Introduction to immune pathways and immune response to therapeutics in Lysosomal Storage Disorders

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Disclaimer: No reportable conflicts of interest

Disclosure

- Oral Alpan, MD, is a consultant for Sanofi.
- ill be made when a product is discussed for an unapproved use.
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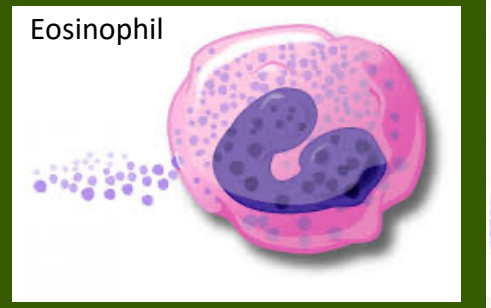
Learning Objectives

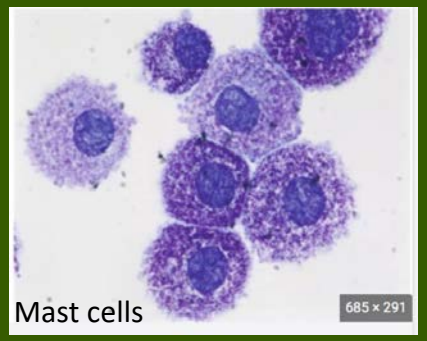
- Review idiosyncratic adverse drug reactions and its immune response mediation.
- Explain the process of inflammatory cell death.
- List the diagnostic approach to suspected drug hypersensitivity.
- Describe the factors that influence drug reactions.

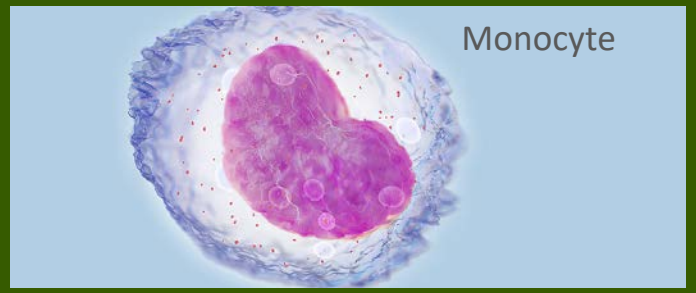
Adverse drug reactions

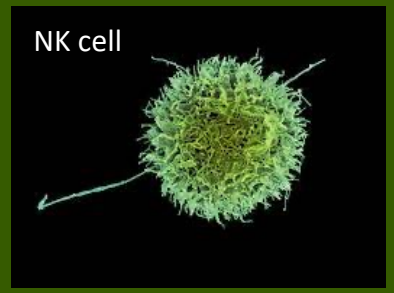
- Any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use.
- Adverse drug reactions are a major clinical problem, accounting for 2-6% of all hospital admissions
- Adverse drug reactions are type A (pharmacological) or type B (idiosyncratic)
- Many idiosyncratic adverse reactions are thought to be mediated by the immune system on the basis of clinical criteria.
- The type of hypersensitivity is partly determined by the nature of the immune response and the site of antigen formation.

Innate immune cells

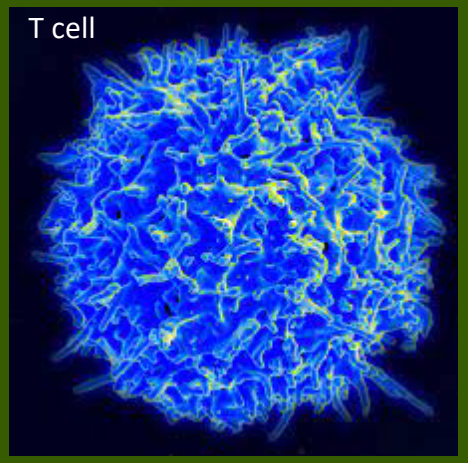






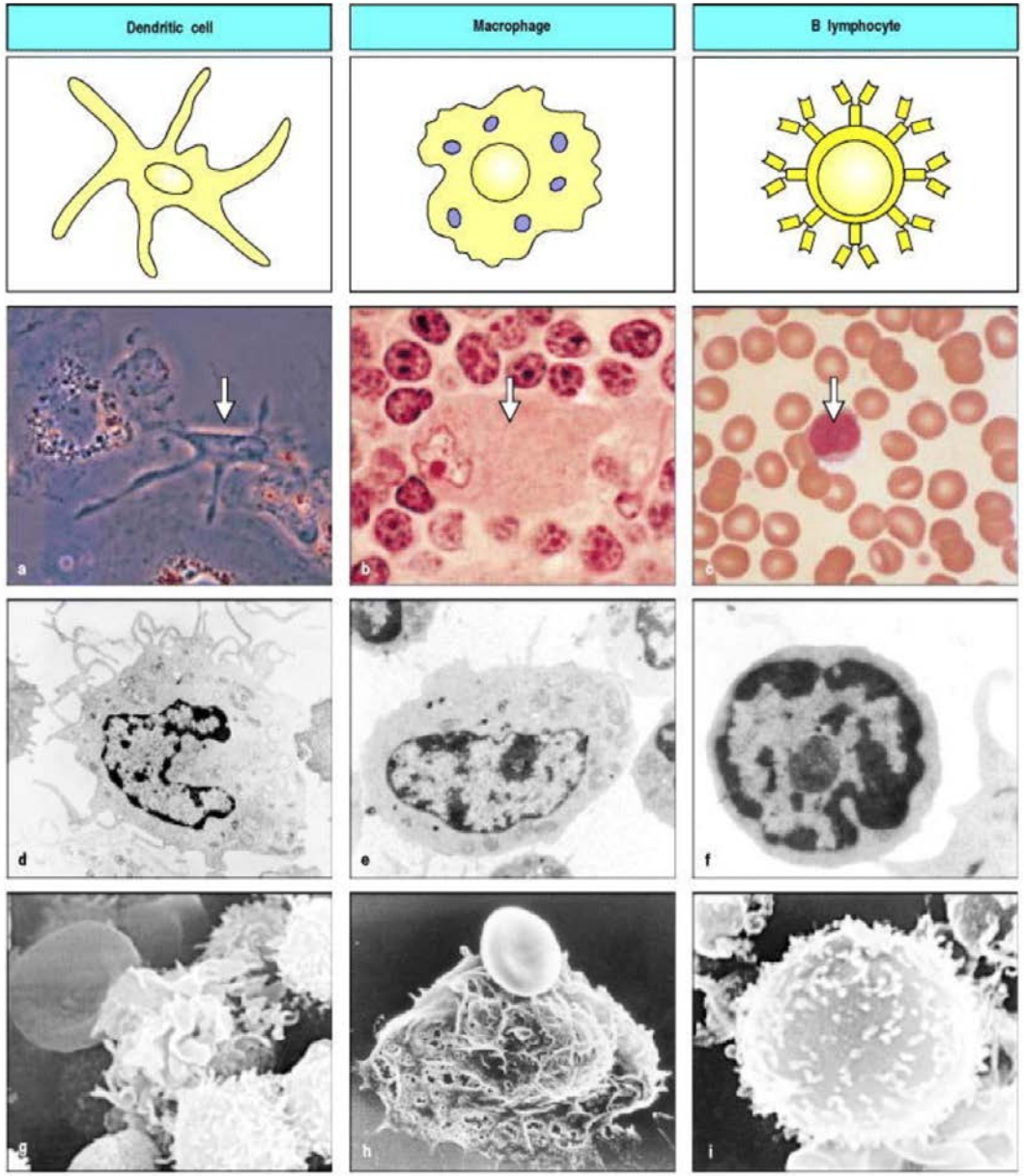


Adaptive immune cells



- Have different functions
- Interact with each other
- Cause distinct pathologies

Professional Antigen Presenting Cells



Immunobiology: The Immune System in Health and Disease. 5th edition.
Janeway CA Jr, Travers P, Walport M, et al.

Antibodies

- Made by B cell that need T cell help
- Prevent or enhance infections
- Cause autoimmunity or anaphylaxis
- Can participate in inflammation

Antigen presenting cells (APCs) and inflammation

- Dendritic cells are professional APCs
- B cells, monocytes and macrophages are non-professional APCs
- APCs can present drug antigens to other immune cells or become activated by them
- Can participate in inflammation

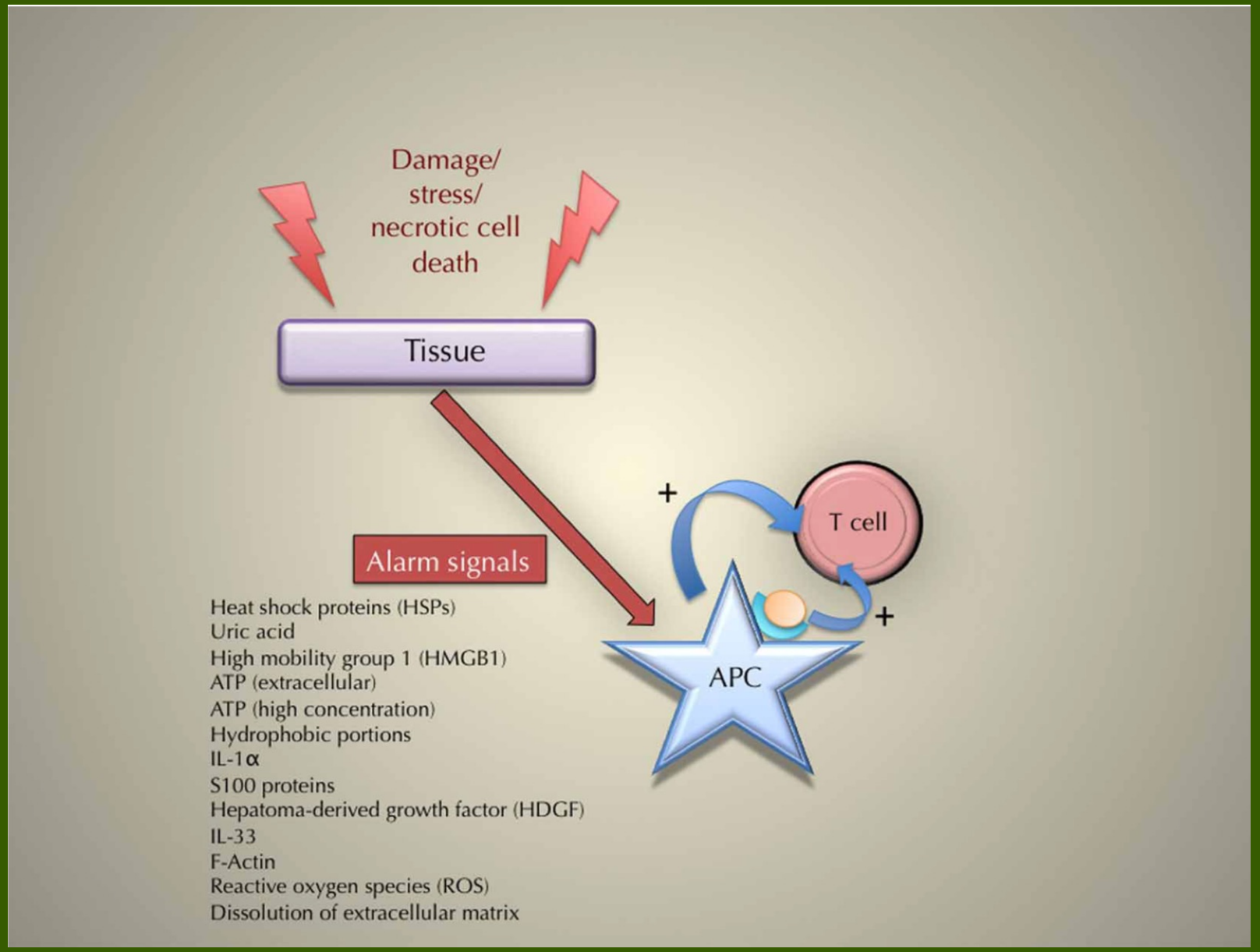
Complement system

- A central component of innate immunity
- Bridges the innate to the adaptive immune response.
- Can be activated in drug reactions
- Several drugs (i.e. IVIG), have dampening effect on complement activation.

Inflammatory cell death

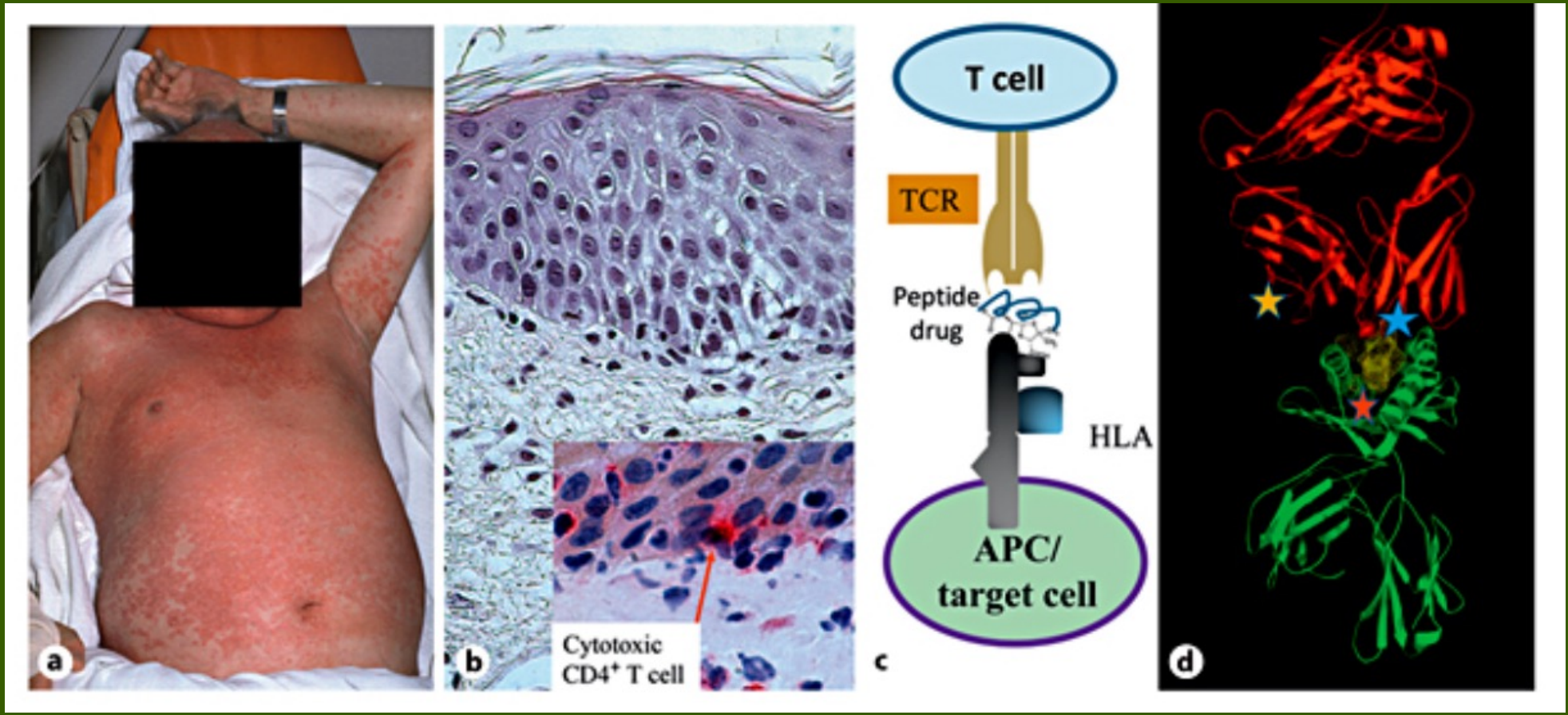
- Pyroptosis
- Necroptosis
- Can be measurable but no inhibitors yet FDA approved

Danger signals



Pradeu T, Cooper EL. The danger theory: 20 years later. Front Immunol. 2012 Sep 17;3:287.

Adaptive Immune responses



Pichler WJ et al.. Int Arch Allergy Immunol. 2015;168(1):13-24.

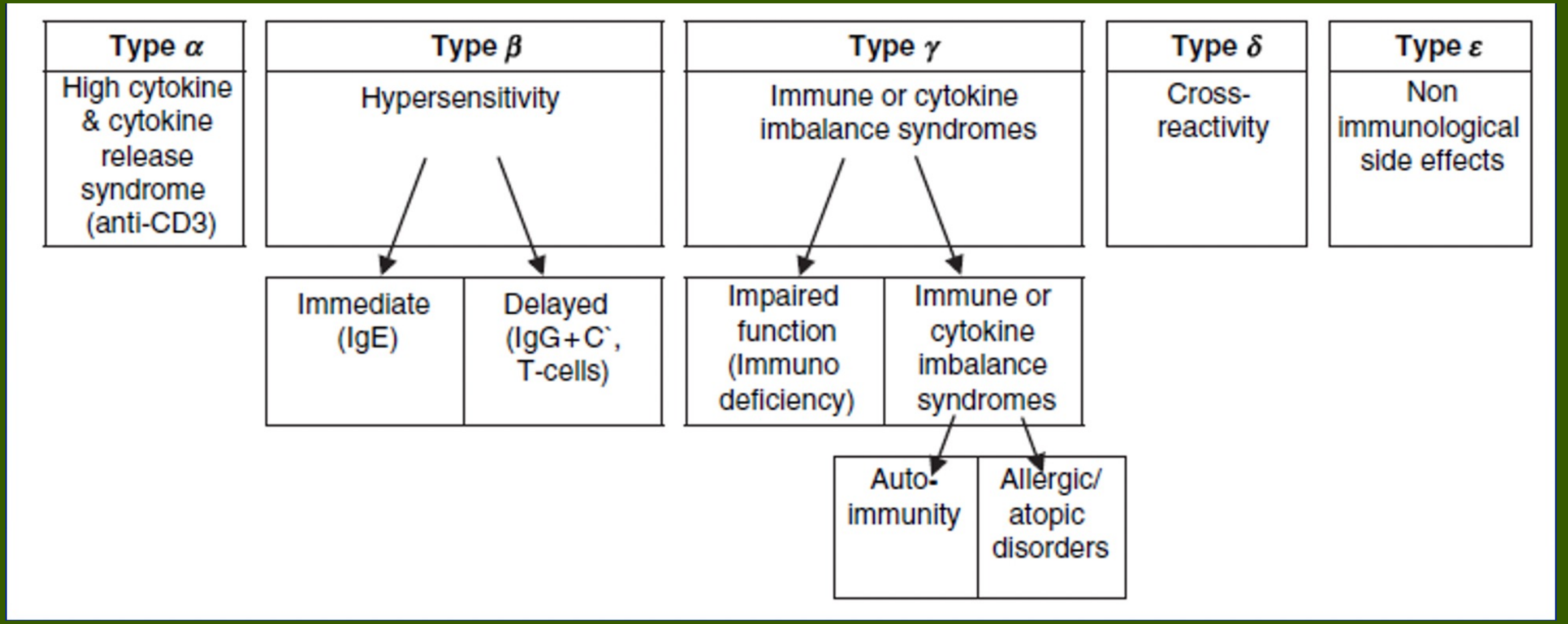
Types of drug reactions (timing and clinical characteristics are key)

- Immediate (anaphylactic and non-anaphylactic)
- Delayed

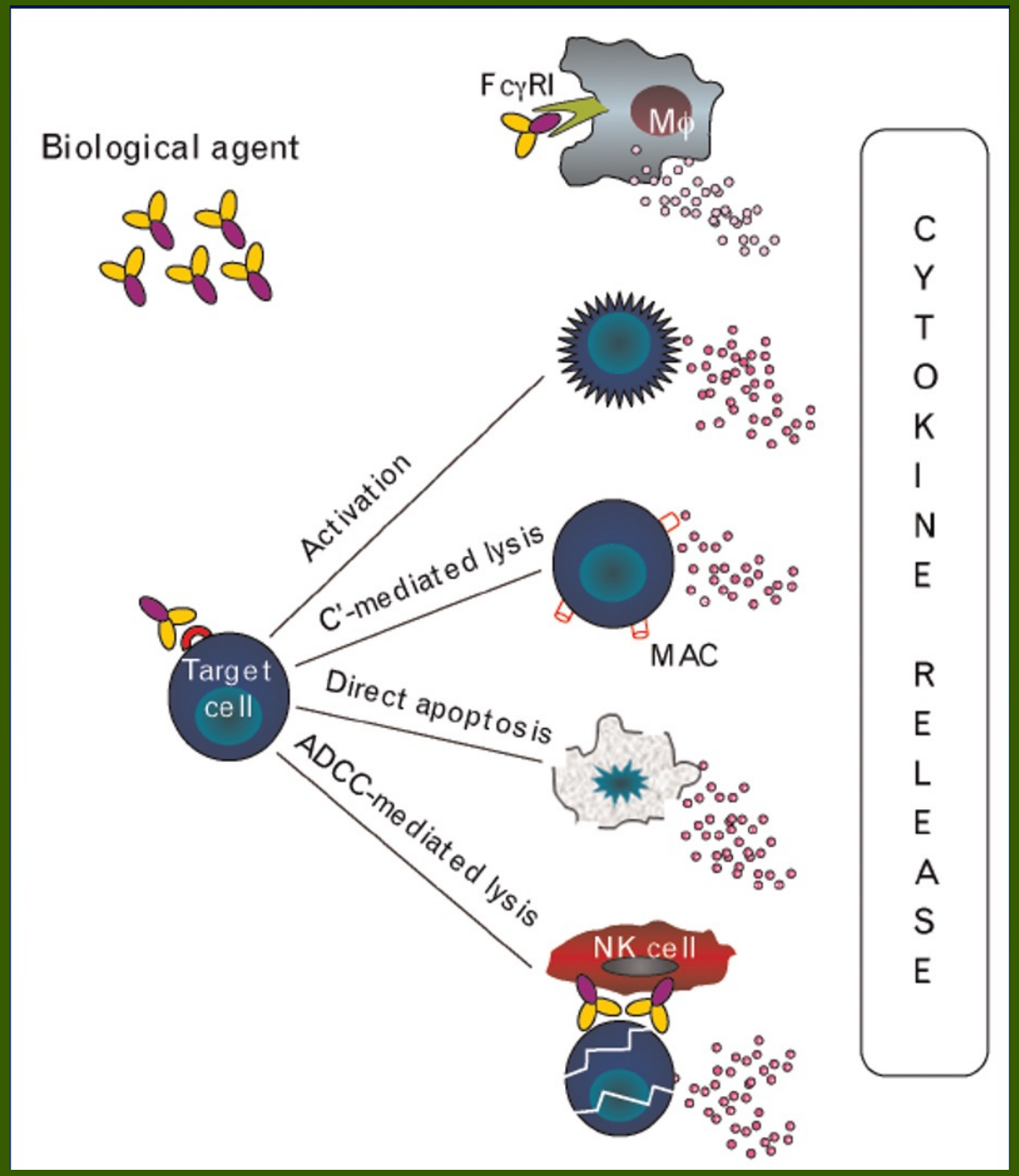
Factors that influence drug reactions

- Drug characteristic (protein, lipid, peptide, small molecule, antibodies, etc...)
- Dose
- Rate of administration
- Duration of use

Types of drug reactions



Cytokine release



Types of drug reactions - Time

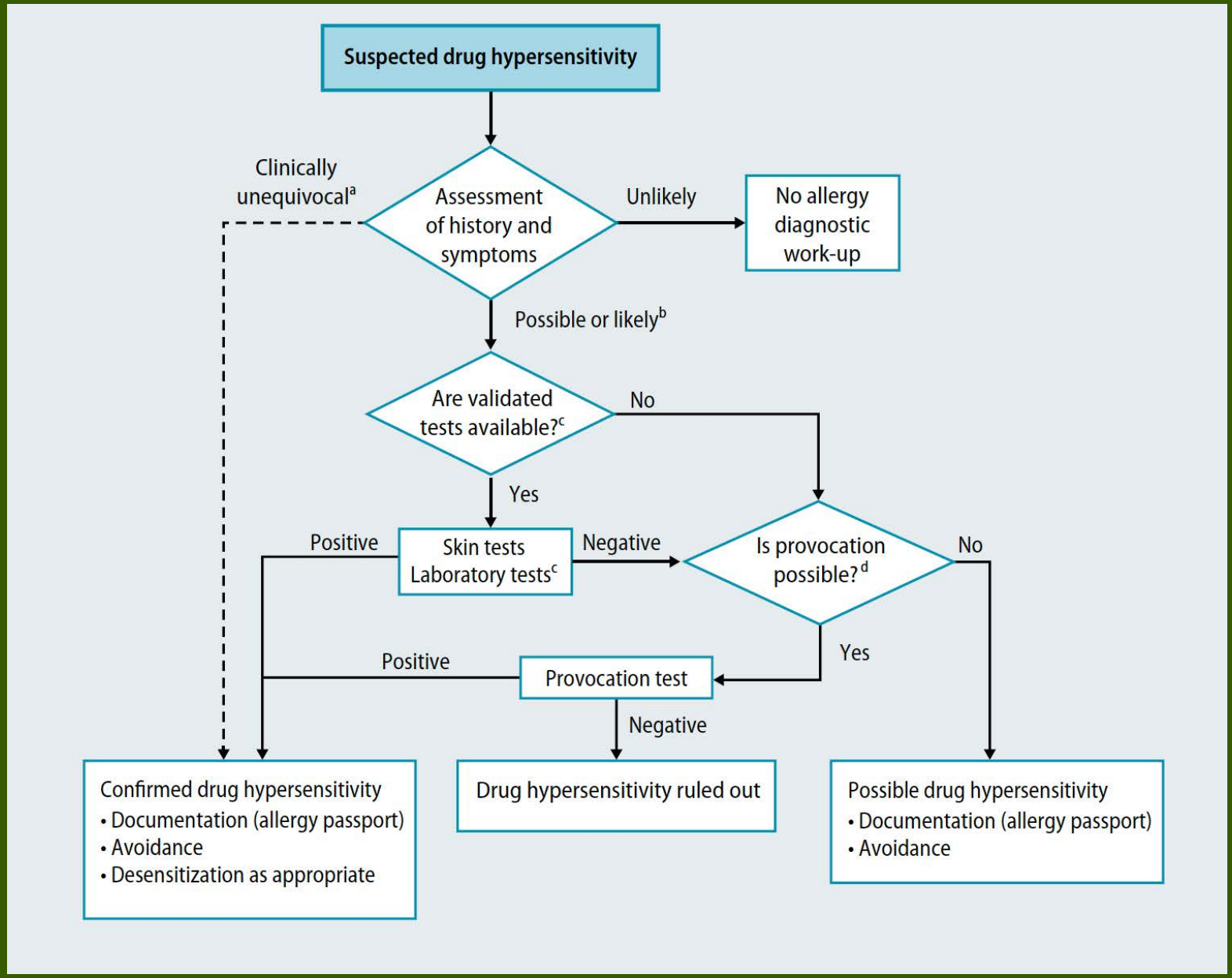
Tab. 3: Typical time intervals between initial drug use and first onset of symptoms

Hypersensitivity reaction	Time interval
Urticaria, asthma, anaphylaxis	typically within 1 h, in rare cases up to 12 h after exposure
Maculopapular drug eruption	4–14 Days after start of use[a]
AGEP	1–12 Days after start of use[b]
SJS/TEN	4–28 Days after start of use[c]
DRESS	2–8 Weeks after start of use

AGEP, acute generalized exanthematous pustulosis; SJS, Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms.

[a]Time interval in repeat reactions typically shorter compared with the first reaction. In maculopapular drug eruptions, reaction typically seen after 1–4 days, typical time interval for repeat reactions has not been investigated in AGEP, SJS, TEN, and DRESS;
[b]mostly 1–2 days with antibiotics, often 7–12 days with other medications; [c]sometimes longer with allopurinol

Diagnostic Approach



Diagnostic Tests

TABLE I. Diagnostic tests of hypersensitivity reactions to drugs

Type of reaction		Type of tests
Immediate	*In vitro*	Specific IgE assays
		Flow cytometric BATs
	In vivo	Skin tests
		Provocation tests
Nonimmediate	*In vitro*	LTTs or LATs
		ELISPOT assays for analysis of antigen-specific, cytokine-producing cells
	In vivo	Delayed-reading intradermal tests
		Patch tests
		Provocation tests

Principles of Desensitization

- Temporary clinical tolerance
- Only in immediate reactions
- Does not need to be IgE mediated
- Protocols vary for drugs and between institutions

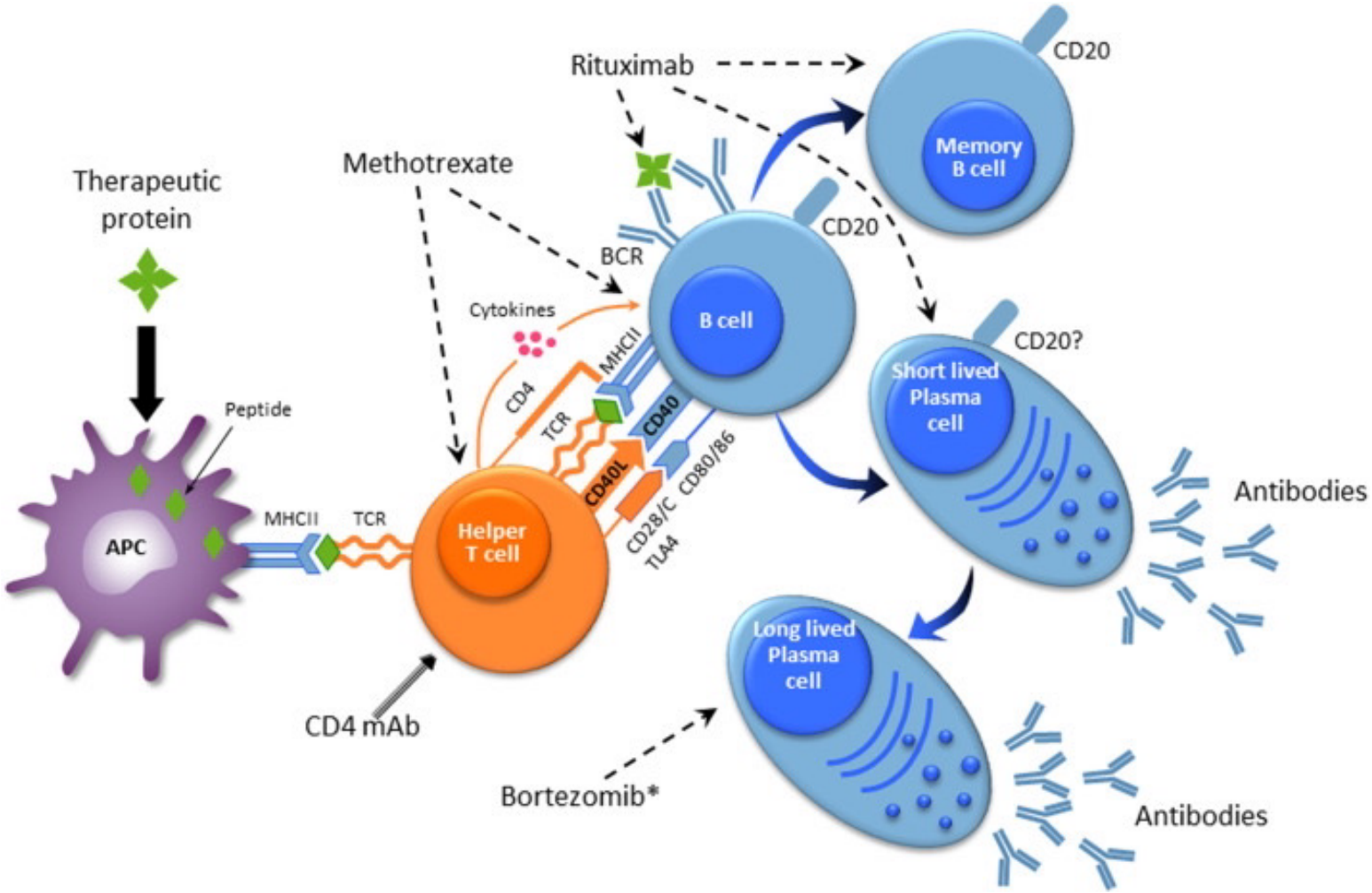
Neutralizing antibodies

Table 1 Overview of the most common ERT-treatable lysosomal storage diseases associated with an immune response and formation of ADAs

Disease	Deficient enzyme	Main accumulated substrate	Approved drug	IARs	Neutralizing ADAs	Agents used for immune tolerance
Gaucher disease	β-Glucosidase	Glucosylceramide	Imiglucerase, Velaglucerase, Taliglucerase-alfa	Yes	Yes	Cyclophosphamide, IVIG
Fabry disease	α-Galactosidase A	Globotriaosylceramide	Agalsidase-alfa, Agalsidase-beta	Yes	Yes	NA
MPS I	α-L-iduronidase	Dermatan sulfate and heparan sulfate	Laronidase	Yes	Yes	Cyclosporine, azathioprine
MPS II	Iduronate-2-sulfatase	Dermatan sulfate and heparan sulfate	Idursulfase-alfa, Idursulfase-beta	Yes	Yes	Rituximab, ofatumumab, bortezomib, methotrexate, IVIG,
MPS IVa	*N*-acetylgalactosamine-6 sulfatase (GALNS)	Keratan sulfate and chondroitin-6-sulfate	Elosulfase	Yes	Yes	Rituximab, methotrexate
MPS VI	N-acetylgalactosamine 4-sulfatase	Dermatan sulfate	Galsulfase	Yes	Yes	Corticosteroids, rituximab, IVIGs, methotrexate.
Pompe disease	Acid α-glucosidase	Glycogen	Alglucosidase-alfa	Yes	Yes	Rituximab, methotrexate, IVIG, methylprednisolone, rapamycin, cyclophosphamide, bortezomib

ADA anti-drug antibody, *ERT* enzyme-replacement therapy, *IARS* infusion-associated reaction, *IVIG* intravenous immunoglobulin, *MPS* mucopolysaccharidosis, *NA* not available

Targeting the immune response in lysosomal storage disorders



Kishnani PS. Mol Genet Metab. 2016 Feb;117(2):66-83.

Summary

- Many factors play into drug reactions; no “one shoe fits all”
- Identification of potential mechanism impacts treatment approaches
- Naïve v Educated immune system to the drug is a critical factor