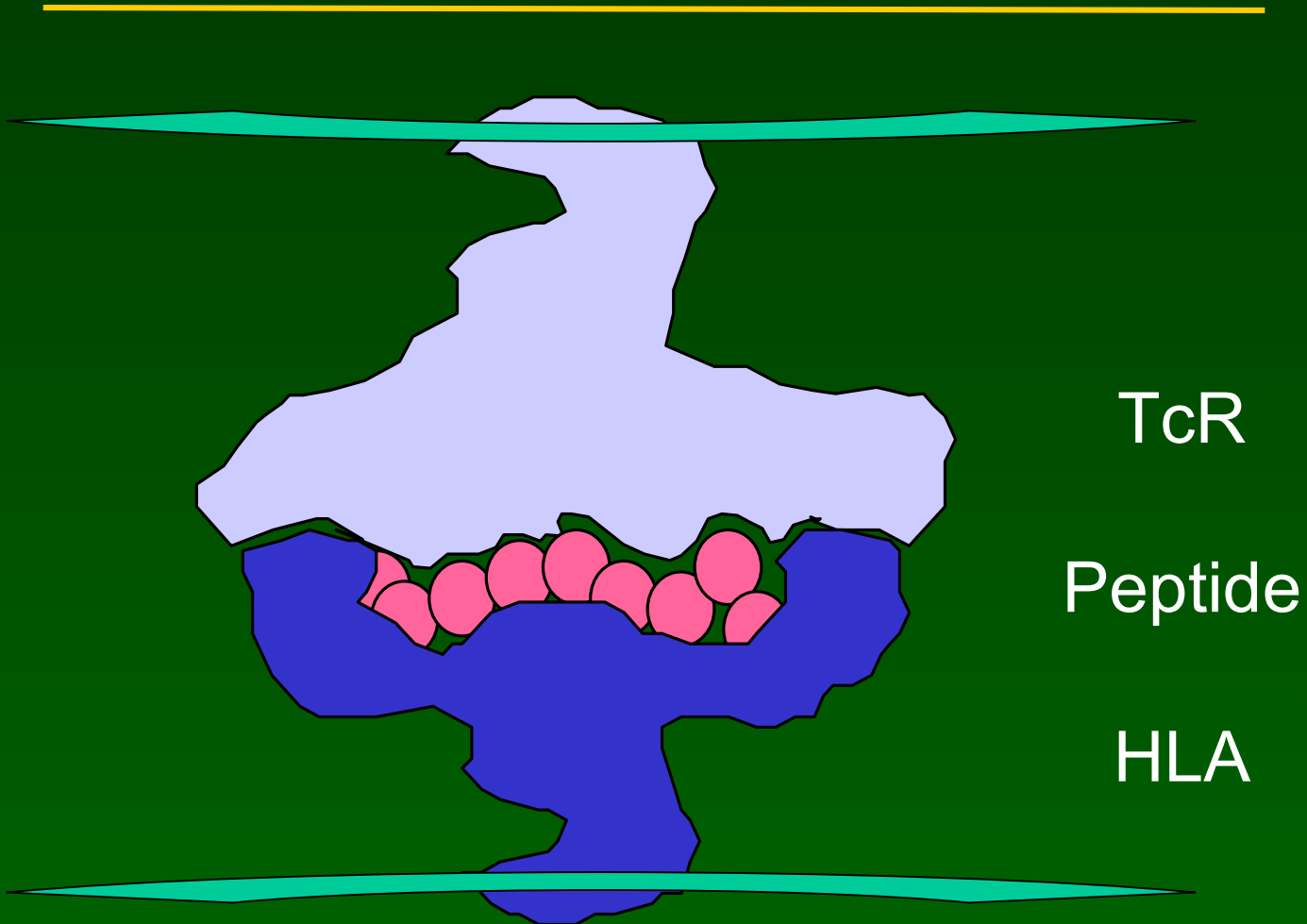


Genome- and HLA-wide search for SARS CTL epitopes

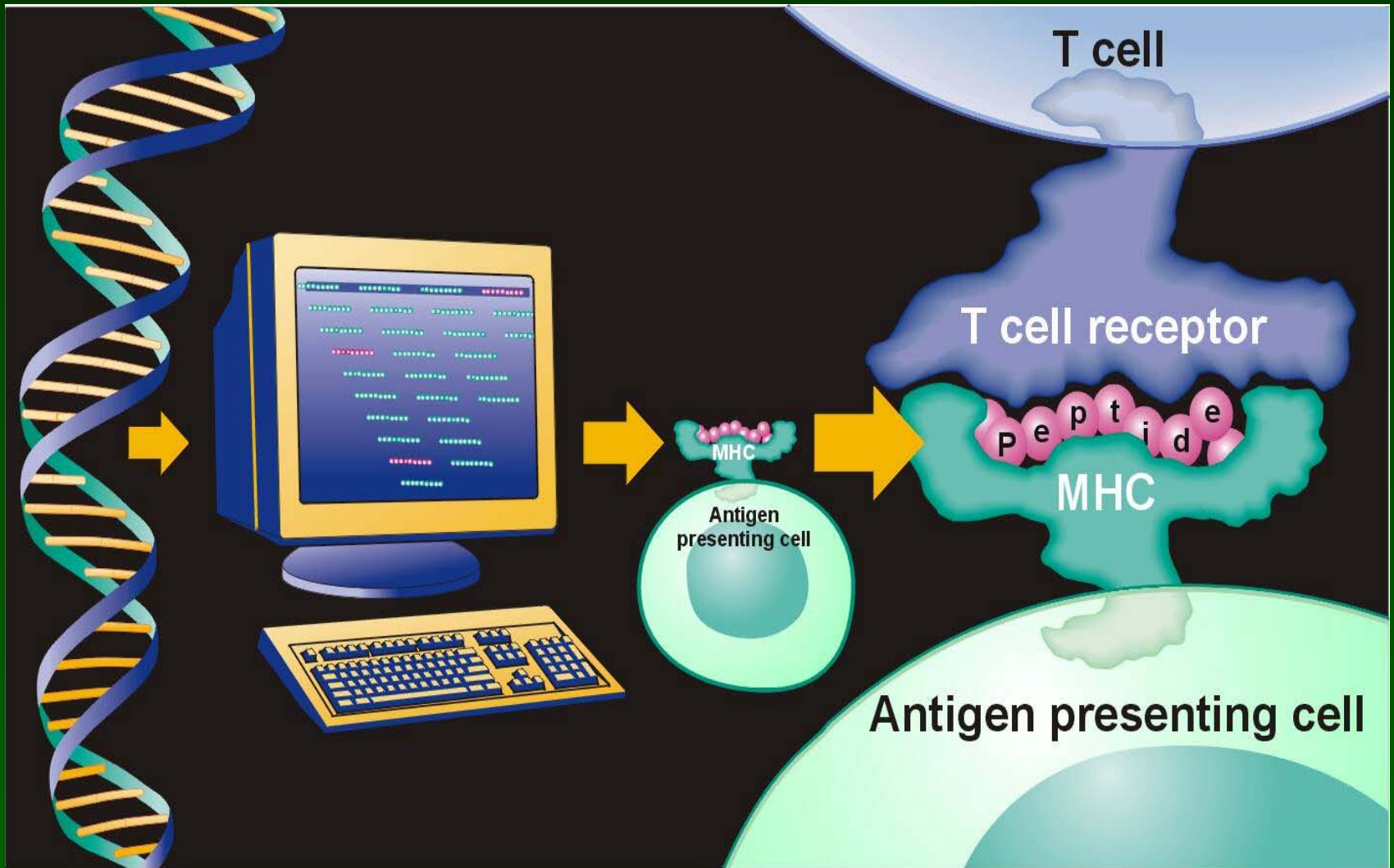
The Peptide Component
of the
International Histocompatibility Working Group (IHWG)

Coordinator
Søren Buus, professor, MD, PhD
University of Copenhagen

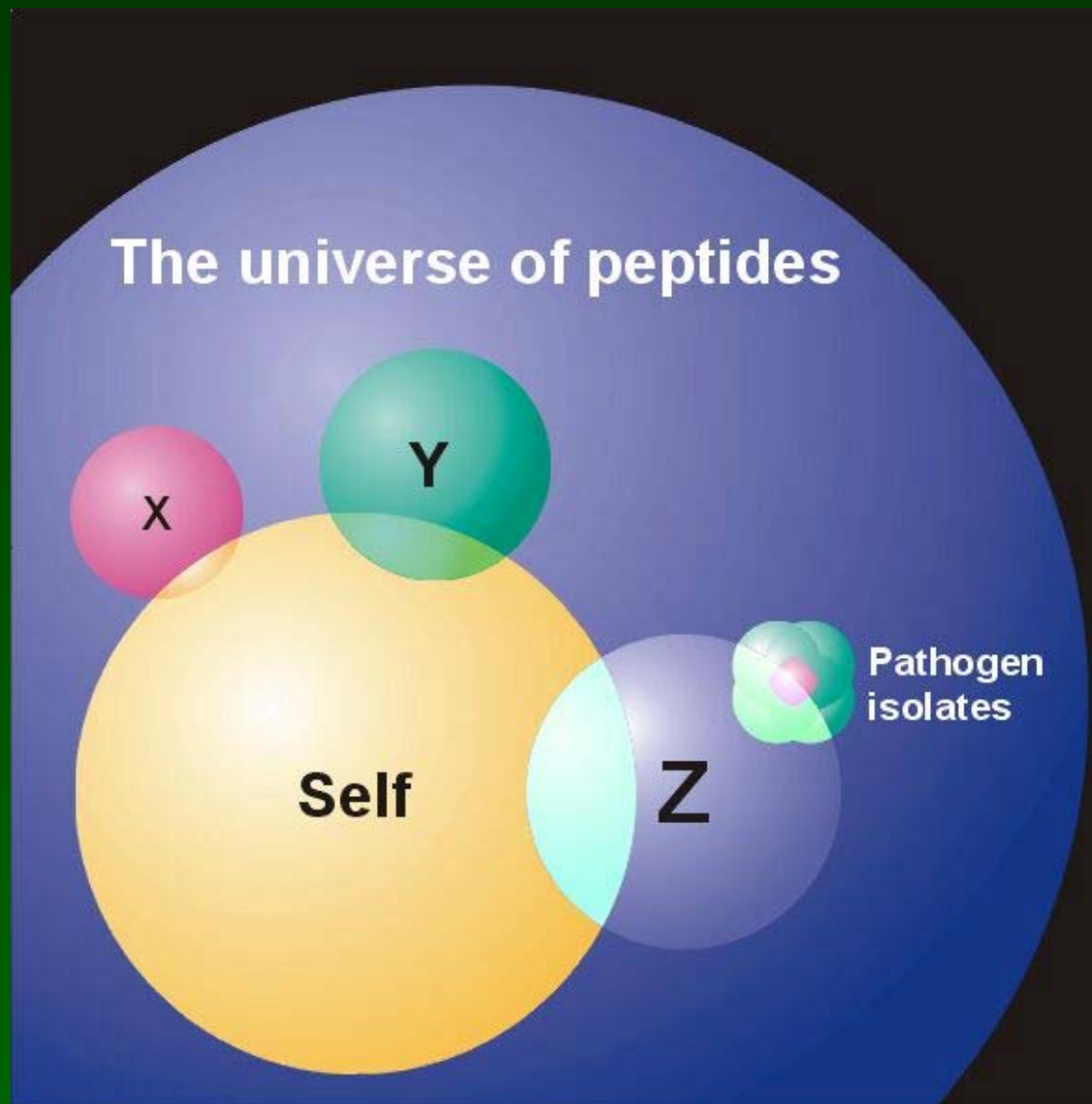
Peptides - prime targets of immune recognition



Translating genome to immunogens



MHC polymorphism and immunity



HLA polymorphism - supertypes

A “supermotif”, a motif which confers the ability to bind to several different HLA molecules

A “supertype”, the corresponding assembly of HLA molecules

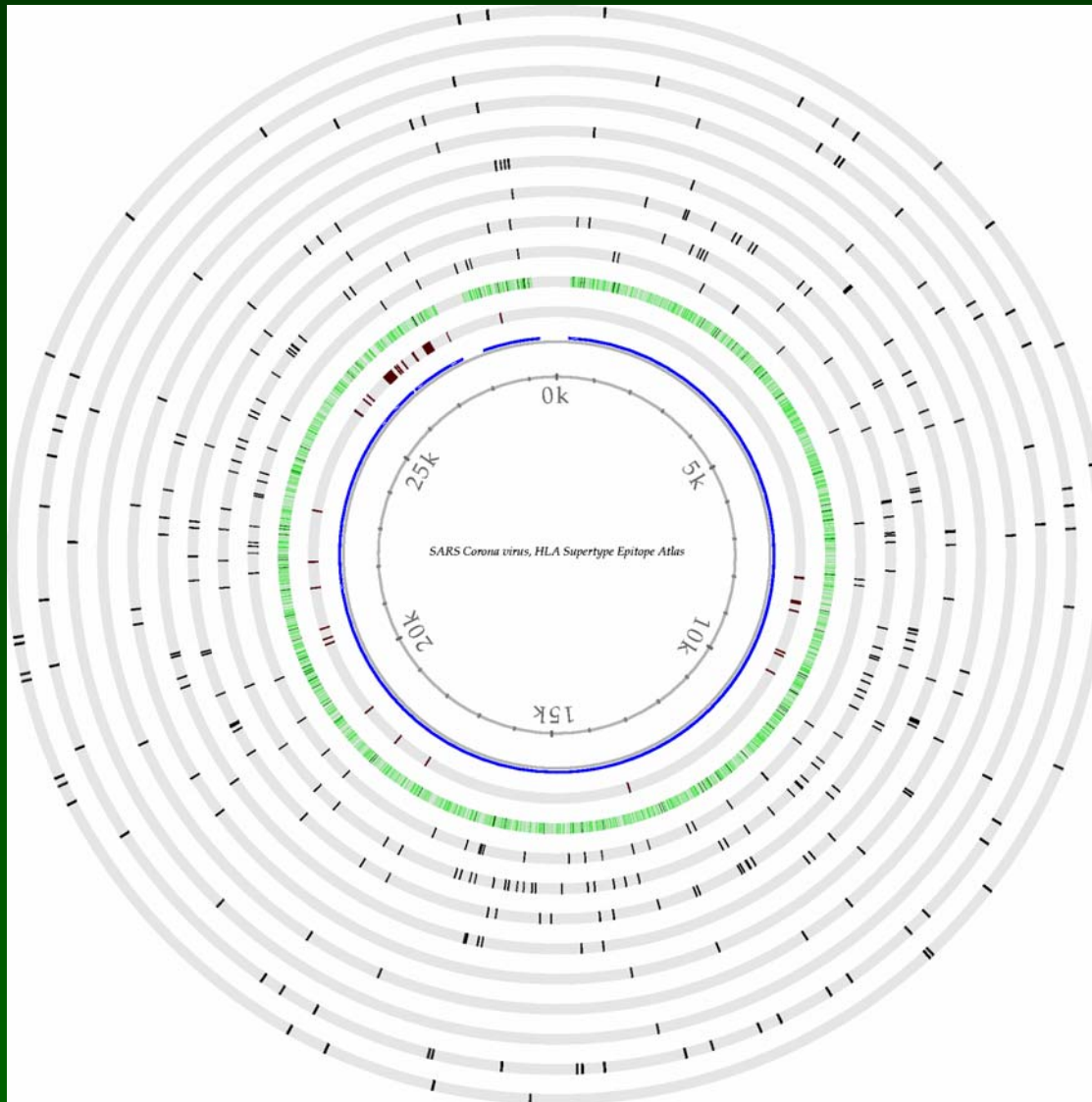
As of October 2001, nine major HLA class I supertypes have been defined

HLA-A1, A2, A3, A24

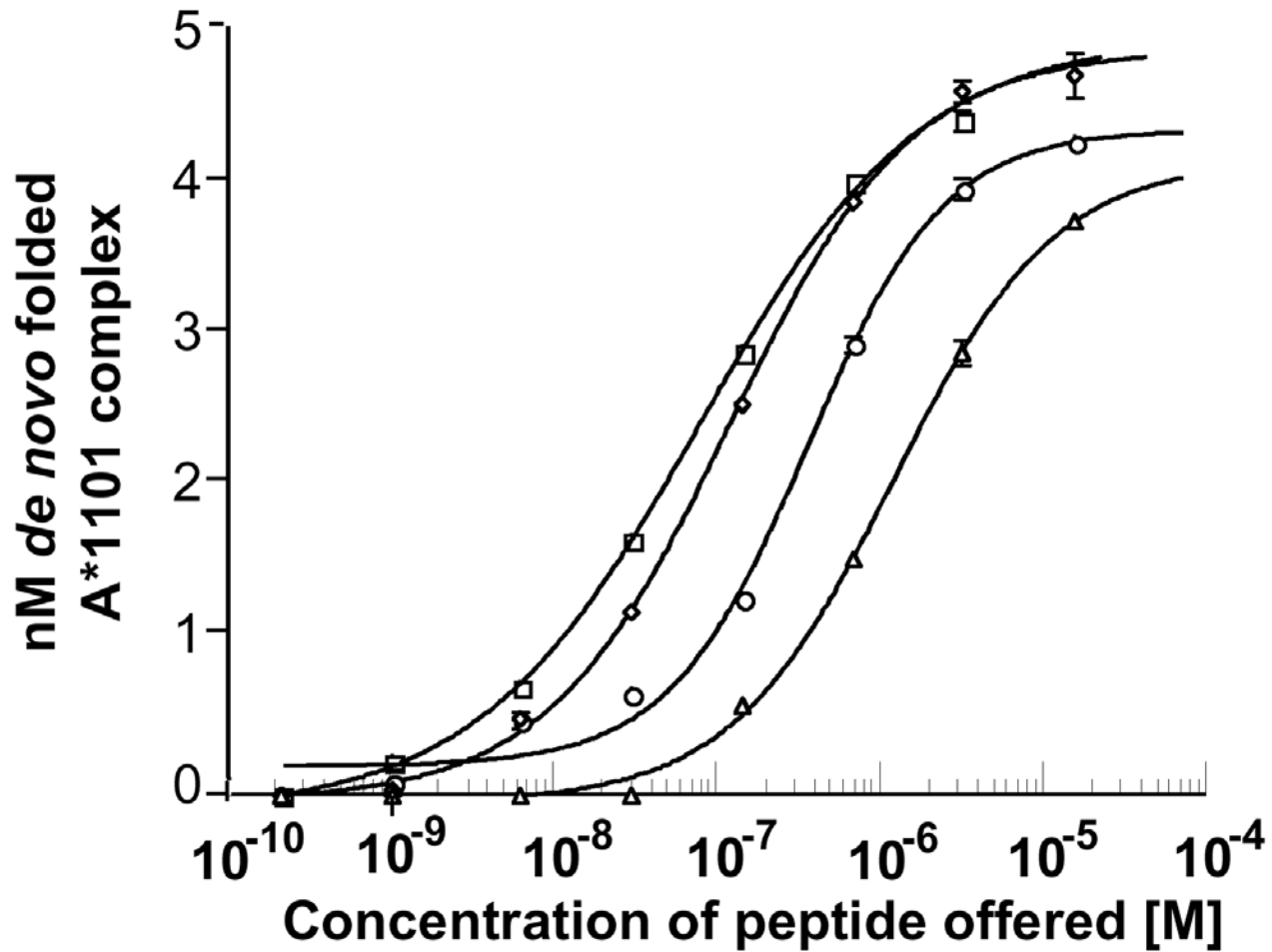
HLA-B7, B27, B44, B58, B62

Sette et al, Immunogenetics (1999) 50:201-212

Bioinformatics tools are available



Biochemical tools are available



Prediction of SARS epitopes (1)

A1 Peptides	HLA Molecule					
	A1 (A*0101)	A2 (A*0201)	A3 (A*0301)	B58 (B*5801)	B7 (B*0702)	B62 (B*1501)
XXXXXXXXXX	█					
XXXXXXXXXX	█					
XXXXXXXXXX	█					
XXXXXXXXXX	█			█		
XXXXXXXXXX	█					
XXXXXXXXXX	█			▴		▴
XXXXXXXXXX	█					
XXXXXXXXXX	█					
XXXXXXXXXX	█					▴
XXXXXXXXXX	█					
XXXXXXXXXX	█					
XXXXXXXXXX	█					
XXXXXXXXXX	█					
XXXXXXXXXX	█					
XXXXXXXXXX	█					
XXXXXXXXXX	▴					
XXXXXXXXXX	▴					

B58 Peptides	HLA Molecule					
	A1 (A*0101)	A2 (A*0201)	A3 (A*0301)	B58 (B*5801)	B7 (B*0702)	B62 (B*1501)
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
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XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX				█		
XXXXXXXXXX	▴			█		▴
XXXXXXXXXX			▴	█		▴
XXXXXXXXXX				█		▴
XXXXXXXXXX				█		

Prediction of SARS epitopes (summary)

The first six HLA supertypes showed:

High accuracy: 93% (498 of 534 examples)

High PPV: 74% (67 of 90 positives)

High NPV: 97% (431 of 444 negatives)

Low cross-reactivity between supertypes: 3%

High cross-reactivity within the A3 supertype: 63%

More than 100 HLA binders found

i.e. expect more than 50 candidate epitopes

Immuno-bioinformatics

- FAST EPITOPE IDENTIFICATION
- COMPLETE GENOME/PROTEOME SCAN
- INCORPORATES PATHOGEN DIVERSITY
- INCORPORATES HUMAN IMMUNE DIVERSITY

Validation of predictions

- **BIOCHEMICAL VALIDATION**

Tissue typing, HLA binding, peptide generation

- **PHYSIOLOGICAL VALIDATION**

In vitro recall (QuantiFeron®, Elispot, IFN γ - overlapping peptide mixtures)

In vivo challenge (transgenic animals, vaccinee's)

Use of epitope information

- DIAGNOSTICS

Monitor immune responses in disease, and in vaccination

QuantiFeron®, Elispot, IFN γ , tetramers, immunohistochemistry

- THERAPEUTICS

Selection of subunits vaccine candidates

Selection of epitope candidates (artificial multi-epitopes)

Challenge to the WHO

- COORDINATE SAMPLING OF PATIENT PBMC
- COORDINATE TESTING, TRAINING
- COORDINATE DATA ANALYSIS

SARS PATIENTS ARE A SCARCE

AND VALUABLE RESOURCE

“The human MHC project”

Institute of Medical Microbiology and Immunology, University of Copenhagen

Christina Sylvester-Hvid, Kasper Lamberth, Sune Justesen, Hanne Thomadsen, Søren Buus

Center for Biological Sequence Analysis, Technical University of Denmark

Ole Lund, Morten Nielsen, Claus Lundegaard, Peder Worning, Can Kesmir, Søren Brunak