myNEO Therapeutics

mySELF

Next-generation immunogenicity prediction for autoimmune disease and immune tolerance

myNEO BV
Ottergemsesteenweg-Zuid 808
9000 Ghent, Belgium

www.myneotx.com
contact@myneotx.com

mySELF - Next-generation immunogenicity prediction in autoimmunity

Executive summary

"Which self-peptides are truly driving disease — and which can be leveraged to restore tolerance?"

Autoimmune and immune-mediated inflammatory diseases arise from loss of immune tolerance to self. In many indications, like type 1 diabetes, vitiligo or multiple sclerosis, autoreactive T cells play a central role in shaping inflammation, providing B-cell help, and directly mediating tissue damage. Yet despite increasing mechanistic insight, therapeutic management remains dominated by broad immunosuppression.

Current treatments dampen immune activity non-specifically. While clinically effective in controlling symptoms, they **do not address the underlying antigen-specific drivers of disease and are associated with systemic adverse effects and infection risk**. Antigen-specific strategies capable of selectively targeting pathogenic T cells or restoring tolerance remain an important unmet need.

A central bottleneck in T-cell–centric autoimmune programs is epitope selection. Even a single autoantigen yields hundreds to thousands of plausible self-epitopes across lengths and HLA backgrounds. MHC binding prediction alone is necessary but insufficient to determine which peptides are most likely to be presented and to elicit biologically meaningful T-cell responses.

mySELF is an autoimmune-focused adaptation of our best-in-class immunogenicity prediction engine, **designed to quantify the immunogenic potential of self-derived peptides across both CD8 and CD4 contexts**. It enables rational prioritization of pathogenic candidates and supports region-level selection for tolerance-oriented strategies.

mySELF shifts autoimmune epitope discovery from heuristic screening to biologically grounded, data-driven prioritization.

Why immunogenic potential matters in autoimmunity

Autoimmune pathology can emerge when **self-reactive T-cells** escape central and peripheral tolerance and encounter their cognate peptides under inflammatory conditions.

In many autoimmune diseases, $CD8^+$ T cells contribute to direct cytotoxic tissue damage, and $CD4^+$ T cells amplify inflammation through helper functions and orchestrate B-cell responses. Accordingly, accurate estimation of immunogenic potential is valuable **for identifying disease-driving epitopes and for practical downstream use cases**. The latter involve **antigen-specific monitoring panels** (e.g., tetramers or activation-marker readouts) to track epitope spreading, quantify treatment response, and potentially flag impending flare-ups as well as **patient stratification** by dominant epitope reactivity to support cohort enrichment and mechanism-of-action interpretation. In addition, CD4 targets can be leveraged in **tolerance-inducing strategies**—where controlled, context-appropriate CD4 recognition is redirected toward regulation rather than inflammation—while CD8 epitopes are

more commonly used to **monitor cytotoxic autoimmune activity and tissue-directed risk** than as primary tolerogenic targets.

The therapeutic objective therefore differs depending on context:

- For **pathogenic driver** identification, prioritizing highly immunogenic CD8 epitopes is critical.
- For **tolerogenic** approaches, **controlled** CD4 engagement may be desirable — maximal inflammatory potential is not necessarily the goal.

Limitations of current epitope selection approaches

Autoimmune epitope discovery remains constrained by several limitations:

- **Large combinatorial search space** across peptide lengths, HLA alleles, and candidates.
- Over-reliance on **MHC-binding predictions**: do not capture T-cell activation probability.
- Limited integration of **presentation, expression, and TCR repertoire data.**
- **Lack of quantitative prioritization frameworks** aligned with therapeutic objectives.

As a result, teams often face an operational challenge of not knowing which of the hundreds or thousands of plausible self-peptides, are most relevant for disease biology or therapeutic exploration.

A systematic, immunogenicity-focused framework is required to move from “plausible” to “actionable.”

mySELF: predictive immunogenicity in autoimmunity

Rather than focusing solely on binding affinity, **mySELF estimates the probability that a self-peptide will elicit a T-cell response within a given biological context**.

mySELF integrates modeling of (1) MHC class I and class II presentation likelihood, (2) peptide-intrinsic immunogenic features, (3) context-aware prioritization using HLA background, and (4) optional integration of expression, immunopeptidomics, and TCR data.

This enables two complementary applications:

Pathogenic epitope prioritization

For mechanistic studies and target discovery, mySELF can (1) rank CD8 and CD4 self-peptides by predicted immunogenic potential, (2) highlight enriched regions within disease-relevant antigens, and (3) reduce large candidate spaces to a focused, testable shortlist.

Tolerance-oriented design support

For antigen-specific therapeutic concepts, mySELF supports (1) region-level evaluation of immunogenic potential, (2) identification of segments with balanced CD8/CD4 signals.

Retrospective validation study

To evaluate the predictive validity of mySELF, we analyzed established type 1 diabetes autoantigens using literature-validated T-cell epitopes as reference points (James *et al.*, 2020). For each antigen, predicted immunogenicity scores were computed across all possible peptides and compared to reported CD8 and CD4 epitopes.

CD8 landscape

Across multiple type 1 diabetes autoantigens, literature-reported CD8-positive epitopes consistently localize toward the higher-scoring end of the predicted distribution relative to other peptides from the same proteins and to MS-detected self-peptides (**Figure 1**).

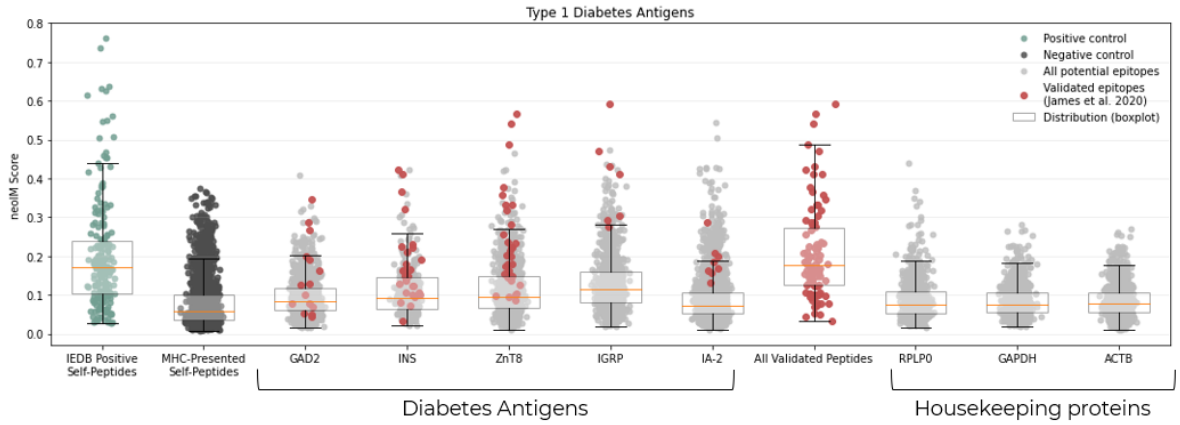

Figure 1. Predicted mySELF CD8 immunogenicity scores across candidate peptides from type 1 diabetes autoantigens, with literature-validated epitopes highlighted.

This enrichment demonstrates that **mySELF captures biologically meaningful CD8 immunogenic signals** and can substantially narrow the candidate space for downstream testing.

In contrast, housekeeping proteins show lower overall predicted immunogenicity, supporting disease-specific signal discrimination.

CD4 landscape

For CD4 peptides, validated epitopes do not concentrate exclusively at the extreme high end of the score distribution. Instead, they overlap with broader peptide populations from the same autoantigens (**Figure 2**).

This pattern reflects known MHC class II biology, where:

- Binding cores are more variable,
- Multiple overlapping registers may be active,
- Region-level enrichment is often more informative than single-peptide ranking.

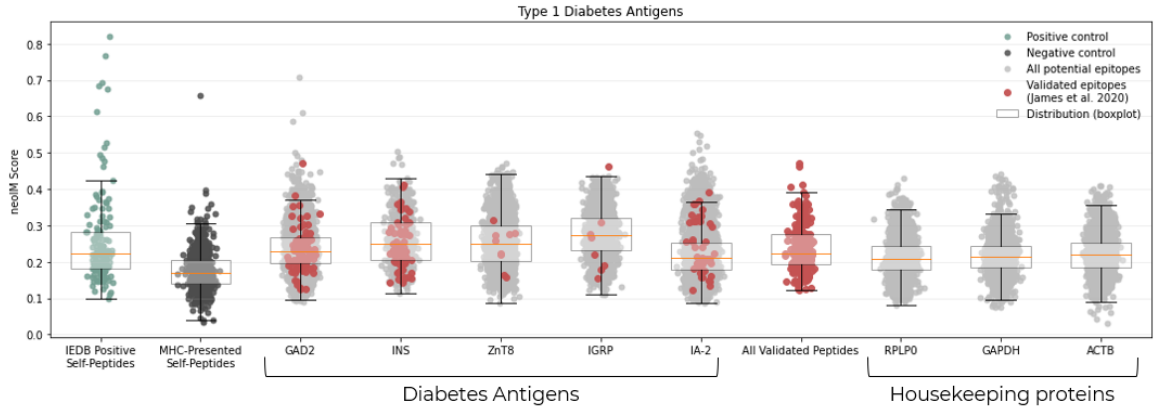

Figure 2. Predicted mySELF CD4 immunogenicity scores across candidate peptides from type 1 diabetes autoantigens, with literature-validated epitopes highlighted.

In tolerance-oriented workflows, this region-level perspective is particularly valuable. **mySELF enables identification of segments capable of controlled CD4 engagement** rather than maximal inflammatory activation. This is important because moderately immunogenic CD4 cues are generally easier to channel into a regulating response: they are strong enough to be recognized and reshaped, but not so intense that they override a tolerogenic context and drift toward an inflammatory trajectory. Put differently, they offer a broader control margin, reducing the risk of inadvertently amplifying the effector response the vaccine is meant to dampen.

Regional selection: balancing CD8 and CD4 signals

For tolerogenic concepts, a practical design challenge is identifying regions that combine strong disease-relevant CD8 signals, and controllable CD4 signals that can be steered through formulation and context.

mySELF enables sliding-window analysis across full protein sequences and **identifies segments where CD8 and CD4 immunogenic profiles co-localize** in a therapeutically meaningful manner supporting rational design of antigen-specific therapeutic strategies (**Figure 3**).

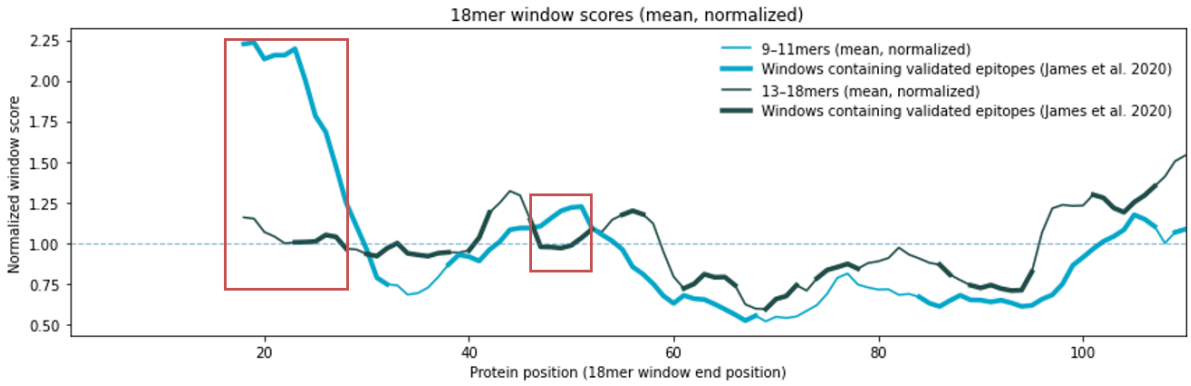

Figure 3. Mean normalized mySELF scores across insulin for CD8-length (9–11mer) and CD4-length (13–18mer) peptides, highlighting regions combining elevated CD8 signal with moderate CD4 potential.

Conclusion

mySELF brings quantitative immunogenicity modeling into autoimmune and immune tolerance discovery pipelines.

By moving beyond MHC-binding and integrating presentation as well as T-cell activation features into a unified scoring framework, mySELF enables:

- Robust CD8 epitope prioritization for pathogenic mechanism and target discovery
- Region-based CD4 analysis aligned with tolerance-oriented concepts
- Rational narrowing of large autoimmune candidate spaces

mySELF transforms autoimmune epitope selection from broad screening to predictive, data-driven engineering — supporting both disease mechanism elucidation and next-generation antigen-specific therapeutic development.

References

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