©NIJRMS
Publications 2025

OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES (NIJRMS)

Volume 6 Issue 2 Page 25-29 2025

https://doi.org/10.59298/NIJRMS/2025/6.2.2529

Immunomodulation in Congenital Immunodeficiencies: Targeting Innate and Adaptive Pathways

Mubanza Zunguka J.

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

Congenital immunodeficiencies, also known as primary immunodeficiency disorders (PIDs), comprise a heterogeneous group of inherited conditions affecting both innate and adaptive immune pathways. These disorders result in increased susceptibility to infections, immune dysregulation, and heightened risk of autoimmunity and malignancies. Advances in immunomodulatory strategies have transformed the management of these conditions, providing targeted therapeutic approaches to enhance immune function. This review explores key immunomodulatory mechanisms, including cytokine modulation, gene therapy, and cellular therapies, that are being developed to correct immune deficiencies. Emerging therapies such as CRISPR-based gene editing, monoclonal antibodies, and microbiome-based interventions hold great potential for improving patient outcomes. Understanding the interplay between innate and adaptive immunity in congenital immunodeficiencies is crucial for optimizing treatment strategies and developing novel interventions. Future research should focus on refining these approaches to achieve durable immune restoration and minimize adverse effects.

Keywords: Congenital immunodeficiencies, primary immunodeficiency, immunomodulation, gene therapy, cytokine therapy

INTRODUCTION

Congenital immunodeficiencies, also known as primary immunodeficiency disorders (PIDs), result from genetic mutations affecting critical components of the immune system [1]. These defects compromise innate and adaptive immunity, leading to increased susceptibility to infections, autoimmunity, and malignancies [2]. The spectrum of congenital immunodeficiencies is broad, encompassing disorders affecting immune cell development, signaling pathways, cytokine production, and complement activation [3]. Traditionally, management has focused on supportive care, including antimicrobial prophylaxis, immunoglobulin replacement therapy, and hematopoietic stem cell transplantation (HSCT) for severe cases [4]. While these strategies mitigate infection risk, they do not directly restore immune function. Recent advances in immunomodulatory therapies have shifted the paradigm of congenital immunodeficiency management [5-7]. Immunomodulation aims to enhance immune responses, correct dysregulated signaling, and improve overall host defense [8]. Targeted therapies, including cytokine supplementation, monoclonal antibodies, and gene-editing technologies, are being explored to modify immune function more precisely [9]. Janus kinase (JAK) inhibitors, for instance, have shown promise in managing immune dysregulation syndromes, while gene therapy is emerging as a curative option for conditions such as severe combined immunodeficiency (SCID) and chronic granulomatous disease (CGD) [10]. Additionally, biologics targeting key immune checkpoints offer novel approaches for modulating immune responses without excessive immune suppression [11]. This review explores the principles of immunomodulation in congenital immunodeficiencies, discussing the mechanisms, benefits, and limitations of current and emerging therapies. By elucidating these advancements, we aim to highlight innovative strategies that not only enhance immune function but also improve long-term patient outcomes. Understanding the evolving landscape of immunomodulation in

OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

congenital immunodeficiencies is crucial for optimizing personalized therapeutic approaches and addressing the unmet needs of affected individuals.

Innate Immune Modulation

The innate immune system serves as the first line of defense against infections, providing rapid and nonspecific responses to pathogens [12]. Genetic defects in innate immunity can result in severe immunodeficiency, increasing susceptibility to recurrent infections and inflammatory disorders [13]. Therapeutic strategies targeting the innate immune system aim to enhance or restore immune function through cytokine supplementation, receptor agonists, and cellular therapies.

Cytokine Therapy

Cytokines are key regulators of innate immunity, modulating immune cell activation and function. Several cytokine-based therapies have been developed to compensate for innate immune deficiencies.

Interferon-Gamma (IFN-γ) Therapy: This therapy is widely used in chronic granulomatous disease (CGD) to enhance macrophage function and oxidative burst activity, improving microbial clearance [14] Granulocyte Colony-Stimulating Factor (G-CSF): G-CSF stimulates neutrophil production and function, benefiting patients with neutropenia-related immunodeficiencies, such as severe congenital neutropenia (SCN) [15] Interleukin-2 (IL-2) Therapy: IL-2 has been explored in conditions involving T-cell dysfunction, promoting regulatory T-cell activity and immune homeostasis [16].

Toll-Like Receptor (TLR) Agonists

Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns (PAMPs) and activate innate immune responses [17]. In congenital immunodeficiencies where pattern recognition receptor (PRR) signaling is defective, TLR agonists may enhance immune activation.

CpG oligodeoxynucleotides (ODNs), synthetic TLR9 agonists, have been studied for their potential to enhance innate immune responses, particularly in patients with impaired dendritic cell function or defective antimicrobial defense [18,19].

Cellular Therapies

Restoring innate immune cell function through cellular therapies represents a promising approach for congenital immunodeficiencies affecting myeloid lineage cells.

Hematopoietic Stem Cell Transplantation (HSCT): HSCT remains the gold standard for severe congenital immunodeficiencies, providing a lifelong source of functional immune cells [4].

Gene-Edited Stem Cells: Advances in gene-editing technologies, including CRISPR-Cas9, have enabled precise correction of mutations in innate immune pathway genes, offering a potential curative approach [6,20].

Adaptive Immune Modulation

Adaptive immunity, mediated by T and B lymphocytes, is essential for pathogen-specific immune responses and immune memory [21]. Defects in adaptive immunity can lead to severe combined immunodeficiencies (SCID) and other primary immunodeficiency disorders (PIDs). Immunomodulatory strategies focus on restoring or enhancing adaptive immune functions through gene therapy, monoclonal antibodies, and immunoglobulin replacement therapy [22].

Gene Therapy

Gene therapy offers a targeted approach to correct genetic defects underlying adaptive immune deficiencies [18]. Ex Vivo Gene Correction: Patient-derived hematopoietic stem cells (HSCs) are genetically modified using lentiviral or retroviral vectors to introduce functional copies of defective genes, as demonstrated in SCID and Wiskott-Aldrich syndrome. CRISPR-Based Gene Editing: CRISPR-Cas9 technology enables precise correction of pathogenic mutations in T and B cells, holding promise for long-term immune reconstitution [23].

Monoclonal Antibodies (mAbs) and Biologics

Monoclonal antibodies and biologics are used to modulate immune responses in primary immunodeficiencies associated with immune dysregulation [24]. Anti-IL-6 and Anti-TNF Therapies: These biologics help control inflammation in immunodeficiencies with autoimmune manifestations, such as autoimmune lymphoproliferative syndrome (ALPS). Checkpoint Inhibitors: Targeting immune checkpoint molecules, such as CTLA-4 and PD-1, is being explored as a strategy to restore immune function in disorders with immune dysregulation [25].

Immunoglobulin Replacement Therapy (IgRT)

B-cell deficiencies result in impaired antibody production, necessitating passive immunity through IgRT. Intravenous or subcutaneous immunoglobulin (IVIG/SCIG) provides essential antibodies, reducing infection risk and improving quality of life in patients with X-linked agammaglobulinemia (XLA) and common variable immunodeficiency (CVID) [26]. Emerging advancements in immunomodulation continue to refine treatment strategies for congenital immunodeficiencies, offering hope for improved patient outcomes and potential curative therapies.

OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

Emerging and Future Therapies

Recent advances in immunomodulation have introduced innovative therapeutic approaches aimed at enhancing immune function, correcting genetic defects, and fine-tuning immune responses. These emerging strategies offer potential breakthroughs in the management of congenital immunodeficiencies.

mRNA-Based Therapies

Messenger RNA (mRNA) technology, widely recognized for its role in vaccine development, is now being explored for personalized immune modulation [27]. mRNA-based therapies can be designed to encode cytokines, immune-modulating proteins, or even gene-correcting enzymes, allowing for transient yet highly specific immune regulation [3]. In congenital immunodeficiencies, mRNA therapy could be used to restore defective immune signaling pathways or boost immune responses against infections.

Synthetic Biology Approaches

Advances in synthetic biology have enabled the engineering of immune cells with enhanced functional capabilities. Chimeric antigen receptor (CAR) T-cell therapy, initially developed for cancer immunotherapy, is being adapted for primary immunodeficiencies to enhance immune surveillance and pathogen clearance [30]. Additionally, synthetic gene circuits are being designed to modulate immune activation dynamically, providing precision control over immune responses.

Microbiome-Based Interventions

The gut microbiome plays a crucial role in shaping immune function. Dysbiosis, or an imbalance in microbial composition, has been implicated in immune dysregulation [31]. Microbiome-based therapies, including probiotics, prebiotics, and fecal microbiota transplantation (FMT), are being investigated as potential strategies to enhance immune resilience and modulate inflammatory pathways in patients with immunodeficiencies [32,33]. These cutting-edge approaches hold promise for revolutionizing the treatment landscape, offering more targeted, durable, and patient-specific immunomodulatory therapies.

CONCLUSION

Immunomodulation in congenital immunodeficiencies has advanced significantly, shifting from purely supportive care to targeted therapies that restore immune function. Gene therapy, biologics, and cell-based approaches offer promising avenues for long-term disease management and potential cures. Emerging innovations, such as mRNA-based therapies and synthetic biology, continue to expand treatment possibilities. Despite these advancements, challenges remain in optimizing efficacy, safety, and accessibility. Ongoing research and clinical trials will refine these strategies, ultimately improving patient outcomes and quality of life. A deeper understanding of immune regulation will drive the development of more precise and personalized therapeutic interventions for congenital immunodeficiencies.

REFERENCES

1. McCusker C, Upton J, Warrington R. Primary immunodeficiency. Allergy Asthma Clin Immunol. 2018; 14(Suppl 2):61. doi: 10.1186/s13223-018-0290-5. PMID: 30275850; PMCID: PMC6157160.
2. Mahbuba Rahman, Mamatha Ramaswamy, Chapter 4 - Metabolomics used in clinical diagnosis related to newborn screening, Editor(s): Mahbuba Rahman,In Developments in Applied Microbiology and Biotechnology, Metabolomics, Academic Press, 2023; 121-171. https://doi.org/10.1016/B978-0-323-99924-3.00007-8.
3. Pessach, I., Walter, J. & Notarangelo, L. Recent Advances in Primary Immunodeficiencies: Identification of Novel Genetic Defects and Unanticipated Phenotypes. *Pediatr Res.*, 2009; **65**, 3–12. https://doi.org/10.1203/PDR.0b013e31819dbe1e
4. Madeleine Taylor, Shaukat Khan, Molly Stapleton, Jianmin Wang, Jing Chen, Robert Wynn et al., Hematopoietic Stem Cell Transplantation for Mucopolysaccharidoses: Past, Present, and Future, Biology of Blood and Marrow Transplantation, 2019; 25(7): e226-e246. https://doi.org/10.1016/j.bbmt.2019.02.012.
5. Ifversen M, Meisel R, Sedlacek P, Kalwak K, Sisinni L, Hutt D, et al., Supportive Care During Pediatric Hematopoietic Stem Cell Transplantation: Prevention of Infections. A Report from Workshops on Supportive Care of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT). Front Pediatr. 2021; 9:705179. doi: 10.3389/fped.2021.705179. PMID: 34395344; PMCID: PMC8358428.
6. Kreins, A.Y., Velasco, H.F., Cheong, KN. *et al.* Long-Term Immune Recovery After Hematopoietic Stem Cell Transplantation for ADA Deficiency: a Single-Center Experience. *J Clin Immunol.*, 2022; **42**, 94–107. https://doi.org/10.1007/s10875-021-01145-w
7. Muraro, P.A., Mariottini, A., Greco, R. *et al.* Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis and neuromyelitis optica spectrum disorder — recommendations from

OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

ECTRIMS and the EBMT. *Nat Rev Neurol.*, 2025; **21**, 140–158. https://doi.org/10.1038/s41582-024-01050-x

8. Lei, T., Wang, Y., Zhang, Y. *et al.* Leveraging CRISPR gene editing technology to optimize the efficacy, safety and accessibility of CAR T-cell therapy. *Leukemia.*, 2024; **38**, 2517–2543. https://doi.org/10.1038/s41375-024-02444-y
9. Feng X, Li Z, Liu Y, Chen D, Zhou Z. CRISPR/Cas9 technology for advancements in cancer immunotherapy: from uncovering regulatory mechanisms to therapeutic applications. Exp Hematol Oncol. 2024; 13(1):102. doi: 10.1186/s40164-024-00570-y. PMID: 39427211; PMCID: PMC11490091.
10. Krzyszczyk P, Acevedo A, Davidoff EJ, Timmins LM, Marrero-Berrios I, Patel M, White C, Lowe C, Sherba JJ, Hartmanshenn C, O'Neill KM, Balter ML, Fritz ZR, Androulakis IP, Schloss RS, Yarmush ML. The growing role of precision and personalized medicine for cancer treatment. Technology (Singap World Sci). 2018; 6(3-4):79-100. doi: 10.1142/S2339547818300020. Epub 2019 Jan 11. PMID: 30713991; PMCID: PMC6352312.
11. Sharma, Y., Arora, M. & Bala, K. The potential of immunomodulators in shaping the future of healthcare. *Discov Med.*, 2024; **1**, 37. https://doi.org/10.1007/s44337-024-00029-3
12. Aristizábal B, González Á. Innate immune system. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From Bench to Bedside [Internet]. Bogota (Colombia): El Rosario University Press; 2013 Jul 18. Chapter 2. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459455/
13. Carrillo JLM, Rodríguez FPC, Coronado OG, García MAM, Cordero JFC. Physiology and Pathology of Innate Immune Response Against Pathogens [Internet]. Physiology and Pathology of Immunology. InTech; 2017. Available from: http://dx.doi.org/10.5772/intechopen.70556
14. Diamond, M.S., Kanneganti, TD. Innate immunity: the first line of defense against SARS-CoV-2. *Nat Immunol.*, 2022; **23**, 165–176. https://doi.org/10.1038/s41590-021-01091-0
15. Oyesola OO, Früh SP, Webb LM, Tait Wojno ED. Cytokines and beyond: Regulation of innate immune responses during helminth infection. Cytokine. 2020; 133:154527. doi: 10.1016/j.cyto.2018.08.021. Epub 2018 Sep 18. PMID: 30241895; PMCID: PMC6422760.
16. Holley CK, Dobrovolskaia MA. Innate Immunity Modulating Impurities and the Immunotoxicity of Nanobiotechnology-Based Drug Products. *Molecules.* 2021; 26(23):7308. https://doi.org/10.3390/molecules26237308
17. Janssens S, Beyaert R. Role of Toll-like receptors in pathogen recognition. Clin Microbiol Rev. 2003; 16(4):637-46. doi: 10.1128/CMR.16.4.637-646.2003. PMID: 14557290; PMCID: PMC207104.
18. Duan T, Du Y, Xing C, Wang HY, Wang RF. Toll-Like Receptor Signaling and Its Role in Cell-Mediated Immunity. Front Immunol. 2022; 13:812774. doi: 10.3389/fimmu.2022.812774. PMID: 35309296; PMCID: PMC8927970.
19. Li, D., Wu, M. Pattern recognition receptors in health and diseases. *Sig Transduct Target Ther.*, 2021; **6**, 291. https://doi.org/10.1038/s41392-021-00687-0
20. Wahlstrom JT, Dvorak CC, Cowan MJ. Hematopoietic Stem Cell Transplantation for Severe Combined Immunodeficiency. Curr Pediatr Rep. 2015; 3(1):1-10. doi: 10.1007/s40124-014-0071-7. PMID: 25821657; PMCID: PMC4371740.
21. Hongbo Chi, Marion Pepper, Paul G. Thomas, Principles and therapeutic applications of adaptive immunity, Cell, 2024; 187 (9):2052-2078. https://doi.org/10.1016/j.cell.2024.03.037.
22. Rivera, A., Siracusa, M., Yap, G. *et al.* Innate cell communication kick-starts pathogen-specific immunity. *Nat Immunol.*, 2016; **17**, 356–363. https://doi.org/10.1038/ni.3375
23. Abdelnour SA, Xie L, Hassanin AA, Zuo E, Lu Y. The Potential of CRISPR/Cas9 Gene Editing as a Treatment Strategy for Inherited Diseases. Front Cell Dev Biol. 2021; 9:699597. doi: 10.3389/fcell.2021.699597. PMID: 34977000; PMCID: PMC8715006.
24. Perez E. Future of Therapy for Inborn Errors of Immunity. Clin Rev Allergy Immunol. 2022; 63(1):75-89. doi: 10.1007/s12016-021-08916-8. Epub 2022 Jan 12. PMID: 35020169; PMCID: PMC8753954.
25. Lu, RM., Hwang, YC., Liu, IJ. *et al.* Development of therapeutic antibodies for the treatment of diseases. *J Biomed Sci.*, 2020; **27**, 1. https://doi.org/10.1186/s12929-019-0592-z
26. Sil A, Basu S, Joshi V, Pilania RK, Siniah S, Suri D, Rawat A, Singh S. Immunoglobulin replacement therapies in inborn errors of immunity: a review. Front Pediatr. 2024; 12:1368755. doi: 10.3389/fped.2024.1368755. PMID: 38425666; PMCID: PMC10902166.
27. Al Fayez N, Nassar MS, Alshehri AA, Alnefaie MK, Almughem FA, Alshehri BY, Alawad AO, Tawfik EA. Recent Advancement in mRNA Vaccine Development and Applications. Pharmaceutics. 2023; 15(7):1972. doi: 10.3390/pharmaceutics15071972. PMID: 37514158; PMCID: PMC10384963.

OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

28. Jain S, Venkataraman A, Wechsler ME, Peppas NA. Messenger RNA-based vaccines: Past, present, and future directions in the context of the COVID-19 pandemic. Adv Drug Deliv Rev. 2021; 179:114000. doi: 10.1016/j.addr.2021.114000
29. Zhang C, Durer S, Thandra KC, et al. Chimeric Antigen Receptor T-Cell Therapy. [Updated 2022 Oct 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537294/
30. Maldini CR, Ellis GI, Riley JL. CAR T cells for infection, autoimmunity and allotransplantation. Nat Rev Immunol. 2018; 18(10):605-616. doi: 10.1038/s41577-018-0042-2. PMID: 30046149; PMCID: PMC6505691.
31. Zhang R, Ding N, Feng X, Liao W. The gut microbiome, immune modulation, and cognitive decline: insights on the gut-brain axis. Front Immunol. 2025; 16:1529958. doi: 10.3389/fimmu.2025.1529958. PMID: 39911400; PMCID: PMC11794507.
32. Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes. 2012; 3(1):4-14. doi: 10.4161/gmic.19320. Epub 2012 Jan 1. PMID: 22356853; PMCID: PMC3337124.
33. Fakharian F, Thirugnanam S, Welsh DA, Kim W-K, Rappaport J, Bittinger K, Rout N. The Role of Gut Dysbiosis in the Loss of Intestinal Immune Cell Functions and Viral Pathogenesis. *Microorganisms*. 2023; 11(7):1849. https://doi.org/10.3390/microorganisms11071849

CITE AS: Mubanza Zunguka J. (2025). Immunomodulation in Congenital Immunodeficiencies: Targeting Innate and Adaptive Pathways. Newport International Journal of Research in Medical Sciences, 6(2):25-29. https://doi.org/10.59298/NIJRMS/2025/6.2.2529