# Knowledge-based systems for assessing immunogenicity

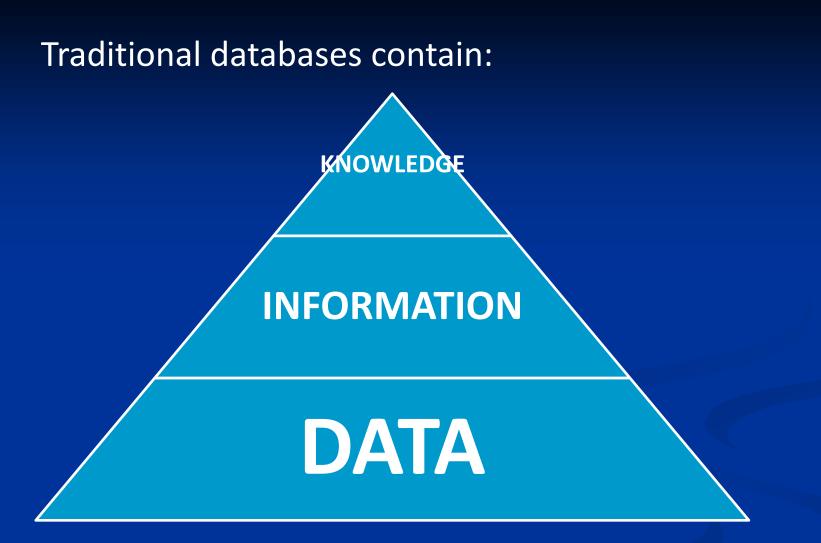
Vladimir Brusic, PhD MBA Director of Bioinformatics Cancer Vaccine Center Dana-Farber Cancer Institute







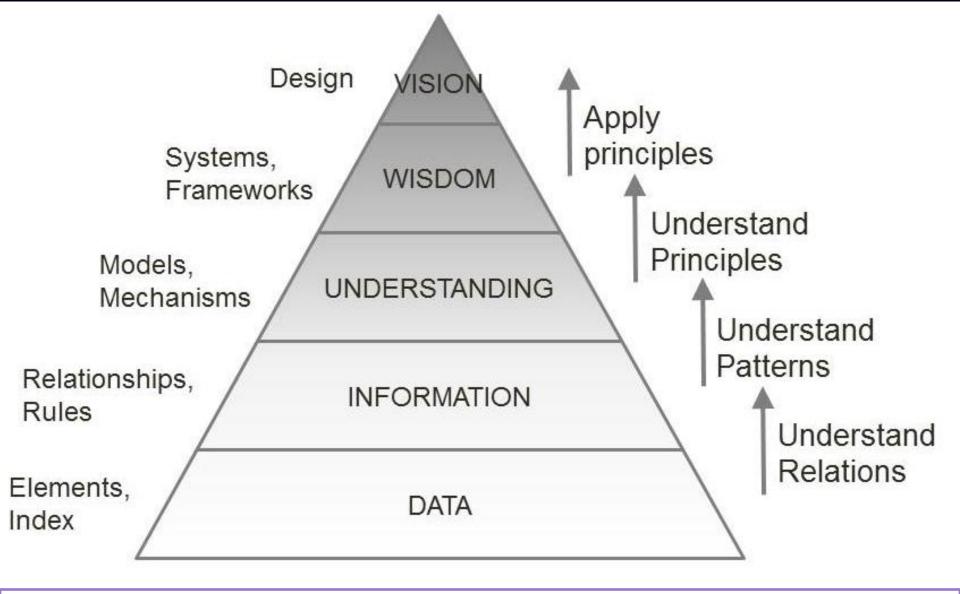
SUMMARY Introduction **Definitions** Framework Immunogenicity **Examples** Malaria **FLAVIdB** Conclusions



Focus on extraction of information. Knowledge extraction and acquisition left to the user.

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1.	166 aa protein	RefSeq (161)	
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3.	interferon-gamma [Homo sapiens]	Cowpox virus (5)	
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ORGANISM       Homo sapiens       production in tubercul [J Formos Med Assoc. 2011]         Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplornhini; Catarrhini; Hominidae; Homo.       Enhanced demethylation of interferon-y gene promoter in peripheral bl [Tohoku J Exp Med. 2011]         REFERENCE 3 (residues 1 to 166)       Functional polymorphism of interferon-y (IFN-y) gene +874T/A polymorphi: [Prague Med Rep. 2011]         TITLE       Structure of the human immune interferon gene JOURNAL       See all         PUBMED       6180322 REFERENCE 7 (residues 1 to 166) AUTHORS       Gray, P.W. and Goeddel, D.V.         TITLE       Human immune interferon (IFN-gamma) gene sequence and structure JOURNAL       Identical proteins for AAB59534.1         Basic Life Sci. 25, 35-61 (1983)       Sequence 20 from patent US 7795210[ADS43270]         Sequence 20 from patent US 774066[ADR87019]       Sequence 212 from patent US 774066[ADR87019]         VIENNEN       Immune interferon (IFN-gamma) shows little homology with leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci       Sequence 212 from patent US 774066[ADR87019]		Homo sapiens (human)	-	а
Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.       Financed denteurymation interfectory gene promoter in peripheral bl [Tohoku J Exp Med. 2011]         REFERENCE       3 (residues 1 to 166)       Functional polymorphism of interferon-y (IFN-y) gene +874T/A polymorphis: [Prague Med Rep. 2011]         TITLE       Structure of the human immune interferon gene JOURNAL       See all         Nature 298 (5877), 859-863 (1982)       See all         PUBMED       6180322         REFERENCE       7 (residues 1 to 166)         AUTHORS       Gray, P.W. and Goeddel, D.V.         TITLE       Human immune interferon (IFN-gamma) gene sequence and structure         JOURNAL       Basic Life Sci. 25, 35-61 (1983)         PUBMED       6305337         COMMENT       Immune interferon (IFN-gamma) shows little homology with leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci         Degraphing <himten>       LNN-genema protein (35 000 to 70 000 mw as</himten>	ORGANISM			
Catarrhini; Hominidae; Homo. REFERENCE 3 (residues 1 to 166) AUTHORS Gray, P.W. and Goeddel, D.V. TITLE Structure of the human immune interferon gene See all JOURNAL Nature 298 (5877), 859–863 (1982) PUBMED 6180322 REFERENCE 7 (residues 1 to 166) AUTHORS Gray, P.W. and Goeddel, D.V. TITLE Human immune interferon (IFN-gamma) gene sequence and structure JOURNAL Basic Life Sci. 25, 35–61 (1983) PUBMED 6305337 COMMENT Immune interferon (IFN-gamma) shows little homology with leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci berinning <humiens. (35="" 000="" 70="" as<="" jen-gamma="" mm="" protein="" td="" to=""><td></td><td></td><td></td><td></td></humiens.>				
AUTHORS       Gray, P.W. and Goeddel, D.V.         TITLE       Structure of the human immune interferon gene       See all         JOURNAL       Nature 298 (5877), 859-863 (1982)       See all         PUBMED       6180322       See all         REFERENCE       7 (residues 1 to 166)       Identical proteins for AAB59534.1       Immune interferon (IFN-gamma) gene sequence and structure         JOURNAL       Basic Life Sci. 25, 35-61 (1983)       Sequence 2 from patent US 7964400 [AEJ75027]         JOURNAL       Basic Life Sci. 25, 35-61 (1983)       Sequence 2 from patent US 7795210[ADS43270]         PUBMED       6305337       Sequence 212 from patent US 77406€[ADR87019]         COMMENT       Immune interferon (IFN-gamma) shows little homology with leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci       Sequence 212 from patent US 77406€[ADR87019]				[1]
AUTHORS       Gray, P.W. and Goeddel, D.V.         TITLE       Structure of the human immune interferon gene       See all         JOURNAL       Nature 298 (5877), 859-863 (1982)       See all         PUBMED       6180322       REFERENCE       7 (residues 1 to 166)         AUTHORS       Gray, P.W. and Goeddel, D.V.       Identical proteins for AAB59534.1       Immune interferon (IFN-gamma) gene sequence and structure         JOURNAL       Basic Life Sci. 25, 35-61 (1983)       Sequence 2 from patent US 7964400 [AEJ75027]         JOURNAL       Gaos337       Sequence 20 from patent US 7795210[ADS43270]         PUBMED       6305337       Sequence 212 from patent US 77406€[ADR87019]         COMMENT       Immune interferon (IFN-gamma) shows little homology with leukocyte       See all         (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci       See all       See all				111
JOURNAL Nature 298 (5877), 859-863 (1982) PUBMED 6180322 REFERENCE 7 (residues 1 to 166) AUTHORS Gray, P.W. and Goeddel, D.V. TITLE Human immune interferon (IFN-gamma) gene sequence and structure JOURNAL Basic Life Sci. 25, 35-61 (1983) PUBMED 6305337 COMMENT Immune interferon (IFN-gamma) shows little homology with leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci beginning < HUMLEN> LEN-gamma protein (35,000 to 70,000 mm as				
PUBMED       6180322         REFERENCE       7 (residues 1 to 166)         AUTHORS       Gray, P.W. and Goeddel, D.V.         TITLE       Human immune interferon (IFN-gamma) gene sequence and structure         JOURNAL       Basic Life Sci. 25, 35-61 (1983)         PUBMED       6305337         COMMENT       Immune interferon (IFN-gamma) shows little homology with leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci       Sequence 212 from patent US 77406€[ADR87019]         Sequence 212 from patent US 77406€[ADR87019]       See all		-	See a	
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Hollows       Oldy, First and Oberder, First         TITLE       Human immune interferon (IFN-gamma) gene sequence and structure       Sequence 2 from patent US 7964400 [AEJ75027]         JOURNAL       Basic Life Sci. 25, 35-61 (1983)       Sequence 20 from patent US 7795210[ADS43270]         PUBMED       6305337       Sequence 20 from patent US 7795210[ADS43270]         COMMENT       Immune interferon (IFN-gamma) shows little homology with leukocyte       Sequence 212 from patent US 77406€[ADR87019]         Comment of the sequence of			Identical proteins for AAB59534.1	<b>.</b>
JOURNAL PUBMED COMMENT Basic Life Sci. 25, 35-61 (1983) 6305337 Tommune interferon (IFN-gamma) shows little homology with leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci beginning CHUMIENS IFN-gamma protein (35,000 to 70,000 mm as				271
PUBMED       6305337         COMMENT       Immune interferon (IFN-gamma) shows little homology with leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci       Sequence 212 from patent US 77406€[ADR87019]         See all       See all	JOURNAL	Basic Life Sci. 25, 35-61 (1983)		
(IFN-alpha) and fibroblast (IFN-beta) interferons. See other loci See all				
heginning /HIMIENN TEN_gamma protein (35 000 to 70 000 mm ag	COPPENI			
	1	heginning ZHIMIENN TEN-gamma protein (35 000 to 70 000 mm ag		•••



The D2V knowledge hierarchy model. The layers from data to vision decrease in quantity of the output but increase in the overall value of knowledge, acquisition cost, and complexity of management. Lower layers are more amenable to algorithmic approach and automation, while higher levels increase in utilization of conceptualization and modeling approaches.

LEVEL	INFORMATION SCIENCE	BASIC SCIENCE	APPLIED SCIENCE	CLINICAL SCIENCE	ENGINEERING/ TECHNOLOGY
Data	data	experiment	model elements	test, observation	product elements
Information	information	statistics	model evaluation	procedure	specifications
Understanding	<i>in <u>silico</u> model</i>	description (structure)	validated model	diagnosis	design
Wisdom	simulation	description (mechanism)	model deployment	treatment	prototype
Vision	prediction, decision	model, theory	design	design	product

D2V hierarchy across disciplines

LEVEL	INFORMATION SCIENCE	BASIC SCIENCE	APPLIED SCIENCE	CLINICAL SCIENCE	ENGINEERING/ TECHNOLOGY
Data	data 🗲	experiment 🗲	model	test, observation	product elements
Information	information	statistics	model evaluation	procedure	specifications
Understanding	<i>in <u>silico</u> model</i>	description (structure)	validated /	diagnosis	design
Wisdom	simulation	description (mechanism)	model / deploymert	treatment	prototype
Vision	prediction, <b>/</b> decision	model, theory	design	design	product

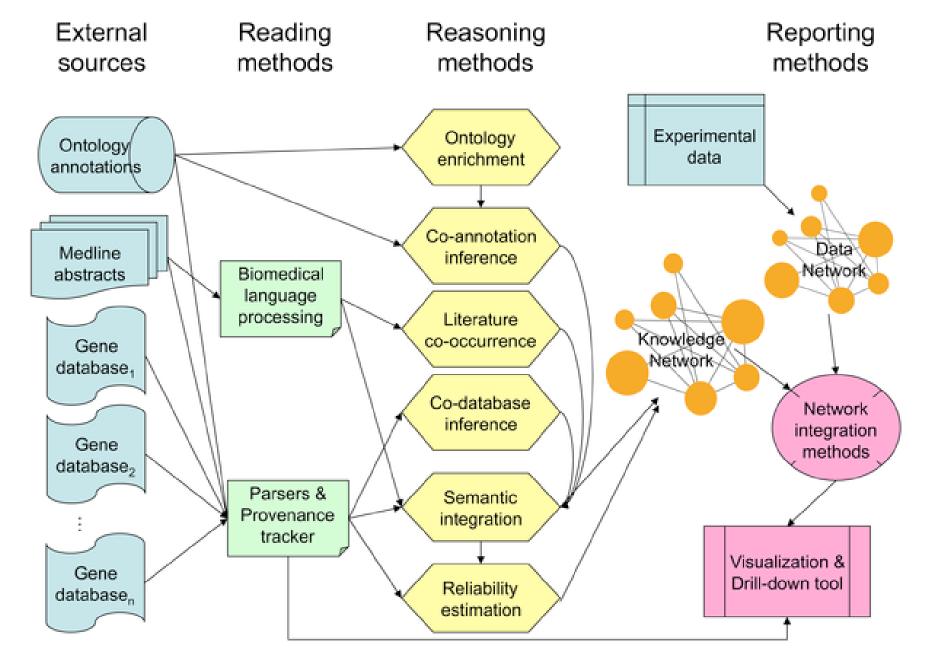
D2V hierarchy across disciplines

# Knowledge based systems (KBS) are:

Tools of Artificial Intelligence applied to a narrow domain to provide analysis, decisions, and explanation. KBS are used for knowledge extraction and decision support.

## KBS use:

- knowledge representation to document knowledge
- conceptual modeling to capture system properties
- learning to acquire new knowledge
- inference mechanisms to produce reasoning and explanation



Leach et al. 2009 PLoS Comput Biol 5(3): e1000215

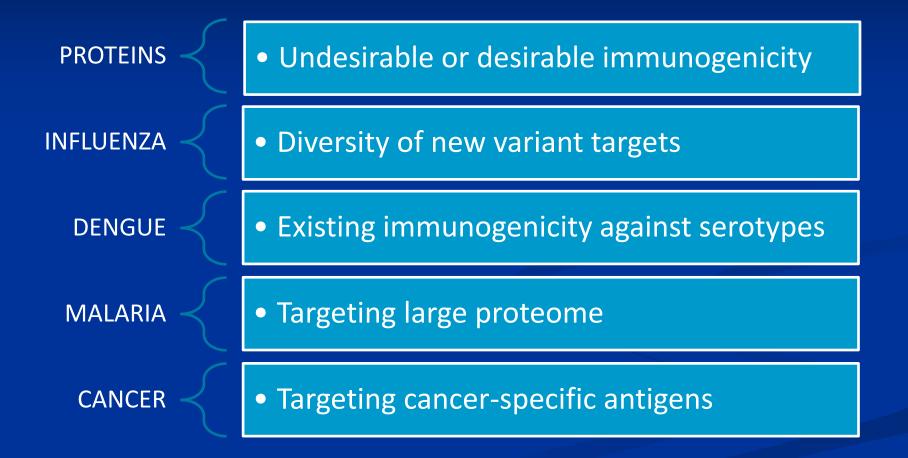
# Immunogenicity

- The ability of a substance (antigen) to induce immune response
- Not inherent property, requires a partner (a T or B cell)
- Individual-, profile-, history-, challenge- specific

# Immunogenicity, a poorly-defined term

- Different types of responses possible, fine tuning
- Every target is immunogenic, given the right context
- Different laboratory, functional, and clinical outcomes
- Differs between individuals

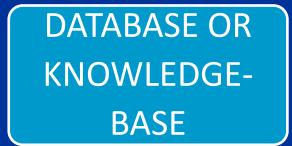
### DIFFERENT OBJECTIVES



# **KBS COMPONENTS**

CONCEPTUAL MODEL

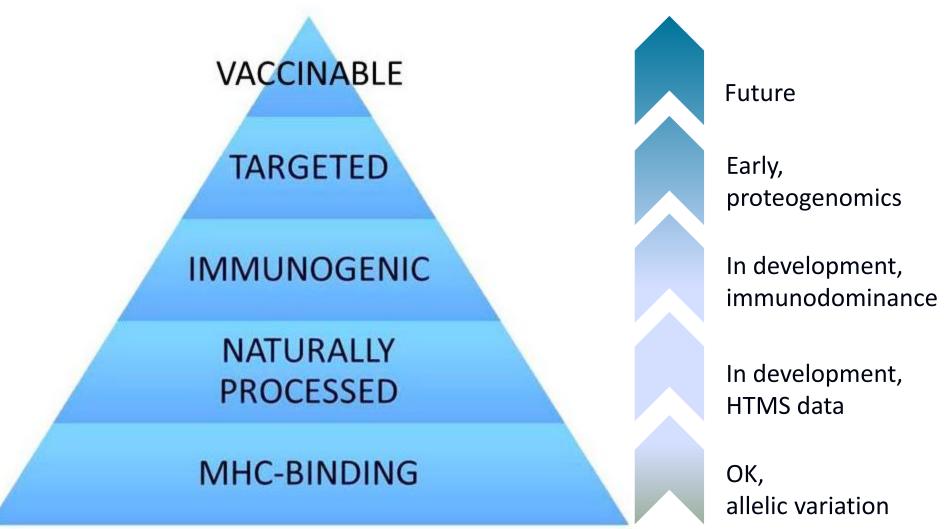


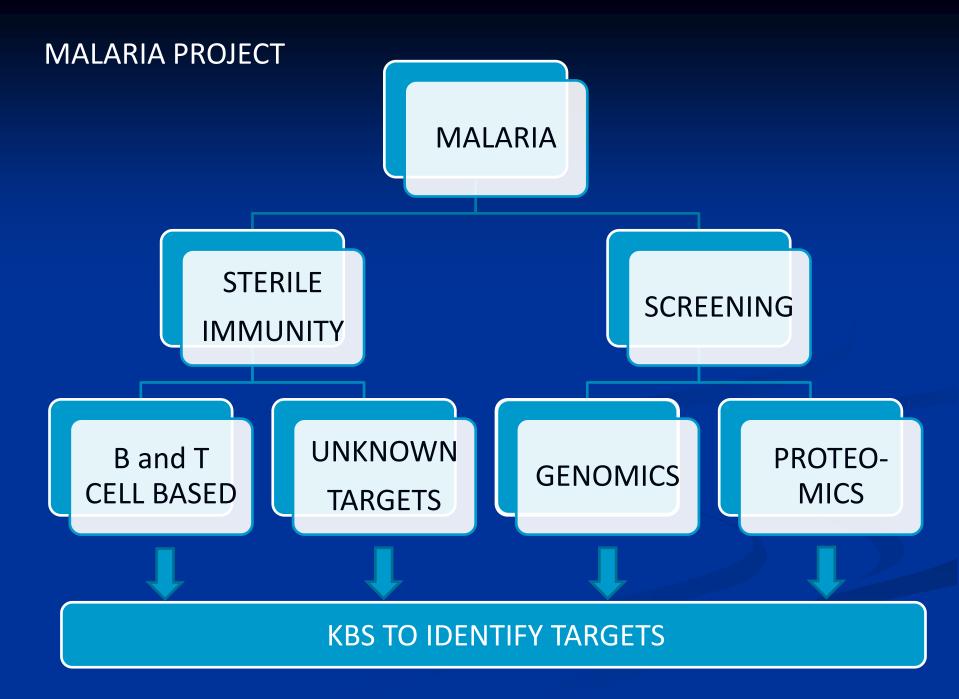




SUMMARY Introduction **Definitions** Framework Examples Malaria **FLAVIdB** Conclusions

### COMBINATORIALLY COMPLEX PROBLEM EPITOPE-BASED TARGET DISCOVERY FILTERS





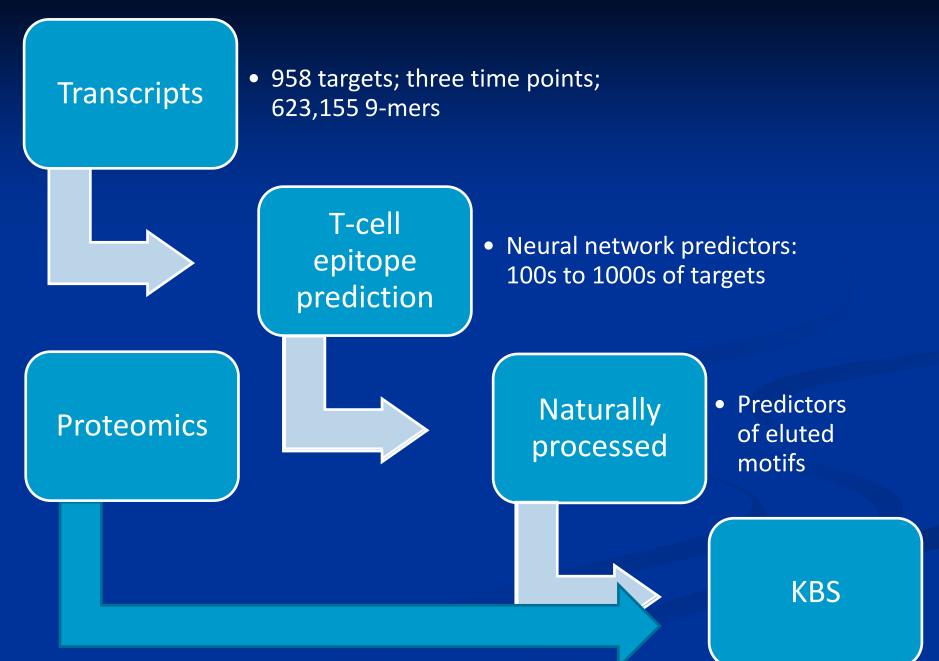
### **Preliminary data**

19 proteins identified as pooled targets of human immune responses against P. *falciparum*. (Trieu et al., 2011)

958 tanscripts identified in the gene expression study in P. *yoelii* (Mackellar et al, 2011).

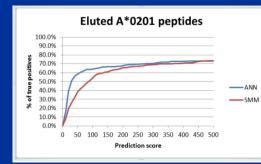
Too many transcripts and too few proteins.

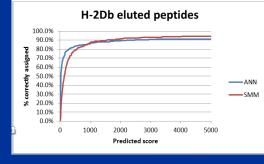
Need for a KBS for identification of vaccine targets.

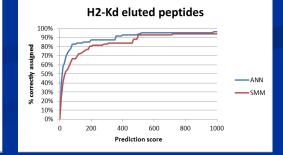


### Number of predicted peptides for YNN (24 hour liver infection)

		Pı	LENGTH	CAPTURE				
	10	20	50	100	200	1000		
A0201	340	1202	2483				9-mer	63.40%
H-2D <sup>d</sup>			1	11	28	152	9-mer	72.70%
H-2K <sup>d</sup>	304	534	870				9-mer	55.20%
H-2D <sup>b</sup>	74	169	331	510			9-mer	69.40%
H-2K <sup>b</sup>	228	433	819				8-mer	77.90%







SUMMARY Introduction **Definitions** Framework Examples Malaria **FLAVIdB** Conclusions

## How to convert data to application?

### A next generation database:

Contains database, knowledgebase, analytical tools, and workflows.

Enables us to extract new knowledge from existing data, information, and knowledge base in automated fashion.

### "Next generation databases"





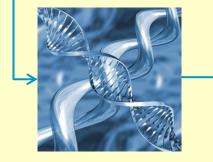
Applied computing



Next generation database Sense the mix of activities
 Sense the mix of activities

Knowledge

Literature

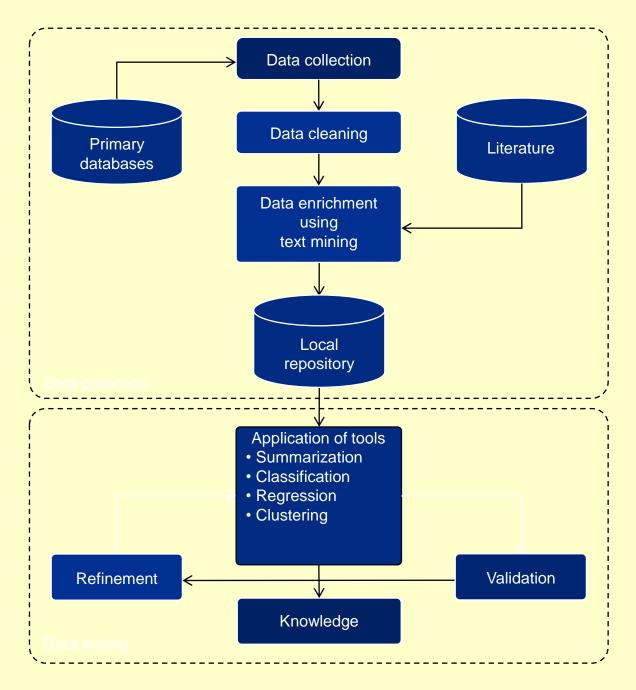


Experimental validation, Clinical testing



Vaccine

# FLAVIdB Architecture



### **FLAVIdb**

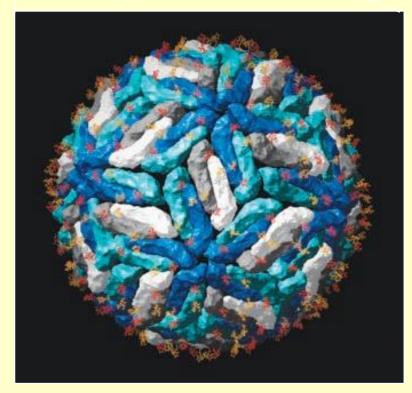
- Of more than 70 species of flaviviruses approx. half causes human disease.
- Five most relevant human flaviviruses alone put half of the world's population at risk of infection.
- Fflaviviruses have small single-stranded RNA genomes, ideal for rapid integration into a KBS.
- Dengue virus present an interesting challenge to vaccinology because of complications associated with secondary infection

# The flavivirus proteome

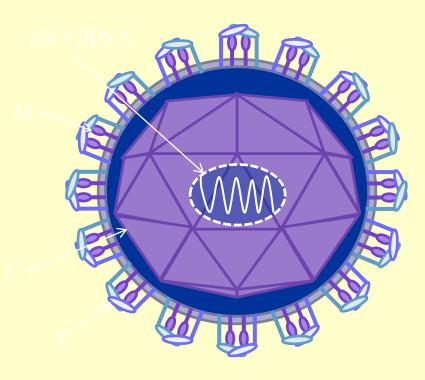
Flavivirus linear RNA proteome:

anC	prM	Е	NS1	NS2A	2B	NS3	4A	NS4B	NS5

Structural proteins



Enveloped nucleocapsid - 50 nm in diameter.



### Three classes of computational tools:

### Data retrieval tools

- Keyword search
- BLAST query

### **Basic analytical tools**

- Species classification
- Multiple sequence alignment
- Conservation and variability analysis
- Block entropy analysis

### **Advanced analytical tools**

- Prediction of T-cell epitopes
- Analysis of shared features of neutralizing B-cell epitopes (BBscore)

### Tools

**Common approach to discovery of T-cell epitopes as vaccine targets** 

- 1. Selection of sequences of interest
- 2. Application of T-cell epitope prediction algorithms

### **Output: Epitope candidates (data + information)**

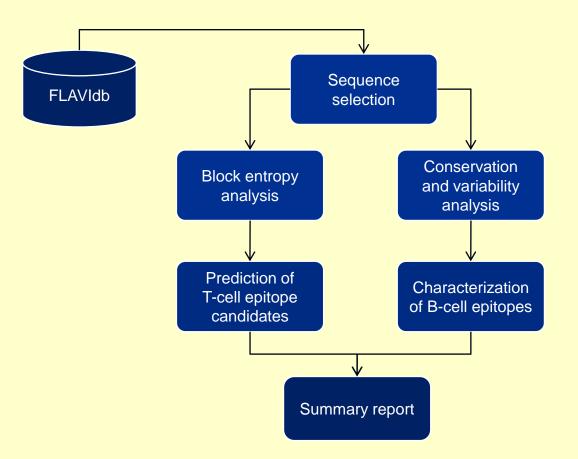
3. Conservation and variability analysis to ensure broad coverage of pathogen population and host population

### **Output: Reduced target set (data + information)**

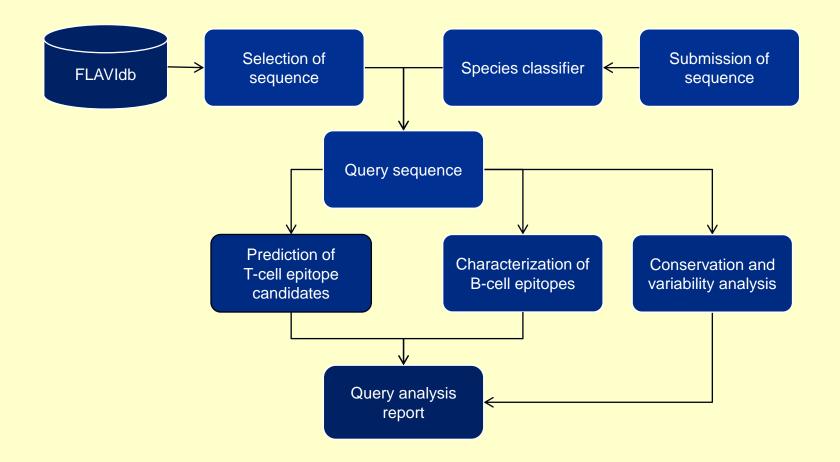
4. Experimental validation of epitope candidates

Output: Validated and characterized targets and their context (knowledge)

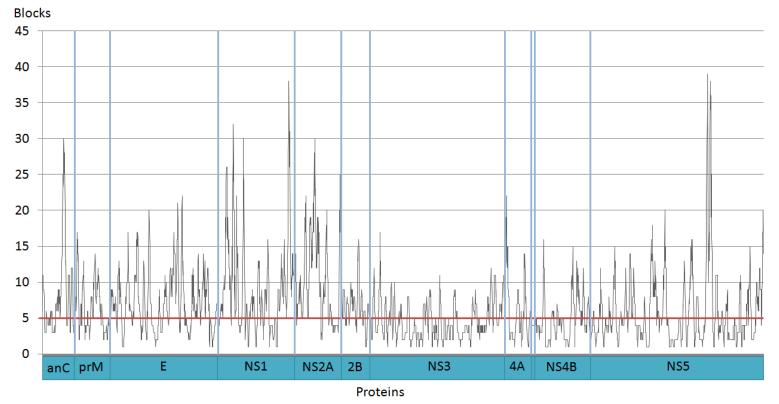
### Workflows: Summary workflow



# Workflows – Query analysis workflow



# **Blocks conservation analysis**



1.551 blocks of 9-mers (5.113 peptides) cover 99% of DENV1-4 with 5 or less peptides

...As compared to 165 conserved 9-mers, by traditional conservation analysis (Khan *et al.*)

10-fold increase in the number of conserved vaccine target candidates

V. Brusic, 2011

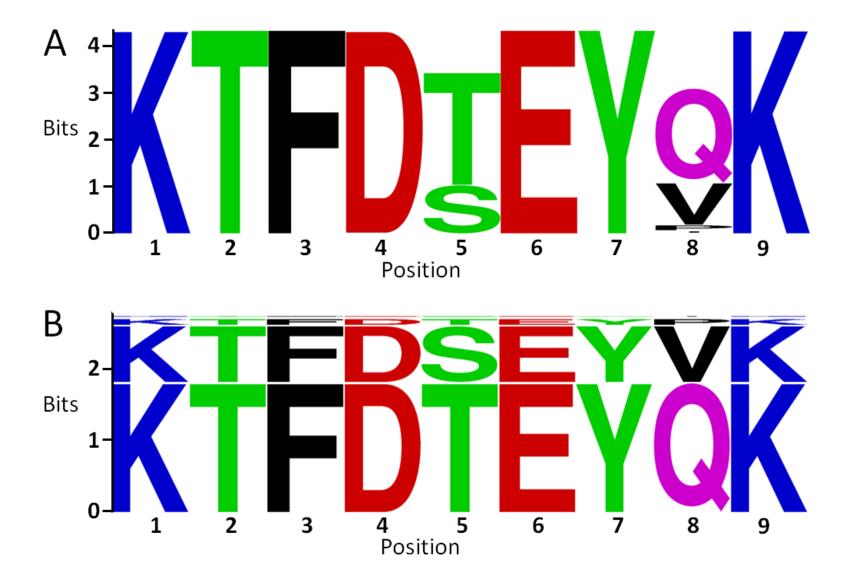
### **Block details**

2722 sequences analyzed, block start: 388, word length: 9

NetMHC predicted

#	peptide	Cons(응)	Accum(%)	bit height	HLA	binding affinity
1	KTFDTEYQK	65.03	65.03	0,84	A0301	
2	KTFDSEYVK	28.69	93.72	0,37	A0301	
3	KTFDTEYPK	3.82	97.54	0,05	A0301	
4	KTFDSEYIK	1.18	98.71	0,02	A0301	
5	KTFDTEYTK	0.29	99.01	0,00	A0301	
6	KTFDSEYAK	0.29	99.30	0,00	-	-
7	KTFDTEYIK	0.26	99.56	0,00	-	-
8	RTFDTEYQK	0.11	99.67	0,00	-	-
9	KTFETEYQK	0.11	99.78	0,00	-	-
10	KTFDAEYVK	0.07	99.85	0,00	-	-
11	KTFNTEYQK	0.07	99.93	0,00	-	-
12	KTFDTEYQR	0.04	99.96	0,00	-	-
13	KTFDFEYIK	0.04	100.00	0,00	-	-

### Sequence Logo vs Block Logo



Home	Search	Tools	Work Flows	FAQ	Contact us
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#### Search Flavivirus Antigen Database

Search Flavivirus records by keywords.

Choose search type

Input keyword

Flavivirus Records	-

#### Refine your search for Flavivirus records

Species	All Dengue virus type 1 Dengue virus type 2 Dengue virus type 3	^ -
Pathology	All The All Th	
Protein	All anC PreM E +	
Strain type	All 👻	
Entry type	All	
Host	All Human All Avian All Mosquito	•

Search Clear

Version 1.0, Feburary 2010. Developed by Bioinformatics Core at Cancer Vaccine Center, Dana-Farber Cancer Institute.

	Home	Search	Tools	Work Flows	FAQ	Contact us	
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#### Search Flavivirus records using Keyword "Clone"

Accession	Species	Entry type
FV000015	Japanese encephalitis virus	complete proteome
FV000697	Tick-borne encephalitis virus	partial proteome
FV000706	Tick-borne encephalitis virus	partial proteome
FV001348	Tick-borne encephalitis virus	partial proteome
FV001437	Japanese encephalitis virus	partial proteome
FV001438	Japanese encephalitis virus	partial proteome
FV001439	Japanese encephalitis virus	partial proteome
FV001453	Japanese encephalitis virus	partial proteome
FV001466	Japanese encephalitis virus	complete proteome
FV001823	Kunjin virus	complete proteome
FV001824	Kunjin virus	complete proteome
FV002117	Tick-borne encephalitis virus	complete proteome
FV002290	Japanese encephalitis virus	partial proteome
FV002291	Japanese encephalitis virus	partial proteome
FV002292	Japanese encephalitis virus	partial proteome
FV002293	Japanese encephalitis virus	partial proteome
FV002294	Japanese encephalitis virus	partial proteome
FV002295	Japanese encephalitis virus	partial proteome
FV002296	Japanese encephalitis virus	partial proteome
FV002297	Japanese encephalitis virus	partial proteome
FV002299	Japanese encephalitis virus	partial proteome
FV002772	Japanese encephalitis virus	partial proteome
FV002778	Japanese encephalitis virus	partial proteome

Home	Search Tools	Work Flows	FAQ	Contact us
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#### Flavivirus record FV003366

Protein accession	FV003366
Genebank accession	AY277665
Genbank Gl	33468370
Reference	15041181
Species	Dengue virus
Туре	1
Host	Human
Country	Paraguay
Year	2000
Isolate	ARG0028
Nomenclature	DENV1 Human PY  ARG0028  2000
Strain Type	wild type strain
Entry type	complete proteome
Proteome annotation	show/hide proteome annotation

show/hide T cell epitopes

#### Predict HLA binders

Protein: anC 🔹

 $\mathbf{T}$ 

#### show/hide T cell epitopes

T-cell Epitope sequence	HLA allele	Reference	in Protein
ILGDTAWDFG	B7	15827181	envelope protein
SVKKDLISY	B62	10453018	nonstructural protein 3
TPEGIIPAL	B35	7544398	nonstructural protein 3
VLMLVAHYA	A2	16493038	nonstructural protein 4B
ILLMRTTWA	A2	16493038	nonstructural protein 4B
MLLALIAVL	A2	16493038	nonstructural protein 4A
FLDLPLPWT	A2	16493038	envelope protein
GTSGSPIVNR	A11	12808447	nonstructural protein 3
KPWDVIPMV	B*5502	17626101	nonstructural protein 5
GTSGSPIVNR	A*1101	17565177	nonstructural protein 3
TPEGIIPAL	B35	18762226	nonstructural protein 3
QYSDRRWCF	A24	16517753	nonstructural protein 3
EIVDLMCHAT	DPw2	7690424	nonstructural protein 3
EIVDLMCHAT	DPw2	9568963	nonstructural protein 3
VDLMCHATFT	DPw2	9568963	nonstructural protein 3
NREGKIVGLYGNGVV	DRB1*1501	16081844	nonstructural protein 3
PTRVVASEMAEALKG	DRB1*1501	16081844	nonstructural protein 3

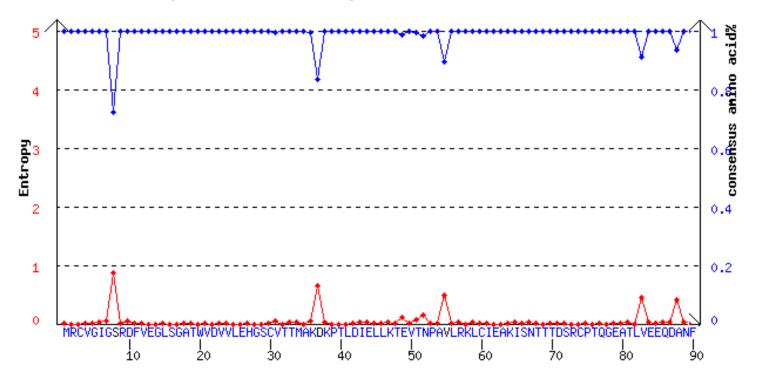
FV006412 Dengue 3 NS3 PGKNPKNFQTMPGTFQTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAQTNAEPD( FV006449 Dengue 3 NS3 PGKNPKNFQTMPGTFQTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAQTNAEPD( FV006523 Dengue 3 NS3 PGKNPKNFOTMPGTFOTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAOTNAEPD( FV006526 Dengue 3 NS3 PGKNPKNFOTMPGTFOTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAOTNAEPD( FV006609 Dengue 3 NS3 PGKNPKNFQTMPGTFQTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAQTNAEPD( FV006638 Dengue 3 NS3 PGKNPKNFOTMPGTFOTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAOTNAEPD( FV006648 Denoue 3 NS3 PGKNPKNFOTMPGTFOTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAQTNAEPD( FV006658 Dengue 3 NS3 PGKNPKNFOTMPGTFOTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAQTNAEPD( FV006667 Dengue 3 NS3 PGKNPKNFOTMPGTFOTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAOTNAEPD( FV006746 Dengue 3 NS3 PGKNPKNFOTMPGTFOTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAOTNAEPD( FV006820 Dengue 3 NS3 PGKNPKNFOTMPGTFOTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAQTNAEPD( FV006882 Dengue 3 NS3 PGKNPKNFQTMPGTFQTTTGEIGAIALDFKPGTSGSPIINREGKIVGLYGNGVVTKNGGYVSGIAQTNAEPD( FV003431 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKASOE( FV004134 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKATQE( FV004459 Dengue 1 NS3 PGKNPKNVQTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKATQE( FV003936 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKASOE( FV004259 Dengue 1 NS3 PGKNPKNVQTAPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKASOE( FV004572 Dengue 1 NS3 PGKNPKNVQTAPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKASQE( FV003745 Dengue 1 NS3 PGKNPKNVQTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKASQE( FV003990 Dengue 1 NS3 PGKNPKNVQTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKASOE( FV004285 Dengue 1 NS3 PGKNPKNVQTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKASQE( FV004355 Dengue 1 NS3 PGKNPRNVQTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKASQE( PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003421 Dengue 1 NS3 FV003575 Dengue 1 NS3 PGKNPKNVQTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKTSQE( FV003730 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003947 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003450 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003502 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003632 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003634 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003698 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKTSQE( FV003812 Dengue 1 NS3 FV003825 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003867 Dengue 1 NS3 PGKNPKNVQTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKTSQE( PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKTSQE( FV003919 Dengue 1 NS3 FV003969 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKTSOE( FV003588 Dengue 1 NS3 PGKNPKNVQTTPGTFKTLEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKASQE( PGKNPKNVOTTPGTFKTLEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKASQE( FV004084 Dengue 1 NS3 FV004189 Dengue 1 NS3 PGKNPKNVOTTPGTFKTLEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKASOE( FV004215 Dengue 1 NS3 PGKNPKNVOTTPGTFKTLEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKASOE( FV004546 Dengue 1 NS3 PGKNPKNVOTTPGTFKTPEGEVGAIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAOAKASOE(

#### Sequence variability analysis result

Consensus sequence is shown below X axis with conserved positions in blue. A conserved position must fulfill: entropy  $\leq 1$ , gap fraction  $\leq 0.1$ , and consensus amino acid% > 90%.

### Entropy and % of consensus amino acid at each position based on 1574 Human Dengue virus type 1 complete envelope sequences in the database

Download full result file | Download consensus sequence file



#### B-cell epitope summary table for 4 dengue virus subtypes (Amino acids highlighted at the positions where neutralizing epitopes appear more often than non-neutralizing epitopes)

pos		W101	G104	G106	L107	F108	K174	P176	W231	Y299	V300	T301	L301	N302	T303	F304	G304	K305	V305	L306	F306	K307	L308	K308	V308	E309	V309
DV1	neutralizing									1	1											1	1			2	
DV1	non-neutralizing	1			1	1											3	1									
DV1	Unknown														1		4	2				2					
DV2	neutralizing	9	9	10	3	1			1	1	1				1		7	8			5	11			5	1	5
DV2	non-neutralizing														1				1	1		1		1		1	
DV2	Unknown	1		5	5	1												2				1					
DV3	neutralizing											4	1	8	3	8			7	8		2		16		8	
DV3	non-neutralizing	1			1	1											3	2				1					
DV3	Unknown														1		3	1				1					
DV4	neutralizing	1	1	1			2	2		1	1																
DV4	non-neutralizing	1			1	1									6		4	2	6	6		7		6		7	
DV4	Unknown														1		3	1				1					

#### Input key neutralizing positions (seperated by comma) of your interest. They will be highlighted on 3D structure.

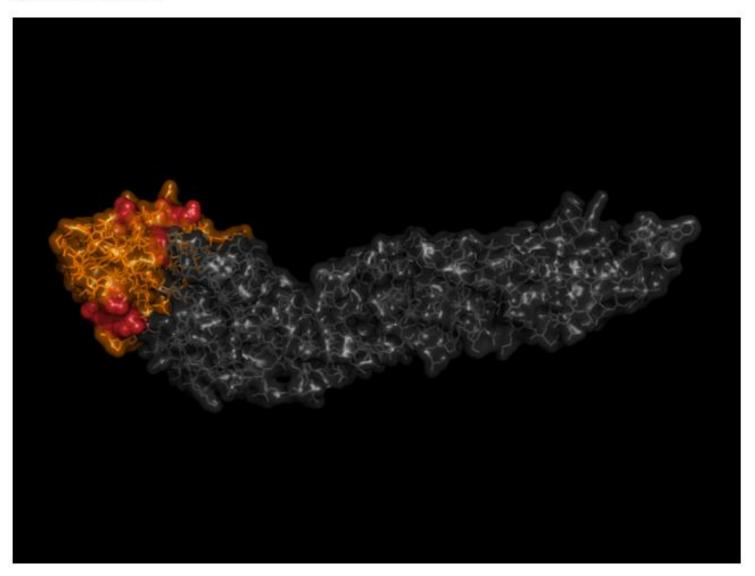
Y299,V300,K307,K310,P332,K334,P364,L389,W391

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	2 (12)		90 - AN		

#### 3D structure

Key positions are in red.



SUMMARY Introduction Definitions Framework **Bioinformatics tools Examples** Malaria **FLAVIdB** Conclusions

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# CONCLUSIONS

Traditional databases are being supplemented by knowledge-based systems

KBS integrate data, knowledge base, analytical tools, and workflows for multiple automated analyses

**KBS** suggest experiments and learn from results

# Acknowledgements

Guanglang Zhang PhD –

system design and implementation

Lars R. Olsen MSc –

FLAVIdB

