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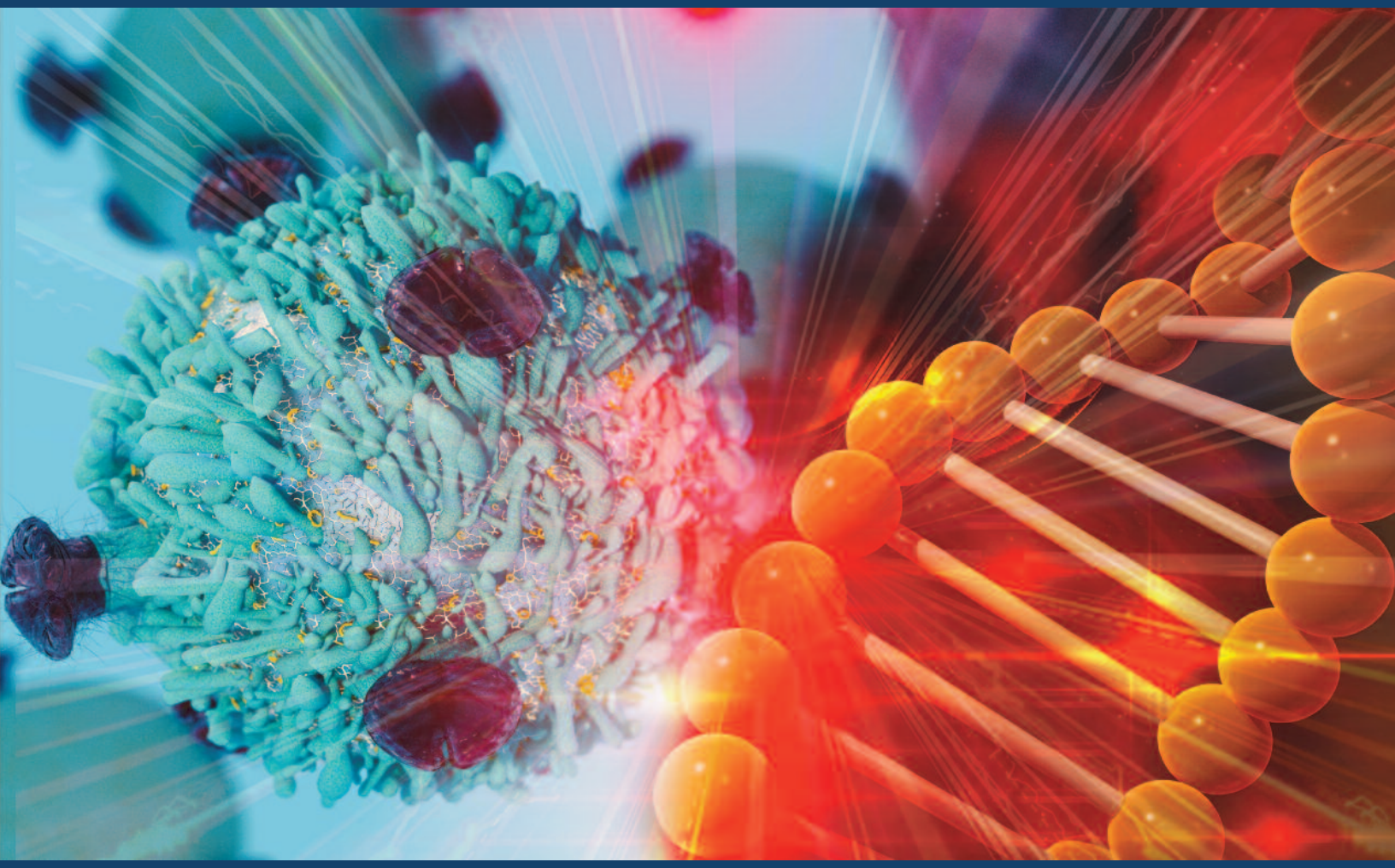
BIO-RAD

An Executive Think Tank Dinner Summary

# Current Challenges and Future Impact of Cellular and Genetic Immunotherapies For Human Health



Frost & Sullivan recently invited academic and industry thought leaders working in immunotherapy development to participate in our Executive Think Tank Dinner, which is a unique thought leadership forum that brings together leading minds to discuss current challenges and the future impact of cellular and genetic immunotherapies for human health.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## THE NEW AGE OF IMMUNOTHERAPY DEVELOPMENT

In 2017, the FDA approval of immunotherapeutics Kymriah and Yescarta officially legitimized the rise of innovative ways to treat cancers by using a patient's own immune cells (T-cells). Since then, the immunotherapy industry has witnessed a spur in research and development (R&D) and subsequent commercialization efforts to bring the next generation of immunotherapies to patients. These "live" drugs have shown promising efficacy and safety profiles in clinical trials, and the immunotherapy industry is focusing R&D toward the development of additional, effective immunotherapies.

According to the World Health Organization (WHO), cancer is currently the second leading cause of death, globally, responsible for 9.6 million deaths in 2018. Despite years of effort to improve outcomes, cancer incidence is estimated to double by 2035. The growth in oncology cost to the health system is expected to rise between 7% – 10% annually throughout 2020, when global oncology costs will exceed $150 billion.

Overcoming the uncertainties surrounding immunotherapies — such as deciding the best path forward for immune cell engineering (viral vs non-viral) and choosing the safest and most efficient therapy development platform (autologous vs allogeneic) — will help to advance these therapies. Additionally, continued development of standardized Good Manufacturing Processes (GMP) and cost reduction measures will support the scaled up immunotherapy production required for millions of cancer patients, ensuring that patients have access to these novel immunotherapies.

## FIVE IMPACTFUL TRENDS

Chemotherapy is the most widely known treatment for cancer in medical history, but it is also infamous for its side effects. For millions of people, living with cancer means hair loss, long-term nausea, drastic weight loss, and extreme fatigue, among many other bodily reactions. These common chemo side effects make the treatment process extremely difficult for not only patients, but also their caregivers.

Scientists are now focusing on the human body's own immune system, shaped for millennia to be equipped to fight against disease. Many researchers are looking toward immunotherapy in an attempt to eliminate and control cancer progression. Yet, current limitations and uncertainties prevent immunotherapies from reaching millions of cancer patients. It is important to understand the key trends impacting the immunotherapy industry.

**Key Trends Impacting the Immunotherapy Industry**

1. Detecting antigens to improve Adoptive Cell Transfer (ACT) therapies
   Collecting and using patients' own immune cells to treat their cancer
2. Overcoming the tumor microenvironment
   Increasing the efficacy of CAR T-cell therapies
3. Relying on 3D models
   Utilizing 3D cancer cell spheroids to develop effective anti-tumor therapies
4. Deciding autologous vs. allogenic platforms
   Understanding which platform holds the key to future cancer immunotherapeutic success
5. Genetically engineering T-cells
   Anticipating increased demand for immunotherapies, what does the industry see as the best method for genetically editing T-cells?

## 1 DETECTING ANTIGENS TO IMPROVE ADOPTIVE CELL TRANSFER (ACT) THERAPIES

### Harnessing the power of immune cells

There are two classes of genetically enhanced T-cell therapies: Chimeric Antigen Receptor (CAR) T-cell therapies and gene–modified T-cell Receptor (TCR) therapies. CAR T-cells are a novel form of immunotherapy where T-cells are collected from patients and genetically modified to destroy cancer cells. These tumor targeting CAR T-cells are grown in the laboratory for two to three weeks before being infused back into the patient. In 2017, the first two CAR T-cell therapies (Kymriah and Yescarta) were approved by the FDA. They were approved again in 2018 by the European Medicines Agency to treat debilitating blood cancers — B-cell acute lymphoblastic leukemia and high-grade B-cell lymphoma.

### TCRs vs CARs

Recently, there has been considerable interest in engineering conventional TCRs, primarily because they are able to recognise a larger array of potential antigens compared with CARs. This feature is possible only because TCRs have evolved the sensitivity to detect low levels of intracellular antigens.

An alternative approach is to avoid adoptive cell therapies that utilize circulating T-cells from the blood and instead use TILs. Neill Mackenzie of Immetacyte/Cellular Therapeutics, shared that TILs have zero toxicity because they are sourced from the patient and are not re-engineered. He states that all antibody combination therapies used in patients have failed, except PD-1 and 4-1BB. When treated with TILs, they demonstrated efficacy.

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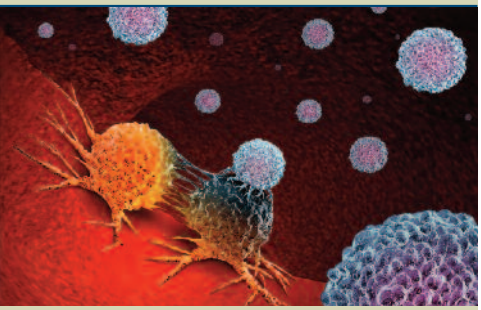

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*"We need to educate immune cells and help it overcome cancer."*

**– Rob Allen,**
Dark Horse Consulting





### Developing new CAR and TCR constructs

There are several approaches for creating new CAR and TCR constructs, including unmasking antigens already present on or within tumors/cancer cells and also enriching T-cells "trained" to detect certain antigens and transfer them to the patient. In either case, it is important to know which antigens are derived from viruses or tumors and which ones may be recognized by T-cells. Such developments will help pave the way for improved cancer detection and therapeutic efficacy.

## 2 OVERCOMING TUMOR MICROENVIRONMENTS

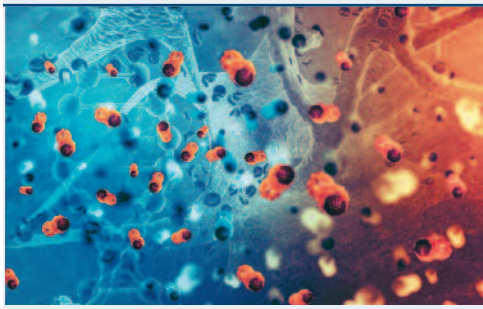
### Solid tumors: The fight from within

New CAR T-cell immunotherapies are offering hope for patients with hematologic malignancies. However, that is not the case for those with solid tumors. Research has shown that sarcomas and carcinomas have proven more resistant to CAR T-cell approaches in part because engineered T-cells progressively lose tumor-fighting capacity once a tumor is infiltrated. Immunologists call this cellular fatigue T-cell "exhaustion" or "dysfunction".

### Staying alive: Helping T-cells persist and recognize in the tumor microenvironment

To improve T-cell persistence and tumor recognition, several research investigations have focused on:

- Regional delivery of CAR T-cells to improve T-cell persistence in solid tumors. Preclinical testing has consistently reported significantly lower CAR T-cell numbers being required to induce tumor responses and limited or abolished systemic toxicities when regional administration is chosen over systemic delivery.
- Empowering CAR T-cells to shape their own cytokine environment. Cytokine support is a crucial factor for the survival and expansion of T-cell therapies. Engineering solutions for transferred T-cells have been developed to allow for both supporting themselves with pro-inflammatory cytokines and shielding themselves from immunosuppressive cytokines within the tumor microenvironment.
- Developing combinatorial antigen recognition approaches. Recently, this technique has been created to address challenges by targeting two or more TAAs with a single CAR T-cell. These tandem CAR T-cells are activated in the presence of either antigen 1 or antigen 2. The strategy helps to increase the density of the target molecules on the tumor surface and therefore may increase CAR T-cell potency.
- Engineering T-cells to safely discriminate between malignant cells and healthy tissues. By expressing both a first-generation CAR which recognizes antigen 1 (inducing inadequate activation) and a chimeric co-stimulatory receptor which recognizes antigen 2 (allowing for full T-cell activation, complementing the co-stimulation needed). For example, sensing of antigen 1 by the synNotch receptor induces transcription of a CAR that is specific for the antigen.



# 3 UNDERSTANDING CANCER IN A NEW DIMENSION

### Appreciating spatial awareness for cancer cells

Traditionally, tumoricidal activity and immune system evasion have been studied by utilizing two-dimensional systems (2D), involving either immortalized cancer cell lines or primary tumor cells cultured as monolayers. Primary testing via 2D methods is often the entry point into preclinical drug screening cascades. Yet, these 2D models do not accurately reflect the complexity of a 3D tumor, the multicellular interactions that direct the immune response against cancer, nor the tumor cell-immune cell interactions. CAR T-cells that show encouraging results using 2D models often produce less effective results at later stages of the development pipeline, meaning time, effort, and resources are wasted. This is particularly important when 85% of new cancer cases are of the solid types.

### New role models: Culturing cancer cells in a spatially relevant manner

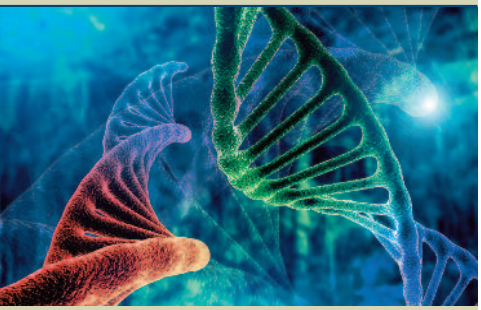
Three dimensional in vitro tumor models, such as spheroids, have recently emerged as a promising tool to replicate many features of solid tumors in vivo. However, the structural complexity of cancer spheroids creates more physiological barriers to immune cells compared to 2D culture. Spheroid models have a layered structure with rapidly proliferating cells surrounding a more quiescent and hypoxic, necrotic core. This structure generates a gradient of nutrients, metabolites, and oxygen in the spheroid — important attributes for the evaluation of drug efficacy in a heterogeneous environment. As of 2018, thanks to work published by Fan et al., it is now possible to grow spheroids in the lab using colorectal cancer (CRC) cells. There is no current effective CAR T-cell therapy available for CRC patients, but this study demonstrated efficacious killing of CRC spheroids targeted by CAR T-cells. Future studies just like this one may continue to show promising paths forward, especially for cancers currently without effective immunotherapies.

### Using 3D models to speed up cancer drugs to market

OncoSolutions, a spin-off from the University of Akron, USA, is developing 3D models for triple-negative breast cancer to bridge the gap between in vitro and clinical testing. OncoSolutions believes that their spheroid-forming technology will help drug companies filter out ineffective cancer drugs earlier in the process. Ultimately, resources can be focused on cancer drugs that are more likely to succeed, allowing better cancer drugs to get to the market faster and cheaper.

*"TILs work long term, they are cheap, have long duration of effect, there is T-cell persistence, avoid costly lentivirus production, no need to focus on a specific target."*

**– Neill Mackenzie,** Immetacyte/Cellular Therapeutics





# 4 AUTOLOGOUS AND ALLOGENIC PLATFORMS

### Challenges faced by autologous therapy

Autologous therapies use immune cells that originate from the patient themselves. The major advantage of autologous CAR T-cell therapy is its ability to overcome rejection by the host's immune system, improving safety and tolerability. While clinically meaningful, this highly personalized approach to medicine has struggled in the face of commercial and scientific realities.

The complex manufacturing process and logistical burden to engineer immune cells contributes to the three main shortcomings of autologous therapies: time, cost, and reliability.

The intensive and bespoke nature of the autologous manufacturing process and the stringent quality controls associated with manufacturing therapies using live cells carries with it a hefty price tag. Because the therapy must be made on-demand following apheresis (separation of white blood cells/leukocytes from blood sample), the manufacturing process is difficult to scale effectively. Patients may also experience delays when waiting for a therapy they may never receive if the manufacturing process fails.

*"There is a tendency to ignore the complexity of the tumor microenvironment."*

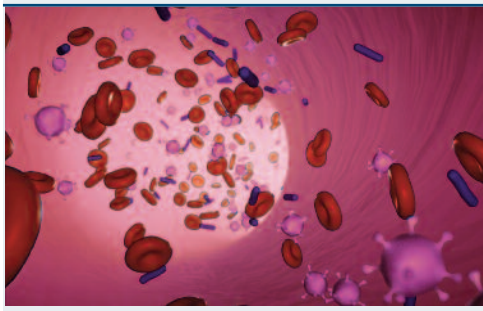
**– Giuseppe Mazza,** Engitix

### The rise of allogeneic therapy

Allogeneic cell therapy uses engineered cells from healthy donors. The main advantage of an allogeneic platform is the universal production of therapies, which enables immediate patient access to treatment. This also means there is minimal risk that a patient fails to receive treatment due to manufacturing failure. Moreover, allogeneic therapies can be manufactured in a batch, which allows manufacturing to scale more effectively.

One unique risk allogeneic therapies have is called Graft-versus-Host Disease (GvHD). With allogeneic CAR-T therapy, transplanted donor T-cells may recognize a patient's healthy cells as foreign and attack. The limitations of both autologous and allogeneic therapies have pushed researched to develop novel cancer therapeutic approaches:

- A 2019 study used sequential allogeneic and autologous CAR T-cell therapy to treat an immune-compromised leukemic patient — a child with B-ALL who failed standard treatments. The patient received CD19 CAR T-cells derived from her mother (allogeneic CAR T), followed by infusion of her own CAR T-cells (autologous CAR T), which resulted in complete remission.
- Another study developed various universal immune receptors (UIRs) that allow for targeting of multiple TAAs by T-cells expressing a single receptor. This may help allogeneic CAR T-cell therapy overcome GvHD by enabling greater discrimination between patient's healthy cells and cancerous cells.



## 5 GENETIC ENGINEERING OF T-CELLS

With demand for immunotherapies anticipated to increase, what does the industry see as the best method for genetically editing T-cells?

### Going viral

At present, there are two ways to deliver genetic material into human cells: viral vector mediated and non-viral systems. Within both basic research and clinical studies, viral vector mediated methods are employed due to:

- **High transfer efficiency**, which reduces the time needed to reach clinically necessary numbers of edited cultured T-cells.
- **Large number of options** with a library of different viruses and different expression characteristics.
- **Supply chain benefits,** including potential for mass production and long term storage of viral vectors and viruses, which reduces risk to companies as they consider which processes to employ for long term manufacturing stability.

However, the potential for insertional mutagenesis caused by the integration of viral vector DNA into host cells can lead to tumorigenesis. Therefore, it is necessary to carefully monitor for adverse events related to viral vectors over a long time period.

*"The three dimensional nature of solid tumors is often ignored when analyzing cells, which are often considered in one dimensional configurations."*

**– Ioannis Papantoniou,** KU Leuven



**Eliminating viruses**

Non-viral methods have maintained their position as an alternative approach to introducing foreign genetic material into a host cell. The key benefits of non-viral methods include increased target specificity, cost effectiveness, a preferable safety profile, lower induction burden, unlimited carrier capacity, controlled chemical constitution, and generous production.

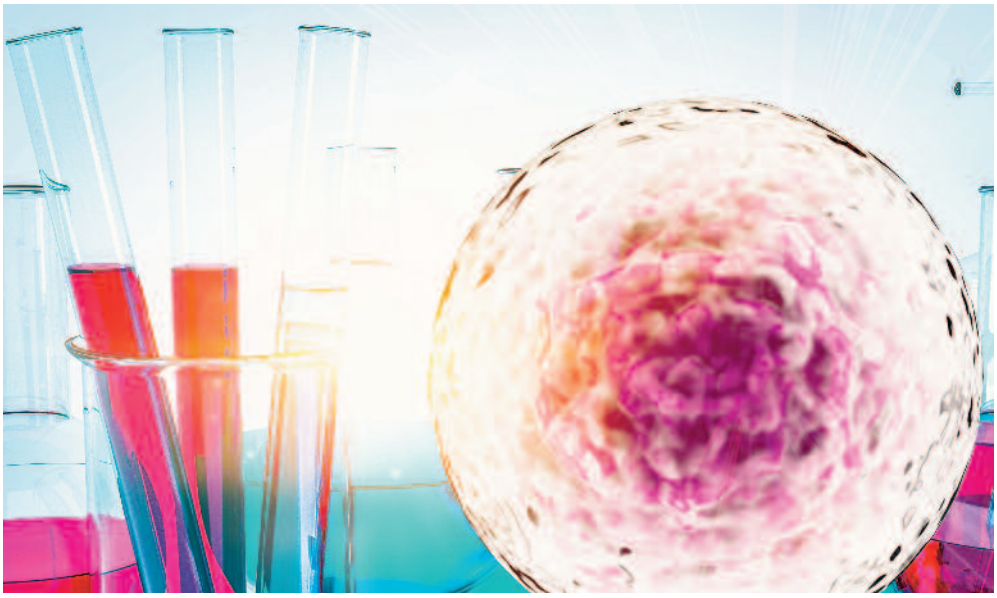
Thus, next generation cell therapies will rely heavily on gene editing techniques that employ safer non-viral integration methods. CRISPR-Cas9 mediated gene editing was first tested in patients with aggressive lung cancer (NCT02793856). In the trial, the immune cells from recipient blood were removed, followed by ex vivo CRISPR-Cas9 editing to disable the PD-1 protein. However, the use of CRISPR-Cas9 for therapeutic targeting remains challenging with CRISPR-Cas9–mediated on-target damage, which may lead to activation of dormant oncogenes. Although these challenges persist, CRISPR-based technologies hold immense potential and are a great addition to the genome editing toolbox for the development of immunotherapies that aim to improve cancer patient outcomes.

*"Autologous cell therapies are scientifically feasible but they are not commercially viable."*

**– Claudia Mitchell,** Astellas

## NAVIGATING UNCERTAINTIES: BEST-PRACTICES AND FOCUS AREAS

Recent advances in ACT and genetic engineering have brought new cancer treatment options to patients. The future of the industry is ambitious, yet still undefined. To fully realize those ambitions, the pharmaceutical industry ought to start addressing how immunotherapy production can be scaled efficiently to ensure uninhibited access to treatment without compromising drug safety. To navigate these uncertainties with trust, there are a few key best-practices and focus areas.



## THE KEY TO MANUFACTURING SUCCESS

### Upscaling the manufacturing of immunotherapies from bench to bedside

As cell-based immunotherapies mature from treating tens to hundreds of patients during clinical trials to hundreds of thousands of patients after regulatory approval, significant manufacturing challenges remain. A number of manufacturing protocols still rely on manual processing steps across workflows, which are heavily susceptible to variability, contamination and errors. There is now a more concerted effort among manufacturers to close, automate, and control manufacturing processes to ensure critical quality attributes of the cell-based product are consistently maintained. This has the added benefit of ensuring manufacturing processes are cost-effective and risk-mitigated.

### Thinking GMP

To reduce downstream issues during clinical testing and manufacturing phases good laboratory/manufacturing practices are critical early on in the R&D workflow. When products fail at the manufacturing stage, it is often not an issue with manufacturing but poor assay development during early research discovery. Research labs may not need to embrace GMP reagents, but should deploy a GMP mindset when developing assays. However, the trade-off for early GMP/GLP enforcement may be the creation of anxiety over new ideas due to the perception of high costs associated with GMP products and processes, throttling research progression.

### Ensuring seamless standards

To validate processes more efficiently, the industry would benefit from developing comprehensive and consistent standards to overcome the disjointed handover of ideas and technologies between early research, clinical, and manufacturing settings. Future system complexities and irregularities could be overcome, which would in turn help improve the manufacturing/QC process. This may consequentially get successful and safer therapies to market more quickly while simultaneously saving millions of dollars for drug developers on ineffective drug targets and/or therapies.

*"Viral vectors will remain the most effective way of introducing genetic inserts into the host's genome."*

**– Shirley Bartido,**
Cellectis



## TREATMENT ACCESS AND TREATMENT COST

**How will the development of immunotherapies influence treatment cost and subsequent treatment access?**

***Drug developers' perspective***

Due to the current reliance on autologous cell-based immunotherapies, prices remain high. The laborious and lengthy manufacturing process involves bespoke CAR T-cells to be developed for each patient. This is also exacerbated by the upward pricing pressure on medicine currently being witnessed within the US. There are two ways of potentially reducing time and costs in the manufacturing process:

1. Increase the adoption of automation, thereby reducing the number of labor intensive steps in CAR T-cell production.
2. The adoption of allogeneic therapies over more personalized autologous therapies will decrease cost.

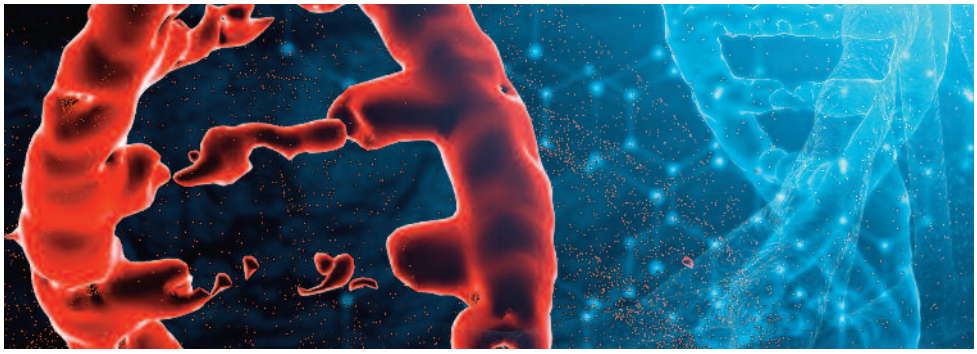
For allogeneic therapies to reach patients, a better understanding of tumor mutations and antigens, Graft-versus-Host Disease, and the wide variation in patients' immune systems will be required. The switch to allogeneic therapies is widely anticipated to result in more patients being able to receive promising immunotherapies.

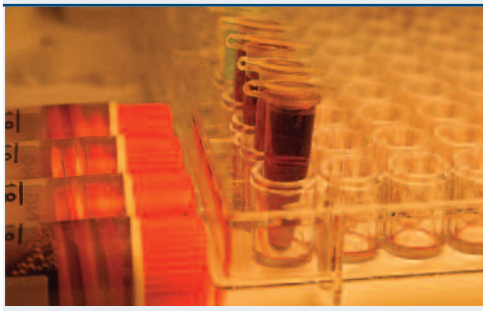
***Payer/Patient perspective***

FDA-approved CAR T-cell therapies have introduced a new era of effective cancer therapies for patients. Yet, they remain the most expensive treatments to date. Now, health systems are faced with financial implications when introducing these novel agents into clinical practice. Current list prices do not include hospitalization fees associated with treatment, which can drive total treatment costs to over $1 million per patient, in some instances. Patient access and reimbursement, in addition to insurance coverage, remain the most prominent rate-limiting steps for the implementation of CAR T-cell treatments. Issues with reimbursement will only increase as additional CAR T-cell therapies are granted regulatory approval and the eligible patient population grows.

*"The quality and quantity of data is limiting CRISPR, but eventually CRISPR will overcome on-target and off-target effects."*

**– Ajan Reginald,**
Cellxir





**Summary of Key Takeaways**

- Innovations in genetic engineering are making immunotherapy an attractive method for treating cancer.
- Cancer cells have intricate mechanisms to avoid detection of immune cells; however, new immunotherapies are designed to overcome the cancer detection barrier.
- Immune cells struggle to overcome the toxic microenvironments of solid tumors, perturbing the development of immunotherapies.
- Greater understanding of tumor microenvironments and the development of 3D cell models are enabling greater success against solid tumors.
- As more immunotherapeutics are anticipated to reach millions of cancer patients, there will need to be a concerted effort to upscale safely, efficiently, and at cost to ensure greater access.
- The need to shift from autologous to allogeneic platforms is still a controversial subject that continues to stoke fierce debate. Future research may be able to draw on the benefits of both platforms.

## LOOKING AHEAD TO THE NEXT DECADE

Immunotherapies, in particular ACTs, as well as advances in genetic engineering are giving new hope to patients, creating the impetus for researchers to develop ever more innovative therapies. Current research endeavors are addressing key issues, such as:

- Developing armored CAR T-cells that reinforce modified CAR T-cells against influences in hostile tumor microenvironments, especially for hard-to-treat hematological or solid tumor malignancies.
- Most clinical trial efforts are evaluating treatment regimens that combine PD-L1 immunotherapies with other cancer therapies, ushering in an era of combination therapies.
- Leveraging autologous and/or allogenic cell platforms to efficiently upscale manufacturing.
- Adopting breakthroughs in gene editing tools such as CRISPR-Cas9.

Embracing comprehensive standards across R&D and manufacturing to validate methodologies and manufacturing processes will create a more robust, seamless, and diligent drug development environment. Millions of cancer patients can benefit as life-saving cancer drugs are increasingly brought to market faster and at lower costs. With these possibilities on the horizon, the future of the immunotherapy toolbox is looking extremely promising.

*"It is a crime to go through the whole research process to find out that it cannot be manufactured."*

**– Ajan Reginald,**
Cellxir