Overcoming the Challenges of Developing Cell and Gene Therapies for Autoimmune Disorders

Autoimmune diseases such as lupus, type 1 diabetes, inflammatory bowel disease (Crohn's disease or ulcerative colitis) and rheumatoid arthritis are complex conditions involving multi-factorial mechanisms of action and patient heterogeneity. Treating them with CGT requires a comprehensive understanding of the specific disease biology and a reliable source of cellular starting materials.

CGT Challenges

As researchers look beyond using cell and gene therapy (CGT) for oncology indications and start to focus on autoimmune disorders, they need to adjust their approach. Autoimmune diseases are highly individualised, and patients have different pathophysiology. Therefore, researchers need to develop personalised therapies that are tailored to the specific immune profiles and needs of each patient. They can be autologous (using the patient's own cells) or allogeneic (using cells from a donor).

A deep understanding of the underlying mechanisms of action is essential. Researchers need to identify specific targets within the immune pathways that can be modulated effectively to restore balance without compromising overall immune function.

Delivery of the CGT must also be optimised for autoimmune disorders. This may involve the use of advanced delivery systems, such as nanoparticles or viral vectors, which can enhance targeting and uptake of the therapies in specific tissues or organs affected by the disease.

Establishing the safety and effectiveness of an advanced therapy medicinal product (ATMP) through pre-clinical and clinical trials is a complex and resource intensive process that requires rigorous planning and execution. As successful cell therapy projects often require interdisciplinary collaboration between immunologists, clinicians, biologists and regulatory experts, they can also be logistically challenging.

In addition, researchers should consider combination therapies that integrate CGT with existing treatments, for example, immunosuppressants or biologics, to enhance their efficacy and reduce relapses.

Gender Disparities

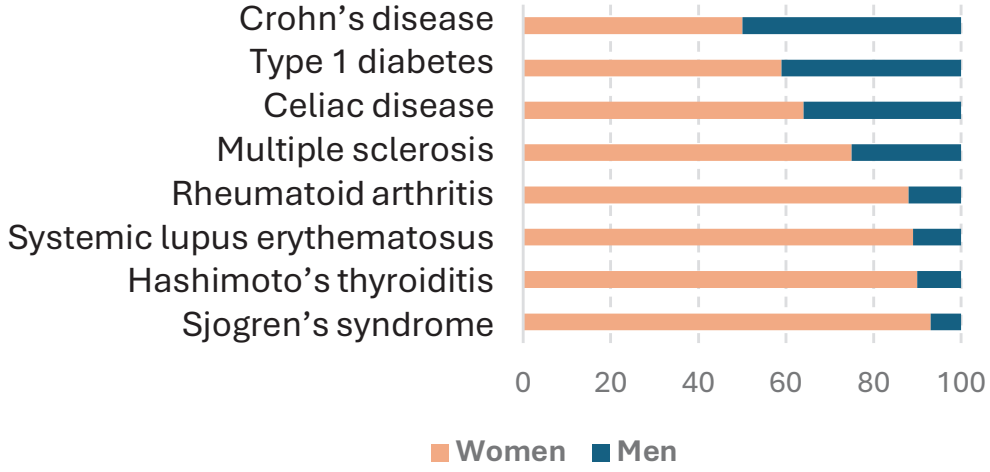
Females are disproportionately affected by autoimmune diseases and there is growing recognition of the need to conduct gender-specific research. Certain genes may be expressed differently in males and females, for example, thus influencing their disease susceptibility and response to therapies.

Researchers are investigating how X-linked genes and their expression might influence autoimmune responses. This could lead to targeted therapies that address specific genetic factors affecting females more than males.

Studying how hormonal fluctuations can affect disease progression and treatment response may also allow the development of therapies that recognise those differences.

In addition, females typically have stronger innate and adaptive immune responses than males, impacting their response to infections. It's critically important that researchers utilise diverse patient cohorts within the early research phases to properly illuminate differences based on gender, race or other demographic aspects. These differences should also be used to inform the design of cell therapies, ensuring they are tailored to harness or modulate these responses effectively.

Balance of the sexes



Lupus Example

Approximately 90% of the diagnoses of lupus are in females aged 15 to 44.[1] This dramatic female sex bias is thought to be due, at least in part, to estrogens.[2] Research has identified several genes associated with lupus susceptibility, some of which may be more actively expressed in females, and environmental exposure to silica, cigarette smoking and oral contraceptives may also play a role.[3]

Further supporting the genetic link, the prevalence of systemic lupus erythematosus (SLE) is higher in patients with supernumerary X chromosome syndromes, such as Klinefelter (XXY) and Triple X syndrome (XXX), and lower with Turner syndrome (XO).[4]

Conducting mechanistic studies at the cellular and molecular levels to understand how sex differences impact immune cell function, cytokine production and overall pathophysiology can provide valuable insights into lupus and other autoimmune diseases.

Differences in drug metabolism, immune response and side effects can influence therapy outcomes. Therefore, tailoring therapies based on gender-specific responses may enhance their effectiveness.

Identifying biomarkers that reflect gender-specific disease mechanisms will also assist in the stratification of patients in clinical trials and the development of personalised therapies.

Diverse Patient Recruitment

Due to the different disease burden and therapeutic responses between males and females, it is imperative that both sexes are adequately represented in autoimmune cell therapy clinical trials. This will lead to a greater understanding of how new therapies will perform, resulting in more effective and safer treatments for all patients.

It is also important that clinical trial populations are diverse in terms of their racial, ethnic and cultural backgrounds to ensure that the findings are applicable to a broad population and represent a real-world scenario.

Researchers should collaborate with community organisations, patient advocacy groups and local healthcare providers to raise awareness of their clinical trials and encourage a representative patient population to enrol. Building trust within these communities is essential for increasing research participation.

To ensure that patients not only enrol in the clinical trial but continue to participate throughout, researchers must design studies that are culturally sensitive and consider the unique social, economic and health-related factors affecting different racial and ethnic groups. This includes considering language barriers, health beliefs and access to care.

Regulatory Hurdles

Navigating the regulatory landscape for ATMPs involves understanding and complying with stringent requirements from agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), which can be time-consuming and costly.

But early and ongoing engagement with those regulatory agencies can help researchers navigate the complexities of the approval processes for novel therapies and ensure that they meet safety and efficacy standards specific to autoimmune indications.

Furthermore, given the chronic nature of autoimmune diseases, long-term monitoring of treatment efficacy and safety is crucial. Researchers need to develop robust strategies to assess the durability of therapeutic responses and manage potential adverse effects.

Sourcing Starting Materials

Identifying suitable donors for an allogeneic autoimmune cell therapy program can be a major hurdle. Finding healthy donors that have specific cell characteristics and are human leukocyte antigen (HLA) matched, or patients with specific autoimmune conditions who are willing to donate cells, can be difficult. This scarcity can limit and delay project timelines and increase costs.

Having ready access to disease-state autoimmune cells is invaluable. These cells can be used to create accurate *in vitro* models of the condition, permitting further study of its mechanisms of action and disease progression and potentially revealing new therapeutic targets. They are also required for pre-clinical testing of potential new drug candidates.

Once a new cell therapy has demonstrated proof of concept and is ready for production, ensuring the quality and viability of the starting materials is critical. Variability in cell quality between donors and even between lots from the same donor can affect the consistency and reliability of the therapy. Stringent quality control measures must be implemented, which can complicate logistics and increase costs.

As the demand for cell therapies grows, ensuring high-quality, consistent cell production and developing reliable, scalable and compliant manufacturing processes is essential. Meeting all those needs becomes increasingly difficult and can hinder the ability to launch larger clinical trials or commercial therapies effectively.

Funding Challenges

Autoimmune diseases are complex, which may deter some investors who prefer clearer, more straightforward therapeutic targets. The path to demonstrating therapeutic efficacy for an autoimmune disease can also be long and complicated, potentially leading investors to perceive them as riskier funding options.

The regulatory landscape for CGTs can also be daunting and investors may be wary of the potential for delays and costs associated with navigating it.

As a result, securing funding for research and development in autoimmune diseases can be difficult, especially during the initial stages when proof of concept is being established.

Public awareness and patient advocacy can also impact funding. Health conditions that have strong patient advocacy

groups, such as oncology and rare genetic disorders, frequently receive more attention and funding compared to autoimmune diseases, which typically do not have the same level of visibility.

While there may be a limited number of traditional funding sources for autoimmune disease research, there is growing interest in public-private partnerships and venture philanthropy, which may help to address funding gaps.

Autoimmune Research Breakthroughs

Despite all the challenges associated with research into autoimmune diseases, there have been some significant breakthroughs. For example, research on regulatory T cells (Tregs) has led to new therapeutic approaches for autoimmune diseases. Recent studies have shown that expanding and infusing Tregs can restore immune tolerance in patients with conditions such as type 1 diabetes and rheumatoid arthritis, potentially halting their disease progression.

Use of a novel modified Treg enabled patients in the UK who had had a liver transplant to come off immunosuppression (IS) medication because their body no longer viewed the transplanted liver as foreign tissue.[5] This approach is also being considered for treating graft-versus-host disease, which occurs when donor stem cells attack the recipient patient's healthy cells.

Innovative therapies targeting B cell depletion, such as obinutuzumab and rituximab, have also shown promise in treating lupus and multiple sclerosis. Recent trials have demonstrated their efficacy both in reducing disease activity and improving patient outcomes.

Furthermore, CRISPR technology is being applied to correct genetic defects associated with autoimmune diseases. Recent studies have demonstrated that it is possible to edit immune cells to enhance their tolerance and reduce autoimmunity.

Novel Approaches

A recent first-in-human stem cell transplant case involved a 25-year-old female patient who suffered from long-term, hard-to-control type 1 diabetes complicated by episodes of severe hypoglycemia.[6] This patient received autologous chemically induced pluripotent stem cell–islet cells, which were generated from mesenchymal stromal cells isolated from her adipose tissue. The stem-cell-derived islets were transplanted into a site in her abdominal anterior rectus sheath. This procedure successfully restored insulin-independent glycemic control for the patient, which was maintained at one-year follow-up.[6]

A female patient has also become the first person with multiple sclerosis to be treated with an "off-the-shelf" CAR T-cell therapy called azercabtagene zapreleucel.[7] While traditional CAR T-cell therapies use the patient's own T cells, which are genetically modified to carry a chimeric antigen receptor (CAR) and target a specific protein, this product uses donor-derived cells, allowing it to be produced faster and more consistently.

Conclusion

Developing CGTs presents significant challenges, but these

products also possess the potential to yield incredible medical advances. Some difficulties can be overcome by partnering with companies that have consistent and reliable access to high-quality, disease-state and normal cells from diverse donors that are both research and Current Good Manufacturing Practice grade. This step allows new products to transition more easily from the pre-clinical to the clinical pipeline and potentially help patients faster.

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