MAPPING THE ANTIBODY RESPONSE TO VACCINES DIRECTLY FROM PATIENT SERUM

Statistical analyses based on NGS and novel library technologies

Michael Szardenings
Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany

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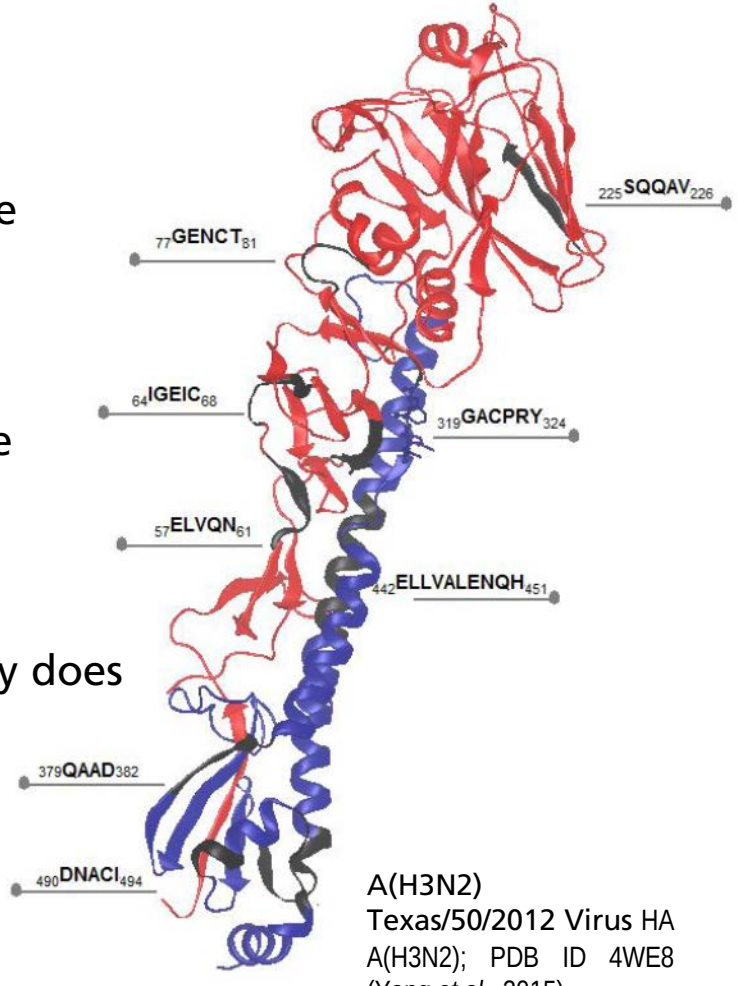
Conflict of interest

- Managing director of the Epitopic GmbH dealing with antibody epitope fingerprinting and leading the Fraunhofer group applying the technology on sera.
- Patentholder on several relevant technology patents

- Always hoped our immune system would not be so ********* complex as it turns out to be

Vaccine Epitopes

- This talk is about how to predict/identify multiple epitopes from a single drop of patient blood.
- Four epitopes of this antigen are described in the literature, four more were identified.
- All based on peptide phage display, which usually does not results in more than a few epitopes.



A(H3N2) Texas/50/2012 Virus HA A(H3N2); PDB ID 4WE8 (Yang *et al.*, 2015)

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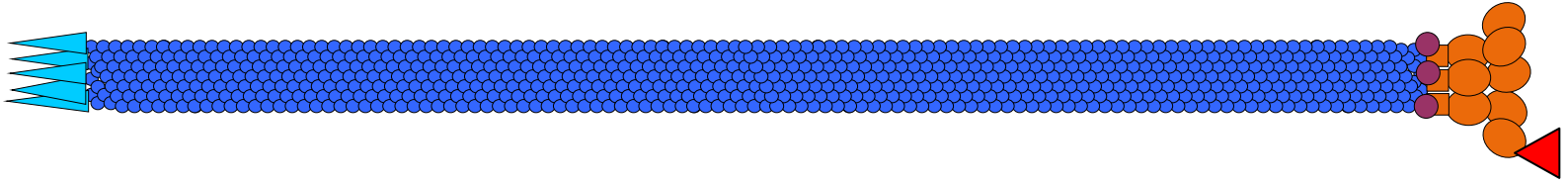
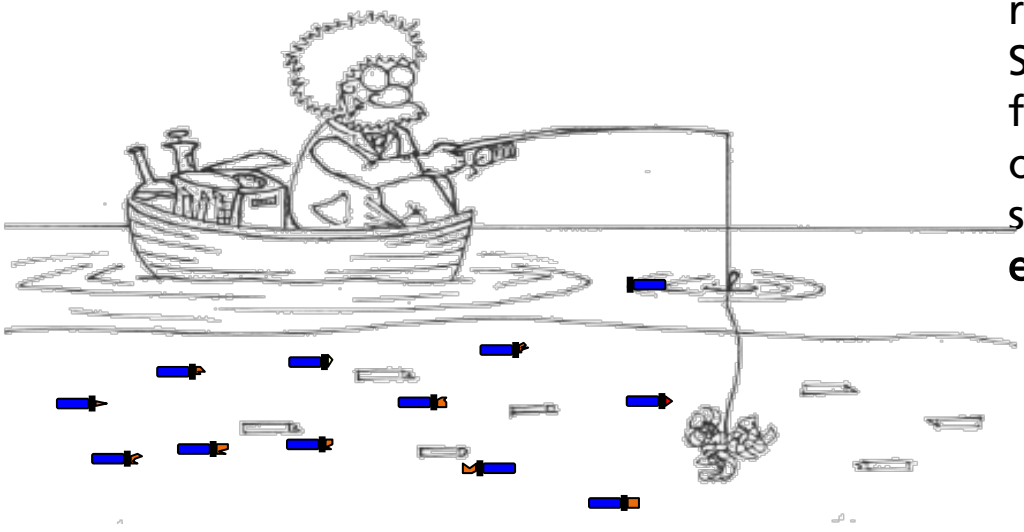


modifying the rules of the game

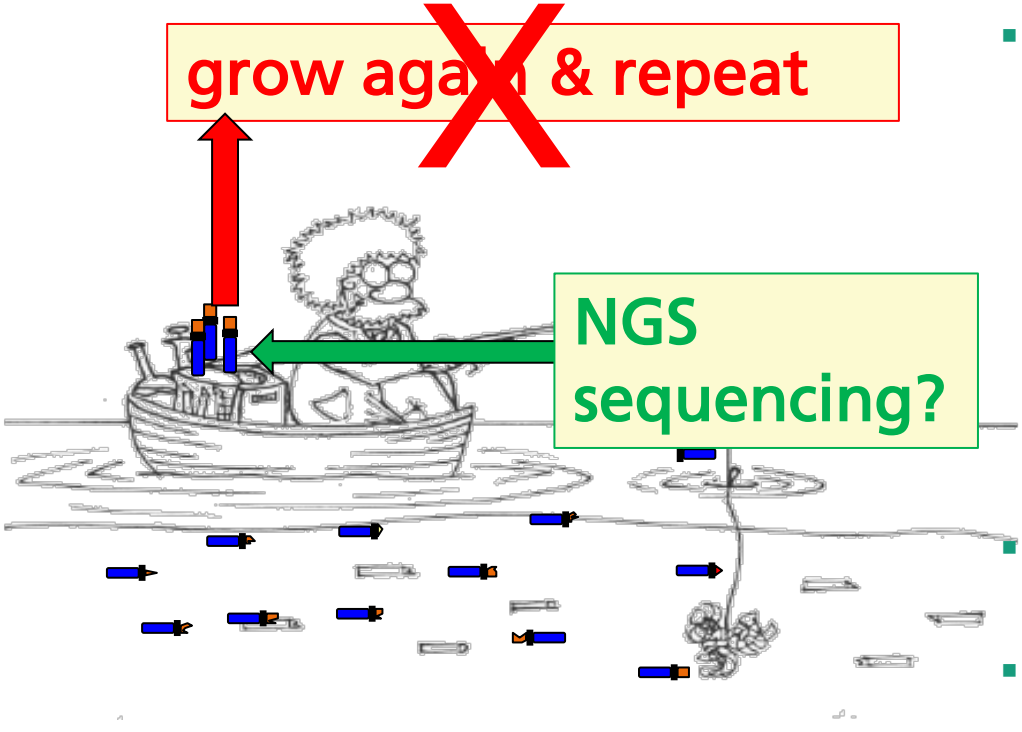
STATISTICAL PEPTIDE PHAGE DISPLAY

Fingerprinting Antibody Epitopes



Standard peptide phage display is, as most people will agree to, a kind of lottery with respect to the sequences finally identified as binders. After many years without real progress Next Generation Sequencing (NGS) is now more frequently being used. But this is only partially improving the results, since it is still **relying on the enrichment of individual clones.**

Fingerprinting Antibody Epitopes



- Applying a new combination of
  - Statistically reliable random peptide phage library
  - Optimized NGS protocols
  - Stringent sequence data filtering
  - Specially designed software for calculating statistics of short motifs
- …this allows to include not only enriched sequences…
- …and gives access to hundreds of sequences in the analyses, which would otherwise be discarded.

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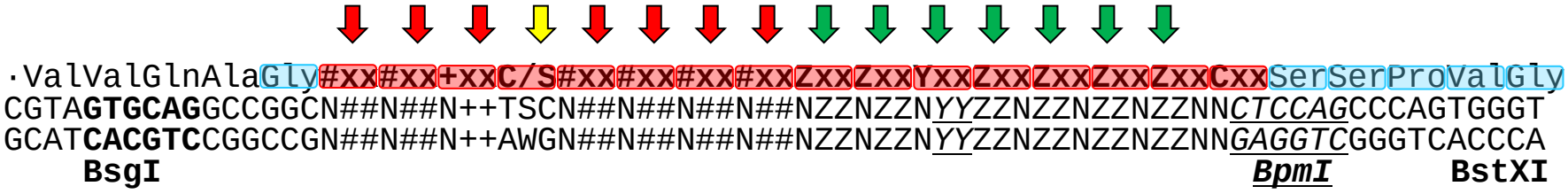
Library Design ENTE-1



NYY: any codon ending on certain non palindromic NN
NZZ: any codon (no Trp no Met)
N##: any codon (no Cys no Met)
N++: any codon MUST end with a K, NO Cys
NNC: any codon ending on C
(or NNK instead of N++)

- NO Cys
- Cys/Ser
- reduced codon set with Cys

- Trinucleotide based synthesis
- Max 18 codons per position
- Reduced probability of too close Cys
- Reduction of Met and Trp codons
- Contains significant fraction of 8-mer combinations

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Statistics of the new library ENTE-1

	Gly	#xx	#xx	+xx	C/S	#xx	#xx	#xx	#xx	Zxx	Zxx	Yxx	Zxx	Zxx	Zxx	Zxx	Cxx	Ser	Ser
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
A	0	39398	90956	186896	522	106968	111974	119732	125638	145486	143878	330	115070	141808	150810	148728	210284	0	0
C	0	416	442	972	1568218	1508	384	382	514	166848	166862	326870	148224	181926	178966	186930	550978	0	0
D	0	121218	147304	448	54	132024	128594	132772	135180	133122	133244	444	125948	119076	122484	89678	373274	0	0
E	0	265552	214760	200	52	181604	168106	166774	173500	171608	183564	361690	164792	154616	157474	156350	120	0	0
F	0	79882	93234	132368	782	121944	133130	124916	123726	135898	135512	388	135932	148972	141866	140308	419896	0	0
G	2580938	118170	102104	123210	288	103164	98142	103158	103184	105932	118254	210228	103892	100738	99158	103104	302	0	0
H	0	183728	210022	276224	218	193046	199854	198690	201420	198948	197830	712	215206	199326	197608	200372	662	0	0
I	0	261530	148836	670	60	152052	131096	125206	131572	121100	125694	166342	125310	121888	120926	117576	307086	0	0
K	0	123962	113660	270	44	96312	88342	82500	84762	85532	90728	141044	88136	78988	75258	70150	92	0	0
L	0	76996	101696	135064	180	107394	121148	123968	121546	126398	114968	454	142988	135062	129778	143870	600	0	0
M	0	136	132	190552	146	90	90	82	118	92	68	44	126	106	72	80	8	0	0
N	0	242394	173660	222964	164	160878	146182	139142	137072	100932	98022	396	99174	94478	96654	91812	225742	0	0
P	0	133074	151342	179242	464	155758	144530	145170	148064	144820	140742	260560	161584	139658	139098	141702	150	0	0
Q	0	167382	203670	276748	198	184028	211236	213484	203750	205056	187362	398642	221298	207610	212524	222028	32	0	0
R	0	59562	111702	155384	522	104284	117846	123140	121788	122634	121240	189740	125332	125692	121258	132628	368	0	0
S	0	97316	107976	145310	1007238	129726	126148	125332	121664	129168	127548	664	130660	138544	134466	131084	868	2580938	2580938
T	0	155464	132292	164596	254	128358	126256	123696	122298	122874	122012	436	125248	121086	124680	125946	320	0	0
V	0	215518	194452	214970	384	197740	191790	190844	194094	197602	214250	324	190598	199846	205314	204654	722	0	0
W	0	83942	127436	174576	336	159568	171438	179928	164760	160	82	280202	562	62	54	26	56	0	0
Y	0	155298	155262	274	814	164492	164652	162022	166288	166728	159078	241428	160858	171456	172490	173912	489378	0	0

No such codon in the oligonucleotide, these are the errors of Illumina MiSeq

Naive ENTE-1 library

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Statistics: Library diversity

	ENTE-1 before expansion	ENTE-1 final library	Ph.D.™-12* (commercial library)	ENTE-1 after mAB 10D2 1st selection	ENTE-1 after mAB 10D2 2nd selection
Total number	**1,241,361**	**2,800,721**	**17,609,210**	**294,193**	**411,931**
Sequence found 1X	1,186,637 (96%)	2,018,083 (72%)	736,953 (4.2%)	76,972 (26.2%)	16,574 (4%)
Sequence found 2X	22,853 (3.7%)	351,921 (25.1%)	114,791 (1.3%)	37,533 (25.5%)	4,401 (2.1%)
Sequence found 3X	2,002 (0.5%)	24,957 (2.7%)	47,187 (0.8%)	16,079 (16.4%)	1,492 (1.1%)
Sequence found 4X	21 (0.1%)	838 (0.1%)	26,184 (0.6%)	7,074 (9.6%)	759 (0.7%)
Sequence found 5X	131 (0.1%)	71	17,098 (0.5%)	3,338 (5.7%)	478 (0.6%)
Sequence found 6X	48	14	11,727 (0.4%)	1,672 (3.4%)	437 (0.6%)
Sequence found 7X	21	6	8,801 (0.3%)	817 (1.9%)	309 (0.5%)
Sequence found 8X	5	5	7,057 (0.3%)	504 (1.4%)	268 (0.5%)
Sequence found 9X	4	1	5,531 (0.3%)	297 (0.9%)	231 (0.5%)
Sequence found 10X	6	2	4,678 (0.3%)	191 (0.6%)	228 (0.5%)
Sequence found 11X	2	1	3,972 (0.2%)	142 (0.5%)	187 (0.5%)
Sequence found 12X	2	1	3,326 (0.2%)	100 (0.4%)	155 (0.5%)
Sequence found 13X	1		2,939 (0.2%)	70 (0.3%)	156 (0.5%)
Sequence found 14X	2		2,542 (0.2%)	56 (0.3%)	119 (0.4%)
Sequence found 15X	1		2,253 (0.2%)	46 (0.2%)	110 (0.4%)
Sequence found 16X			2,074 (0.2%)	45 (0.2%)	95 (0.4%)
Sequence found 17X			1,825 (0.2%)	36 (0.2%)	98 (0.4%)
Sequence found 18X			1,713 (0.2%)	32 (0.2%)	110 (0.5%)
Sequence found 19X			1,495 (0.2%)	22 (0.1%)	90 (0.3%)
Sequence found 20X			1,366 (0.2%)	31 (0.2%)	85 (0.4%)
Sequence found **> 20X**			65,305 (89.1%)	308 (5.6%)	2,224 (84.5%)
Sequence found **> 100X**			20,241 (82.1%)	26 (1.6%)	631 (67.1%)
Sequence found **> 1000X**			2,844 **(56.6%)**	0	45 (29%)

*Matochko et al. Methods 58 (2012) 47–55

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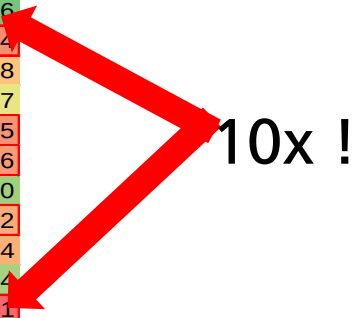
Statistics: Amino Acid Distribution in „Normal“ Libraries

Almost 10x difference in amino acid statistics: C7C library , NNK synthesis (312,352 sequences)

data from: Dias-Neto et al:Next-generation phage display: integrating and comparing available molecular tools to enable cost-effective high-throughput analysis. PLoS One. 2009 Dec 17;4(12)

	A1	A2	A3-	A4	A5	A6	A7
A	3398	3223	3422	3475	3592	3697	4161
R	4564	5649	5669	5316	4691	4484	5326
N	826	701	755	888	750	822	834
D	1531	1385	1636	1101	1472	1654	1288
C	2387	2171	2188	2215	2635	2402	2227
Q	902	1131	1159	656	750	816	885
E	1253	1318	1368	1009	1265	1362	936
G	5308	5196	4750	4652	5350	5273	4220
H	1062	1089	1273	715	901	880	1082
I	1143	1045	1064	1616	1223	1167	1124
L	4233	4402	4484	3440	3934	3941	3994
K	614	585	564	766	568	682	531
M	928	858	669	1080	773	876	658
F	1906	1648	1613	1441	1783	1597	1190
P	1723	1882	2059	1751	1769	1704	3384
S	3909	3881	3768	5875	4564	4382	5047
T	1334	1310	1298	2595	1555	1591	2143
W	1701	1824	1460	1823	1802	1847	1309
Y	1267	1170	1163	918	1124	1121	1003
V	4629	4149	4254	3283	4117	4320	3276



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Preparing For Statistical Data Mining

- Phage Display selection is done with an optimised immunotube procedure.
- NGS is done on tagged PCR products in an illumina MiSeq
- Remaining data is indexed and stored in a data base …
- STOP!
- The error rate in NGS is prohibitive for analyzing individual sequences:
  - 0.1% on the illumina machines under optimal conditions
  - In our 180 bp reads >18% of all sequences would contain a wrong base, plus additional artefacts from PCR and cloning…
- In standard approach procedure we purge the data of low quality reads and in an additional step remove all sequences containing a single read error compared to the library's trinucleotide set up:

Dataset	All Seq	Valid Seq	Motif Count
it2_0214-1pr	541,613	353,725	138,673
it2_0214-2pr	571,359	358,291	137,181
it2_1014-1pr	406,754	272,396	139,095
it2_1014-2pr	356,731	231,764	135,209

Preparing For Statistical Data Mining

- In standard approaches all 3-mer and 4-mer motifs are indexed, frequency and probability are calculated, compared and related sequences can be retrieved and analyzed.
- For monoclonal antibodies a single selection round is usually not enough to enrich sequences but the enrichment is seen on the shorter motif level:

Id	Motif	Count	Freq	Expect	Enrichment (log!)
66091	DPEN	2445	3,17412	5,12765	1,95354
65785	DPPN	2365	3,18856	5,12765	1,93909
4168	NEVY	2340	3,19318	5,12765	1,93447
66128	DPDN ★	1459	3,39834	5,21223	1,81389
4740	NEAY ★	1727	3,3251	5,12765	1,80255
65998	DPHN	1272	3,45791	5,21223	1,75433
100344	PPNE	1387	3,42032	5,16191	1,74159
33118	EWIW	125	4,46548	6,13503	1,66955
5080	NDEY	1252	3,46479	5,12765	1,66286

First selection round on mAB 10D2!

Mapping of mAB 10D2, epitope in synuclein:
DMPV**DPDNEAY**EMPS

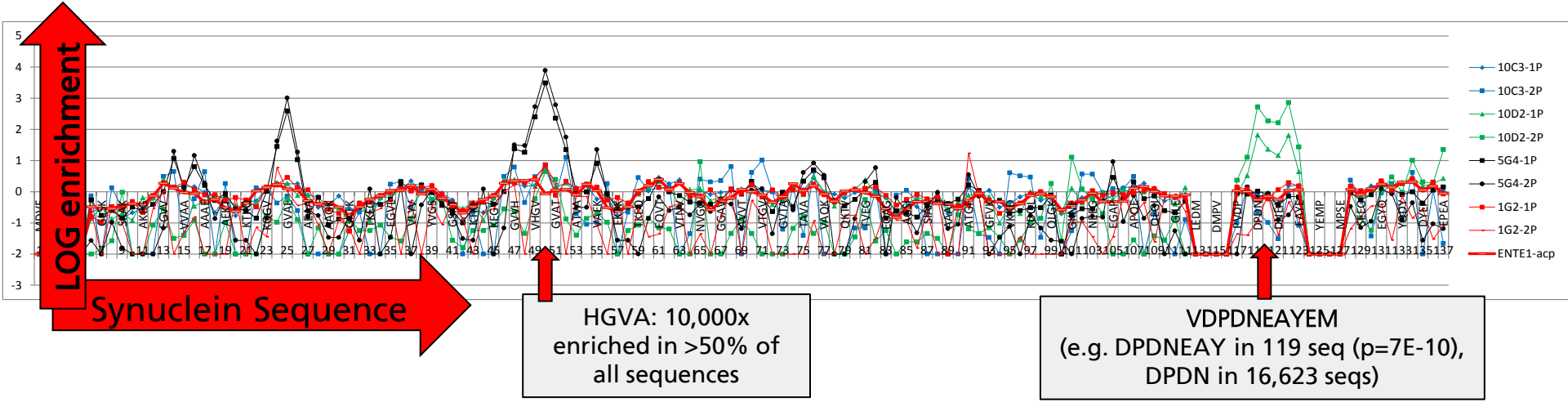
Count = Total number in data set
Freq = -log(count/total sequences)
Expect = -log(theoret./total sequences)
Enrichment = (Expect-Freq)

- Knowing the antigen's sequence allows direct search for it's shorter motifs ★ in the data base

Motif Search in NGS Data –Example Three Synuclein mABs

- The motif enrichment (NOT THE FREQUENCY) in data sets from selection experiments can be plotted against the entire alpha synuclein protein's 4-mer sequences. This curve reveals potential epitopes. (Antibodies from AJ Roboscreen GmbH)

Explanation: blue/green/black different monoclonal antibodies; red non specific data sets; Y-axis is **log** enrichment over expected values.



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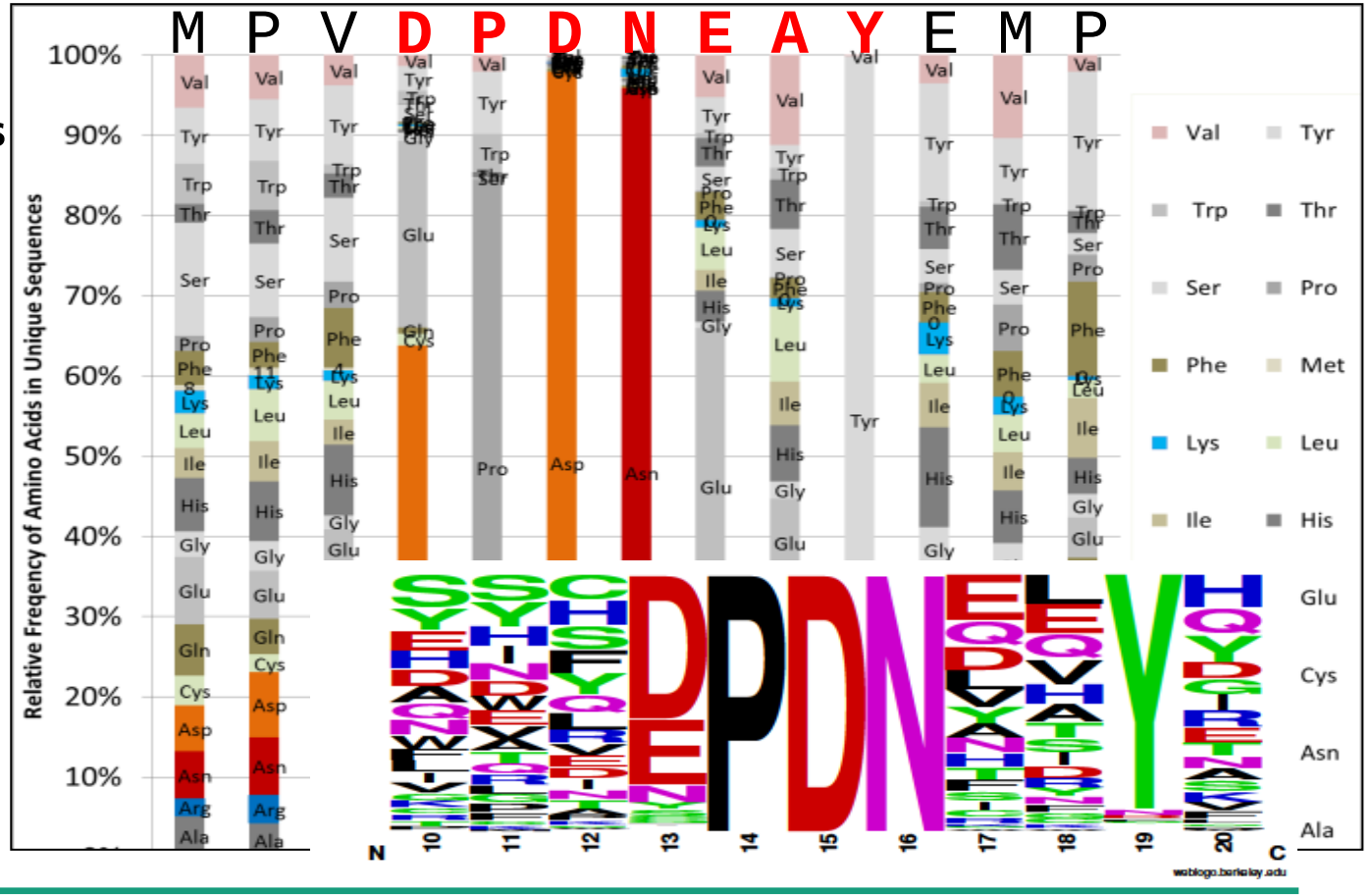
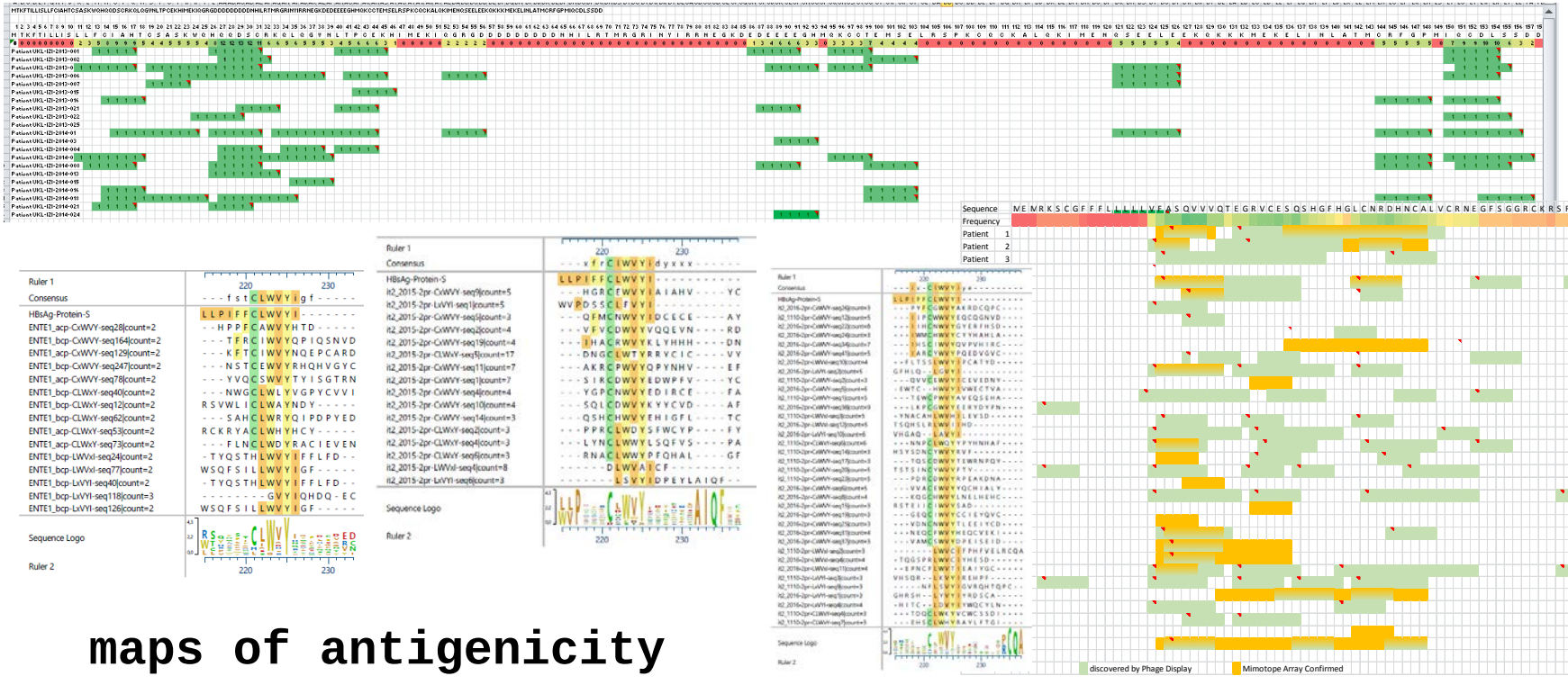
Epitope Fingerprinting mAB 10D2

Here a broad analyses of all **1149 individual Sequences with either DPD, PDN or DNE motif**.

Sequences were aligned and the frequency of the amino acids is listed. These are corresponding to

> 15,000 observed sequences from the second selection round.





maps of antigenicity

FINGERPRINTING ANTIBODY EPITOPES IN SERUM

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Fingerprinting Vaccine Antibody Epitopes in Serum

- Serum samples collected from one patient over several years have been used for this immunome study. The results have been compared for vaccine antigens received in this time period.
- Hepatitis Antigen epitope signal strength varies before and after vaccination, epitopes shift with the time
- Epitopes from influenza virus immunisation can be also mapped. In addition an infection can be seen with a different H3N2 virus.

Male

> 40 years old

Sample ID	Collection date	
S-10	11.2010	← 42 weeks after Hepatitis B boost (Engerix-B)
S-12	12.2012	
S-0214	02.2014	
S-1114	11.2014	← 5 weeks after Influenza vaccination (Vaxigrip 2014/2015)
S-15	12.2015	← Low anti-HBsAg titer
S-16	01.2016	← 5 weeks after second Hepatitis B boost (Engerix-B)

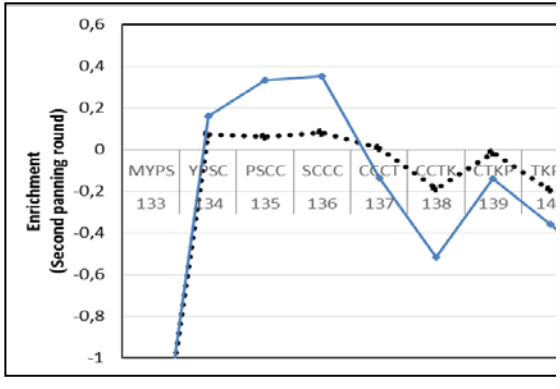
Example HBsAg – Epitope PSCCC

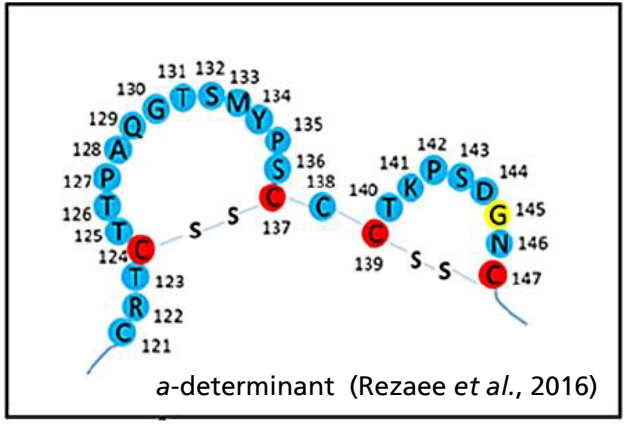
Several motif related to the Hepatitis B epitope have been identified. The significant but very unusual epitope below showed an interesting change with respect to motif frequencies.

Antigen	Motif	First panning round		Second panning round			
		Enrichment	Unique seq	Enrichment	Unique seq	Found motifs	Count
	PSCC	0,08287	17	0,25451	24	VVTSYGIFSQCPSCCC	1**
GTSMYPSCCCTKPSDGNC	SCCC	0,17992	19	0,33903	20	WVNCNIYR**SCCCT**RKD	4
	CCCT	0,23766	14	0,29074	13		

**more single sequences with this motif found

Sample ID	Date
Engerix-B 03.2010	
S-10	25.11.2010
S-12	18.12.2012
S-0214	02.2014
S-1014	22.10.2014
S-1114	26.11.2014
S-15	07.12.2015
Engerix-B 12.2015	
S-16	17.01.2016





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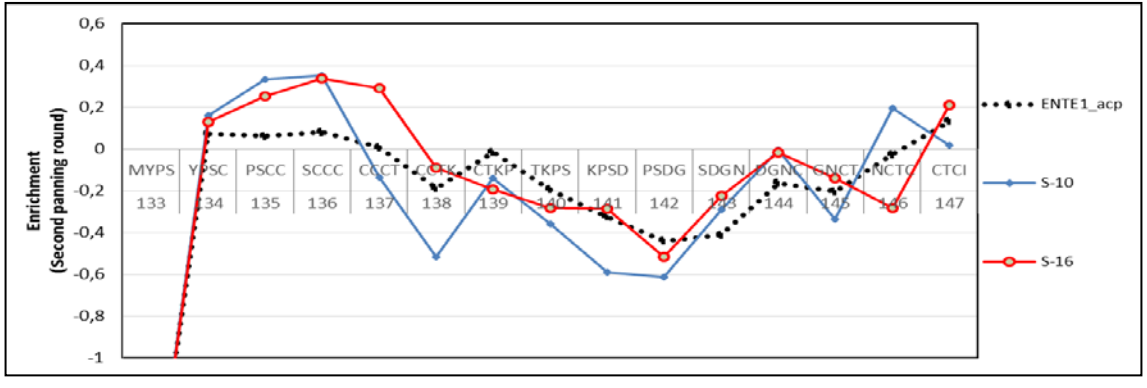

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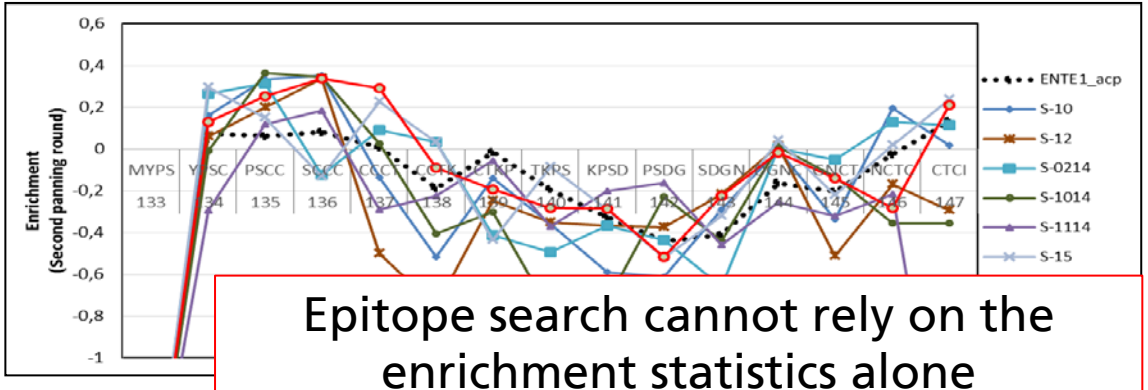

Epitope search cannot rely on the enrichment statistics alone

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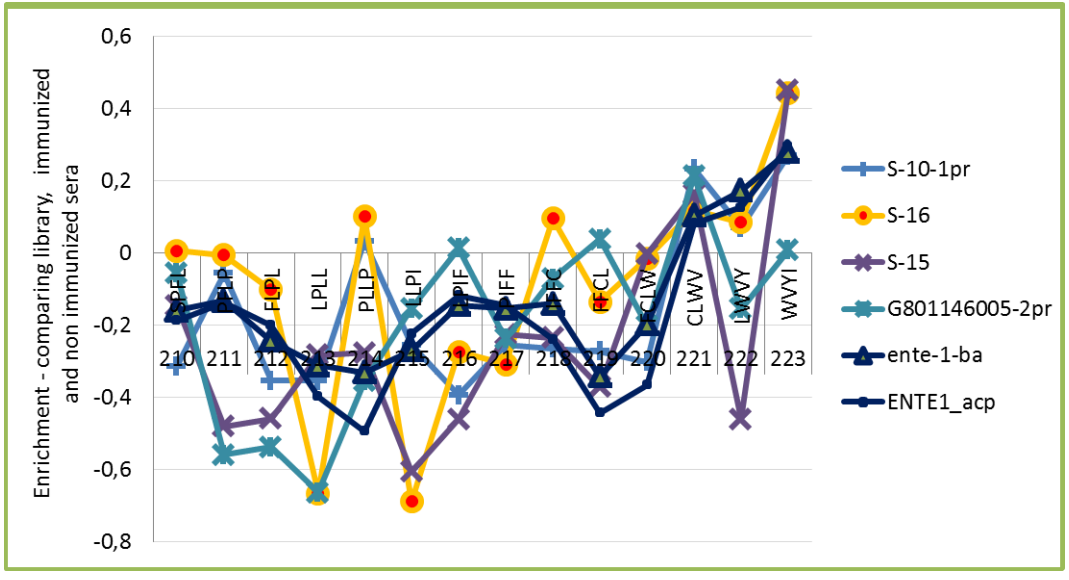
Example HbsAg C-Terminal Epitope

- A C-terminal epitope is described in the literature,
- Statistical significance is reduced because of less stringent conservation of amino acids, i.e. if not all four amino acids of a 4-mer motif are required for binding enrichment of the motif alone is not the only tool:



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S-15	07.12.2015
Engerix-B 12.2015	
S-16	17.01.2016

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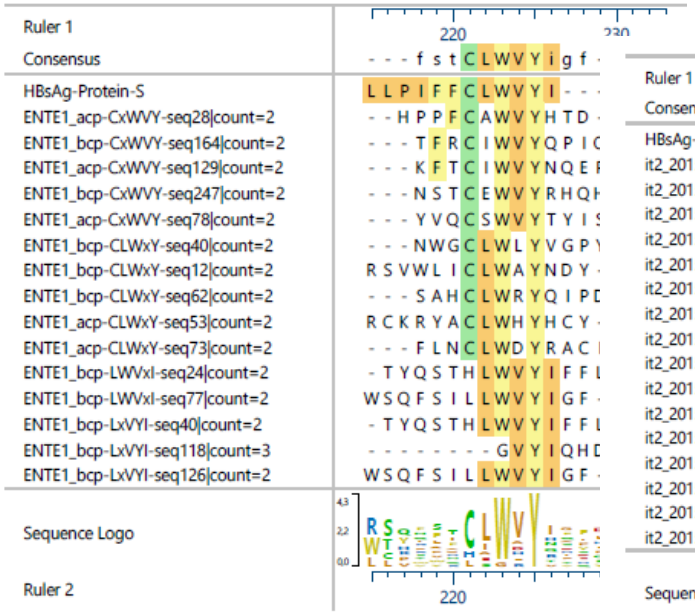
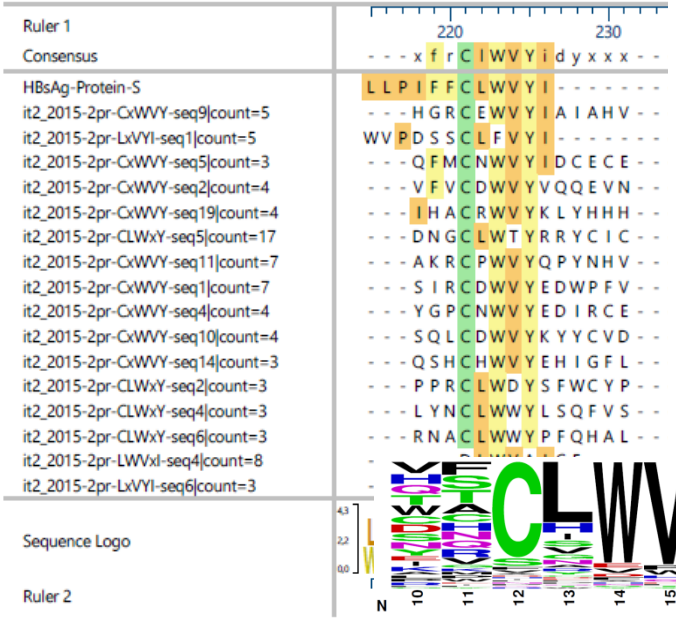
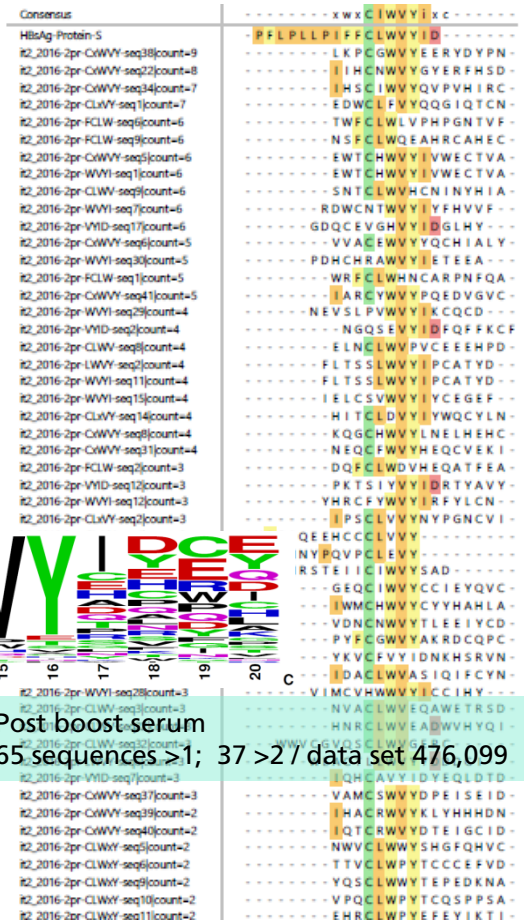
Example HbsAg C-Terminal Epitope

Comparing naive library vs. pre-boost vs. post boost sera: Only sequences found with at least 4 aa identity to the antigen's C-terminal epitope are listed.







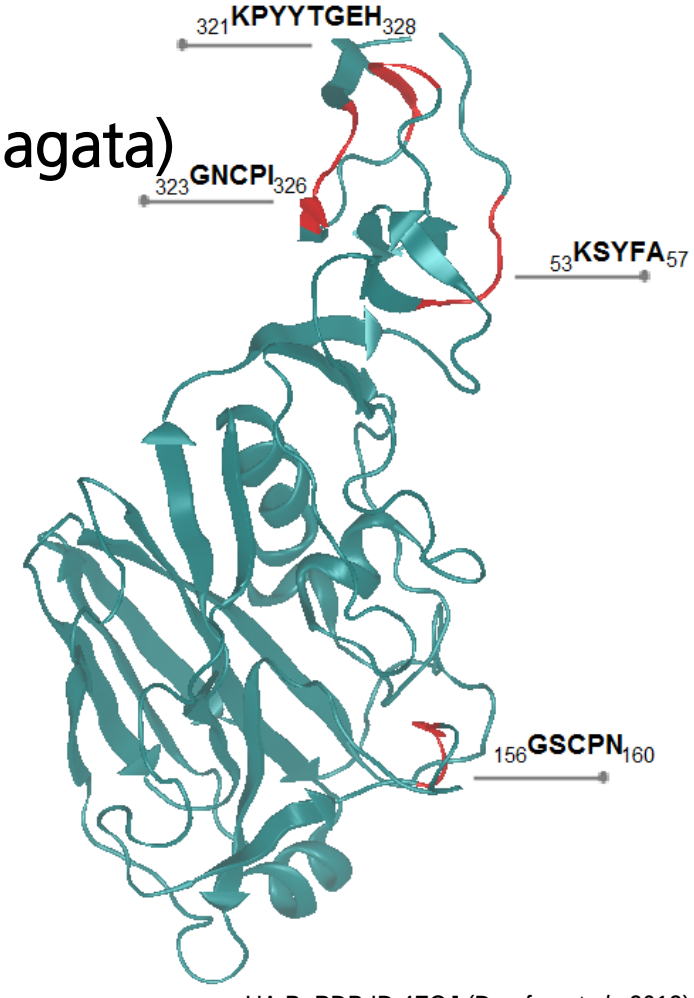
Naïve library
15 sequences >1x; 1 >3x / data set 2,191,037

Pre vaccine boost serum
27 sequences >1x ; 16 >2x / data set 253,288

Post boost serum
65 sequences >1; 37 >2 / data set 476,099

Identified Epitopes from Influenza: HA - B Massachussetts/02/2012 (Yamagata)

- Five potential epitopes identified
- Four epitopes decribed in the literature
- Cross-reactive neutralizing epitopes



HA B; PDB ID 4FQJ (Dreyfus *et al.*, 2013)

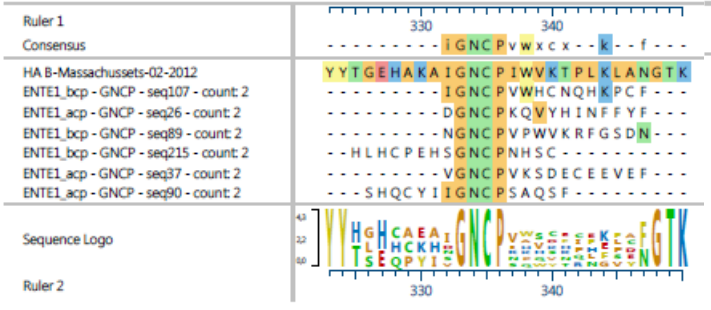
Fraunhofer IZI

Identified Epitopes from Influenza: HA - B Massachussetts/02/2012 (Yamagata)

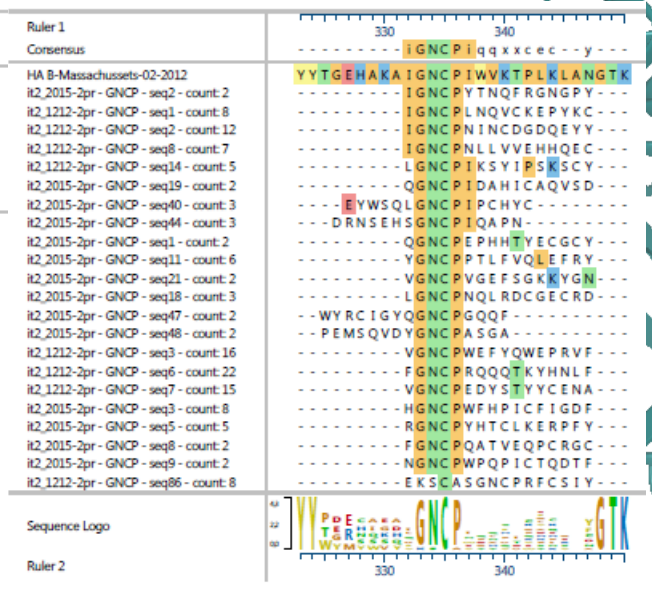
- Comparing naive and selected library

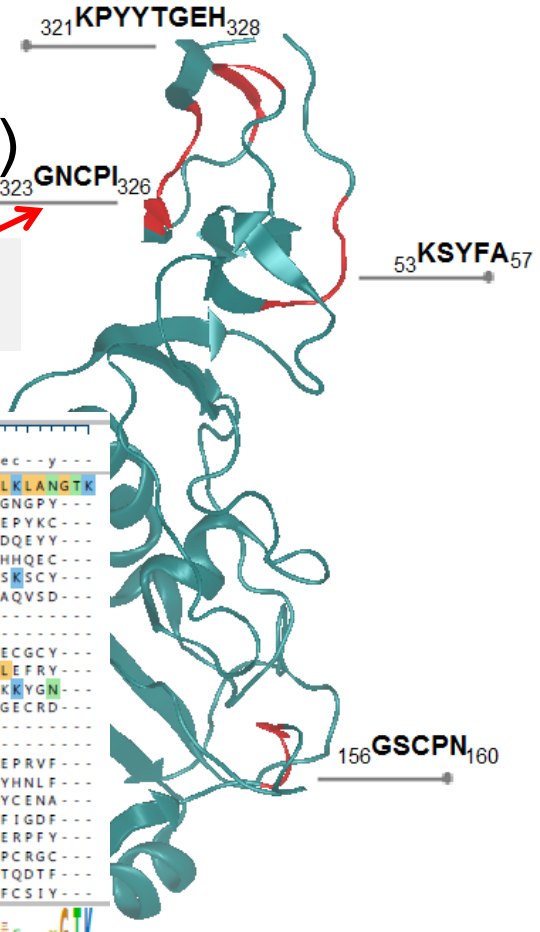
$_{332}$IGNCPIWVKT$_{341}$
Yasugi *et al.*, 2013

Naïve Dataset: 2,191,037 sequences



Selection Dataset: 511,986 sequences





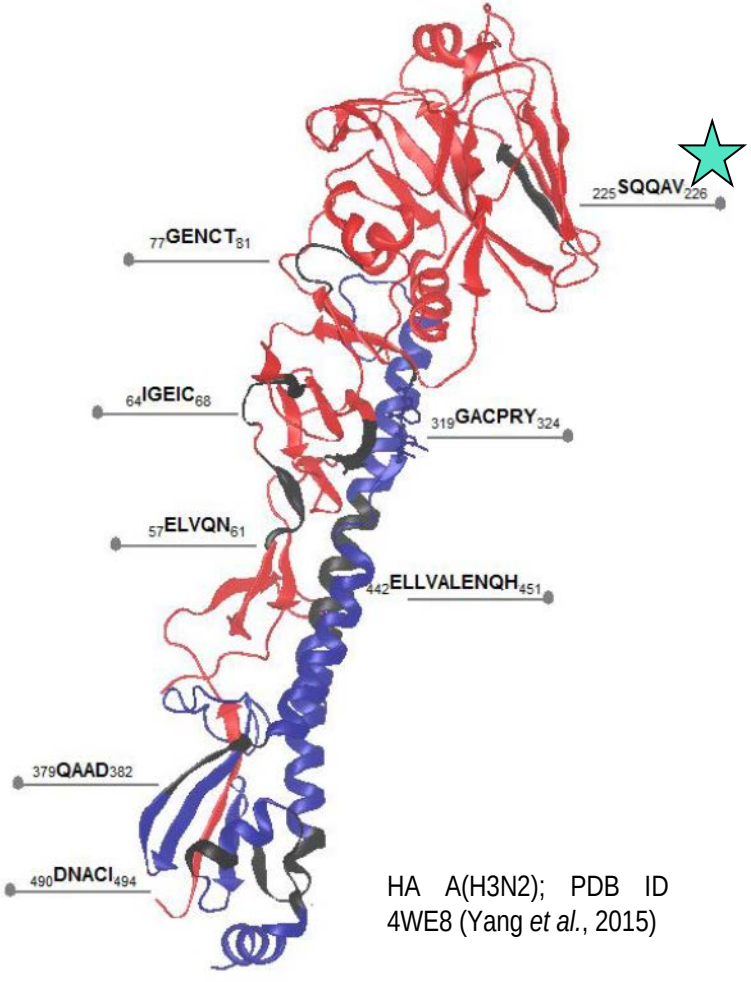
HA B; PDB ID 4FQJ
(Dreyfus *et al.*, 2013)

Fraunhofer IZI

Identified Epitopes from Influenza: HA - A(H3N2) Texas/50/2012 virus

- Nine potential epitopes identified
- Four epitopes described in the literature
- One epitope in the receptor binding site ★

(residues 219-228) [Yang et al., 2015; 10.1016/j.virol.2014.12.024]



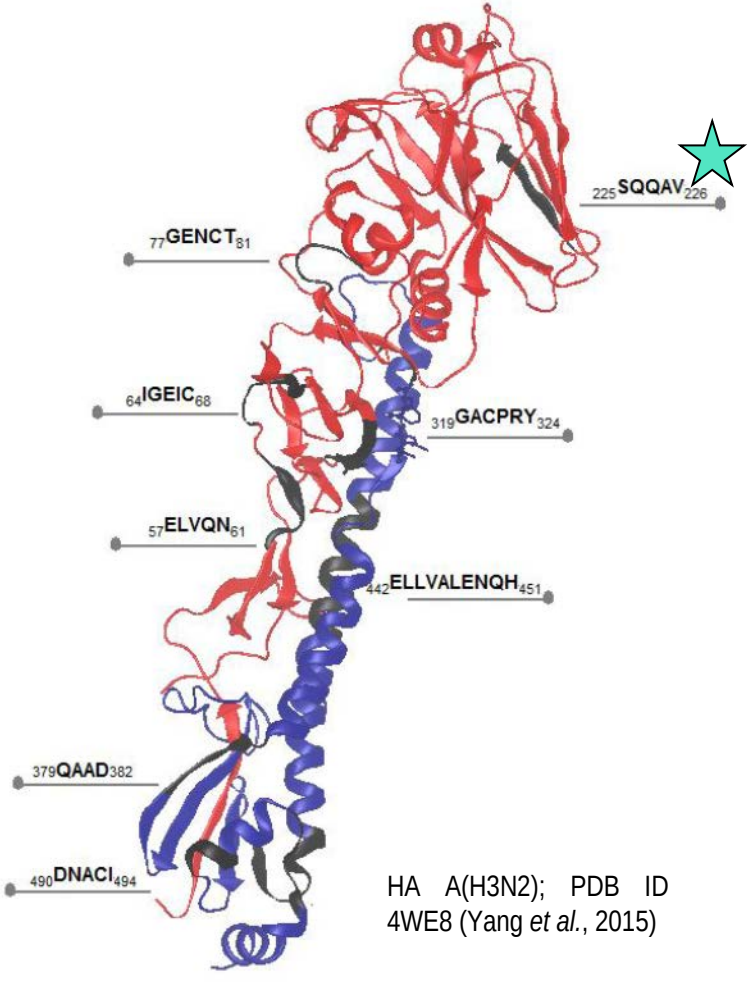
HA A(H3N2); PDB ID 4WE8 (Yang *et al.*, 2015)

Fraunhofer IZI

Identified Epitopes from Influenza: HA - A(H3N2) Texas/50/2012 virus

Ruler 1	220	230	240
Consensus	- - - - - - q i v - q S Q Q A V x - - - - - - - - -
HA A-Texas-50-2012 H3N2	S G R I T V S T K - R S Q Q A V I P N I G F R P R I R
it2_1114-2pr - QQAV - seq28 - count: 9	- - - H H N S Y D A Q A Q Q A V R F Y - - - - - - - -
it2_1114-2pr - QQAV - seq18 - count: 8	- - - - - - - S T P C V T Q Q A V I E V P D F - - - - -
it2_1014-2pr - QQAV - seq8 - count: 11	- Q W H C K Q E - - N H Q Q A V I V C - - - - - - - -
it2_1114-2pr - SQQA - seq59 - count: 10	- - K H Q C Y T L - Q S Q Q A H I A Y - - - - - - - -
it2_1114-2pr - SQQA - seq4 - count: 5	- - - - - - - - I D - A S Q Q A P H E Q Y H F F D - - -
it2_2015-2pr - QQAV - seq12 - count: 4	- - - - - - Y D H S T G Q Q A V E P C D L Y - - - - -
it2_2015-2pr - QQAV - seq11 - count: 5	- - - - - - W I W S Y L Q Q A V K G Y I I - - - - -
it2_1114-2pr - QQAV - seq4 - count: 4	- - - - - - - - E S - R S Q Q A V A R G A L P E A - - -
it2_1114-2pr - SQQA - seq87 - count: 5	- R G S S V G I Q - S S Q Q A N Y N - - - - - - - - -
it2_1114-2pr - QQAV - seq32 - count: 5	- K F R C Y Q Q - - D Y Q Q A V C Q A - - - - - - - -
it2_2015-2pr - QQAV - seq26 - count: 5	- I L F C I E H V - P C Q Q A V G C - - - - - - - - -
it2_2015-2pr - QQAV - seq29 - count: 7	- - P S H S A G E S T L Q Q A V Q Y - - - - - - - - -
it2_2015-2pr - QQAV - seq33 - count: 4	T A N C - E V L Y - Q L Q Q A V R N - - - - - - - - -
it2_1114-2pr - SQQA - seq3 - count: 7	- - - - - - - - H H - T S Q Q A H D L W Y H Q D C - - -
it2_1114-2pr - SQQA - seq5 - count: 4	- - - - - - - - S E - W S Q Q A Y C A G F K C P C - - -
it2_1114-2pr - SQQA - seq45 - count: 4	- - - - - - E F V - S S Q Q A L V E D L - N Y A - - -
it2_1114-2pr - SQQA - seq52 - count: 5	A Q C Y S Q Q A A - W S A Q C F - - - - - - - - - -
it2_1114-2pr - SQQA - seq88 - count: 5	- E V V S S F P T - V S Q Q A Q V C - - - - - - - - -
it2_1114-2pr - SQQA - seq60 - count: 14	- - V G M C I N W - E S Q Q A Q L Q F - - - - - - - -
it2_2015-2pr - QQAV - seq25 - count: 14	- F L Q C N V Q S - D T Q Q A V C D - - - - - - - - -
it2_1014-2pr - SQQA - seq4 - count: 4	- - - - - - - - V P - A S Q Q A W T H P E Y S L F - - -
it2_1014-2pr - SQQA - seq28 - count: 4	- - - - - - Q H T - C S Q Q A A V Y S P Y P F - - - -
it2_1014-2pr - SQQA - seq30 - count: 4	- - - - - - D S V - C S Q Q A H C W F T - L A Y - - -
it2_1014-2pr - SQQA - seq54 - count: 8	W S Q W S T I I Q - P S Q Q A - - - - - - - - - - - -
it2_1014-2pr - QQAV - seq10 - count: 4	- D N F C Y Q A - - P V Q Q A V E V C - - - - - - - -
it2_1014-2pr - QQAV - seq27 - count: 5	- R T A S W Q F V - G P Q Q A V N N - - - - - - - - -
it2_1014-2pr - QQAV - seq28 - count: 9	- T Q W S Y R F Q - Q G Q Q A V E D - - - - - - - - -

72 sequences with the active site motif, only those >3x are shown (vs 17 2x in larger naive data set)



HA A(H3N2); PDB ID 4WE8 (Yang *et al.*, 2015)

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Applications

- This study was the first time we applied our method to a single person's serum samples collected over several years.
- Food allergies and infectious disease have been our major areas of interest and peptide (consensus) mimotopes have been confirmed with about 50% success rate by applying peptide arrays. But in all those cases we used data from many different patients to compare and extract epitope information.
- For any antigen or allergen maps of antigenicity can be prepared.

Gly m 2S Albumin Antigenicity Map

aa sequence of Gly m 2S Albumin

Epitopes

Patient ID

Maps of all major soy allergens have been generated!

possible cross-reactivity with other proteins because of similar sequences

Epitopes of Soybean potein	Epitopes of peanut	Epitopes of Ricinus
LFCIAHTCS		LLFIIAN
SASKWQH		
QQDSCR		
SCRKQL		
KQLQGVN		
NLTPCEK	NLKPCE	
QGRGD		
EDEEEEG		
QKCCT	QRCCD	
TEMSEL		
CKALQK		
NQSEELEEK		
MCRFGP		
IQCDLS	RCDLD	

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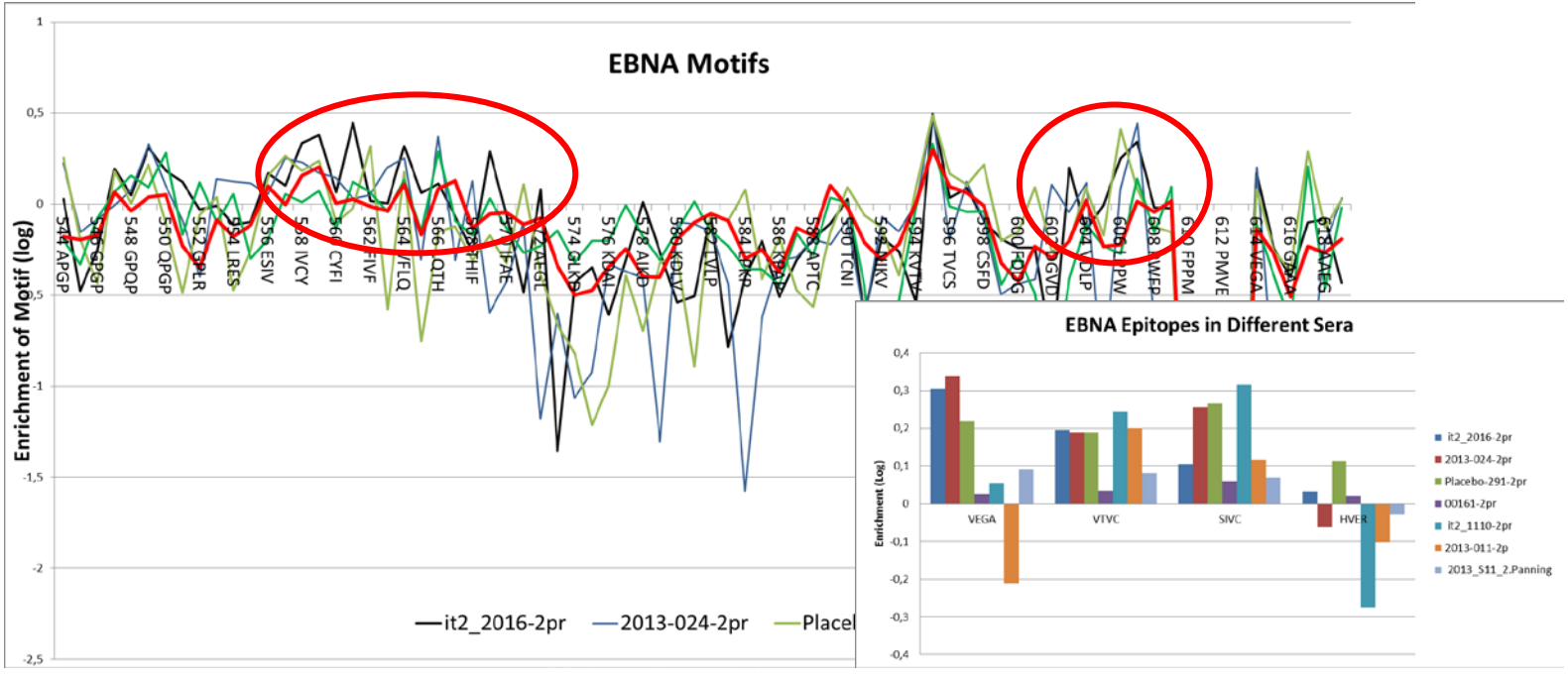
Epstein-Barr-Virus Signatures

- Being present in most of the population, EBNA1 C-terminal signatures have been found in almost every serum and are useful as internal markers



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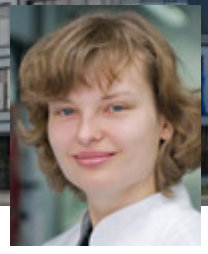
Preliminary Conclusions

- Technical: It works….
- Practical: Detection limit about 50-100 antibody molecules in 1 µl of serum, enough to even detect IgE
- Theoretical: Even the immunome of a single patient is undergoing permant changes.

Thank you for listening & Thanks to….



Lisbeth Ramírez Caballero, Nicolas Delaroque, Karolin Kern, Dorothe Wehrmann, Maria Helm, Aastha Jain, Markus Puder and many more…
PolyQuant GmbH: Markus Fischer, Iris Kobl (Bad Abbach, Germany)
Prof. Ines Neundorf (Cologne University) for peptide synthesis; IZI-BB, Potsdam (peptide array preparation): E. Ehrentreich-Förster; AJ Roboscreen GmbH: I. Lachmannn, U. Wagner; Veterinary Faculty, Leipzig: A. Rückner, T. Vahlenkamp;

POLYQUANT EPITOPIC

These studies are funded by
- Fraunhofer Gesellschaft, MAVO project LowAllergen
- Federal Ministry for Economic Affairs and Energy, (grant. no. KF2302706).

ZIM Zentrales Innovationsprogramm Mittelstand

Supported by: Federal Ministry for Economic Affairs and Energy on the basis of a decision by the German Bundestag

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Contacts

Michael Szardenings
Fraunhofer IZI
(Fraunhofer Institute for Cell Therapy and Immunology)
Ligand Development Unit

Perlickstr. 1, 04103 Leipzig, Germany
Tel: +49-341-35536 2805
Fax: +49-341-35536 82805
Cell: +49 159 044 268 49
michael.szardenings@izi.fraunhofer.de
www.izi.fraunhofer.de

EPITOPIC GmbH
Perlickstr. 1, 04103 Leipzig, Germany
www.epitopic.com
info@epitopic.com
Phone: +49 341 23028939
Cell: +49 160 97953148

in North America:
Catapult Intelligence, LLC
One Kendall Sq Bldg 200 Ste 2203
Cambridge, MA 02139
www.catapultintel.com
info@catapultintelligence.com

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