Immunology and causes of unwanted immunogenicity

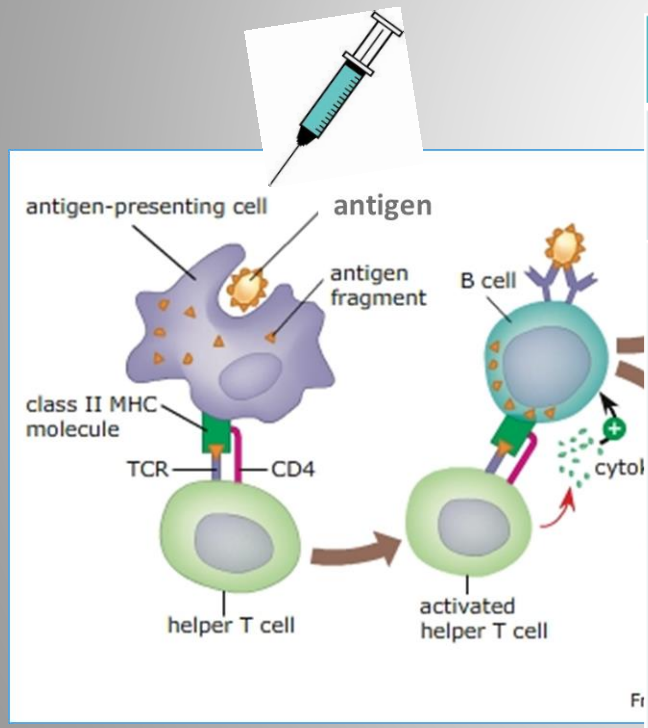
Sofie Pattijn

EIP Symposium

February 25th 2019

Immunogenicity

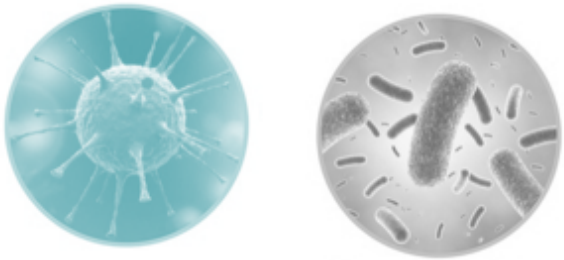
"the ability of a particular substance, such as an antigen or epitope, to induce an immune response"



WANTED	UNWANTED	
Vaccines	**Therapeutic protein**	**Stem Cell products**
Immune response against the pathogen (virus, bacteria) aiming at protecting the organism	Production of antidrug- antibodies (ADAs) possibly neutralising the therapeutic effects of the treatment and, in rare cases, inducing adverse effects	Cellular and humoral responses Anti HLA antibodies Immune rejections Potential safety effect

Our Immune System

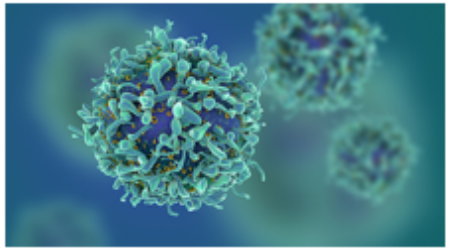
Virus, bacteria



Over-reactive
Auto immune diseases

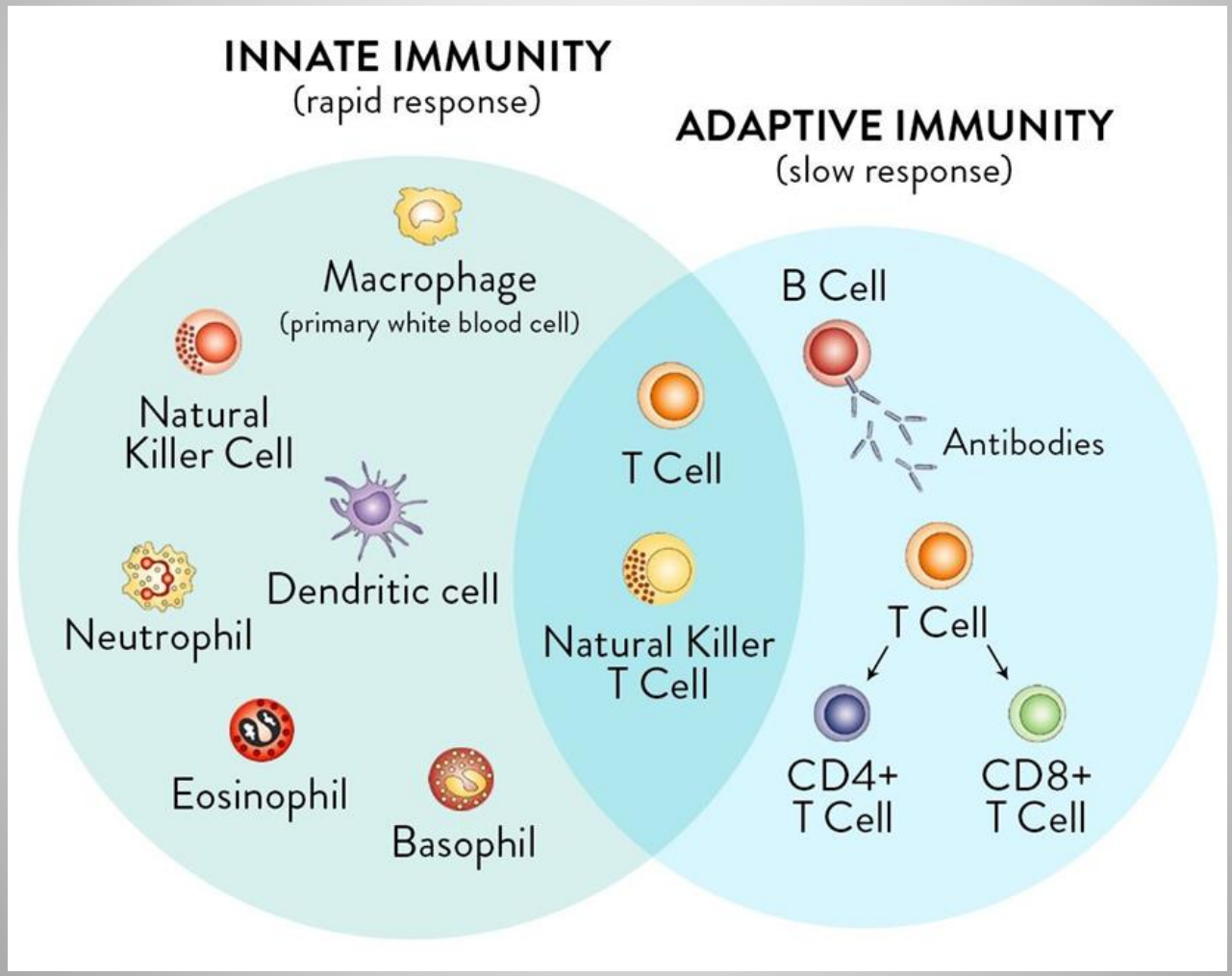


Tumor cells

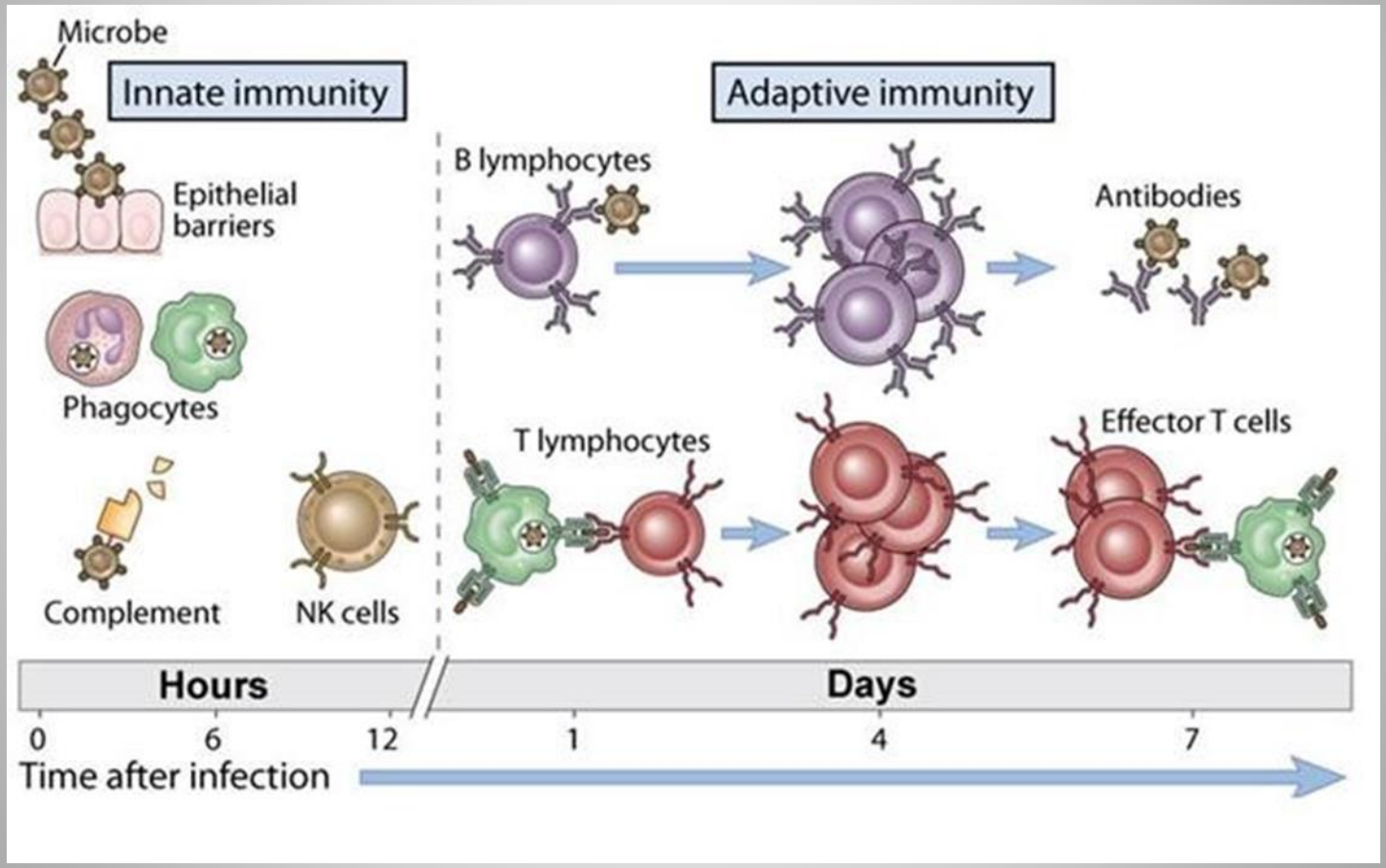


Immune deficiencies
Infections, malignancies

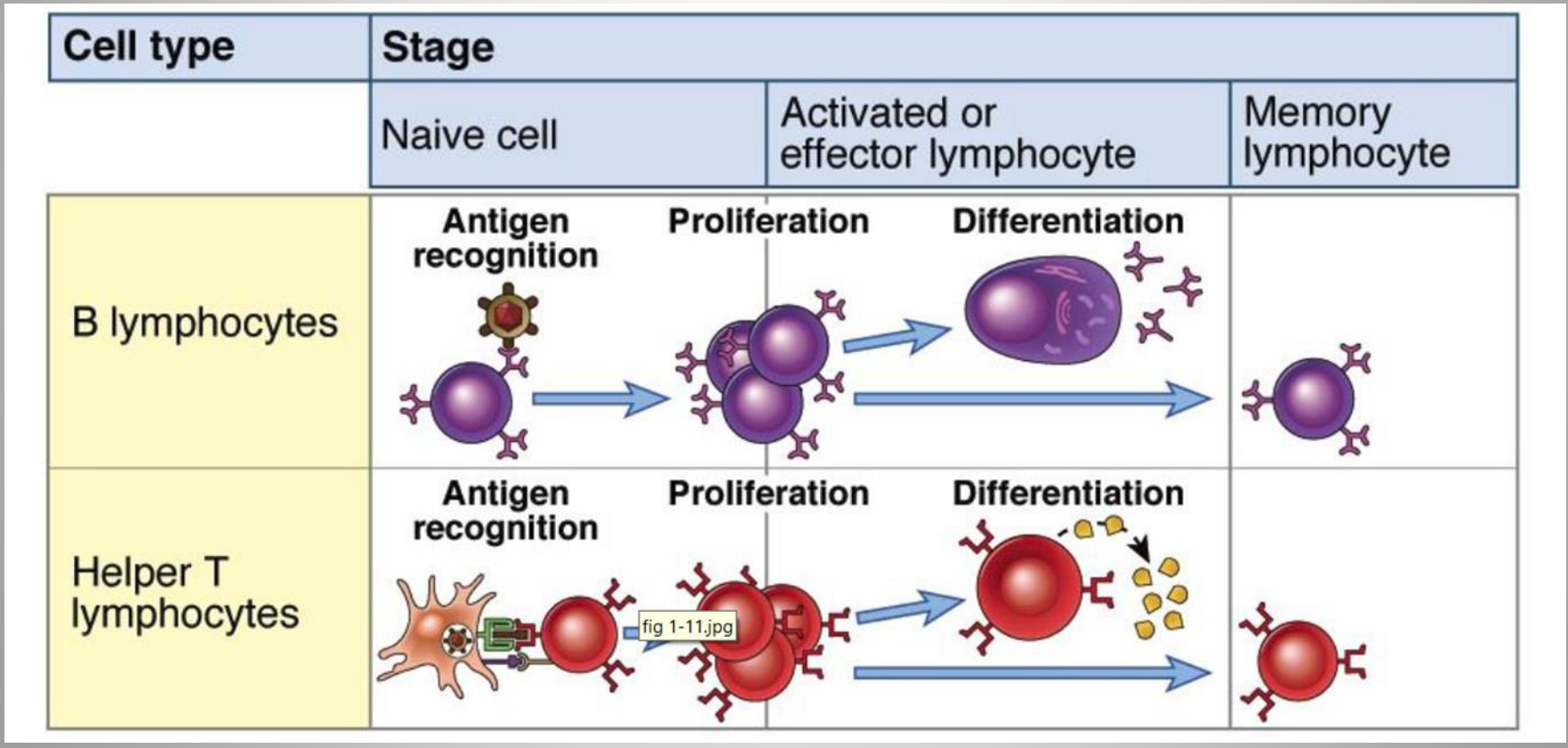
The central players



The maturation

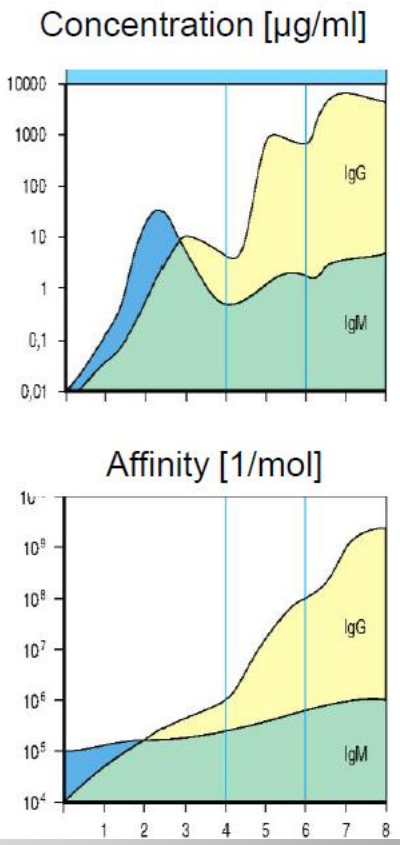


The life cycle of lymphocytes

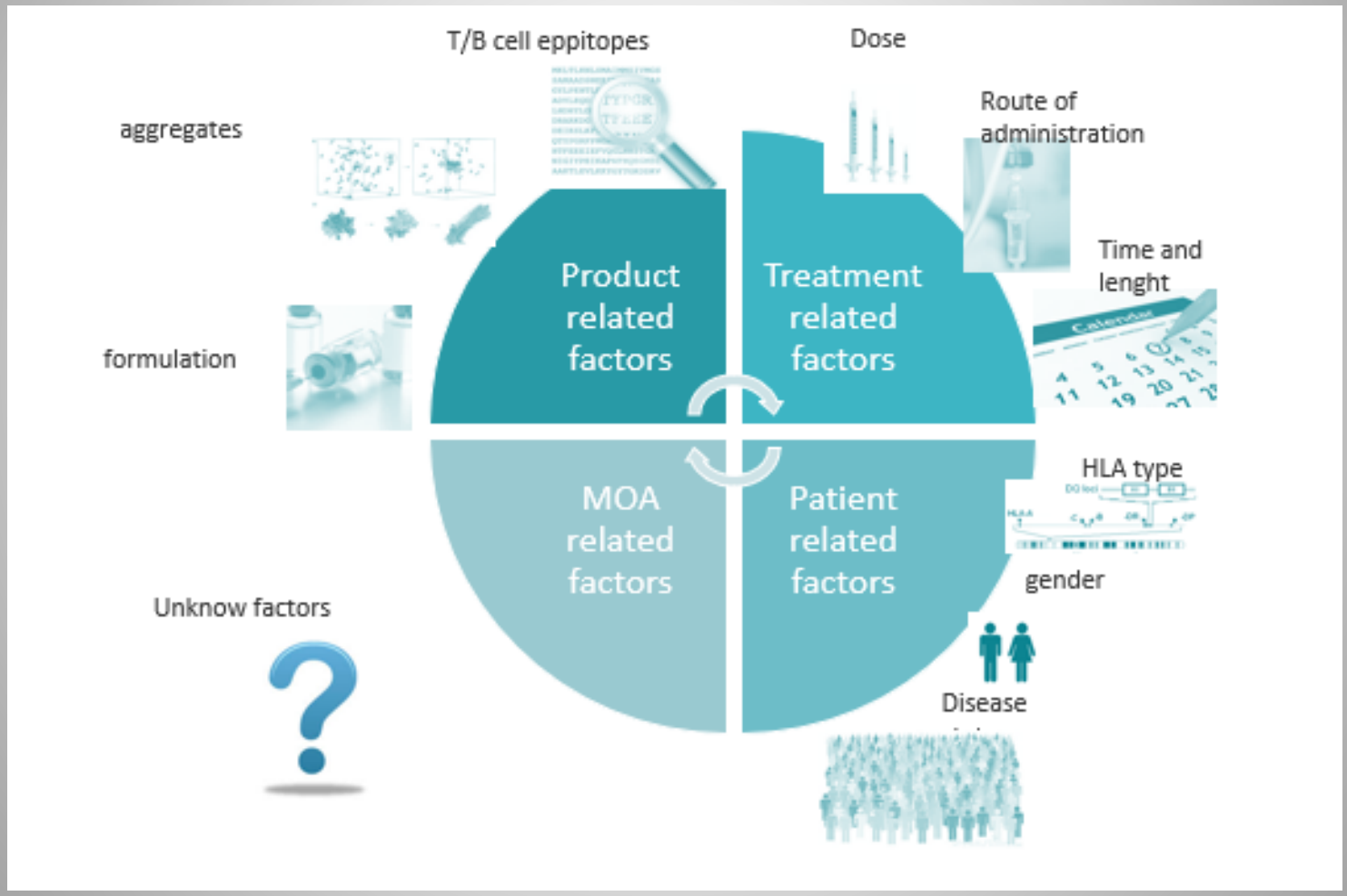


The antibodies

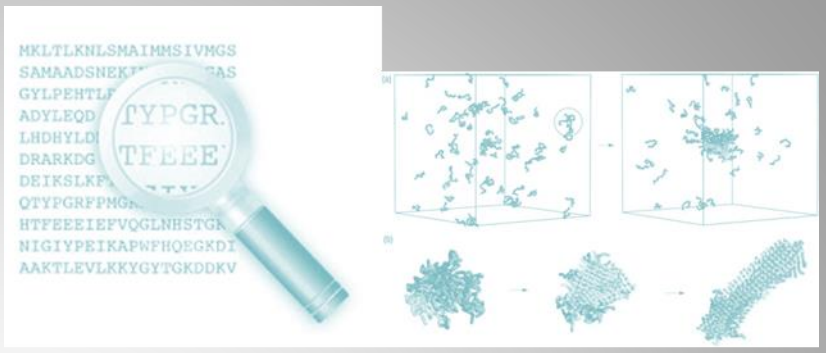
	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Heavy chain	γ1	γ2	γ3	γ4	μ	α1	α2	δ	ε
Molecular weight (kD)	146	146	165	146	970	160	160	184	188
Concentration [mg/ml]	9	3	1	0,5	1,5	3,0	0,5	0,03	5×10^{-5}
Half life time [days]	21	20	7	21	10	6	6	3	2
Complement activation	++	+	+++	–	+++	–	–	–	–
Alternative pathway	–	–	–	–	–	+	–	–	–
Placenta transfer	+++	+	++	–/+	–	–	–	–	–
Binding to MΦ	+	–	+	–/+	–	+	+	–	+
Binding to mast cells	–	–	–	–	–	–	–	–	+++
Reactivity to Protein A	+	+	–/+	+	–	–	–	–	–



Factors influencing unwanted Immunogenicity



Drug related factors



- **Drug-related factors:**
  - ✓Primary sequence, structure
  - ✓Novel epitopes
  - ✓Glycosylation, deamidation, oxydation, …
  - ✓Product impurities, aggregation and degradation products
  - ✓Formulation and storage conditions



Drug related factors

Table 3. Origin of Biological Drugs[a]

Murine Cell Line	Chinese Hamster Ovary Cell	*Escherichia coli*	Rat/Mouse
Eculizumab	Rituximab	Ranibizumab	Catumaxomab
Natalizumab	Fusion protein	Certolizumab p	
Ustekinumab	IFN β 1a	Anakinra	
Canakinumab	Lenograstim	Cytokines	
Chimeric mAb	Humanized and human mAb	Pegfilgrastim	

[a]Most chimeric mAbs are derived from murine cell lines, while many of the humanized and human mAbs are obtained from Chinese hamster ovary cells. The exceptions are detailed in the table.

Table 4. Excipients With Allergenic Potential in Biological Drugs

Mannitol	Albumin	Polysorbate 80	Latex	Papain	Trometamol
Adalimumab	Interferon beta-1a (Avonex)	Adalimumab	Adalimumab	Abciximab	Etanercept
Basiliximab	Interferon beta-1b (Betaferon)	Infliximab	Etanercept		
Palivizumab	Interferon alfa-2b (IntronA)	Omalizumab	Anakinra		
Etanercept		Alemtuzumab			
Interferon beta-1a (Rebif)		Natalizumab			
Interferon beta-1b (Betaferon)		Tocilizumab			
Interferon gamma-1b		Canakinumab			
Lenograstim		Belimumab			

Therapy related factors







- **Therapy related factors**
  - ✓Duration and length
  - ✓Dose
  - ✓Route and frequency of administration

Therapy related factors

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Effect of route of administration of human recombinant Factor VIII on its immunogenicity in Hemophilia A mice

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Abstract

Factor VIII is a multi-domain glycoprotein and is an essential cofactor in the blood coagulation cascade. Its deficiency or dysfunction causes Hemophilia A, a bleeding disorder. Replacement using exogenous recombinant Factor VIII (FVIII) is the first line of therapy for Hemophilia A. Immunogenicity, the development of binding (total) and neutralizing (inhibitory) antibody against administered protein is a clinical complication of the therapy. There are several product related factors such as presence of aggregates, route and frequency of administration and glycosylation have been shown to contribute to immunogenicity. The effect of route of administration of Factor VIII on antibody development in Hemophilia A is not completely understood. Here we investigated the effect of route of administration (sc or iv) on immunogenicity in Hemophilia A mice. The total and inhibitory titers were determined using ELISA and modified Bethesda Assay respectively. The results indicated that sc is more immunogenic compared to iv route in terms of total antibody titer development (binding antibodies) but no significant differences in inhibitory titer levels could be established.

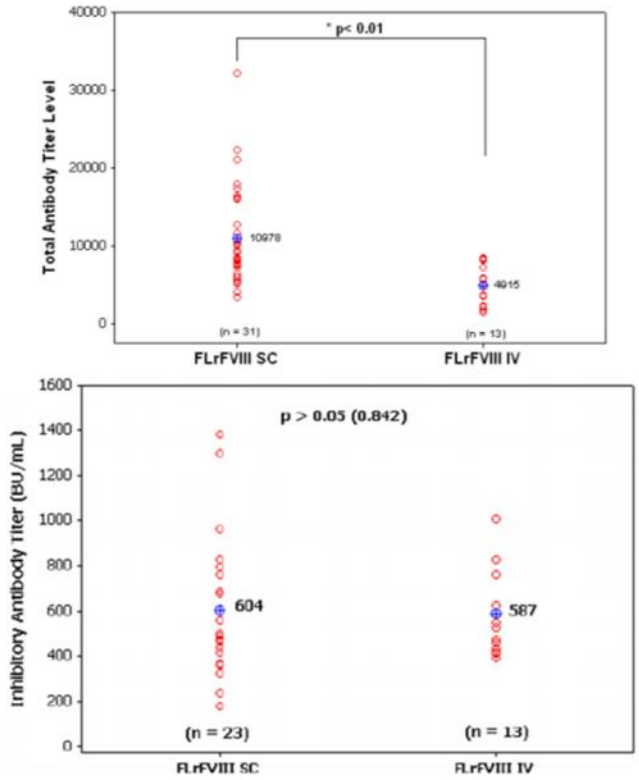


Figure 1.
Total and inhibitory antibody titers following sc and iv administration of full length factor VIII in hemophilia A mice.

Table 1

Effect of route of administration of recombinant Factor VIII on total and inhibitory titers

Titers	Group		n	Mean±S.E.M	p value	N (for Power 0.95)
Total	FL rFactor VIII	IV	13	4915 ± 723	< 0.01	7
		SC	31	10978 ± 1153		
Neutralizing	FL rFactor VIII	IV	13	587 ± 54	> 0.05 (0.84)	3421
		SC	23	604 ± 66		

Patient related factors



- **Patient related factors**
  - ✓Age
  - ✓Gender
  - ✓Disease status
  - ✓Genetic make up
  - ✓Immune status
  - ✓Pre-exposure, pre-existing (cross-reactive) antibodies



Patient related factors

Curr Opin Immunol. 2016 Oct;42:31-40. doi: 10.1016/j.coi.2016.05.003. Epub 2016 Jun 2.

Allotype specific interactions of drugs and HLA molecules in hypersensitivity reactions.

Illing PT[1], Mifsud NA[2], Purcell AW[2].

Author information

Abstract

It is hypothesised that associations between adverse drug reactions and specific alleles of the human leukocyte antigens arise due to specific interactions between the human leukocyte antigen molecules and the causative drug that stimulate immune responses targeting drug exposed tissues. To date this has only been definitively demonstrated for abacavir, an antiretroviral that causes a systemic adverse drug reaction, abacavir hypersensitivity syndrome, solely in HLA-B*57:01^{+} individuals. Whilst this has informed the modification of abacavir to remove immunogenicity, there remains an imperative to define other interactions between drugs and specific HLA in order to understand the scope of interactions that can drive T cell mediated drug hypersensitivity. Here we review the current state of understanding of these interactions.

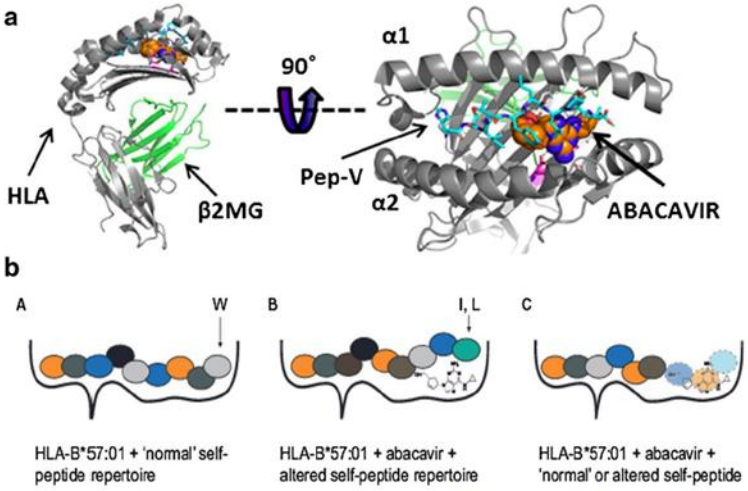
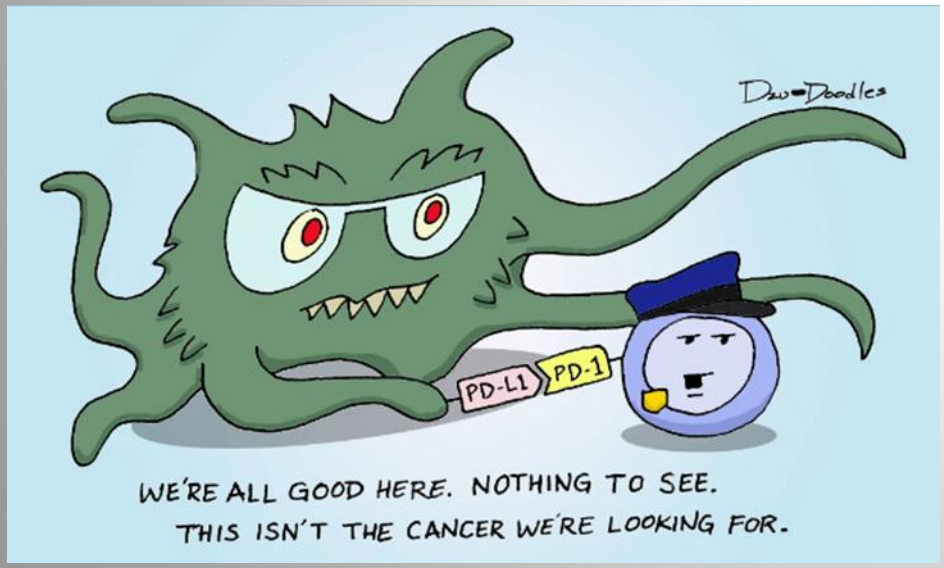
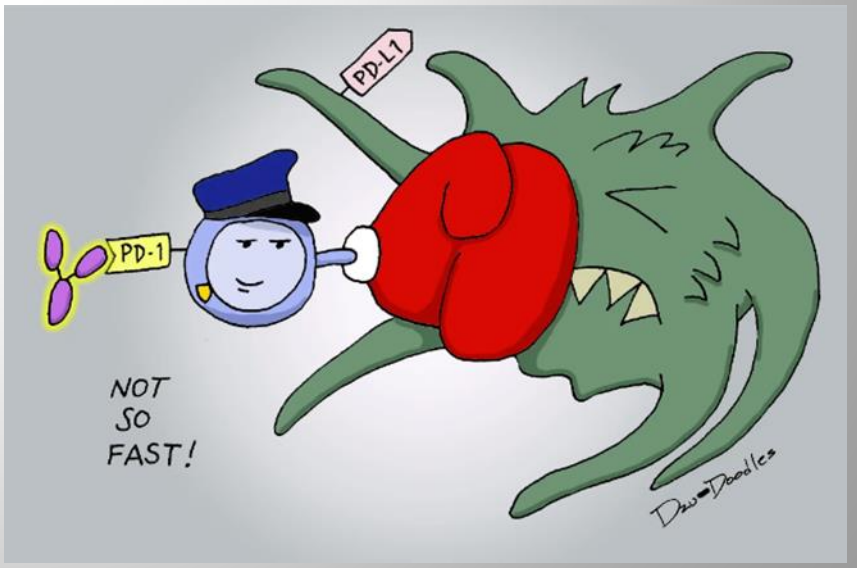


Fig. 2 Abacavir-induced altered self-peptide presentation (adopted from Ostrov et al. [16] and Yun et al. [25]). **a** Crystal structure of a peptide, HSITYLLPV or Pep-V (*cyan*) bound to HLA-B*57:01 (*gray*) together with abacavir (shown as *spheres*, *orange* for carbon, *blue* for nitrogen, and *red* for oxygen) [16]. **b** Without abacavir, the HLA-B*57:01 presents the 'normal' self-repertoire peptides and thus does not trigger an immune response (*left*). In the presence of abacavir, the drug can be incorporated in the F pocket of the HLA molecule thereby altering the peptide repertoire that is loaded onto this molecule. Abacavir binding favors binding of peptides with tryptophan (W) or phenylalanine at the C-terminus (position 9) rather than the small aliphatic residues (e.g., valinine, alanine, or isoleucine) which are normally bound to unmodified HLA-B*57:01 [16, 28]. This results in recognition of neo-antigens by neo-antigen primed CD8+ T-cells (*middle*). On the *right*, a hypothetical model of how abacavir might result in the selection of shorter peptide or is recognized itself by the TCR [25].

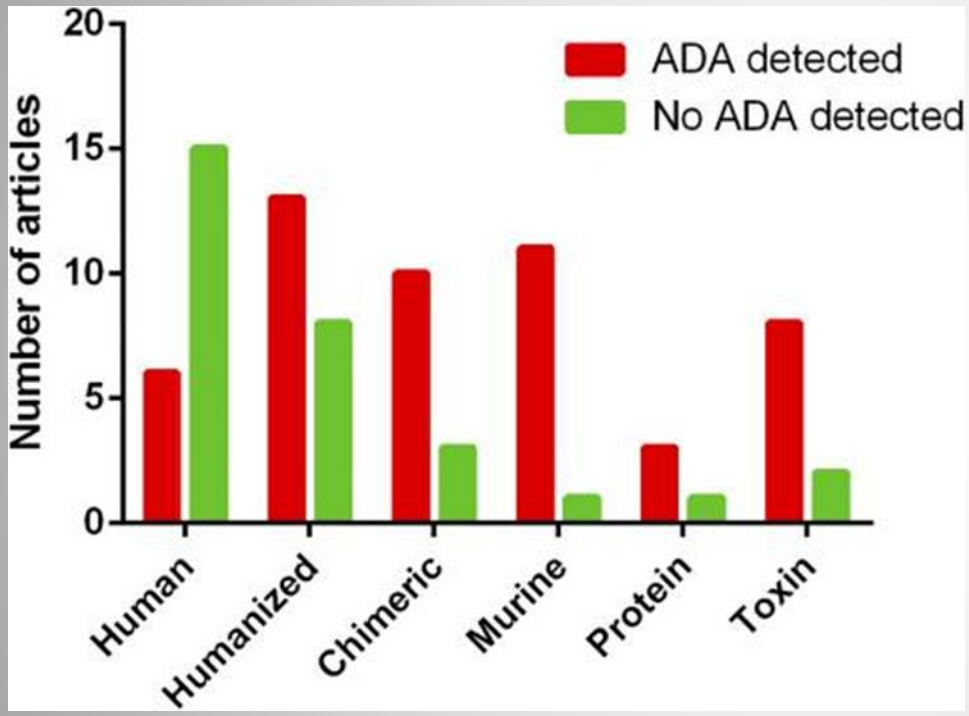
Mechanism of action related factors

- **Mechanism of action related factors:**
  - ✓Immune cell targets
  - ✓Immuno-oncology drugs
    - ✓Check-point inhibitors





Mechanism of action related factors



Among the 81 reviewed studies with biological anticancer agents, ADAs were detected in 63%

Antidrug Antibody Formation in Oncology: Clinical Relevance and Challenges Oncologist. 2016 Oct; 21(10): 1260–1268

Mechanism of action related factors

Product	Target(s)	ADA
Tecentriq (Atezolizumab)	PDL-1	41.5-54.1%
Bavencio (Avelumab)	PDL-1	4.1%
Opdivo (Nivolumab)	PD-1	11.2%
Keytruda (pembrolizumab)	PD-1	2.1%
Yervoy (ipilimumab)	CTLA-4	1.1% w/ECL* 4.9% ipilimumab, 4.5% placebo w/improved assay
Empliciti (Elotuzumab)	SLAMF7	18.5%
Opdivo + Yervoy	PD-1 + CTLA-4	37.8% vs nivolumab 8.4% vs ipilimumab

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125554s055lbl.pdf

Interplay between factors

