myNEO Therapeutics

myADA

Next-generation Anti-Drug Antibody risk prediction

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myADA - Next-generation ADA-risk prediction

Executive summary

“Will this biologic trigger an anti-drug antibody (ADA) response?” is a central question in biologic drug development. For monoclonal antibodies, cytokines, fusion proteins, and enzyme replacement therapies alike, unintended immunogenicity can lead to loss of efficacy, hypersensitivity reactions, safety liabilities, treatment discontinuation, and, in severe cases, market withdrawal. Yet despite its critical importance, ADA risk is still too often discovered late—during clinical trials or even post-approval—when mitigation strategies are complex, costly, and frequently ineffective.

Current preclinical approaches to ADA risk assessment rely largely on empirical testing or on computational predictions that **focus on isolated aspects of immunogenicity, capturing only part of the biological determinants of T-cell–dependent antibody formation**. As a result, many biologics enter the clinic with substantial, yet unrecognized, immunogenic risk.

myADA is a next-generation, in-silico ADA risk predictor **centered on advanced MHC class II epitope modeling**. By accurately identifying $CD4^+$ T-cell epitopes capable of initiating T-cell–dependent ADA responses, myADA supports proactive, design-stage control of biologic immunogenicity rather than reactive, late-stage mitigation.

Benchmarking against clinically validated biologics with known high- and low-ADA incidence demonstrates that myADA reliably discriminates between high-risk and low-risk therapeutics and pinpoints immunogenic hotspots consistent with real-world ADA outcomes. In doing so, myADA enables developers to prioritize intrinsically low-immunogenicity designs, rationally engineer safer and more effective biologics, and substantially reduce late-stage development, manufacturing, and regulatory risk.

myADA delivers what current approaches cannot: accurate, scalable, biologically grounded ADA risk prediction shifting biologic drug development from reactive immunogenicity management to proactive, data-driven design.

Why anti-drug antibodies matter

Anti-drug antibodies are immunoglobulins produced by a patient’s immune system in response to therapeutic protein drugs. These antibodies arise when the immune system recognizes a biologic as foreign and mounts an adaptive immune response analogous to those elicited by pathogens or vaccines. ADAs are generally classified as either binding antibodies, which associate with the therapeutic molecule without directly blocking its function, or neutralizing antibodies, which interfere with the drug’s mechanism of action by preventing target engagement.

The clinical consequences of ADA formation are substantial. For patients, ADAs can lead to **diminished or complete loss of therapeutic efficacy**, necessitating dose escalation, treatment switching, or discontinuation—sometimes leaving patients without viable alternatives. ADAs can also trigger **hypersensitivity** reactions ranging from mild injection site responses to severe, life-threatening anaphylaxis. In rare but serious cases, neutralizing antibodies may cross react with endogenous proteins, resulting in **autoimmune complications** such as pure red cell aplasia.

From a development and regulatory perspective, ADA-related issues impose a significant burden on pharmaceutical companies.

The immunological basis of ADA formation

The generation of ADAs is fundamentally **driven by CD4⁺ T-cell responses**. Following administration, therapeutic proteins can be internalized by antigen-presenting cells such as dendritic cells, processed into peptide fragments, and presented on MHC class II molecules. Recognition of these peptide–MHC-II complexes by CD4⁺ T helper cells leads to T-cell activation and the provision of essential help to B-cells through cytokine secretion and co-stimulatory signaling. This interaction promotes B-cell differentiation into antibody-secreting plasma cells and long-lived memory B-cells, ultimately resulting in ADA production.

Consequently, **a prerequisite for T-cell–dependent ADA formation is the presence of immunogenic MHC class II epitopes within the biologic drug sequence**. Identifying and mitigating such epitopes therefore represents a rational and mechanistically grounded strategy for reducing ADA risk.

Limitations of current preclinical ADA risk assessment

Contemporary preclinical approaches to ADA risk mitigation increasingly rely on computational immunogenicity assessments. These in-silico tools typically focus on predicting MHC class II binding peptides within therapeutic protein sequences, enabling the identification of peptide regions that may be presented to CD4⁺ T-cells. Publicly available resources such as the Immune Epitope Database (IEDB), as well as proprietary platforms including EpiMatrix and TCED, screen protein sequences across panels of common HLADR, HLADQ, and HLADP alleles to generate immunogenicity risk scores.

However, despite their conceptual appeal, these approaches have delivered mixed results in practice. Most tools **emphasize MHC-II binding affinity alone, which is necessary but insufficient to accurately predict** downstream T-cell activation and clinical ADA outcomes. As a result, many predicted epitopes **do not translate into meaningful immunogenicity in vivo**, limiting the reliability of current in-silico ADA risk assessments.

In this context, there is a clear unmet need for more precise, biologically grounded computational approaches that move beyond binding predictions to capture true T-cell immunogenic potential.

myADA: early and accurate ADA risk prediction

Through expansion of myNEO's immunogenicity prediction platform to include a dedicated suite of advanced MHC class II algorithms, yielding myADA: an ADA risk predictor able to identify and prioritize CD4⁺ T-cell epitopes with high immunogenic potential.

myADA was evaluated in a benchmark study where therapeutic antibodies were used with well characterized clinical immunogenicity profiles. The following steps were performed:

- Extraction of all possible 15- to 18-mer epitopes from 4 antibodies known to elicit high ADA rates (adalimumab, bococizumab, abciximab, infliximab) and 2 antibodies associated with low ADA incidence (etanercept, tocilizumab).
- Assessment of both the MHC-II presentation likelihood across the 10 most frequent European HLA-DR and HLA-DQ alleles, and the probability to elicit a CD4+ T-cell response upon presentation.
- Integration of these parameters into a unified Immunogenicity Score (IS).
- Normalization of the proportion of ADA-risk epitopes was normalized to the total number of epitopes per molecule to enable fair comparison across antibodies of different sizes.

As shown in **Figure 1**, antibodies with high clinical ADA incidence exhibited a substantially greater burden of predicted MHC-II–immunogenic epitopes than antibodies with low ADA rates. This clear separation demonstrates that **myADA reliably captures immunogenic features aligned with real-world clinical outcomes, enabling robust early-stage ADA risk stratification**.

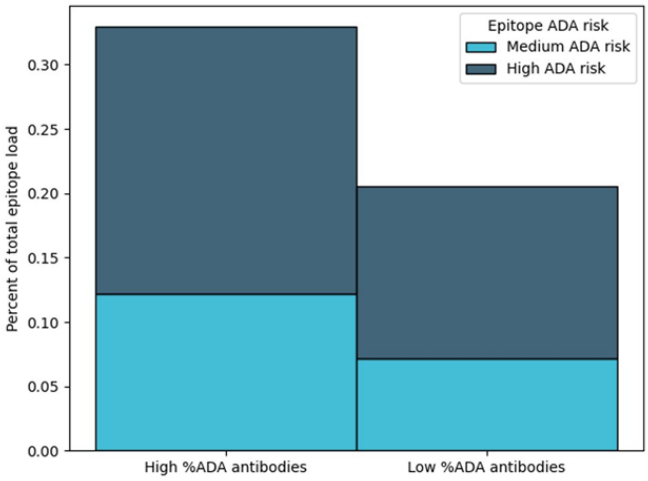

Figure 1. Distribution of MHC class II epitope risk categories stratified by anti-drug antibody (ADA) prevalence. Stacked bar chart depicting the proportion of therapeutic epitopes with medium (Immunogenicity Score of >0.95 for 1 MHC-II allele: light blue) and high (Immunogenicity Score of >0.95 for more than one MHC-II allele: dark blue) ADA risk. Two cohorts are shown: therapeutic antibodies with a high rate of ADA-positive patients (left) versus those with a low percentage of ADA-positive patients (right).

Identification of immunogenic hotspots to guide biologics engineering

Beyond global ADA risk assessment, **myADA enables fine-grained mapping of immunogenic hotspots within therapeutic protein sequences**. By profiling immunogenicity scores along the full length of a biologic, clusters of overlapping high-risk epitopes can be identified and prioritized for targeted engineering interventions.

To demonstrate this, the following benchmark study was performed:

- Analysis of the full sequence of adalimumab
- Ordering of the epitopes sequentially along the heavy and light chains
- Computation of the Immunogenicity Scores for each position
- Clustering of medium- and high-risk epitopes defined as overlapping epitopes forming uninterrupted high-risk region

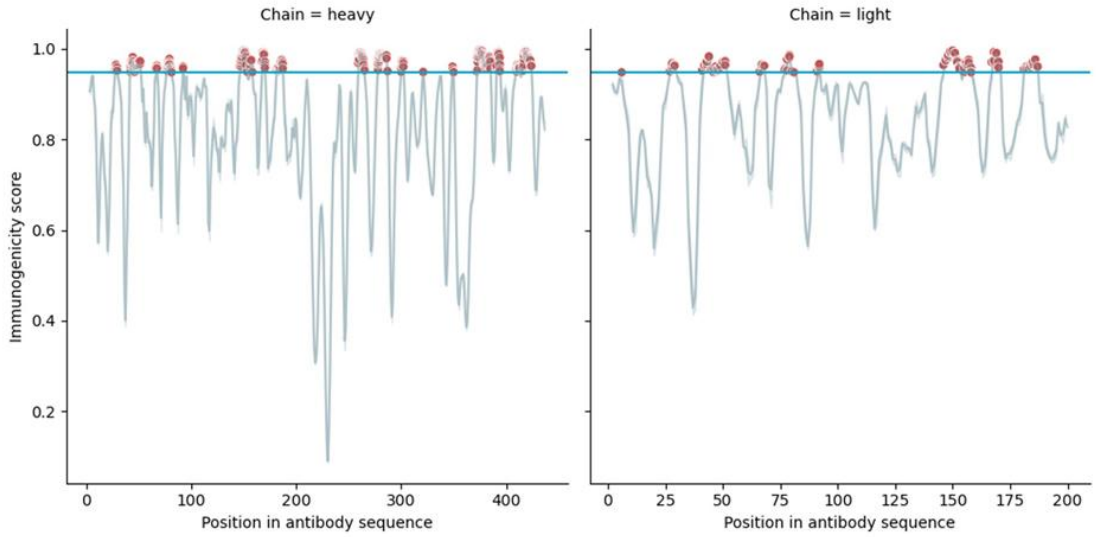

Figure 2. In-silico immunogenicity profiling of heavy and light chains in a therapeutic monoclonal antibody. Position-specific immunogenicity scores across the complete amino acid sequences of the antibody heavy chain (left panel) and light chain (right panel). Clusters are shown in red. The horizontal blue line is the Immunogenicity score threshold of 0.95, over which epitopes are deemed at risk of triggering ADA.

This revealed distinct immunogenic clusters within both the heavy and light chains, representing likely sources of ADA formation (**Figure 2**). Such localized risk profiles provide actionable guidance for rational sequence optimization, enabling **selective modification of high-risk ADA regions while preserving structural integrity and therapeutic function**.

Conclusion

myADA allows rational and data-driven biologics engineering minimizing ADA-risk at pre-clinical development stage.

By accurate quantification of $CD4^+$ T-cell–driven immunogenic potential and localization of discrete immunogenic hotspots in therapeutic proteins combined with known clinical ADA outcome alignment, myADA enables reliable discrimination between high- and low-ADA risk biologics.

Integration of myADA into preclinical pipelines allows to prioritize superior lead candidates and accelerates the development of safer, more effective therapies for patients.

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