Prediction and Validation of Immunogenicity and Tolerance to Generic Peptides & Impurities

Anne S. De Groot MD

CEO/CSO, EpiVax, Inc.
Professor, Senior Scientist
Center for Vaccines and Immunology
University of Georgia (Athens)

Prepared for FDA OGD January 26th 2021

Annie De Groot M.D. CEO/CSO

https://www.fda.gov/drugs/news-events-human-drugs/non-clinical-immunogenicity-assessment-generic-peptide-products-development-validation-and-sampling

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FDA Draft Guidance 2017: T cell epitopes

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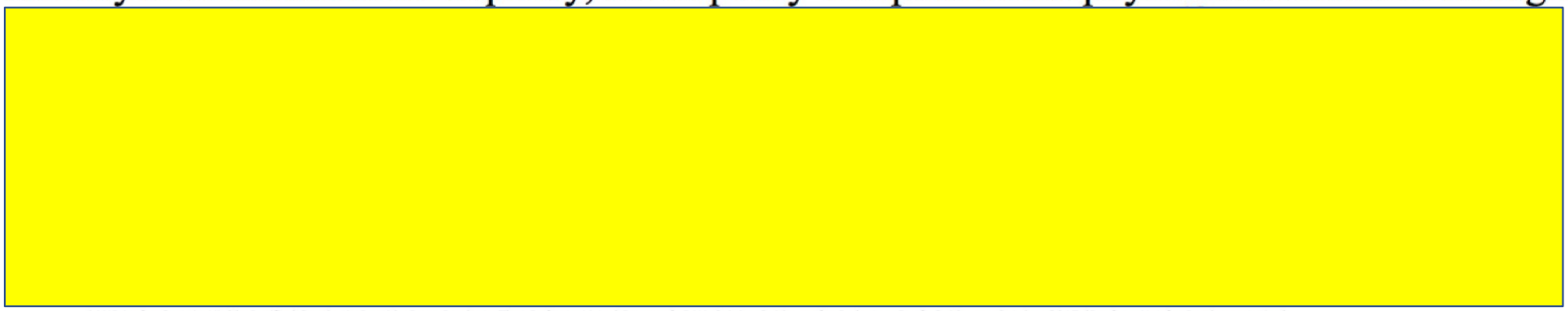
ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*

For each new specified peptide-related impurity that is not more than 0.5 percent of the drug substance, the ANDA applicant should characterize the impurity. Further, the ANDA applicant should provide justification for why such impurity does not affect the safety of the proposed generic synthetic peptide (including with respect to immunogencity) and why it does not affect its effectiveness. This justification should take into consideration, among other things, the identity and amount of an impurity, the impurity's impact on the physicochemical and biological



*ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin, Guidance for Industry, Draft Guidance, October 2017 (Draft — Not for Implementation), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578365.pdf

Immunogenicity Risk Assessment Of Peptides (using tools developed for Proteins)

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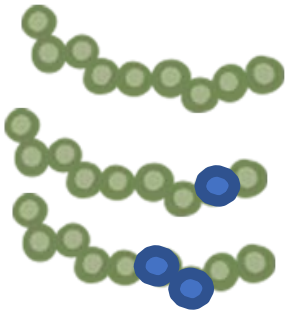
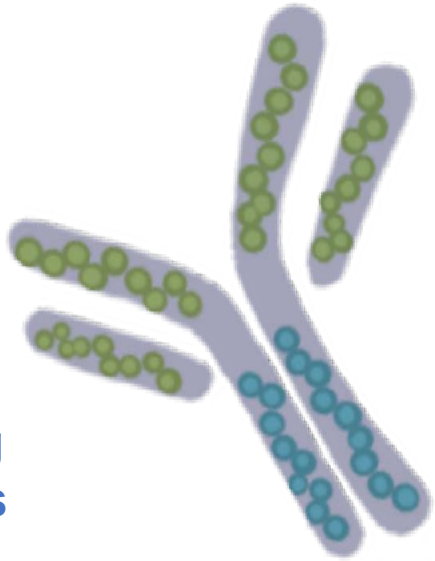


FDA:
Generic Peptide Impurities... should be assessed for T cell epitope-related Immunogenicity risk.

OK, so,
Develop a comprehensive program for assessing immunogenicity risk building on decades of experience with biologics



Peptide Accelerated New Drug Application

Latest AAPS "White Paper" on Immunogenicity Risk Assessment

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Impact Factor 5.085 | CiteScore 5.4
More on impact ›

frontiers in Immunology | Vaccines and Molecular Therapeutics

SYSTEMATIC REVIEW ARTICLE
Front. Immunol., 30 June 2020 | https://doi.org/10.3389/fimmu.2020.01301

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7,011
TOTAL VIEWS

Am score 159

View Article Impact

T-Cell Dependent Immunogenicity of Protein Therapeutics Pre-clinical Assessment and Mitigation—Updated Consensus and Review 2020

Vibha Jawa[1], Frances Terry[2], Jochem Gokemeijer[3], Shibani Mitra-Kaushik[4], Brian J. Roberts[2], Sophie Tourdot[5] and Anne S. De Groot[2,6*]

EpiVax PANDA (Peptide ANDA) Team Members

Annie De Groot, MD
Founder, CEO/CSO, EpiVax Inc

Brian J Roberts, PhD
Associate Scientific Director,

Frances Terry, MPH
Director of Analysis in Immunoinformatics

William Martin,
COO/CIO

EpiVax PANDA team members: Christine Boyle, Holly Clifford, Beth McGonigal, Shah Miah, Sandra Lelias, Chris Talbot, Olivia Morin, Heather Stuart, Mitchell McCallister, Jacob Tiven, and Matt Ardito.

Analyzing Immunogenicity in Peptides/Impurities

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- Why do Immunogenicity Screening of Peptides?
- How to do it – In Silico and In Vitro
- Special tools that evaluate “tolerance” and find Treg Epitopes
- FDA Case Studies: Calcitonin and Teriparatide (Impurities)

Start with In Silico Analysis
Change to HLA binding affects T cell activation

Epitope Prediction
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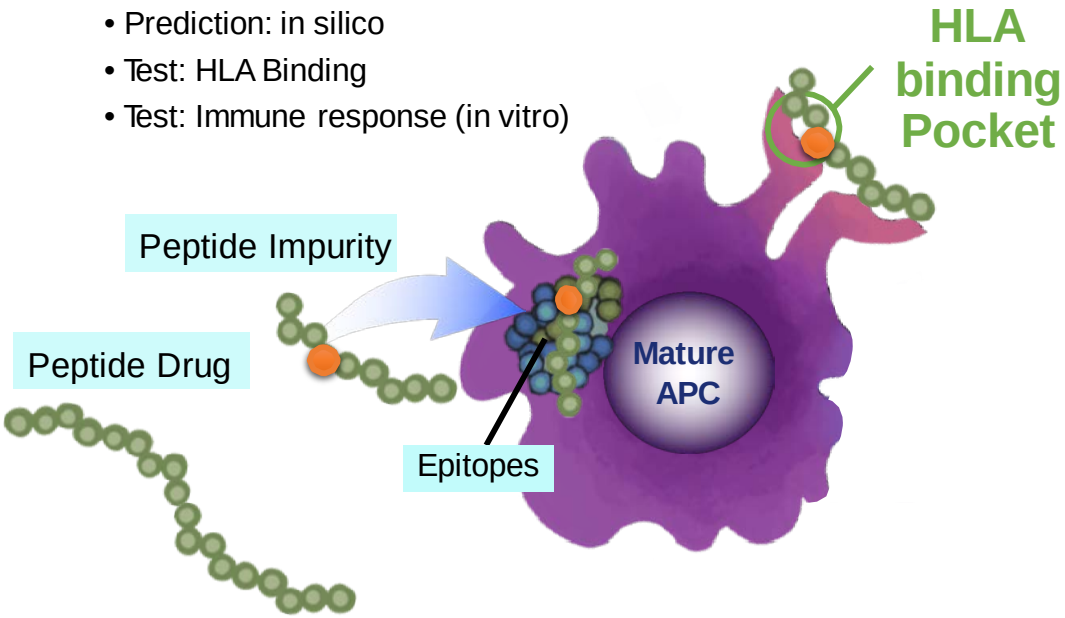
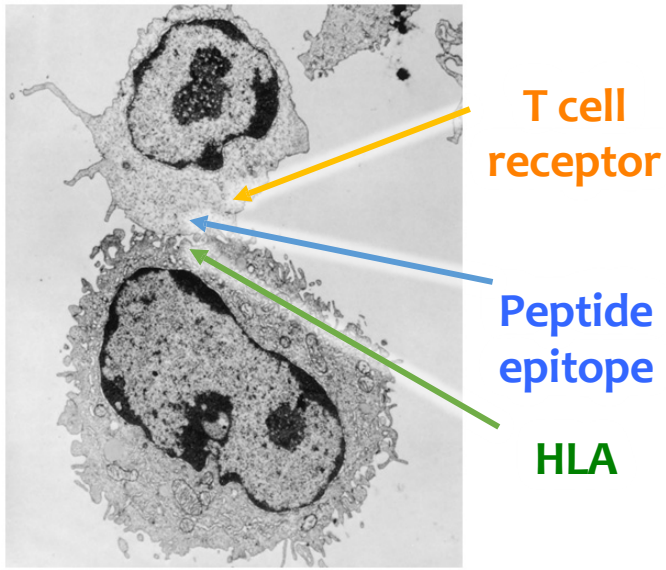
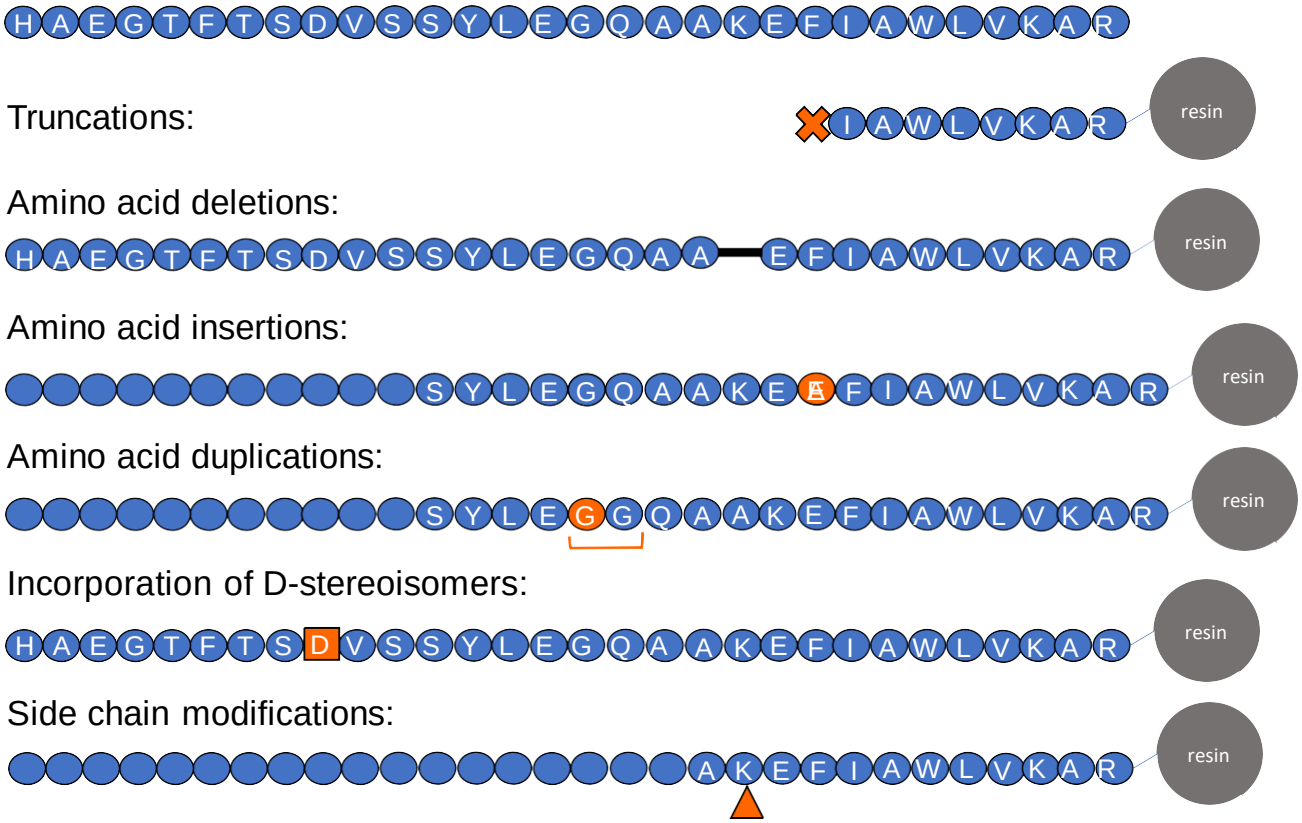
- Impurity can bind and trigger immune response
  - Prediction: in silico
  - Test: HLA Binding
  - Test: Immune response (in vitro)

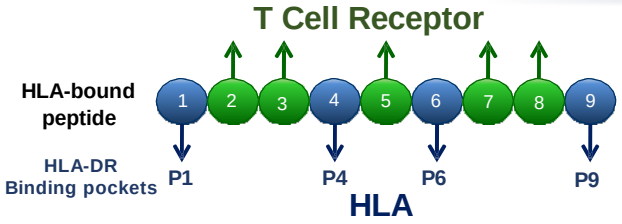




Peptide Drugs and their Manufacturing-related Impurities

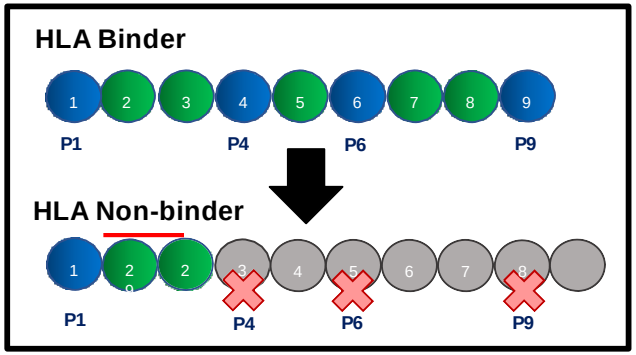


Peptide Impurities modify HLA binding
E.g. Duplications, on Potential for Immunogenicity



Example Impurity - Duplication of Amino Acid 2:

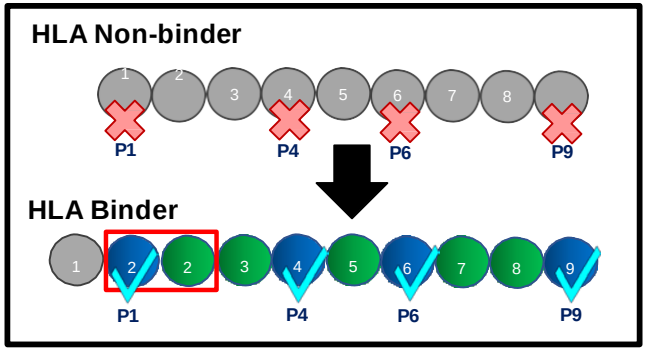
Scenario 1: Binderà **Non-binder**



results in a peptide that will no longer bind HLA by shifting subsequent amino acids out of phase

Loss of immune response?

Scenario 2: Non-binderà **Binder**



results in a peptide that will now bind HLA by shifting subsequent amino acids into phase

New Immunogenic Impurity

Outline – Analyzing Immunogenicity in Peptide Drugs

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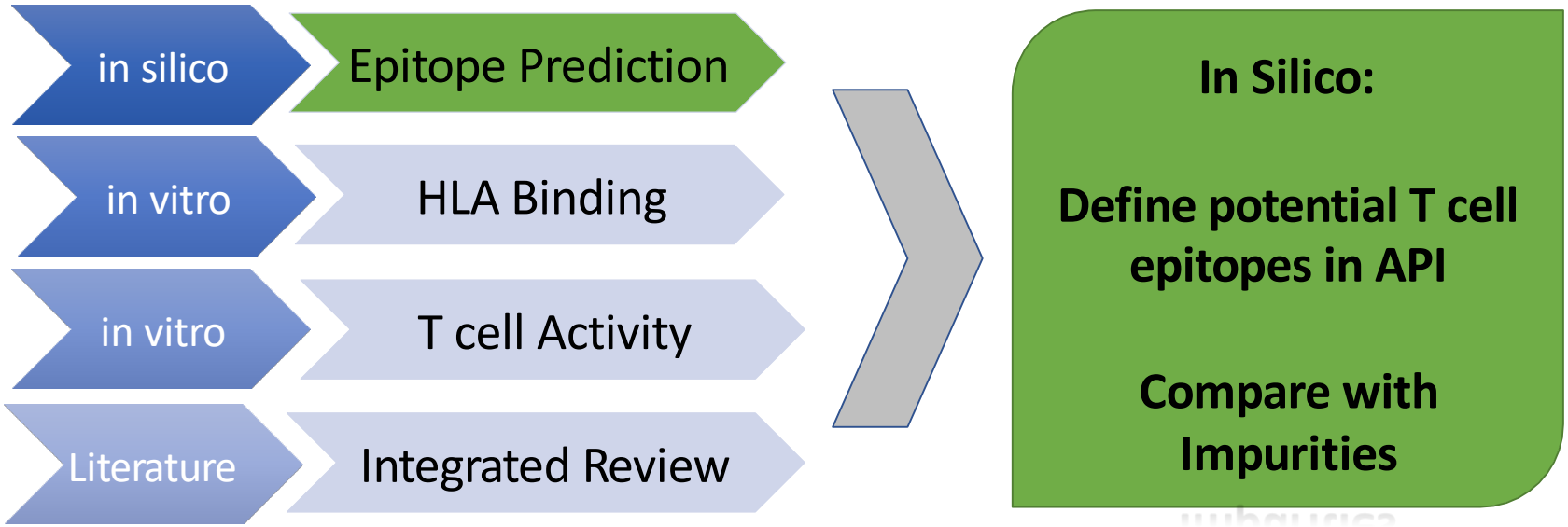
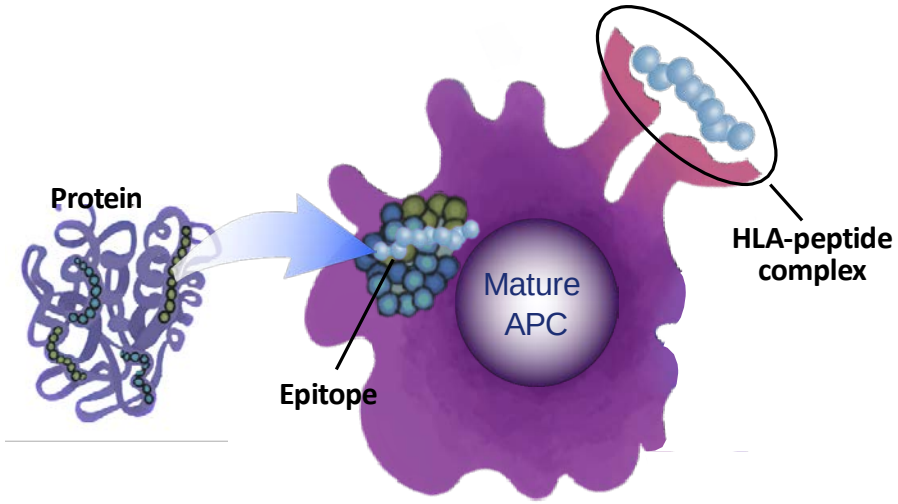
- Why do Immunogenicity Screening of Peptides?
- How to do it – In Silico and In Vitro
- Special tools that evaluate “tolerance” and find Treg Epitopes
- Case Studies: Calcitonin and Teriparatide (Impurities)

Four step approach to Peptide Drug Impurities

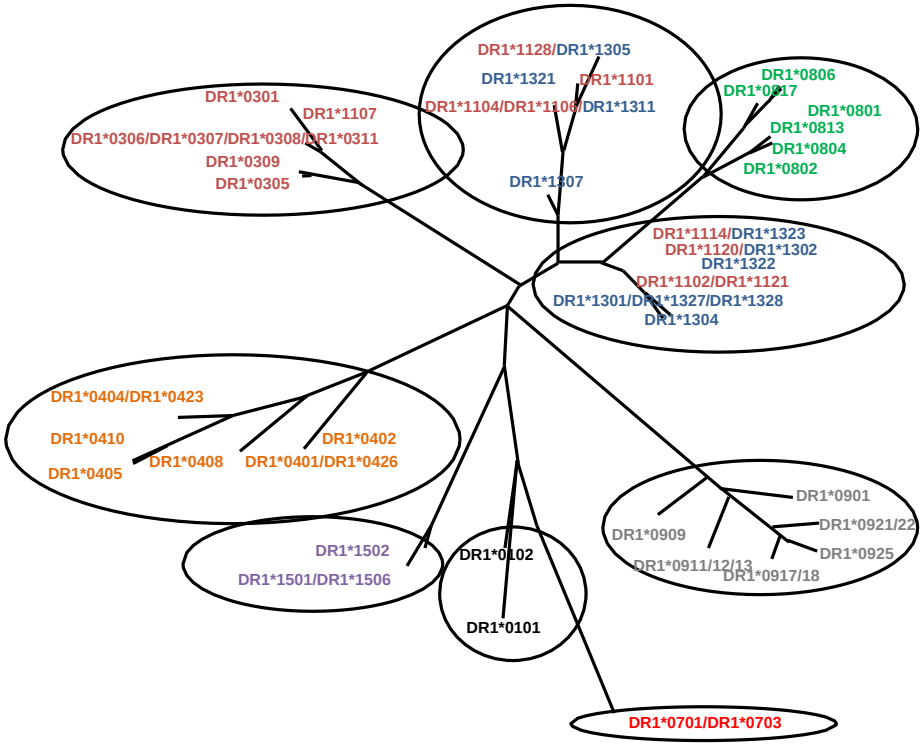


How to predict HLA binding of impurities EpiMatrix was developed and is curated by EpiVax

- EpiVax proprietary algorithm: **EpiMatrix**
  - Matrix-based algorithm for predicting linear T cell epitopes
- EpiMatrix™ predicts both class I and **class II HLA** binding potential



Class II HLA DR "Supertypes"



EpiMatrix tests for binding potential to the most common HLA molecules within each of the "supertypes"* shown to the left.

Supertypes comprise families that have similar binding pocket preferences – specific amino acid side chains fit into their HLA binding pockets.

*Lund et al. Definition of Supertypes for HLA Molecules Using Clustering of Specificity Matrices. Immunogenetics. 2004; 55(12):797–810.

**Southwood et al. Several Common HLA-DR Types Share Largely Overlapping Peptide Binding Repertoires. J Immunol. 1998; 160(7):3363–73.

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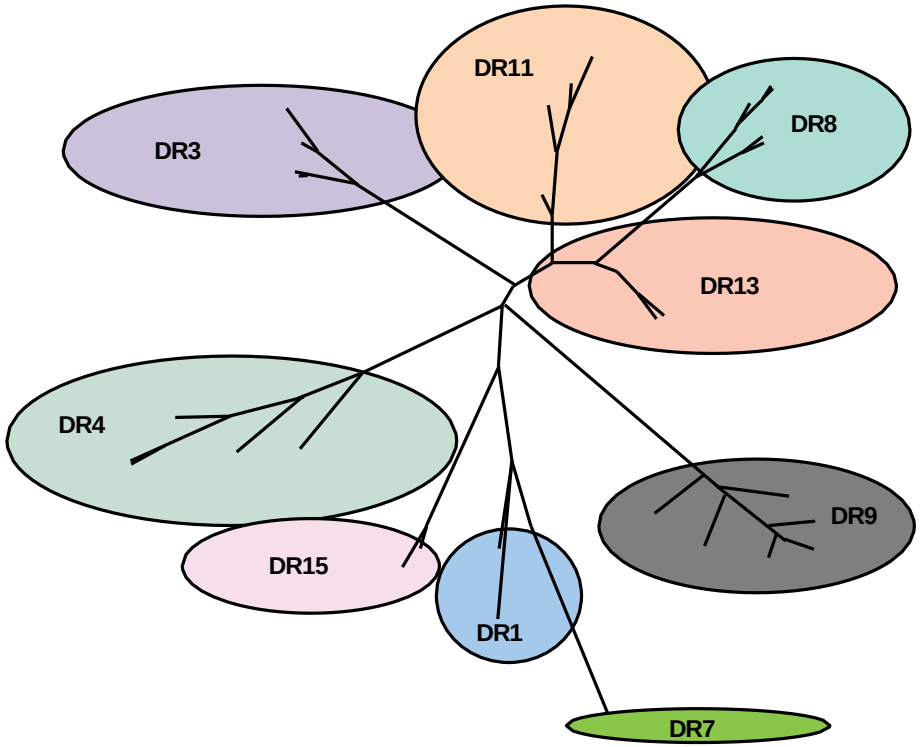

Analyzing sequences for "supertype" HLA DR binding motifs allows us to provide results that are representative of >95% of human populations worldwide without needing to test each haplotype individually.**

*Lund et al. Definition of Supertypes for HLA Molecules Using Clustering of Specificity Matrices. Immunogenetics. 2004; 55(12):797–810.

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EpiMatrix: Screening a Peptide

Sequence for T Cell Epitopes

Assessment (Z Score)

Z Score ≥ 1.64
Hit

≥4 hits for a 9-mer
EpiBar

Frame Start	AA Sequence	Frame Stop	Hydro-phobicity	DRB1*0101 Z-Score	DRB1*0301 Z-Score	DRB1*0401 Z-Score	DRB1*0701 Z-Score	DRB1*0801 Z-Score	DRB1*0901 Z-Score	DRB1*1101 Z-Score	DRB1*1301 Z-Score	DRB1*1501 Z-Score	Hits
1	DLQVAFRAL	9	0.74	-0.02	-0.04	-0.73	0.76	-0.59	0.54	0.40	-0.29	-0.24	0
2	LQVAFRALL	10	1.56	1.96	2.41	0.94	1.67	2.00	2.70	1.93	2.56	1.92	8
3	QVAFRALLL	11	1.56	1.67	0.28	1.72	1.78	1.17	0.89	1.36	1.65	2.19	5
4	VAFRALLLL	12	2.37	0.49	0.64	-0.26	0.86	1.05	0.40	0.89	1.84	1.72	2
5	AFRALLLLA	13	2.10	0.04	1.14	0.65	0.23	0.53	1.27	0.95	1.26	1.42	0
6	FRALLLLAL	14	2.32	2.28	2.20	1.93	2.44	2.50	2.38	2.82	2.53	2.95	9
7	RALLLLALP	15	1.83	-0.54	0.11	-0.14	-0.96	0.39	0.47	0.86	0.55	0.15	0
8	ALLLLALPG	16	2.29	1.75	0.89	1.81	0.61	1.63	0.72	1.74	1.25	1.63	3

Summarized Results	DRB1*0101	DRB1*0301	DRB1*0401	DRB1*0701	DRB1*0801	DRB1*0901	DRB1*1101	DRB1*1301	DRB1*1501	Total
Maximum Single Z-score	2.28	2.41	1.93	2.44	2.50	2.70	2.82	2.56	2.95	--
Sum of Significant Z-scores	7.66	4.61	5.46	5.89	4.50	5.08	6.49	8.58	8.78	57.05
Count of Significant Z-Scores	4	2	3	3	2	2	3	4	4	27
Total Assessments Performed: 72	**Hydrophobicity: 1.36**			**EpiMatrix Score: 49.64**			**EpiMatrix Score (w/o flanks): 49.64**			
Scores Adjusted for Tregitope:	**--**			**EpiMatrix Score: 49.64**			**EpiMatrix Score (w/o flanks): 49.64**			

EpiMatrix Immunogenicity Score

1.28 < Z Score ≤ 1.64
Near-Miss

Total Number of Hits

Risk Assessment Approach
Epitope Density per Length

Protein or Peptide Therapeutic:

1 + 1 + 1 = Response

T cell response depends on:

T cell epitope content + HLA of subject

➢ immunogenicity can be ranked

De Groot A.S. and L. Moise. Prediction of immunogenicity for therapeutic proteins: State of the art. Current Opinions in Drug Development and Discovery. May 2007. 10(3):332-40.

"Immunogenicity Scale" for proteins
Potential immunogenicity risk

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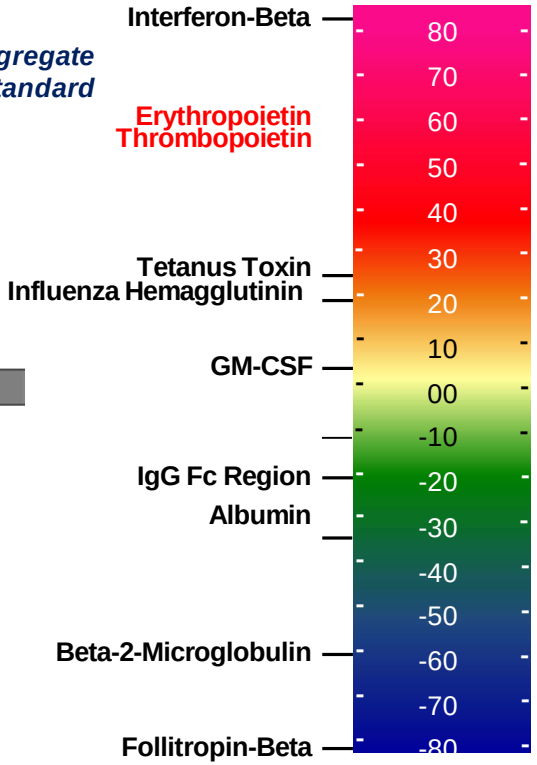
EpiMatrix Predicted Excess/Shortfall in Aggregate Immunogenicity Relative to a Random Peptide Standard



Have been known to be immunogenic

Protein Therapeutic:

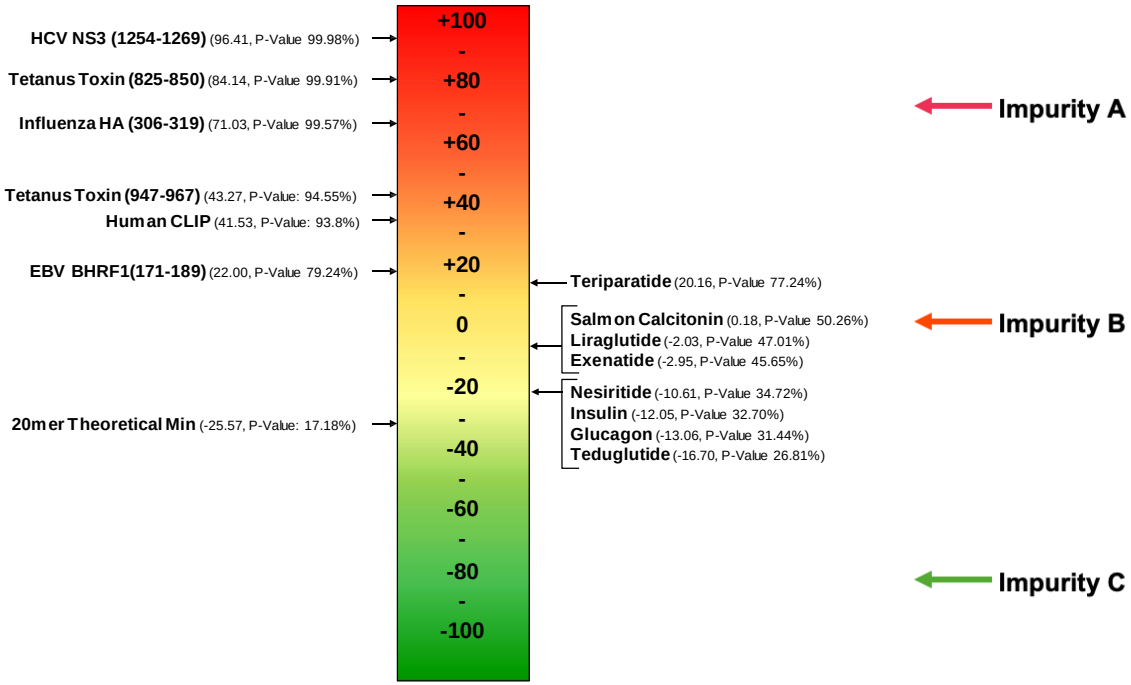
1 + 1 + 1 = Response

T cell response depends on:

T cell epitope content + HLA of subject

- protein immunogenicity can be ranked

New “PANDA” Peptide Immunogenicity Scale



The first step to assessing Immunogenicity risk of Impurities is to evaluate peptide epitope density on the immunogenicity scale.

ClustiMer – "EpiBar"

Screen Peptide Sequence for T Cell Epitopes

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EpiMatrix Cluster Report for GAD65 555-566

Frame Start	AA Sequence	Frame Stop	Hydro-phobicity	DRB1*0101 Z-Score	DRB1*0301 Z-Score	DRB1*0401 Z-Score	DRB1*0701 Z-Score	DRB1*0801 Z-Score	DRB1*0901 Z-Score	DRB1*1101 Z-Score	DRB1*1301 Z-Score	DRB1*1501 Z-Score	Hits
555	NFFRMVISN	563	0.43										0
556	FFRMVISNP	564	0.64			1.54	1.76		2.07	1.78			3
557	FRMVISNPA	565	0.53	2.67	2.43	2.83	3.12	2.02	3.27	2.95	1.82	2.81	9
558	RMVISNPAA	566	0.42										0

Assessments Performed: 36	Deviation from Expectation: 27.66

Z-score indicates the potential of a 9-mer frame to bind to a given HLA allele; the strength of the score is indicated by the blue shading.

Cluster Regions Outlined:	Top 10%*	Top 5%	Top 1%

Figure 5. EpiMatrix analysis of a promiscuous epitope. *The GAD65 peptide is an epitope known to be promiscuously immunogenic. It scores extremely high for all 9 alleles in EpiMatrix. Its EpiMatrix Score is 28. Scores higher than 10 are considered to be significant. The band-like EpiBar pattern is characteristic of promiscuous epitopes.*

Approach to analyzing unnatural amino acids
Details to be published in manuscripts in preparation

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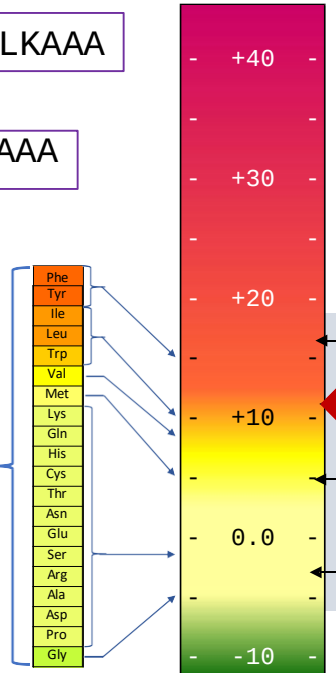
1 Neutral placeholder:
Replace unnatural AA(1Nal) with **X**

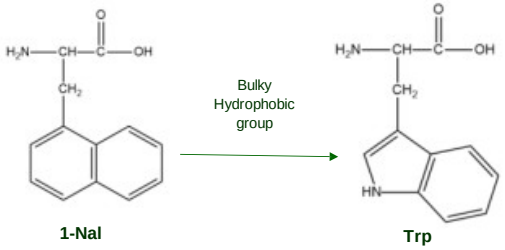
AK**1Nal**VAAWTLKAAA

AK**X**VAAWTLKAAA

2 Replacement Analysis:
Replace **X** with all 20 natural L-amino acids



3 Best Proxy:
Choose best-matching natural L-amino acid based on structural and/or chemical properties



AK**F**VAAWTLKAAA Most conducive to binding (i.e. worst-case scenario) 2

Best Risk Estimate

AK**X**VAAWTLKAAA Neutral Placeholder 1

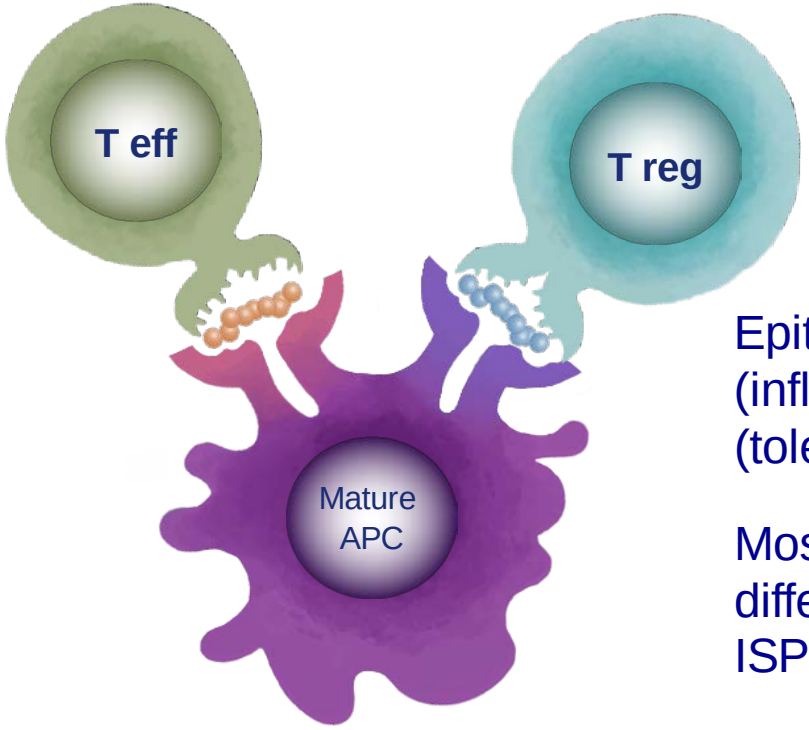
Risk Estimate Range

AK**G**VAAWTLKAAA Least conducive to binding (i.e. best-case scenario) 2

Outline – Analyzing Immunogenicity in Peptide Drugs

- Why do Immunogenicity Screening of Peptides?
- How to do it – In Silico and In Vitro
- Special tools that evaluate “tolerance” and find Treg Epitopes
- Case Studies: Calcitonin and Teriparatide (Impurities)

Some generic peptides are not immunogenic
Are they potentially tolerated or tolerogenic?



Epitopes can be *either* effector (inflammatory) or regulatory (tolerogenic).

Most in silico algorithms cannot differentiate between these two. ISPRI uses JanusMatrix.

The T cell epitope has two faces: One that binds HLA, and one that faces up to the T Cell Receptor (TCR)

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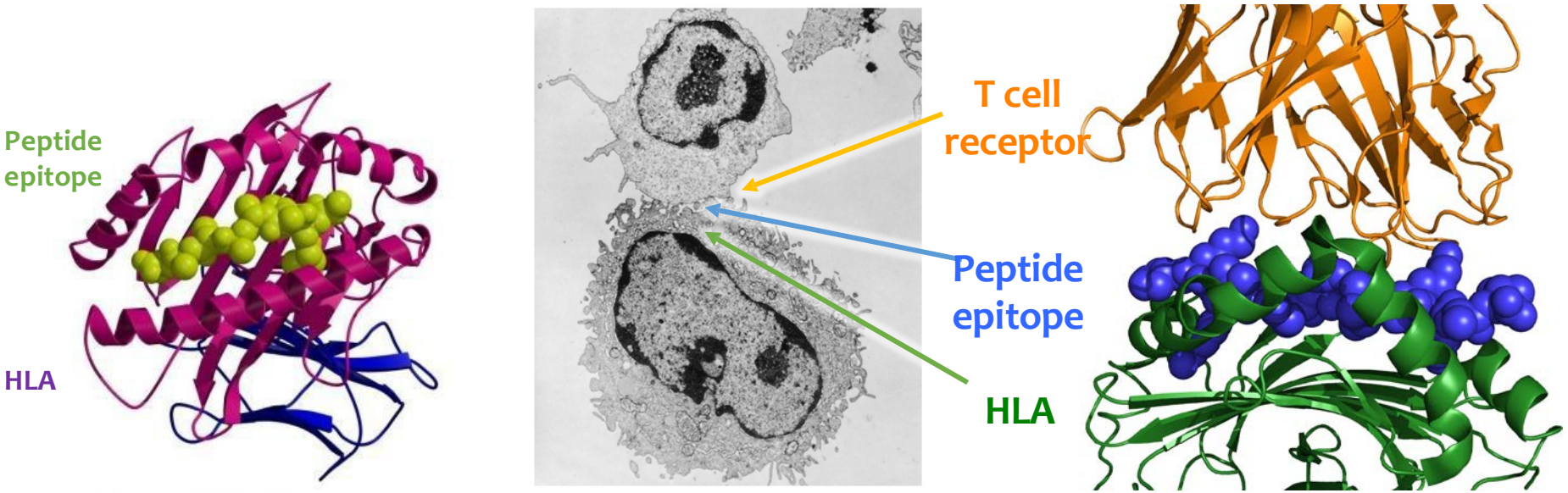


The T cell epitope is linear when bound to the HLA molecule that presents it to the TCR

JanusMatrix™ 2013

A New Way to Search for Homology with Self

EpiVax

Each MHC ligand has two faces:

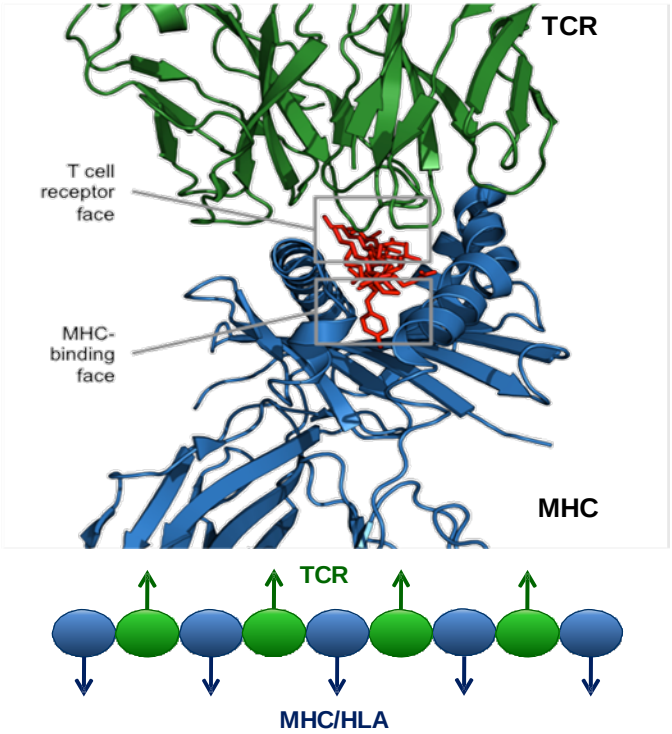
1. The MHC-binding face (agretope) and
2. The TCR-interacting face (epitope)

JanusMatrix™ is designed to predict the potential for cross-reactivity between epitope clusters and the human genome, based on conservation of TCR-facing residues in their putative HLA ligands.

JanusMatrix

Find predicted 9-mer ligands with:

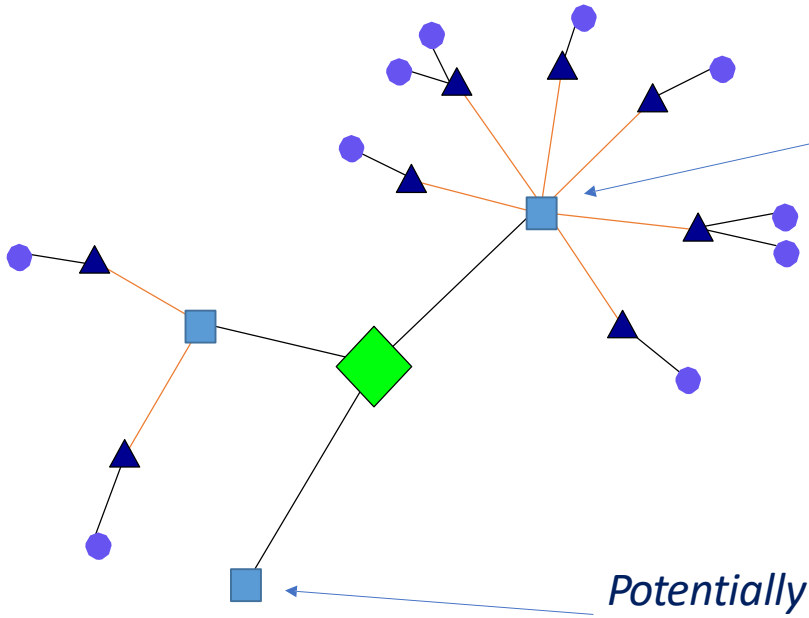
- **Identical T cell-facing residues**
- **Same HLA allele and minimally different MHC-facing residues**



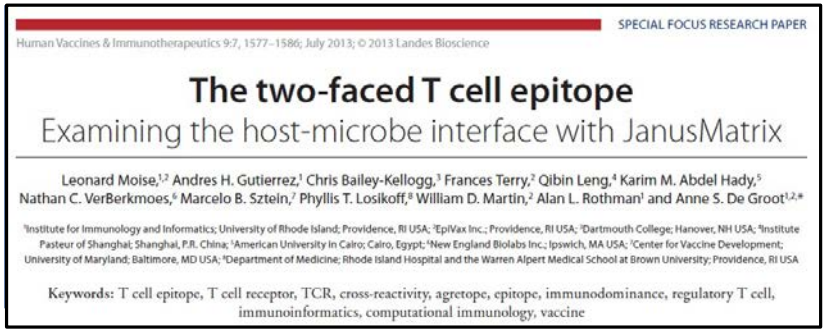
Moise L et al. Hum Vaccin Immunother. 2013 Jul;9(7):1577-86

Epitope networks used to provide visual map of epitope cross-conservation to identify tolerogenic (Treg) epitopes

Cytoscape: Visual map of epitope cross-conservation



Potentially <u>non</u>-immunogenic due to high cross-conservation with "self"



SPECIAL FOCUS RESEARCH PAPER

Human Vaccines & Immunotherapeutics 9:7, 1577–1586; July 2013; © 2013 Landes Bioscience

The two-faced T cell epitope

Examining the host-microbe interface with JanusMatrix

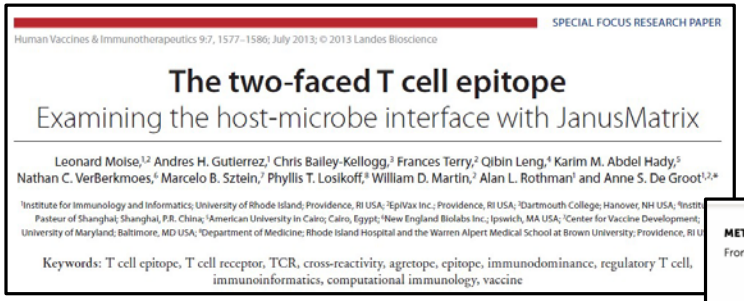
Leonard Moise,[1,2] Andres H. Gutierrez,[1] Chris Bailey-Kellogg,[3] Frances Terry,[2] Qibin Leng,[4] Karim M. Abdel Hady,[5] Nathan C. VerBerkmoes,[6] Marcelo B. Sztein,[7] Phyllis T. Losikoff,[8] William D. Martin,[2] Alan L. Rothman[1] and Anne S. De Groot[1,2,*]

[1]Institute for Immunology and Informatics; University of Rhode Island; Providence, RI USA; [2]EpiVax Inc.; Providence, RI USA; [3]Dartmouth College; Hanover, NH USA; [4]Institute Pasteur of Shanghai; Shanghai, P.R. China; [5]American University in Cairo; Cairo, Egypt; [6]New England Biolabs Inc.; Ipswich, MA USA; [7]Center for Vaccine Development; University of Maryland; Baltimore, MD USA; [8]Department of Medicine; Rhode Island Hospital and the Warren Alpert Medical School at Brown University; Providence, RI USA

Keywords: T cell epitope, T cell receptor, TCR, cross-reactivity, agretope, epitope, immunodominance, regulatory T cell, immunoinformatics, computational immunology, vaccine

Potentially immunogenic due to low cross-conservation with "self"

JanusMatrix Publications



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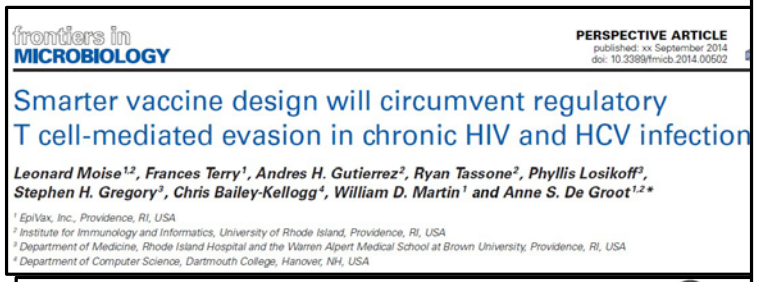

frontiers in MICROBIOLOGY

PERSPECTIVE ARTICLE

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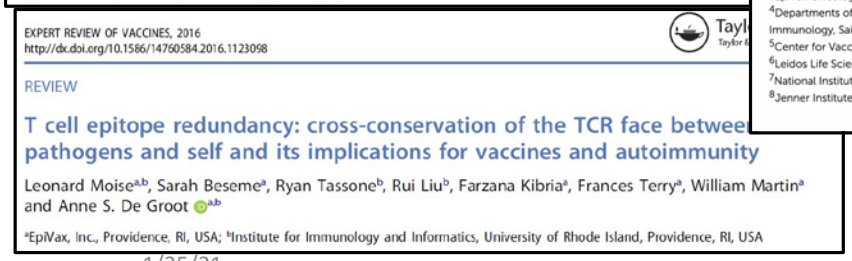
Smarter vaccine design will circumvent regulatory T cell-mediated evasion in chronic HIV and HCV infection

*Leonard Moise[1,2], Frances Terry[1], Andres H. Gutierrez[2], Ryan Tassone[2], Phyllis Losikoff[3], Stephen H. Gregory[3], Chris Bailey-Kellogg[4], William D. Martin[1] and Anne S. De Groot[1,2]**

[1] EpiVax, Inc., Providence, RI, USA
[2] Institute for Immunology and Informatics, University of Rhode Island, Providence, RI, USA
[3] Department of Medicine, Rhode Island Hospital and the Warren Alpert Medical School at Brown University, Providence, RI, USA
[4] Department of Computer Science, Dartmouth College, Hanover, NH, USA



EXPERT REVIEW OF VACCINES, 2016
http://dx.doi.org/10.1586/14760584.2016.1123098

REVIEW

T cell epitope redundancy: cross-conservation of the TCR face betwee pathogens and self and its implications for vaccines and autoimmunity

Leonard Moise[a,b], Sarah Beseme[a], Ryan Tassone[b], Rui Liu[b], Farzana Kibria[a], Frances Terry[a], William Martin[a] and Anne S. De Groot[a,b]

[a]EpiVax, Inc., Providence, RI, USA; [b]Institute for Immunology and Informatics, University of Rhode Island, Providence, RI, USA

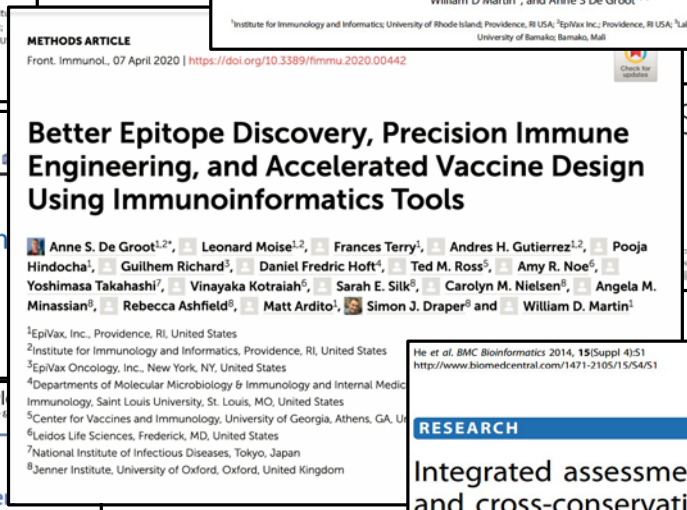
RESEARCH PAPER

Human Vaccines & Immunotherapeutics 11:9, 2241–2252; September 2015; Published with license by Taylor & Francis Group, LLC

H7N9 T-cell epitopes that mimic human sequences are less immunogenic and may induce Treg-mediated tolerance

Rui Liu[1], Leonard Moise[1,2], Ryan Tassone[1], Andres H Gutierrez[1], Frances E Terry[2], Kotou Sangare[3], Matthew T Ardito[2], William D Martin[2], and Anne S De Groot[1,2,*]

[1]Institute for Immunology and Informatics; University of Rhode Island; Providence, RI USA; [2]EpiVax Inc.; Providence, RI USA; [3]Laboratory of Applied Molecular Biology (LBMA); University of Bamako; Bamako, Mali



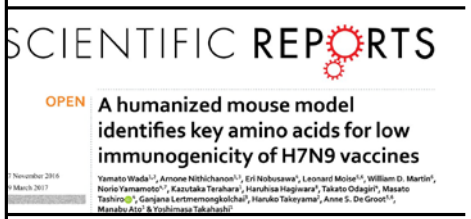
METHODS ARTICLE

Front. Immunol., 07 April 2020 | https://doi.org/10.3389/fimmu.2020.00442

Better Epitope Discovery, Precision Immune Engineering, and Accelerated Vaccine Design Using Immunoinformatics Tools

Anne S. De Groot[1,2*], Leonard Moise[1,2], Frances Terry[1], Andres H. Gutierrez[1,2], Pooja Hindocha[1], Guilhem Richard[3], Daniel Fredric Hoft[4], Ted M. Ross[5], Amy R. Noe[6], Yoshimasa Takahashi[7], Vinayaka Kotraiah[6], Sarah E. Silk[8], Carolyn M. Nielsen[8], Angela M. Minassian[8], Rebecca Ashfield[8], Matt Ardito[1], Simon J. Draper[8] and William D. Martin[1]

[1]EpiVax, Inc., Providence, RI, United States
[2]Institute for Immunology and Informatics, Providence, RI, United States
[3]EpiVax Oncology, Inc., New York, NY, United States
[4]Departments of Molecular Microbiology & Immunology and Internal Medic Immunology, Saint Louis University, St. Louis, MO, United States
[5]Center for Vaccines and Immunology, University of Georgia, Athens, GA, U
[6]Leidos Life Sciences, Frederick, MD, United States
[7]National Institute of Infectious Diseases, Tokyo, Japan
[8]Jenner Institute, University of Oxford, Oxford, United Kingdom

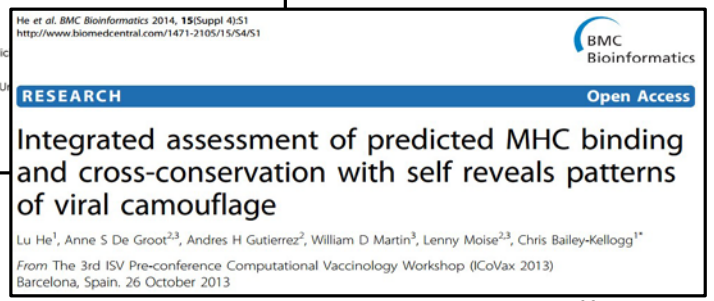


SCIENTIFIC REPORTS

OPEN

A humanized mouse model identifies key amino acids for low immunogenicity of H7N9 vaccines

Yamato Wada[1,2], Arnone Nithichanon[1,2], Eri Nobusawa[3], Leonard Moise[1,4], William D. Martin[4], Norio Yamamoto[5,6], Kazutaka Terahara[7], Haruhisa Hagiwara[8], Takato Odagiri[9], Masato Tashiro[9,*], Ganjana Lertmemongkolchai[10], Haruko Takeyama[2], Anne S. De Groot[1,4], Manabu Ato[2] & Yoshimasa Takahashi[1]



He *et al. BMC Bioinformatics* 2014, **15**(Suppl 4):S1
http://www.biomedcentral.com/1471-2105/15/S4/S1

BMC Bioinformatics

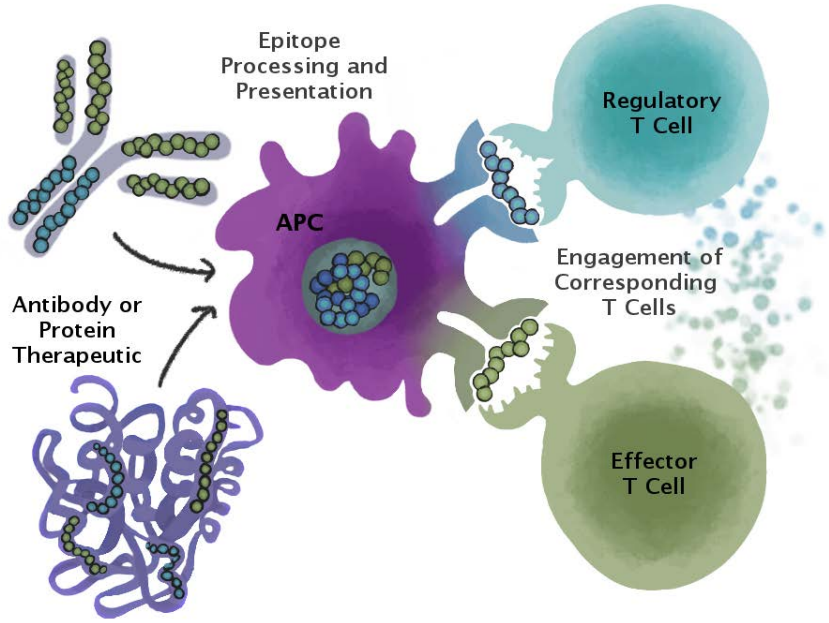
RESEARCH Open Access

Integrated assessment of predicted MHC binding and cross-conservation with self reveals patterns of viral camouflage

Lu He[1], Anne S De Groot[2,3], Andres H Gutierrez[2], William D Martin[3], Lenny Moise[2,3], Chris Bailey-Kellogg[1*]

From The 3rd ISV Pre-conference Computational Vaccinology Workshop (ICoVax 2013)
Barcelona, Spain. 26 October 2013

Published Treg epitopes in IgG: Tregitopes Also highly conserved by JanusMatrix



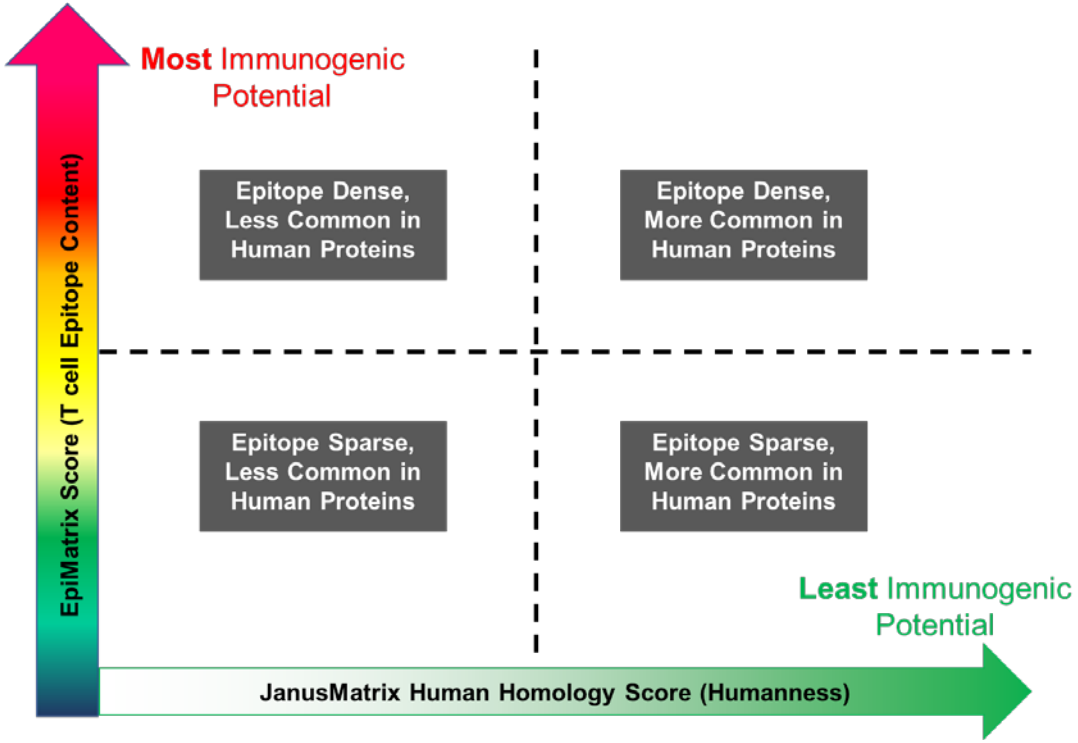
De Groot A.S., et al., Activation of Natural Regulatory T cells by IgG Fc-derived Peptide "Tregitopes". Blood, 2008,112: 3303. http://tinyurl.com/ASDeGroot-Blood-2008

- Tregitopes
- Discovered by EpiVax
- Highly conserved peptide sequences in Fc and Fab regions of antibodies
- High affinity, promiscuous binders across HLA alleles
- **One mechanism of action of IVIG?**
- **Activate antigen-specific regulatory T cells**
- **Do other self-proteins have tolerogenic epitopes?**

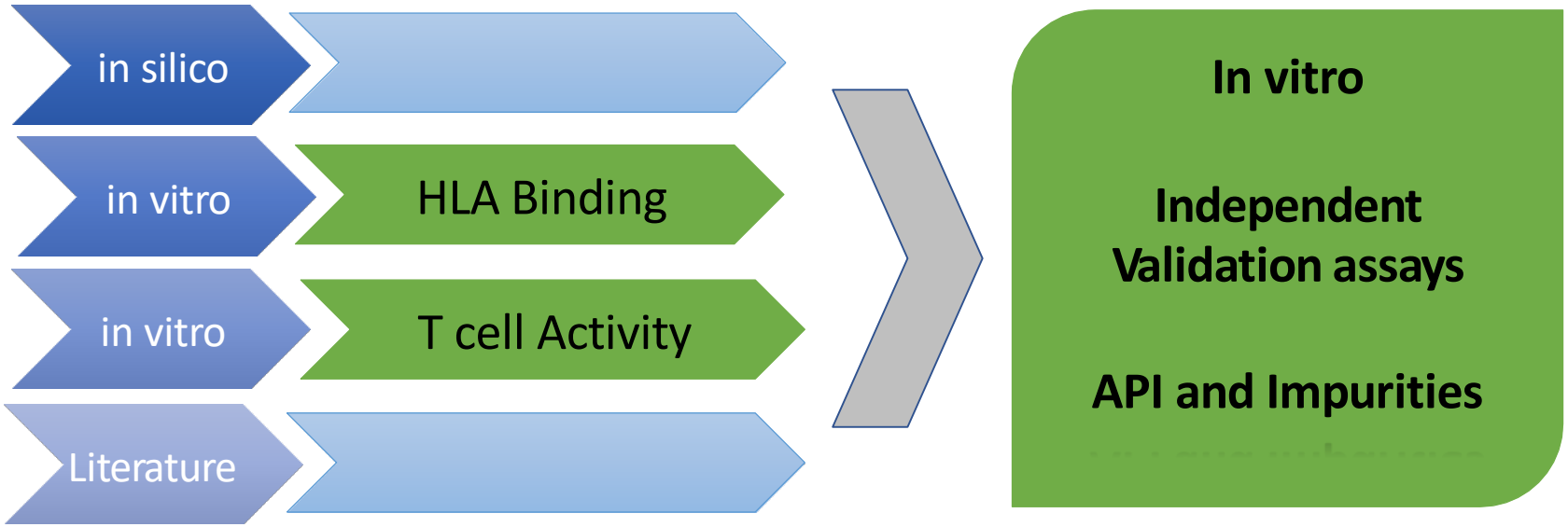
Evaluation of Immunogenicity: Consider the potential for tolerance

EpiVax

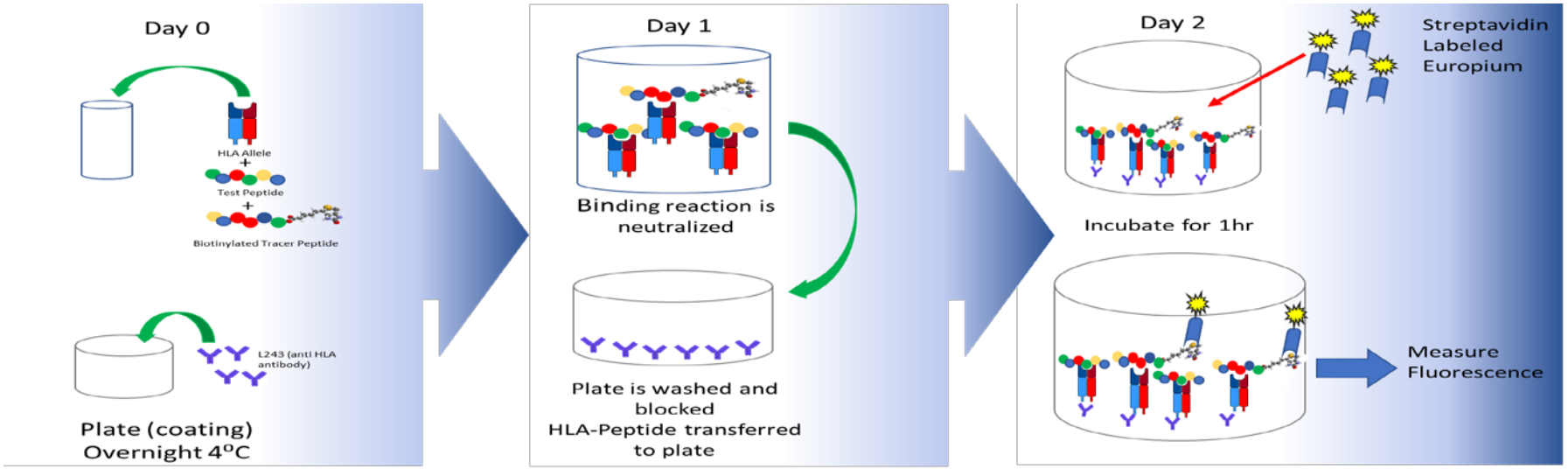
- Immunogenic peptides have high EpiMatrix scores and low JanusMatrix scores.
- Based on these two parameters, API and their sequence-related impurities can be divided into four quadrants:



Four step approach to Peptide Drug Impurities

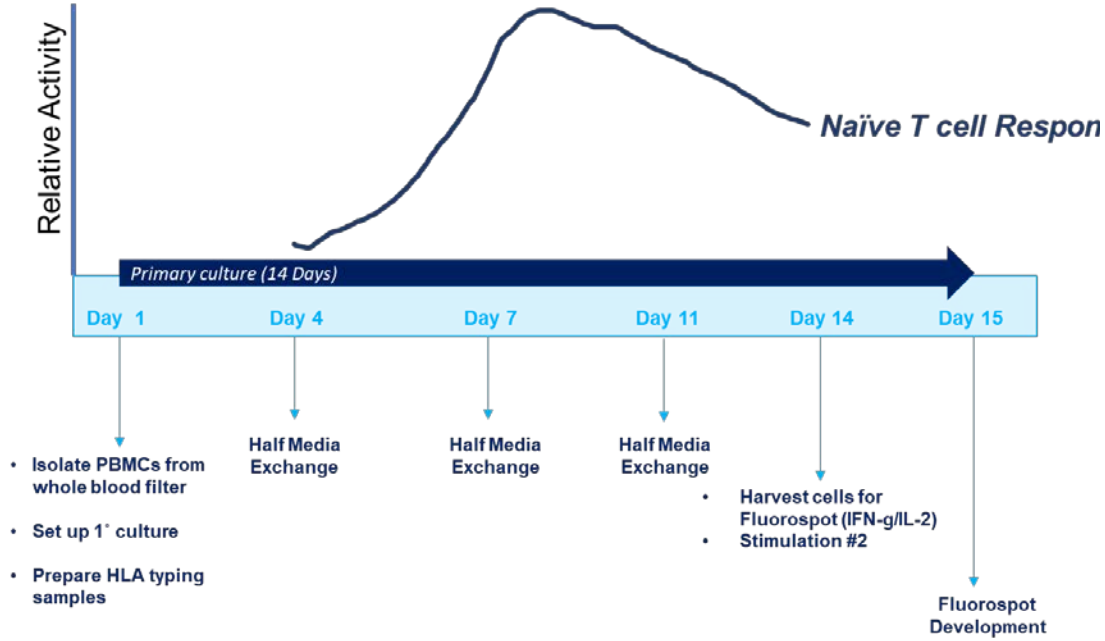


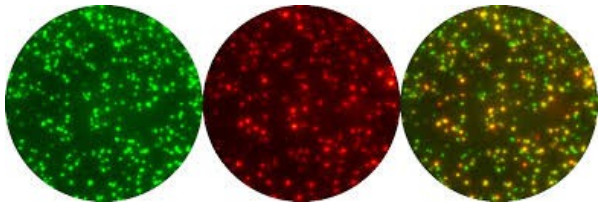
Validation: HLA Binding yle



In brief, the peptide of interest is incubated with an allele-specific labeled tracer peptide and a soluble HLA supertype monomer are incubated to equilibrium. The following day the binding reaction is halted and the mixture is transferred to assay plates precoated with a pan anti-HLA-DR antibody and incubated overnight. Following this incubation, the plates are developed and peptide binding is indirectly measured by time resolved fluorescence spectroscopy. By using a fixed concentration of the labeled tracer peptide and a range of concentrations for the test peptide, one can generate a multi-point dose ranging curve that enables the calculation of an IC50 value which provides information not only about the ability of the peptide to bind HLA (yes/no) but also about the relative affinity of the peptide to a given HLA-DR supertype. Once can utilize the IC50 values to divide peptides into categories based on their affinity for a given HLA allele, such as high, moderate, low and non-binding. As new technology becomes available and accessible, it will be useful to look at the kinetics of the binding reaction as well.

In Vitro Assay to measure T cell response "IVIP" (Similar assay for Treg response "TTBSA"





Evaluate for Treg induction –
Tetanus Toxoid bystander suppression assay

Outline of the assay

Stimulation (day 1)

- Media (negative control)
- TT 0.5 μg/ml
- TT + peptide (289/FV621 or Teriparatide)

Concentration 10, 20, 40 μg/ml

End points (day 7)

- Proliferation and activation of Teff (CFSE, CD25)
- Characterization markers (CD4 and CD3e)

TTBSA Assay + New Tregitope

EpiVax

ELSEVIER

Clinical Immunology

Volume 224, March 2021, 108661

Full Length Article

Identification of a potent regulatory T cell epitope in factor V that modulates CD4+ and CD8+ memory T cell responses

Anne S. De Groot [a, b], Amy Rosenberg [c], S.M. Shahjahan Miah [a], Gail Skowron [a], Brian J. Roberts [a], Sandra Lélias [a], Frances E. Terry [a], William D. Martin [a]

Outline – Analyzing Immunogenicity in Peptide Drugs

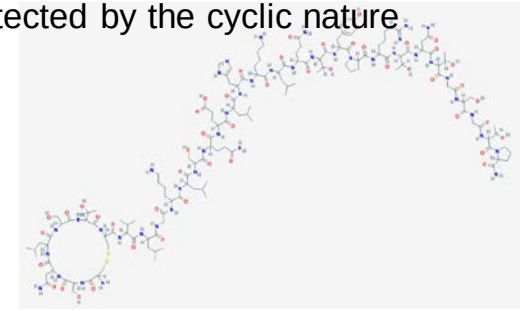
- Why do Immunogenicity Screening of Peptides?
- How to do it – In Silico and In Vitro
- Special tools that evaluate “tolerance” and find Treg Epitopes
- Case Studies: Calcitonin and Teriparatide (Impurities)

Case Studies / OGD Contract 2018-2020

EpiVax

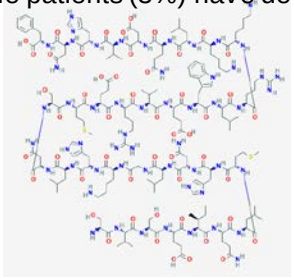
Salmon Calcitonin

- ➢ A **Foreign** Peptide
  - only 50% sequence homology with human calcitonin
- ➢ Is **slightly immunogenic**
  - 40-70% patients develop ADA to SCT[1,2,3]
- ➢ Some **impurities** are potentially **immunogenic**
- Ø The N-terminal human calcitonin-like active site region of SCT contains no epitopes and may be protected by the cyclic nature



Teriparatide

- ➢ Fully **Human** Peptide
- ➢ Is less immunogenic, may even be ***tolerogenic***
  - Only 3% of patients develop ADA to teriparatide[4]
  - Teriparatide was shown to increase the number of Tregs by threefold[5]
  - EpiMatrix & JanusMatrix[6] identified a promiscuous binding epitope with high degree of human homology to another widely expressed human protein, tubulin.
- ➢ Some **impurities** are potentially **immunogenic**
  - This may explain why some patients (3%) have developed transient antibodies



1. Grauer A, Ziegler R, Raue F. Clinical significance of antibodies against calcitonin. Exp Clin Endocrinol Diabetes 1995; 103: 345–351.
2. Muff, R;Dambacher M and FJ. Formation of neutralizing antibodies during intranasal synthetic salmon calcitomin treatment of postmenopausal osteoporosis. Osteoporos Int 1991; 1: 72–75.
3. LEVY F, MUFF R, DOTTI-SIGRIST S, et al. Formation of Neutralizing Antibodies During Intranasal Synthetic Salmon Calcitonin Treatment of Paget's Disease*. J Clin Endocrinol Metab 1988; 67: 541–545.
4. Eli Lilly. FORTEO Package Insert.
5. Yu M, D'Amelio P, Tyagi AM, et al. Regulatory T cells are expanded by Teriparatide treatment in humans and mediate intermittent PTH-induced bone anabolism in mice. EMBO Rep 2018; 19: 156–171.
6. Moise L, Gutierrez AH, Bailey-Kellogg C, et al. The two-faced T cell epitope: Examining the host-microbe interface with JanusMatrix. Hum Vaccin Immunother 2013; 9: 1577–1586.

Salmon Calcitonin Immunogenicity Analysis
In silico analysis confirms what is known about this drug

EpiVax

EpiMatrix Cluster Detail Report

File: SALMON_CALCITONIN Sequence: SALMON_CALCITONIN Cluster: 1

Frame Start	AA Sequence	Frame Stop	Hydro-phobicity	DRB1*0101 Z-Score	DRB1*0301 Z-Score	DRB1*0401 Z-Score	DRB1*0701 Z-Score	DRB1*0801 Z-Score	DRB1*1101 Z-Score	DRB1*1301 Z-Score	DRB1*1501 Z-Score	Hits
1	CSNLSTCVL	9	1.22	1.03	-0.85	0.07	1.18	-0.51	0.52	-0.72	0.04	0
2	SNLSTCVLG	10	0.9	0.21	0.99	1.13	-0.20	0.32	0.01	0.64	0.04	0
3	NLSTCVLGK	11	0.56	0.17	-0.58	0.94	0.52	0.32	0.12	0.39	-0.27	0
4	LSTCVLGKL	12	1.37	-0.54	0.41	-0.55	0.13	1.24	-0.23	-0.53	0.65	0
5	STCVLGKLS	13	0.86	1.05	-0.10	0.59	0.53	0.05	0.60	0.32	0.69	0
6	TCVLGKLSQ	14	0.56	-0.18	-0.22	0.12	-0.69	0.82	1.39	0.17	0.15	0
7	CVLGKLSQE	15	0.24	-1.29	0.53	-0.87	-0.96	0.36	-0.61	-0.03	-0.29	0
8	VLGKLSQEL	16	0.39	1.37	1.75	0.60	2.22	1.70	0.79	0.97	1.43	3
9	LGKLSQELH	17	-0.43	0.82	0.49	0.72	0.40	1.49	1.16	0.24	-0.22	0
10	GKLSQELHK	18	-1.29	-0.40	0.36	0.19	0.34	-0.19	0.59	0.18	0.06	0
11	KLSQELHKL	19	-0.82	0.68	0.99	0.30	0.71	0.35	0.82	1.72	0.66	1
12	LSQELHKLQ	20	-0.78	1.17	1.00	1.57	1.32	0.90	1.65	0.98	0.70	1
13	SQELHKLQT	21	-1.28	0.47	0.01	0.11	-0.13	0.85	1.38	0.38	1.19	0
14	QELHKLQTY	22	-1.33	-1.27	-0.10	-1.12	-0.47	-1.30	-1.08	0.22	-0.61	0
15	ELHKLQTYP	23	-1.12	-1.03	-0.88	-1.36	-0.54	-0.12	-1.18	-0.41	-2.15	0
16	LHKLQTYPR	24	-1.23	2.11	2.03	2.36	1.49	2.51	2.13	2.08	1.97	7
17	HKLQTYPRT	25	-1.73	1.23	-0.85	0.27	0.17	0.36	0.75	-0.01	0.94	0
18	KLQTYPRTN	26	-1.77	0.72	-0.70	0.19	0.79	0.53	0.26	-0.34	0.13	0
19	LQTYPRTNT	27	-1.41	0.13	-0.35	-0.63	0.40	1.01	-0.08	0.97	1.11	0
20	QTYPRTNTG	28	-1.88	0.05	0.11	1.05	-0.44	0.41	0.25	0.00	0.06	0
21	TYPRTNTGS	29	-1.58	0.19	-0.96	-0.12	-0.88	0.06	-0.73	0.11	-0.23	0
22	YPRTNTGSG	30	-1.54	1.11	0.31	1.30	0.84	1.54	0.60	0.04	0.87	0
23	PRTNTGSGT	31	-1.48	0.62	-0.90	0.22	0.20	-0.48	-0.21	-0.97	-0.01	0
24	RTNTGSGTP	32	-1.48	-0.52	-0.51	-0.36	0.50	-0.45	-0.96	-0.77	0.38	0

Summarized Results	DRB1*0101	DRB1*0301	DRB1*0401	DRB1*0701	DRB1*0801	DRB1*1101	DRB1*1301	DRB1*1501	Total
Maximum Single Z-score	2.11	2.03	2.36	2.22	2.51	2.13	2.08	1.97	--
Sum of Significant Z-scores	2.11	3.78	2.36	2.22	4.21	3.78	3.80	1.97	24.23
Count of Significant Z-Scores	1	2	1	1	2	2	2	1	12

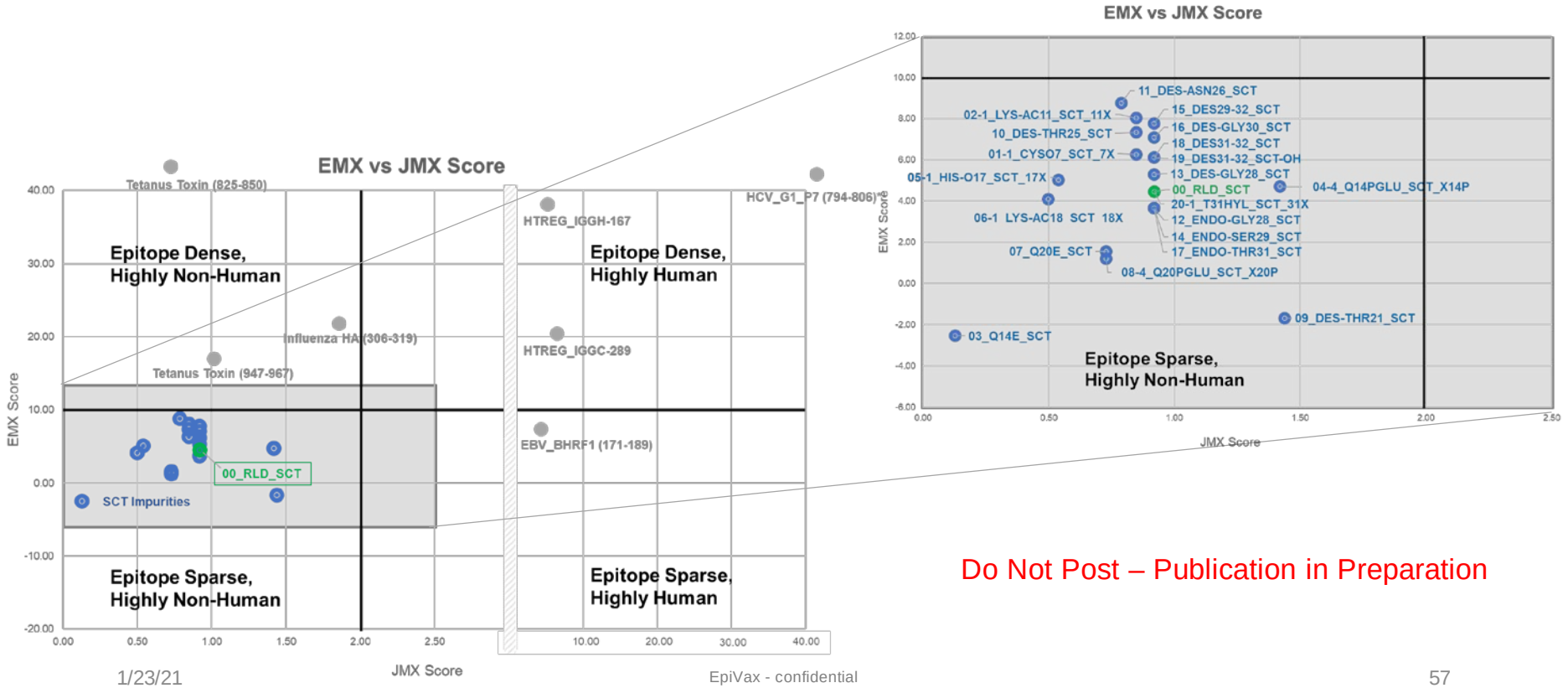
Total Assessments Performed: 192	Hydrophobicity: -0.54	EpiMatrix Score: 4.46	EpiMatrix Score (w/o flanks): 4.46
Scores Adjusted for Tregitope:	--	EpiMatrix Score: 4.46	EpiMatrix Score (w/o flanks): 4.46

Human Calcitonin-like region – no T cell epitopes

Antibody Binding Site

Fully Foreign immunogenic region

Salmon Calcitonin and Impurities
Immunogenicity vs Humanness



Do Not Post – Publication in Preparation

Salmon Calcitonin: Impurities

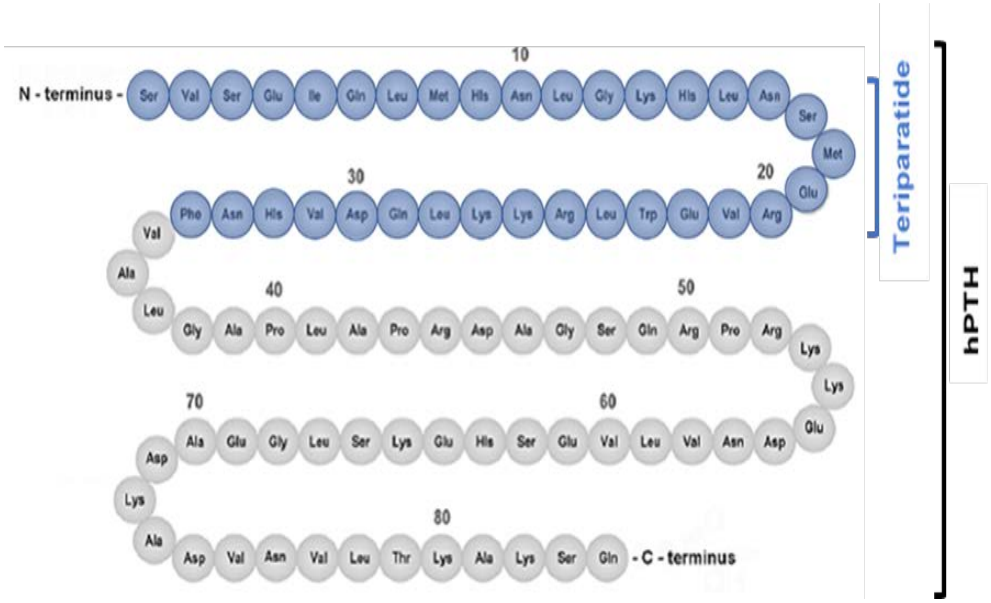
EpiVax

Peptide	Sequence	EpiMatrix Score	JanusMatrix Score	% of Responding Donors	# of Responding Donors
Salmon Calcitonin API	***CSNLSTCVLGKLSQELHKLQTYPRTNTGSGTP***	***1.99***	***0.92***	***44%***	***7 of 16***
LYS-AC18_SCT	CSNLSTCVLGKLSQELH**(Ac-K)***LQTYPRTNTGSGTP	3.33	0.46	56%	9 of 16
Q20E_SCT	CSNLSTCVLGKLSQELHKL**E**TYPRTNTGSGTP	-0.92	0.73	56%	9 of 16
ENDO-GLY28_SCT	CSNLSTCVLGKLSQELHKLQTYPRTNT**G**GSGTP	1.06	0.92	63%	10 of 16
ENDO-THR31_SCT	CSNLSTCVLGKLSQELHKLQTYPRTNTGSG**T**TP	1.06	0.92	69%	11 of 16

- Salmon Calcitonin (SCT) API is demonstrated and known to be, immunogenic.
- SCT impurities have similar EpiMatrix (moderate) and JanusMatrix (non-human) scores.
- Each impurity had similar immunogenicity in silico and ex vivo relative to the API.
- ***SCT impurities are immunogenic as predicted, but not significantly more so than the API.***

Teriparatide

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF

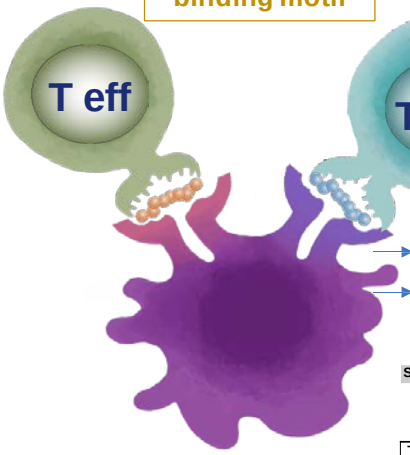


- Sold under the name Forteo® (RLD, rDNA).
- Approved for the treatment of Osteoporosis for men and women in the USA.
- Comprised of the N-terminal 34 amino acids of hPTH.
- Primary regulator of Calcium and Phosphate metabolism in the bone and kidney.

Teriparatide
In Silico Evaluation of Immunogenicity

EpiMatrix Hits in Frames 4, 5, 7, 8, 11, 21, 23
(Medium and Dark blue shading)

EpiBar in Frame 5= promiscuous binding motif



EpiMatrix Detail Report

File: FDA_YR2_TERIPARATIDE Sequence: 00_TERIPARATIDE_RLD : 1

Frame Start	AA Sequence	Frame Stop	Hydro-phobicity	DRB1*0101 Z-Score	DRB1*0301 Z-Score	DRB1*0401 Z-Score	DRB1*0701 Z-Score	DRB1*0801 Z-Score	DRB1*0901 Z-Score	DRB1*1101 Z-Score	DRB1*1301 Z-Score	DRB1*1501 Z-Score	Hits
1	SVSEIQLMH	9	0.29	0.21	0.28	0.57	-0.15	-0.27	-0.16	0.39	0.21	-0.87	0
2	VSEIQLMHN	10	-0.01	-0.37	-0.41	-0.04	-0.65	0.22	0.10	0.82	-0.99	1.11	0
3	SEIQLMHNL	11	-0.06	-0.02	-0.24	-0.41	-0.14	-1.10	-0.83	-0.60	0.52	-0.67	0
4	EIQLMHNLG	12	-0.01	1.00	0.83	1.15	0.28	1.77	0.72	1.78	0.27	1.31	2
5	IQLMHNLGK	13	-0.06	2.47	1.71	2.88	1.67	2.01	1.62	2.89	1.69	2.42	8
6	QLMHNLGKH	14	-0.91	-1.16	-0.46	-0.44	0.20	0.37	0.12	0.01	-0.02	-0.29	0
7	LMHNLGKHL	15	-0.1	2.27	1.06	1.26	2.17	1.17	1.44	1.18	1.26	1.41	2
8	MHNLGKHLN	16	-0.91	1.41	1.26	0.84	0.64	1.84	0.95	1.93	1.49	1.21	2
9	HNLGKHLNS	17	-1.21	0.38	1.07	1.11	-0.04	0.55	-0.10	1.17	0.75	1.45	0
	NSM	18	-0.64	-0.85	0.93	-1.12	0.03	0.21	0.35	0.28	0.59	-0.24	0
		19	-0.64	0.06	0.67	0.66	1.09	0.71	0.12	-0.32	2.08	0.30	1
		20	-1.57	1.00	0.78	1.05	0.33	1.38	0.36	1.06	0.06	1.30	0
		21	-1.06	0.28	0.34	0.16	0.47	-0.05	0.00	0.25	-0.12	-0.34	0
		22	-1.01	-1.07	0.26	-1.12	-0.23	-0.12	0.26	-0.13	-0.53	-1.38	0
14 15	[illegible]	23	-0.76	1.38	1.33	0.20	1.54	0.91	0.80	1.09	1.16	0.91	0
16	NSMERVEWL	24	-0.76	0.35	-0.03	0.31	0.41	-1.17	-0.73	-0.61	-0.70	-1.75	0
17	SMERVEWLR	25	-0.87	-1.07	-0.90	-2.16	-0.92	-0.79	-1.56	-0.55	-0.36	-0.58	0
18	MERVEWLRK	26	-1.21	0.00	0.13	0.68	0.90	-0.03	-0.43	0.71	0.49	1.27	0
19	ERVEWLRKK	27	-1.86	-0.55	-0.29	-0.25	-1.04	-0.77	-0.95	0.55	-0.96	-1.27	0
20	RVEWLRKKL	28	-1.04	-0.05	0.10	-0.47	0.98	-0.22	-0.05	0.23	1.30	0.67	0
21	VEWLRKKLQ	29	-0.93	1.23	1.09	0.96	0.86	2.34	0.23	2.51	1.51	1.38	2
22	EWLRKKLQD	30	-1.79	-0.64	-0.68	-1.47	-0.92	1.47	-0.88	0.09	0.54	-0.07	0
23	WLRKKLQDV	31	-0.93	0.71	1.03	0.16	1.65	2.04	0.88	1.42	0.27	0.48	2
24	LRKKLQDVH	32	-1.19	0.19	0.39	-0.25	-0.14	1.05	0.40	0.61	0.32	-1.21	0
25	RKKLQDVHN	33	-2	0.29	-0.02	0.82	-0.04	0.62	-0.44	-0.07	0.20	1.15	0
26	KKLQDVHNF	34	-1.19	0.19	0.46	0.84	0.60	-0.13	-0.10	0.35	1.20	-1.30	0

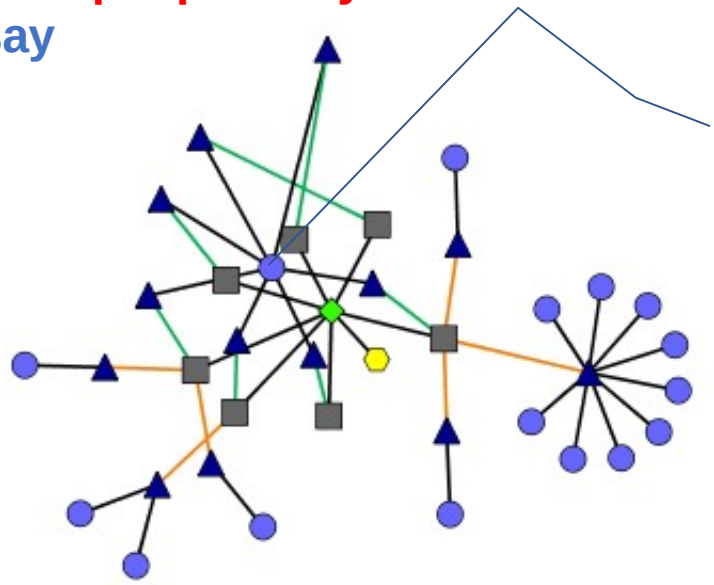
Summarized Results	DRB1*0101	DRB1*0301	DRB1*0401	DRB1*0701	DRB1*0801	DRB1*0901	DRB1*1101	DRB1*1301	DRB1*1501	Total
Maximum Single Z-score	2.47	1.71	2.88	2.17	2.34	1.62	2.89	2.08	2.42	--
Sum of Significant Z-scores	4.74	1.71	2.88	5.49	10.00	0.00	9.11	3.77	2.42	40.12
Count of Significant Z-Scores	2	1	1	3	5	0	4	2	1	19

Total Assessments Performed: 234	Hydrophobicity: -0.67	EpiMatrix Score: 16.03	EpiMatrix Score (w/o flanks): 16.03
Scores Adjusted for Tregitope:	--	EpiMatrix Score: 16.03	EpiMatrix Score (w/o flanks): 16.03

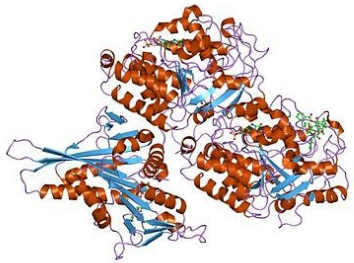
The EpiBar in frame 5 has a **high JanusMatrix Human Homology Score** suggesting potential for **homology-induced tolerance**
(homology is to the widely expressed human protein tubulin)

Example: JanusMatrix Analysis of Teraparatide

Immunogenic by T cell epitope analysis.
But both in vitro assay and clinical data (3% ADA) . . . much Less Immunogenic than predicted . . .Do JanusMatrix Analysis:



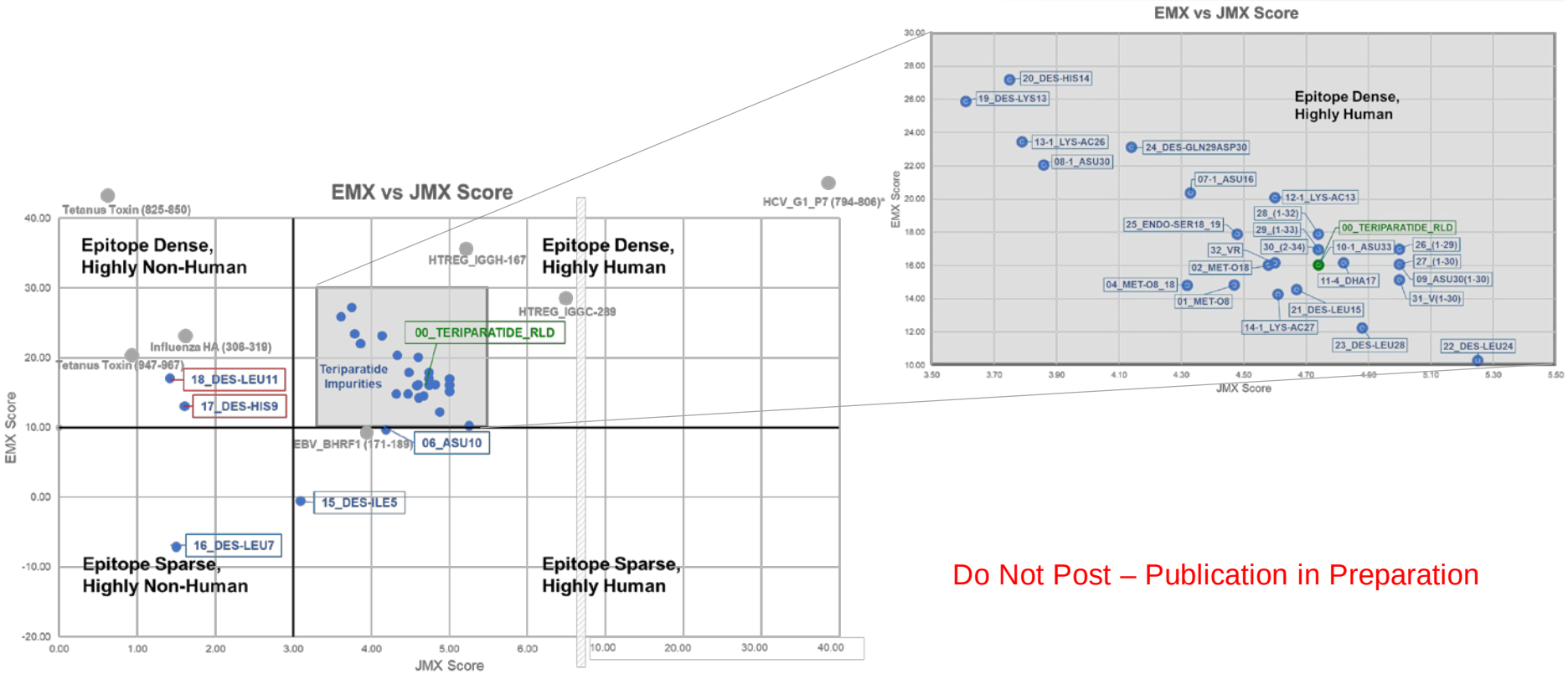
Tubulin
tubulin protein superfamily of globular proteins, or one of the member proteins of that superfamily. α- and β-tubulins polymerize into microtubules, a major component of the eukaryotic cytoskeleton.



Conserved with very common intracellular protein, Tubulin.

DO NOT POST – UNPUBLISHED

Teriparatide and Impurities
Immunogenicity vs Humanness



Do Not Post – Publication in Preparation

Teriparatide Summary

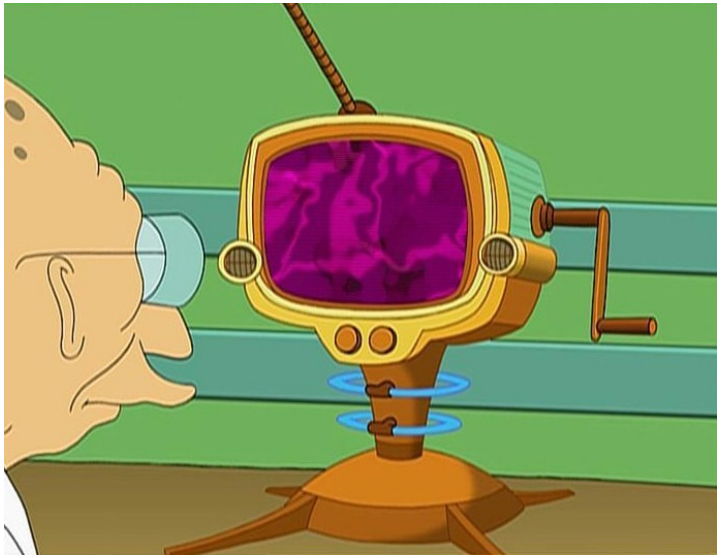
- **Teriparatide peptide has tolerogenic behavior in vitro, as predicted**
  - ***The putative Teriparatide "Tregitope" inhibits CD4+ T cell proliferation and activation in TTBSA in healthy donor PBMCs***
- **Impurities that retain the same TCR facing sequences are not more immunogenic than Teriparatide (API) in vitro.**
- **Impurities that remove the TCR cross-conservation but still bind are more immunogenic (publication in preparation)**
- **Future studies: Does the Teraparatide "Tregitope" tolerize against potential immunogenic impurities when administered together?**

Outline – Analyzing Immunogenicity in Peptide Drugs

EpiVax

- Why do Immunogenicity Screening of Peptides?
- How to do it – In Silico and In Vitro
- Special tools that evaluate “tolerance” and find Treg Epitopes
- Case Studies: Calcitonin and Teriparatide (Impurities)
- What if we could prospectively predict and rank all peptide impurities?

"Yes We Can" Predict the impact of Impurities: The "What If Machine"



Prof. Farnsworth contemplates what could be using the What if Machine (in "Futurama")

Image attributed to *"Futurama,"* 20th Century Fox Broadcasting

EpiVax has a **"What If " Machine** for peptide impurities.

When generic drug impurities are **unknown**, modifications at each amino acid position in the peptide can be performed in silico, their immunogenicity risk predicted and they can be assigned an **impurity risk score**.

The "**What if Machine", performs all possible changes to the natural amino acid sequence of the drug substance** and measures their impact on the epitope content of the peptide.

The WhIM then calculates the predicted immunogenicity of the impurities and flags the most worrisome for special consideration. Generics manufacturers may be able to use this information to reduce the cost of their ANDA preparation. **This list could be used to identify impurities that should be removed.**

WHAT IF.. (WhIM) Summary of one iteration: Taspoglutide AA Duplication EXAMPLE (insertion)

EpiVax

Input Sequence	Peptide Sequence	EpiMatrix Hits	EpiMatrix Score	EpiBars? (#)	Number of HUMAN Matches	Janus HMLGY Score
00_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKAR	9	0.86	Yes (1)	9	1.67
01_ENDO-HIS7_HGLP-1	HHAEGTFTSDVSSYLEGQAAKEFIAWLVKAR	9	0.04	Yes (1)	9	1.67
02_ENDO-ALA8_HGLP-1	HAAEGTFTSDVSSYLEGQAAKEFIAWLVKAR	9	0.04	Yes (1)	9	1.67
03_ENDO-GLU9_HGLP-1	HAEEGTFTSDVSSYLEGQAAKEFIAWLVKAR	9	0.04	Yes (1)	9	1.67
04_ENDO-GLY10_HGLP-1	HAEGGTFTSDVSSYLEGQAAKEFIAWLVKAR	9	0.04	Yes (1)	9	1.67
05_ENDO-THR11_HGLP-1	HAEGTTFTSDVSSYLEGQAAKEFIAWLVKAR	9	0.04	Yes (1)	9	1.67
06_ENDO-PHE12_HGLP-1	HAEGTFFTSDVSSYLEGQAAKEFIAWLVKAR	10	1.72	Yes (1)	9	1.50
07_ENDO-THR13_HGLP-1	HAEGTFTTSDVSSYLEGQAAKEFIAWLVKAR	5	-9.91	No	6	1.40
08_ENDO-SER14_HGLP-1	HAEGTFTSSDVSSYLEGQAAKEFIAWLVKAR	6	-7.75	No	7	1.33
09_ENDO-ASP15_HGLP-1	HAEGTFTSDDVSSYLEGQAAKEFIAWLVKAR	5	-9.22	No	7	1.60
10_ENDO-VAL16_HGLP-1	HAEGTFTSDVVSSYLEGQAAKEFIAWLVKAR	8	-3.12	No	28	**6.63**
11_ENDO-SER17_HGLP-1	HAEGTFTSDVSSSYLEGQAAKEFIAWLVKAR	8	-2.19	Yes (1)	27	**8.38**
12_ENDO-TYR19_HGLP-1	HAEGTFTSDVSSYYLEGQAAKEFIAWLVKAR	7	-4.55	No	8	1.43
13_ENDO-LEU20_HGLP-1	HAEGTFTSDVSSYLLEGQAAKEFIAWLVKAR	8	-1.66	Yes (1)	6	1.50
14_ENDO-GLU21_HGLP-1	HAEGTFTSDVSSYLEEGQAAKEFIAWLVKAR	8	-1.66	Yes (1)	6	1.50
15_ENDO-GLY22_HGLP-1	HAEGTFTSDVSSYLEGGQAAKEFIAWLVKAR	8	-1.66	Yes (1)	6	1.50
16_ENDO-GLN23_HGLP-1	HAEGTFTSDVSSYLEGQQAAKEFIAWLVKAR	10	2.23	Yes (1)	6	1.20
17_ENDO-ALA24_HGLP-1	HAEGTFTSDVSSYLEGQAAAKEFIAWLVKAR	10	2.15	Yes (1)	10	1.60
18_ENDO-LYS26_HGLP-1	HAEGTFTSDVSSYLEGQAAKKEFIAWLVKAR	12	5.25	Yes (1)	11	1.58
19_ENDO-GLU27_HGLP-1	HAEGTFTSDVSSYLEGQAAKEEFIAWLVKAR	9	0.04	Yes (1)	9	1.67
20_ENDO-PHE28_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFFIAWLVKAR	12	5.72	Yes (1)	9	1.25
21_ENDO-ILE29_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIIAWLVKAR	11	4.34	Yes (2)	7	1.09
22_ENDO-ALA30_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIAAWLVKAR	10	2.32	Yes (2)	6	1.10
23_ENDO-TRP31_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWWLVKAR	7	-3.62	Yes (1)	6	1.57
24_ENDO-LEU32_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLLVKAR	8	-1.60	Yes (1)	8	1.63
25_ENDO-VAL33_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVVKAR	9	1.09	Yes (1)	8	1.56
26_ENDO-LYS34_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKKAR	12	6.35	Yes (2)	9	1.33
27_ENDO-ALA35_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKAAR	13	8.04	Yes (2)	9	1.15
28_ENDO-ARG36_HGLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKARR	13	7.78	Yes (2)	9	1.15

EMX Hits:
- aa duplication impurities with more EMX than baseline (9) are in **red** à **increase** in overall putative T cell epitope content
- aa duplication impurities with less EMX hits than baseline (9) in **green** à **decrease** in overall putative T cell epitope content

Original Sequence.. Not immunogenic

JMX HMLGY Score:
- JanusMatrix Human Homology Score.
- **Scores >3** are considered significant for potential homology induced tolerance

Large number of hits
High EpiMatrix Score
Low JanusMatrix Score

DO NOT POST – Manuscript in Preparation

FDA Contract with CUBRC and EpiVax 2018-2020 (and 2020-2022…)

2018

Office of Generic Drugs (OGD/FDA) Awards $1M FDA Contract to CUBRC and EpiVax for Demonstration and Validation of Immunogenicity Risk Assessment Methods for Generic Peptide Drugs and Their Impurities

Providence, R.I., October 2, 2018 – EpiVax, Inc. ("EpiVax") and CUBRC, Inc. ("CUBRC") announced today that they have been awarded a two-year $1 million contract from the Food and Drug Administration (FDA) in response to a Broad Agency Announcement (BAA), FDA BAA-17-00123.

The research program will identify best practices and procedures for assessing generic peptides and related impurities for immunogenic potential. "EpiVax has worked hard to be at the forefront of the immunogenicity assessment field. Our proprietary immunoinformatics tools make it possible to perform risk assessments accurately and expeditiously. We look forward to working with FDA scientists to set new standards for immunogenicity risk assessment for generic peptide drug products," stated Annie De Groot, MD, EpiVax's CEO/CSO.

The FDA recently issued a draft guidance for generic peptide drugs and issued a BAA for immunogenicity risk assessment tools. In response to this BAA, EpiVax scientists will demonstrate and validate risk assessment methods for generic peptides. OGD scientists will also have access to the EpiVax ISPRI Toolkit for selected peptide drugs and their impurities.

CUBRC will leverage its technical expertise in biomedical research and development along with its experience leading large federal government grants and contracts in collaboration with EpiVax to execute the research. "CUBRC plans to leverage our 3+ year partnership with EpiVax to provide systems integration and program management expertise to advance EpiVax's highly specialized immunoinformatic tools which will help the FDA with evaluation of new generic peptide drugs," stated Katie Edwards, Ph.D., CUBRC's Prime Technical Program Lead.

2020

#22 WhIM: The What-If-Machine

EpiVax Advances "PANDA" Peptide Therapeutic Immunogenicity Screening Program

PROVIDENCE, RI, December 29, 2020 /PRNewswire/ -- EpiVax, Inc. ("EpiVax") today provides an update on the advancement of the company's peptide therapeutic immunogenicity assessment program.

Peptide Impurity Risk Assessment

The PANDA (Peptide Abbreviated New Drug Application) immunogenicity assessment program was originally developed for screening generic peptide drugs and their impurities following the publication of the ANDA draft guidance by the Food and Drug Administration (FDA). EpiVax performed validation studies of the in silico tools and in vitro validation methods used in the PANDA program in collaboration with CUBRC under contract to the FDA between 2018 and 2020. Work performed by EpiVax under this initial FDA contract is in preparation for publication. Meanwhile, EpiVax announced a new FDA OGD contract in Octo

"What if" Machine (WhIM)

In pa ptide
immu renty
percent of total revenue between 2017 and 2020. In the past 12 months, EpiVax worked with over fifteen pharmaceutical and biotechnology companies developing both novel and generic peptide therapeutics, applying in silico screening, HLA binding assays, and T cell assays to assess the immunogenic risk of their products utilizing the PANDA approach.

EpiVax's CEO/CSO, Annie De Groot, MD, says, "Having performed protein immunogenicity risk assessment for more than 20 years, we're thrilled to not only be able to add immunogenicity risk assessment of generic peptides and their impurities to our repertoire of services, but also to see the PANDA approach becoming increasingly useful for assessing the potential immunogenicity of novel peptide therapeutics. The application of our PANDA research aims to help peptide drug developers reduce the risk of failure in the clinical phase of development. We look forward to learning more about the immunogenicity of generic and novel peptide therapeutics and growing our program further in 2021."

Publications cited in this presentation

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•HCV epitope, homologous to multiple human protein sequences, induces a regulatory T cell response in infected patients. Losikoff PT, Mishra S, Terry F, Gutierrez A, Ardito MT, Fast L, Nevola M, Martin WD, Bailey-Kellogg C, De Groot AS, Gregory SH. J Hepatol. 2015 Jan;62(1):48-55. doi: 10.1016/j.jhep.2014.08.026. Epub 2014 Aug 23. PMID: 2515798

•Modulation of CD8+ T cell responses to AAV vectors with IgG-derived MHC class II epitopes. Hui DJ, Basner-Tschakarjan E, Chen Y, Davidson RJ, Buchlis G, Yazicioglu M, Pien GC, Finn JD, Haurigot V, Tai A, Scott DW, Cousens LP, Zhou S, De Groot AS, Mingozzi F. Mol Ther. 2013 Sep;21(9):1727-37. doi: 10.1038/mt.2013.166. Epub 2013 Jul 16. PMID: 23857231 Free PMC article.

•Application of IgG-derived natural Treg epitopes (IgG Tregitopes) to antigen-specific tolerance induction in a murine model of type 1 diabetes. Cousens LP, Su Y, McClaine E, Li X, Terry F, Smith R, Lee J, Martin W, Scott DW, De Groot AS. J Diabetes Res. 2013;2013:621693. doi: 10.1155/2013/621693. Epub 2013 Apr 23.

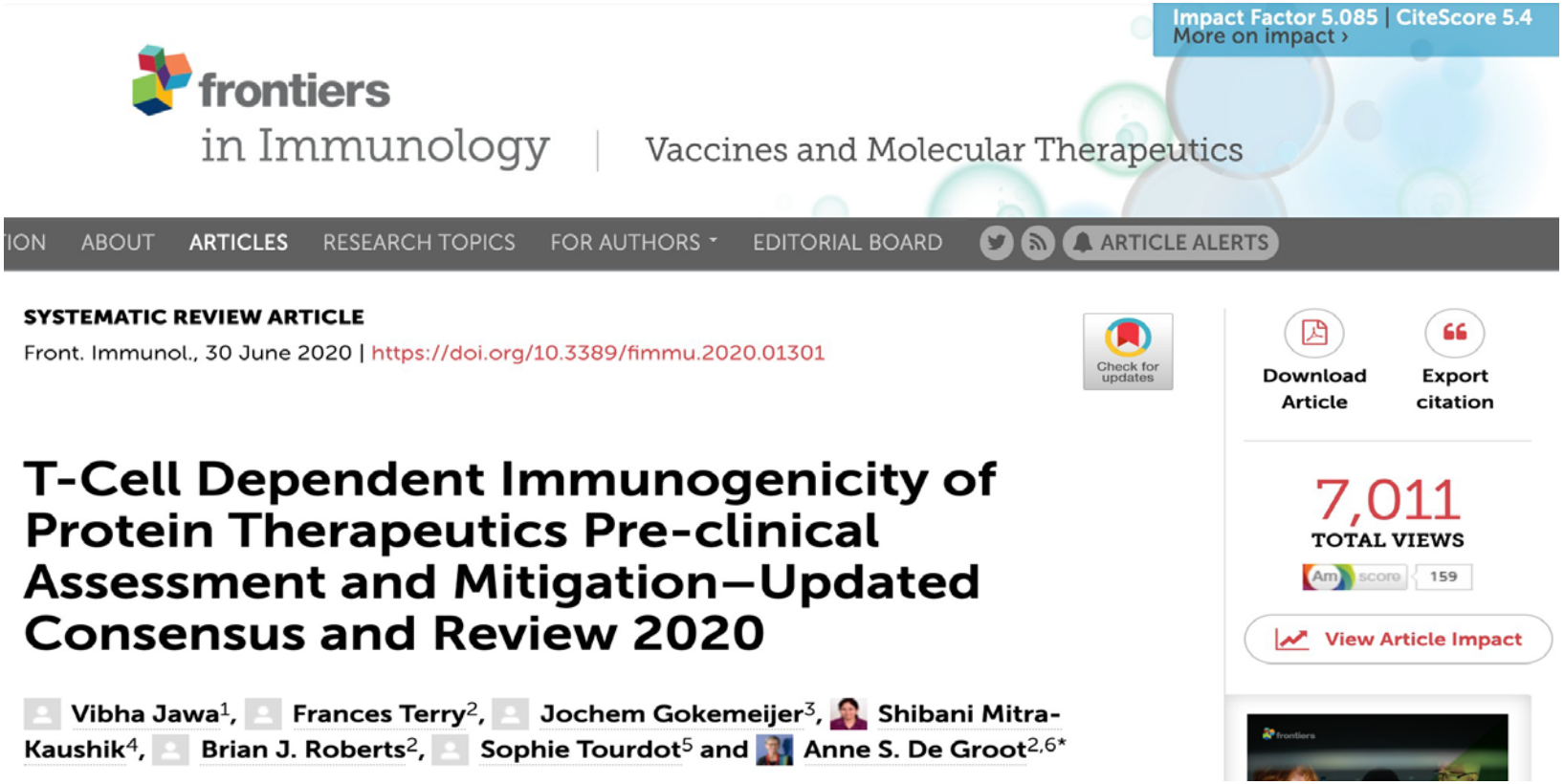
•The two-faced T cell epitope: examining the host-microbe interface with JanusMatrix. Moise L, Gutierrez AH, Bailey-Kellogg C, Terry F, Leng Q, Abdel Hady KM, VerBerkmoes NC, Sztein MB, Losikoff PT, Martin WD, Rothman AL, De Groot AS. Hum Vaccin Immunother. 2013 Jul;9(7):1577-86. doi: 10.4161/hv.24615. Epub 2013 Apr 12. PMID: 23584251 Free PMC article.

•H7N9 T-cell epitopes that mimic human sequences are less immunogenic and may induce Treg-mediated tolerance. Liu R, Moise L, Tassone R, Gutierrez AH, Terry FE, Sangare K, Ardito MT, Martin WD, De Groot AS. Hum Vaccin Immunother. 2015;11(9):2241-52. doi: 10.1080/21645515.2015.1052197. PMID: 26090577 Free PMC article.

The EpiVax Team makes this work possible!

EpiVax & AAPS TPGIF Immunogenicity Experts TCWP Version 2.0 Published June 2020

EpiVax



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T-Cell Dependent Immunogenicity of Protein Therapeutics Pre-clinical Assessment and Mitigation–Updated Consensus and Review 2020

Vibha Jawa[1], Frances Terry[2], Jochem Gokemeijer[3], Shibani Mitra-Kaushik[4], Brian J. Roberts[2], Sophie Tourdot[5] and Anne S. De Groot[2,6*]

EpiVax & AAPS TPGIF Immunogenicity Experts
TCWP Version 2.0 Published June 2020

EpiVax

ELSEVIER

Clinical Immunology

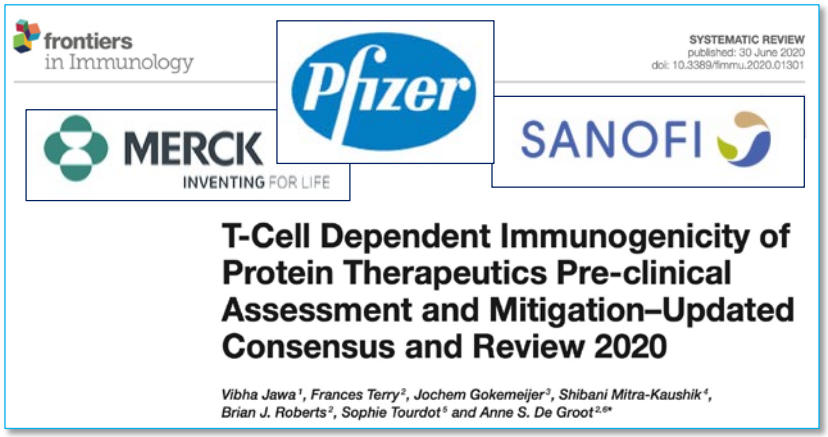
Volume 224, March 2021, 108661

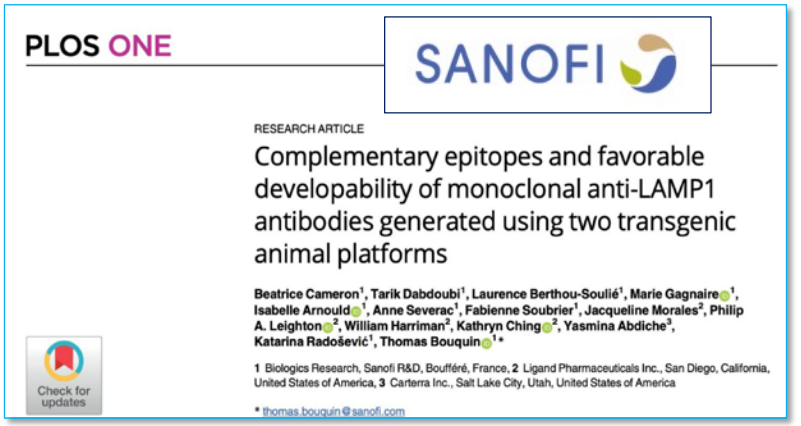
Full Length Article

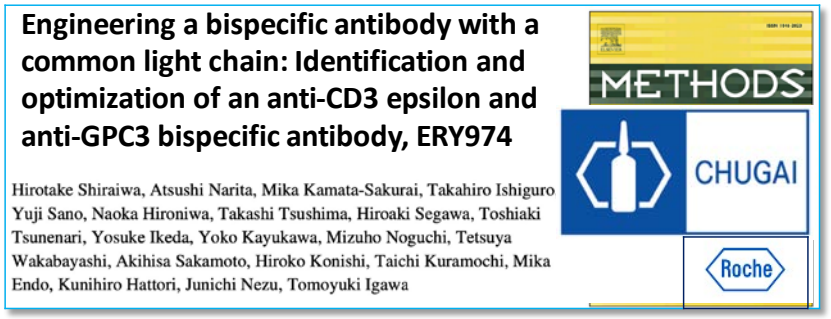
Identification of a potent regulatory T cell epitope in factor V that modulates CD4+ and CD8+ memory T cell responses

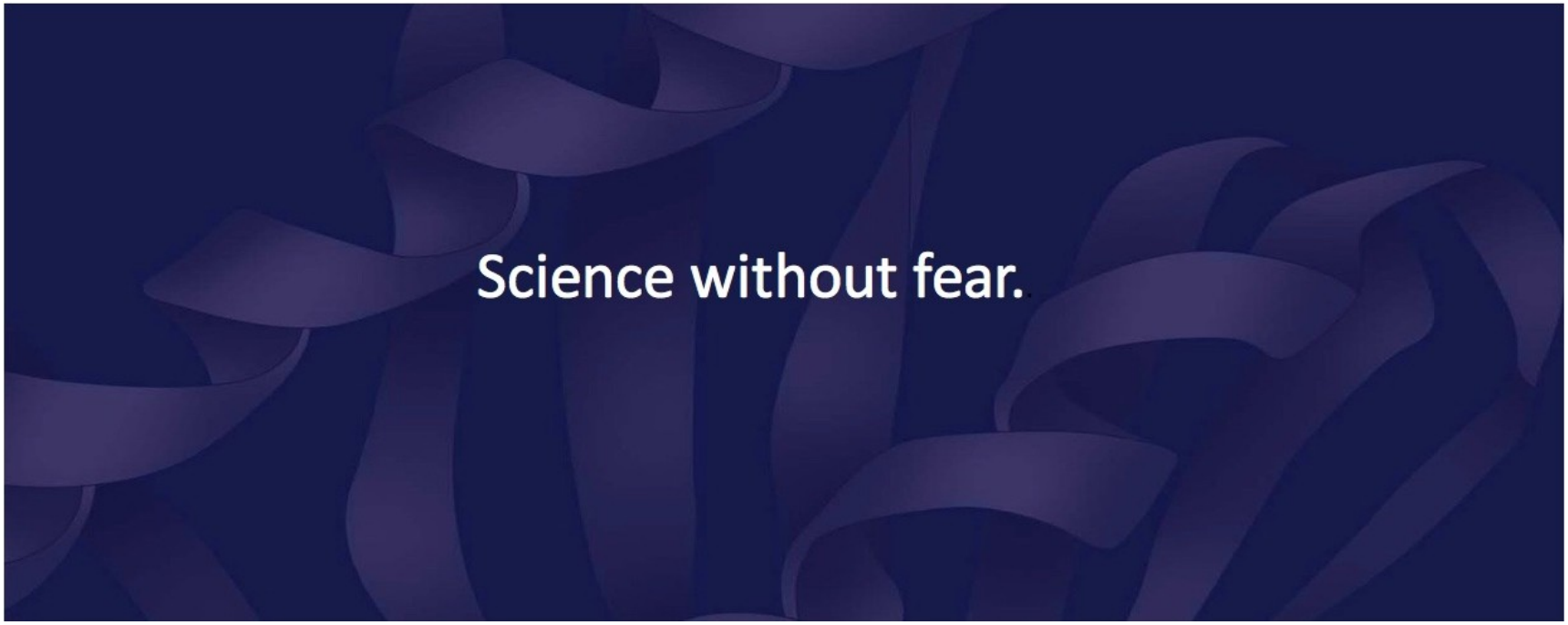
Anne S. De Groot [a, b], Amy Rosenberg [c], S.M. Shahjahan Miah [a], Gail Skowron [a], Brian J. Roberts [a], Sandra Lélias [a], Frances E. Terry [a], William D. Martin [a]

Recent Publications Describing EpiVax Tools









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