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From Assays to Benefit/Risk Assessment: A European Assessors Perspective on Unwanted Immunogenicity

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EIP Lisboa

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Introduction

The evolution of protein expression for biopharmaceuticals

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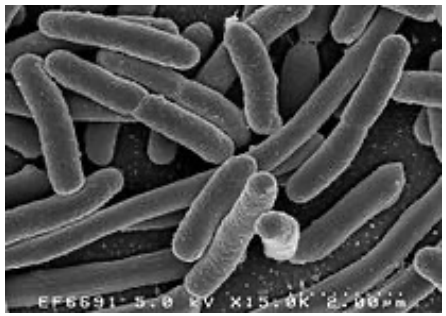

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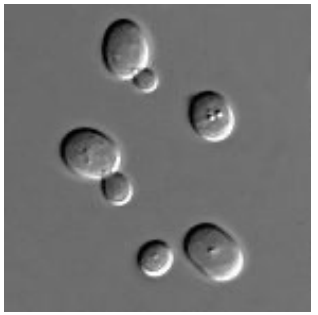

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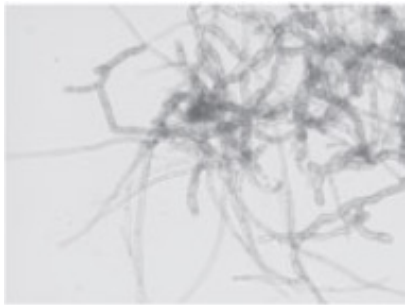
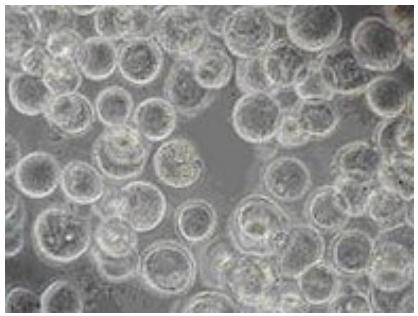


Büttner-Mainik et al. 2011



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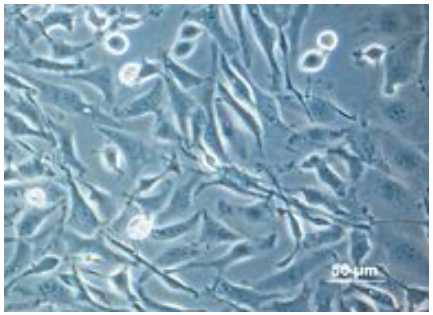

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What´s the issue?

Why immunogenicity testing in the clinic?

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Positive B/R ratio profile is required;

Does it matter if the risk is a consequence of an immunogenicity driven event?

- YES: to apply the appropriate risk mitigation strategy

e.g. FVIII, rhGAA, Epo, Insulin, mAbs,…

Identify risk: glycosylation, in silico tools, models,…

Assess risk: control risk factors, test for IgMs and loss of efficacy

Mitigate risk: Extent of post-marketing activities, extent of analysis (IgG, IgM,…), power studies for safety rather than efficacy,…

See Büttel et al. 2011: Taking immunogenicity assessment of therapeutic proteins to the next level

What drives immunogenicity?

Extrinsic and intrinsic risk factors

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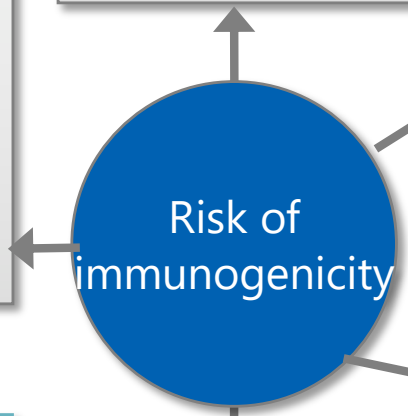
Nature of the biopharmaceutical

Size and structural complexity
Sequence variation from endogenous protein
Aggregates
Post-translational & chemical modification (e.g., glycosylation, pegylation).
Neoepitopes due to denaturation or fragmentation
Adjuvant potential of inactive ingredients
Other impurities

Target disease and population

Patient characteristics such as genetic background
Comorbidity
Natural tolerance to protein
Pre-existing immunodeficiency
Use of immunosuppressive drugs or chemotherapy



T-cell epitopes

e.g. TCPro

B-cell epitopes

Treatment regimen

Route of administration
Dose
Frequency of treatment
Duration of treatment

Adapted from Doevendans and Schellekens 2019

What drives immunogenicity?

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Evidence for AGGREGATION driven immunogenicity

- Inhibitory antibodies to rFVIII following treatment

Anzengruber et al. 2018

- Eprex and pure red cell aplasia after formulation changes

Hermeling et al. 2003, Boven et al. 2005, EMEA/CHMP/BPWP/123835/2006

- ADA/aggregate correlation for β-interferon and h-Insulin

Farrell et al. 2012, Barnard et al.. 2013, Robbins et al. 1987

- Inhaled human insulin… more immunogenic than sc insulin

Fineberg et al. 2007

- In the 50s and 60s aggregated IVIGs triggered severe hypersensitivity responses. (also HSA/pasteurized plasma)

Rosenberg, The AAPS Journal 2006; 8 (3) Article 59

What do we know?

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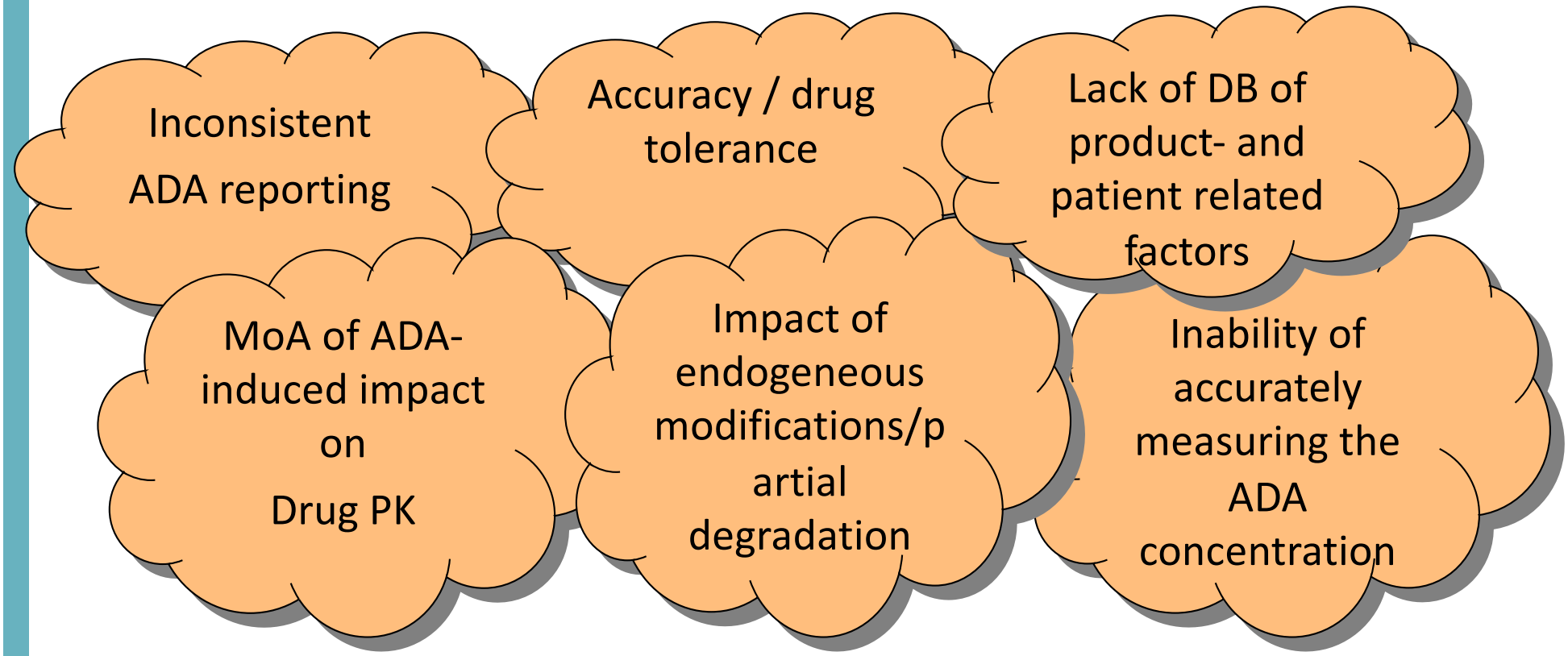
Gaps in knowledge on the impact of immunogenicity on PK/PD



Chirmule et al. 2012

What do we know?

Dealing with Uncertainties

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Hazard identification and Risk assessment

Risk governance

Term	Explanation	Example	Reference
variability	uncertainty intrinsic to biology, cannot be reduced with further knowledge	different species and protocol variants will produce results that vary from each other to a certain extent, may be described as probability distribution	WHO, 2014; ECHA, 2012
"pure" uncertainty	uncertainty due to limited knowledge, can be reduced with further knowledge (at least theoretically)	knowledge of variability of results from different species and protocol variants is uncertain , may be described qualitatively and quantitatively in terms of a confidence interval to the probability descriptor	
reliability	variability plus uncertainty	see above	OECD, 2005
complexity	uncertainty stemming from multi-causal effect relationships	derivation of a reference value is the result of a series of decisions in the process of data generation, assessment and integration, e.g., decisions on animal numbers and top doses, definition and grouping of tumors, statistics and use of historical controls	Renn et al., 2011; IRGC, 2005
ambiguity	uncertainty stemming from the plurality of scientifically legitimate viewpoints	different expert groups weighting and integrating the same data differently and thereby come to different conclusions	
ignorance	any uncertainty that we are not aware of and cannot name: 'what we don't know that we don't know'	epigenetic modes of action were "ignorance" until relatively recently, but are now moved to being recognized as uncertainty	EEA, 2010

Paparella et al. ALTEX 34(2), 2017

"Absence of evidence of harm is not the same as evidence of absence of harm"

Risk = Probability x Consequence (Severity)

☞ **Risk-based approach**

CHMP GL Guideline on Immunogenicity assessment of therapeutic proteins

What do we know?

Association – Aggregation - Precipitation

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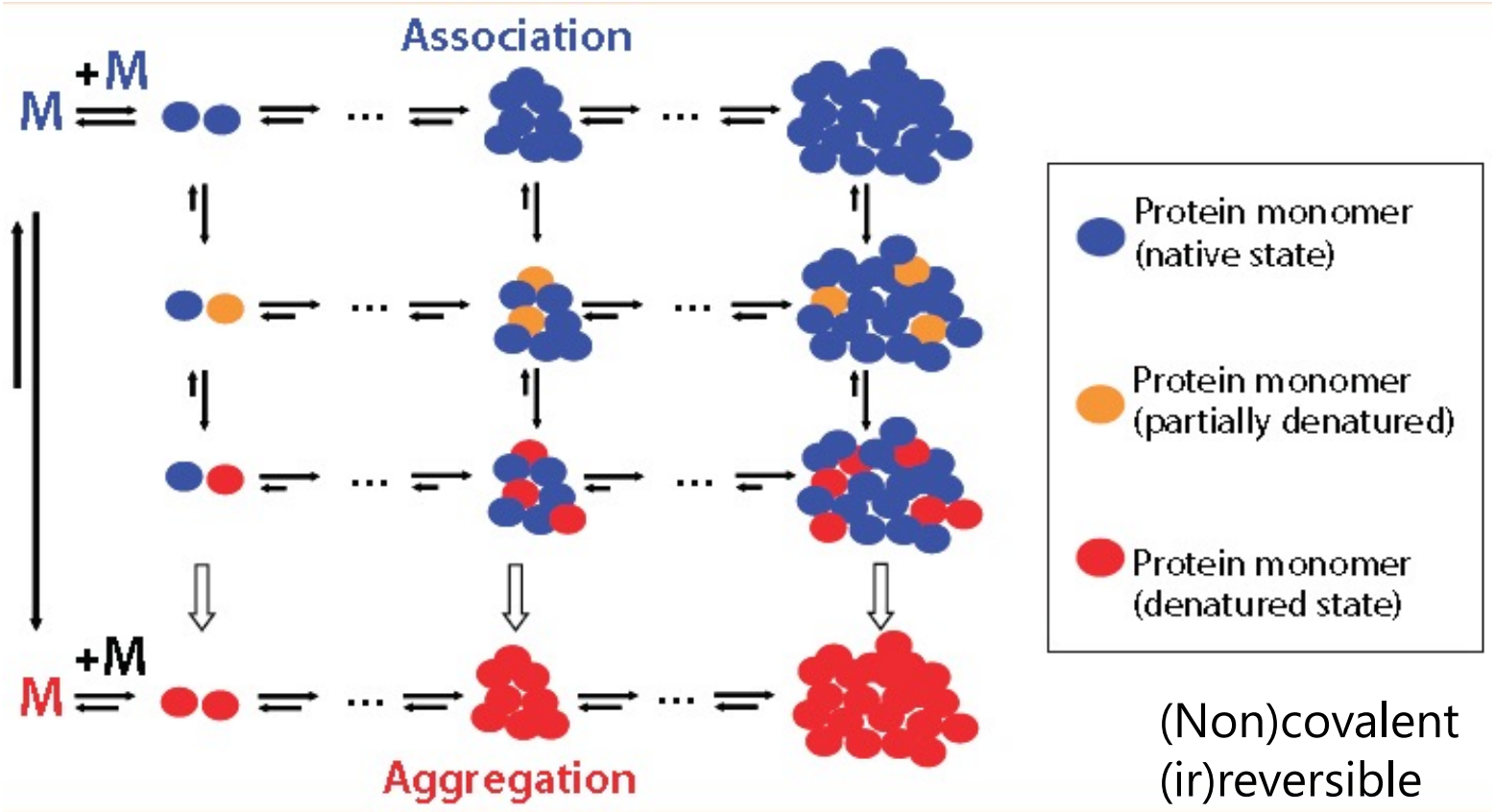
Aggregation is not black and white, hard to define and difficult to analyze



BioProcess International, Vol. 8, No. 3, March 2010, pp. 38–46

(Non)covalent
(ir)reversible
(in)soluble
(non-)native

Aggregates

The complexity of Immune complexes

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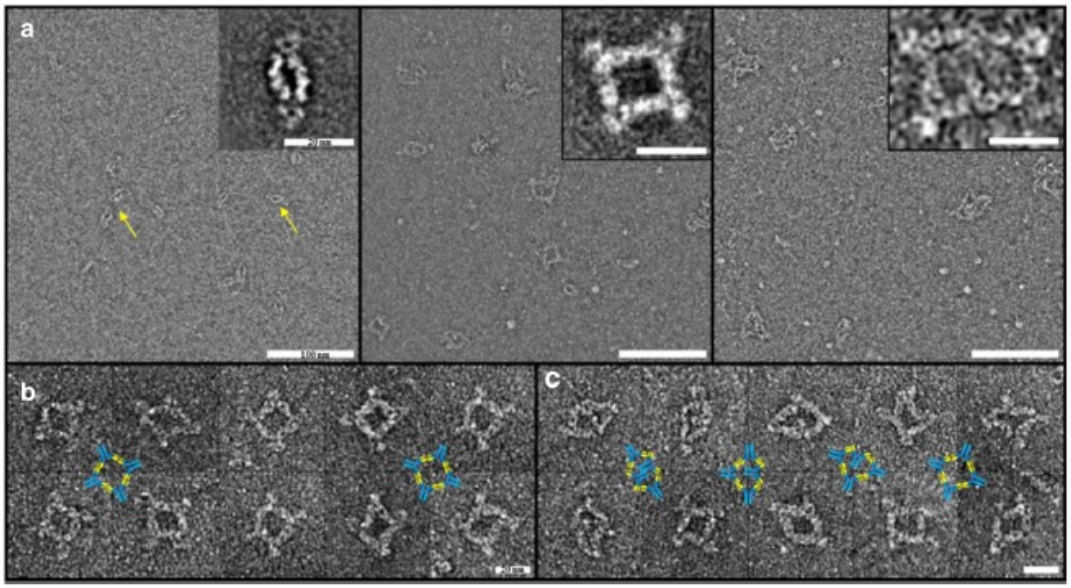
ICs are frequently not standardized



ICs were generated, separated by SEC and defined fractions were collected containing IC species to be analyzed via Negative Staining Transmission Electron Microscopy

Generation, Characterization, and Quantitative Bioanalysis of Drug/Anti-drug Antibody Immune Complexes to Facilitate Dedicated In Vivo Studies
Hoffmann et al. 2019

☞ Are many published conclusions misleading?

Aggregates

Need for orthogonal methods

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Single methods cannot cover the whole size range

Monographical methods for subvisible particle detection were originally developed for assessing **foreign** particles in parenterals

Focus on >10 and >25 µm is not adequate to address immunogenicity concerns of particles between 1 and 10 µm

-> soluble protein aggregates up to 100 nm

-> undissolved, subvisible particles (0.1 – 50 µm)

Cao et al. Pharmeuropa Bio & Scientific Notes 2009-1
John den Engelsman et al. Pharm Res 2011

Aggregates

Proteins are sensitive: e.g. leachables

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Like for instance

Monoethylhexylphthalate (MEHP)

Di-2-ethylhexyl phthalate (DEHP)

exctractable trimellitate (Rubber)

Metals (magnetic stirring)

Salt crystals, glass particles

Silicone oil droplets

Tungsten

Polycyclic aromatic hydrocarbons

Alkyl phenols

Peroxide formation Polysorbate 80

Al, Fe,…

may

- ☞ directly form particles
- ☞ modify proteins: adduct formation, oxidation, degradation with subsequent aggregation
- ☞ interact with excipients inducing formation of particulates
- ☞ affect upstream steps: altering protein folding, post-translational events
- ☞ act immunologically (w or w/o HCPs)
- ☞ …

Modified from Paskiet et al. 2013

Aggregates

Post-production issues

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- Shaking instead of swirling (increases FVIII particle levels)

Ueda et al. 2019

- Pumping: (in combination with metal contamination)

Tyagi et al. 2009

☞ The majority of patients do not store their biologic disease-modifying antirheumatic drugs within the recommended temperature range

Vlieland et al. 2016

☞ Rarely true correlation of aggregates with immunogenicity data or clinical adversity shown

☞ Bedside filtration

Werner and Winter 2018

Responsibilities….?

Immunogenicity assays

Challenging for mAbs: HAMA, HACA, HAHA

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How to detect a human antibody binding to a human antibody?

GL on immunogenicity assessment of mAbs (EMA/CHMP/BMWP/86289/2010)

<u>Considerations:</u>

- ☞ Neutralizing capacity of **anti idiotypic** ADAs
- ☞ Relevance of ADAs against **constant region of Fc and Fab**? (e.g. Rheumatoid factor paradox; Jones et al. 2013)
- ☞ Unclear level of evidence for clinical impact:

  e.g. Development of anti-drug antibodies is associated with shortened survival in patients with metastatic melanoma treated with ipilimumab

Kverneland et al. 2018

Immunogenicity assays

Innovative assays: e.g. Human MO-derived DC

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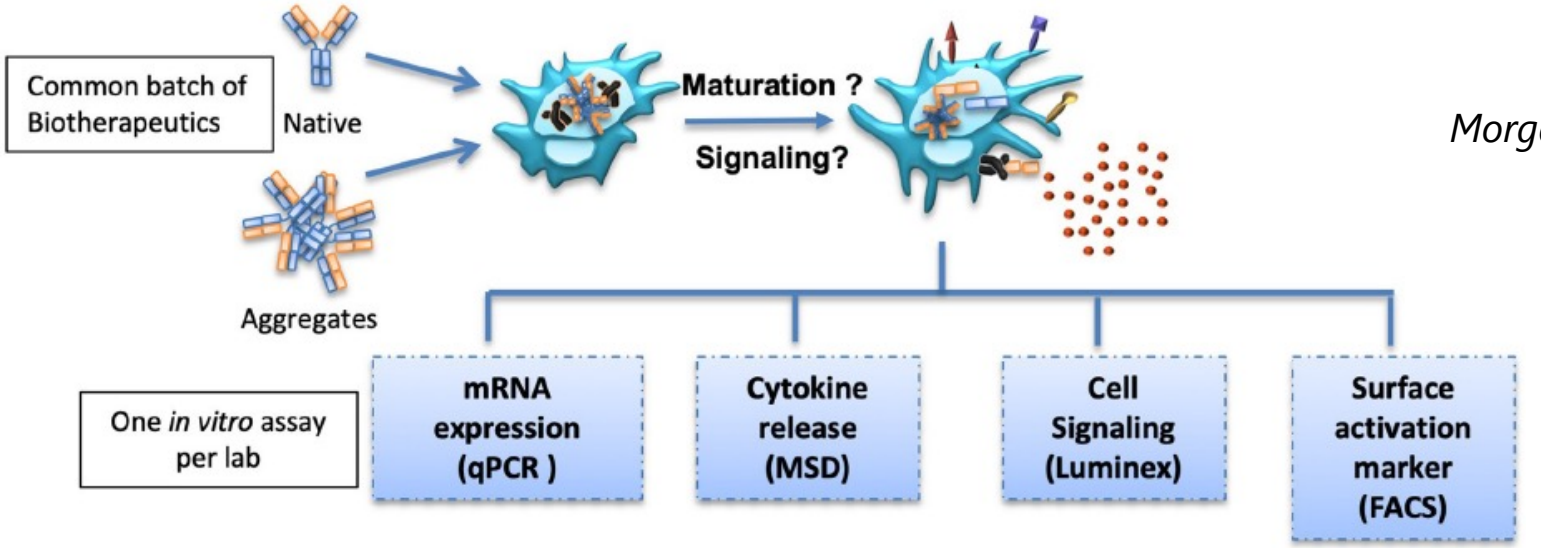
- Tested native and aggregated preparations of infliximab, natalizumab, adalimumab, or rituximab
- Results indicated marked DC activation by heat aggregated infliximab, in contrast to natalizumab

☞ Screening of mAb candidates?

☞ Monitor drug-intrinsic propensities to drive <u>maturation of DC</u>



Morgan et al. 2019

Immunogenicity assays

Innovative assays: calculations and rankings

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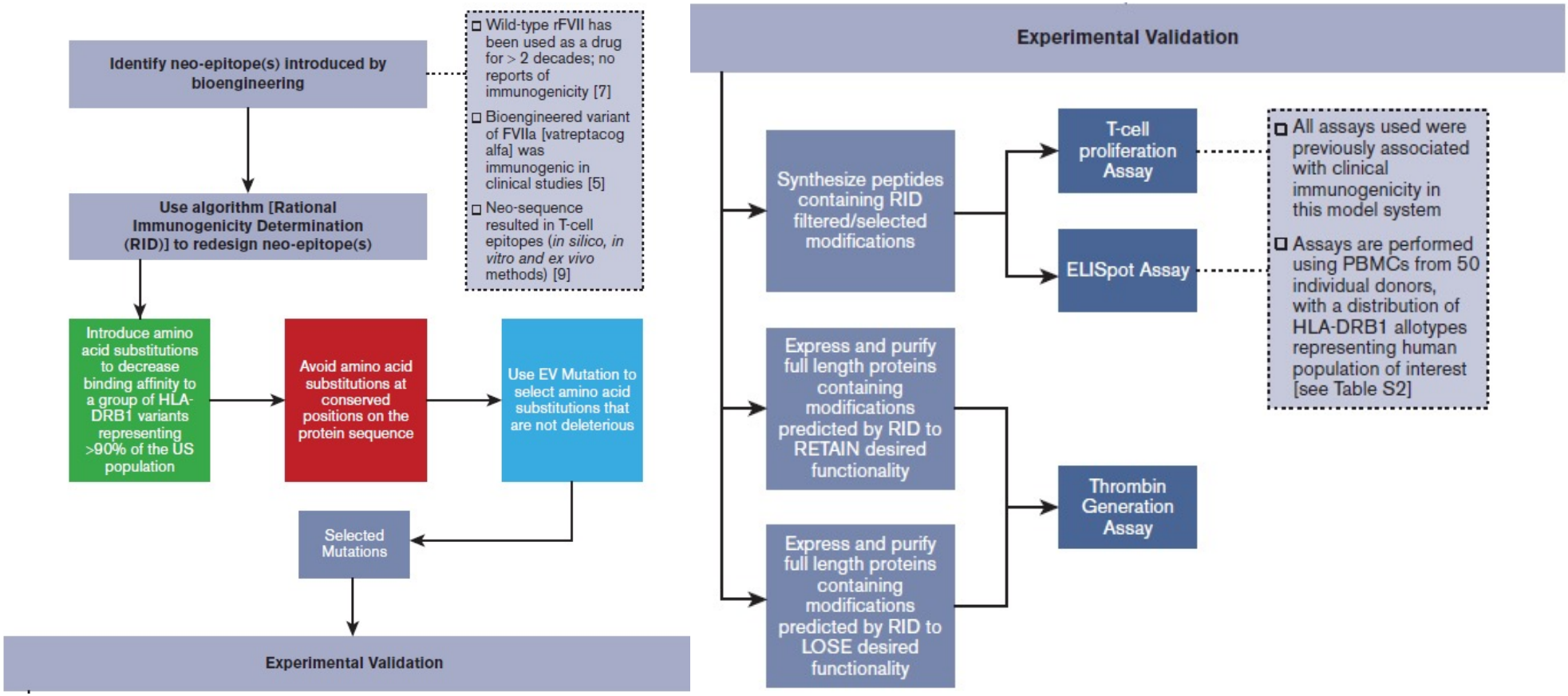
AAPS J. 2019 Aug 2;21(5):96. doi: 10.1208/s12248-019-0368-0.

TCPro: an In Silico Risk Assessment Tool for Biotherapeutic Protein Immunogenicity.

Yogurtcu ON[1], Sauna ZE[2], McGill JR[2], Tegenge MA[1], Yang H[3].

- test virtual pools of subjects based on MHCII frequencies and estimate immunogenicity risks for different populations.
- rapid and inexpensive initial screen
- validated TCPro using an experimental immunogenicity dataset, making predictions on the population-based immunogenicity risk of 15 protein-based biotherapeutics.
- Immunogenicity rankings generated using TCPro are consistent with the reported clinical experience with these therapeutics.



Redesigned rFVIIa analogs exhibit both desired functional activity and reduced immunogenicity risk.

Mitigation of T-cell dependent immunogenicity by reengineering factor VIIa analogue; Wojciech Jankowski et al. 2019

Immunogenicity assays

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Assaying immunogenicity against…

- DP
- DS
- Excipients (esp. novel)
- Product related impurities
- Process-derived impurities: HCP, insulin…

} May be an issue for otherwise "low risk products"

☞ Provide **background data** to support / justify data interpretation

☞ If you go for extended studies with hyperimmune sera…
don´t forget to **validate the method** (or at least apply appropriate controls).

Immunogenicity assays

Need for more standardization?

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Experience from several immunogenicity assessments tells us that **Cut point determination** is often conducted inconsistently …

- False positive rate
- Sample size (and percentiles)
- Beware of matrix effects from / interference with serum components
- Heterogeneity in ADA standards: Positive controls are surrogates!

☞ **Failure to distinguish noise from signal:** More focus on optimized assay conditions BEFORE (w/o positive control) final assessment of the overall assay performance (including assay PC-based sensitivity, drug, and target tolerance characteristics).

Gorovits et al. 2019

☞ See also Kubiak et al. 2018: Excessive Outlier Removal May Result in Cut Points That Are Not Suitable for Immunogenicity Assessments

Immunogenicity assays

Considerations

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Since **preclinical** studies are performed on animals, the **translational value of neutralizing Ab assays** is questionable. Nevertheless, if a biologic is high risk… testing for neutralizing antibodies at a preclinical level can support evaluation of the biologics' safety.

Is the tiered immunogenicity testing of biologics the adequate approach in preclinical development?
Sauerborn et al. 2013

(Immunogenicity of mAbs in non-human primates during nonclinical safety assessment
Van Meer et al. 2013)

- 👎 Supplying nonclinical safety testing species with artificially enriched amount of polymers likely generates artificial results
- 👎 Ignorance of mucosal immunity for intranasal applications:

  Effects may potentially be influenced by aggregates – check for mucosal immunity („Lets call them nano")

Further aspects on ADAs

Assaying anti-PEG antibodies

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We confirm that some healthy individuals and some patients with hemophilia express specific antibodies against PEG which are not associated with any pathology and do not bind to human tissues.

The Mystery of Antibodies Against PEG – What do we Know?
Lubich et al. Pharm Res (2016) 33:2239-2249

A Cell Assay for Detecting Anti-PEG Immune Response against PEG-Modified Therapeutics.
Shimizu et al. Pharm Res. 2018 Oct 2;35(11):223.

Sensitive and Quantitative Detection of Anti-PEG Antibodies by Methoxy-PEG-Coated Surface Plasmon Resonance Sensors. *Zhang et al. Anal Chem. 2017 Aug 15;89(16):8217-8222.*

Accelerated Clearance of Ultrasound Contrast Agents Containing Polyethylene Glycol is Associated with the Generation of Anti-Polyethylene Glycol Antibodies.
Fix et al. Ultrasound Med Biol. 2018 Jun;44(6):1266-1280.

Further aspects on ADAs

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Ophthalmologicals

- Local antibody production in the vitreous humor of patients with severe uveitis

  Baarsma et al. 1991
- Vitreous Inflammation Associated with Intravitreal Anti-VEGF Pharmacotherapy;

  Agrawal et al. 2013
- Sterile endophthalmitis after intravitreal injection of bevacizumab obtained from a single batch

  Yamashiro et al. 2010
- Presence of adaptive immunity in the eye in certain pathologies like AMD; measuring free ADAs while mostly found in bound state;

  Sharma et el. 2019
- Safety and compatibility considerations for Leachables and Extractables in biologics

  Paskiet et al. 2013

Biosimilars

Assay Limitations and Confounding Factors

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- ADA assays merely scratch the surface of humoral immune responses: assays optimized based on patient population, (not at the individual patient level)
  - ☞ risk of underestimating the total ADA population
- ADA assays are not standardised and assay details are not publically available:
  - ☞ comparisons of the ADA incidences are not appropriate
- ADA Assay performance has improved over time
- Poor ADA assay design may cause serious bias: drug tolerance, matrix interference
- Neutralising ADAs:
  - ☞ in-vitro cell-based assay vss. competitive LBAs

Reinivuori et al. 2018

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From herbals to novel modalities

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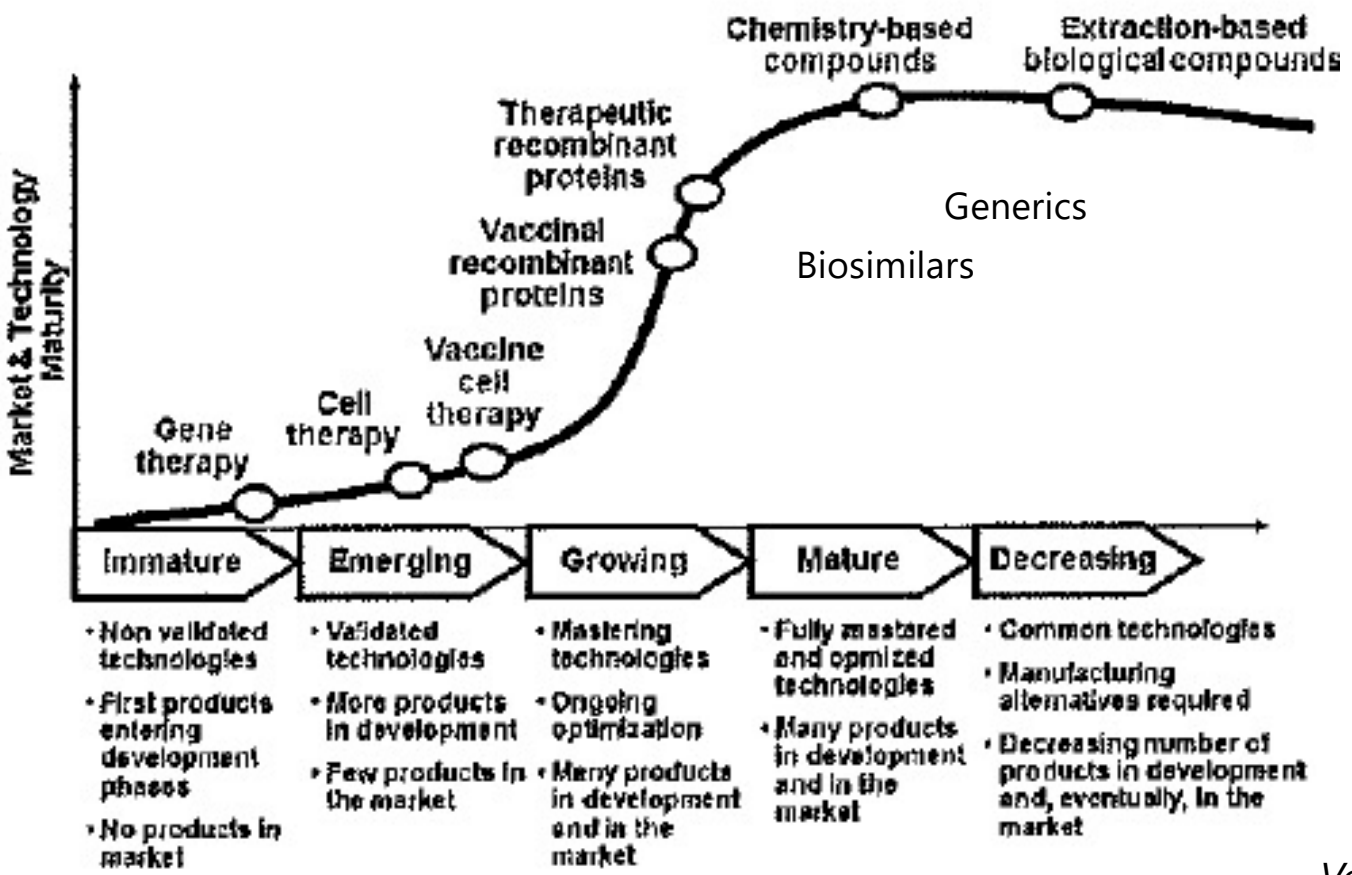

Van Meer et al. 2015

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Immunogenicity of novel modalities

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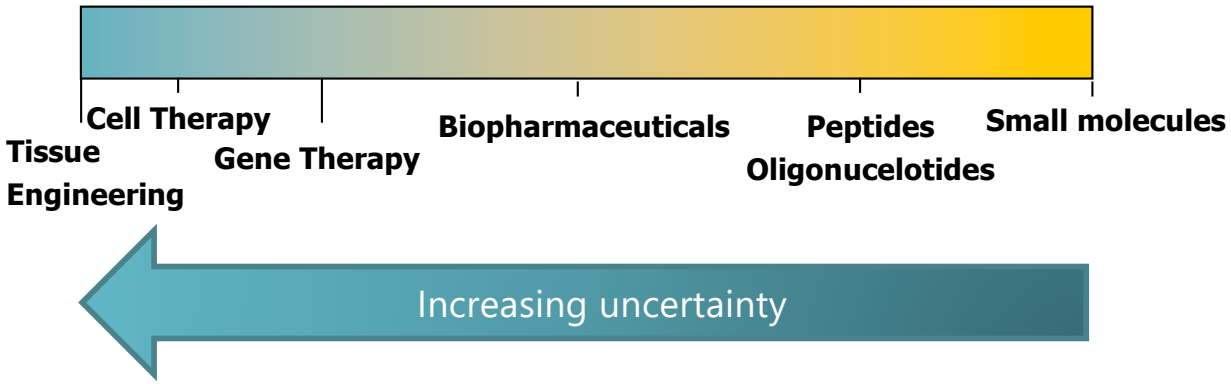

Guideline on the risk-based approach according to Annex I, part IV of Directive/2001/83/EC applied to advanced therapy medicinal products

Avoiding Black swan conjecture:

(i) rare, (ii) extreme 'impact', and (iii) retrospective (though not prospective) predictability.

Nassim Nicholas Taleb: Fooled by Randomness (2001)
The Black Swan (2007)

ATMPs are…

…mainly Orphan

Initial Evaluation
of MAAs for ATMPs

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	2016		2017		2018		2019†	
	Started	Finalised	Started	Finalised	Started	Finalised	Started	Finalised
Non-orphan medicinal products								
New products	40	28	32	33	31	34	20	15
Advanced-therapy medicinal products	0	0	0	1	1	0	0	0
Paediatric-use (PUMA) products	1	1	2	1	0	2	0	0
Well-established use, abridged, hybrid and informed consent products	7	5	5	6	5	6	10	7
Generic products	24	22	10	22	18	9	9	7
Similar biological products	14	7	17	14	9	15	8	3
Sub-total product applications	**86**	**63**	**66**	**77**	**64**	**66**	**47**	**32**
Orphan medicinal products◇								
New products	27	16	19	20	17	26	18	6
Advanced-therapy medicinal products	1	2	4	1	2	3	0	1
Total product applications	**114**	**79**	**89**	**101**	**83**	**89**	**65**	**39**

https://www.ema.europa.eu/en/documents/report/medicinal-products-human-use-monthly-figures-june-2019_en.pdf

Negative opinions: lack of clinical efficacy and severe safety risks.

Unmet medical need often outweighed scientific uncertainties.

Setting appropriate standards for ATMP authorization in Europe, similar to elsewhere, is a learning experience.

EU-decision making for MA of ATMPs Sofieke de Wilde et al. 2018

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Lack established safety models…

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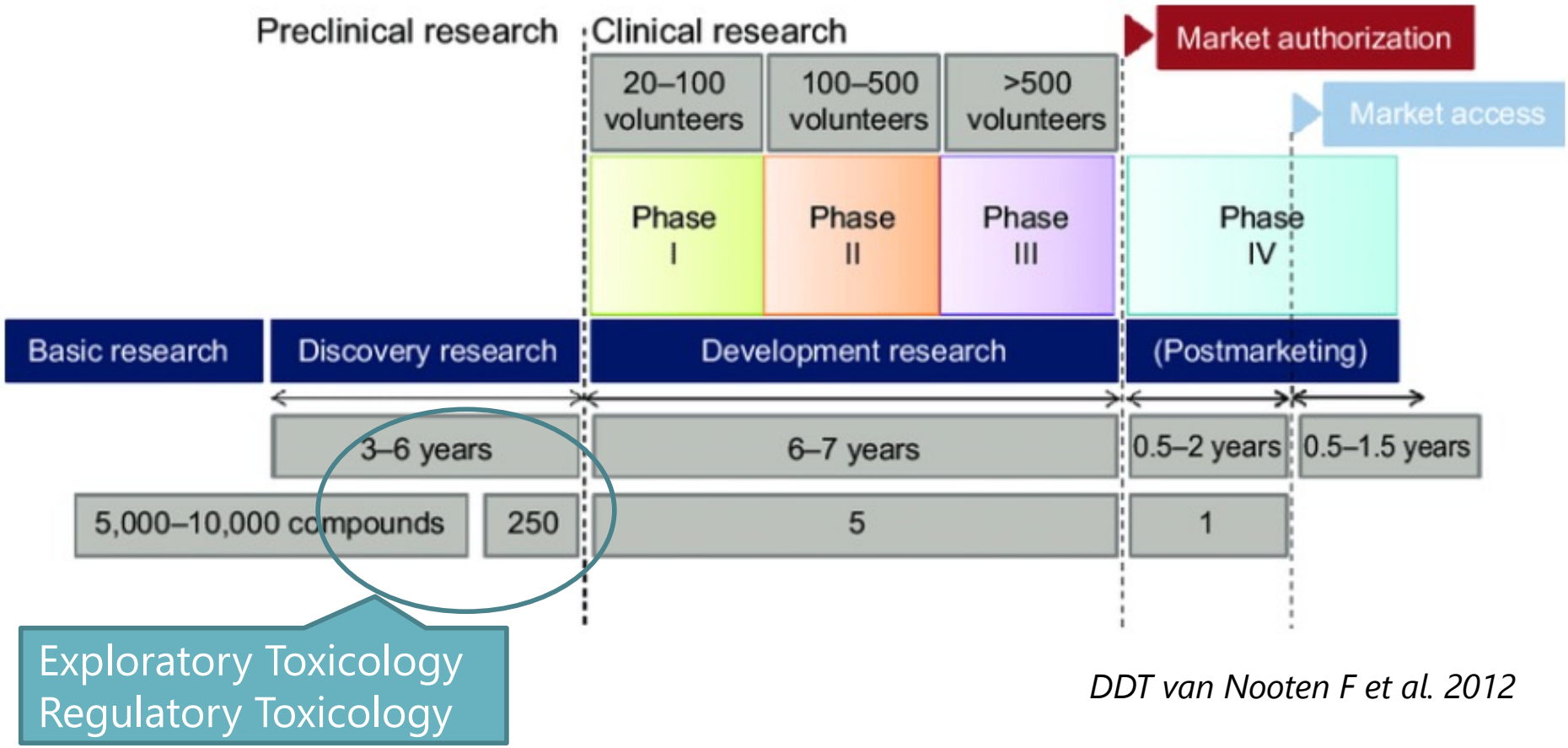
…accelerate drug development caused by the absence of established nonclinical safety models



DDT van Nooten F et al. 2012

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An example for non-clinical de-risking

Strategies to identify cancer hazard across different modalities

	Genotoxicity	Rodent lifetime cancer bioassay	Cancer-prone transgenic mouse model	Human tumor growth in rodent xenograft model	Indicators of neoplastic risk in chronic toxicology studies	*In vitro* cell growth and proliferation	Association of tumorigenic phenotype with drug target modulation	*In vitro* and/or *in vivo* cellular transformation	Clonality assessment	Viral vector integration site mapping or gene editing fidelity
Small molecule General medicines (>6 months treatment)	+	+	+	–	+	–	+	–	–	–
Small molecule Advanced cancer-phase I	+	–	–		+		+	–	–	–
Biologic General medicines (not rodent cross-reactive)	–	–	–	+/–	+	+/–	+	–	–	–
Biologic General medicines (rodent cross-reactive)	–	W	W	+/–	+	+/–	+	–	–	–
Cell and gene therapies All indications	–	–	–	–	–	+/–	–	+	+	+

(+) frequently deployed; (–) rarely/never used; (+/–) deployed if relevant to mechanism of action; (W) waiver may be appropriate based on lack of feasibility or relevance

Identify cancer hazard (drug-induced tumors and/or indicators of neoplastic risk)

↓

Safety margin between drug exposure causing tumors in animals and anticipated human therapeutic exposure

↓

Assess mode of action and human relevance via mechanistic studies

↓

Weight of evidence approach for cancer risk assessment

↓

Clinical risk management plan and product labelling

Moggs et al. 2016 Derisking Drug-Induced Carcinogenicity for Novel Therapeutics

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Apply a risk-based approach

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Immunogenicity

A number of patients may develop clinically relevant immune responses to the transgene product and/or to the transduced cells thus, data should be collected to characterise the immune response taking into account variability among patients. If multiple treatments are considered, the treatment schedule should be discussed also under the light of the pharmacokinetic properties of the transgene product.

Draft:

Assessment of immunogenicity needs to take into account clinically relevant immune responses to the transgene product and/or to the transduced cells. The risk for immunogenicity is influenced by the origin of transduced cells (allogeneic versus autologous), the nature of the disease (immune deficient versus immune competent patient, total absence vs. defective gene product), the type of conditioning regimen, the pre-existing immune response against the transgene product as well as the location of the transgene product (intracellular versus extracellular/secreted). An immune response to the cells and/or the transgene product may compromise efficacy and have an impact on safety, also in cases of single administration. Thus, the immunogenicity testing should be conducted throughout the development.

EMA/CAT/GTWP/671639/2008 Rev. 1 Committee for Advanced Therapies (CAT) Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

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Preclinical safety of AAV based gene therapy products

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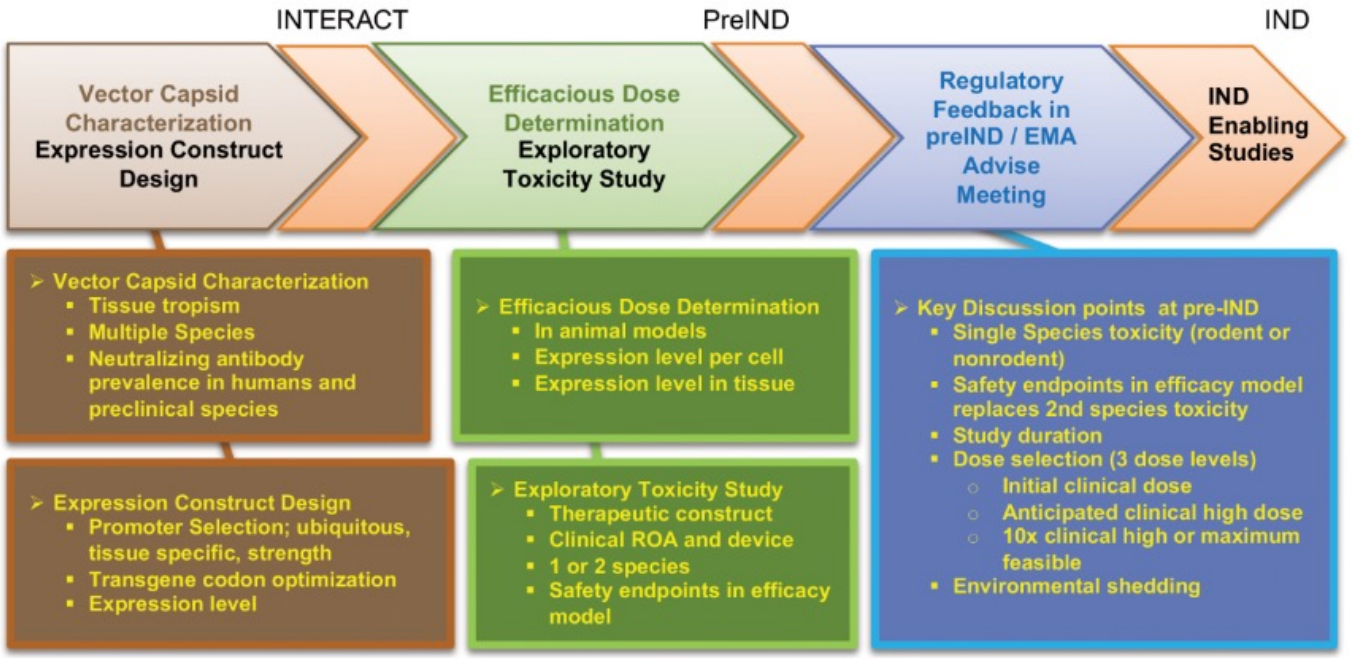

Assaf and Whiteley 2018

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Immunogenicity: Still a learning exerience

Gene Therapies:

- IR against transgene, therapeutic protein, vector
- Viral gene delivery
  - Innate IR (Danger- or pathogen-associated molecular patterns (D/PAMPs)
  - Pre-existing antibodies and memory B- and T-cells (CE-marked CDx)
  - Treatment-induced /-boosted cellular/humoral IR (transient,…)

Cellular products:

- Allogeneic reactivity due to mismatches in major/minor histocompatibility antigens

☞ Examples of approved ATMPs, immunogenicity risks, testing strategies.

☞ Overview of bioanalytical methods used to monitor IRs

Immunogenicity of advanced therapy medicinal products: risk factors and mitigation measures
Paula Salmikangas, Paul Chamberlain, Beatriz Silva Lima & Markku Toivonen Cell & Gene Therapy Insights 2019; 5(7), 829–857

ATMPs

Nonclinical Assessment of T-cell Immunotherapies

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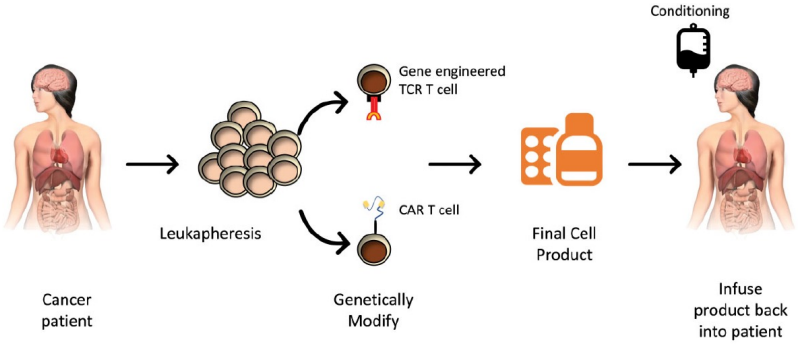
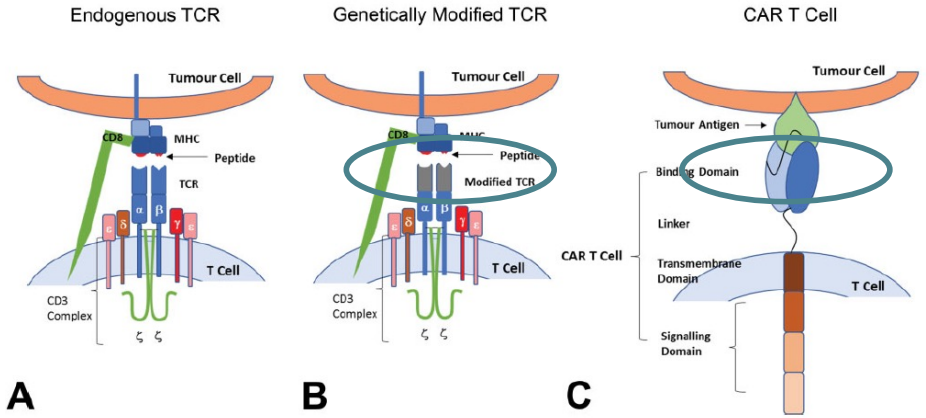


Manufacturing of and treatment using gene-engineered T cells



Genetically modified T cells for cancer immunotherapy

- Use of Animal Models for Target Specificity Assessment of Adoptive T-cell Therapies
- Use of Immunodeficient Animals in Efficacy and Safety Assessments

wanted immunogenicity

- Safety Related to Genetic Modification of T Cells
- Cytokine release syndrome
- Tumor lysis syndrome
- Neurological toxicities

Michaela E. Sharpe 2018 Tox Path

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Regenerative medicine

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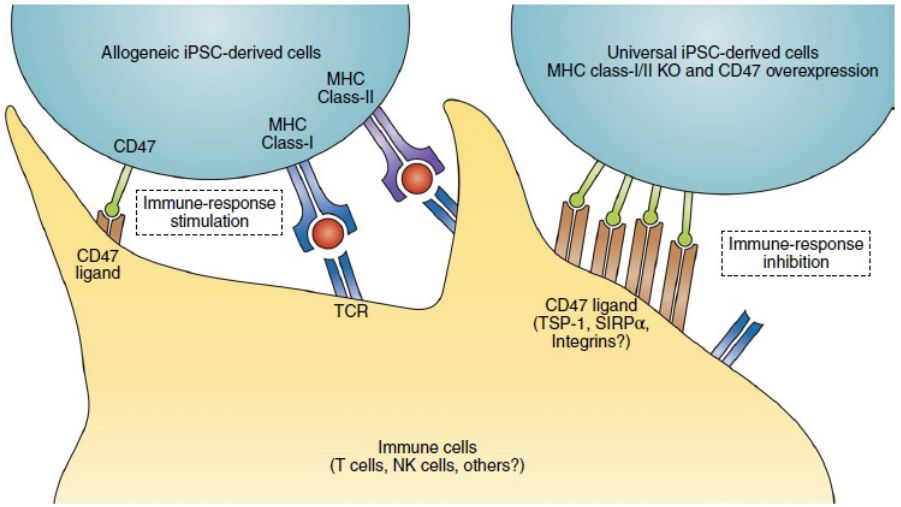
Personalized cell-based therapies are time consuming, laborious and costly.

☞ Approaching universally non-immunogenic iPSCs?



Inactivation of the major histocompatibility complex and overexpression of the transmembrane protein CD47

renders induced pluripotent stem cells invisible to the immune system of the host.

Engineered hypoimmunogenic iPSCs via MHC class-I/II knockout and CD47 overexpression.
Tom Shani and Jacob H. Hanna
Nature Biomedical Engineering | VOL 3 | MAY 2019 | 337–338

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Immunogenicity spoilers genome editing

CRISPR associated protein 9 (Cas9) is now enabling

a new generation of precision gene therapies, but the potential for immunotoxicity remains a concern.

T-cell and B-cell immunity to *Sp*Cas9 triggered hepatic inflammation and liver damage within14 days of injection

confirmed that the Cas9 protein itself was broadly immunogenic.

…

pre-existing IgG antibodies to the S. pyogenes6–9 and Staphylococcus aureus9 Cas9 proteins in humans

Weakly immunogenic CRISPR therapies

Orthologues of CRISPR-associated proteins and of viral vectors evade immune recognition in mice, enabling repeated gene therapy.

Eric A. Wilson and Karen S. Anderson 2019

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Nonclinical studies are of value

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rAAV-2 F.IX vector transduced human hepatocytes destroyed by cell-mediated immunity targeting antigens of the AAV capsid

Manno et al. 2006 Nature Medicine volume 12

Studied AAV5-based FVIII-SQ vector in cynomolgus monkeys with varying pre-dose levels of neutralizing anti-AAV antibodies and non-antibody transduction inhibitors.

- ☞ animals without AAV5 antibodies are likely responders to AAV5 gene therapy, regardless of other inhibiting plasma factors.

Long et al. 2019 Molecular Therapy: Methods & Clinical Development Vol. 13

- ☞ Prednisolone Does Not Regulate Factor VIII Expression in Mice Receiving AAV5-hFVIII-SQ

Zhang et al. 2020 Molecular Therapy: Methods & Clinical Development Vol. 17

Risk management

Concomitant medication with biotherapeutics

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- concomitantly administered passive immunotherapies
- addition of recombinant proteins on the basis of plasma derived proteins
  - Preexisting Abs in the plasma derived biotherapeutic?
- biological derived excipient

➢ **Polypharmacy!**

➢ **growing home-care segment (Self-administration)**

Risk management

Post-marketing tool box

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Pivotal clinical trials need to be powered to allow overall benefit / risk assessment

- and can rarely be powered for immunogenicity driven AEs

➢ *potential immunogenicity and clinical consequences should be included in the safety specification*

➢ strengthened Pharmacovigilance

PASS / RM Plans / Registries (standardized assays?)

Dir 2010/84/EC, Good Pharmacovigilance Practice

"Immunogenicity of XY to be followed post-authorization"

Summary

Complicating factors in immunogenicity assessment

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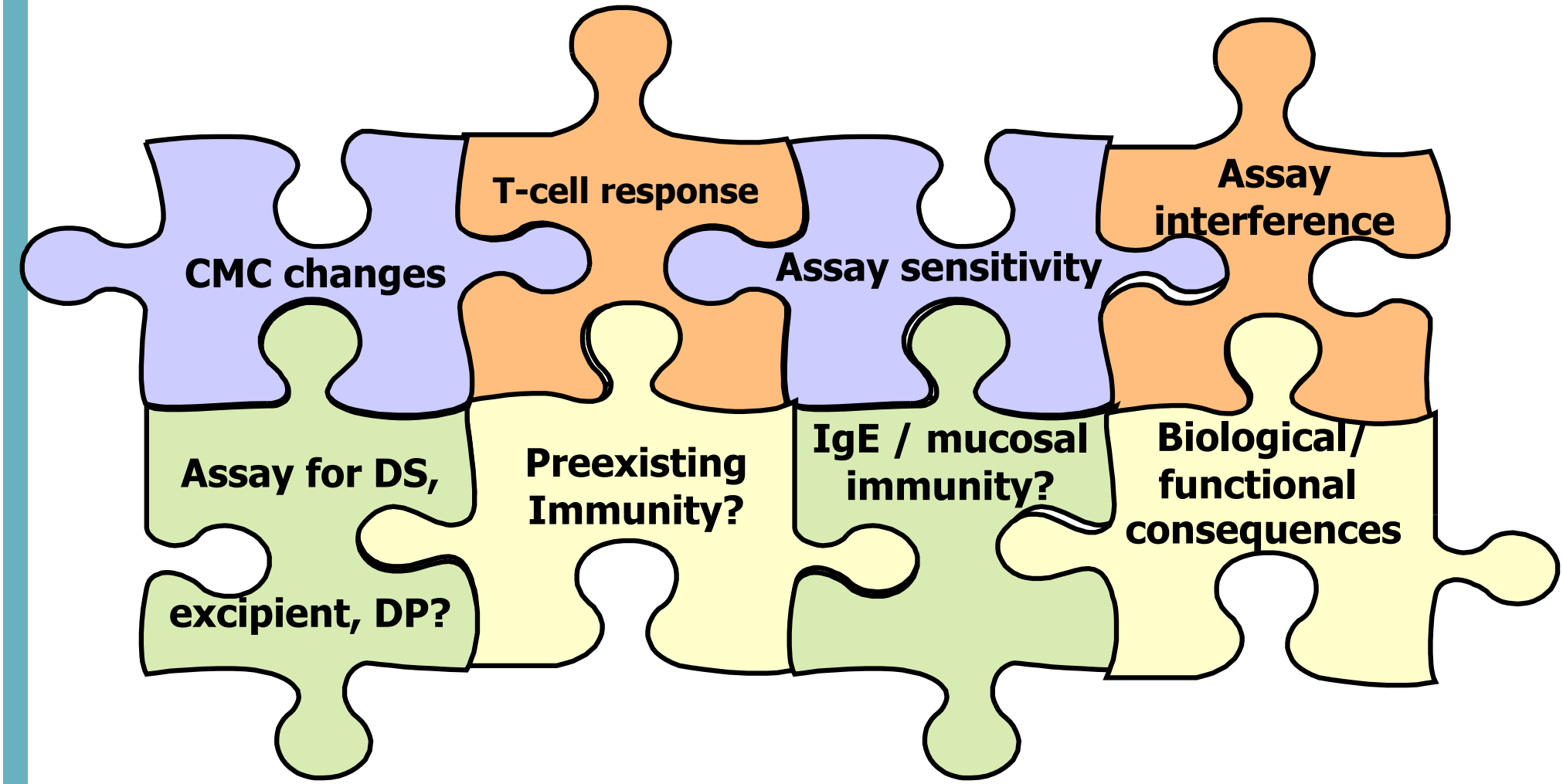


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