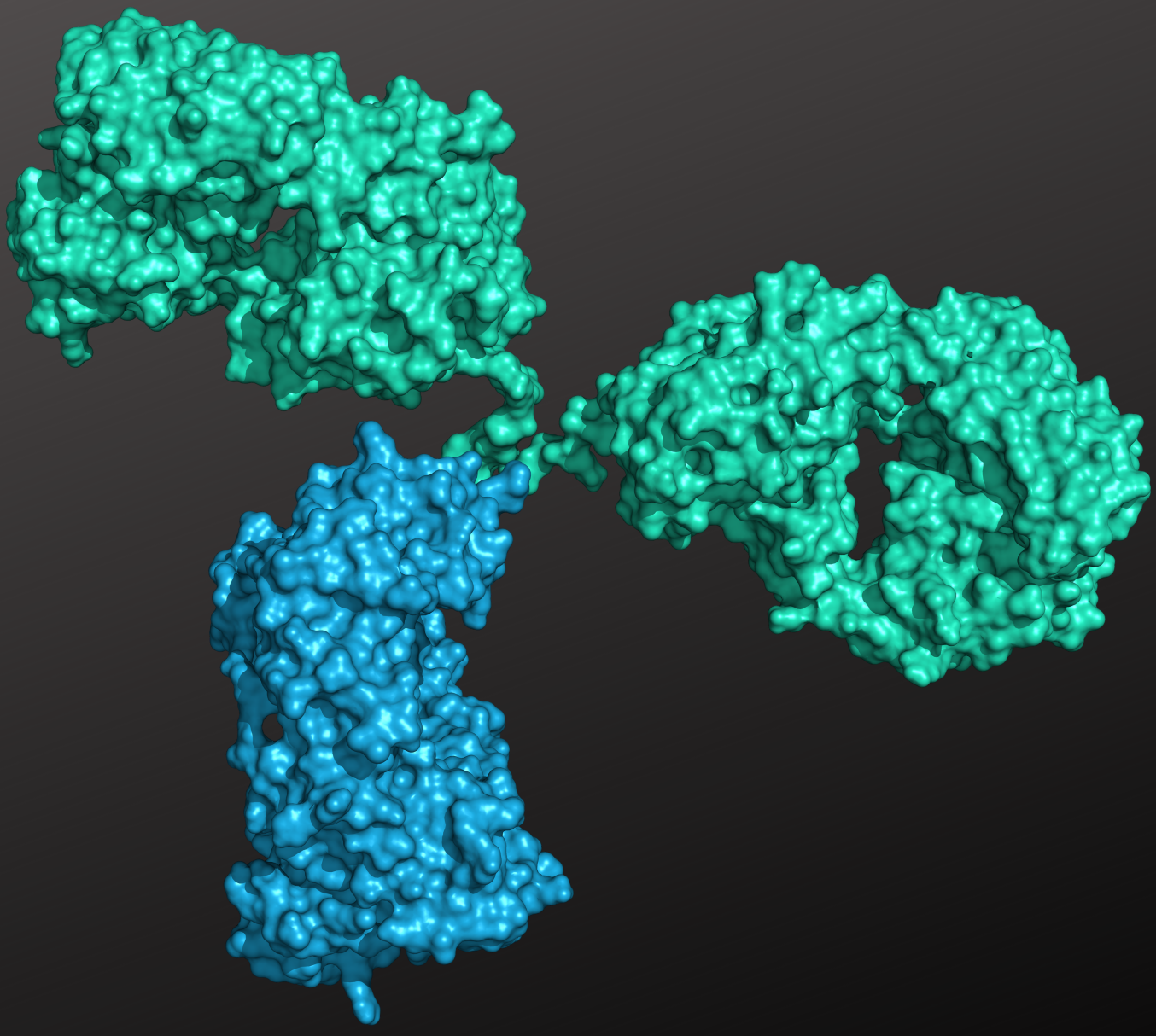
fusionantibodies

Humanization.

Much more than a handle turning exercise.



Therapeutic antibody development

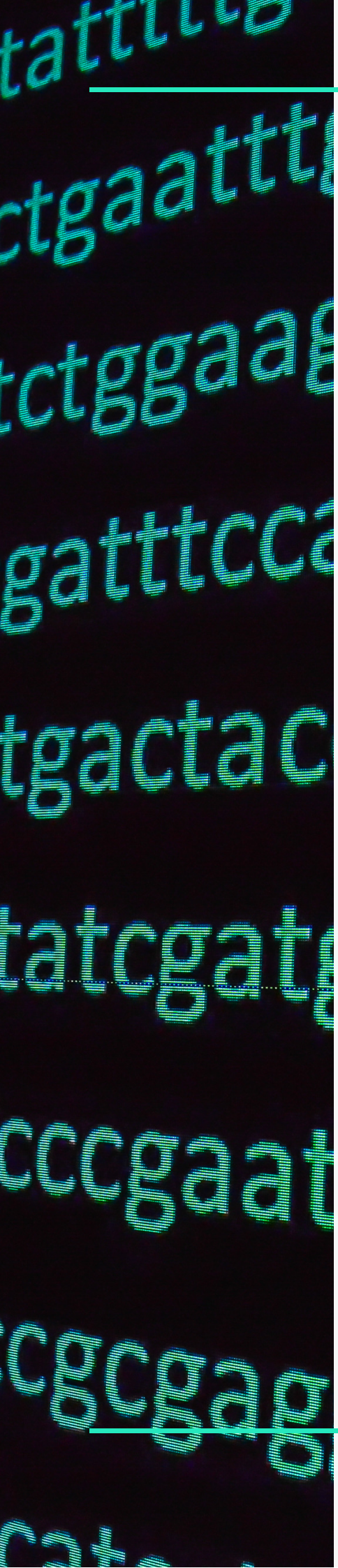
THE CHALLENGES OF NON-HUMAN MOLECULES

Monoclonal antibodies raised from non-human sources can be harnessed as powerful and specific therapeutic molecules, targeting almost every area of human disease.

However, they have limitations in that they illicit the human immune response which can limit the efficacy of such therapies.

To become a therapeutic molecule antibodies raised in animal systems must be humanized.

Often viewed as a handle turning exercise, we explore best practice in antibody humanization to deliver the best outcome for your molecule.



Looking beyond the sequence

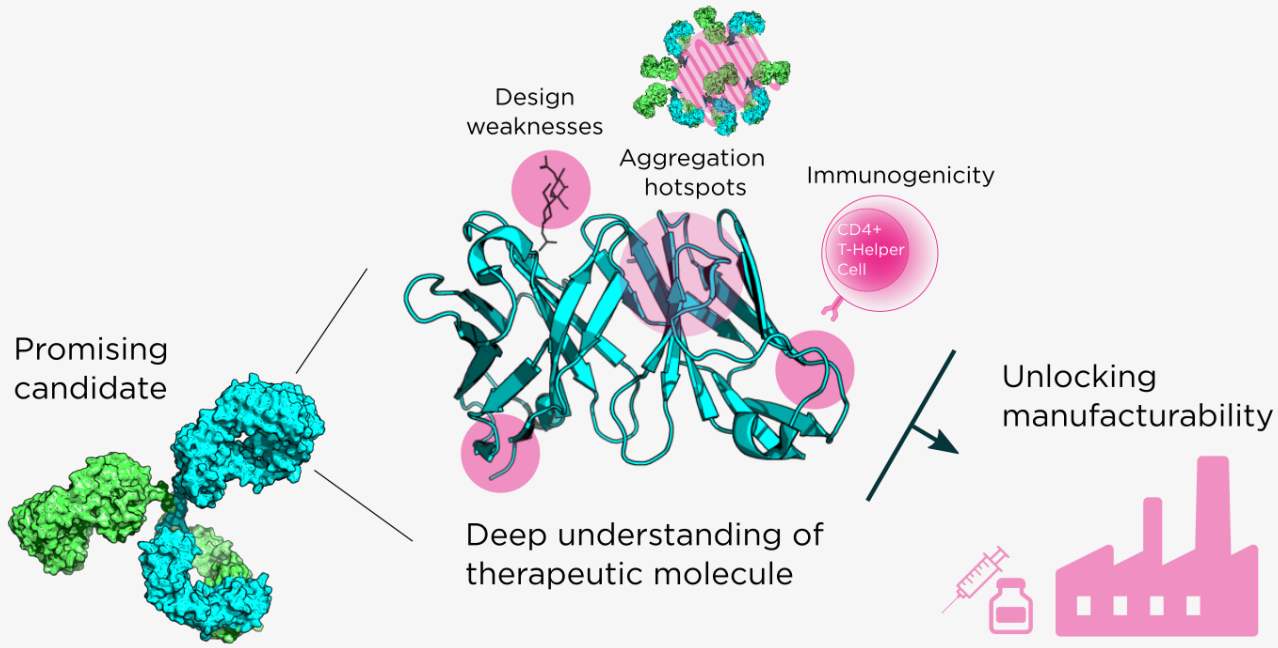
A very limited service could be described as "humanization" if the output simply yields an antibody sequence that is more closely related to human than to any other species.

However, if you are serious about getting your molecule to the clinic here are things you should consider:

- Immunogenicity - Has your sequence been checked against T-cell epitope databases? Is this validation offered as standard?
- Scaffold developability - Have you considered biophysical properties alongside antibody function?
- Sequence liabilities - have you purged liabilities to mitigate downstream risk?
- Diversity - Have you explored the experimental space?
- Affinity - Will the antibody bind as expected?

If you haven't considered these factors as part of your process you are more likely to yield dead-end molecules.

Eliminating the burden of sequence liabilities



Eliminating sequence liabilities at the earliest stage in your drug development journey will give you the best chance at overcoming hurdles on the path to the clinic.

A successful humanization project should be purged of the following liabilities:

- Free cysteines - These have the potential to staple the antibody structure with incorrect conformations inducing misfolding or increasing mulitimerization.
- Glycosylation motifs can lead to masking of antibody binding regions, or lead to a less homogenous product.
- Fragmentation motifs in the primary sequence can lead to a slew of problems in downstream purification and can potentially contaminate a therapeutic product.
- Deamidation may adversely effect binding or lead to a less homogenous product.
- Oxidation of methionine and tryptophan may occur in CDRs, or effect shelf life and manufacturability.

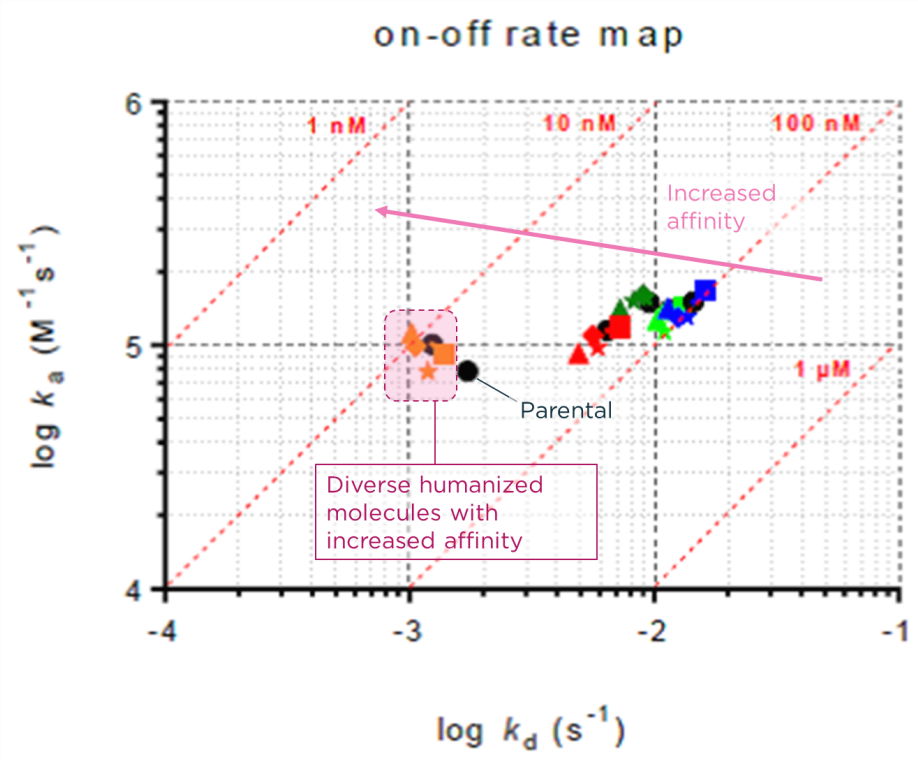
Introducing diversity

AND COMBATING AFFINITY LOSS

Humanization is synonymous with affinity loss. Introducing diversity in the design process ameliorates this potential issue which would necessitate more rounds of costly optimization with an increased risk associated with each step.

A matrix of humanized molecules generated through a panel approach allows for sampling of some of the complex structure-function relationship space in presentation of the CDRs.

The example below shows a humanization project which builds in this diversity, resulting in a range of observed affinities. The approach can even give rise to humanized antibodies with measurable improvements in binding. In this way, a panel approach increases the change of obtaining drug-like molecules.

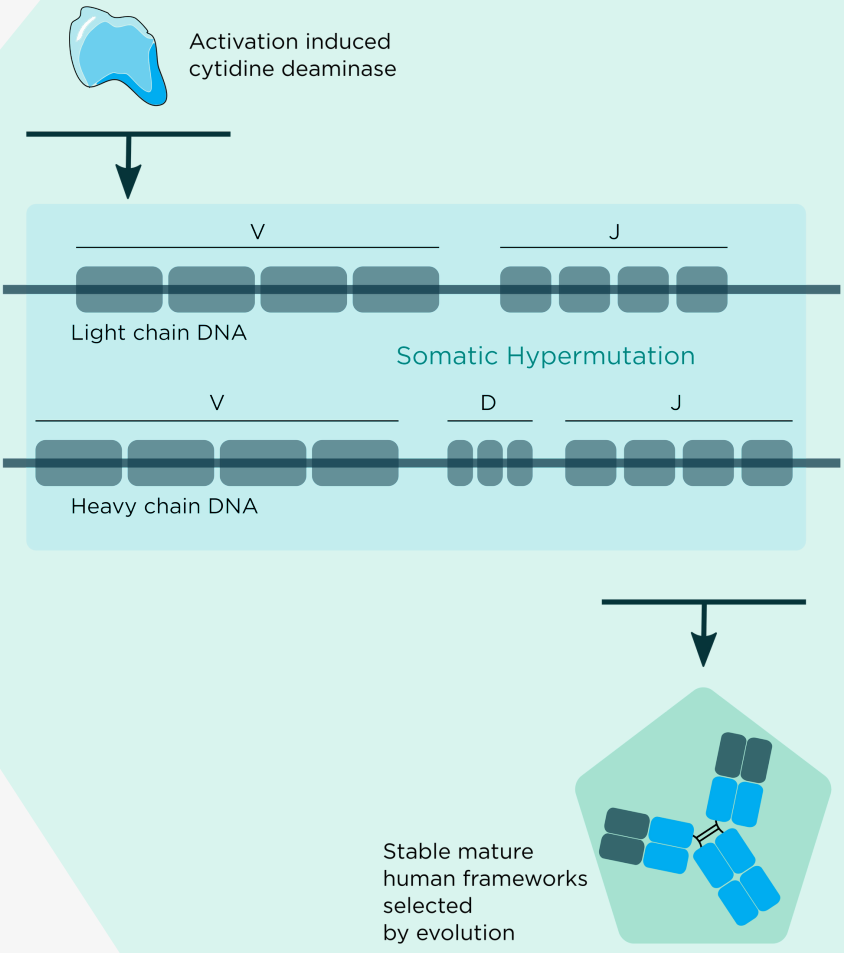


Focus on mature human frameworks

Exploiting natural evolution for ideal therapeutics.

By focusing on mature human frameworks rather than a germline approach, the properties of naturally evolved sequences, which have already undergone somatic hypermutation, can be harnessed.

These sequences have been subjected to natural selective interrogation usually generating antibodies with higher expression, greater stability and subsequently more manufacturable candidates.



Want to learn more?

Fusion Antibodies are an R&D antibody development partner. We focus on developing the best possible therapeutic antibody considering developability and manufacturability at every turn.

We offer services throughout each stage of the pre-clinical journey including discovery, engineering and supply.

Our expertize in this area means that we can humanize your molecule retaining function and maintaining affinity to within 2-fold.

We would love to hear more about your antibody development challenges. Email us at info@fusionantibodies.com

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