Immunogenicity assessment at Novartis

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Lisbon
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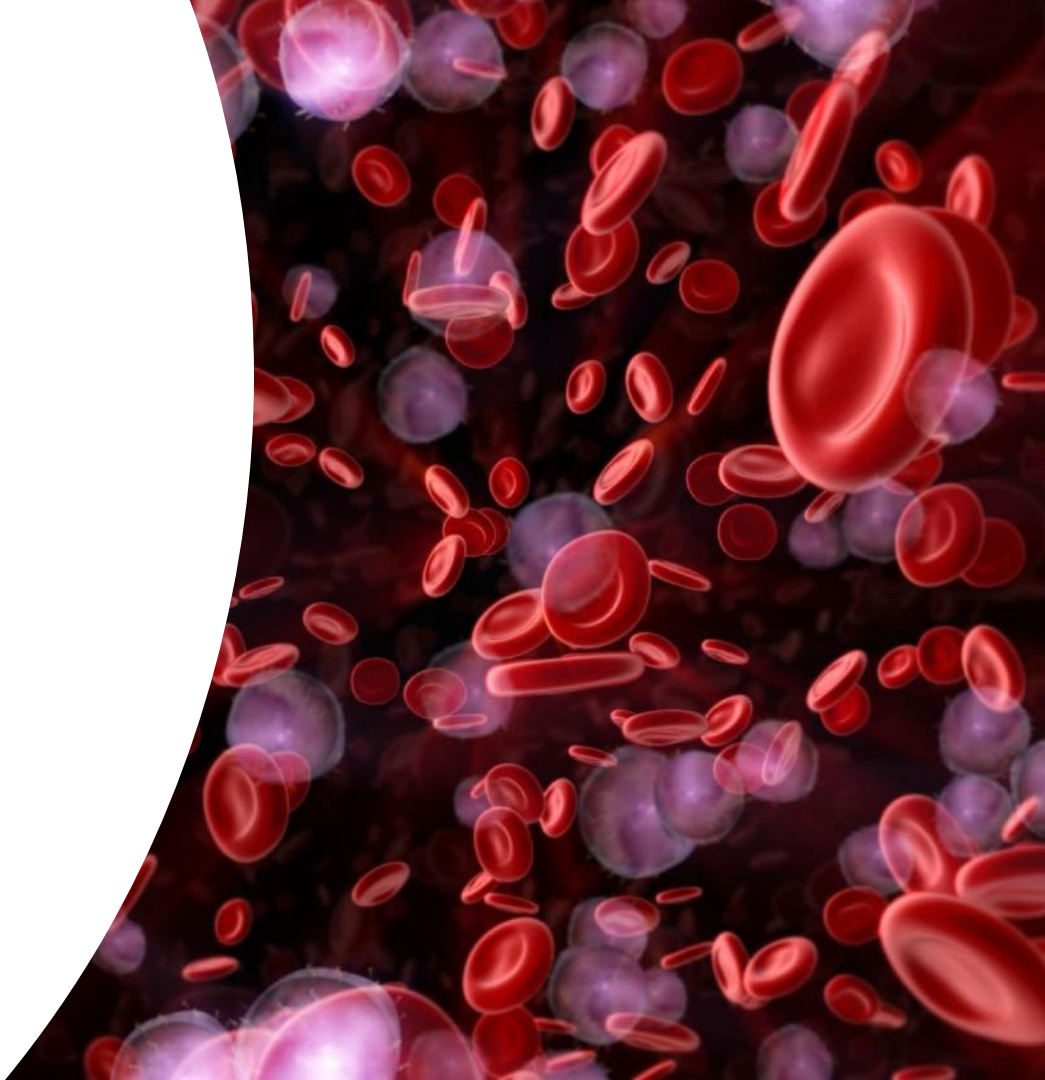

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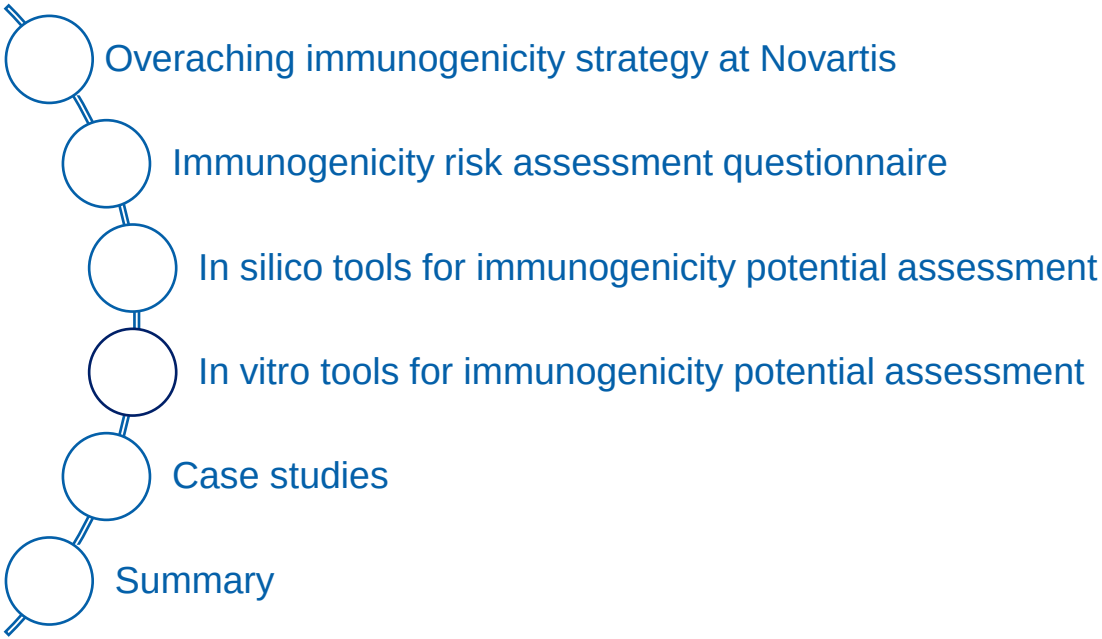
Agenda


Overaching immunogenicity strategy at Novartis
Immunogenicity risk assessment questionnaire
In silico tools for immunogenicity potential assessment
In vitro tools for immunogenicity potential assessment
Case studies
Summary

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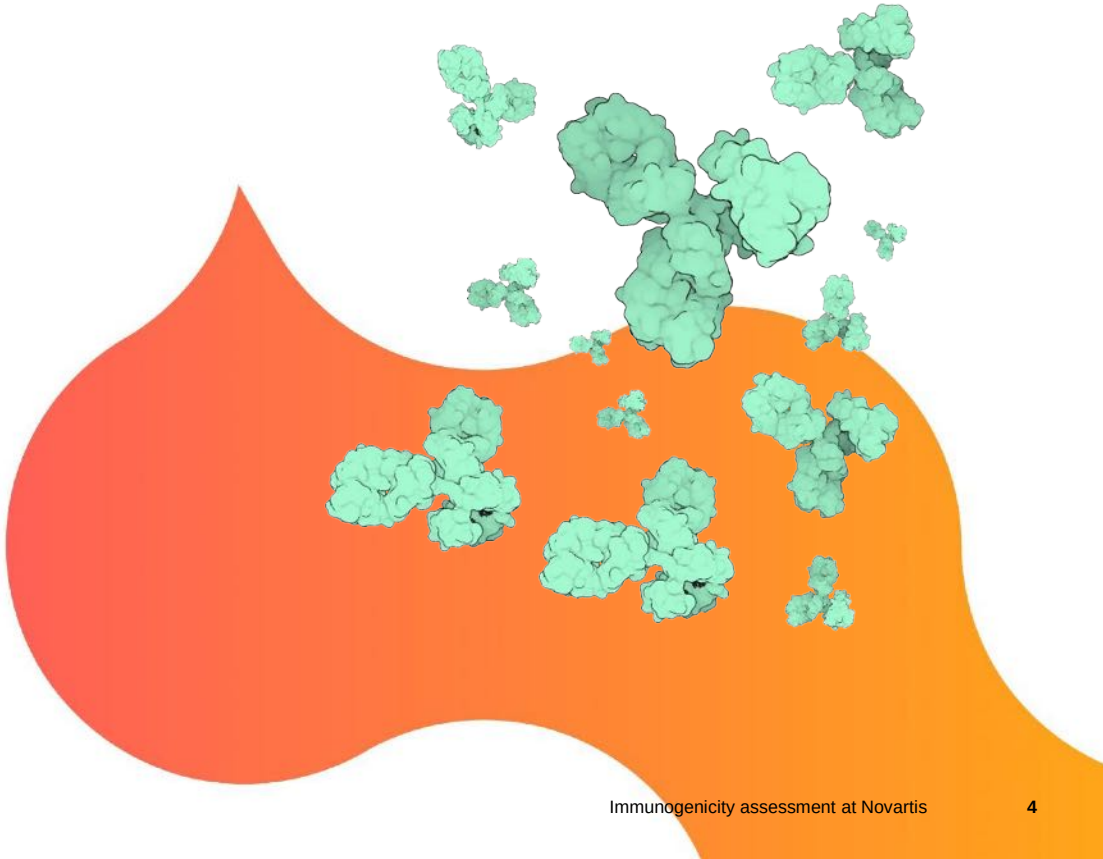
Overaching immunogenicity strategy at Novartis



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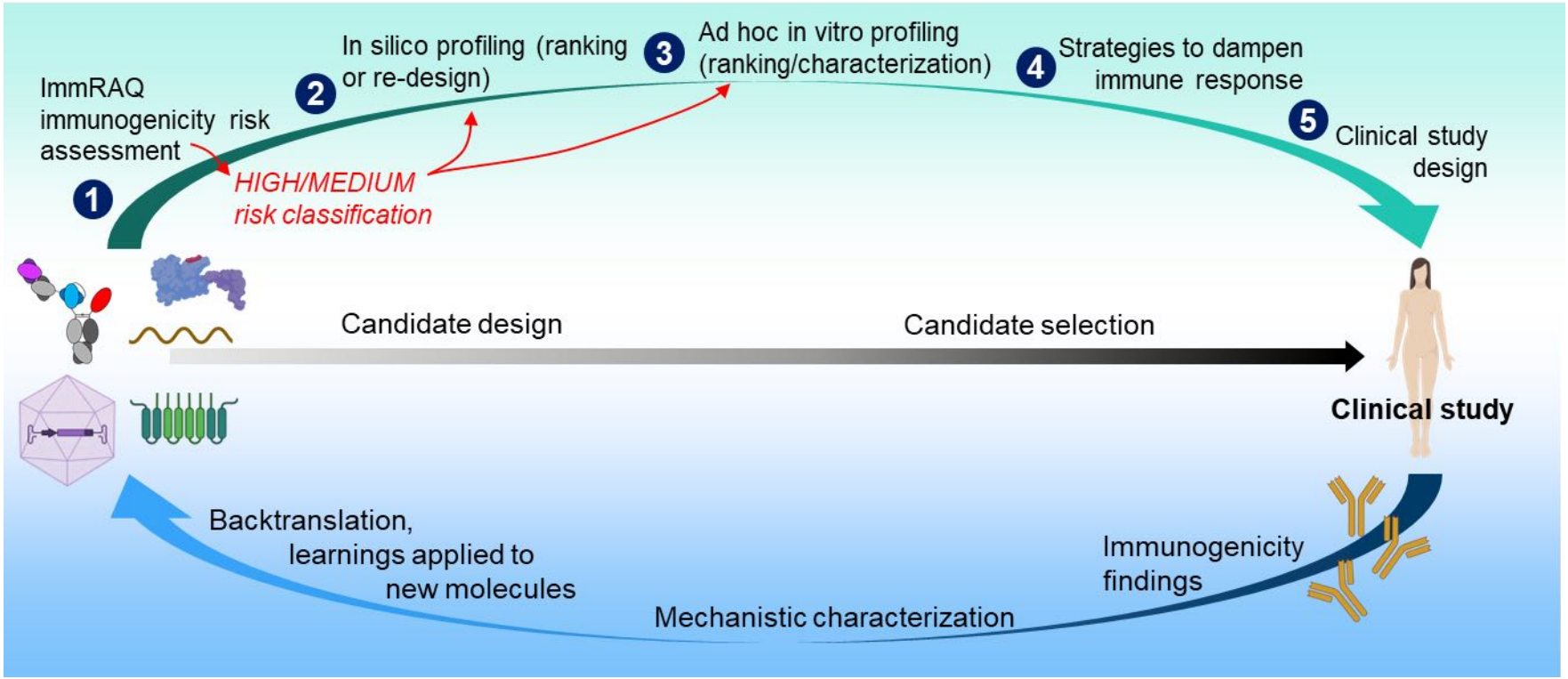
Immunogenicity strategy for biotherapeutics



ImmRAQ (Immunogenicity risk assessment questionnaire

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- **Novartis fills out the questionnaire once a target and tentative indication have been proposed, even though some questions particularly related to candidate design and material critical quality attributes cannot be addressed at this stage.**
- **The ImmRAQ is considered a living document and is updated once additional relevant information is available.**
- **The risk assessment covers the ability to generate an immune response based on a multitude of factors that will be discussed in the following slides, as well as the safety consequence of generating immunogenicity based on the target, MoA and drug modality.**

ImmRAQ key aspects

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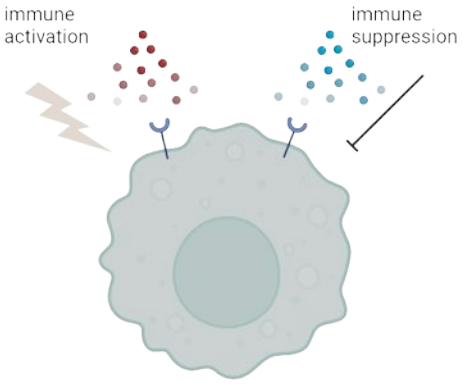
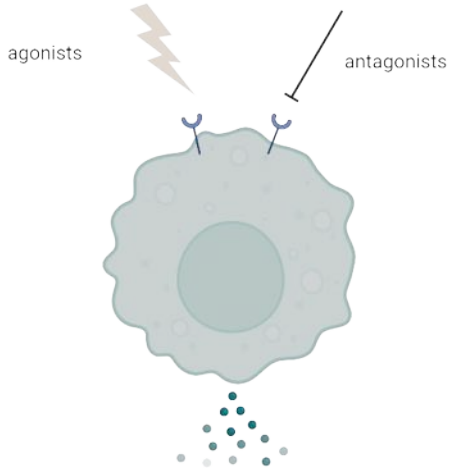
Mechanism of action

- Is the compound immune activating or suppressing?
- Is the compound agonistic/antagonistic?





ImmRAQ key aspects

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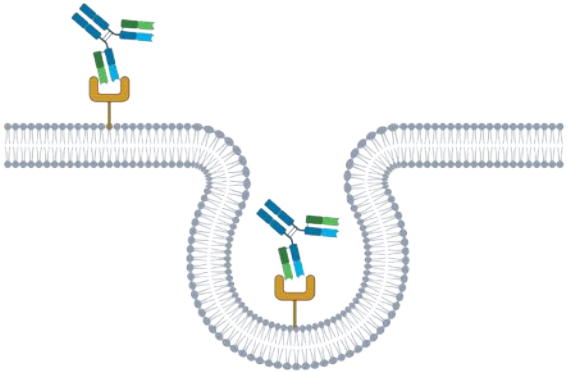
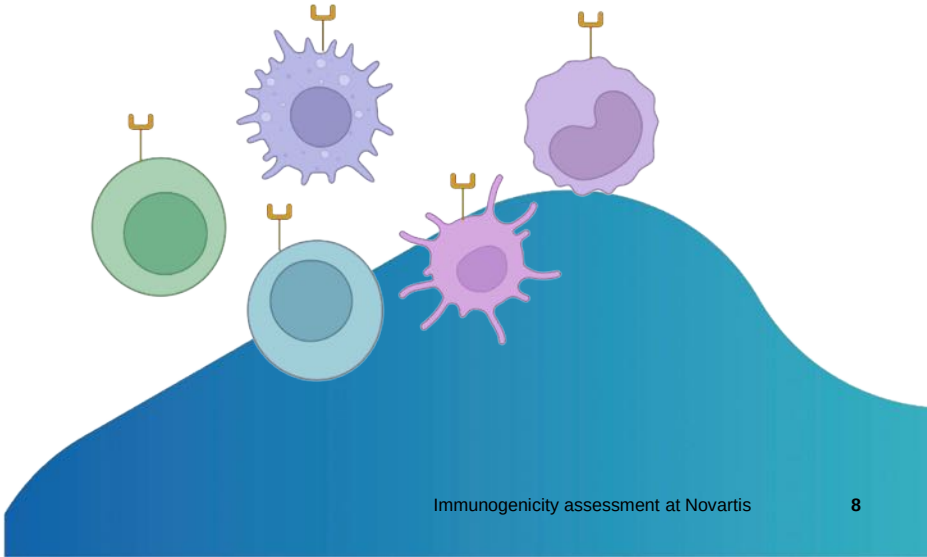


Target location

- Will target engagement trigger internalization?
- Is the target expressed on immune cells?



ImmRAQ key aspects

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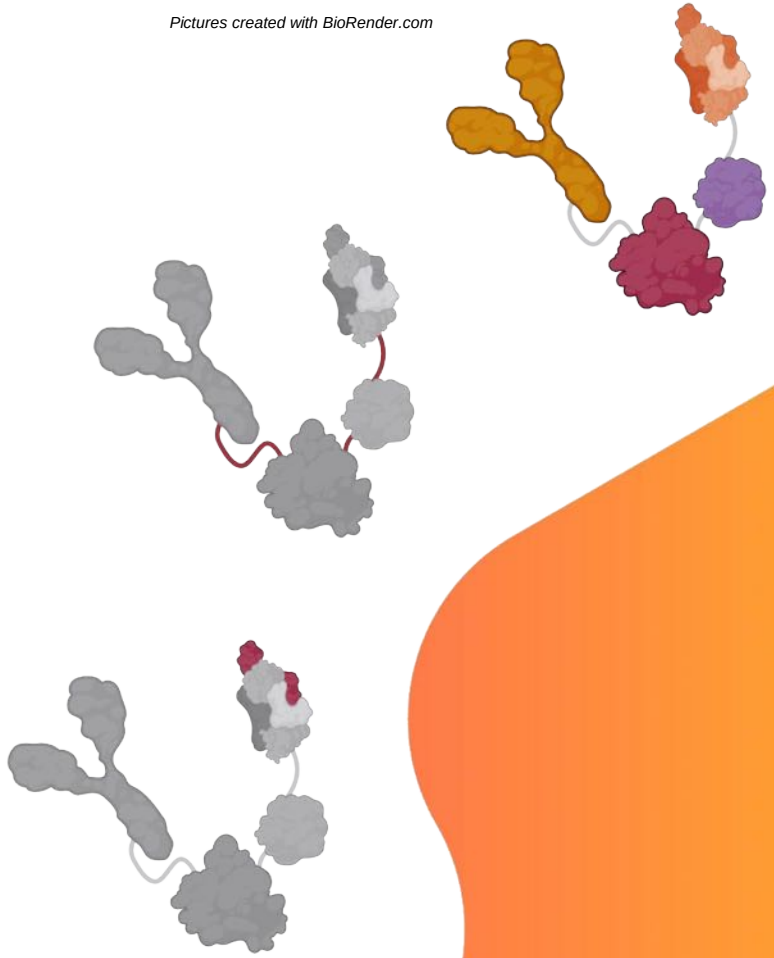

Design

- What is the format of the molecule, is part of it endogenous?
- Does the compound contain neo-epitopes or non-natural junctions?
- Can the sequence be optimized?
- What is the extent of sequence humanness?
- Are there sequence stretches with pathogen similarity?
- What is the size of the drug
- What is the half-life of the compound?

ImmRAQ key aspects

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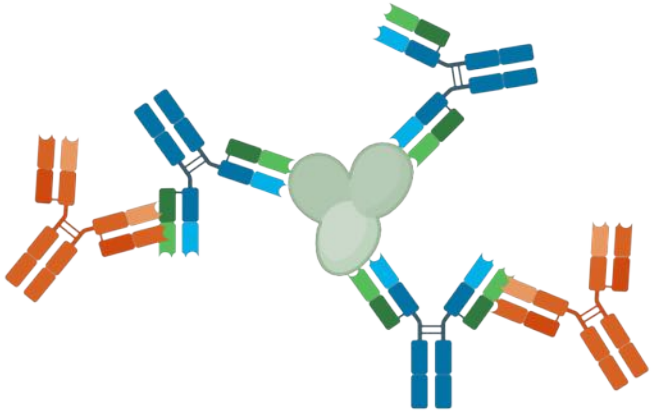


Immune complex formation

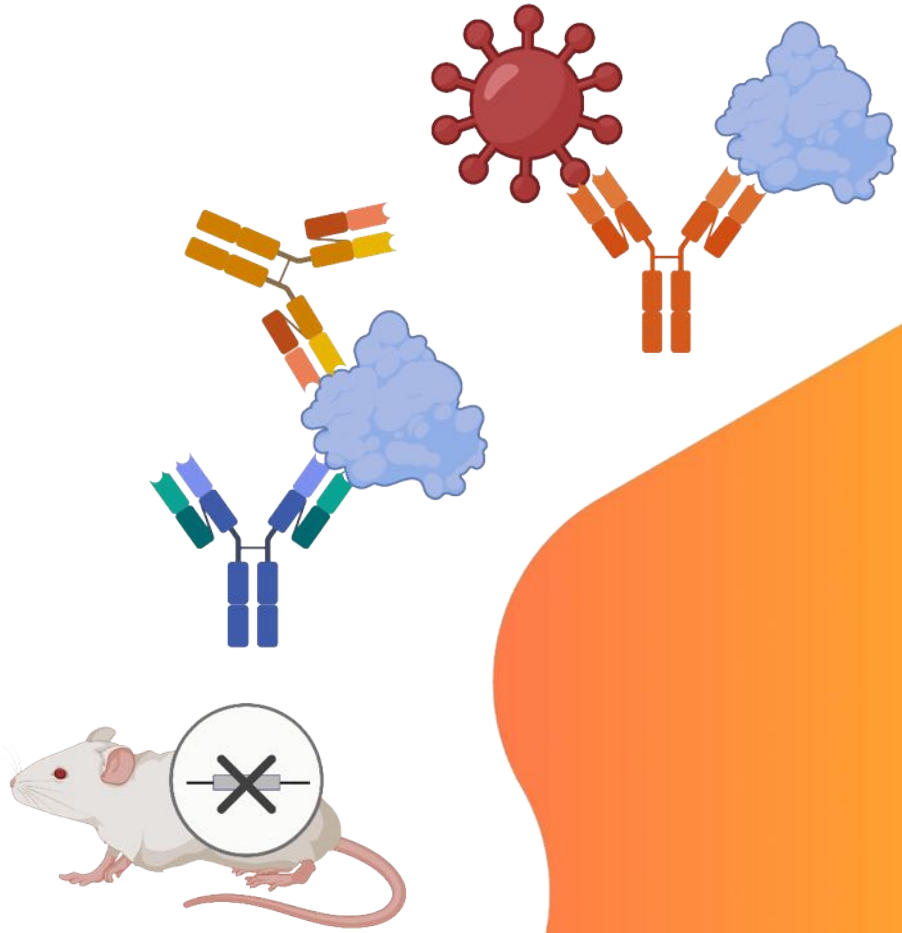
- Are there multimeric soluble ligands?
- Can formats be chosen with lower cross-linking potential?
- Does the drug contain repetitive structures?

ImmRAQ key aspects

Pictures created with BioRender.com

Literature screen

- Any data on pre-existing immunity?
- What is known from approaches hitting same target?
- What can we learn from knock-out models or human diseases?



ImmRAQ key aspects

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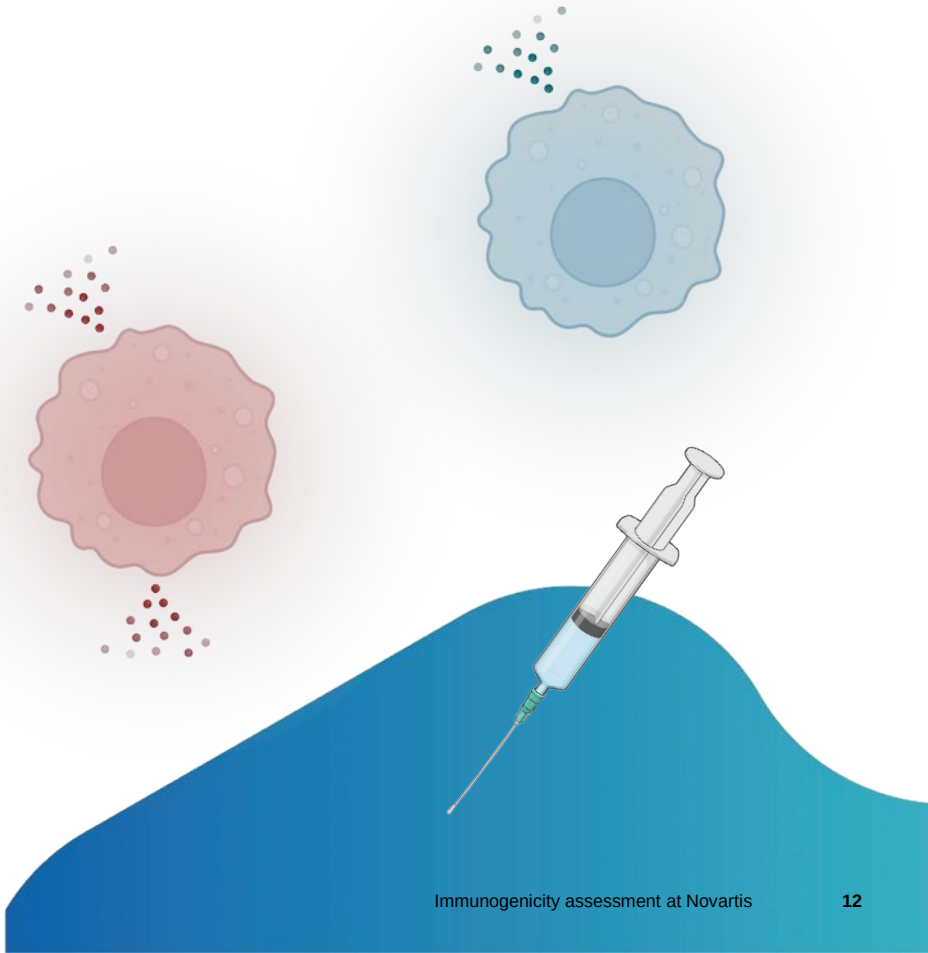
Immune status of the patient

- Is the indication an immunosuppressive/autoimmune condition?
- Are concomitant medications applied?
- What is the location and route of administation?



ImmRAQ key aspects

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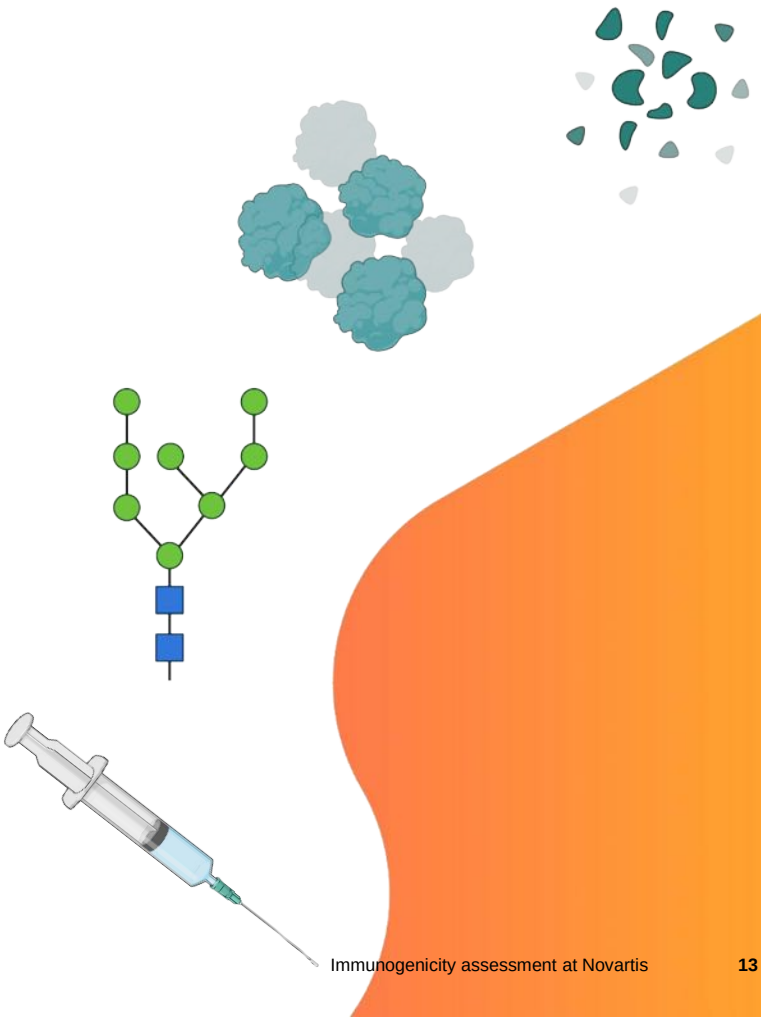

Critical quality attributes

- What is the level of degradataion and aggregation products?
- Are there PTMs that need to be considered?
- Consider glyco patterns
- What is the level of impurities?
- Consider formulation

In silico tools for immunogenicity potential assessment

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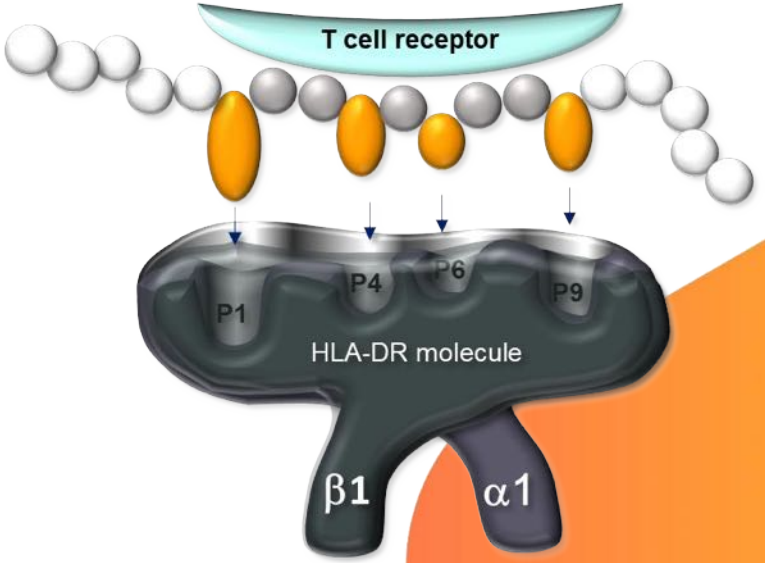
Addressing potential HLA class II binders

1. **Predict HLA class II binding hotspots via MAPPs-based iSHAPe algorithm and use to rank large candidate sets. Assign higher weight on CDRs (usually higher T cell presursor rates)**
2. **Randomize sequences also identified via MAPPs to find non-binders.**
   - iSHAPe algorithm is used but other algorithms are used if appropriate.
   - Consider structural aspects.
   - Reconfirm absent binding via MAPPs.



Addressing sequence similarity to proteins

1. **Identify stretches with sequence identity**
2. **Identify analogous sequences that may be recognized by same T cells (slightly modified but containing the same T cell facing residues)**

➢ **Compare...**

- drug and human proteins (abundant or low concentration?)
- Drug and host cell proteins
- Drug and pathogens

➢ **Main challenge: Is there a «normal level» of sequence identity or analogy?**

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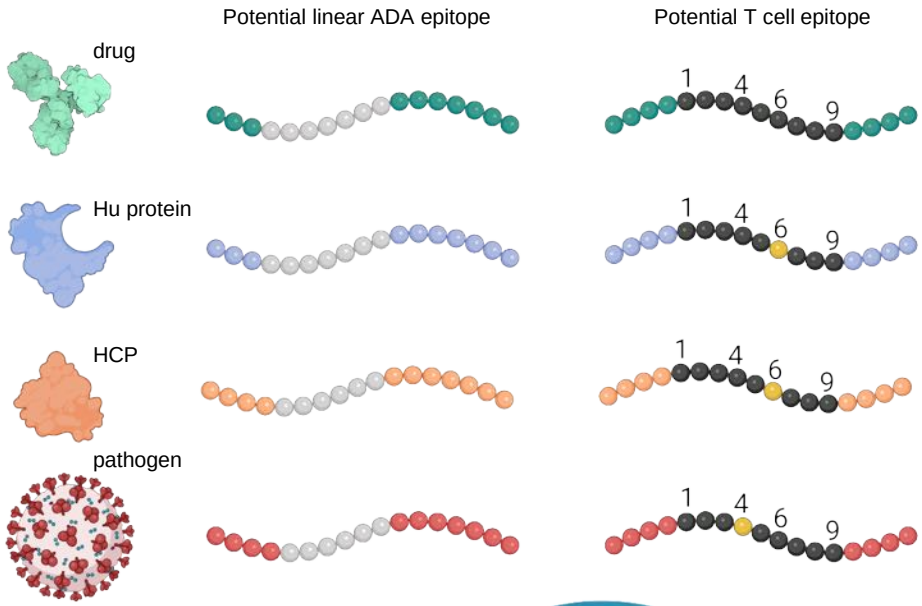
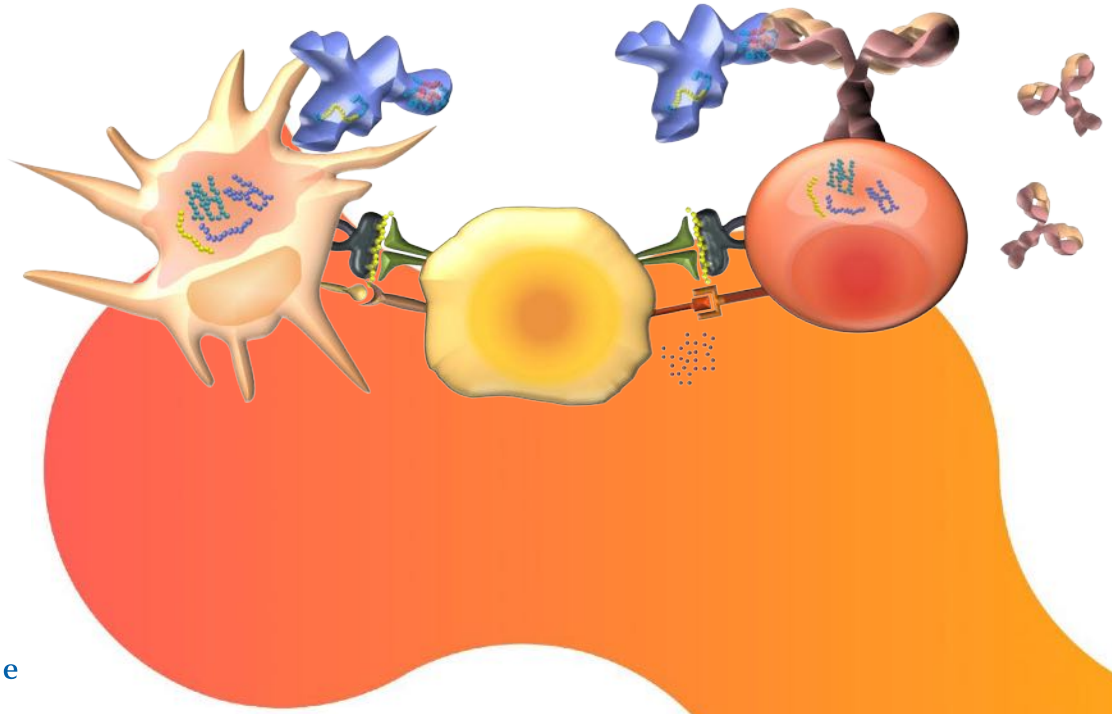


In vitro assays for immunogenicity potential assessment



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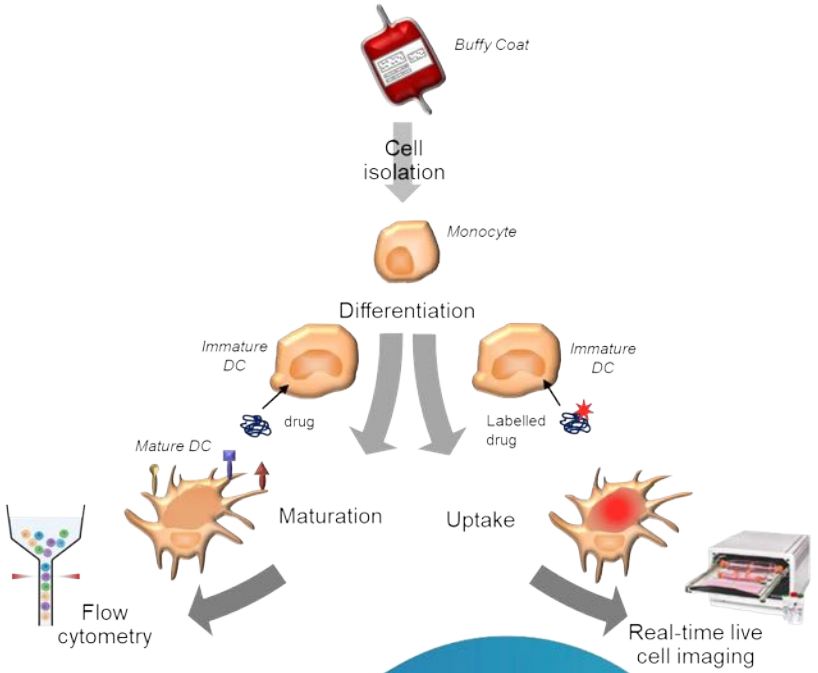
In vitro assays applied to assess IG potential

DC maturation assay

- Mostly applied together with MAPPs
- Applied for «high risk» and partially also for «intermediate risk» projects
- Used to evaluate whether drugs have cell maturation as risk factor

DC uptake assay (exploratory)

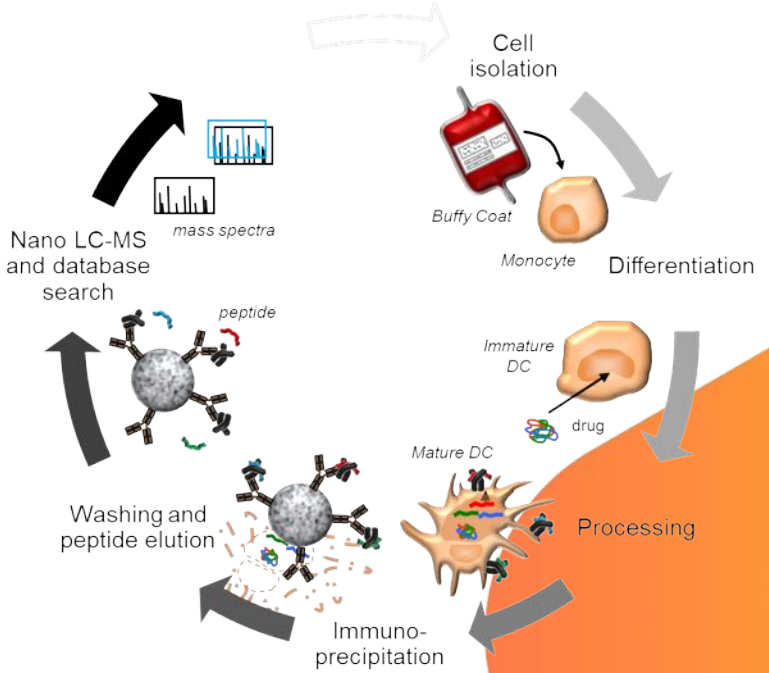
- Mostly applied together with MAPPs
- Applied for «high risk» and partially also for «intermediate risk» projects
- Promising correlation with antigen presentation via MAPPs observed



In vitro assays applied to assess IG potential

MAPPs assay:

- **Applied for «high risk» and partially also for «intermediate risk» projects**
- **Applied to rank candidates, study protein fusion effects and novel scaffolds and to support root cause investigations**
- **More and more deimmunization efforts are supported by MAPPs in conjunction with in silico tools**



In vitro assays applied to assess IG potential

Pre-existing ADA assay

- The impact of pre-existing anti-drug-antibodies (pADA) is not fully understood. Currently, the assay is applied on projects to gather knowledge that may help to better understand the relevance of pADA.
- Based on the theoretical concern regarding pADA, the data is used for candidate ranking in case drug candidates can't be differentiated by other parameters or assays.
- Applied for «high risk» and partially also for «intermediate risk» projects

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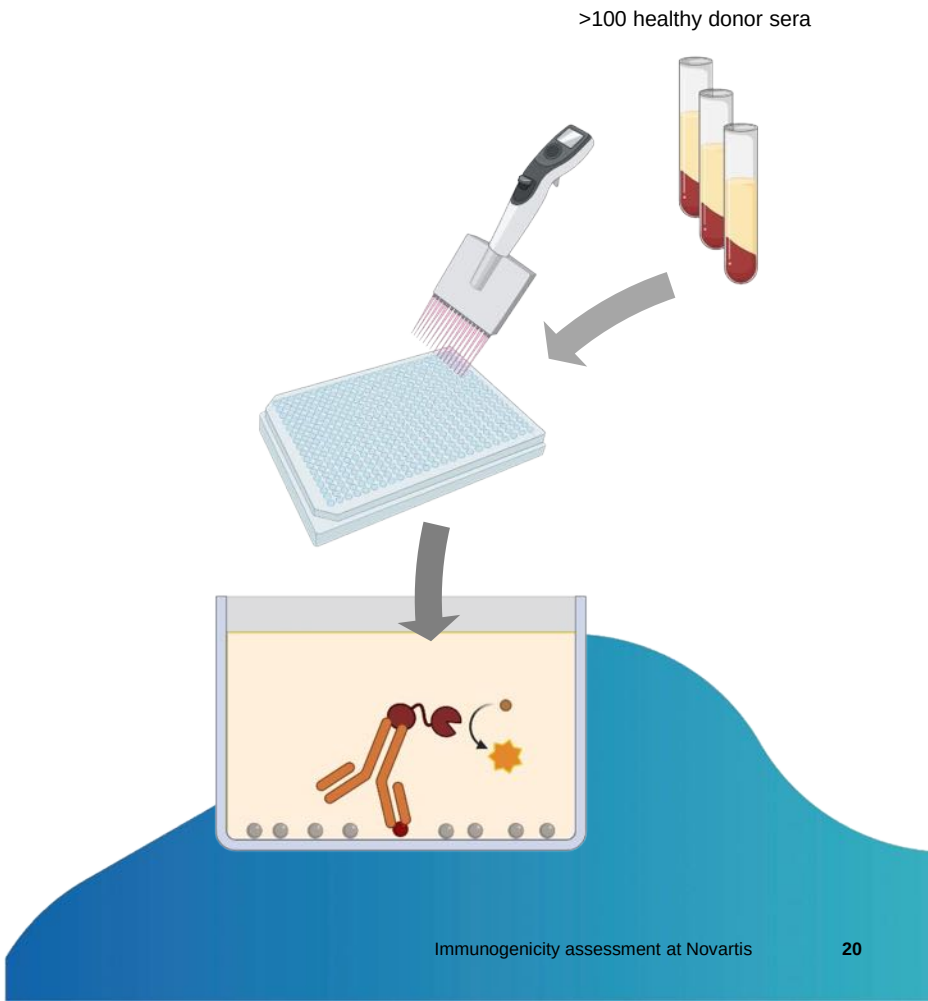
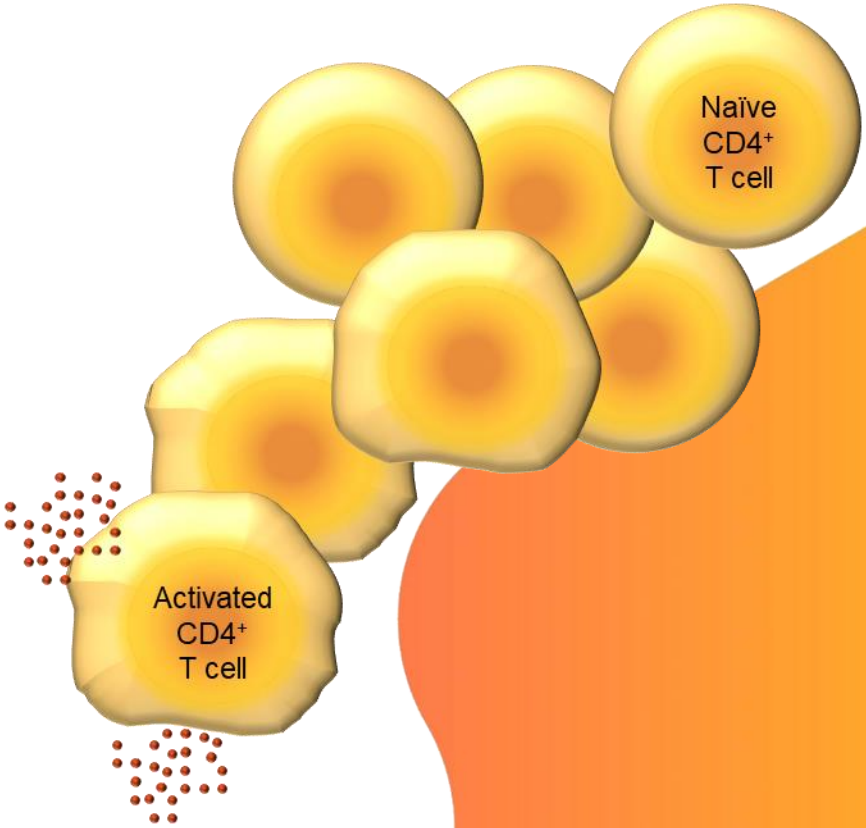


In vitro assays applied to assess IG potential

T cell assay

- Currently in internal implementation
- Difficult to find reliable assay setup that can be applied on the same cells as MAPPs
- Not yet applied regularly
- Aim is to apply for «high risk» projects in the future and to support de-immunization approaches in conjunction with MAPPs and in silico tools



Timing and depth of investigation in pre-clinical and clinical stages

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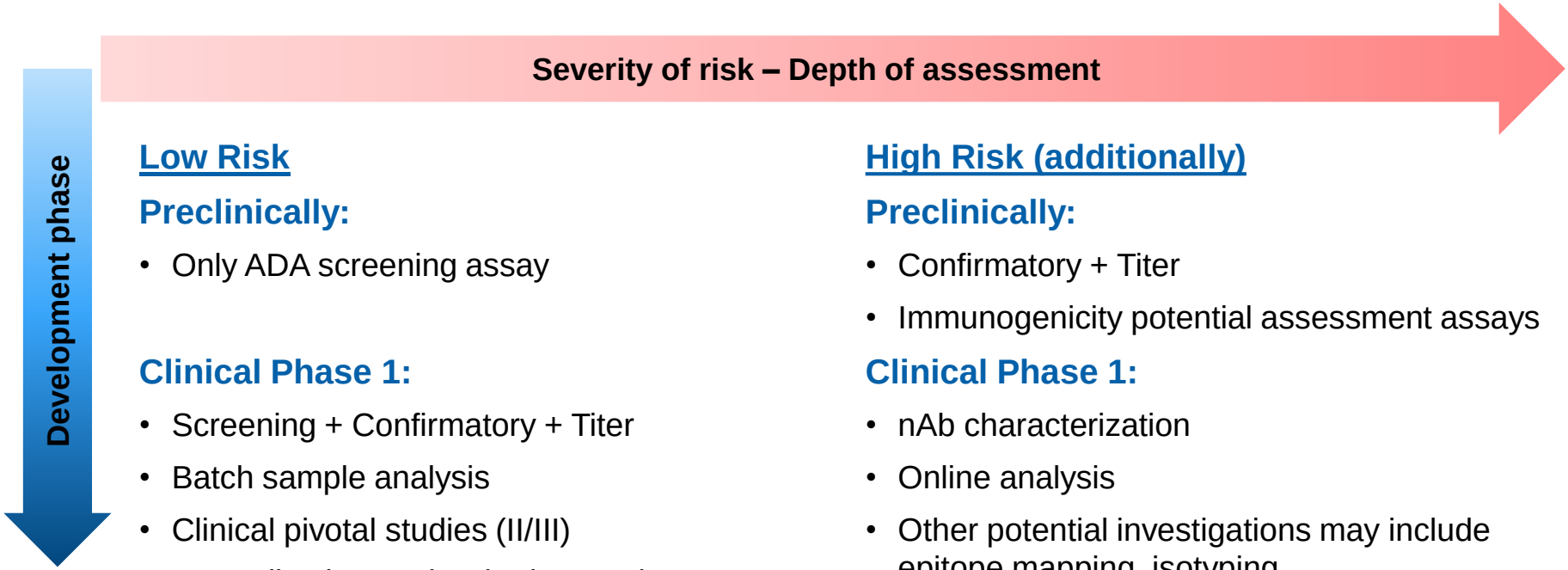
Timing and depth of investigation depends on the risk assessment of the biologics



Low Risk

Preclinically:

- Only ADA screening assay

Clinical Phase 1:

- Screening + Confirmatory + Titer
- Batch sample analysis
- Clinical pivotal studies (II/III)
- Neutralization testing (nAb assay)

High Risk (additionally)

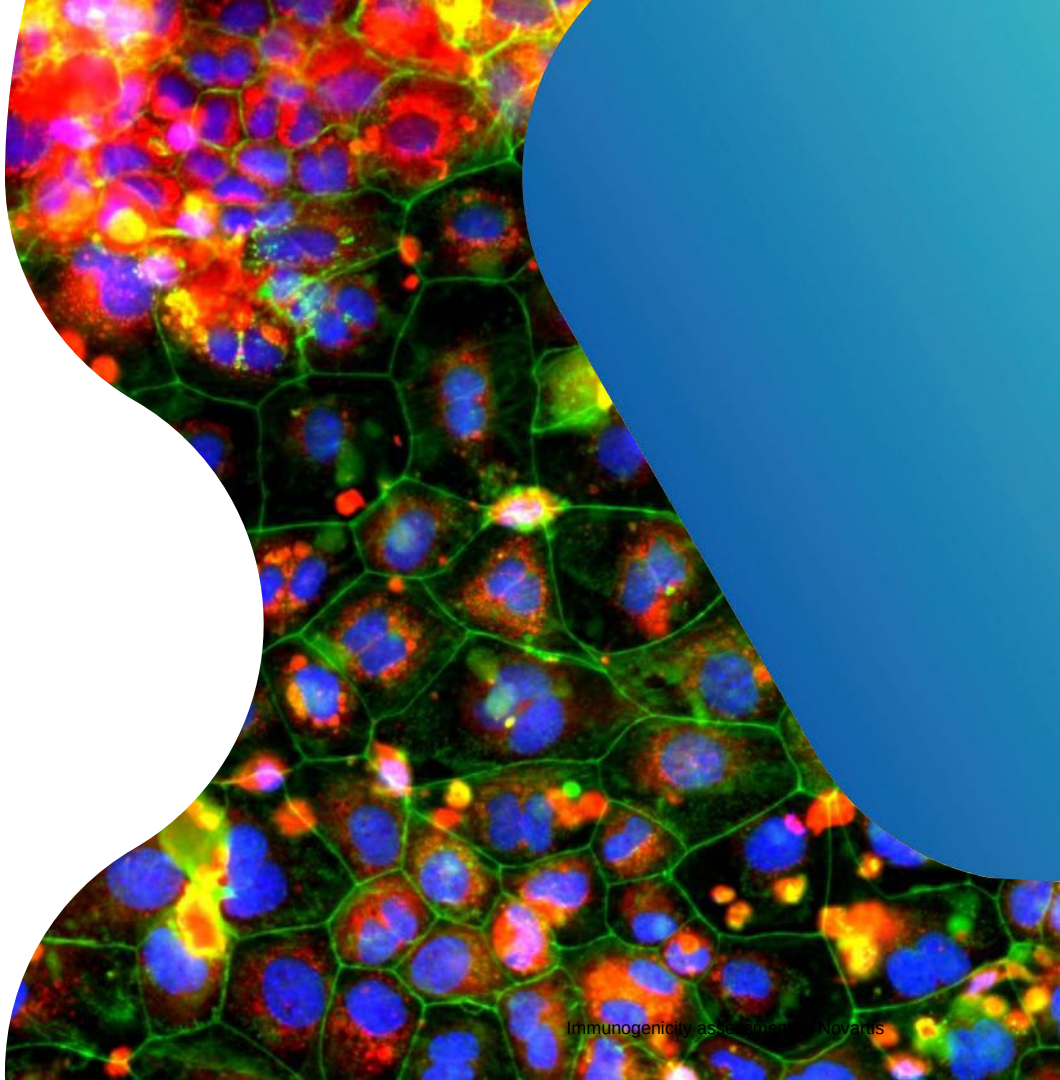
Preclinically:

- Confirmatory + Titer
- Immunogenicity potential assessment assays

Clinical Phase 1:

- nAb characterization
- Online analysis
- Other potential investigations may include epitope mapping, isotyping ...

Case studies



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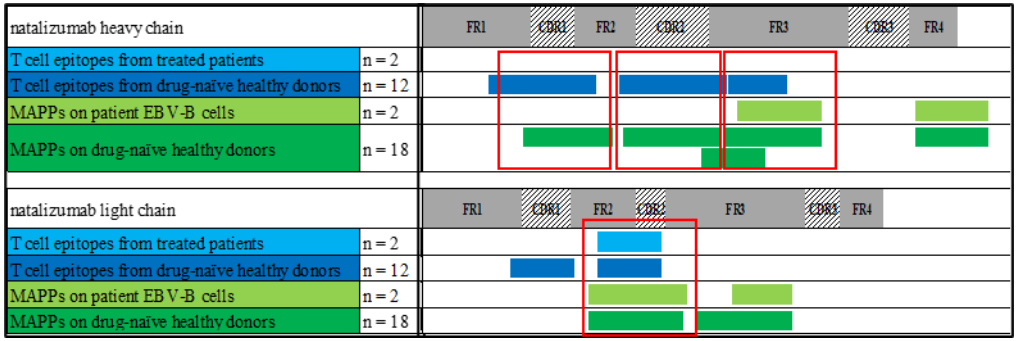
Immunogenicity assessment – Novartis

Biological relevance of MAPPs

- Meunier/Hamze et al.: IMI-ABIRISK project with healthy donors. MAPPs by Novartis. T cell epitope mapping by Bernard Maillère.
- Cassotta et al.: MAPPs + T cell epitope mapping on natalizumab-specific EBV B cell clones from 2 patients with immunogenicity.

➢ Natalizumab-specific B cells able to recognize/internalize natalizumab via BCR and present peptide sequence verified as natalizumab-specific T cell epitope.

➢ Strong overlap between presented peptides and T cell epitopes and high similarity between the two studies



Karle AC. , doi: 10.3389/fimmu.2020.00698.

[1] Cassotta A et. al. , doi: 10.1038/s41591-019-0568-2.

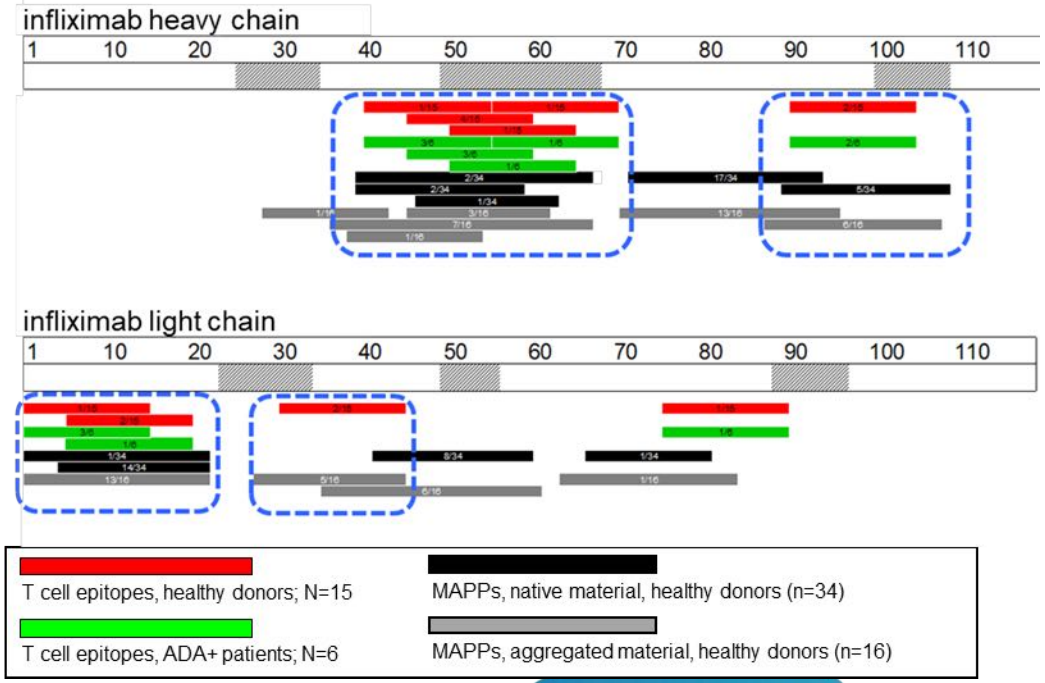
[2] Meunier S et al., doi: 10.1038/s41423-019-0304-3.

Biological relevance of MAPPs

ABIRISK project:

- **MAPPs by Novartis on healthy donors.**
- **T cell epitope mapping by Bernard Maillère on a different set of healthy donors as well as patients with IBD or RA that had developed immunogenicity against infliximab.**

➢ **Despite the use of different donors, a high degree of similarity observed for both datasets in terms of the location of presented sequence regions and T cell epitopes**



Hamze M et al., . doi: 10.3389/fimmu.2017.00500.

Summary

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Summary

- **Immunogenicity comes with varying degrees of clinical consequences, and it is important to assess the likelihood for immunogenicity and potential associated risks early on.**
- **Risk assessment documents can be useful tools for project teams to assess and reduce risks.**
- **Different cell-based assays can be applied to evaluate the immunogenicity potential of biotherapeutics although absolute translation to the clinics remains difficult.**

Acknowledgement

Key members that were involved in the presented case studies

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Thank you