AAPS perspective on predictive assays
Vibha Jawa , Merck

AAPS-BIOTEC Section

Therapeutic Product Immunogenicity Focus Group (TPIFG)

Immunogenicity Prediction Action Program Area (IPAPA)

- **Foreign Sequence Subteam**

Mission:
Increase utilization and acceptance of pre clinical derisking immunogenicity methods in drug development

29
Members from
Industry and academia

- Discuss standardization of immunogenicity profiling
- Promote sharing of pre clinical data / clinical data
- Discuss gaps in understanding and obstacles to deployment in drug development
- Promote new technologies

Gaps Identified in a 2011 AAPS Survey

- Clinical Validation
- Lack of Correlation of Predictive Tools with ADA incidence
- Lack of consideration of other factors that contribute to ADA

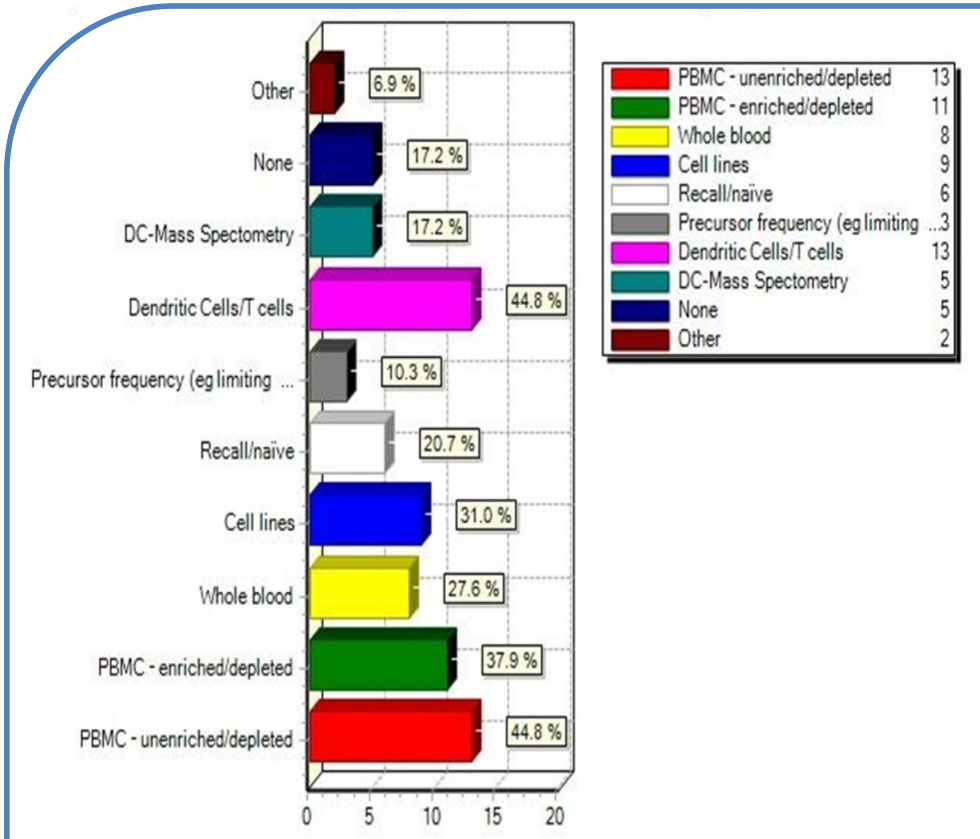
Intended Purpose(s)	VALIDATION EXPTS
Ranking candidates for selection/deselection Guiding de-immunization process Assessing risk of product variants	**Analytical validation** Precision (inter/intra-assay, within and across donor panels) Consistent ranking of candidates Robustness – different incubation times, reagent lots, donor pools etc. Ruggedness – different laboratories (proficiency testing?)
	Biological correlation MAPPS assay?
	Clinical validation T cell recall assays? HLA types

Slide Courtesy: Dr Bonnie Rup's talk at Immunogenicity Summit October 2017

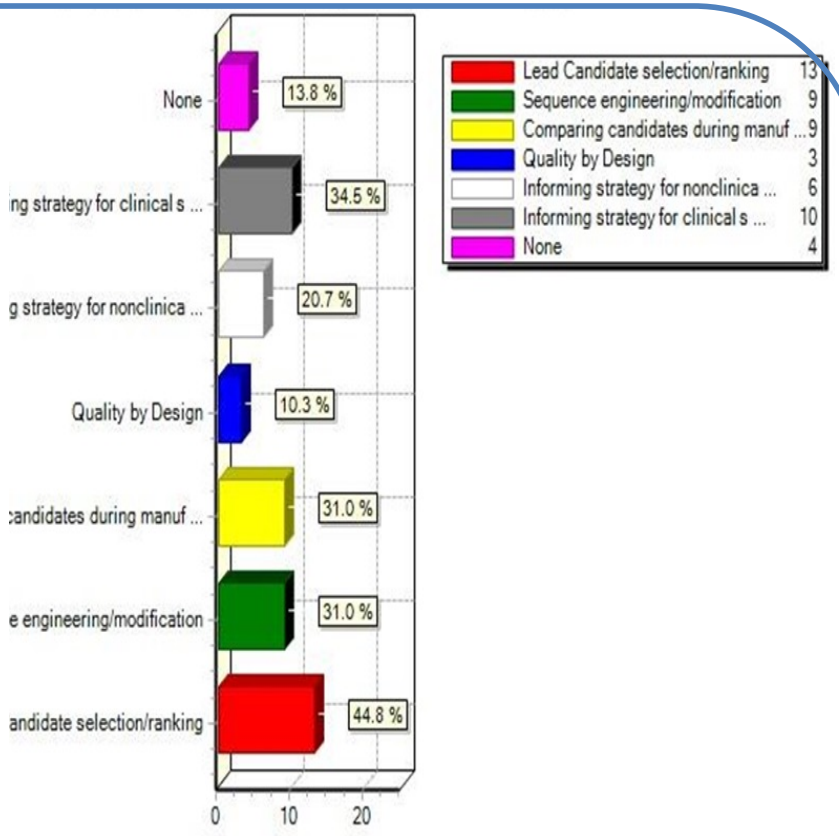
AAPS Immunogenicity Survey

Users of *in vitro* immunogenicity risk assessment assays in drug development within AAPS and EIP members N=29 (60% Pharma and Biotech)

Are you using in vitro assays?



How are in vitro assays used?



Slide Courtesy Shibani Mitra Kaushik; IPAPA FSS www.aaps.org/national biotech 2017

Pre Clinical Immunogenicity Risk Assessment: Emerging Regulatory Perspective

- Not a requirement for IND submissions
- But . . . Would like to see data!
  - Including analytical validation, repeatability , robustness……
  - (Immunogenicity Summit, Baltimore 2016)

338 **6. Non-clinical assessment of immunogenicity and its**
339 **consequences**

340 Therapeutic proteins show species differences in most cases. Thus, human(ised) proteins will be
341 recognised as foreign proteins by animals. For this reason, the predictivity of non-clinical studies for
342 evaluation of immunogenicity in humans is considered low. Non-clinical studies aiming at predicting
343 immunogenicity in humans are normally not required.

344 However, ongoing consideration should be given to the use of emerging technologies (novel *in vivo*, *in*
345 *vitro* and *in silico* models), which might be used as tools during development or for a first estimation of
346 risk for clinical immunogenicity. *In vitro* assays based on innate and adaptive immune cells could be
347 helpful in revealing cell-mediated responses.

Draft guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins. London, UK (2015). EMEA/CHMP/BMWP/14327/2006 Rev.1

2. *Primary Molecular Structure/Posttranslational Modifications*

Primary sequence, higher-order structure, species origin, and molecular weight of therapeutic protein products are all important factors that may contribute to immunogenicity. Primary sequence analysis can reveal potentially immunogenic sequence differences in proteins that are otherwise relatively conserved between humans and animals. In some cases, nonhuman epitopes may elicit T-cell help or facilitate epitope spreading to generate an antibody response to the conserved human sequences (Dalum et al. 1997). Per section V.A.4, it is important to note that therapeutic protein products of human origin may elicit immune responses in subsets of patients with distinct HLA haplotypes as well as in patients whose endogenous protein amino acid sequence differs from that of the therapeutic protein product, even by single nucleotide polymorphisms.

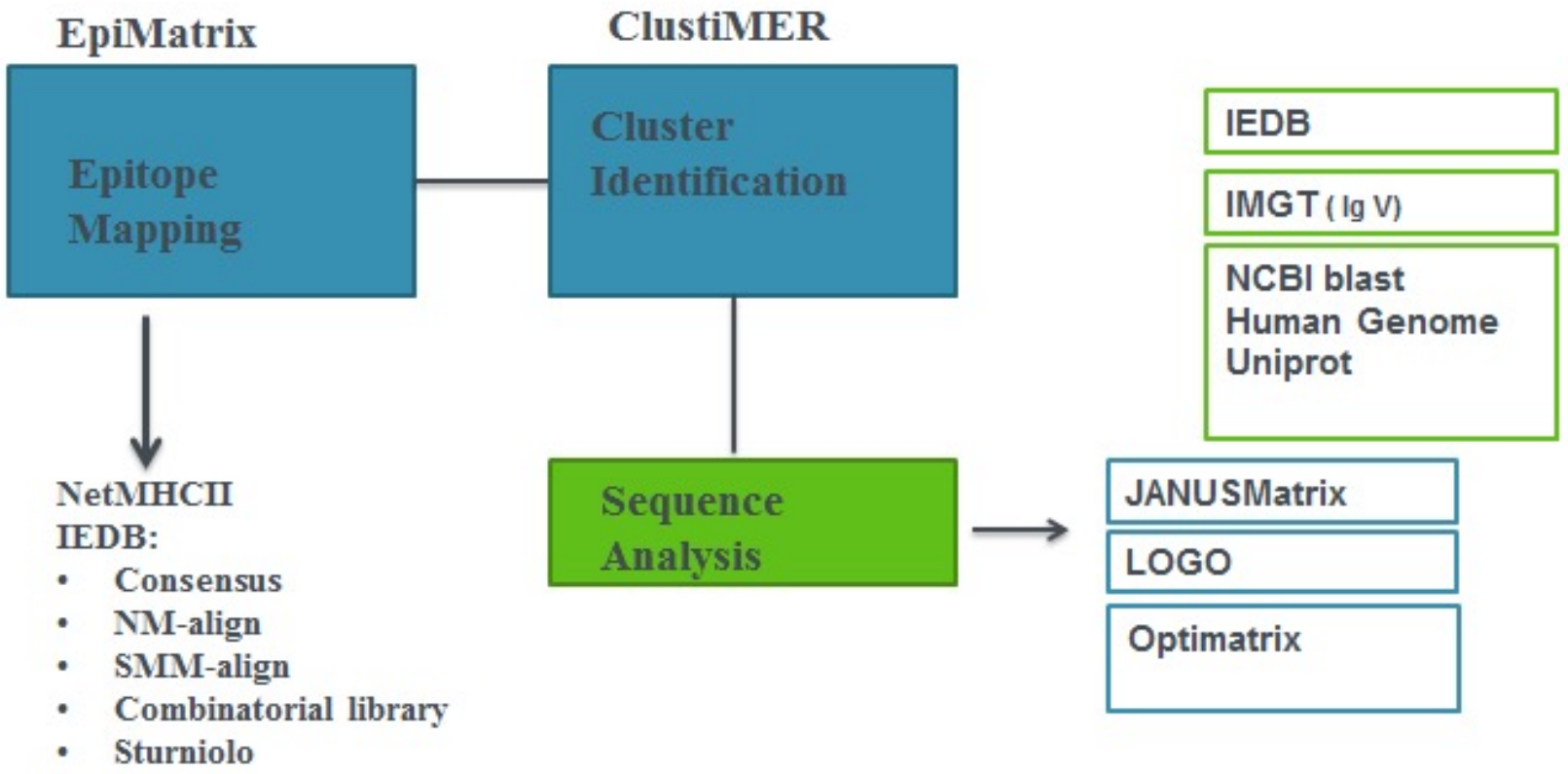
Additional advanced analyses of primary sequence are also likely to detect HLA class II binding epitopes in nonpolymorphic human proteins. Such epitopes may elicit and activate regulatory T-cells, which enforce self-tolerance, or, opposingly, could activate T-helper (Th) cells when immune tolerance to the endogenous protein is not robust (Barbosa and Celis 2007; Tatarewicz

Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products. Rockville, MD, USA (2014)

Preclinical Immunogenicity

RISK ASSESSMENT TOOLS IN USE

Algorithm Based Tools



Slide : Courtesy Jad Maamary, Merck

Predicting Antigen Processing And Presentation : In Vitro/Ex Vivo Human Immune Cell Based Tools

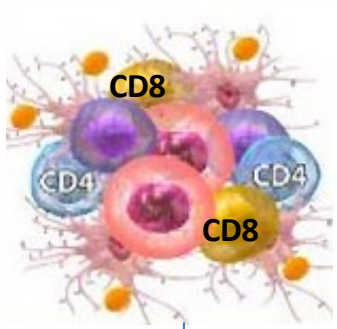
MAPPS Assay

MHC immunoprecipitation

MS sequencing of peptides

Value added: peptide processing/competition

PBMC Assay



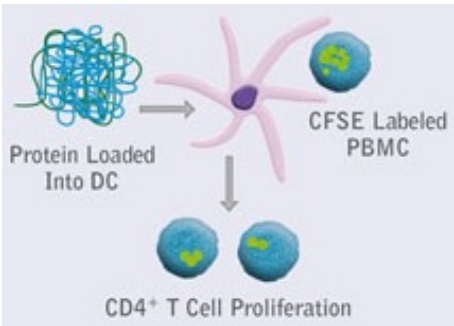
TNFa, IL2, IFNg

Luminex/Elispot/ICS/Proliferation

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

DC/T cell Assay

Generate moDC

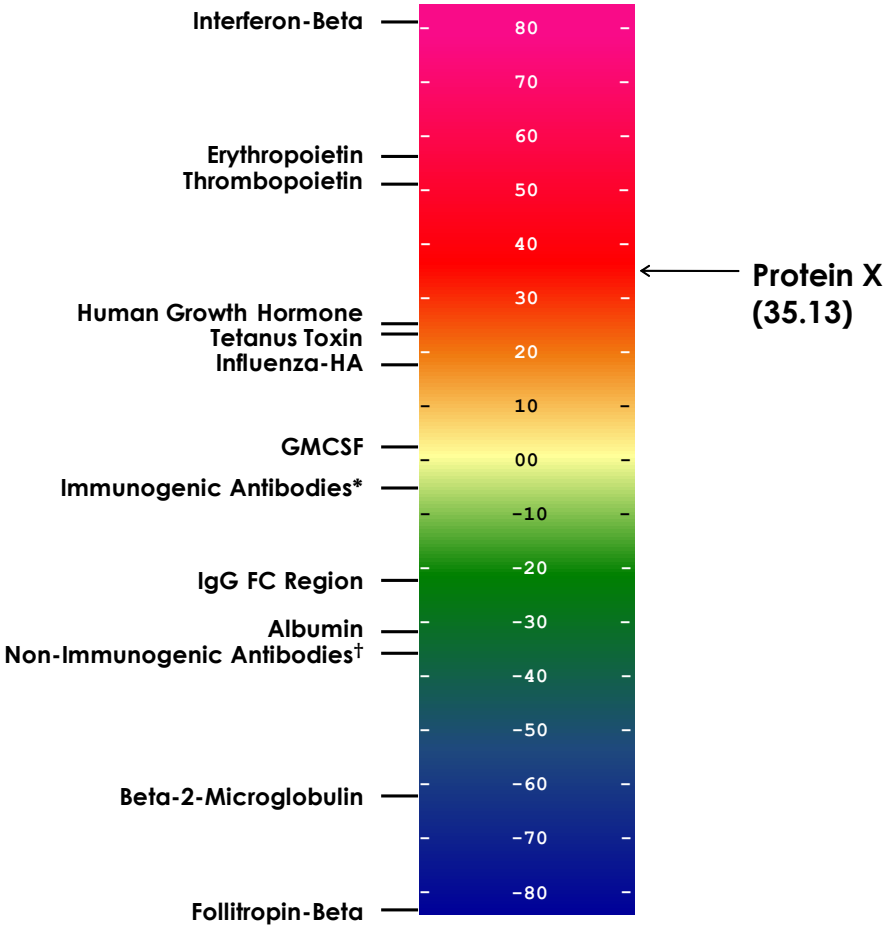


Slide : Courtesy Jad Maamary, Merck

Algorithm-based predictions: Clinical Utility

Protein Therapeutics:	FPX 1	FPX 2	FPX 3	FPX 4
EpiMatrix Score	**21.97**	1.76	-0.76	1.63
Tregitope-adjusted EpiMatrix Score	**21.97**	1.62	-1.76	-111.25
Binding Antibodies	**37%**	7.80%	5.60%	4.50%
Neutralizing Antibodies	**40%**	0.50%	Not Analyzed	0%

Correlation with Observed Immunogenicity Where all confounding factors were controlled in this analysis



Rank ordering of Early Development Candidates

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

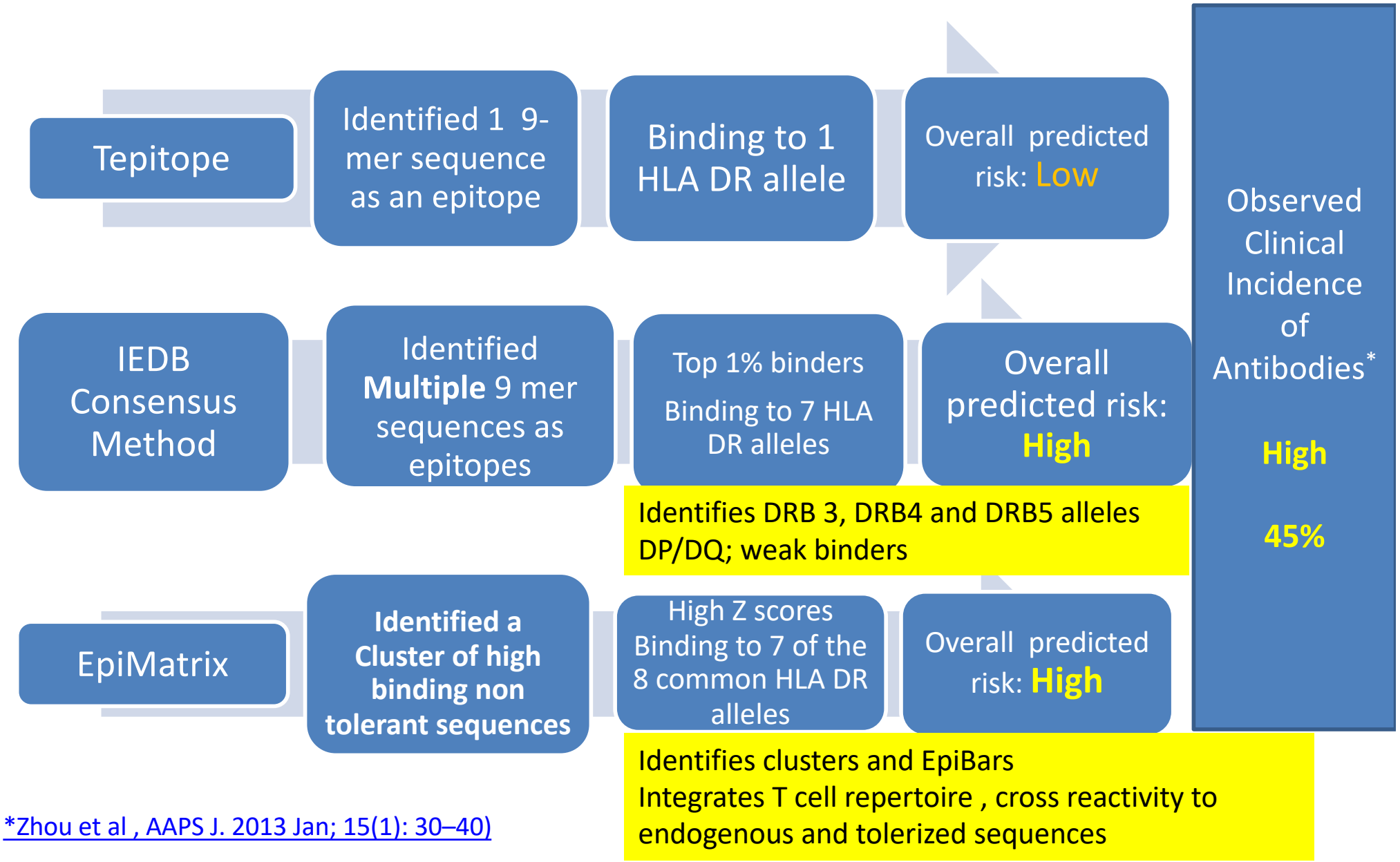
Increasing Prediction Accuracy Using Multiple Platforms

Assessing T-cell dependent immunogenicity

Use in silico with in vitro

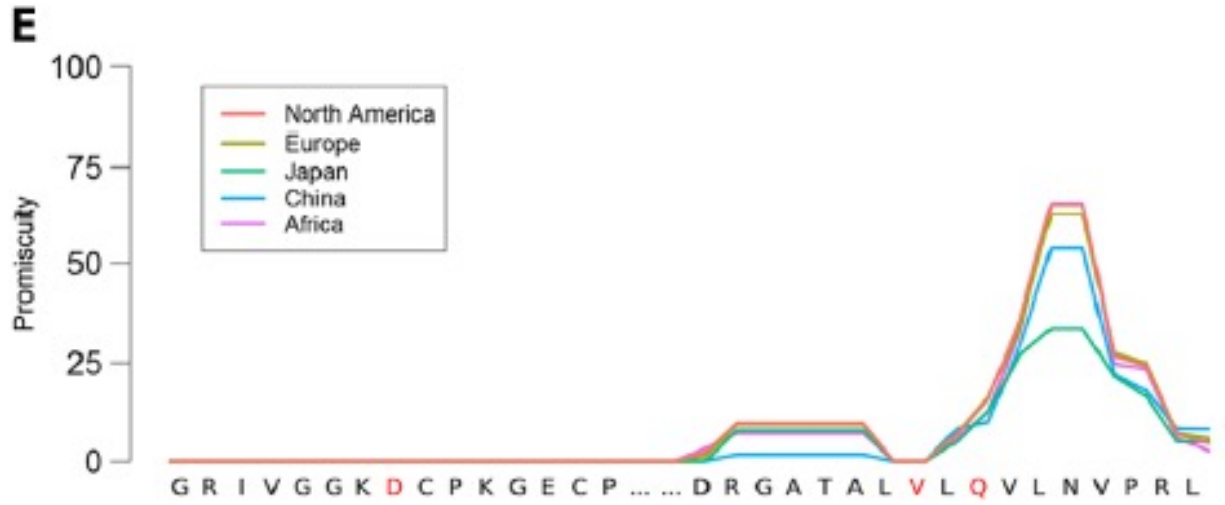
- In silico analysis insures inclusion of diverse HLA alleles and populations (DRB1,DRB3,DP and DQ)
- Understand target mediated immune modulation
- De risk sequences that are cross reactive with endogenous proteins
- Assessing binding at both MHC pocket and T cell receptor binding faces
- Identifying promiscuity scores and binding affinities
- In vitro studies are complementary

Combining Outputs from Multiple Algorithms Help Predict Risk of a Human mAb



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

Identifying Risk of Immunogenicity in a specific population: Good Correlation of Algorithm with Identified HLA Alleles with In Vitro and Clinical Data



Regional and geographic differences are important when planning global clinical trials and in understanding that the potential immunogenicity risk of sequence-engineered molecules might be different for different populations.

The promiscuity scores have been weighted for the MHC-II allele frequency of the North American, European, Japanese, Chinese, and African populations.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH AR T I C L E
Lamberth et al., Sci. Transl. Med. 9, eaag1286 (2017) 11 January 2017 3 of 11

In Vitro T cell assay outputs and their alignment with Clinical Incidence of Immunogenicity

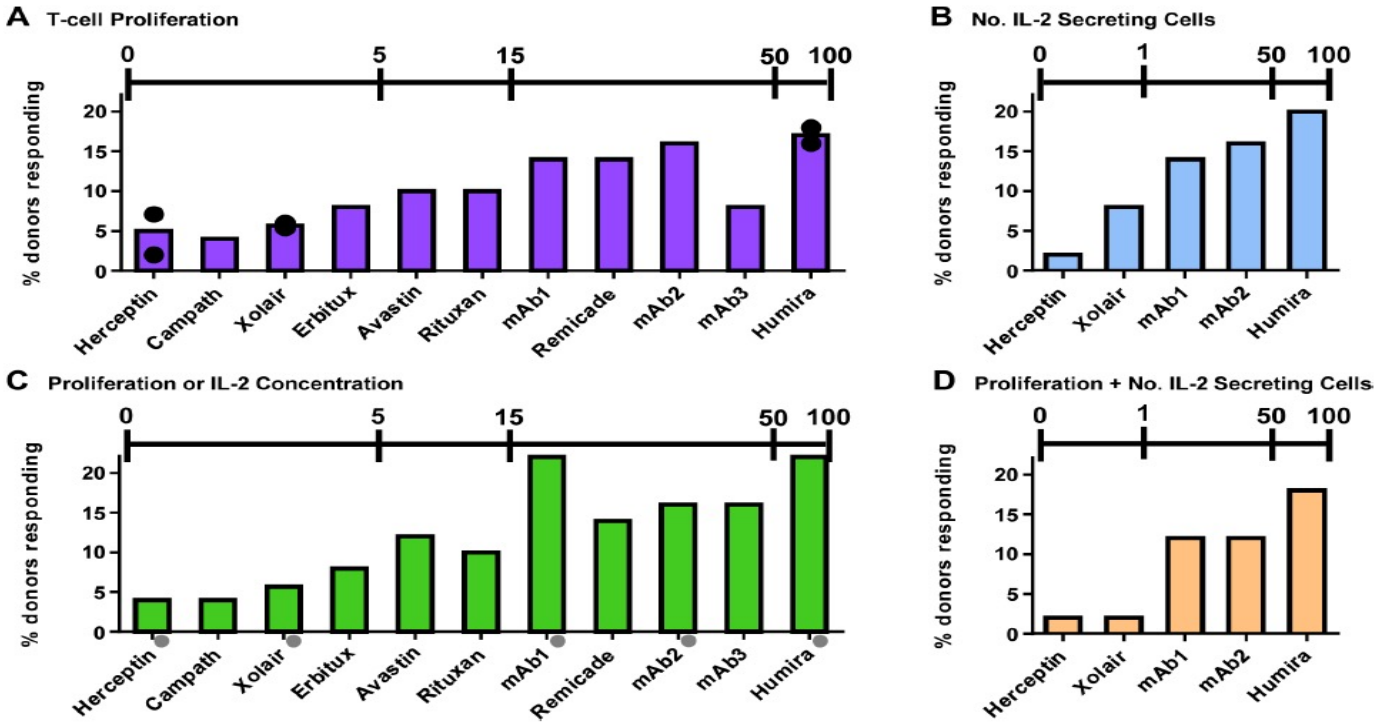
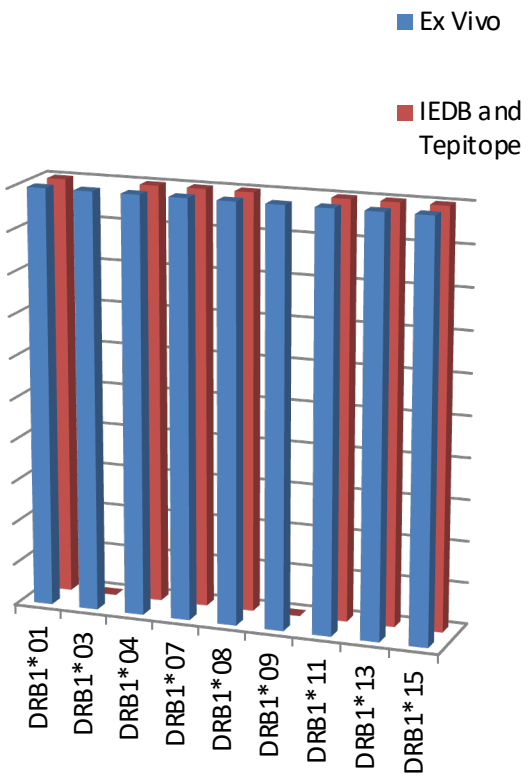


Table 1. Biotherapeutic mAb rates of clinical immunogenicity.

mAb	*Generic*	*Subtype*	*Rate of Clinical Immunogenicity* [a]
Herceptin	trastuzumab	IgG1	0.1% * [b]
Campath	alemtuzumab	IgG1	1.9% **
Xolair	omalizumab	IgG1	0.1%
Erbitux	cetuximab	IgG1	5% *
Avastin	bevaciszumab	IgG1	0–8% *,[c]
Rituxan	rituximab	IgG1	1–23% *,[c,d]
mAb1	NA	IgG2	NT
Remicade	Infliximab	IgG1	13–27% *,[c,e]
mAb2	NA	IgG2	12–16% [f]
mAb3	NA	IgG1	14–50% [f]
Humira	adalimumab	IgG1	1–87% *,[c,e]

Joubert MK, Deshpande M, Yang J, Reynolds H, Bryson C, Fogg M, et al. (2016) Use of In Vitro Assays to Assess Immunogenicity Risk of Antibody-Based Biotherapeutics. PLoS ONE 11(8)

HLA DR alleles confirmed in In Vitro Assays and correlation with Algorithm predicted high binders for Humira (Adalimumab)



78% agreement from Algorithm to In Vitro Observed Responders

Tepitope HLA Predictions

Non-self Sequence: WVSAITWNS
HLA predictions:
DRB1*04
DRB1*11
DRB1*13
Non-self Sequence: VSYLSTASS
HLA predictions:
DRB1*04
Non-self Sequence: IRNYLAWYQ
HLA predictions:
DRB1*08

IEDB HLA Predictions

Non-self Sequence: WVSAITWNS
HLA predictions:
DRB1*04
DRB1*08
DRB1*13
Non-self Sequence: VSYLSTASS
HLA predictions:
DRB1*04
DRB1*11
Non-self Sequence: IRNYLAWYQ
HLA predictions:
DRB1*08
DRB1*13
DRB1*15

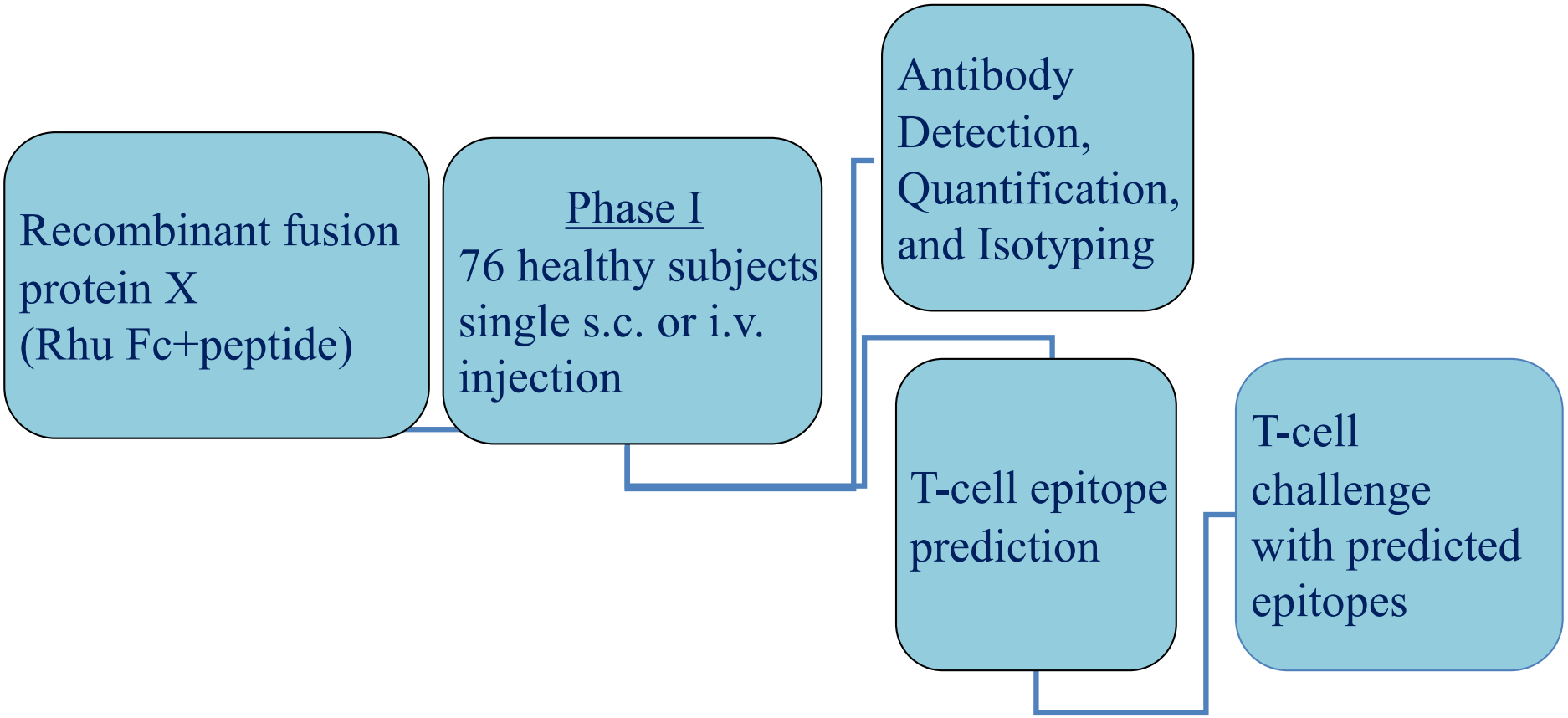
Most of the predicted HLA DR alleles aligned within the 2 algorithms (highlighted green); IEDB was able to identify additional HLA DR Alleles

In Vitro Assay Predicted Additional HLA DR alleles that were not covered by Algorithms

Clinical Phase Studies

VALIDATIONS

Validation of Prediction Strategy: Correlation with Clinical Outcomes



From Koren E,Clinical Immunol (2007);124: 26-32

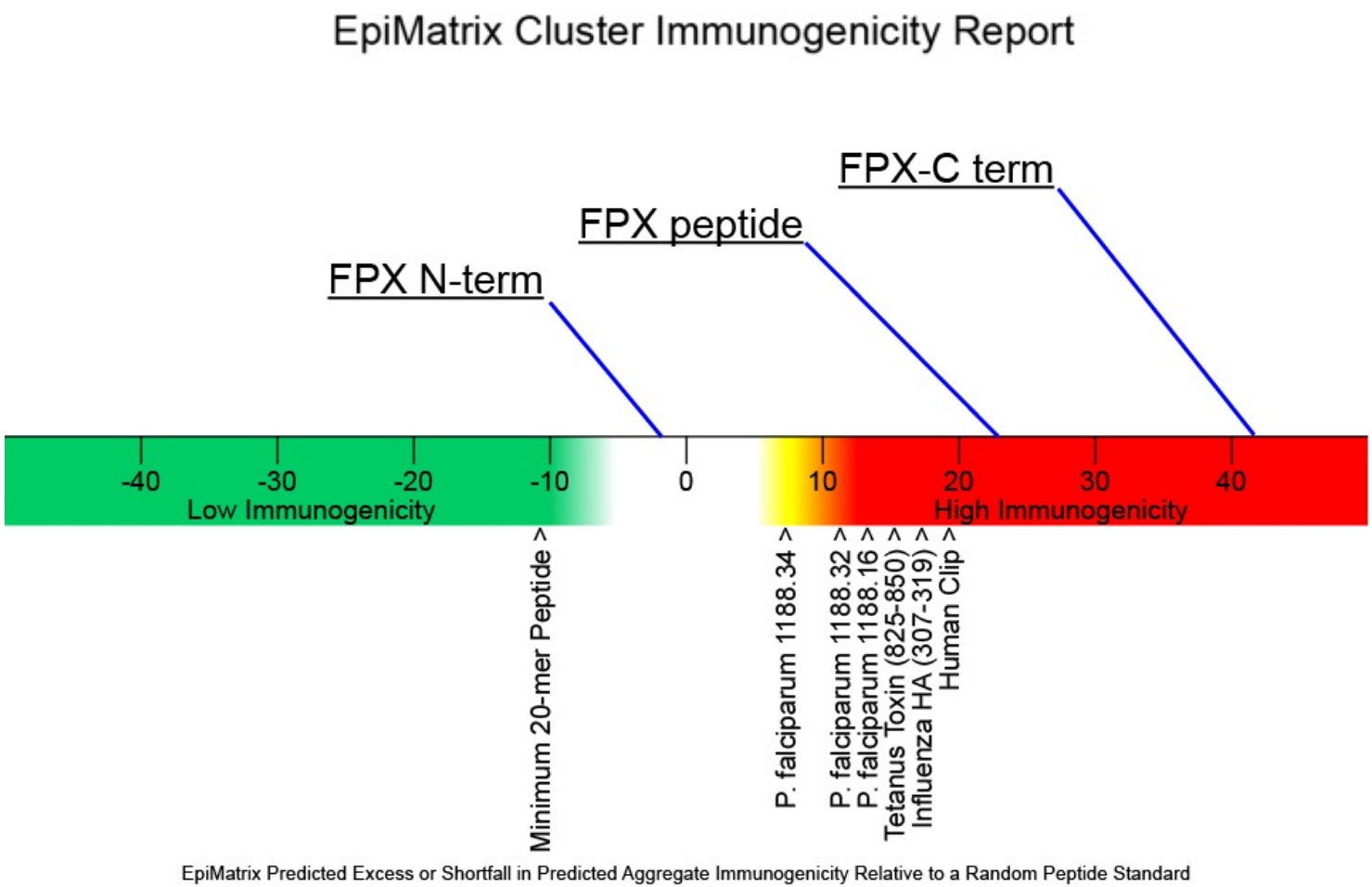
In Silico prediction of T-helper epitopes of the FPX peptides molecule

Class II alleles	DRB1*0101	DRB1*0301	DRB1*0401	DRB1*0701	DRB1*0801	DRB1*1101	DRB1*1301	DRB1*1501
AA Sequence	Z-Score	Z-Score	Z-Score	Z-Score	Z-Score	Z-Score	Z-Score	Z-Score
1 - 9	-0.25	-0.51	-0.38	0.23	1.05	-0.24	0.3	-0.2
2 - 10	-2.83	0.7	-2.03	-0.89	-1.3	-1.72	-1.53	-1.36
3 - 11	0.17	-0.4	-0.54	-0.78	-1.92	-1.54	-0.77	-0.44
4 - 12	-0.36	-1.01	-1.15	-0.01	-1.25	0.47	-0.17	-0.72
5 - 13	-0.85	-1.45	-0.54	-1.07	-0.58	-0.84	-2.55	0.06
6 - 14	-1.15	1.79	-0.01	-0.83	-0.75	-1.17	0.07	-0.78
7 - 15	-1.57	-0.07	-0.24	0.03	-1.04	-0.36	0.52	-0.43
8 - 16	0.63	0.47	-0.05	-1.14	-0.39	-0.11	0.96	0.38
9 - 17	1.34	-0.78	-0.64	1.16	-0.18	-0.61	-0.34	0.61
10 - 18	1.66	0.69	0.94	1.61	1.06	1.73	1.21	-0.07
11 - 19	0.2	1.84	-0.2	-0.19	1.85	0.95	2.49	2.31
12 - 20	0	0.8	0.09	-0.45	0.8	0.62	1.02	1.64
13- 21	0	-0.43	0.39	-0.27	1.24	0.2	0.41	0.33
14 - 22	2.75	0.83	1.87	1.57	1.69	2.1	0.9	1.01
15 - 23	2.53	1.9	1.19	3.35	1.89	2.44	1.5	2.94
16 - 24	0.47	-0.69	-0.91	-0.59	-1.19	-2.02	-0.54	0.06

Koren E, et al Clinical Immunol (2007);124: 26-32

Top 10%* Top 5% Top 1%

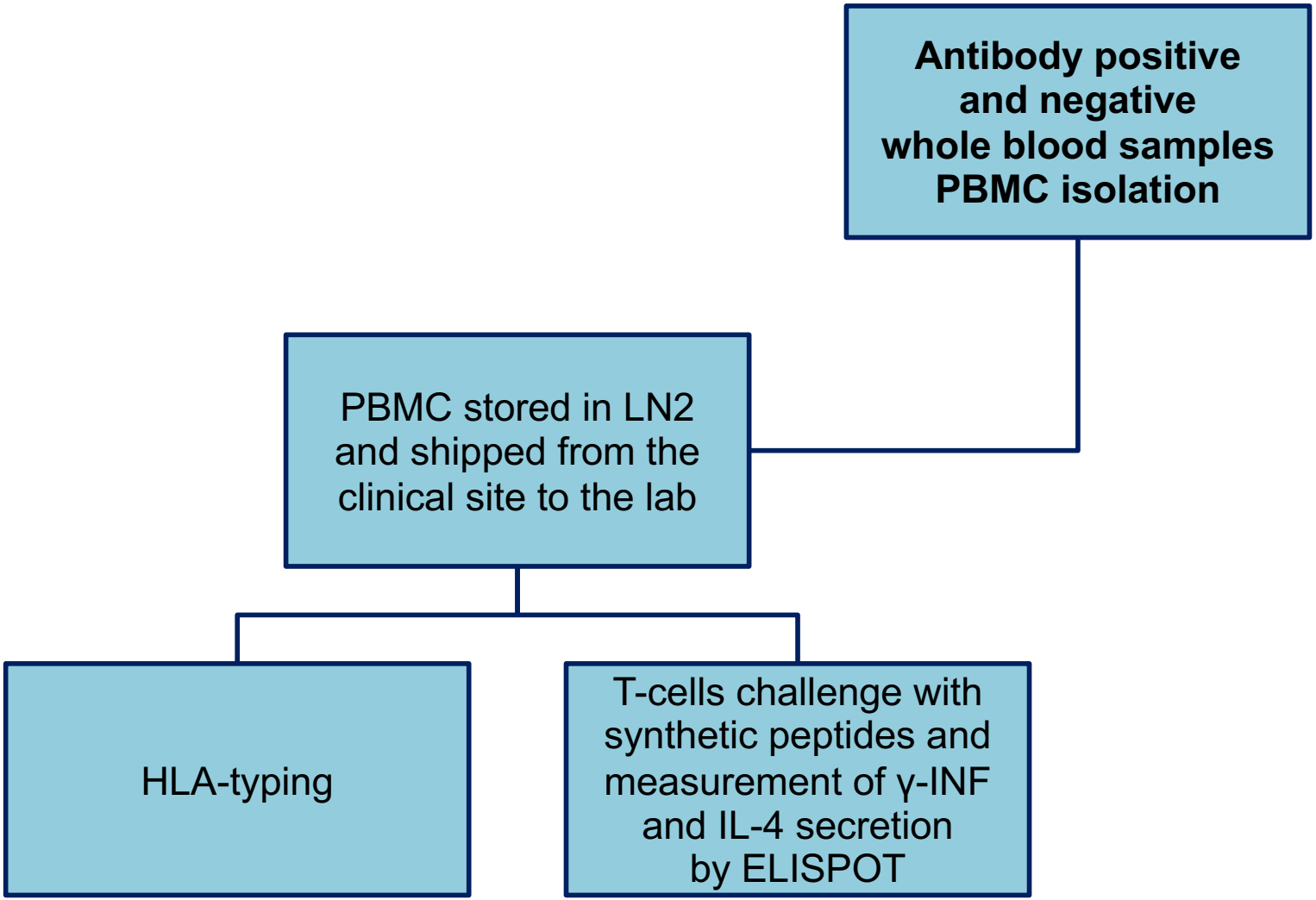
FPX peptide – Preclinical Analysis: Immunogenicity at C terminus



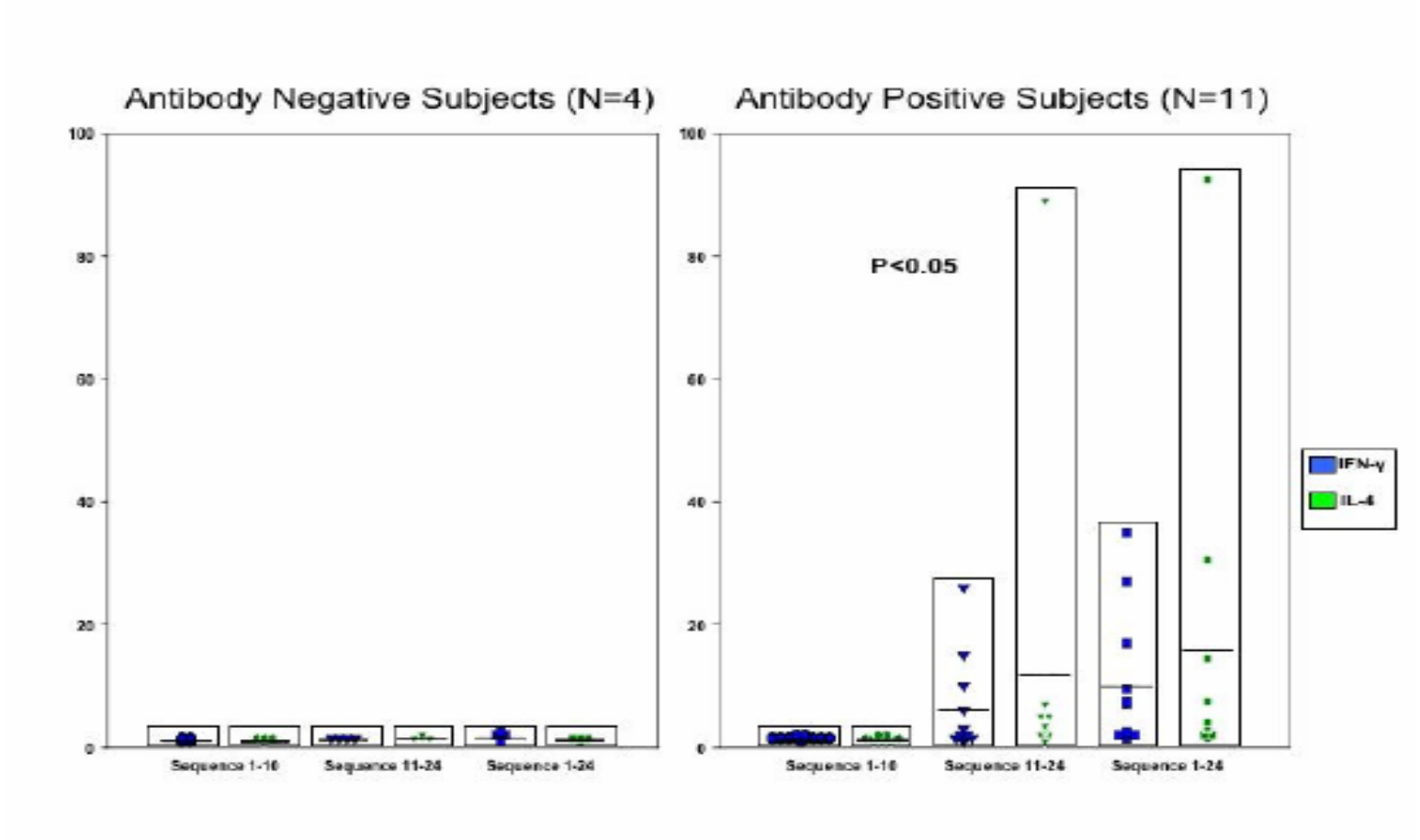
FPX was immunogenic in Phase 1 Clinical Study

	FPX treated			Placebo
	i.v	s.c.	Overall Incidence	
Number of Subjects	36	40	76	24
Antibody Positive Subjects	11 30.6%	15 37.5%	26 34.2%	0

In Vitro T-cell Challenge Study Recall Response from Dosed Subjects (Blinded Study)



An Antigen-Specific T cell Response was observed in Antibody Positive Donors



From Koren E, et al Clinical Immunol (2007);124: 26-32

Strong T Cell response to FPX Peptides was associated with high anti-FPX titers

Subject ID	HLA DRB1	Antibody Concentration (μg/mL)	aa 1-10		aa 11-24		aa 1-24	
			IFN-γ	IL-4	IFN-γ	IL-4	IFN-γ	IL-4
1	*0301/0701	20.2	1.8	0.8	26.0	89.0	34.0	92.0
2	*0101/0103	1.5	1.5	1.8	9.9	4.7	26.6	30.1
3	*0701/1501	1.0	0.6	1.4	14.6	6.8	16.8	14.5
4	*0301	1.1	1.4	1.2	6	4.7	9.4	7.1

Correlation between HLA Haplotype, iTEM , Antibody Concentration and Cytokine secretion

Seq 11-24

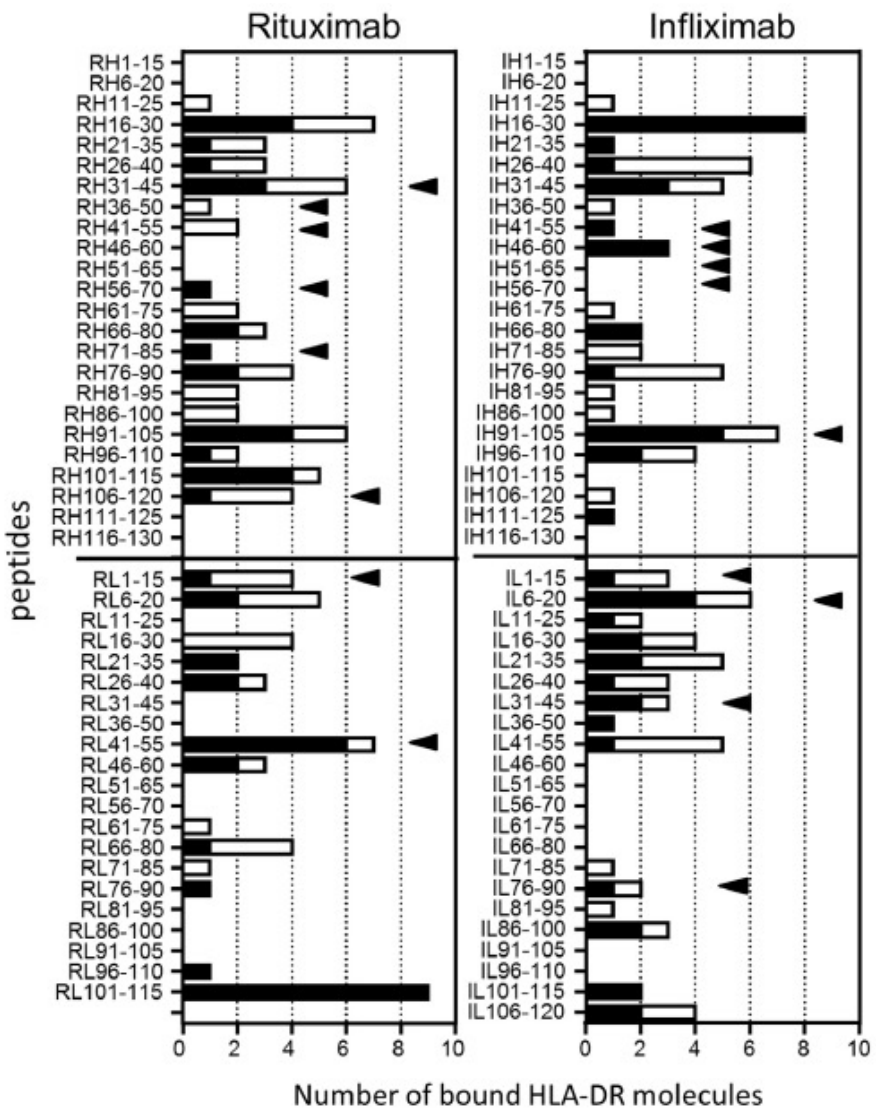
HLA DRB1	iTEM	Ab conc (mg/mL)	IFN-g SFC ratio	IL-4 SFC ratio
*0301/0701	4.75	5.60	1.74	2.60
*0101/0103	2.83	2.80	2.00	3.34
*0701/1501	6.25	20.20	26.0	89.0
*0301	1.67	NA	1.04	1.30

iTEM: Individualized T cell epitope measure

Methods to Improve Correlations

APPLYING MULTIPLE PLATFORM APPROACH TO DATA PUBLISHED IN HAMZE ET AL 2017

Do *in silico* predictions align with *in vitro HLA Binding Affinity* findings?



Hamze et al. 2017

Methods: The observed binders in publication were compared to in silico predictions for the same (15 mer, overlapping) peptides, using EpiMatrix and IEDB consensus prediction methods.

Infliximab and Rituximab

Type of Correlation*	Correlation (Rho)
EpiMatrix / IEDB	**0.60**
EpiMatrix/ Publication	0.42
IEDB/ Publication	0.44

*Note that IEDB (11) has three more predictive models than EpiMatrix and so the correlations are not directly comparable between EMX/IEDB

Results

Overall, EpiMatrix and IEDB show moderate correlations with each other.

Publication results show weak correlation with EpiMatrix or IEDB.

Slide Courtesy: EpiVax

Evaluating Prediction/Binding Discordance

Could the poor correlations be due to assay technique or poor centering of binding motifs in the overlapping 15 mer peptides?

Approach 1: A subset of the peptides tested in publication were synthesized for re-validation in binding assays.
Approach 2: Optimized peptides (with centered motifs) were tested.

- Methods: We synthesized peptides for which published HLA binding assays did not correlate with the in silico (IEDB or EpiMatrix) analysis.

  - Assay technique may have been insensitive.

  → Perform repeat binding assay with same peptides, 7 point curve.

  - Weak binding may be due to poor centering of the binding core.

  → Optimize the peptides. Both Original and Optimized were tested.

Slide Courtesy: EpiVax

Optimizing the Binding Motif in Peptides Improves Binding Results

ORIGINAL

EpiMatrix Cluster Detail Report

RH36-50 Cluster: 36

Frame Start	AA Sequence	Frame Stop	Hydro-phobicity	DRB1*0101 Z-Score	DRB1*0401 Z-Score	DRB1*0701 Z-Score	DRB1*1101 Z-Score	DRB1*1501 Z-Score
36	WVKQTPGRG	44	-1.3	2.26	1.93	1.24	2.31	1.22
37	VKQTPGRGL	45	-0.78	1.89	0.82	1.9	0.56	1.33
38	KQTPGRGLE	46	-1.63	-1.45	-1.83	-1	-0.9	-0.61
39	QTPGRGLEW	47	-1.3	-0.3	-0.29	0.22	-1.07	-0.45
40	TPGRGLEWI	48	-0.41	-1.98	-2.91	-1.66	-1.94	-1.72
41	PGRGLEWIG	49	-0.38	-1.19	-1.31	-1.56	-0.44	-0.59
42	GRGLEWIGA	50	0	-0.14	0.11	0.3	-0.04	0.34

Summarized Results	DRB1*0101	DRB1*0401	DRB1*0701	DRB1*1101	DRB1*1501
Maximum Single Z score	2.26	1.93	1.9	2.31	1.33
Publication Results	B	NB	NB	NB	NB
EpiVax Binding Data IC50 (nM)	1237	32143	TBD	1424	TBD
EpiVax Assessment	B	B	--	B	--

Strong binding motif located at flanks

EpiVax observes two more binders in original peptide

OPTIMIZED

EpiMatrix Cluster Detail Report

RH36-50MOD Cluster: 33

Frame Start	AA Sequence	Frame Stop	Hydro-phobicity	DRB1*0101 Z-Score	DRB1*0401 Z-Score	DRB1*0701 Z-Score	DRB1*1101 Z-Score	DRB1*1501 Z-Score
33	NMHWVKQTP	41	-0.27	-1.53	-0.52	-1.08	-0.07	-0.55
34	MHWVKQTPG	42	-0.19	1.07	0.48	0.26	0.36	0.71
35	HWVKQTPGR	43	-0.35	-0.64	-0.52	-1.05	-0.11	-1.02
36	WVKQTPGRG	44	-1.3	2.26	1.93	1.24	2.31	1.22
37	VKQTPGRGL	45	-0.78	1.89	0.82	1.9	0.56	1.33
38	KQTPGRGLE	46	-0.35	-1.45	-1.83	-1	-0.9	-0.61
39	QTPGRGLEW	47	-0.28	-0.3	-0.29	0.22	-1.07	-0.45
40	TPGRGLEWI	48	-0.09	-1.98	-2.91	-1.66	-1.94	-1.72

Summarized Results	DRB1*0101	DRB1*0401	DRB1*0701	DRB1*1101	DRB1*1501
Maximum Single Z score	2.26	1.93	1.9	2.31	1.33
EpiVax Binding Data IC50 (nM)	192	4444	422	206	TBD
EpiVax Assessment	B	B	B	B	--

Optimized Peptide has a centered binding motif

With optimized version, we find **more** binders with **stronger** affinities

Slide Courtesy: EpiVax

Reassessment of Correlations with Optimized HLA binding Assays and Peptides

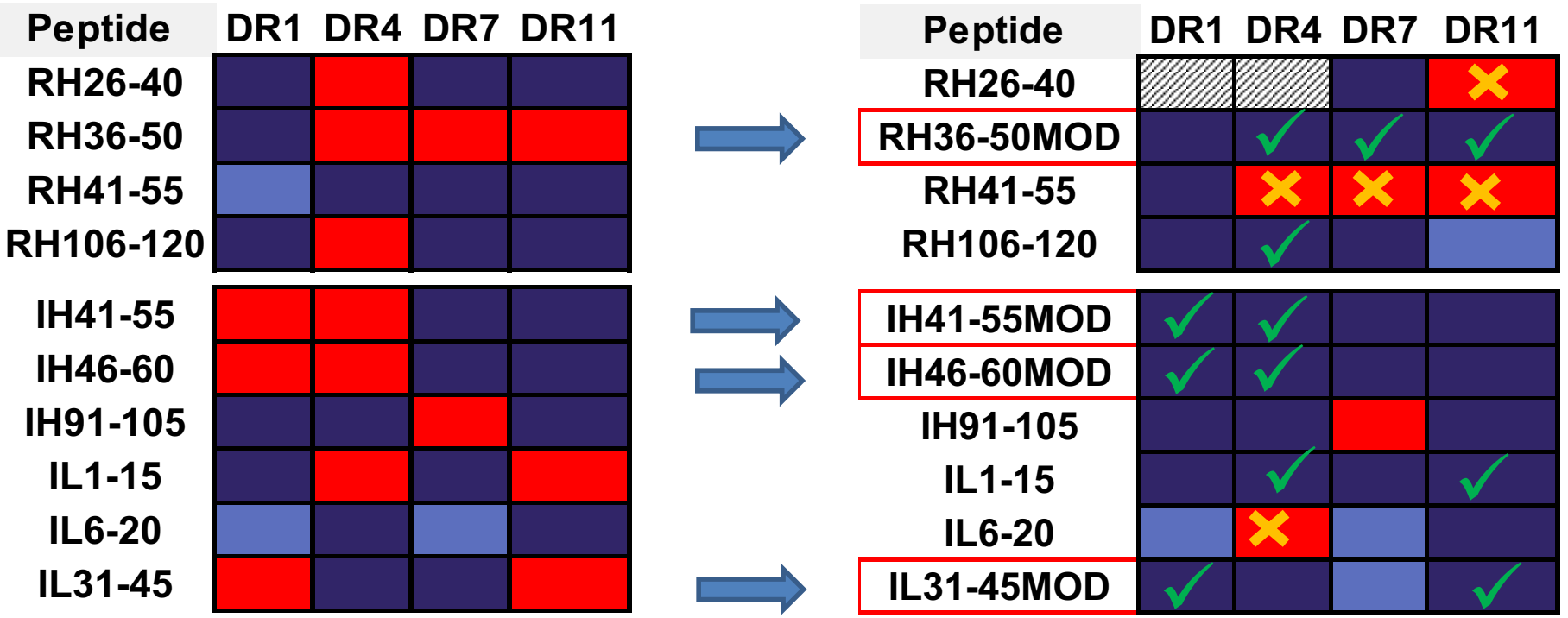
Published

EpiMatrix predictions vs. publication binding results

New Binding and Optimized

Two Variables tested:

- Our Binding Assay
- Modified Peptides



Agreement at top 5 and 10%: 65% (26/40)

Agreement at top 5 and 10%: 84% (32/38)**

True Predictions (TP, TN)

Binders Agree at 10% "Near-miss"

False Predictions (FP, FN)

**Data Collection in Process

Slide Courtesy: EpiVax

Slide Courtesy: EpiVax

*Modified for charge/avoid synthesis flags

Algorithms and In Vitro Assay Outcomes

Population level threshold for peptide immunogenicity

Rituximab	TP	FP	FN	TN	Accuracy	Odds Ratio	Fisher's Exact (2 tailed)
EpiMatrix Cluster Score≥10	**2**	3	7	**33**	**78%**	**>1**	0.57
Accounting for High human cross-conservation	**2**	2	7	**34**			
Considering patient HLA (5%)	**5**	2	4	**34**			
Considering patient HLA (10%)	**8**	2	1	**34**	**93%**	**>1**	**P<0.01**

Considering responding donor HLA, we can explain 5 of 9 positive responses at a strict EpiMatrix threshold of 5%, and 8 of 9 at a more relaxed threshold of 10%.

Using JanusMatrix Algorithm, adjust for human cross-conservation (tolerated epitopes) and improve True Negative count

Infliximab	TP	FP	FN	TN	Accuracy	Odds Ratio	Fisher's Exact (2 tailed)
EpiMatrix Cluster Score≥10	**3**	1	6	**36**	**85%**	**>1**	**0.02***
Accounting for High human cross-conservation	**3**	0	6	**37**			
Considering patient HLA (5%)	**8**	0	1	**37**			
Considering patient HLA (10%)	**8**	0	1	**37**	**98%**	**>1**	**P<0.01**

Most IFX positive responses were explained by donor HLA at EpiMatrix standard threshold. JanusMatrix reclassified one FP to TN.

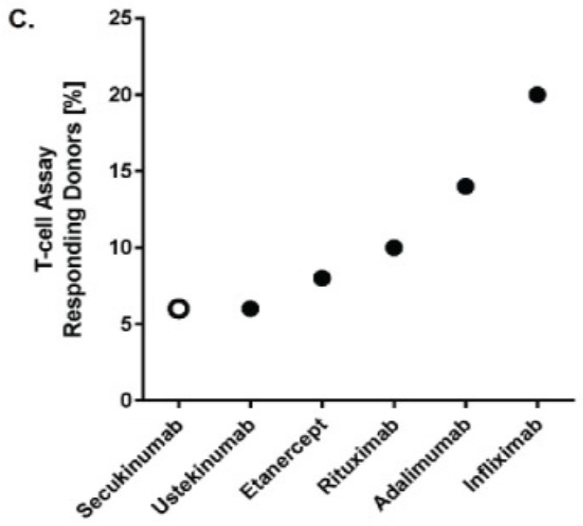
Slide Courtesy: EpiVax

Summary of T cell Assay Findings

- Overall, predictive accuracy ranges from **78% to 85%*** for Rituximab and Infliximab, respectively.
- False Positive and False Negative correlations are due to HLA-specificity; post-hoc evaluation accounting for HLA restrictions in the results improves correlations as can be expected.
- In vitro T cell assays as performed **correlated with in silico analysis for 16/18 of the** CD4 T cell epitopes found in the study.
- Take away message: **In silico assessment is a useful first step to immunogenicity analysis, and evaluations such as the one performed here, post hoc, reveal significant correlation with in vitro results.**

MAPPS and In Silico – *Different Timelines* Complementary Technologies / Similar results

- MAPPS – Months?



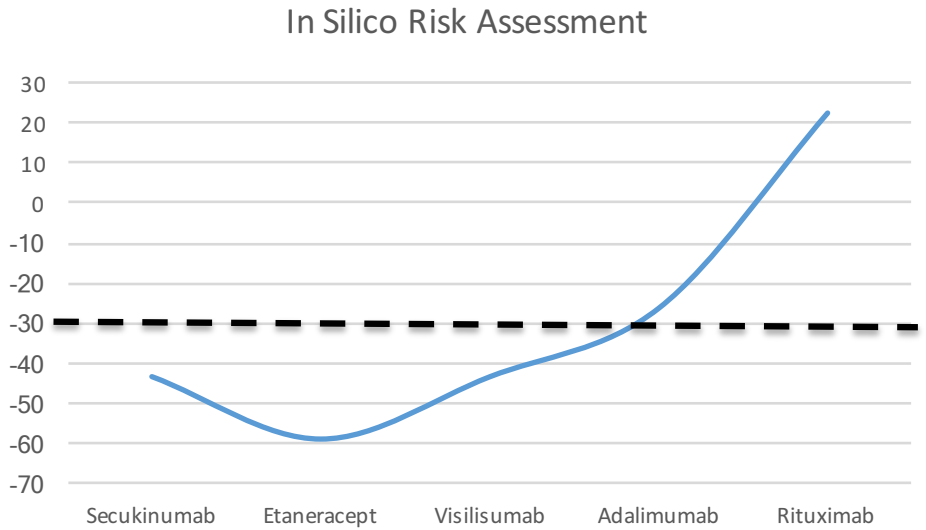
MAbs. 2016 Apr; 8(3): 536–550. PMCID: PMC4966846
Published online 2016 Jan 28.
doi: 10.1080/19420862.2015.1136761

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 ▶

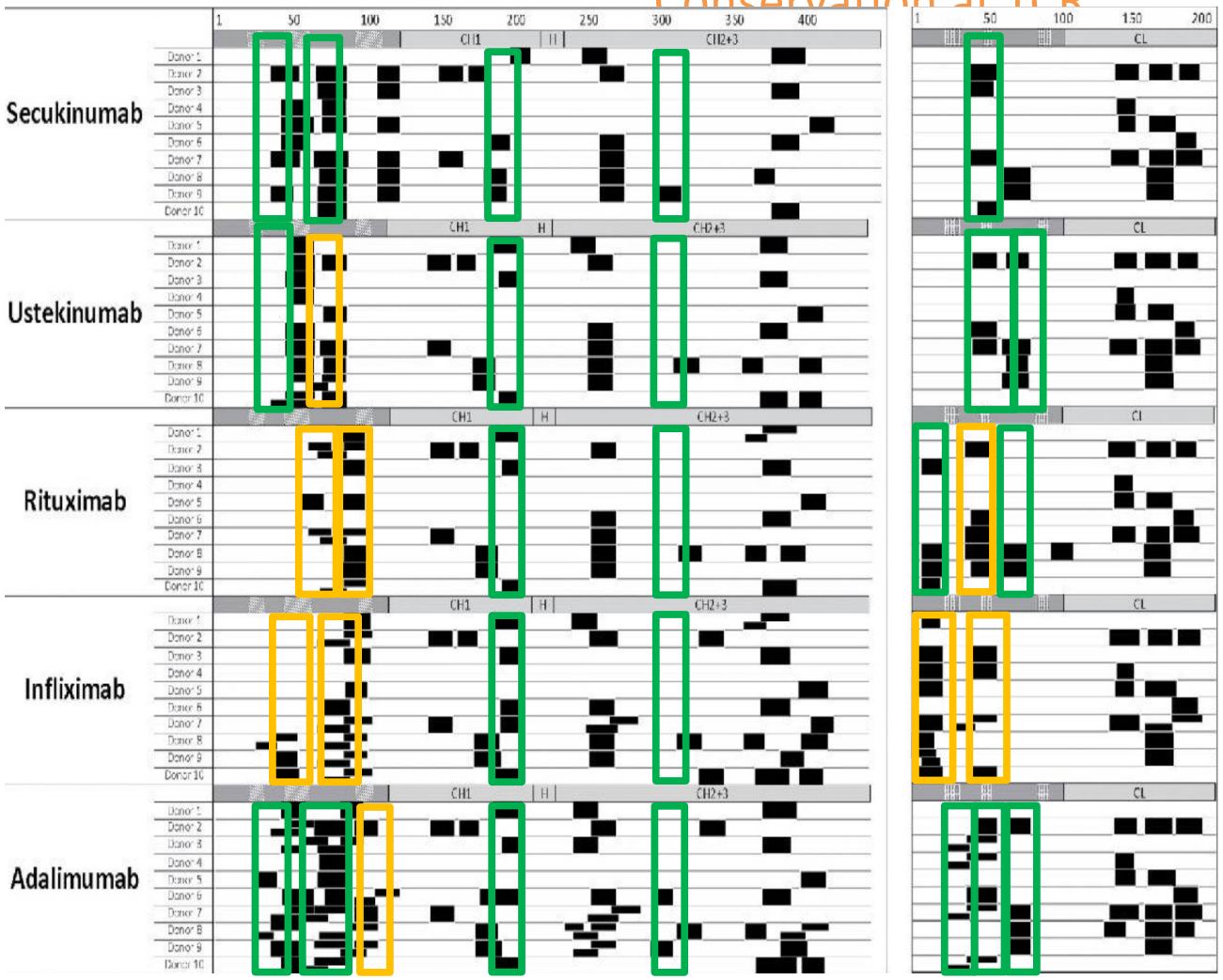
- ISPRI in silico assessment 60 minutes



In silico Risk Assessment can be higher throughput and lower cost while giving similar results to MAPPS

MAPPS vs. ISPRI-Predicted "Public" Epitopes

Yellow = Low Human X-conservation at TCR. Green – Tregitope or High Human X Conservation at TCR

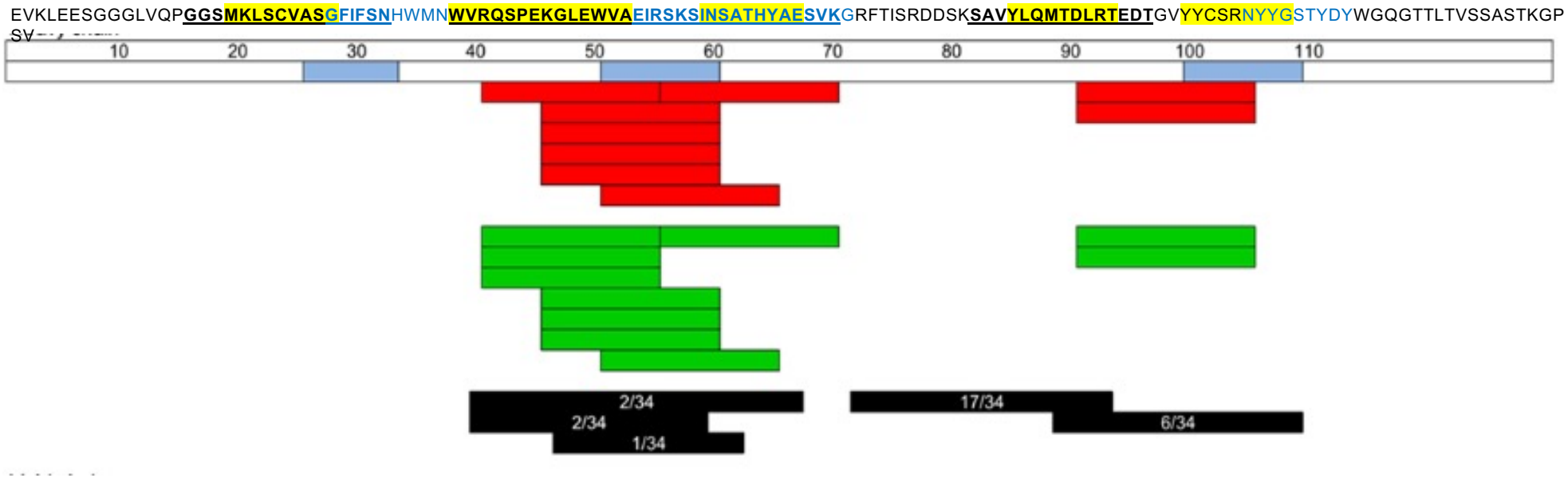


Green Box:
JanusMatrix ≥3 or Tregitope

Yellow Box:
JanusMatrix <3

HLA DR Binding T cell epitopes and Consistency Across In Silico, In Vitro and Clinical Readouts for Infliximab

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. Yellow highlighted regions are clusters with a >4 HLA DR allele binding and high Z score

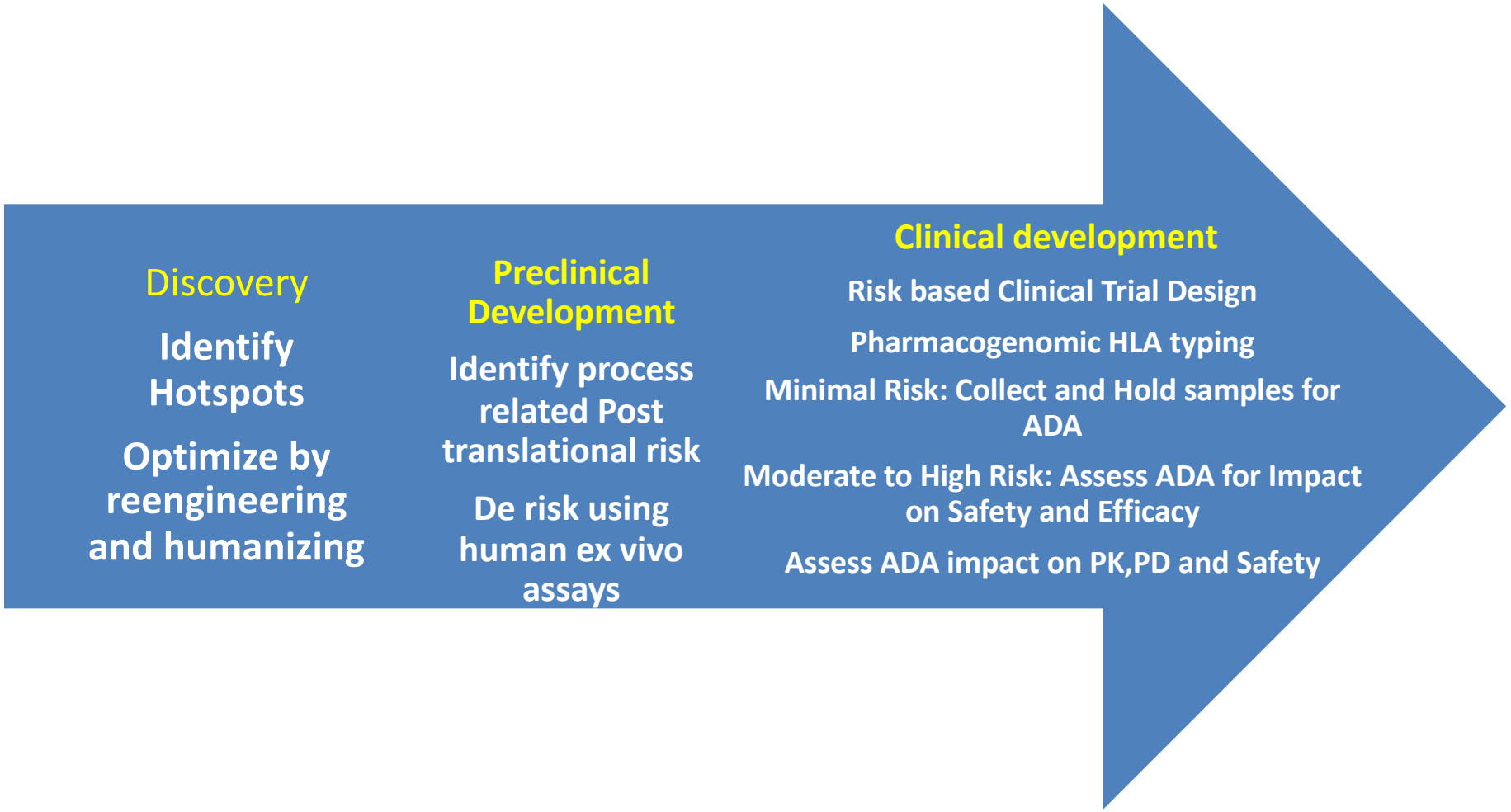
Hamze M, Meunier S, Karle A, Gdoura A, Goudet A, Szely N, Pallardy M, Carbonnel F, Spindeldreher S, Mariette X, Miceli-Richard C and Maillère B (2017) Characterization of CD4 T Cell Epitopes of Infliximab and Rituximab Identified from Healthy Donors. Front. Immunol. 8:500. doi: 10.3389/fimmu.2017.00500

Summary of Algorithms and MAPPS Assay Findings

- For both Infliximab and Rituximab, given relative positions of eluted sequences, **in silico analysis "population-based epitope clusters" do overlap with eluted peptides** and CD4 T cell epitopes, but exact address not given, and we are missing the HLA type of the donors which could skew results.

Slide Courtesy: EpiVax

Decision Flow and Impact on Clinical Trial Design



Inclusion of patient HLA alleles in the statistical analyses of the clinical data from the patient

Considerations for Standardization/Benchmarking Algorithm Based Tools

- Source of Data for Machine Learning Tools
  - Curated sequences from literature : Are they reliable or do they need further validation?
    Quality of sequences would drive the quality of machine learning tools
  - Should there be standard sequences for benchmarking?
    - Promiscuous HLA binding sequences; known T cell epitopes
    - Germline sequences; tolerated /induce tolerance?
- Reporting
  - Consistency across tools
  - Z scores vs. Top binders based on affinity vs. Allele promiscuity
  - Coverage of alleles from global population
- Validation
  - Peptide design (overlapping peptides vs. optimized peptides)
  - Confirm with HLA binding in vitro assays
  - MAPPS assays to confirm if predicted sequence is also eluted at the predicted HLA DR pocket
  - T cell activation readouts (memory and recall) with peptides designed based on algorithm based predictions

Better Benchmarking Effort would lead to Strong Correlation between Algorithm based Predictions to In Vitro and Clinical Readouts

Considerations for Standardization/Benchmarking In Vitro Tools

- Source of Peptides/Proteins
  - Identify Control proteins/peptides with high promiscuity and affinity for HLA binding
  - Identify control proteins/peptides with low/no promiscuity and affinity for HLA binding
- Specific HLA DR binder controls
- Healthy and Diseased State Influence
  - HLA DR predisposition
  - Homozygous vs Heterozygous HLA DR allele binders
  - Weak, intermediate and strong binding affinities
  - Antigen Processing and Proteolytic activity
- T cell Repertoires
  - Cross reactivity to previously exposed antigens

Take Home Messages

- Robust Immunogenicity Risk Assessment Can Enable a more Informed Clinical trial
- AAPS Focus Groups Have Been Actively Involved in Standardization and Benchmarking Efforts of the Predictive Tools and their correlation to Clinical Outcome
- Value of Preclinical risk assessment tools is Evident in
  - Identification of problem regions and opportunity to optimize during early discovery
  - Rank ordering of variants to pick the least risky candidate for further development
  - Estimating the proportion of the population at potential risk for immunogenicity
  - Stratifying patients in clinical trials for more effective monitoring of safety and efficacy
- Discordance between predictive tool outputs has been noted and need further optimization
- Lack of understanding around antigen processing aspect of the immune response
- Prediction of an ADA positive responses does not mean it is impactful and relevance of the response requires additional analysis

- **Value Provided**
  - Drive a more informed clinical trial where subjects at risk based on their HLA can be monitored for safety related endpoints
  - Stratification of data and the possibility of using HLA typing as a biomarker if some HLA variants are associated with high prevalence of immunogenicity.

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      - Jochem Gokemeijer

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