Scaling Hope: Growth of the Allogeneic Cell Therapy Sector

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Scaling Hope: Growth of the Allogeneic Cell Therapy Sector

*This article was originally published on **This Month in Transformative Medicine** on August 30, 2023. **Anshul Mangal** President of Project Farma and Precision ADVANCE and **John Khoury**, Executive Vice President of Project Farma (PF) discuss the growth of the allogeneic cell therapy sector and its impact on patient access.*

In the rapidly evolving landscape of advanced therapies, allogeneic cell therapies have emerged as a promising avenue for addressing various disorders, including hematological malignancies, neurological conditions, and autoimmune or inflammatory diseases. With a number of clinical trials underway to evaluate their efficacy, allogeneic cell therapies hold significant potential in reshaping the way we approach treating numerous diseases. These therapies offer distinct advantages over their autologous counterparts as allogeneic cell therapy presents a streamlined alternative. These 'off the shelf' therapies utilize cells from healthy donors that are genetically modified and stored in large batches, ready for use. This innovative approach allows for quicker treatment initiation, larger-scale preparation, and potentially broader accessibility. The unique benefits of allogeneic cell therapies have the potential to revolutionize treatment and provide new hope for many patients living with devastating diseases.

Allogeneic cell therapies emerges as a promising avenue for various disorders

Allogeneic vs. Autologous

Allogeneic cell therapy offers several advantages over its autologous counterpart. With autologous therapy, the process involves drawing cells from the patient, modifying them genetically, and then multiplying them before readministering to the patient to combat cancer cells. This elaborate procedure can take a month or even longer to complete, making it a highly customized and time-consuming therapy. Although six autologous CAR-T cell immunotherapy products have been approved by the FDA since 2017, the high level of customization and lengthy manufacturing process have limited its widespread adoption. Additionally, the high cost of autologous cell therapy poses challenges in positioning it as a viable first-line treatment option.

On the other hand, allogeneic cell therapy offers a more streamlined approach as an "off the shelf" method. This method utilizes cells from healthy donors, which are then genetically modified and stored in large batches. The key advantage lies in the ability to match the best donor cell batch to a patient's tissue type, a process that takes only a few days. By enabling large-scale preparation and application, allogeneic cell therapy holds the potential to make CAR T therapies more accessible. Allogeneic CAR T cells also show potential for **enhanced proliferation and antitumor effects**, while reducing the burden on the patient and ultimately decreasing time to treatment.

This innovative approach has the power to revolutionize treatment by providing quicker, more efficient, and cost-effective solutions for patients. As research in this area progresses, further breakthroughs have the potential to change the landscape of cell therapy and improve outcomes for countless patients.

Challenges of Allogeneic Products

Despite the potential for allogeneic cell therapy to solve for logistical and manufacturing considerations, **challenges remain** including obstacles in cell quality, homogeneity, integrity, differentiation, and maintaining aseptic conditions.

Cellular Starting Material

Allogeneic cell therapy holds great promise in the field of immune cell-based treatments, but like its autologous counterpart, faces notable challenges in scaling up processes. One of the key obstacles lies in obtaining sufficient and stable "raw material" supplies to create industrial value through economies of scale. Furthermore, the quality and composition of donated cellular starting material significantly impacts the safety and efficacy of allogeneic cell therapies.

Allogeneic immune cell therapy products can be derived from three sources: adult healthy donors, induced pluripotent stem cells (iPSCs), and umbilical cord blood. While umbilical cord blood appears to be the most promising option for large-scale production due to its collection and storage at birth, providing a relatively stable and safe means of immune cell procurement, iPSCs raise significant ethical and safety concerns.

The process of maintaining a stable supply of immune cells from healthy donors is both expensive and challenging, as the cell source from a single donor is limited and cannot be used on a larger scale. Relying on a group of healthy donors can lead to concerns about sourcing quality, consistency, and standardization issues in the production processes. Standardized and validated cell-processing methods are crucial to ensure consistent and effective outcomes.

Potential for Rejection

The biggest hurdle in allogeneic cell therapies is the potential for rejection. Challenges like graft-versus-host disease (GvHD) have been associated with allogeneic cell infusions. Researchers are using methods of immune cloaking to essentially hide and protect the CAR T from the patient's immune system. Gene editing technologies like TALENs and CRISPR-Cas9 can eliminate αβ T cell receptor expression, thereby reducing the risk of GvHD. These advancements are paving the way for safer and more efficient CAR T cell therapies that could be accessible to a broader patient population in the near future.

Advancements are paving the way for safer and more efficient CAR T cell therapies

The aforementioned obstacles have prompted industry leaders like the head of Kite, a Gilead company, to note they believe **allogeneic therapies have a long way to go** before they could compete with autologous offerings. Despite these obstacles, continuing the work to advance allogeneic cell therapy is a worthwhile cause as it ultimately increases access while reducing the burden on the patient and has immense potential for efficacy. As research and technology continue to advance, addressing these hurdles will be crucial in order to advance the effectiveness, safety, and scalability of allogeneic cell therapies.

Caribou Biosciences, co-founded by Nobel winner and CRISPR pioneer Jennifer Doudna and Rachel Haurwitz, CEO and President, specializes in CRISPR gene editing technology. The company has turned their focus towards developing allogeneic CAR-T and CAR-NK cell therapies in the hopes of **serving a much broader patient population**. While autologous methods show immense promise, allogeneic cell therapies have the potential to improve patient access through faster treatment and reduced costs.

The Current Industry and Expected Growth

The allogeneic cell therapy industry is poised for immense growth. Currently, there are about 195 companies engaged in the development of allogeneic cell therapies targeting various therapeutic domains, with oncology leading the way. Among these therapies, the prominent categories are stem cell therapies, followed closely by T-cell therapies. In terms of market dominance, North America takes the lead, capturing over 60% of the total market share.

As we look to the future, forecasts suggest that the allogeneic cell therapy market is poised for significant expansion due to increasing demand for innovative medical solutions, a robust pipeline of developmental projects, and favorable outcomes from clinical trials. As of 2023, the **global allogeneic cell therapy market** is valued at around $0.9 billion. Projections indicate a robust compound annual growth rate (CAGR) of 14% by 2035. As the industry works to overcome the various obstacles facing the allogeneic cell therapy sector, the potential for growth and the number of patients that can be impacted is exponential.

Currently Approved Indications

Atara's Ebvallo for EBV+ PTLD

In December of 2022 Atara made history with the marketing authorization of Ebvallo, the **first ever approval of an allogeneic T-Cell therapy**. Their treatment for Epstein-Barr virus-positive (EBV) was granted approval in Europe for the treatment for relapsed or refractory EBV-positive post-transplant lymphoproliferative disease (EBV+ PTLD) in patients aged two and above. EBV+ PTLD is a rare but serious condition that can manifest in individuals who have received solid organ or hematopoietic stem cell transplantation. This disorder falls under the category of lymphoproliferative disorders, where there is an anomalous increase in lymphoid cells across different organs, growth is frequently influenced by EBV.

Since then, the marketing authorization for Ebvallo has been transferred from Atara to Pierre Fabre which will lead all commercialization, distribution, medical and regulatory efforts for the allogeneic treatment in Europe, the Middle East, Africa, and other selected markets. Atara will continue to oversee the pivotal ALLELE study and Phase II multi-cohort study for EBVALLO®. Atara retains full rights to EBVALLO® in other major markets, including North America, Asia Pacific, and Latin America. The launch of this treatment offers new hope for patients living with this challenging disease.

Gamida Cell Omisirge for Blood Cancer

In a groundbreaking achievement, **Gamida Cell achieved FDA approval** in April for their allogeneic cell therapy Omisirge, which hopes to reduce the risk of infection in blood cancer patients. This marks the FDA's first approval of an allogeneic cell therapy product designed for stem cell transplantation (SCT), addressing a crucial need for patients who face challenges in finding suitable donor matches. Allogeneic SCT is commonly used in treating blood-related cancers, offering a curative potential but carrying significant risks, particularly related to donor-recipient compatibility. Omisirge is engineered to accelerate the recovery of neutrophils, vital white blood cells that combat infections, reducing the risk of severe infections linked to SCT. Initially targeting patients lacking closely matched donors, particularly those relying on umbilical cord blood, Gamida Cell envisions expanding the therapy's application to other SCT-risk populations, including those with mismatched donors or minimal residual disease. With its FDA clearance, Omisirge has the potential to set a new standard of care for SCT in individuals without a suitable donor match.

The Allogeneic Pipeline

FDA Grants IND Clearance for AlloNK in Lupus Nephritis - Artiva Biotherapeutics

Last week the **FDA granted the first IND clearance** for an allogeneic NK cell therapy for an autoimmune disease. The recent FDA approval of an IND for AlloNK, in combination with rituximab, to treat active lupus nephritis in systemic lupus erythematosus (SLE) patients is a groundbreaking development. SLE is a chronic and severe autoimmune disease characterized by abnormal B-cell function and autoantibody production that leads to a range of health issues including organ damage and can be fatal. Among those with SLE, roughly 40% are affected by lupus nephritis and more than 40% of individuals who experience the most severe form of LN face the threat of end-stage renal disease within a span of 15 years.

> **40% of those with SLE** are affected by lupus nephritis

Artiva hopes to change this somber reality with their cell therapy candidate for this autoimmune disease. AlloNK represents a non-genetically modified, cord blood-derived allogeneic natural killer (NK) cell therapy, designed to enhance antibody-dependent cellular cytotoxicity. The combination of AlloNK and rituximab seeks to improve B-cell depletion seen in this indication, presenting potential advantages for SLE and lupus nephritis patients. The therapy has demonstrated the ability to achieve complete responses in advanced B-cell non-Hodgkin lymphoma patients, further underscoring its efficacy. With this **first of its kind approval**, Artiva has high hopes that this innovative allogeneic therapy will improve treatment outcomes for individuals living with SLE.

Mesoblast's Pursuit of Allogeneic Cell Therapy for GVHD

The Australian cell therapy company Mesoblast is working to gain regulatory approval of its remestemcel-L for children with steroid-refractory acute graft-versus-host disease (SR-aGVHD). Over the years the company has faced several regulatory roadblocks, with the latest FDA rejection earlier this month. With their resubmission, the agency has been prompted to **request additional data** from adult patients for reconsideration of the decision. However, the FDA acknowledged no safety issues among the substantial patient group that had received remestemcel-L and recognized

improvements in its potency assay. To meet the FDA's requirements, Mesoblast intends to conduct a controlled study in at-risk adults. This setback follows previous support from the FDA's Oncologic Drugs Advisory Committee. The company's resubmission, which featured long-term survival findings and outcome data, led to scheduling a Type A meeting with the FDA to discuss the design of the planned adult study.

Promising Clinical Results for Multiple Myeloma

The first off-the-shelf allogeneic CAR T cell therapy targeting the protein BCMA has demonstrated **safety and efficacy for multiple myeloma patients**. In a groundbreaking phase 1 clinical trial, allogeneic CAR T cells from healthy donors were used instead of the patient's own cells. Among the patients who received the optimal treatment dosage, an impressive 71% experienced positive responses lasting at least eight months, indicating a halt in disease progression. Almost 90% of trial participants received these innovative allogeneic CAR T cells just five days after enrolling, a significantly shorter timeline compared to traditional autologous CAR T cell therapy. The therapy's success lies in its ability to suppress graft-versus-host disease (GVHD) by manipulating T cell proteins. Although further research is needed, this off-the-shelf strategy holds renewed hope and potential for not only multiple myeloma but also other blood cancers and solid tumors.

CAR T for Blood Cancer Patients Who Relapsed with Autologous

Last week Australian-based **Imugene announced it has acquired the license** to develop and commercialize an allogeneic (CAR) T cell therapy from US based Precision Biosciences. This acquisition of the therapy indicated for diffuse large B-cell lymphoma (DLBCL) patients who have relapsed following autologous (auto) CAR T cell treatments is a significant move in the field of cancer treatment. Imugene's plan to initiate a registrational study for azer-cel in 2024 underscores its ambition to establish itself as a pioneer in the realm of allogeneic CAR T cell therapy and hopes to land the first approval for an allo-CAR T therapy for cancer. Encouraging results from the ongoing Phase Ib clinical trial, which showcase a 58% overall response rate and 41% complete response rate across various doses, bolster its potential. Of note, azer-cel has displayed particularly promising outcomes for DLBCL patients who experienced relapse after auto-CAR T cell therapy. Imugene's vision positions this therapy as a complement to its proprietary onCARlytics platform, focused on enhancing CAR T cell effectiveness in treating solid tumors. While facing competition from other allogeneic CAR T cell therapies, azer-cel's potential and Imugene's strategic approach hold promise in the continually evolving landscape of CAR T cell treatments.

In the dynamic landscape of advanced therapies, the emergence of allogeneic cell therapies offers a new hope for addressing a number of indications, ranging from hematological malignancies to autoimmune conditions. The ongoing clinical trials attest to the fervent exploration of their potential efficacy. This trajectory holds transformative potential for disease treatment, enabling faster, efficient, and cost-effective solutions for patients.

Though challenges exist, the commitment of industry leaders and the promise of scalable solutions drive allogeneic cell therapy's advancement. With an ever-growing number of companies harnessing its potential, the allogeneic cell therapy market is set for substantial expansion. Forecasts predict a robust growth rate, positioning this approach to be a valuable solution for both patients and CAR T developers.

With each approval there is renewed hope for patients, who desperately need innovative solutions. As this journey continues, it's evident that allogeneic cell therapies hold the potential to revolutionize the advanced therapy landscape, offering novel avenues for treatment, accessibility, and improved quality of life. With a global market poised for expansion and forecasts indicating significant growth, the future of allogeneic cell therapy is indeed promising.

About the Authors

Anshul Mangal, President Project Farma (PF) & Precision ADVANCE

Anshul founded and grew PF into a leading global biologics and advanced therapy engineering consulting firm. Under Anshul's leadership, PF pioneered the industrialization of advanced therapies including two notable, commercially approved cell and gene therapies. PF was acquired by Precision Medicine Group in 2020 to be the cornerstone of Precision ADVANCE. ADVANCE is a collection of Precision's services uniquely focused on the complexities of research and clinical development, regulatory, manufacturing, and commercial needs to successfully bring an advanced therapy to market.

John Khoury, Executive Vice President Project Farma (PF)

John Khoury is a 20+ year veteran and leader in the biotech / pharmaceutical industry. As a member of the Project Farma Leadership Committee, John has spearheaded Project Farma's growth in the gene and cell therapy space. He has led and provided strategy on key partner initiatives including make vs. buy analysis, site and vendor selection, tech transfer execution strategies, and facility start-ups.

In addition to his experience in advanced therapies, John has extensive experience with small and large molecules including biologics and biosimilars. Over the past four years, he has led facility builds totaling over $500MM. During this time, he has worked with small and large biotech and pharmaceutical companies including gene and cell therapy startups and CMOs/CROs.

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Rev. 01