинской науке и прикладных технологиях. Клеточная и генная терапия позволили добиться выдающихся результатов этих разработок в течение очень коротких сроков. С начала первой волны заболеваемости, пандемия COVID-19 создала препятствия для пациентов в плане доступа к диагностике и лечению в госпитальных условиях. С другой стороны, этот годичный период был ознаменован беспрецедентными технологическими достижениями, особенно – в аспекте терапии, основанной на применении мРНК и ее законодательного регулирования. В настоящей обзорной статье обращается особое внимание на CAR-T-клетки в качестве клинической модели со всеми ключевыми атрибутами их внедрения в рамках сложных цепочек – от первичных научных исследований к многообразию моделей и тенденций их применения в клинической практике.

Ключевые слова

Клеточная и генная терапия, CAR-T–клеточная терапия, планирование управлением рисками, гибкое развитие.