Case Study

MindWalk™

LensAI™ Immunogenicity Screening

LensAI predictionof Anti-Drug Antibody incidence: evidence for clinical utility of ADA risk assessment

Overview:

Immunogenicity remains a crucial factor in biologics development. The presence of Anti-Drug Antibodies (ADAs) can reduce a drug's effectiveness, alter its pharmacokinetics, or introduce safety risks. Early stage reliable prediction of ADA development is important for derisking and supports smart design decisions.

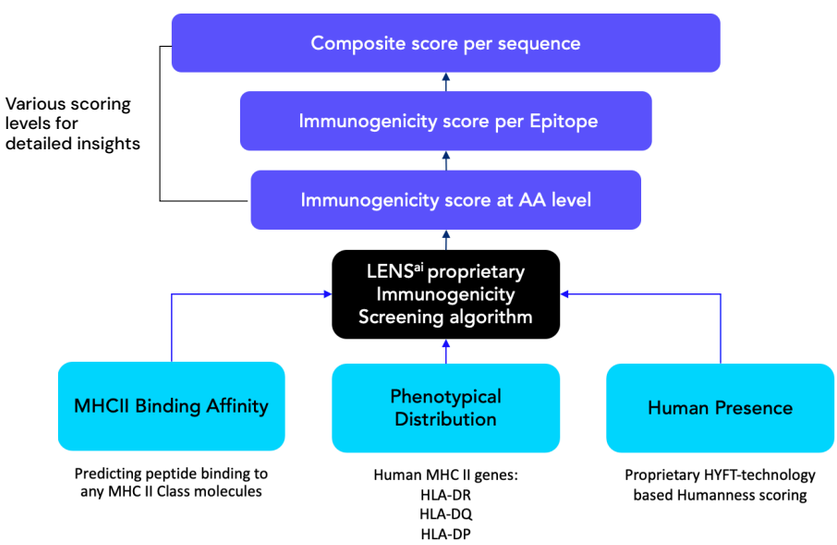
Study background:

To understand how well LensAI Immunogenicity Screening can predict whether patients will develop ADAs, we analyzed:

- **The general association**—between LensAI immunogenicity composite score and the actual ADA incidence in a set of 217 antibodies.
- **Risk group separation**—we tested whether the immunogenicity composite score can separate antibodies with a high risk of causing ADAs from those with a low risk.

How immunogenicity risk is scored and classified

LensAI Immunogenicity Screening combines MHCII-binding prediction tools with a HYFT-based proprietary algorithm and demonstrates reliable ADA risk classification. We generate multiple scores per sequence, including a composite score that aggregates all detailed underlying metrics to reflect the overall risk of an immunogenic reaction.



LensAI Immunogenicity Screening core features

- Demonstrates reliable ADA risk classification
- Full transcriptome-based human proteome scanning that balances breadth of screening with MHC II binding
- Customizable for region-, genotype-, and indication-specific patient populations
- Expanded allele coverage with ~900 additional alleles beyond the MHCII superfamily

Prediction of ADA incidence:

To demonstrate predictive performance, we analyzed the association between LensAI immunogenicity composite score and observed ADA incidence, and assessed whether the score distinguishes high- from low-risk antibodies.

ADA incidence refers to the proportion of treated individuals who developed an ADA response.

We used Bayesian modeling, which allows for incorporation of prior knowledge in the statistical predictive model of ADA incidence. Instead of a single prediction, the model provides a range of likely outcomes—shown by the blue area (89%HDI)—reflecting the model's confidence. A narrower blue area means higher predictive certainty. Bayesian modeling is widely recognized as a more realistic and informative approach for risk assessment in drug discovery than traditional statistical modeling.

Relationship between ADA incidence and LensAI immunogenicity score

Method

We used beta-logistic regression to model the relationship between the actual observed immune responses to 217 antibodies* and their LensAI immunogenicity composite score.

Result

A clear positive association was found: higher LensAI scores correspond to higher predicted ADA incidence. The reported clinical ADA data show substantial variability, as indicated by the red bars for some therapeutic antibodies. Hence, while the predicted ADA incidence aligns well with the overall trend, the observed clinical ADA incidence is widely dispersed around the mean predicted ADA incidence.

Fig. 1

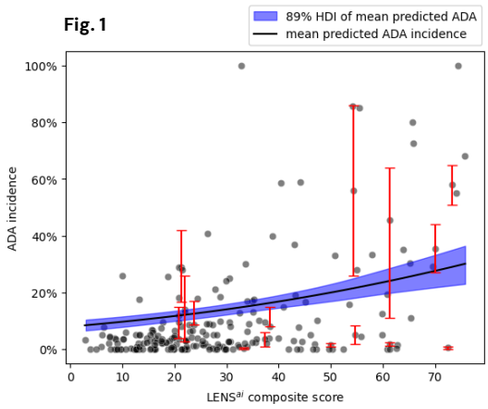


Fig. 1: ADA incidence* vs. LensAI composite score.

- Each grey dot represents an individual therapeutic antibody with its observed ADA incidence.
- The black line shows the mean predicted ADA incidence given the LensAI composite score.
- The blue shaded area is the 89% highest density interval (HDI) for the mean predicted ADA incidence, which indicates the model uncertainty.
- For some antibodies, multiple ADA incidence values were reported in literature; the range of these values is shown by red vertical lines.

*ADA incidence data derived from Bioinformatics. 2021 Jun 10;37(22):4041–4047

ADA risk classification with LensAI: high vs. low risk

Method

We tested the LensAI composite score's ability to classify the same 217 antibodies* by ADA risk, using two thresholds to define low risk: <10% and <30% ADA incidence.

- The 10% cut-off is often used in published literature.**
- The 30% cut-off might be more appropriate for early stage risk assessment purposes.

Our goal was to predict whether the clinical ADA incidence is above or below this 10% or 30% threshold. To do this, we used binary logistic regression with the LensAI composite score as the sole predictor.

Result

Our modeling shows a clear association between the LensAI composite score and the probability of clinical ADA incidence >10% (p(ADA > 10%)). AUC=0.79. AUC=0.8 is considered excellent. The association is even more pronounced for the probability of clinical ADA incidence >30% (p(ADA > 30%)). AUC=0.92. We consider a LensAI immunogenicity composite score of 54 or higher as indicative for high ADA risk (ADA incidence >30%). This indicator score was obtained using the probability that maximizes F1 score (p~0.27).

Fig. 2: Logistic regression fit for probability of ADA incidence > 10% vs. LensAI composite score.

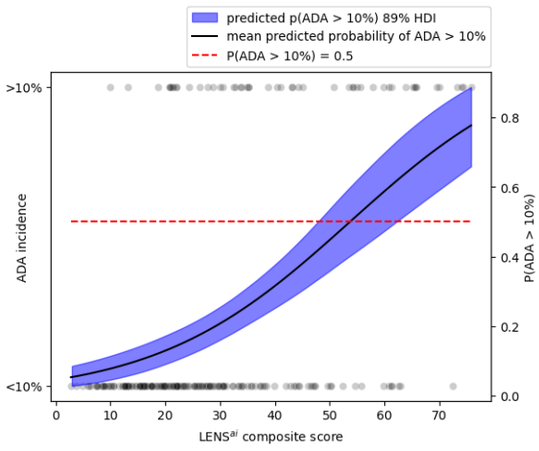
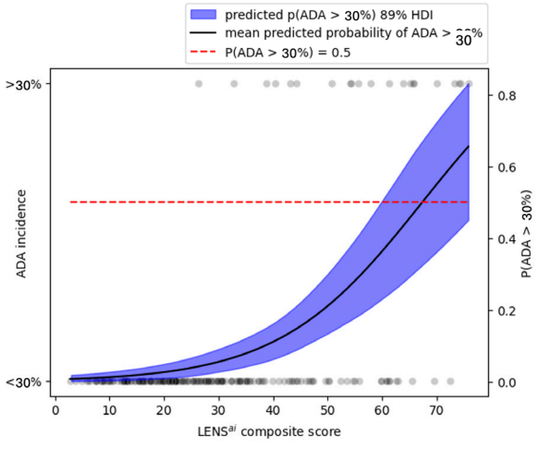


Fig. 3: Logistic regression fit for probability of ADA incidence > 30% vs. LensAI composite score.



- Each grey dot represents an individual therapeutic antibody, assigned to one of two classes: ADA incidence <10% or >10% (Fig 2) and <30% or >30% (Fig 3).
- The black line shows the mean predicted probability of ADA% >10% (Fig 2) and >30% (Fig 3) for a given LensAI composite score.
- The blue shaded area is the 89% highest density interval (HDI) for the predicted probability of ADA% >10% (Fig 2) and >30% (Fig 3), which indicates the model's uncertainty.

**https://academic.oup.com/bioinformatics/article/37/22/4041/6295884

Summary:

1. LensAI immunogenicity composite score enables reliable ADA incidence risk classification. For predicting ADA incidence >10%, the model achieves an AUC=0.79, indicating strong discriminative capability. For predicting ADA incidence >30%, which might be more suitable for early stage risk assessment purposes than the 10% cut-off, AUC rises to 0.92. A LensAI immunogenicity composite score of 54 or higher is considered as indicative for high ADA risk (ADA incidence >30%).
2. Drug developers can use LensAI to:
   - Quickly and reliably estimate immunogenicity risk in early stages, reducing costs
   - Focus development efforts on candidates with lower LensAI scores
   - Apply additional caution when working with candidates showing higher LensAI scores

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