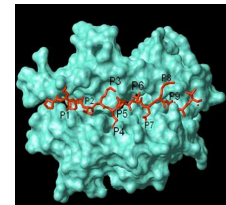




Evaluer l'immunogénicité des protéines thérapeutiques

Bernard MAILLÈRE, PhD

Institute of Biology and Technologies
Service d'ingénierie moléculaire de protéines (SIMOPRO)



Therapeutic proteins

- ❖ **95 of the 265 pharmaceutical products** approved by European commission since 1995 (36%)
- ❖ **Diversity of proteins**
Antibodies, hormones, cytokines, blood factors, enzymes
- ❖ **Market**



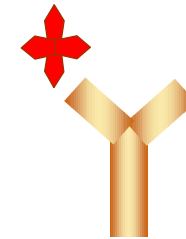
Product	Indications	Sales value (US\$, millions)
Epo	anemia	8000
G-CSF	Neutropenia	2500
IFN- β	Multiple sclerosis	1200
Anti-TNF	Crohn's disease Rheumatoid arthritis	3300
Anti-Her/2	Bresat cancer	425

From Walsh, 2005

Immunogenicity of therapeutic proteins

❖ Consequences

- Altered pharmacokinetics
- reduced efficacy (neutralizing antibodies)
- Safety concerns (neutralization of endogenous proteins)



❖ Occurrence

Non human proteins: **High**

- Bovine and porcine insulin
- Salmon calcitonin
- Streptokinase, staphylokinase

Human proteins: **Variable**

- Factor VIII (hemophiliacs 35%)
- IFN α et β <25%
- Anti-TNF <20%

Immunogenicity and protein engineering

- ❖ **Humanisation** Conversion of foreign sequences to humanized sequences
Use of human sequences

Reduces the risk of immunogenicity

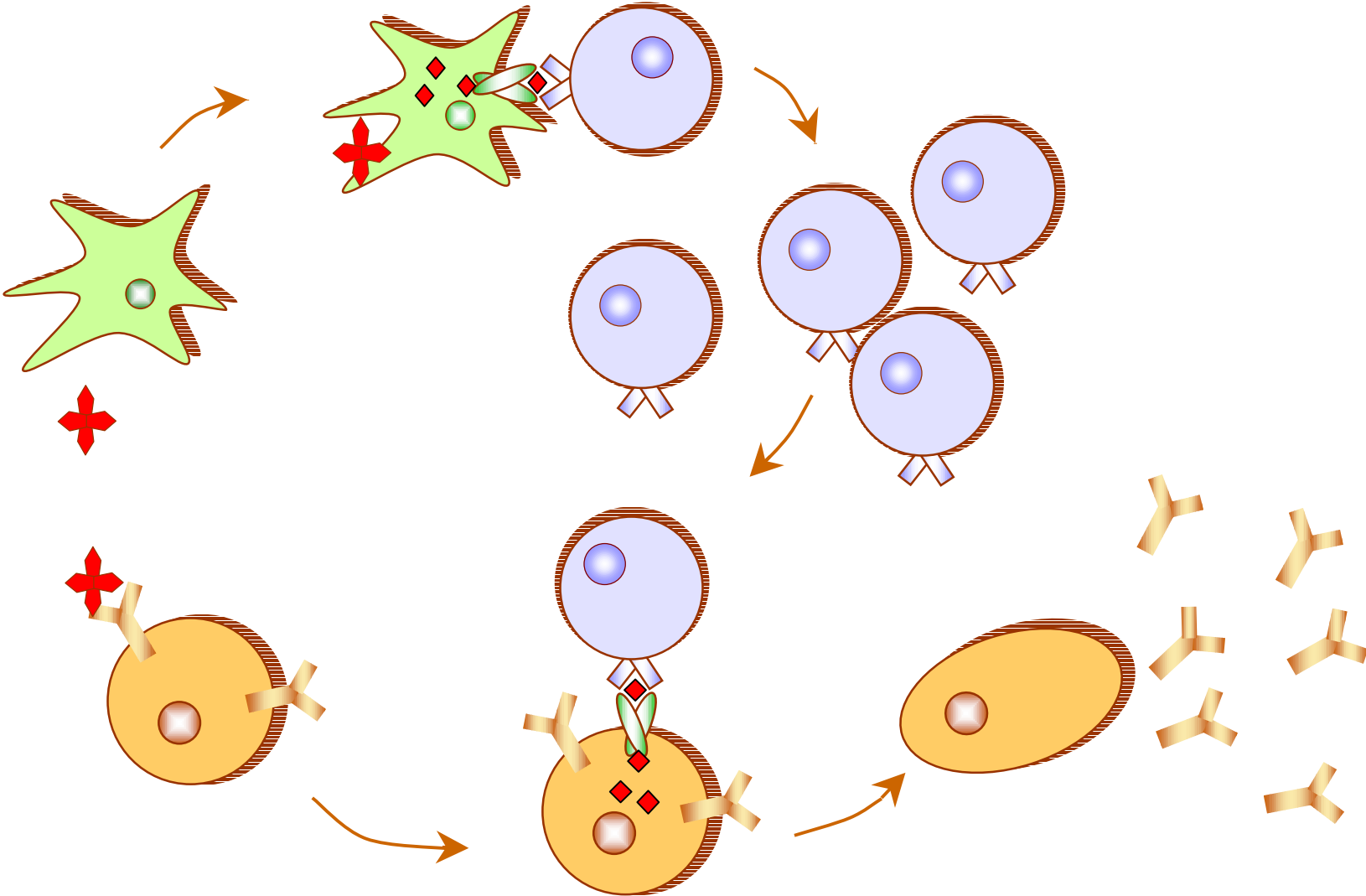
Human proteins could be immunogenic
Limitation for protein engineering

- ❖ **Future advances**

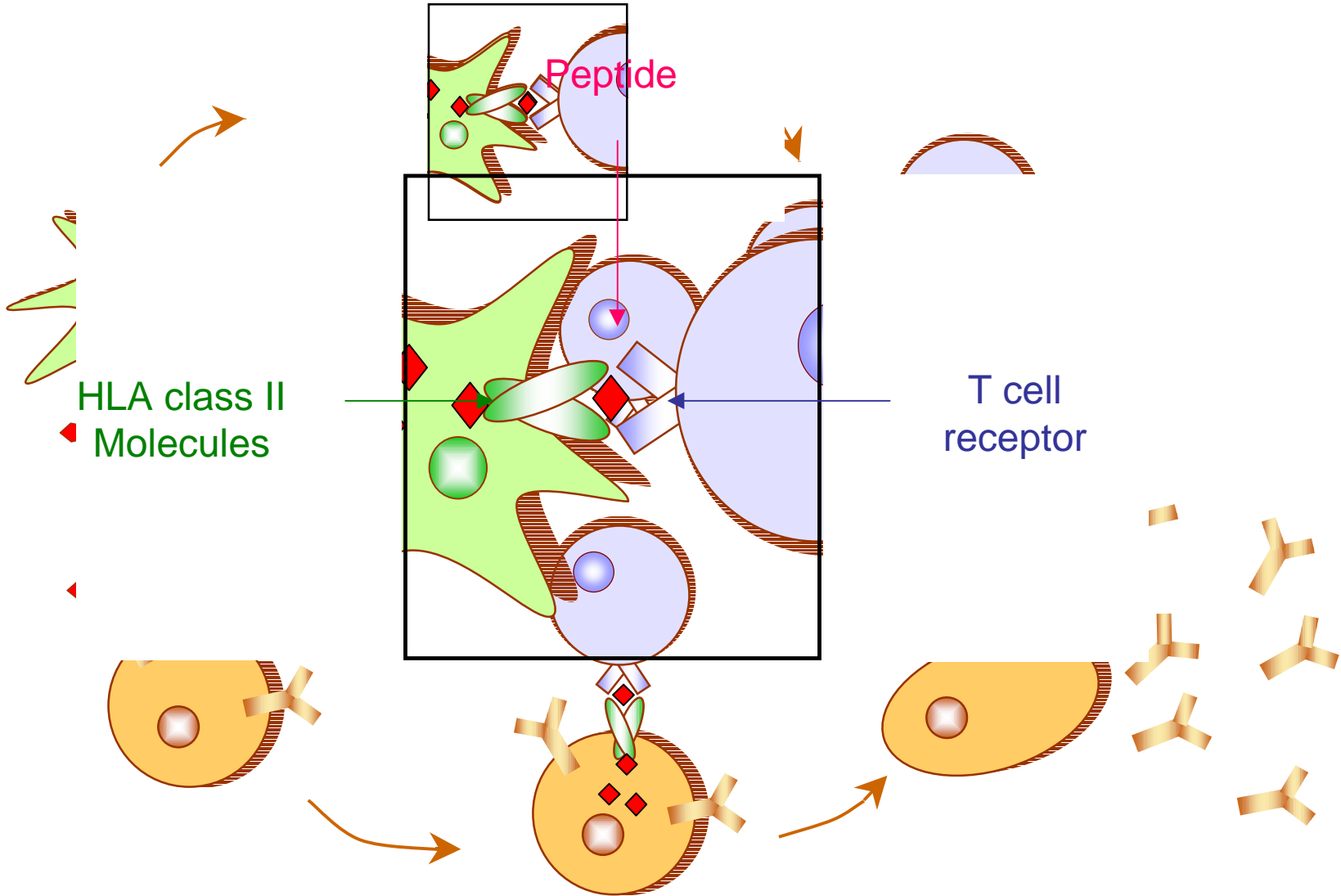
- Engineered sequences: Kinetics, stability, enhanced activity ...
- Biosimilars

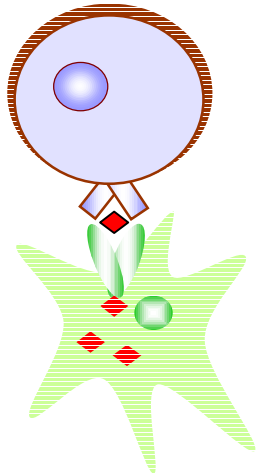
→ immunogenicity evaluation of therapeutic proteins
before the clinical phases

Antibody response specific for therapeutic proteins



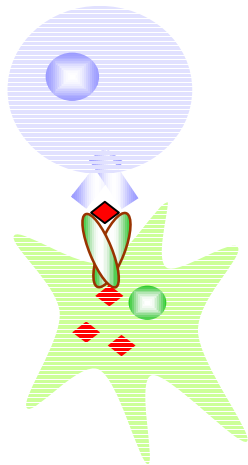
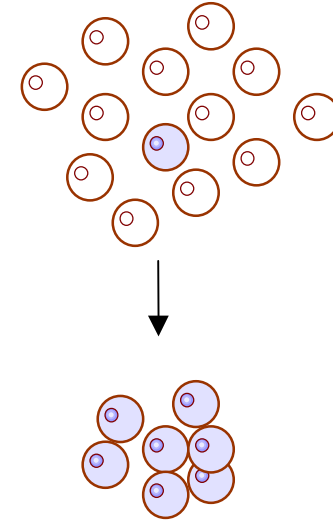
Antibody response specific for therapeutic proteins





❖ T cell activation assay

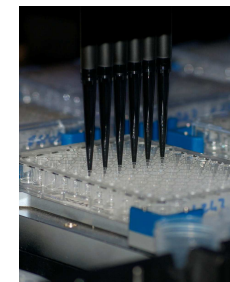
Amplification of therapeutic protein-specific T cells of naïve donors



❖ Automated HLA class II specific binding assays

Collection of immunopurified HLA class II molecules

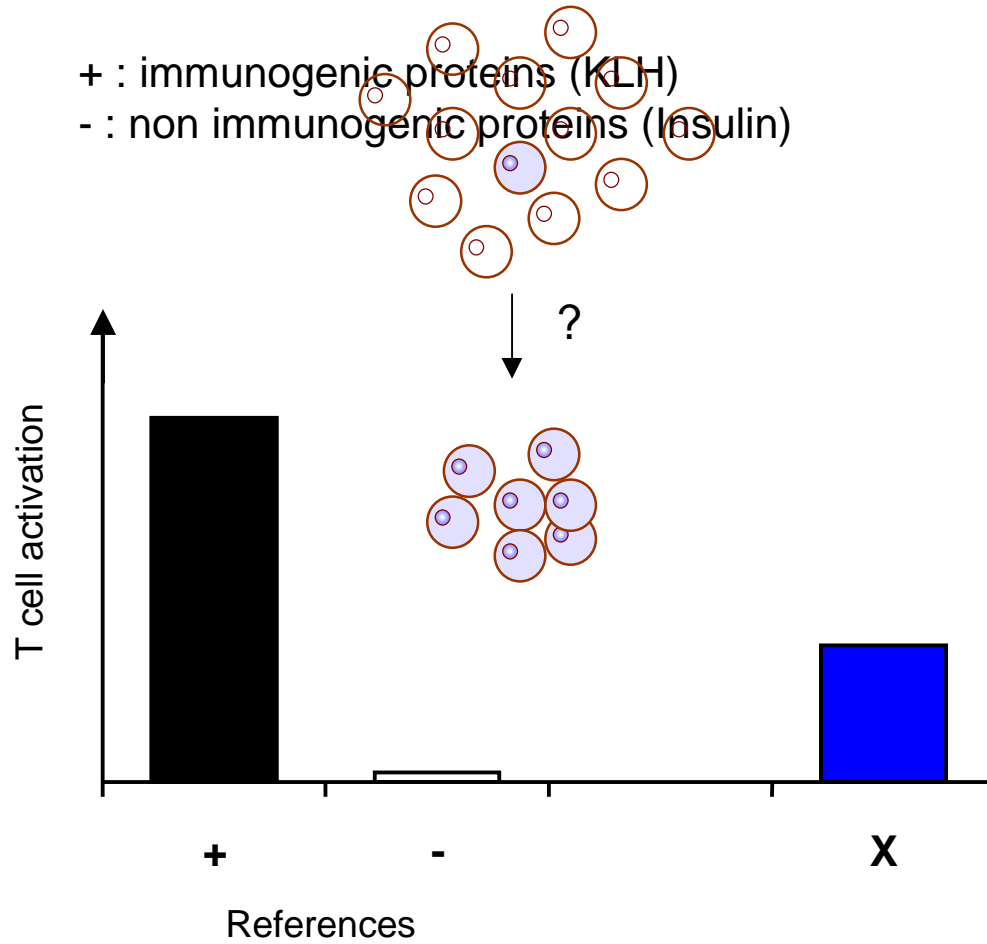
The most frequent molecules in the European and North-American populations



Evaluate immunogenicity of therapeutic proteins

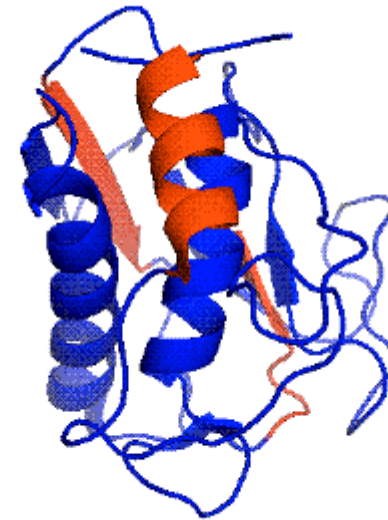
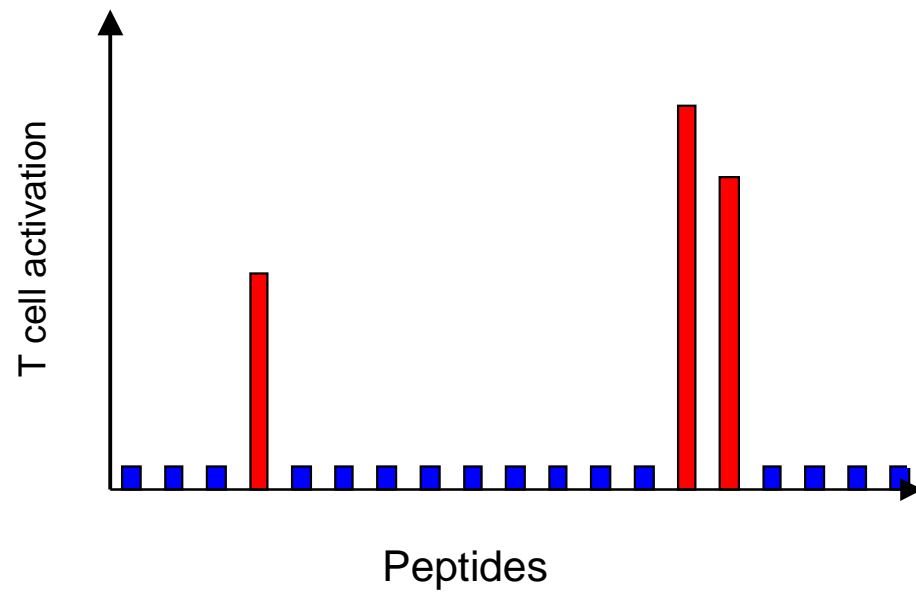
Comparison with reference proteins

+ : immunogenic proteins (KLH)
- : non immunogenic proteins (Insulin)



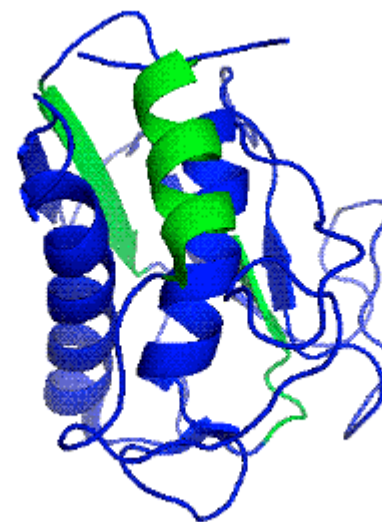
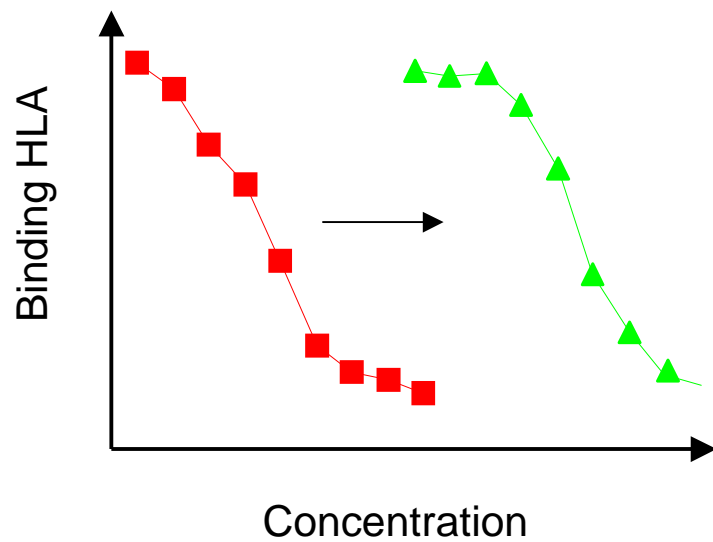
Minimise immunogenicity of therapeutic proteins

Identification of immunogenic sequences
In therapeutic proteins



Minimise immunogenicity of therapeutic proteins

Modification of immunogenic sequences
In therapeutic proteins



proteus



Immuno'lineTM

Evaluate and minimise
immunogenicity of therapeutic proteins