Case Study

Rabbit mAb humanization

The Challenge

Therapeutic lead campaigns strongly benefit from diversity, not only from a sequence and epitope perspective, but also from a functional and affinity point of view. Given the unique biology of antibody maturation in rabbits, this species is an excellent source for identifying diversified panels of target binding antibodies using IPA's proprietary B Cell Select® platform. However, rabbit-derived antibodies might require more extensive engineering for clinical application compared to traditionally used mouse-derived antibodies. Smart strategies are needed to take full advantage of diversity-focused discovery and amplify the therapeutic potential of rabbit-derived antibodies.

The Solution

A smart strategy combines industry-leading high-throughput technologies for selecting leads from a diverse panel of rabbit antibodies with IPA's rapid and scalable *in silico*-driven humanization platform. This platform integrates in-depth risk assessment, early de-risking, and high-throughput *in vitro* kinetic profiling. Our scalable workflow is designed to empower diversity-driven discovery, enabling data-driven decision-making and improving clinical suitability with optimal speed.

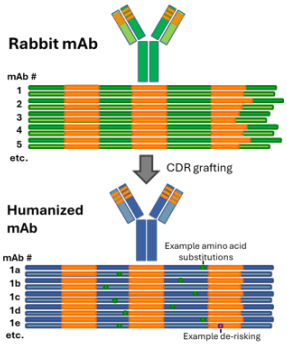
Single-step engineering increasing clinical suitability through efficient, data-driven processes

***In silico*-driven, scalable, species-agnostic humanization** > **Integrated highly scalable *in silico* risk assessment** > **High-throughput SPR-based affinity determination**

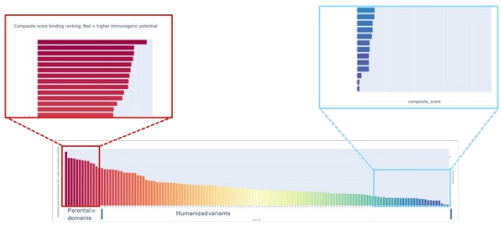
6 weeks

Humanization

CDR grafting and amino acid substitutions based on advanced structural analysis. Early de-risking addressing high risk liabilities.



Immunogenicity Screening



Developability Assessment

Including structural model AggScore, Solvent-exposed liabilities

Ranking towards clinical mAb library

Protein Production

Crude small-scale recombinant production supernatants

High-throughput profiling of kinetic parameters

Program Summary

Optimizing rabbit antibodies to increase clinical suitability

Following diversity-focused discovery leveraging IPA's rabbit B Cell Select® technology combined with high-throughput epitope landscape profiling, 10 lead candidates with confirmed mode of action were selected for further development and subjected to IPA's humanization workflow to increase clinical suitability.

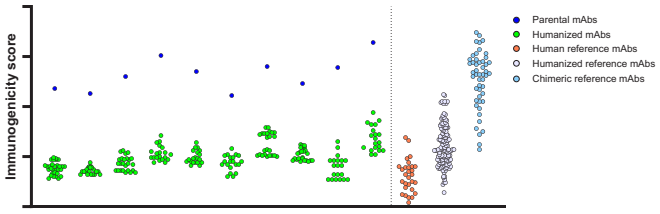
In silico humanization of 10 parental lead candidates in parallel

- Design of up to 6 variants per parental v-domain
- High-throughput *in silico* risk assessment and benchmarking

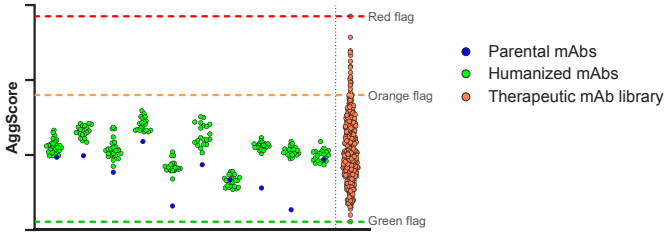
In vitro high-throughput SPR-based affinity determination

- Small-scale recombinant expression of humanized variants
- Profiling of kinetic parameters of each variant using crude supernatant

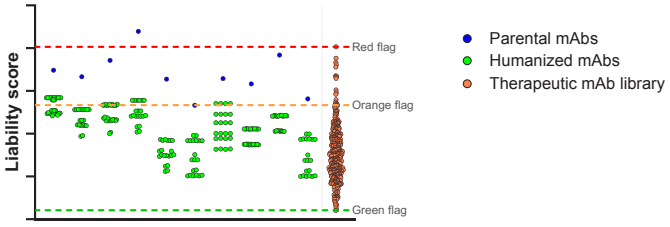
Immunogenicity Screening



Developability – Structural model AggScore

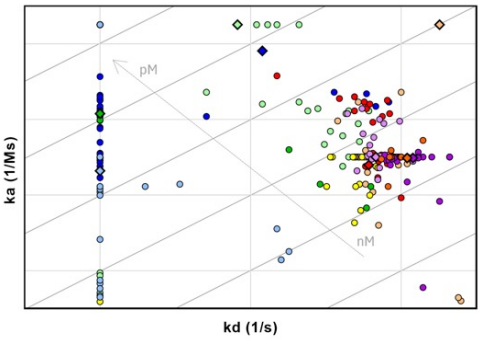


Developability – Solvent-exposed liabilities

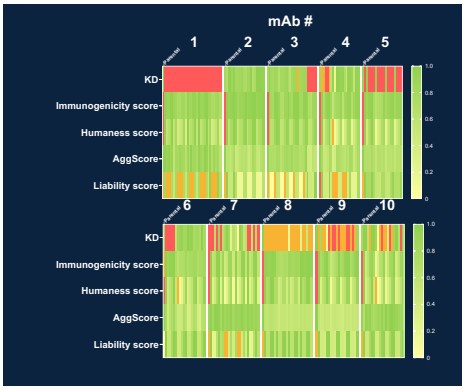


Therapeutic mAb-like immunogenicity score, AggScore, and solvent-exposed liability score for majority of humanized variants

Iso-affinity plot of parental (diamonds) and humanized antibodies (circles)



Multi-parametric output following single-step engineering

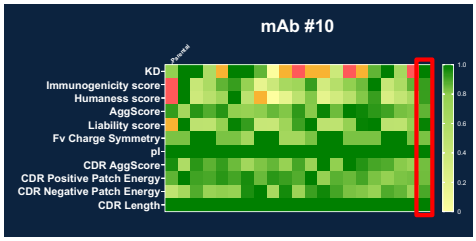


Conclusion

IPA boosts the therapeutic potential of rabbit-derived antibodies without compromising timelines leveraging its unique high-throughput, multi-parametric approach for single-step antibody engineering:

- Early engineering combined with in-depth risk assessment
- Highly scalable *in silico* technologies matched with high-throughput *in vitro* techniques

Highly scalable technologies advancing lead selection



IpA

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