Current Perspectives on Preclinical Predictive Tools for Immunogenicity Risk Assessment and Clinical Translation

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Merck & Co., Inc.
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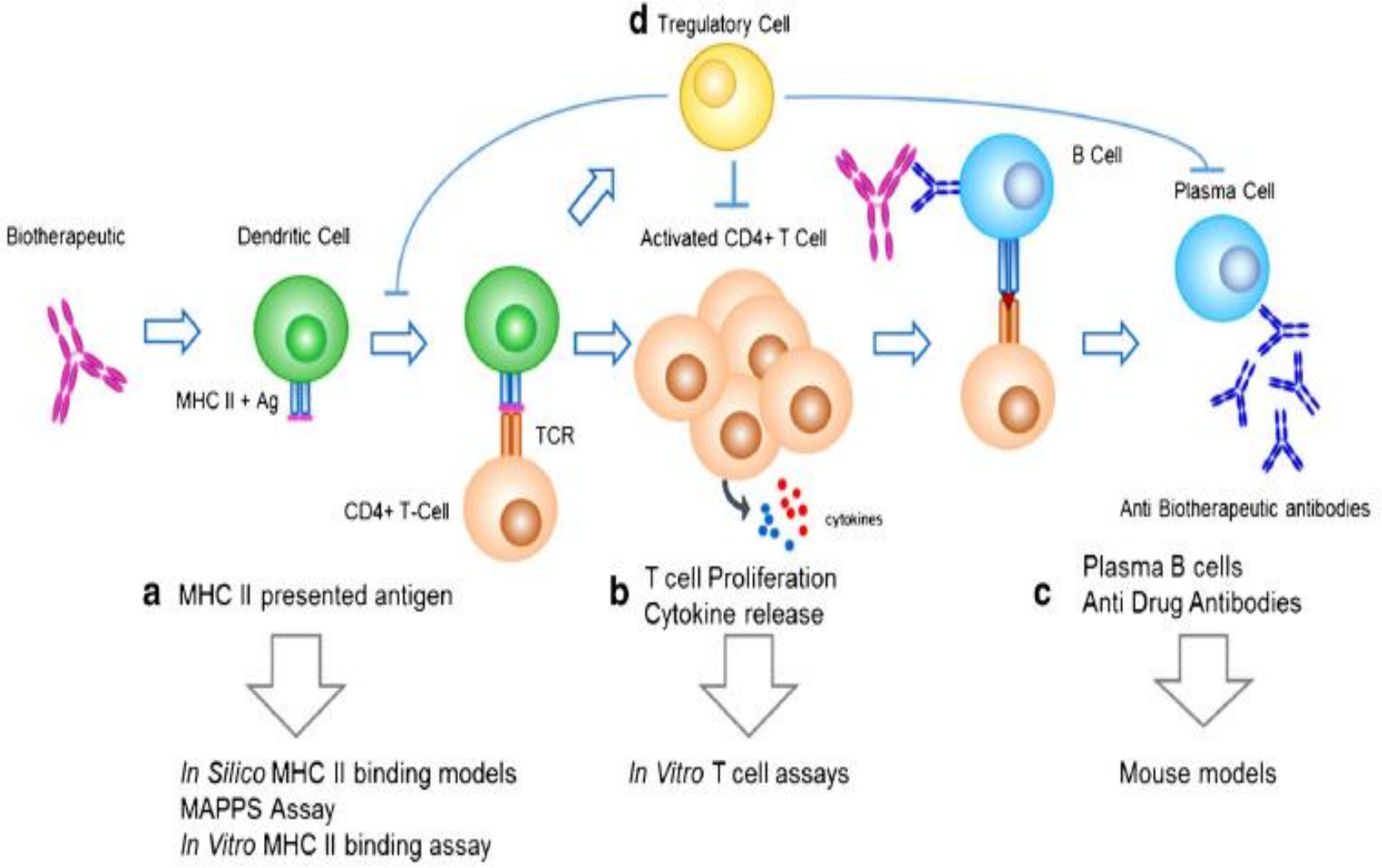
- Jad Maamary
- Carly Tasker
- Michael Swanson
- Diana Montgomery
- Vikram Sinha

Collaborators

EpiVax

Abzena

Implementing Risk Assessment Tools

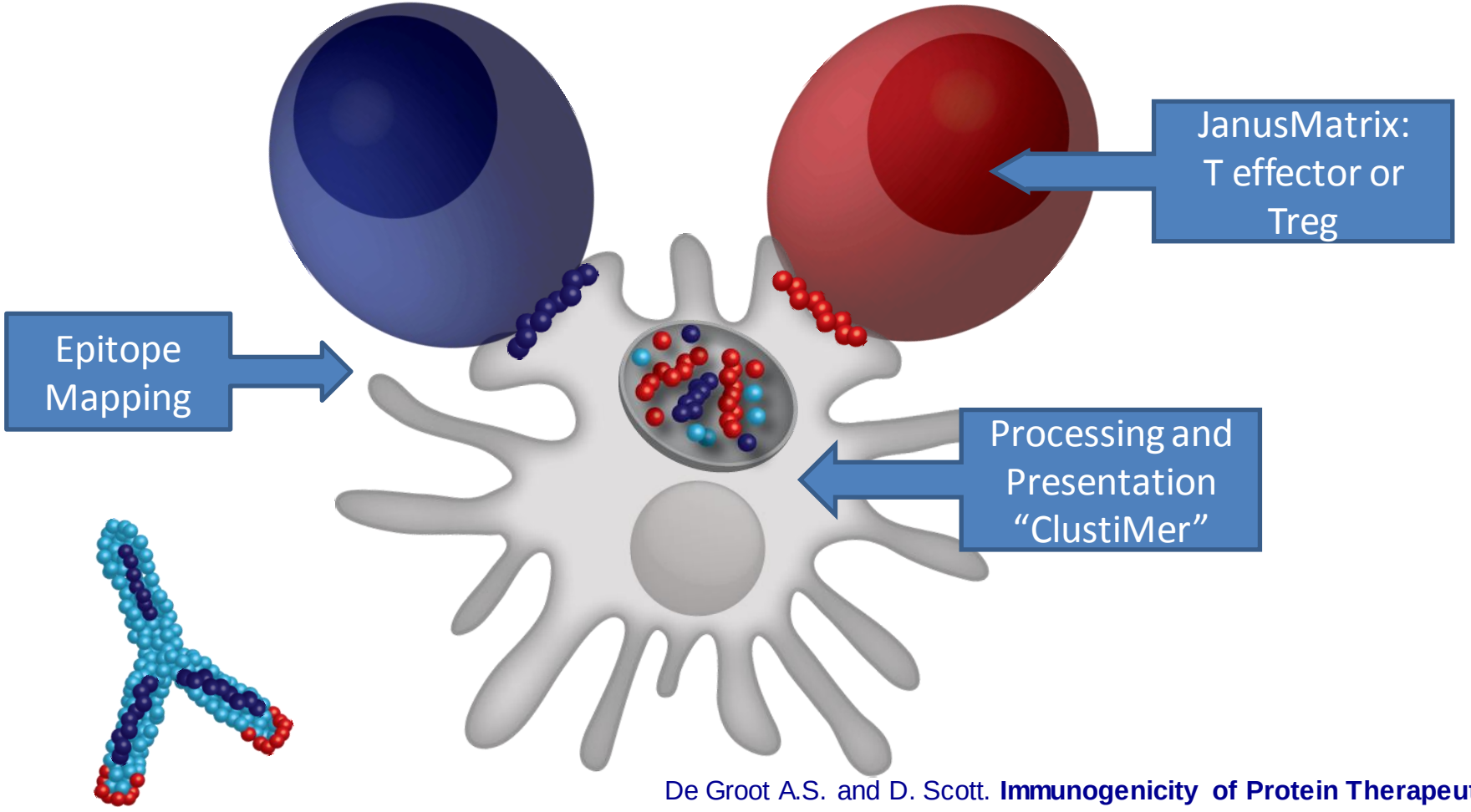


Gokemeijer J, Jawa V and Mitra-Kaushik S. The AAPS Journal (# 2017)

Outline

- Implementation of Predictive Tools during Development
- Integrating outputs from predictive tools
  - Algorithm based outputs and their applications
  - Improving the Prediction Accuracy
- In vitro assays and their correlation to algorithms and clinical data
- Prediction to clinical outcome
  - Case Studies
  - Understand association with HLA DR alleles

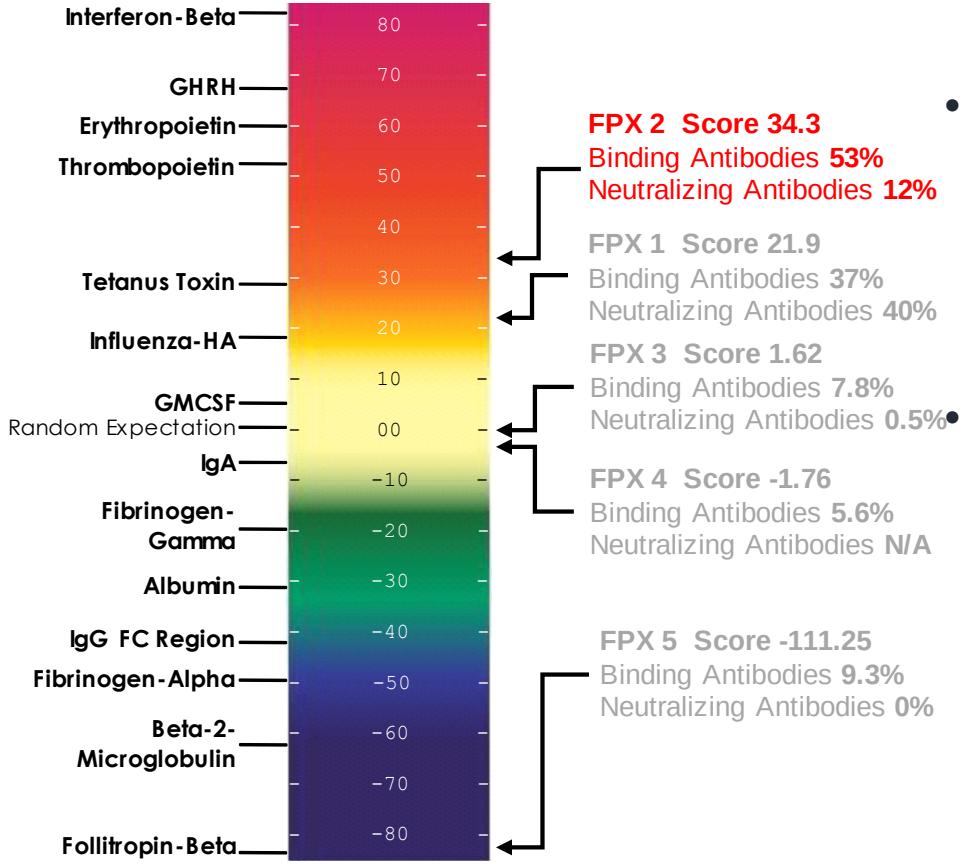
Where Algorithm-based Tools Can Assist with Immunogenicity



De Groot A.S. and D. Scott. **Immunogenicity of Protein Therapeutics**. Trends in Immunology. Invited Review. Trends Immunol. 2007 Nov;28(11):482-90.

Examples: FPX

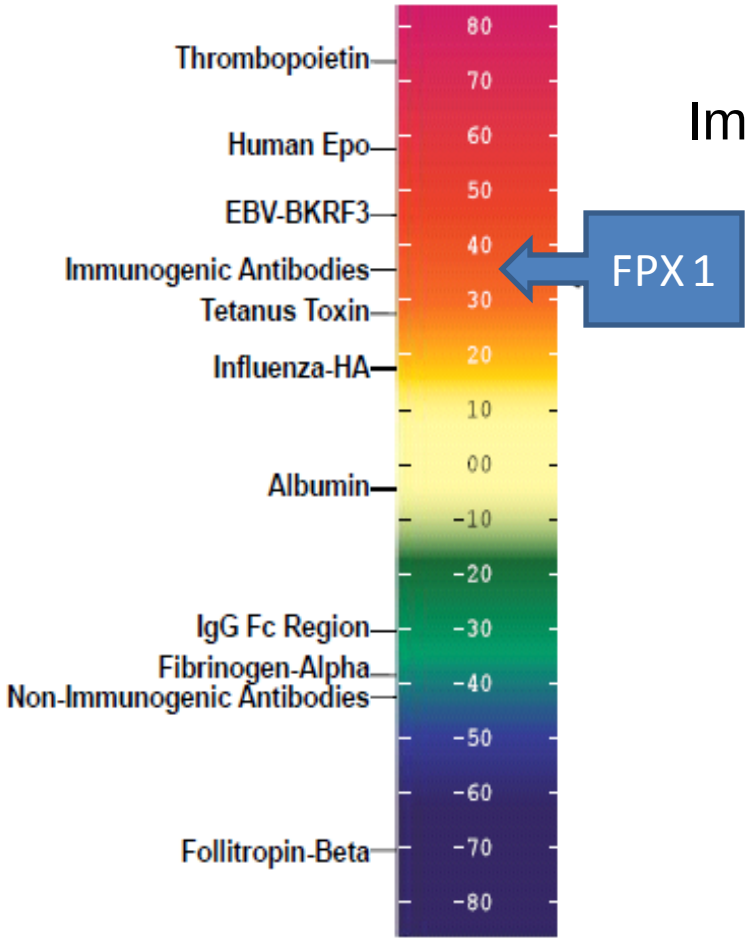
Correlation between Imunogenicity Scores and Immune Response is Excellent



- Amgen FC Fusion peptides (FPX 1 and 2) in clinic. **Blind EpiMatrix retrospective analysis**
- **"PEPTIBODY"**

Koren E, De Groot AS, Jawa V, Beck KD, Boone T, Rivera D, Li L, Mytych D, Koscec M, Weeraratne D, Swanson S, Martin W. Clinical validation of the "in silico" prediction of immunogenicity of a human recombinant therapeutic protein Clin Immunol. 2007 Jul.

Case Study: FPX Demonstrates Utility of In Silico Risk Assessment



Correlation of EpiMatrix Scores and Immunogenicity of Therapeutic proteins in Clinic

Peptibody	FPX 1	FPX 2	FPX 3	FPX 4	FPX 5
EpiMatrix score	21	25.0	1.76	-0.76	1.63
Binding Antibodies	37%	53%	7.8%	5.6%	9.3%
Neutralizing Antibodies	40%	12%	0.5%	na	0%

Vibha Jawa, Leslie Cousens, and Anne S. De Groot. Immunogenicity of Therapeutic Fusion proteins: Contributory Factors and Clinical Experience ; Chapter in: Fusion Protein Technologies for Biopharmaceuticals: Applications and Challenges, John Wiley and Sons, Inc

Examples: Monoclonal Antibody

Comparison of In Silico Outputs and Candidate Ranking

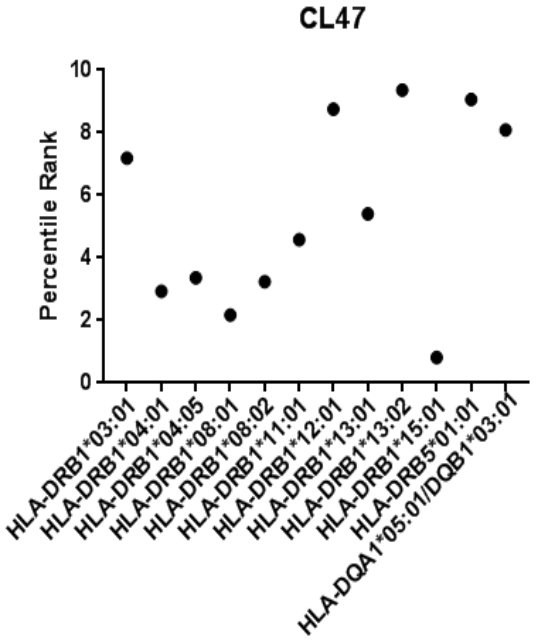
VH

QLVQSGPEVKKPGTSVKVSCKASGYTFTDYNVDWVRQARGQRLEWIGDIN
PNDGGTIYAQKFQERVTITVDKSTSTAYMELSSLRSEDTAVYYCARNYRWFGAM
DHWGQGTTVTVSSA

VL

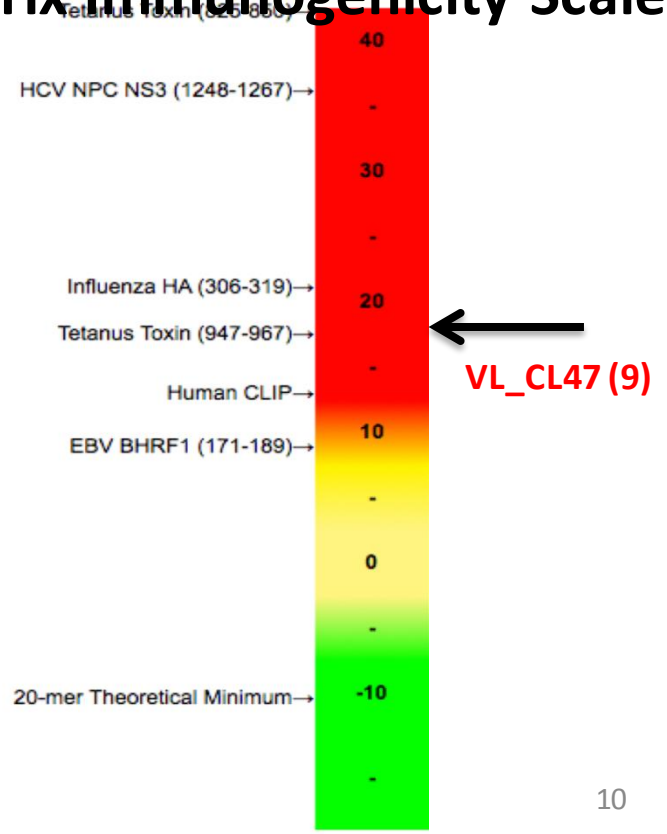
DIVMTQTPLSLSVTPGQPASISCKASQSLDYEGDSDMNWYLQKPGQPPQLLIYG
ASNLESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSTEDPRTFGGGTKV
EIK

IEDB



VL_CL47:
Intermediate/High, cluster is very likely to be processed/ presented since it shares a high similarity to therapeutic antibody derived peptides shown experimentally to be presented on APCs

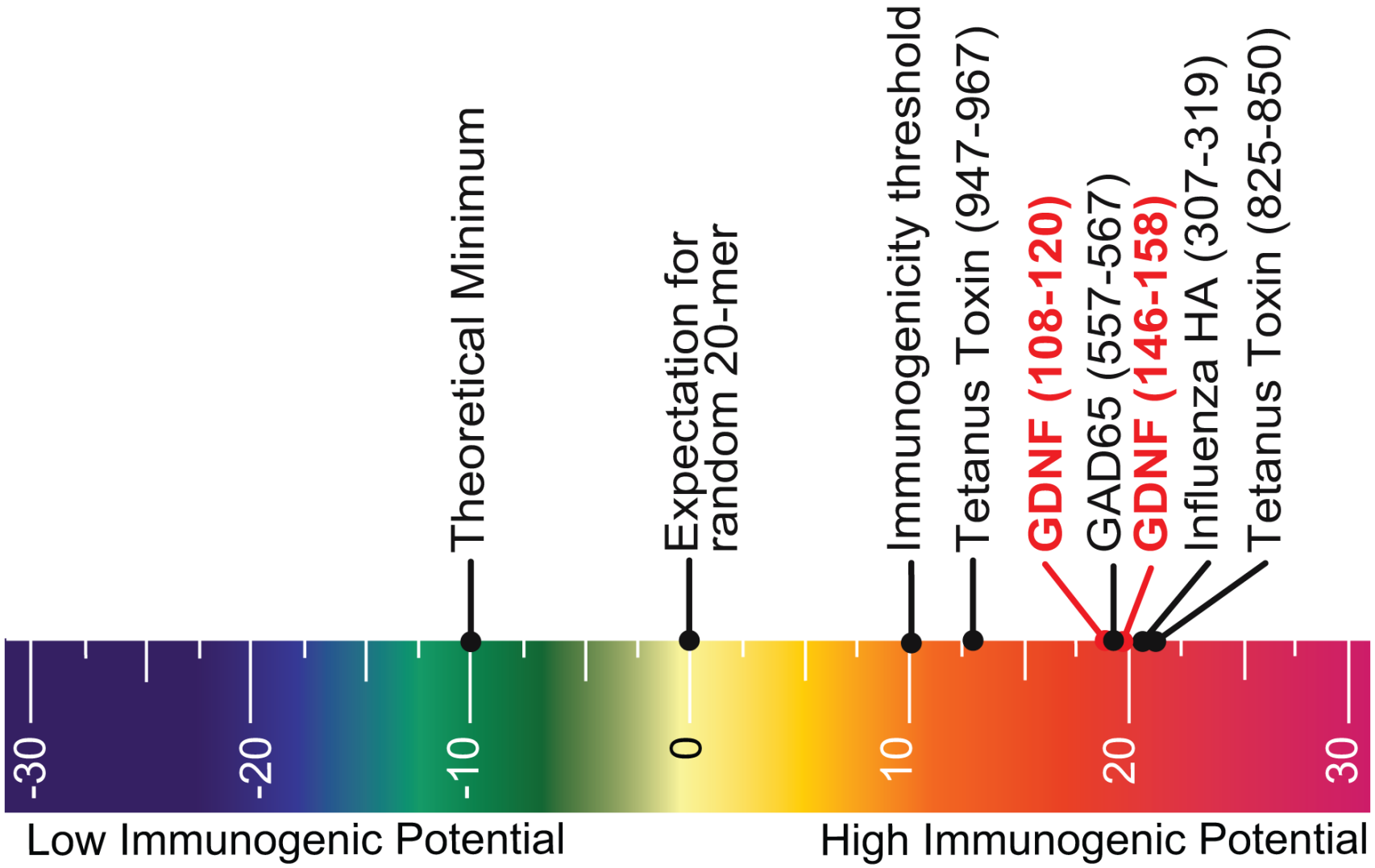
EpiMatrix Immunogenicity Scale



Examples: GDNF

GDNF epitope clusters:

Immunogenic potential as predicted by EpiMatrix



GDNF Immunogenicity in Phase 2 Trial

Study (Treated / Placebo)	Pre-Existing Binding Ab	Pre-Existing Neutralizing	Post-Exposure Binding Ab	Post-Exposure Neutralizing
6 mo (17/17)	18%	0%	**53%**	**6%**
Rollover (34/0)	18%	0%	**53%**	**12%**

IgG increased in 7 pts

– Four of these developed neutralizing Ab

Correlation of EpiMatrix Scores and Immunogenicity of Therapeutic proteins in Clinic

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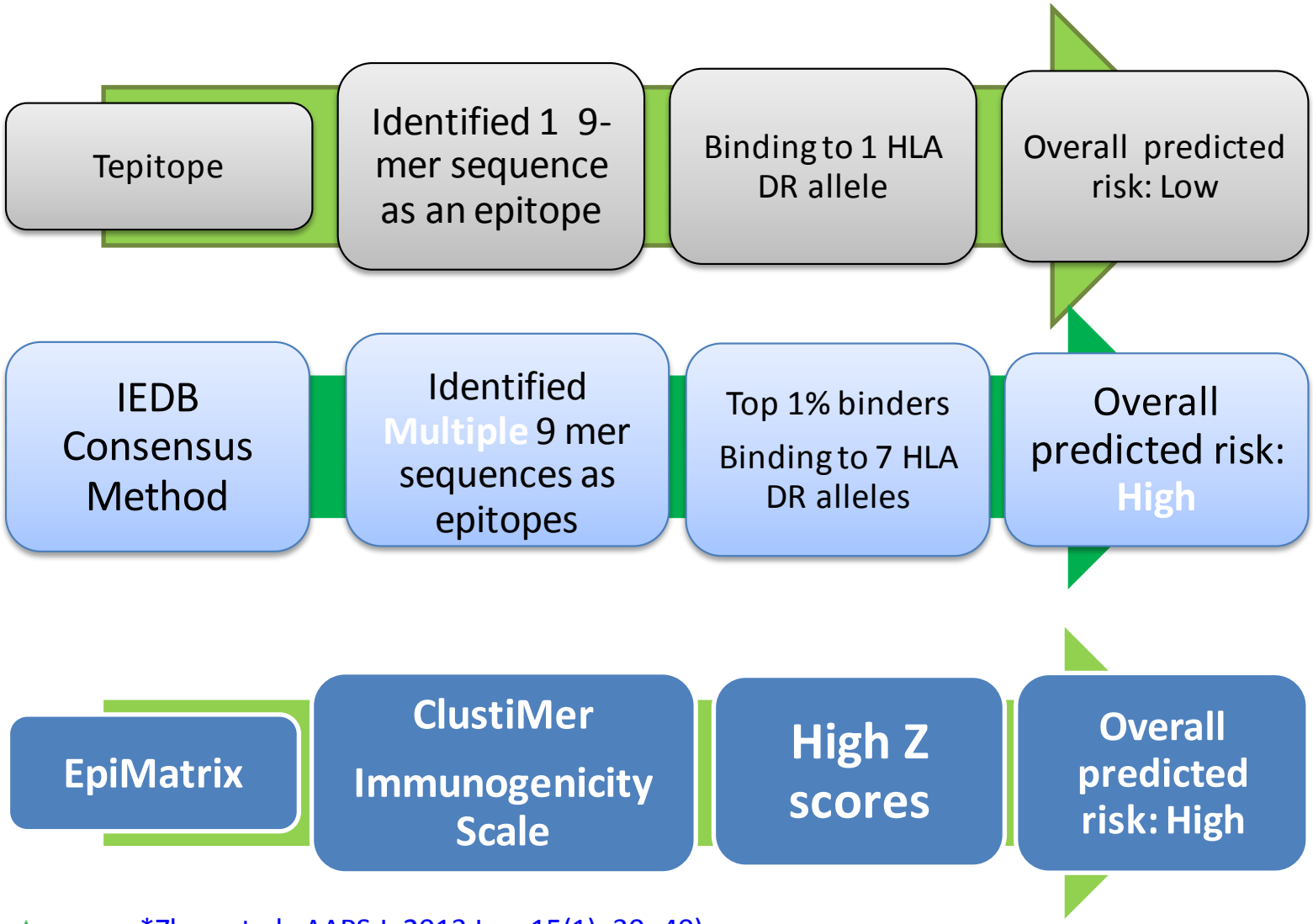
One Option: Layering with Multiple Algorithms Help Predict Risk of a Human mAb



Clinical Incidence of ADA

High

45%

*Zhou et al , AAPS J. 2013 Jan; 15(1): 30–40)

Increasing Prediction Accuracy

Integrating readouts from multiple algorithms

- Ensures inclusion of diverse HLA alleles
  (DRB1,DRB3,DP and DQ)
- Removal of molecules with a potential target effects can improve correlation
- De risk sequences that are cross reactive with endogenous proteins
- Assessing binding at both MHC pocket and T cell receptor binding faces
- Inclusion of MAPPS processed peptides (APPL)

Variety of T cell assays used by Industry

In vitro immunogenicity Protocol or "IVIP"

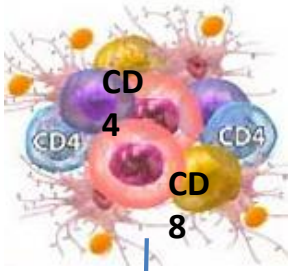
MAPPS Assay

MHC immunoprecipitation

MS sequencing of peptides

Value added: peptide processing/competition

PBMC Assay - IVIP



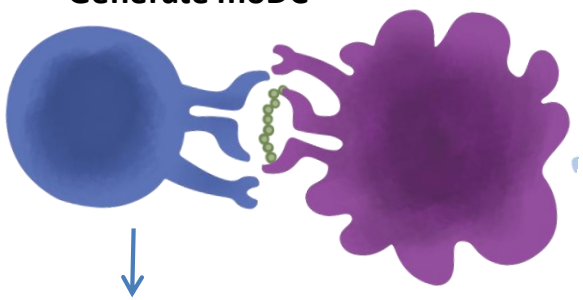
TNFa, IL2, IFNg

Luminex/Elispot/ICS /Proliferation

Validation of immunogenicity/ high sample numbers;; low sensitivity for primary responses

DC/T cell Assay

Generate moDC



TNFa, IL2, IFNg

Luminex/Elispot/ICS /Proliferation

High Sensitivity, Technically Complex

In Vitro Validation of In Silico Output

MAPPS: Antigen Presentation and Processing

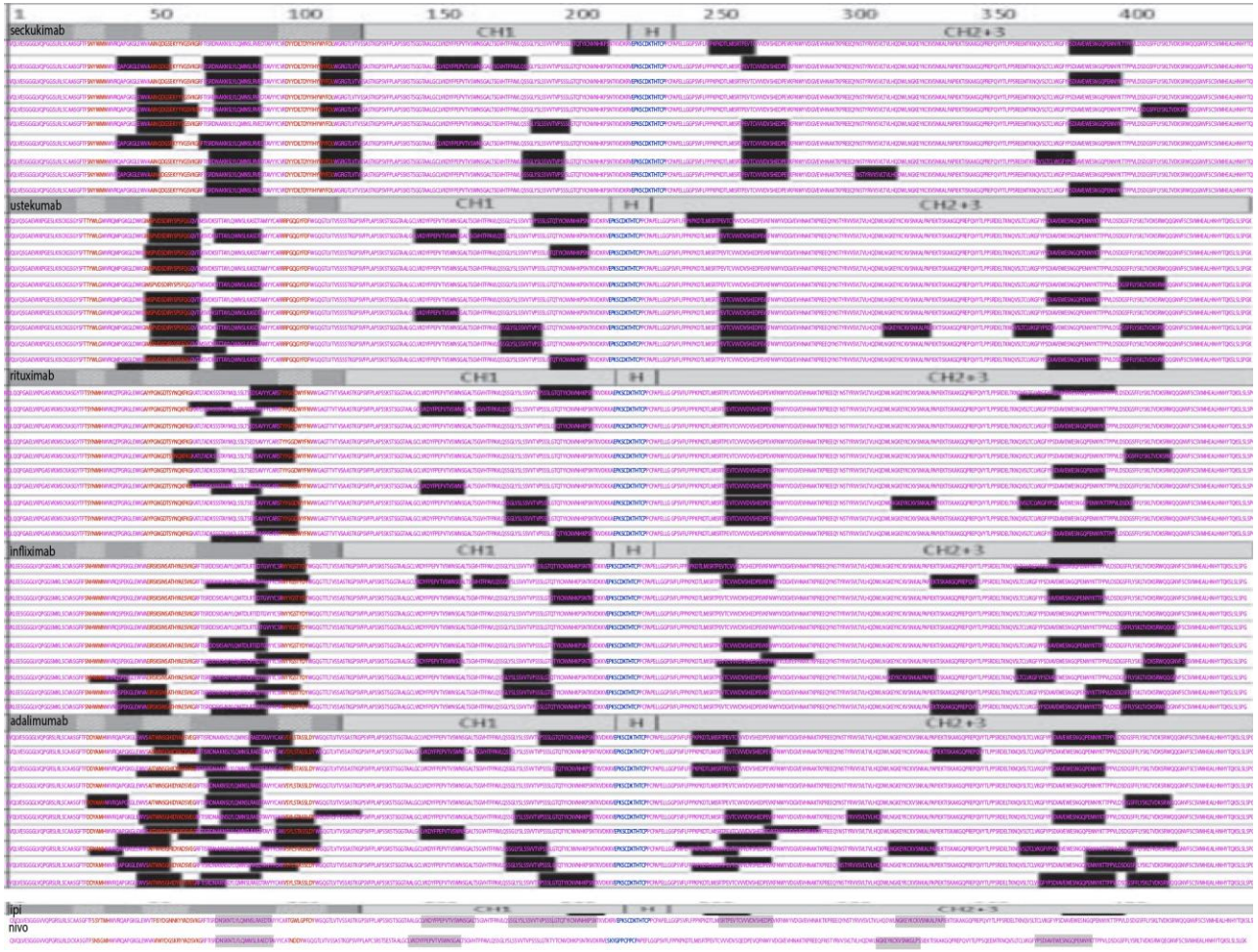
MHC Class II Associated Peptide Proteomics

MAPPS Assay

MHC immunoprecipitation

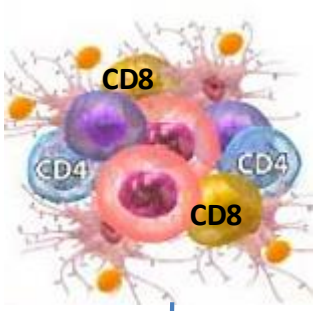
MS sequencing of peptides

Value added: peptide processing/competition



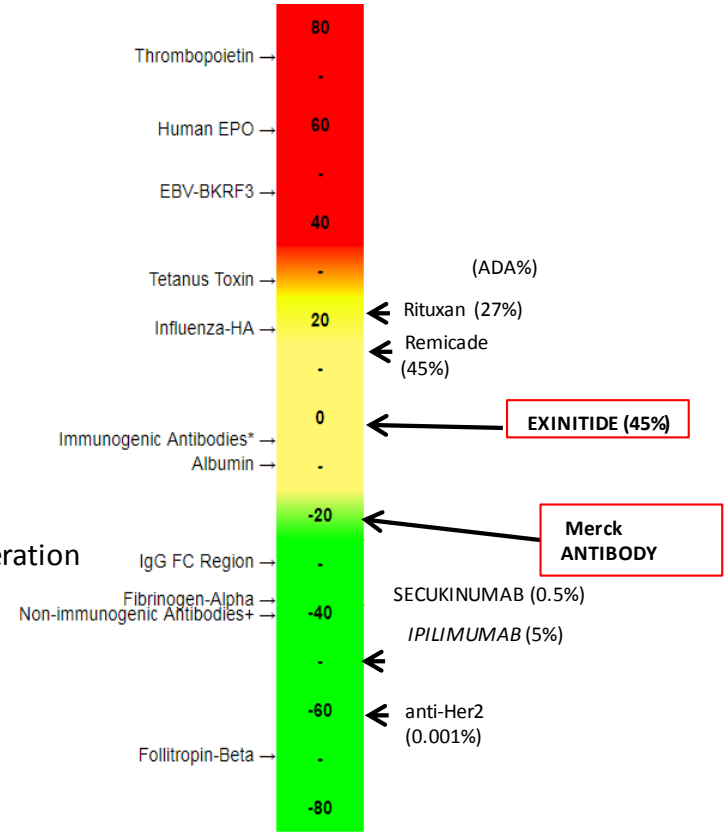
In Vitro Validation of In Silico Output

PBMC Assay



TNFa, IL2, IFNg

Luminex/Elispot/ICS/Proliferation



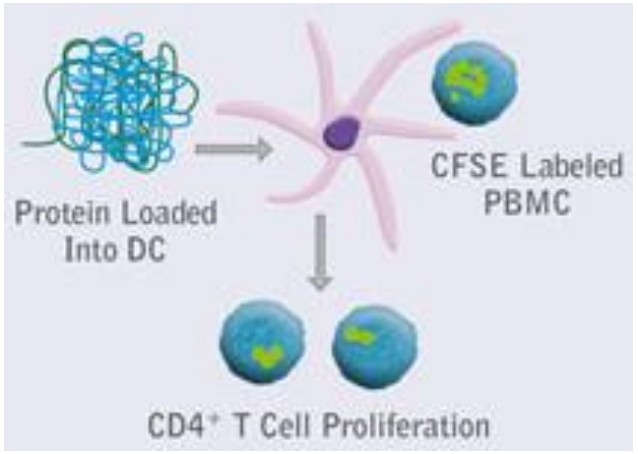
ABZENA
Enabling better biopharmaceuticals

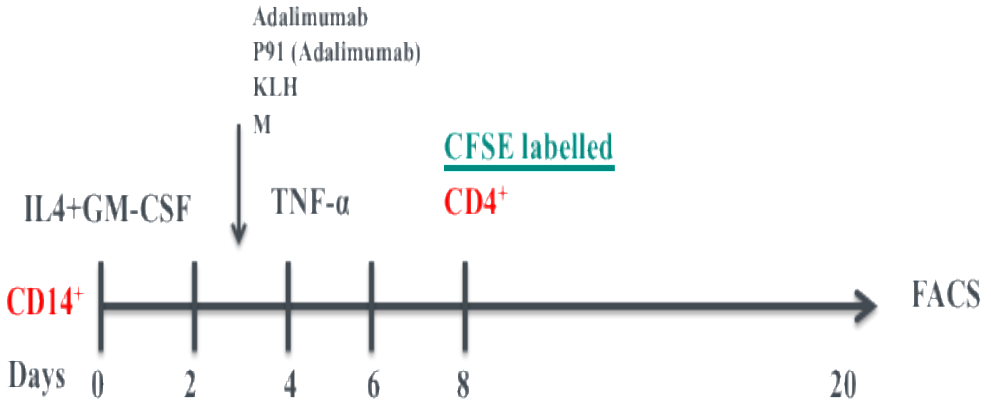
	Proliferation %	ELISpot %	Proliferation and ELISpot %	Correlation %
KLH	100	100	100	100
Exenatide	32	4	2	6
ANTIBODY	10	4	2	20

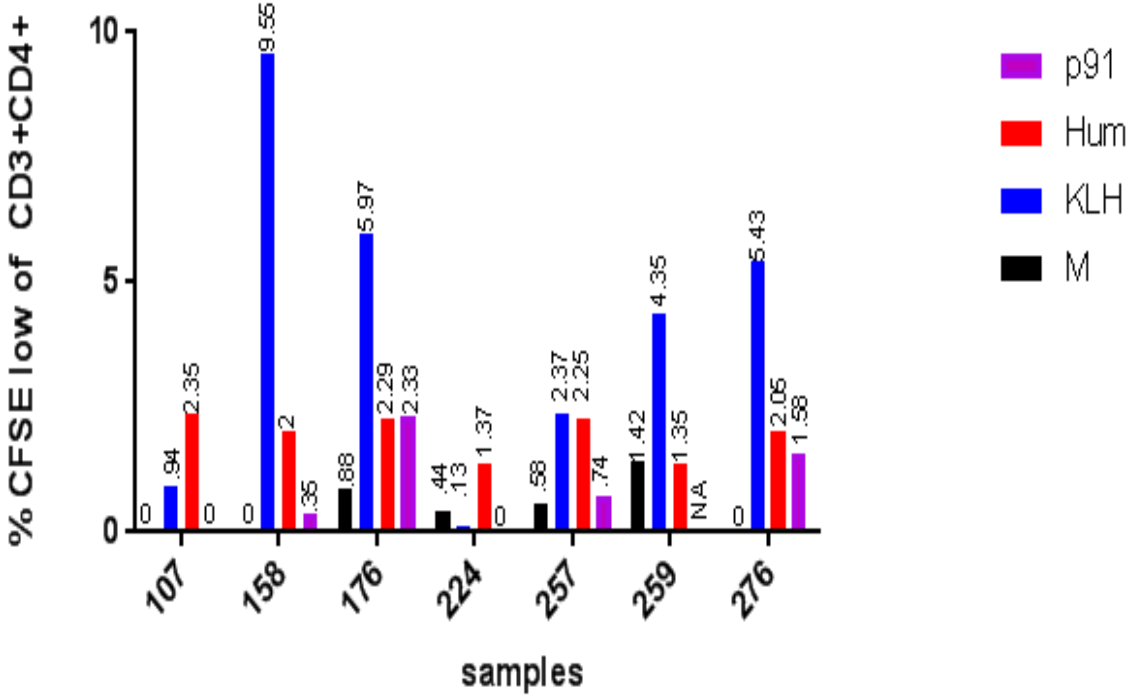
In Vitro Validation of In Silico Output

DC/T Cell Assay

Generate moDC







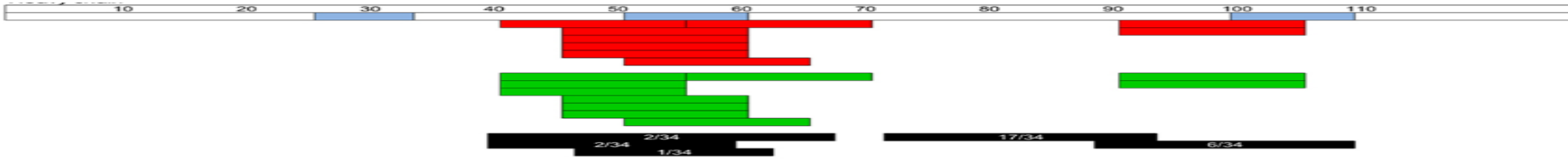
Correlation: *in Silico* Ex Vivo Immunogenicity Assessment

INFLIXIMAB (Remicade anti-TNFα) : ADA rate 10-51%

VH

Cluster score/Janus 13.34/7.63 9.17/0.75 26.32/2.94 10.24/2.5 6.70/0

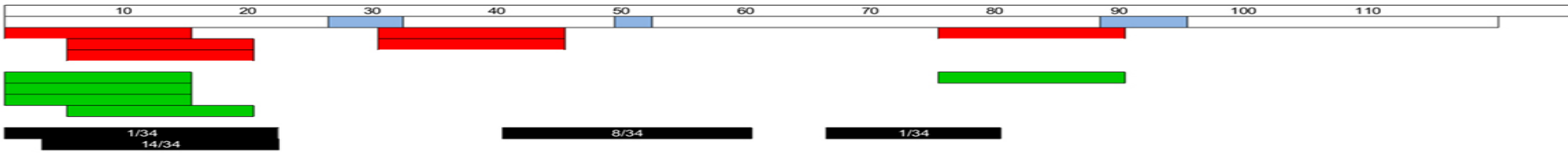
EVKLEESGGGLVQP**GGSMKLSCVAS**GFIFSNHWMN**W**VRQSPEK**GLEWVA**EIRSKSINSATHYAESVKGRFTISRDDSK**SAVYLQMTDLRTEDT**GVYYCSRNYYGSTYDYWGQGTTLTVS



VL

27.4/2.75 9/0.75 14.9/0.2 11.61/1

DILLTQSPAILSVSPGERVSFSC**RASQFVGSSIH**WYQQRT**NGSPRLLIKYASESMSGIP**SRFSGSGSGTDFTLSINTVESEDIADYYC**QQSHSWPFT**FGSGT**NLEVKRTVAAPSVFI**FPP



Hamze et al., Front Immunol. 2017

RED: CDR

Yellow: promiscuous epitopes

Bolded and Underlined: clusters

Red Bars: T cell epitope sequences identified using cells collected in healthy donors (15 donors)

Green bars: T cell epitope sequences identified using cells collected in patients with antidrug antibodies (5 patients)

Black Bars: Epitopes presented on HLA-DR

Secukinumab Case Study:
MAPPS/T cell assays vs. In Silico Prediction

MAbs. 2016 Apr; 8(3): 536–550.
Published online 2016 Jan 28.
doi: 10.1080/19420862.2015.1136761
PMCID: PMC4966846

Secukinumab, a novel anti–IL-17A antibody, shows low immunogenicity potential in human in vitro assays comparable to other marketed biotherapeutics with low clinical immunogenicity

Anette Karle, Sebastian Spindeldreher, and Frank Kolbinger

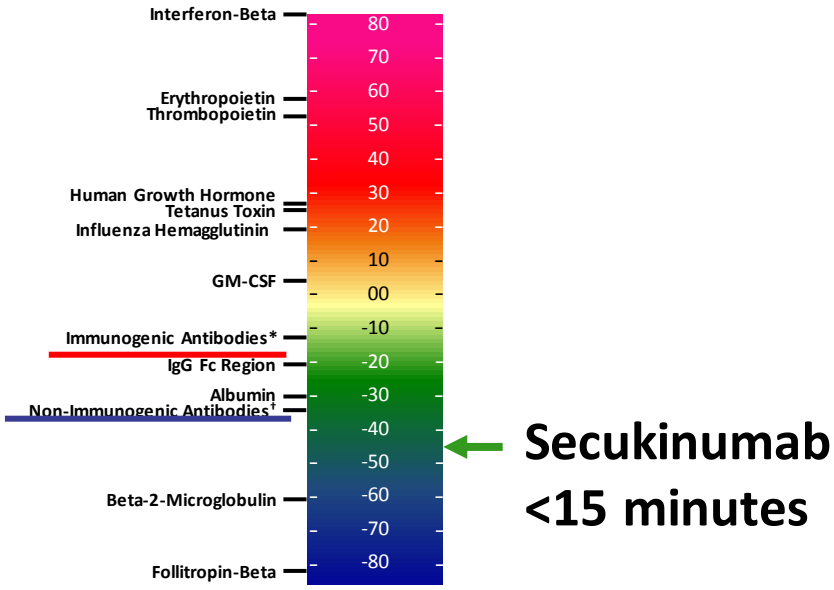
Author information ▶ Article notes ▶ Copyright and License information ▶

Annette Karle – Months of hard work!

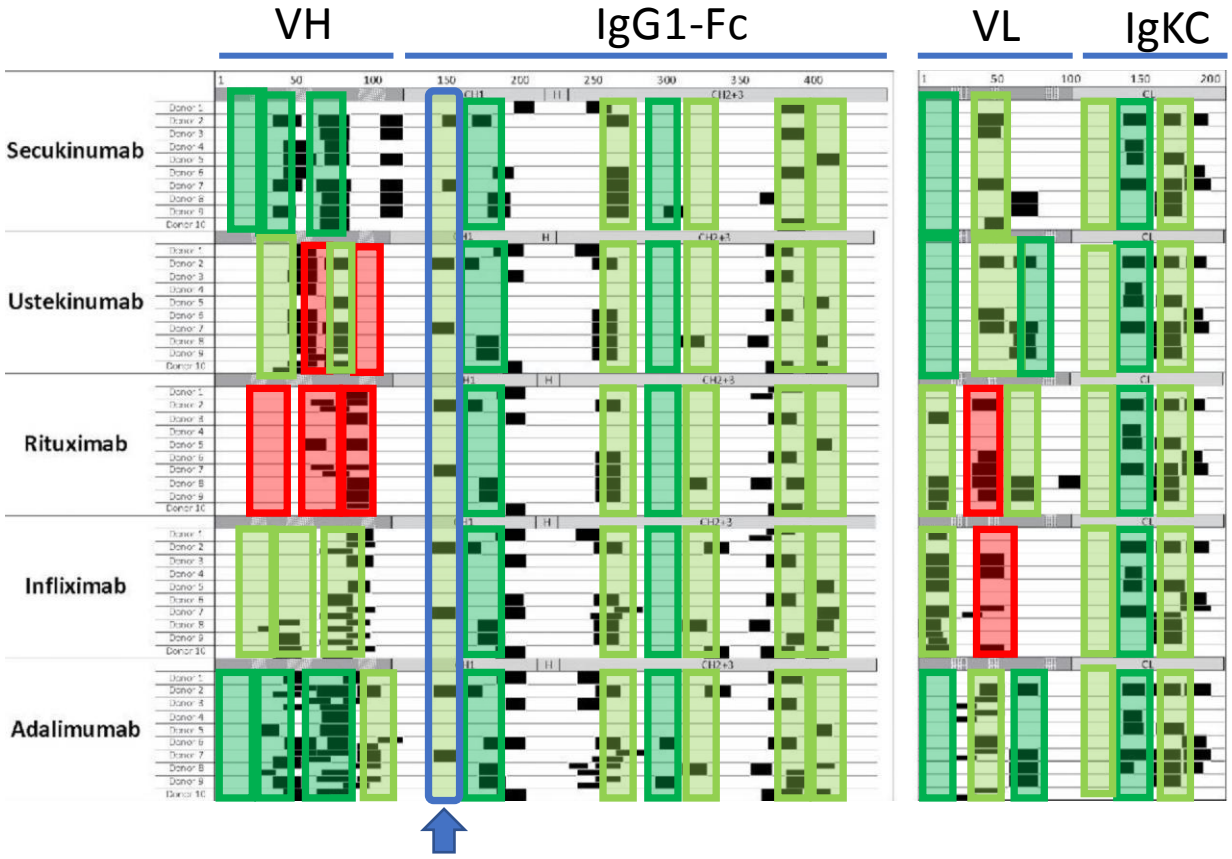
MAPPS assays give patient-level data.

In silico analysis is fast and gives a very good assessment of immunogenicity risk.

In silico data can also give population-level risk.



MAPPS vs. ClustiMer-Predicted Epitopes

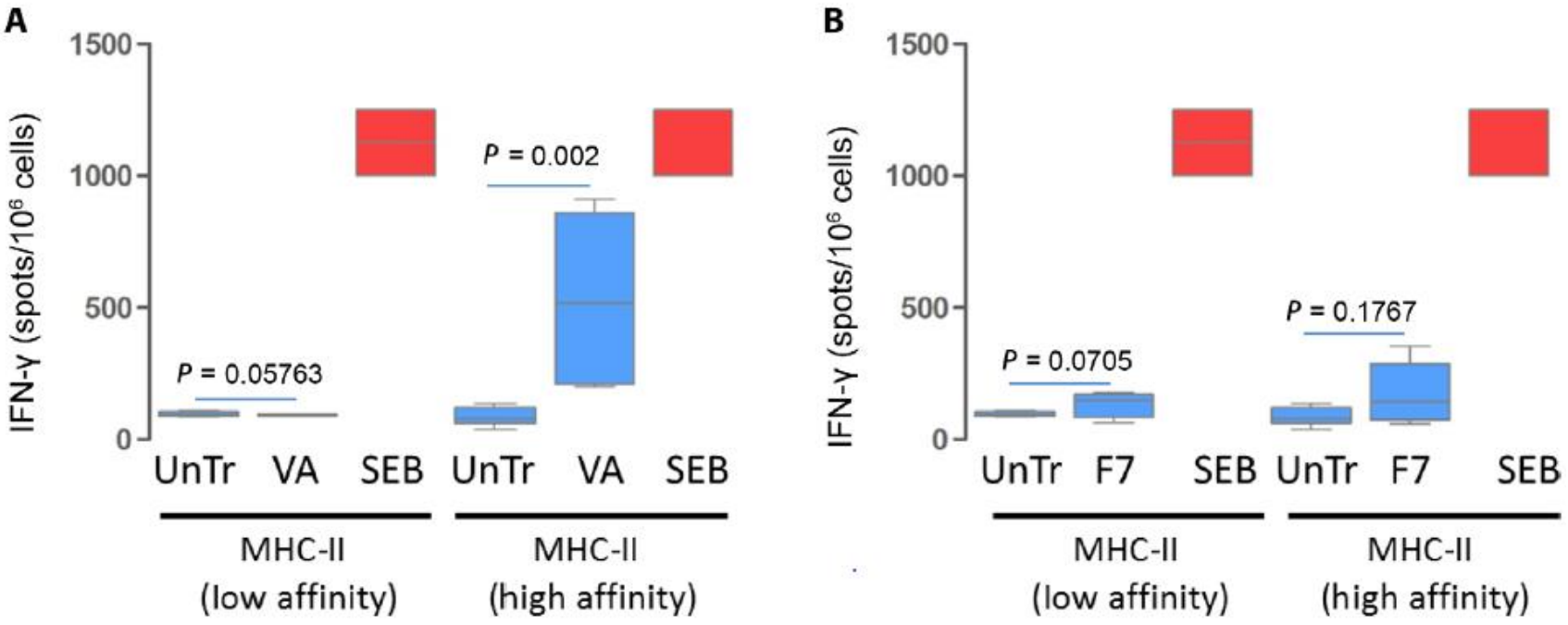


Green Box: Tregitope
Green Box: JanusMatrix ≥2; potential regulatory
Red Box: JanusMatrix <2; potential effector
All positions are relative

Epitope Clusters derived in the context of eight common HLA-DR alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*0801, DRB1*1101, DRB1*1301, DRB1*1501

Figure 4. MAPPS results for five monoclonal antibodies from the publication by augmented with ClustiMer and JanusMatrix results. Peptides eluted from five different therapeutic antibodies (black bars) compared to EpiMatrix-derived T cell epitope clusters (colored boxes). Green Box: contains known and previously validated and/or published Tregitope 9-mer(s); Light Green Box: contains potential tolerated or regulatory peptide based on JanusMatrix analysis; Red Box: potential effector or inflammatory peptide according to JanusMatrix. Blue arrow indicates HLA-restricted epitopes. Differences between the immunogenicity of these products were validated in in vitro assays performed by Karle et al.; EpiMatrix-adjusted immunogenicity scores generated using the ISPRI toolkit (immunoinformatics only) were closely matched to these in vitro, published results.

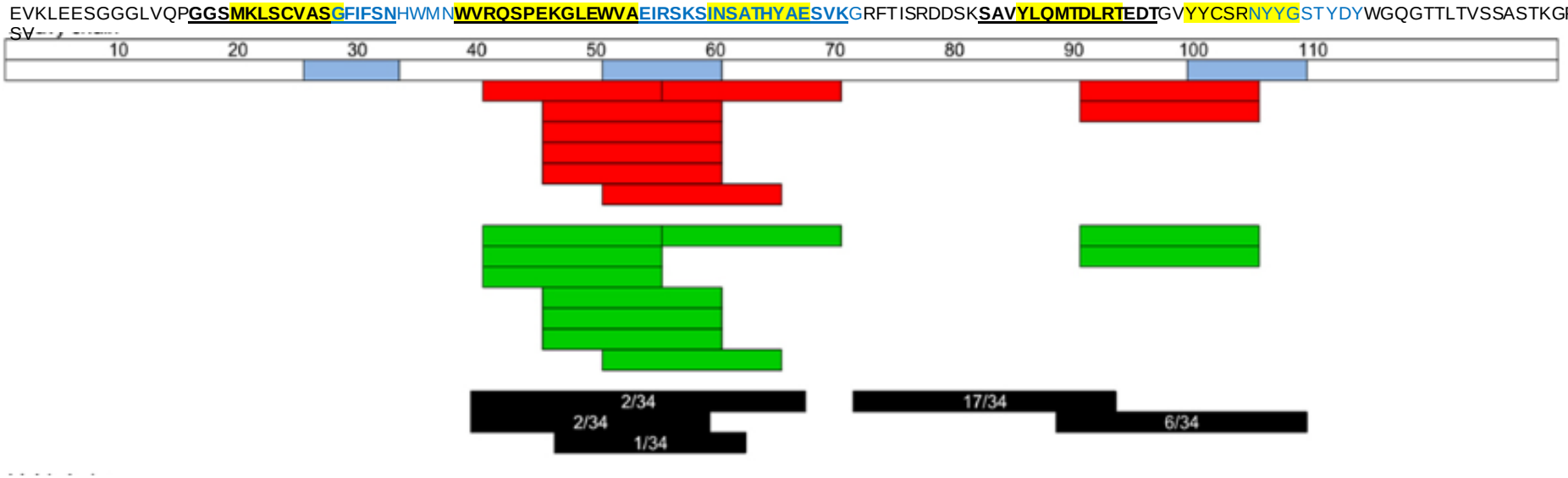
Association of HLA with T cell response to Vatreptacog alfa



Donors with MHC-II alleles that bound with either low [MHC-II (low affinity)] or high [MHC-II (high affinity)] affinity to neosequences engineered into vatreptacog alfa were evaluated for T cell functional response
Lamberth et al., Sci. Transl. Med. 9, eaag1286 (2017)

HLA DR Binding T cell epitopes and Consistency Across Readouts

INFLIXIMAB_VH

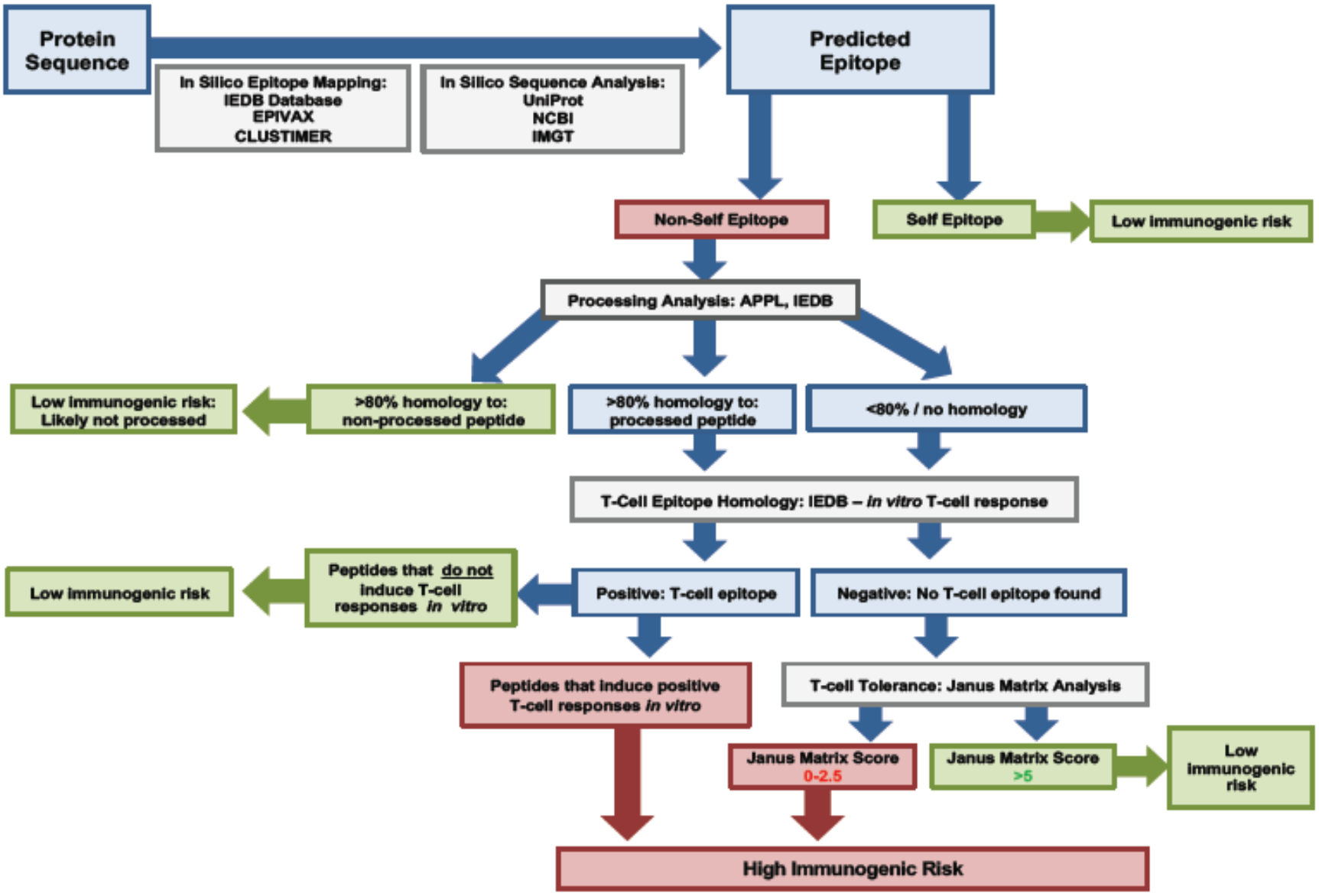


T cell epitope sequences identified using cells collected in healthy donors (red) (15 donors in total) or in patients with antidrug antibodies (green) (5 patients for infliximab) were reported, each bar corresponding to an individual response. Black: cluster identified by MHC-associated peptide proteomics assay. Occurrence of each cluster among the donors tested is indicated inside each bar.

Characterization of CD4 T Cell Epitopes of Infliximab and Rituximab Identified from Healthy Donors

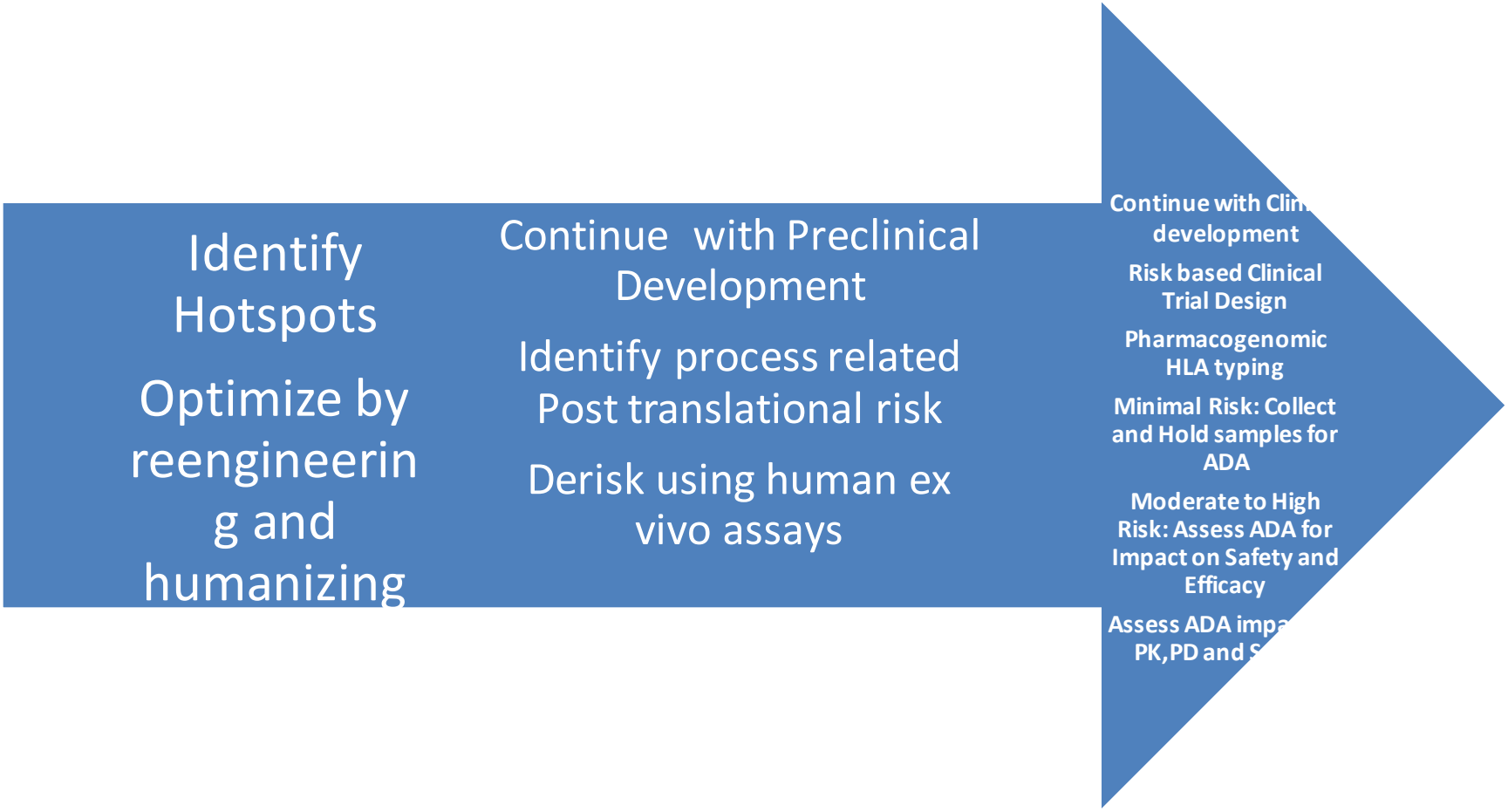
*Moustafa Hamze[1], Sylvain Meunier[1], Anette Karle[2], Abdelaziz Gdoura[1], Amélie Goudet[1], :ha Szely[3], Marc Pallardy[3], Franck Carbonnel[4], Sebastian Spindeldreher[2], r Mariette[5], Corinne Miceli-Richard[5] and Bernard Maillère[1]**

Risk Designation Flow Chart Based On Algorithm Outputs



Drive Clinical Strategy based on Risk Designation

Decision Flow and Impact on Clinical Trial Design



Conclusions

- Developed an in silico methodology to assess potential immunogenicity of Biotherapeutics
- Correlation between in silico prediction and in vitro assays
- Correlation between in silico prediction and clinical ADA incidence
- Scientific Impact:
  - **Supports Quality by Design and Development of a molecule with minimal risk**