Mastering the Immune Response: Immunogenicity Management in Biologics

The advent of therapeutic proteins and gene therapies has been a beacon of hope for treating complex diseases. Yet, these innovative treatments often face the significant hurdle of immunogenicity – when the drug administered provokes an immune response in the body. This biological response occurs when the immune system identifies these therapies as foreign, potentially undermining their therapeutic target. Understanding and managing immunogenicity is a key factor in the development of biologics; it impacts not just the treatment's effectiveness but also its safety profile.[1] Starting from the early stages of drug development it is essential to predict and reduce the immune response, ensuring that the therapies can perform their intended functions without eliciting adverse reactions.

The presence of anti-drug antibodies (ADA) produced as a result of an immune response against biologic therapeutic agents can lead to clinical challenges, ranging from diminished efficacy to adverse immunological reactions. ADAs can neutralise the therapeutic activity of drugs, alter their pharmacokinetic profiles, and even trigger immune responses that mimic autoimmune disorders.[2] These consequences make it critical for drug developers to anticipate the immunogenic potential of new therapies and incorporate strategies that minimise ADA development. Understanding the interaction between the drug and the immune system allows for the design of therapies that not only achieve their therapeutic goals but also maintain a favourable safety profile.[3]

Regulatory bodies across the globe, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have emphasized the necessity of comprehensive immunogenicity risk assessment for the approval of biologic therapies.[4] The goal is to ensure that potential immunogenicity issues are identified and mitigated before clinical trials and market entry. This is not merely a regulatory compliance issue but a core component of patient safety. A thorough assessment can help drug developers make informed decisions that enhance the clinical success and patient acceptance of new biologic treatments. Ultimately, thorough immunogenicity testing shapes the path to innovative therapies that can be safely integrated into patient care.

The Rise of *In Silico* and *In Vitro* Tools

In silico tools – computational methods to simulate biological processes – are essential for predicting immunogenicity risk in drug development. These computational platforms facilitate the identification of peptide sequences that could potentially bind to Human Leukocyte Antigens (HLA) alleles – variants of genes that encode for cell surface proteins that are critical for the immune system's recognition of foreign proteins.[5] By identifying such "hot spots" within therapeutic protein sequences, these tools can predict regions likely to trigger immune responses. Various platforms, such as the Immune Epitope Database (IEDB) offer the capability to rapidly screen numerous variants for their potential to bind to a broad range of HLA alleles.[6] This screening is pivotal for narrowing down candidates early in the drug discovery process, allowing researchers to focus on those with the lowest predicted immunogenicity risk.

Despite continuous improvements, *in silico* tools have a tendency to over-predict which can result in unnecessary engineering, therefore *in vitro* assays are used to complement *in silico* predictions by validating the immune response to therapeutic proteins. Complementary assays such as peptide mapping and proteomics-based approaches can combine to map individual T-cell epitopes, which are regions of the protein that can be recognised by T-cells, potentially leading to an immune response. These assays can provide insight into understanding the immunogenic potential of regions and are invaluable during later stages of candidate optimisation. Further along the discovery process, assays such as the peripheral blood mononuclear (PBMC) cell time course assay measure T-cell proliferation in response to a whole molecule. Taken together, by identifying which variants exhibit the lowest immunogenicity risk, these *in vitro* studies aid in the selection of the most promising drug candidates.[7]

Having a broad range of capabilities like the Abzena's EpiScreen® platform allows the integration of *in silico* and *in vitro* methods and offers a robust strategy for immunogenicity risk assessment. *In silico* algorithms serve as a first pass, screening out drug candidates with high immunogenicity risk based on their primary amino acid sequence. Subsequently, *in vitro* assays provide empirical data on immune response, verifying the computational predictions.[8] This combined approach not only streamlines the selection of drug candidates but also provides a comprehensive understanding of their immunogenicity profile. Such integrated methodologies are essential for developing safe and effective therapeutic proteins, as they allow for the de-risking of candidates early in the development process. Furthermore, the data from these assays can be included in Investigational New Drug (IND) applications, making them a critical component of the regulatory approval pathway.[9]

Applying Tools Across Protein Classes

There are some inspiring success stories that showcase the effective mitigation of immunogenicity in drug development. A remarkable example is the evolution of antibody technology from murine to fully human antibodies. Along the way, one significant breakthrough came in the mid '80s in the form of humanising murine antibodies, a meticulous process that involves redesigning the antibody to make it appear more human-like, thereby minimising its immunogenicity.[10] Subsequently, through the use of epitope prediction algorithms, scientists are now able to identify and alter parts of the antibody that are likely to be recognised by the human immune system. This approach has led to the creation of antibodies with significantly lower immunogenic potential. The evidence lies in the substantial decrease in T-cell epitope scores following the computational redesign, a triumph further validated by *in vitro* testing. These humanised antibodies not only exhibit reduced immunogenicity but also retain their essential binding properties, striking a balance between safety and functionality.

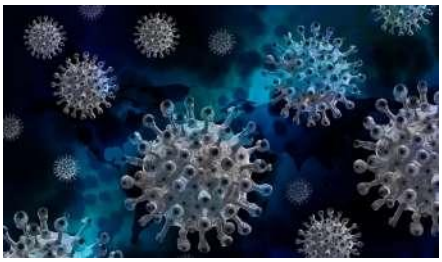
The journey to reduce immunogenicity has imparted valuable lessons and best practices in the field of biologics. It has become clear that even antibodies that are fully human in sequence can sometimes evoke immune responses, highlighting the need for ongoing innovation in therapeutic candidate design.[11] A critical best practice emerging from this challenge is the early adoption of a rational design strategy. By applying computational predictions at the outset, it's possible to pre-emptively identify and engineer out potential immunogenic epitopes. This proactive approach streamlines the development process, avoiding the need for later-stage revisions that can be both costly and time-consuming.[12]

Early Design and Developability Technologies

Understanding immunogenicity forms part of a broader philosophy of 'designing for success'. Developability assessments are a critical component of this philosophy. In addition to safety, these assessments evaluate a drug candidate's function, the specificity and manufacturability, thus the overall suitability for development. By adopting this holistic view, developers can identify candidates that not only have the desired therapeutic effect and safety profile but are also viable for large-scale manufacturing.[13] Such assessments are integral to the early stages of drug development, as they inform decisions on which candidates to progress through the development pipeline. This strategic evaluation ensures that resources are focused on the candidates with the highest likelihood of clinical and commercial success, ultimately contributing to a more efficient and targeted drug development process.

The Evolving Landscape of Immunogenicity Assessment

The last decade has seen a surge in the creation of innovative tools and methodologies designed to address the complex challenge of immunogenicity in therapeutic protein development. Advances such as artificial lymph nodes using 3D organoid models and the development of synthetic skin and subcutaneous tissue models, whilst in their infancy, mark a significant leap forward in our ability to understand an immune response.[14,15] These tools are not mere scientific novelties; they are becoming part of an integrated approach to better predict how the human body might respond to new therapies. By simulating the human immune response more accurately, these technologies allow for more precise immunogenicity assessments.[16]



Ongoing research is dramatically shaping the landscape of immunogenicity assessment. As we delve deeper into the molecular and cellular mechanisms that underpin the immune responses to biologics, our capacity to forecast and circumvent adverse immunogenicity improves. Current research is honing in on the development of more sophisticated *in silico* tools that can scrutinise potential immunogenic regions with greater accuracy, and *in vitro* assays that can mimic the human immune environment with unprecedented fidelity. The aim is to refine these predictive models so that they can offer more definitive guidance on immunogenicity risks, thus facilitating the creation of safer and more effective therapeutic proteins.[17]

The potential for these technologies to transform therapeutic protein development is immense. With tools that can provide early warnings about immunogenicity risks, the path towards developing safe and effective biologics becomes more certain. These technologies not only help in fine-tuning the safety profiles of prospective therapies but also contribute to a more efficient design and optimisation process.[16] By enabling the early identification and redesign of immunogenic elements within therapeutic proteins, these tools can significantly reduce the time and cost associated with bringing new therapies to market.[18]

A Unified Path Forward: Industry and Regulatory Harmonisation

Drug development has been reshaped by the evolving synergy between industry practices and regulatory frameworks. A pivotal aspect of this transformation is the harmonisation of the efforts to address immunogenicity.[19] This collaboration is not merely a convergence of goals but a strategic alignment that enhances the efficacy and safety of biologic therapies.

Industry experts, using *in silico* and *in vitro* tools, have advanced the methodologies used to predict and mitigate immunogenic risks. Regulatory agencies have paralleled this progress by setting rigorous standards for immunogenicity assessment, ensuring that only the most thoroughly evaluated drugs reach the market. This regulatory oversight acts as a catalyst for innovation, driving the industry to continually refine its assessment tools. The dynamic nature of these regulatory requirements reflects an ever-deepening understanding of the complex interplay between biologics and the immune system, emphasizing patient safety and treatment efficacy.[20]

The convergence of industry innovation and regulatory guidance has culminated in an unified path forward. This partnership aims to establish robust and scientifically sound practices that transcend individual corporate goals and address the collective need for safe and effective biologic therapies. Through harmonised efforts, the biopharmaceutical sector is better equipped to navigate the intricacies of immunogenicity, ultimately leading to more successful patient outcomes and a broader reliance on biologic treatments.[21]

Ultimately, however, the unified path forward is more than just a convergence of industry and regulatory bodies; it is a commitment to the shared vision of advancing healthcare. This collective effort is vital in ensuring that new treatments are both safe for patients and effective in combating diseases.

REFERENCES

1. Schellekens H. The immunogenicity of therapeutic proteins. Discov Med. 2010 Jun;9(49):560-4.
2. Pizano-Martinez O, Mendieta-Condado E, Vázquez-Del Mercado M, Martínez-García EA, Chavarria-Avila E, Ortuño-Sahagún D, Márquez-Aguirre AL. Anti-Drug Antibodies in the Biological Therapy of Autoimmune Rheumatic Diseases. J Clin Med. 2023 May 4;12(9):3271.
3. Sathish JG, Sethu S, Bielsky MC, de Haan L, French NS, Govindappa K, Green J, Griffiths CE, Holgate S, Jones D, Kimber I, Moggs J, Naisbitt DJ, Pirmohamed M, Reichmann G, Sims J, Subramanyam M, Todd MD, Van Der Laan JW, Weaver RJ, Park BK. Challenges and approaches for the development of safer immunomodulatory biologics. Nat Rev Drug Discov. 2013 Apr;12(4):306-24
4. Vandivort TC, Horton DB, Johnson SB. Regulatory and strategic considerations for addressing immunogenicity and related responses in biopharmaceutical development programs. J Clin Transl Sci. 2020 Jun 15;4(6):547-555.
5. Garcia KC, Adams EJ. How the T cell receptor sees antigen--a structural view. Cell. 2005 Aug 12;122(3):333-6.
6. Vita R, Overton JA, Greenbaum JA, Ponomarenko J, Clark JD, Cantrell JR, Wheeler DK, Gabbard JL, Hix D, Sette A, Peters B. The immune epitope database (IEDB) 3.0. Nucleic Acids Res. 2015 Jan;43.

7. Joubert MK, Deshpande M, Yang J, Reynolds H, Bryson C, Fogg M, Baker MP, Herskovitz J, Goletz TJ, Zhou L, Moxness M, Flynn GC, Narhi LO, Jawa V. Use of *In Vitro* Assays to Assess Immunogenicity Risk of Antibody-Based Biotherapeutics. PLoS One. 2016 Aug 5;11(8):e0159328.
8. Cohen S, Chung S, Spiess C, Lundin V, Stefanich E, Laing ST, Clark V, Brumm J, Zhou Y, Huang C, Guerrero J, Myneni S, Yadav R, Siradze K, Peng K. An integrated approach for characterizing immunogenic responses toward a bispecific antibody. MAbs. 2021 Jan-Dec;13(1):1944017.
9. U.S. Food and Drug Administration. Investigational New Drug (IND) Application. https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
10. Gorman SD, Clark MR. Humanisation of monoclonal antibodies for therapy. Semin Immunol. 1990 Nov;2(6):457-66.
11. Zinsli LV, Stierlin N, Loessner MJ, Schmelcher M. Deimmunisation of protein therapeutics - Recent advances in experimental and computational epitope prediction and deletion. Comput Struct Biotechnol J. 2020 Dec 29;19:315-329.
12. Jawa V, Terry F, Gokemeijer J, Mitra-Kaushik S, Roberts BJ, Tourdot S, De Groot AS. T-Cell Dependent Immunogenicity of Protein Therapeutics Pre-clinical Assessment and Mitigation-Updated Consensus and Review 2020. Front Immunol. 2020 Jun 30;11:1301.
13. Zhang W, Wang H, Feng N, Li Y, Gu J, Wang Z. Developability assessment at early-stage discovery to enable development of antibody-derived therapeutics. Antib Ther. 2022 Nov 11;6(1):13-29.
14. Yufeng Shou, Sarah C. Johnson, Ying Jie Quek, Xianlei Li, Andy Tay. Integrative lymph node-mimicking models created with biomaterials and computational tools to study the immune system. Materials Today Bio. Volume 14, 2022.
15. Bédard P, Gauvin S, Ferland K, Caneparo C, Pellerin È, Chabaud S, Bolduc S. Innovative Human Three-Dimensional Tissue-Engineered Models as an Alternative to Animal Testing. Bioengineering (Basel). 2020 Sep 17;7(3):115.
16. Sauna ZE, Jawa V, Balu-Iyer S, Chirmule N. Understanding preclinical and clinical immunogenicity risks in novel biotherapeutics development. Front Immunol. 2023 May 12;14:1151888.
17. Gokemeijer J, Jawa V, Mitra-Kaushik S. How Close Are We to Profiling Immunogenicity Risk Using *In Silico* Algorithms and *In Vitro* Methods?: an Industry Perspective. AAPS J. 2017 Nov;19(6):1587-1592.
18. Bauer J, Rajagopal N, Gupta P, Gupta P, Nixon AE, Kumar S. How can we discover developable antibody-based biotherapeutics? Front Mol Biosci. 2023 Aug 7;10:1221626.
19. Ducret A, Ackaert C, Bessa J, Bunce C, Hickling T, Jawa V, Kroenke MA, Lamberth K, Manin A, Penny HL, Smith N, Terszowski G, Tourdot S, Spindeldreher S. Assay format diversity in pre-clinical immunogenicity risk assessment: Toward a possible harmonisation of antigenicity assays. MAbs. 2022 Jan-Dec;14(1):1993522.
20. Chang RB, Beatty GL. The interplay between innate and adaptive immunity in cancer shapes the productivity of cancer immunosurveillance. J Leukoc Biol. 2020 Jul;108(1):363-376.
21. Wadhwa M, Thorpe R. Harmonisation and standardisation of immunogenicity assessment of biotherapeutic products. Bioanalysis. 2019 Sep;11(17):1593-1604.

Campbell Bunce

Campbell Bunce is the Chief Scientific Officer (CSO) and Cambridge Site Head at Abzena. He leads a talented team of scientists across a diverse range of expertise and capabilities to support drug discovery, design, developability, and cell line development. With over 25 years of experience working in the biotech and diagnostics sectors, he ensures Abzena's strong innovation focus and depth of scientific expertise are maintained through technological developments.