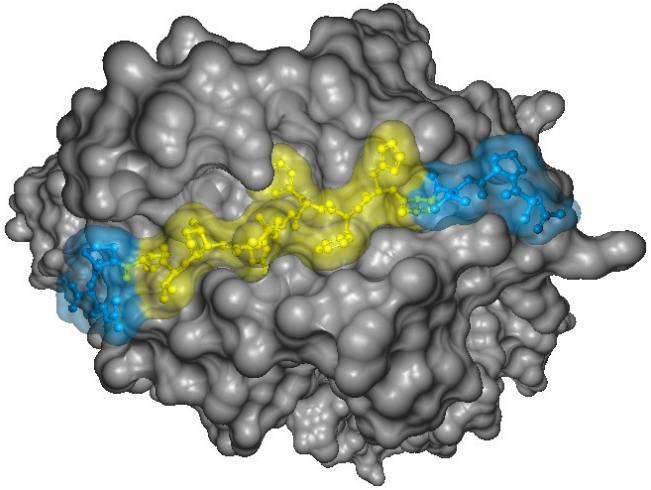
Predicting Binding Affinities of MHC Class II Epitopes Across Alleles

Nico Pfeifer and Oliver Kohlbacher

Center for Bioinformatics

Eberhard Karls University Tübingen



Roadmap

- Background
  - Major Histocompatibility Complex Class II (MHCII)
  - Problem Definition
- Methods
  - Multiple Instance Learning
  - Normalized Set Kernel
  - Positionally-weighted RBF Kernel
- Results

MHCII

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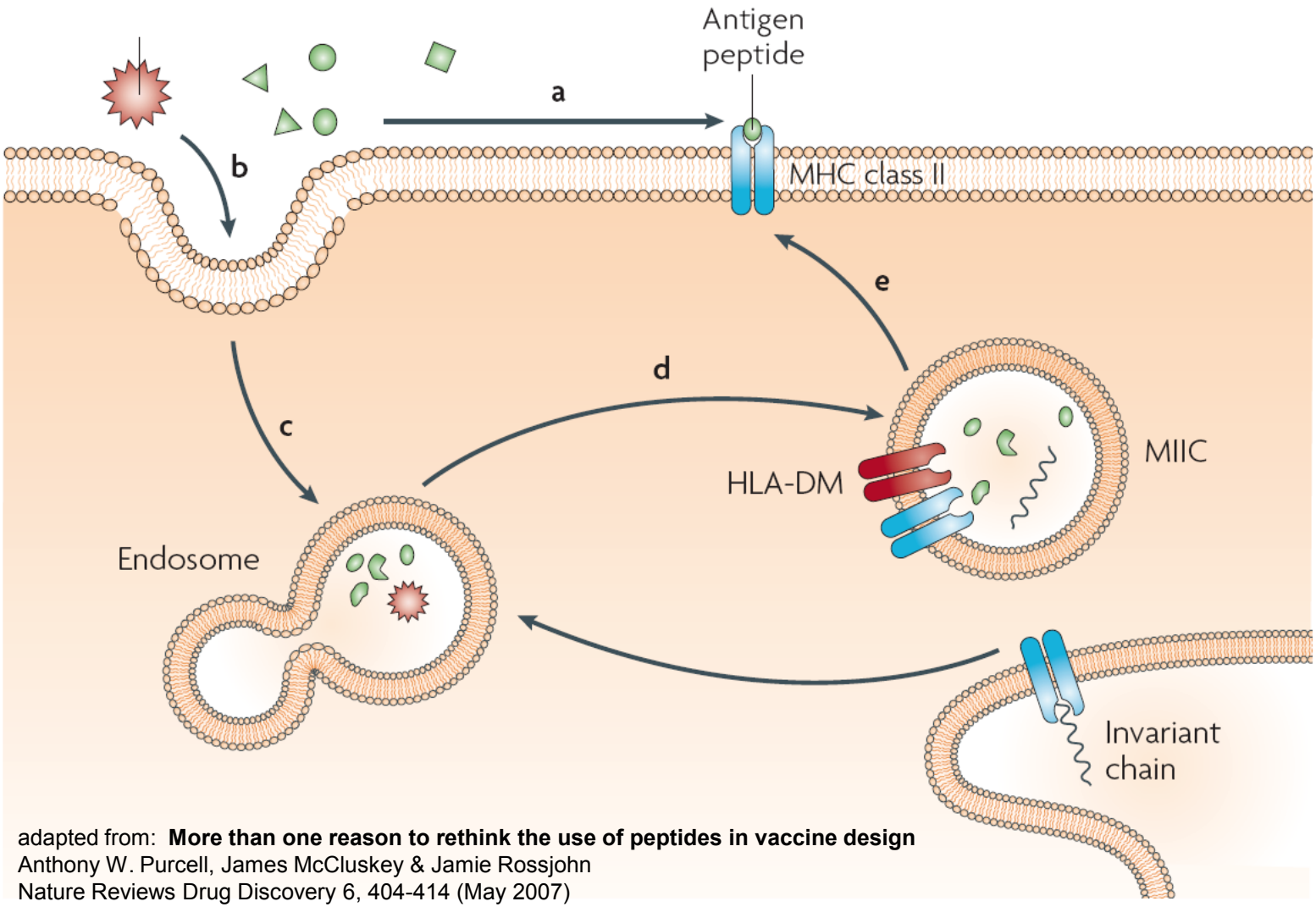
- Can be found primarily on antigen-presenting cells (macrophages, dendritic cells and B-cells)
- Presents peptides which are derived from exogenous proteins to trigger an immune response

MHCII



adapted from: **More than one reason to rethink the use of peptides in vaccine design**
Anthony W. Purcell, James McCluskey & Jamie Rossjohn
Nature Reviews Drug Discovery 6, 404-414 (May 2007)

Why is MHCII interesting?

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$\Rightarrow$ Good predictors for peptide binding needed

Definitions

Peptide-MHCII binding prediction

Given: Peptide sequence *s* and sequence *m* of an MHCII molecule

Problem: Decide whether *s* binds to *m* or not

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Peptide-MHCII binding *affinity* prediction

Given: Peptide sequence *s* and sequence *m* of an MHCII molecule

Problem: Decide how strong *s* binds to *m*

MHCII

- More than 700 different MHCII alleles are known [1]

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- For less than 3% there is sufficient experimental data from binding studies
- Problems of peptide-MHCII binding and affinity prediction are not solved yet

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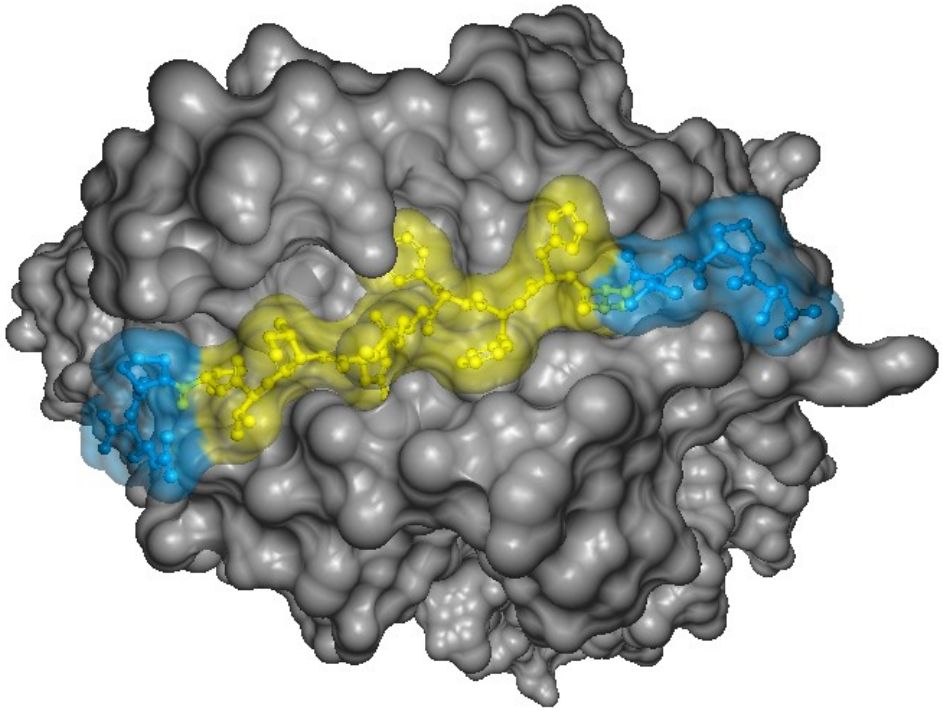
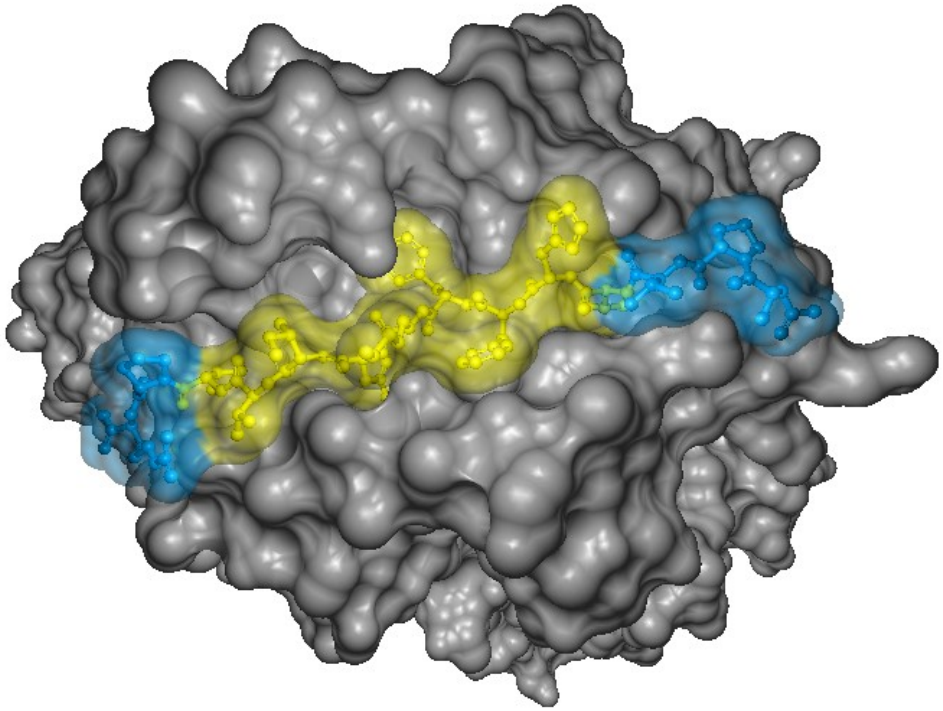
What makes the problems difficult?

- Varying peptide length since binding clefts are open



What makes the problems difficult?

- Varying peptide length since binding clefts are open
- The binding core (9 residues) is, in most of the cases, unknown



Related work

- Positional Scoring Matrices
- Gibbs Samplers
- Hidden Markov Models
- Artificial Neural Networks
- Partial Least Squares
- Support Vector Machines
- Consensus approach

For more information on related work have a look at the paper

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Lecture Notes in Bioinformatics: Proceedings of WABI 2008

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Predictors only for a small fraction of all MHCII alleles

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$\Rightarrow$ Lots of noise in the bags

- Better idea: represent sequence *s* by a bag *X* containing all reasonable [2,3] putative binding cores: aromatic (F,W,Y) or aliphatic (I,L,M,V) amino acid at position 1

2. Hammer, J. et al.: High-affinity binding of short peptides to major histocompatibility complex class II molecules by anchor combinations. Proc Natl Acad Sci U S A 91(10) (1994) 4456-4460
3. Sturniolo, T. et al.: Generation of tissue-specic and promiscuous HLA ligand databases using DNA microarrays and virtual HLA class II matrices. Nat Biotechnol 17(6) (1999) 555-561

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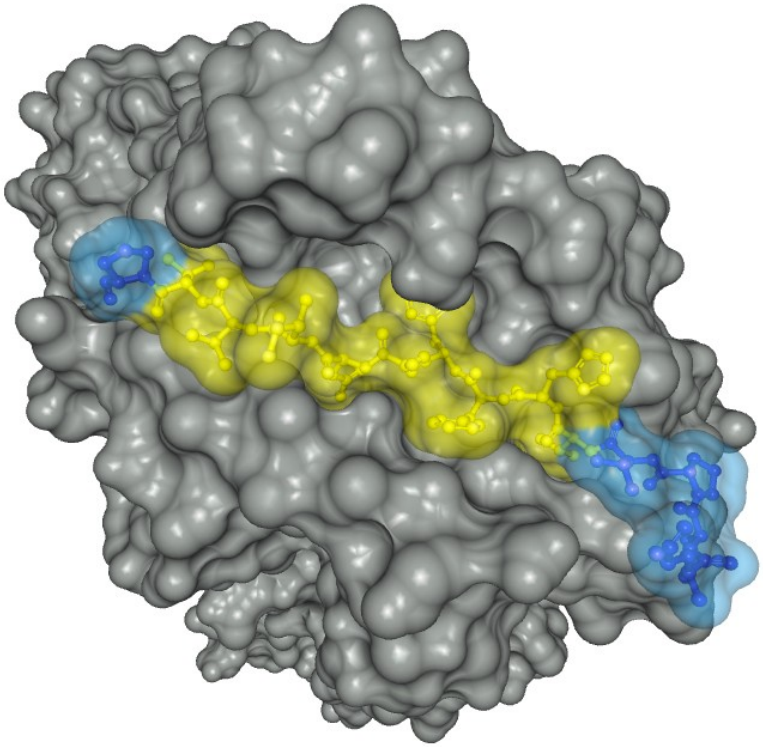


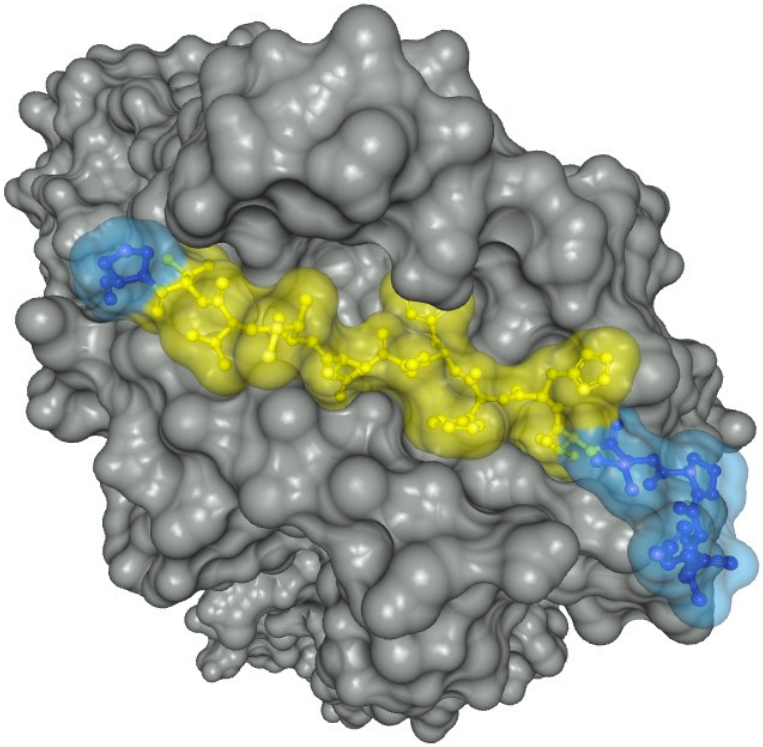
ENPVVHFFKNIVTPR

VVHFFKNIV

VHFFKNIVT

FFKNIVTPR

Peptide-MHCII binding affinity prediction



ENPVVHFFKNIVTPR

VVHFFKNIV

VHFFKNIVT

FFKNIVTPR

Represent sequence ENPVVHFFKNIVTPR by bag

$$X = \{\text{VVHFFKNIV}, \text{VHFFKNIVT}, \text{FFKNIVTPR}\}$$

Multiple Instance Learning

- Binary classification:

$$S = \{(x_1, y_1), (x_2, y_2), ..., (x_n, y_n) | x_i \in \mathcal{X} \wedge y_i \in \{-1, 1\} \; \forall i = 1, 2, ..., n\}$$

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4. Dietterich, T.G. et al.: Solving the multiple instance problem with axis-parallel rectangles. Artif Intell 89(1-2) (1997) 31-71

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- Multiple instance regression [5,6]:

$$S = \{(X_1, y_1), (X_2, y_2), ..., (X_n, y_n) | X_i \subseteq \mathcal{X} \wedge y_i \in \mathbb{R} \; \forall i = 1, 2, ..., n\}$$

4. Dietterich, T.G. et al.: Solving the multiple instance problem with axis-parallel rectangles. Artif Intell 89(1-2) (1997) 31-71
5. Dooly, D.R. et al..: Multiple-instance learning of real-valued data. J Machine Learn Res 3 (2002) 651-678
6. Ray, S. and Page, D.: Multiple instance regression. In: ICML '01: Proceedings of the Eighteenth International Conference on Machine Learning, San Francisco, CA, USA, Morgan Kaufmann Publishers Inc. (2001) 425-432

Normalized Set Kernel [7]

$$k(X, X') := \frac{\sum_{x \in X, x' \in X'} k_{\mathcal{X}}(x, x')}{f_{\text{norm}}(X) f_{\text{norm}}(X')}$$

with $k_{\mathcal{X}}$ being a kernel on $\mathcal{X}$ and

$$f_{\text{norm}}(X) = \sqrt{\sum_{x \in X, x' \in X} k_{\mathcal{X}}(x, x')}$$

7. Gärtner, T. et al.: Multi-instance kernels.
In Sammut, C., Hoffmann, A.G., eds.: ICML, Morgan Kaufmann (2002) 179-186

Single Predictor

- Create a bag X for every sequence of the training set

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- Encode the $x \in X$ reflecting physicochemical properties [9]

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Single Predictor

- Create a bag X for every sequence of the training set
- Encode the $x \in X$ reflecting physicochemical properties [9]
- Perform ν-Support Vector Regression (ν-SVR) with the normalized set kernel

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MHCIIMulti

- *Single Predictor* can only be used if there is sufficient experimental binding data for the target allele (~3% of all MHCII alleles)

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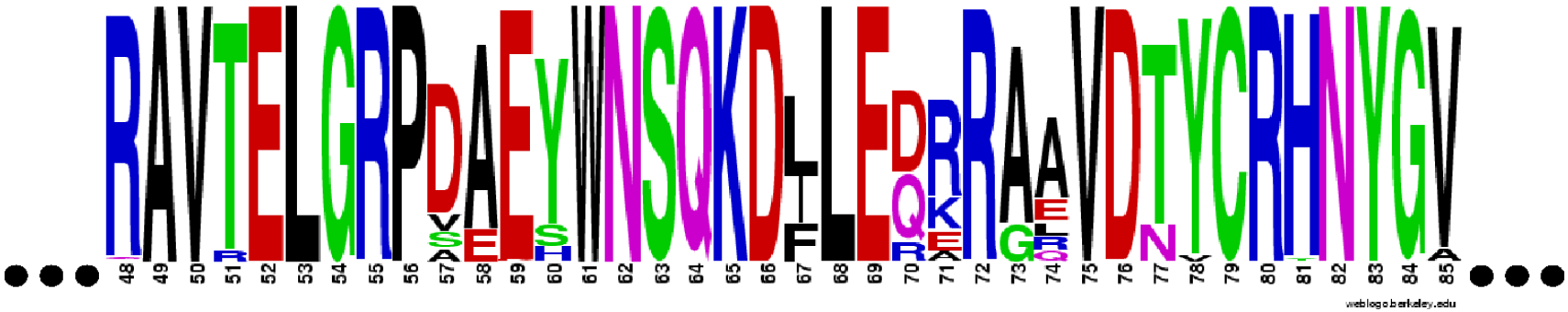
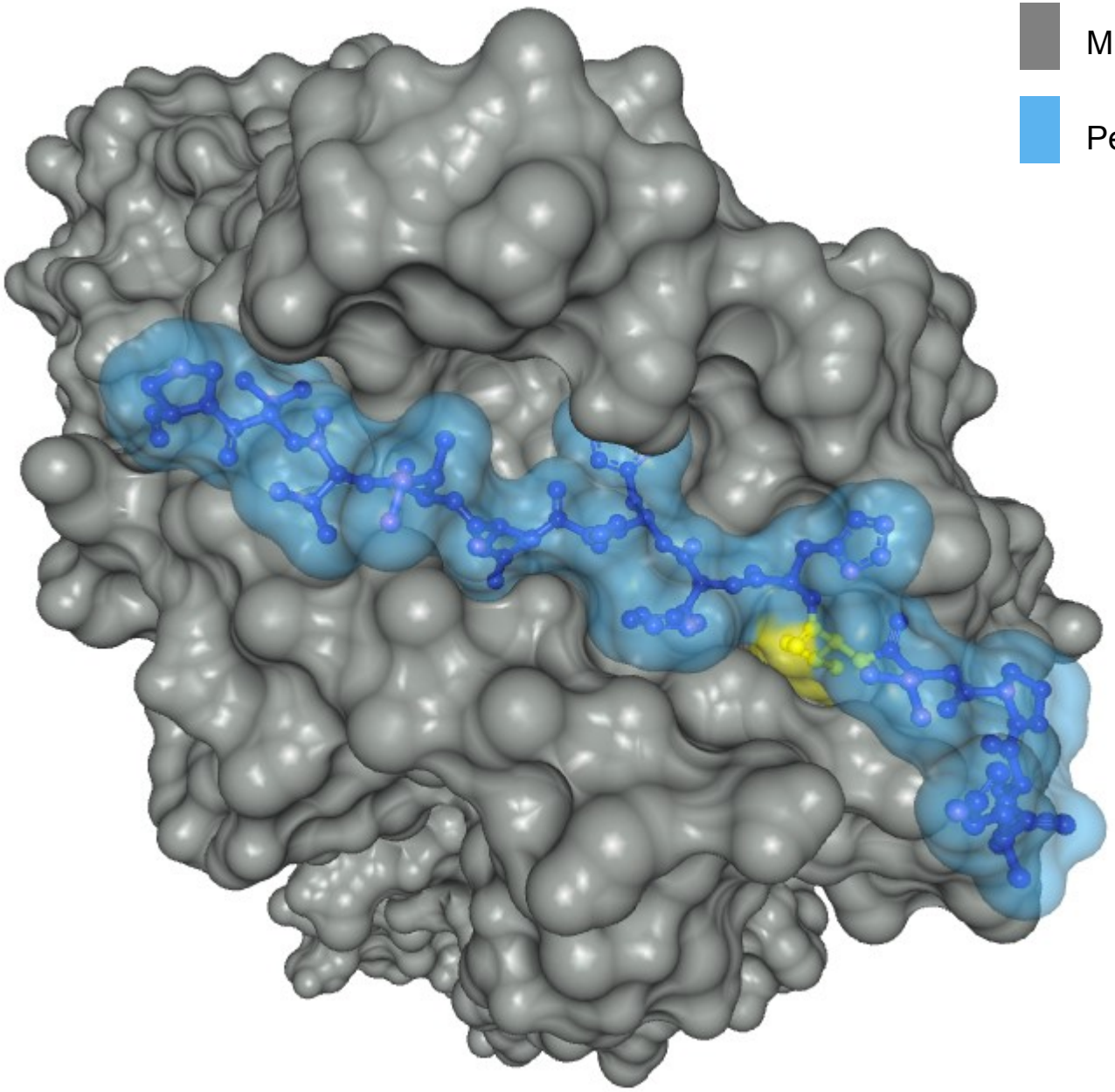
- Predictor for more alleles desirable
- HLA-DRB1, HLA-DRB3, HLA-DRB4 and HLA-DRB5 alleles differ only at very few positions



Methods



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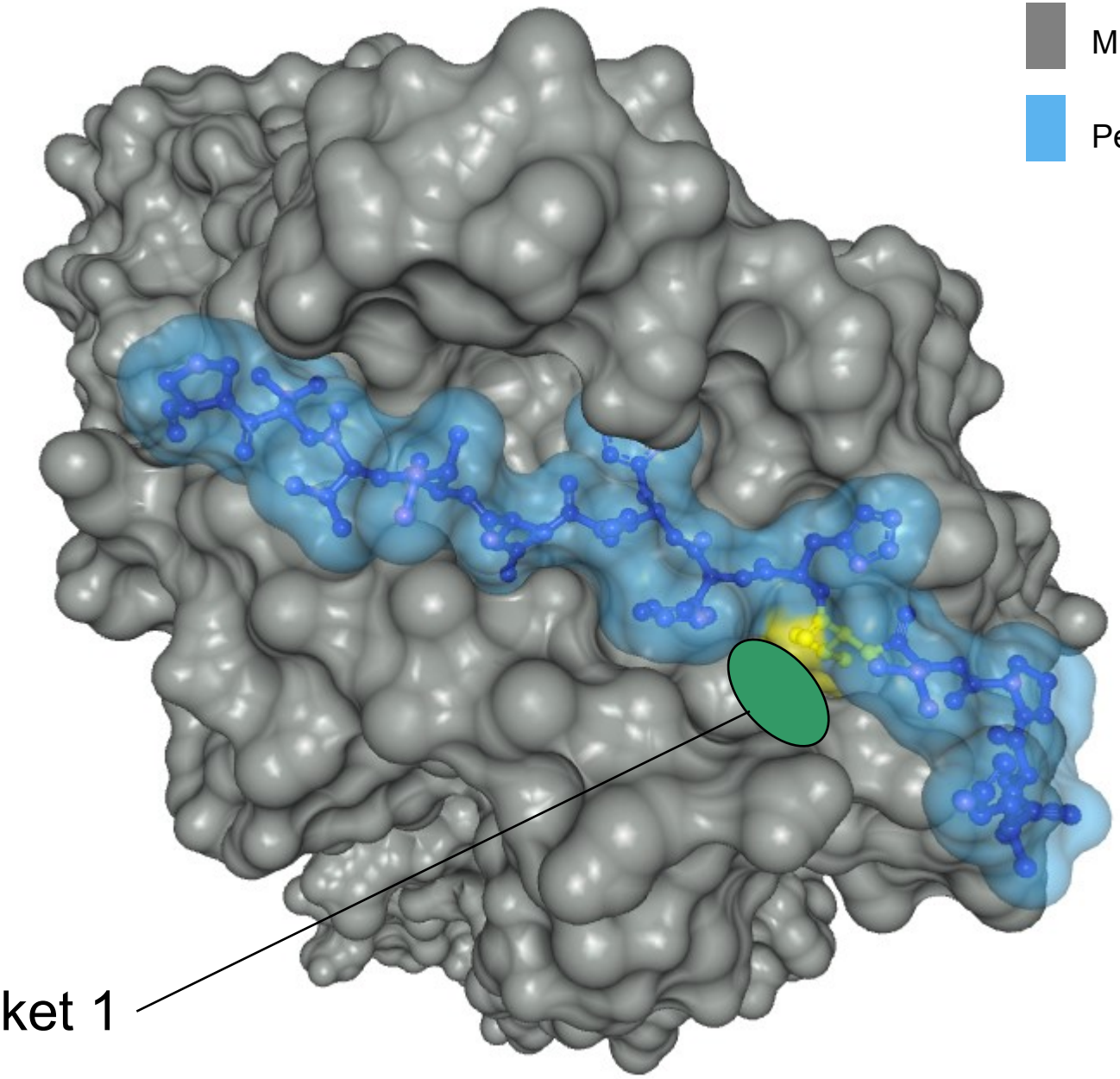

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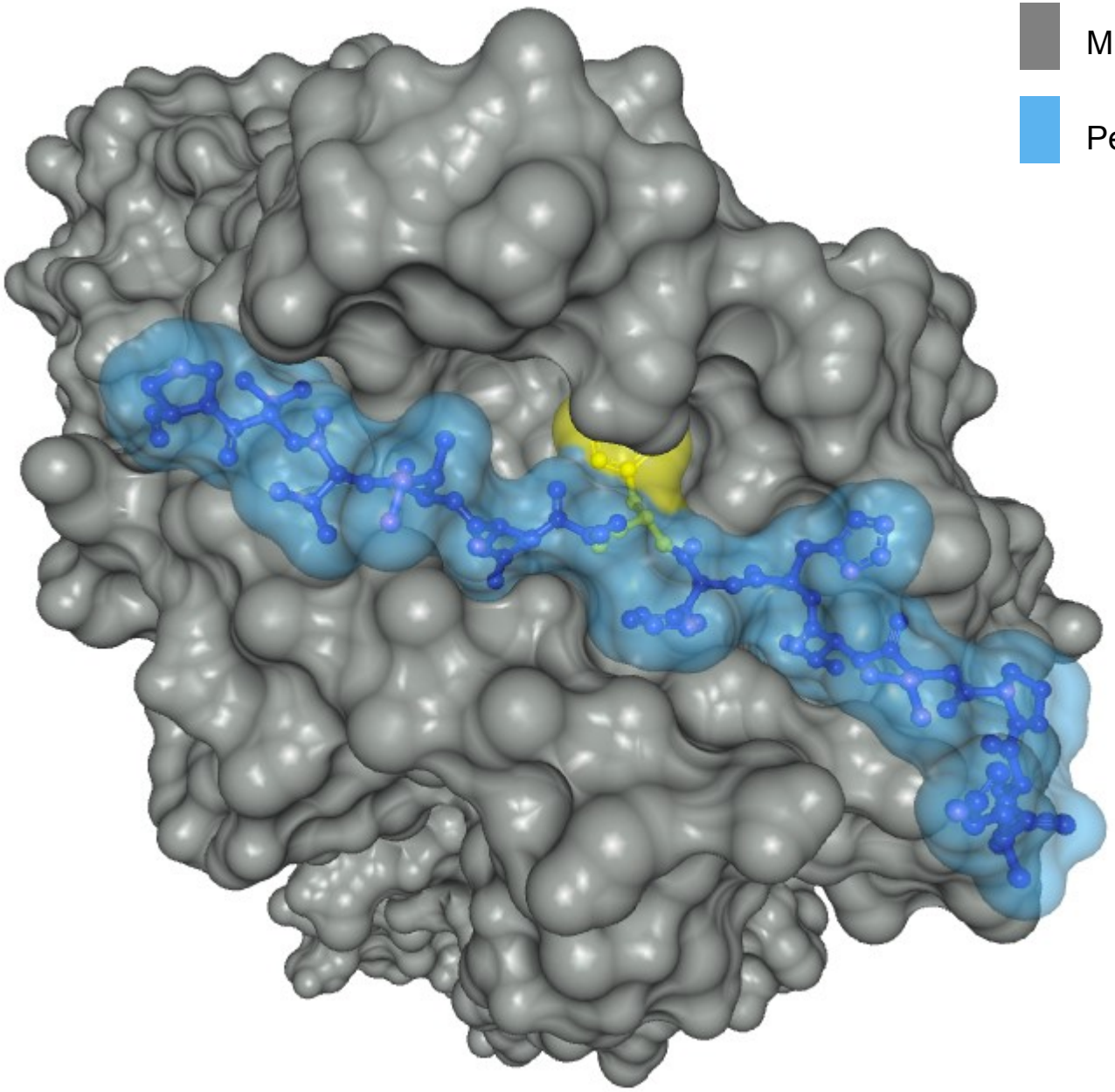

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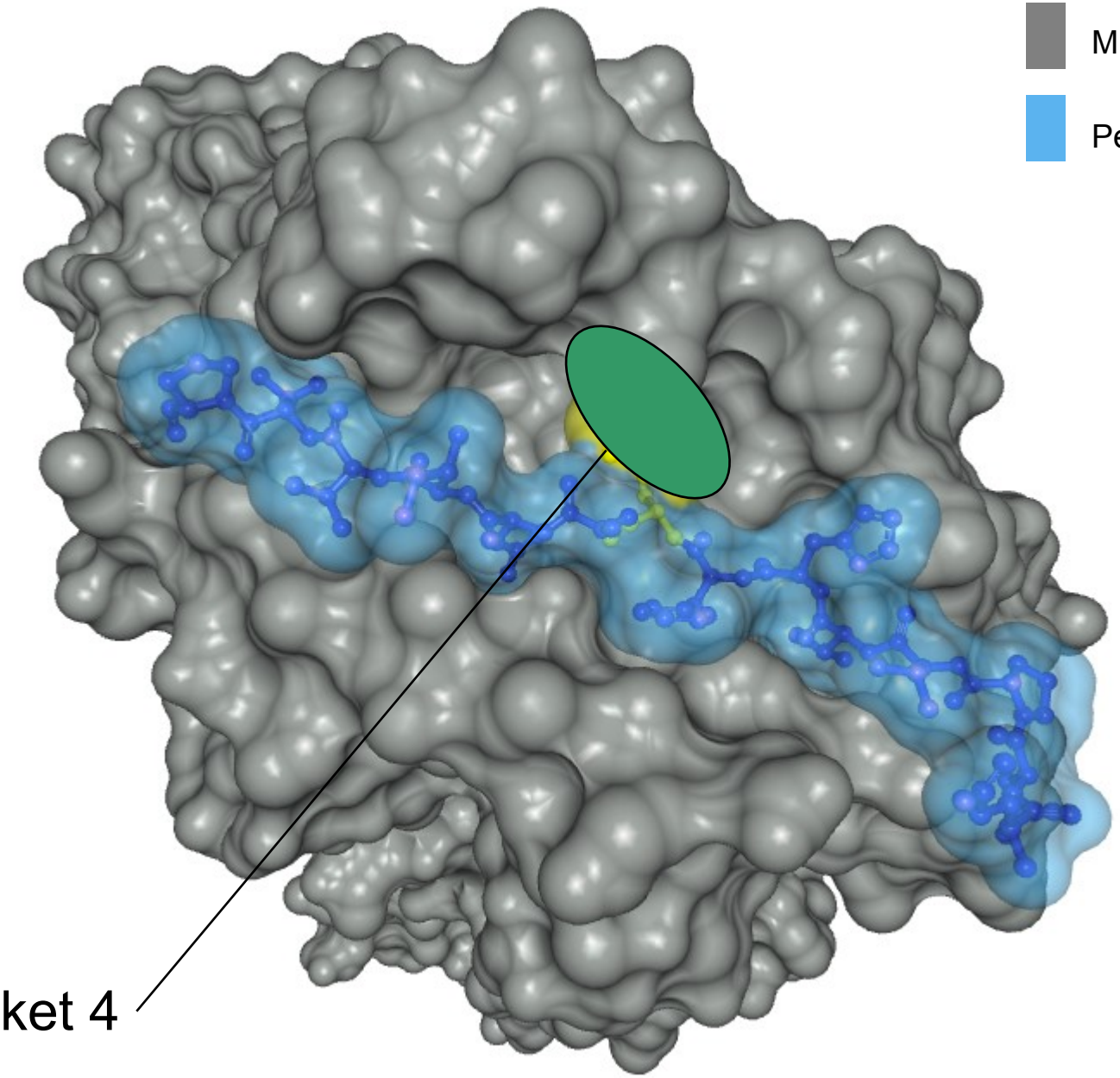

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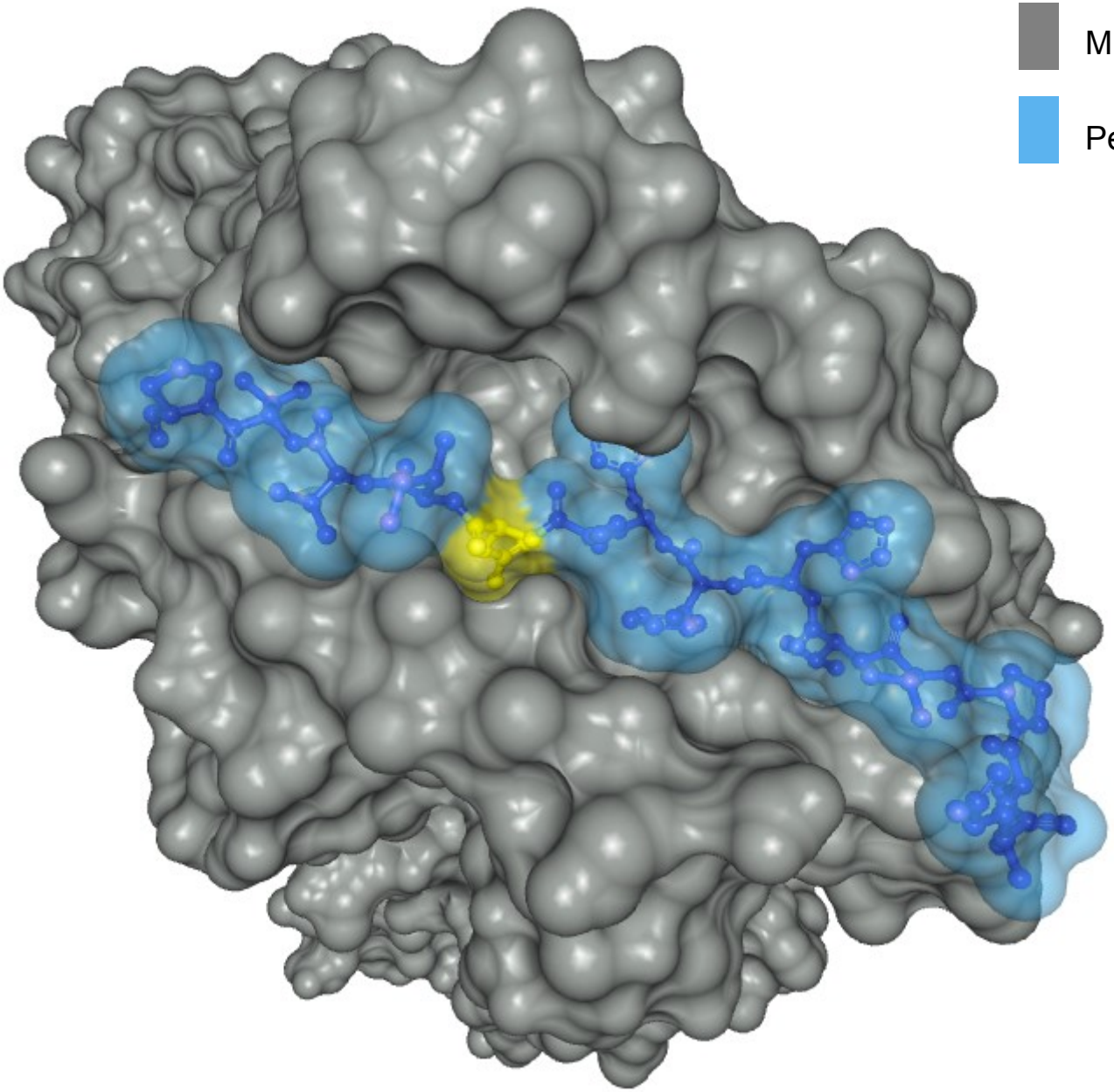

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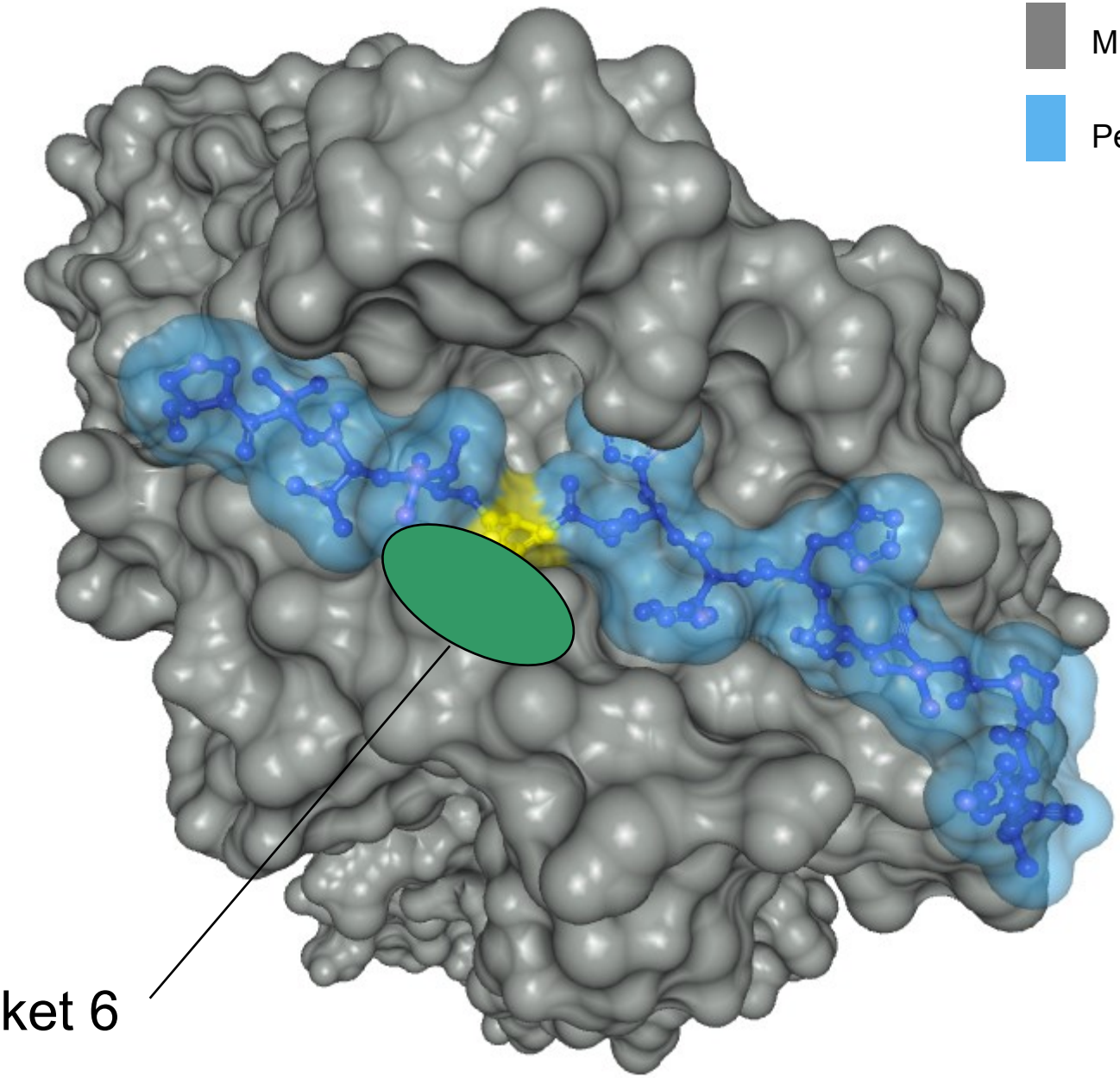

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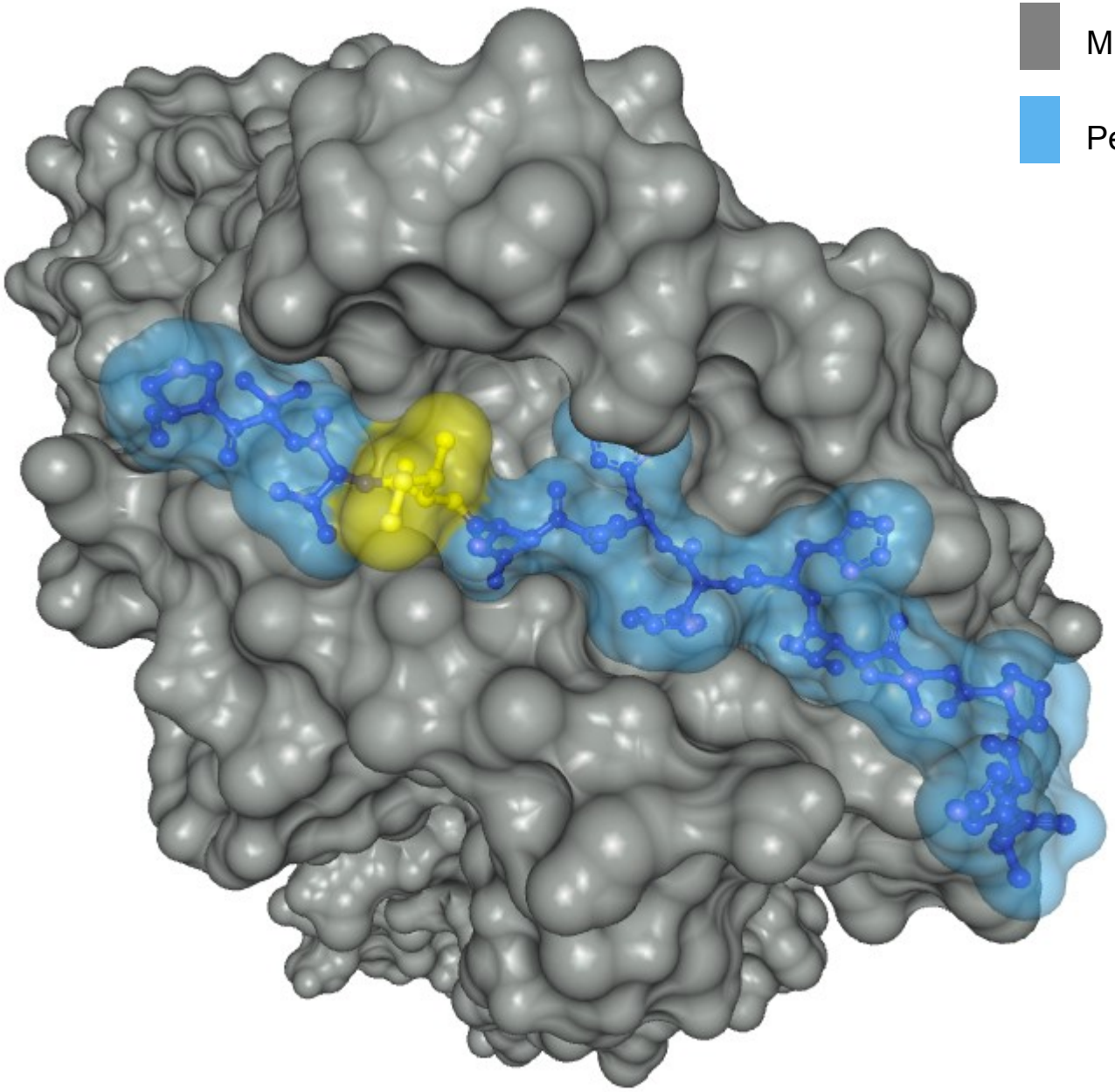
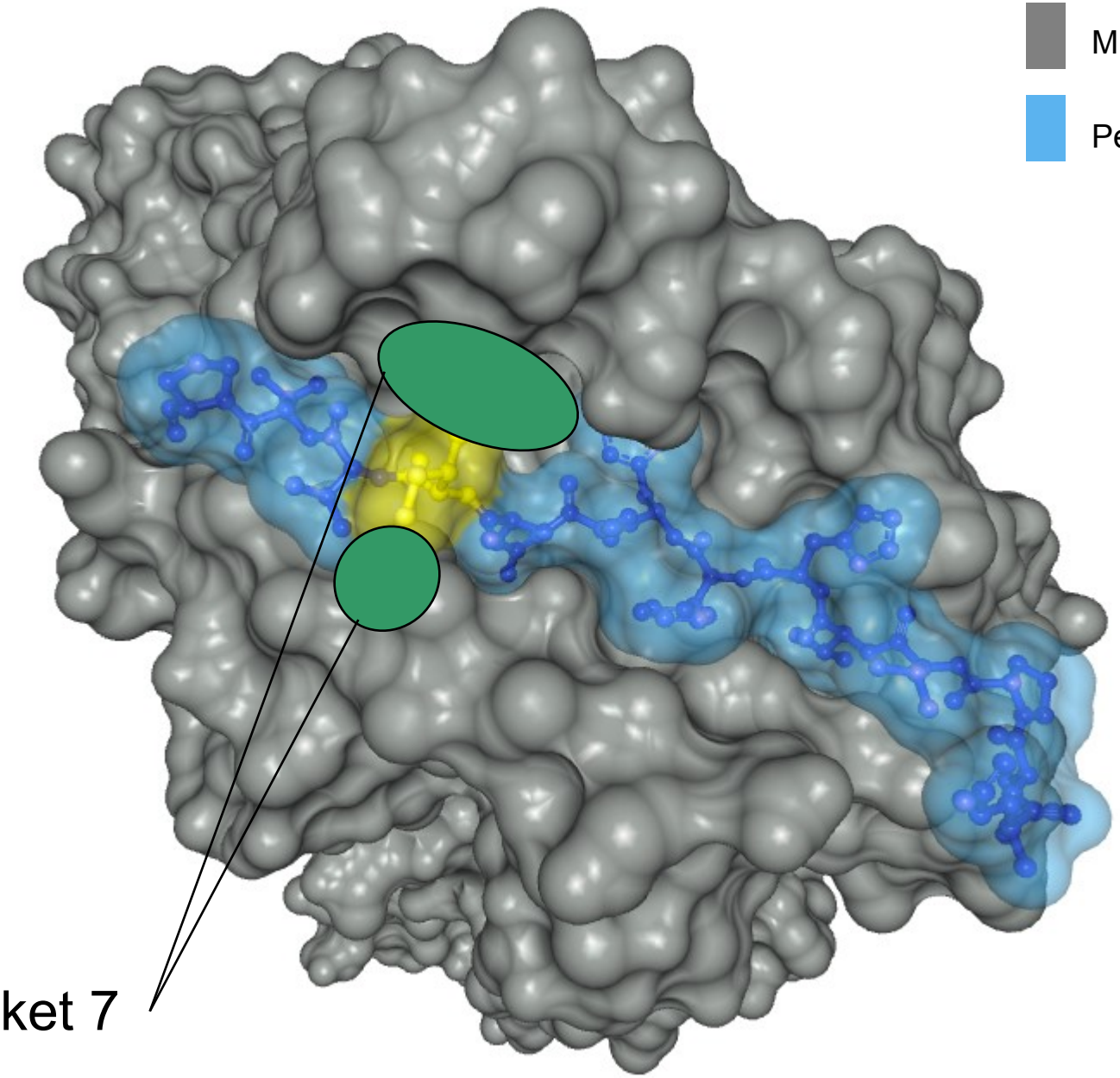
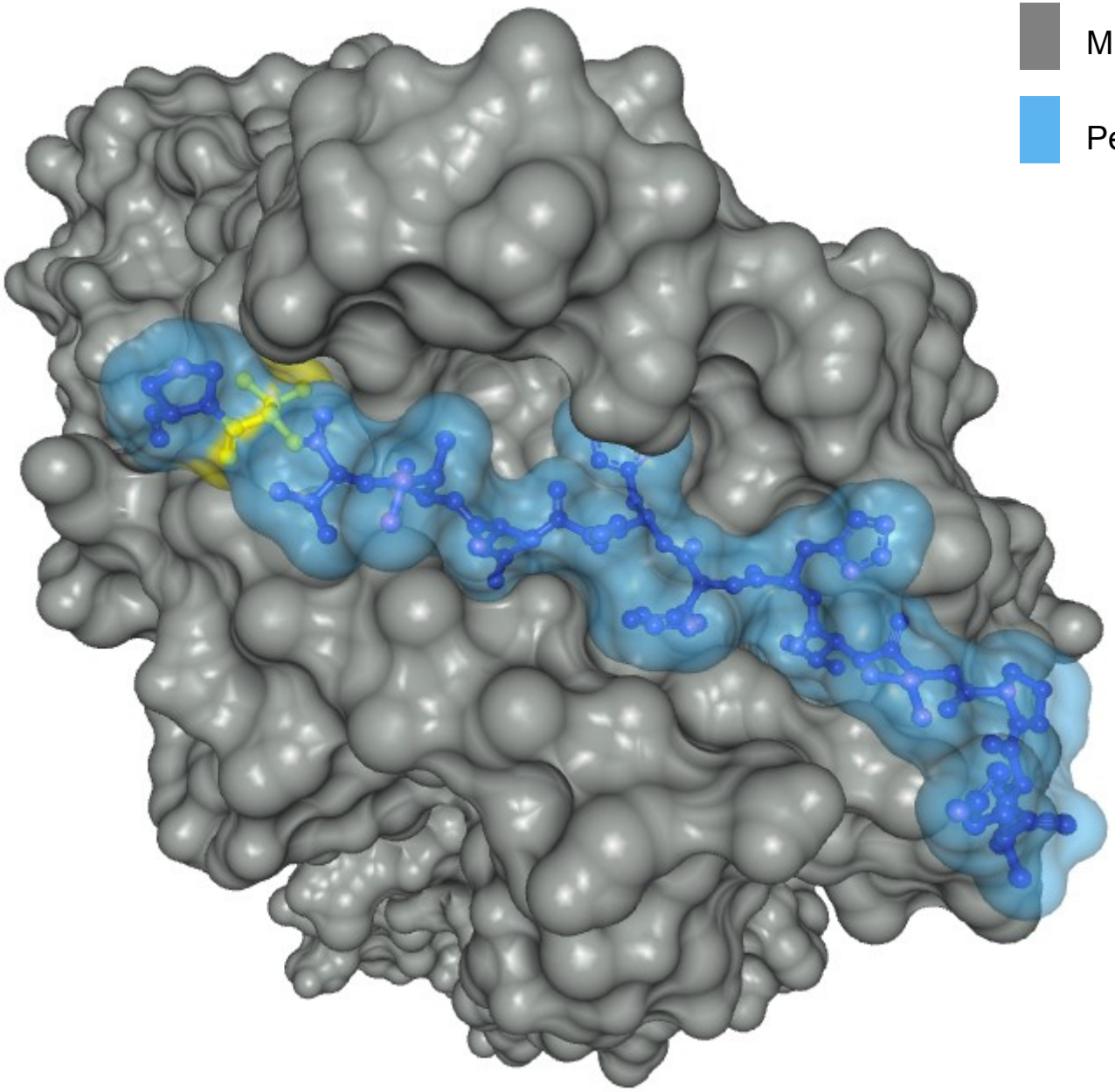



MHCII molecule
Peptide
Pocket 7

Methods



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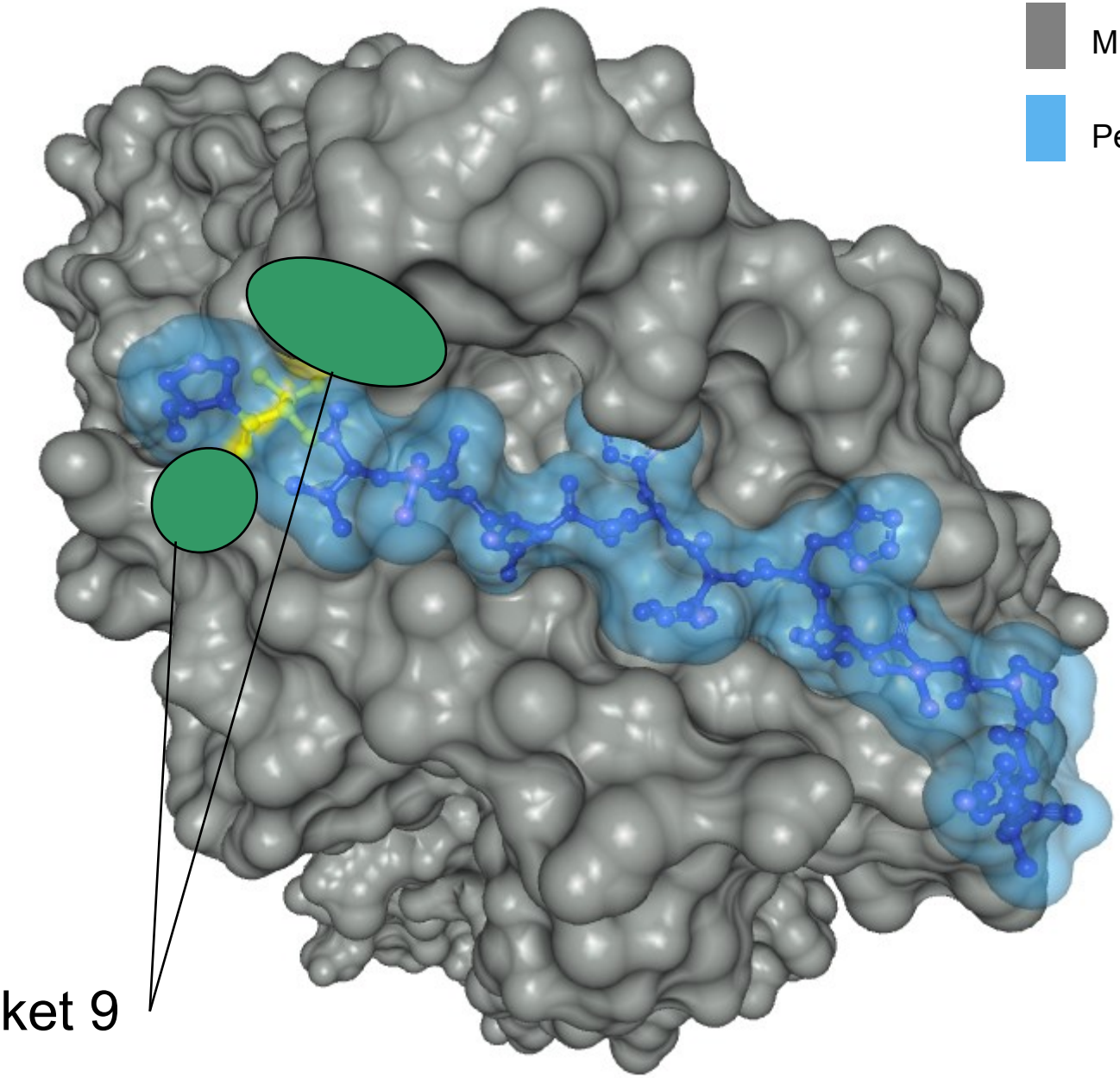
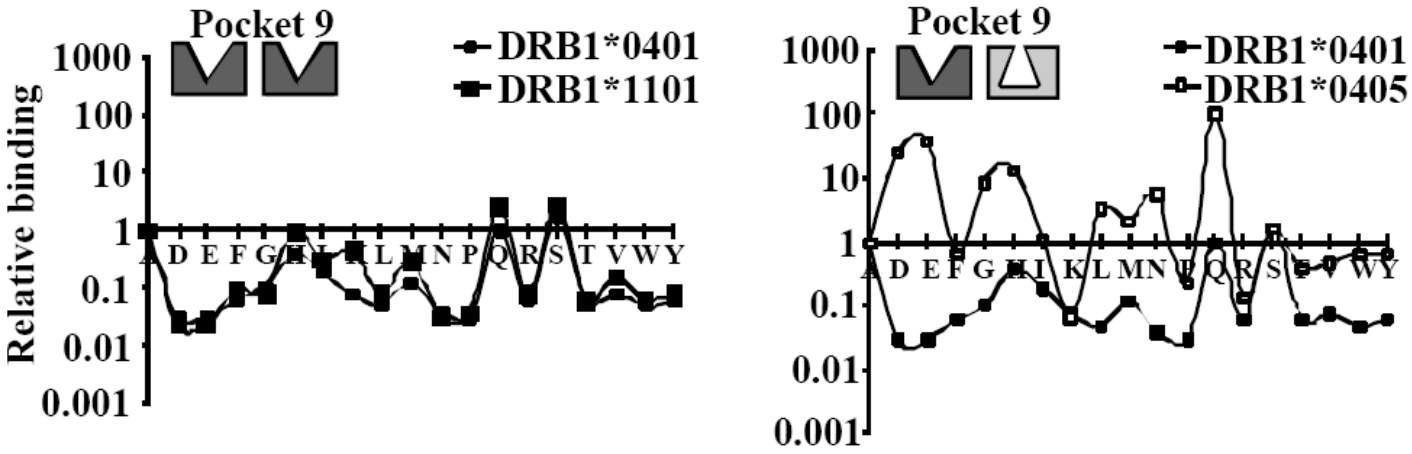


Virtual Matrices [3]



Adapted from [3]

- It was shown that alleles which have the same amino acids in a pocket region show similar binding affinities for the corresponding amino acid of the peptide

3. Sturniolo, T., Bono, E., Ding, J., Raddrizzani, L., Tuereci, O., et al.: Generation of tissue-specic and promiscuous HLA ligand databases using DNA microarrays and virtual HLA class II matrices. Nat Biotechnol 17(6) (1999) 555-561

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- Calculate a mean pocket vector for pockets 1, 4, 6, 7, and 9 using the same encoding as for the peptides

$$p = \left[p_1^T, p_4^T, p_6^T, p_7^T, p_9^T\right]^T$$

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Multitask learning for MHC class I peptide binding [10]

- Kernel-based prediction of peptide MHC class I binding prediction:

$$K\left((x,a),(x',a')\right) = K_{pep}(x,x') \times K_{all}(a,a')$$

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- Our approach: weight positions according to similarities of the binding pockets $p = [p_1^T, p_4^T, p_6^T, p_7^T, p_9^T]^T$

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with

$$w_i := \begin{cases} \mathrm{Pearson}(p_i, p'_i) + 1 & \text{if } i = 1,4,6,7,9 \\ 0.5 & \text{otherwise} \end{cases}$$

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- Recent study to compare peptide-MHCII binding predictors [11] on a new benchmark dataset

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- Performance measure: area under ROC curve

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Comparison

our methods

Allele	ARB	ProPred	SMM-align	Consensus	Single Predictor	MHCIIMulti
DRB1*0101	0.76	0.74	0.77	0.79	0.81	0.75
DRB1*0301	0.66	0.65	0.69	0.72	0.73	0.72
DRB1*0401	0.67	0.69	0.68	0.69	0.67	0.78
DRB1*0404	0.72	0.79	0.75	0.80	0.79	0.80
DRB1*0405	0.67	0.75	0.69	0.72	0.83	0.79
DRB1*0701	0.69	0.78	0.78	0.83	0.82	0.90
DRB1*0802	0.74	0.77	0.75	0.82	0.76	0.79
DRB1*0901	0.62	-	0.66	0.68	0.64	0.66
DRB1*1101	0.73	0.80	0.81	0.80	0.85	0.87
DRB1*1302	0.79	0.58	0.69	0.73	0.74	0.73
DRB1*1501	0.70	0.72	0.74	0.72	0.72	0.75
DRB3*0101	0.59	-	0.68	-	0.72	0.57
DRB4*0101	0.74	-	0.71	0.74	0.79	0.78
DRB5*0101	0.70	0.79	0.75	0.79	0.81	0.90
mean	0.70	0.73	0.73	0.76	0.76	0.77

Comparison

our methods

Allele	ARB	ProPred	SMM-align	Consensus	Single Predictor	MHCIIMulti
DRB1*0101	0.76	0.74	0.77	0.79	0.81	0.75
DRB1*0301	0.66	0.65	0.69	0.72	0.73	0.72
DRB1*0401	0.67	0.69	0.68	0.69	0.67	0.78
DRB1*0404	0.72	0.79	0.75	0.80	0.79	0.80
DRB1*0405	0.67	0.75	0.69	0.72	0.83	0.79
DRB1*0701	0.69	0.78	0.78	0.83	0.82	0.90
DRB1*0802	0.74	0.77	0.75	0.82	0.76	0.79
DRB1*0901	0.62	-	0.66	0.68	0.64	0.66
DRB1*1101	0.73	0.80	0.81	0.80	0.85	0.87
DRB1*1302	0.79	0.58	0.69	0.73	0.74	0.73
DRB1*1501	0.70	0.72	0.74	0.72	0.72	0.75
DRB3*0101	0.59	-	0.68	-	0.72	0.57
DRB4*0101	0.74	-	0.71	0.74	0.79	0.78
DRB5*0101	0.70	0.79	0.75	0.79	0.81	0.90
mean	0.70	0.73	0.73	0.76	0.76	0.77

Leave-One-Allele-Out (LOAO) Prediction

- Train Leave-One-Allele-Out (LOAO) version of *MHCIIMulti* on binding data of all alleles but the target allele (10 times randomly drawn subset)

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- Train Leave-One-Allele-Out (LOAO) version of *MHCIIMulti* on binding data of all alleles but the target allele (10 times randomly drawn subset)
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Leave-One-Allele-Out (LOAO) Prediction

- Train Leave-One-Allele-Out (LOAO) version of *MHCIIMulti* on binding data of all alleles but the target allele (10 times randomly drawn subset)
- Build aggregating predictor *MHCIIMulti** from all 10 random draws (mean prediction value)
- Compare to *Single Predictor* of most similar allele

$\Rightarrow$ Measure performance on the target allele

Comparison

Allele	Single Predictor Trained on Nearest Neighbor	LOAO MHCIIMulti	LOAO MHCIIMulti*
DRB1*0101	0.74	0.64	0.69
DRB1*0301	0.61	0.69	0.70
DRB1*0401	0.64	0.76	0.78
DRB1*0404	0.70	0.79	0.82
DRB1*0405	0.78	0.76	0.77
DRB1*0701	0.72	0.89	0.91
DRB1*0802	0.71	0.77	0.79
DRB1*0901	0.57	0.64	0.65
DRB1*1101	0.79	0.87	0.9
DRB1*1302	0.62	0.68	0.69
DRB1*1501	0.66	0.75	0.77
DRB3*0101	0.51	0.54	0.54
DRB4*0101	0.77	0.69	0.72
DRB5*0101	0.73	0.89	0.92
mean	0.68	0.74	0.76

Summary

- Methods for peptide-MHCII binding affinity prediction perform quite well on alleles with sufficient data

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- Presentation of method for building predictor for about 2/3 of all MHCII alleles (instead of ~7%)
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Summary

- Methods for peptide-MHCII binding affinity prediction perform quite well on alleles with sufficient data
- Presentation of method for building predictor for about 2/3 of all MHCII alleles (instead of ~7%)
- LOAO performance results are quite promising
  $\Rightarrow$ Can be assumed that the methods perform well for alleles for which no experimental data exist
- Methods are integrated into the EpiToolKit [12] (http://www.epitoolkit.org/mhciimulti)

[12] Feldhahn, M., Thiel, P., Schuler, M.M., Hillen, N., Stevanovic, S., et al.: EpiToolKit-a web server for computational immunomics. Nucleic Acids Res (2008) 6 (Web Server issue): W519-522

graduating soon
looking for postdoc position

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SFB 685
Immuntherapie

... you for listening

Comparison to NetMHCIIPan

Allele	Number of training samples (MHCIIMulti*)	MHCIIMulti*	Number of training samples (NetMHCIIPan)	NetMHCIIPan
1_0101	4430	0.670	9441	0.778
1_0401	4609	0.765	13583	0.775
1_0405	4595	0.777	13977	0.808
1_1101	4604	0.863	13657	0.799
1_1302	4224	0.651	14109	0.658
1_1501	2900	0.744	13673	0.738
1_0301	3240	0.738	13587	0.746
1_0404	3426	0.796	13944	0.852
1_0701	4076	0.833	13754	0.825
1_0802	4538	0.789	14187	0.841
1_0901	3779	0.684	14077	0.653
3_0101	4302	0.630	14058	0.716
4_0101	3206	0.746	14161	0.724
5_0101	4511	0.848	13683	0.831
mean:	4031	0.752	13564	0.768

Positive Definiteness

THEOREM (SCHOENBERG THEOREM). Let $\mathcal{X}$ be a space in which a distance function $d(x, y)$ is defined subject to the following conditions:

1. $d(x, y) = d(y, x) \geq 0$
2. $d(x, x) = 0$

for all $x, y \in \mathcal{X}$. The function $\exp(-d^p(x, y))$ is positive definite if $0 < p \leq 2$ and not positive definite if $p > 2$.

Li, H., Jiang, T.: A class of edit kernels for SVMs to predict translation initiation sites in eukaryotic mRNAs. In: RECOMB. (2004) 262-271
Schoenberg, I.J.: Metric spaces and positive denite functions. Trans Amer Math Soc 44(3) (1938) 522-536