Pre-existing ADA

A look beyond ADA assays

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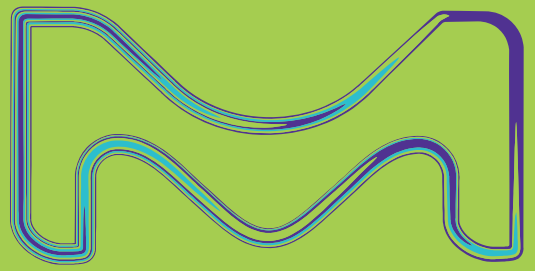
EBF Training Day "Practical Aspects of Immunogenicity"

23rd of March, 2021



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Outline

- What is pre-existing ADA?
- Examples
- Why do I care? A look beyond ADA assays

Introduction

Pre-existing anti-drug antibodies are:

- **ADA present before a subject or an animal is treated with a biotherapeutic**
- Specific (e.g. anti-PEG, anti-FVIII; anti-Glycans) or cross-reactive (e.g. Rheumatoid factors, anti-HCP)
- Either part of the natural antibody population or antibodies of an adaptive immune response to similar biotherapeutics or environmental antigens
- May affect PK, efficacy, safety or be without clinical impact

Specificity of pre-existing antibodies

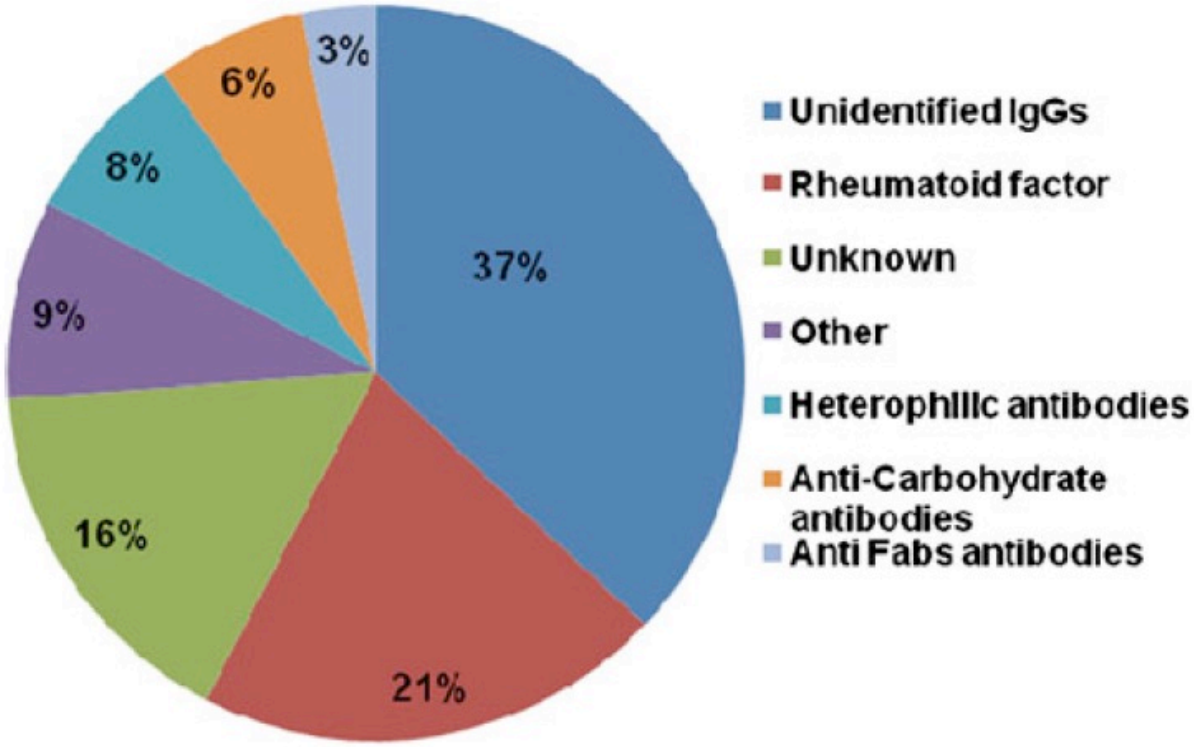
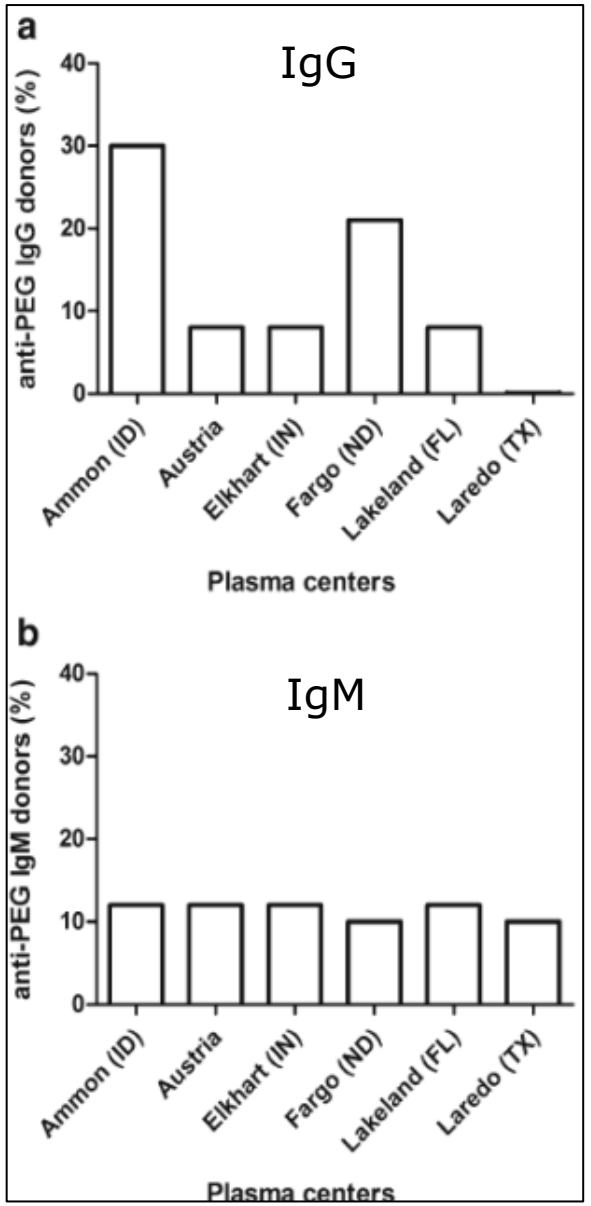


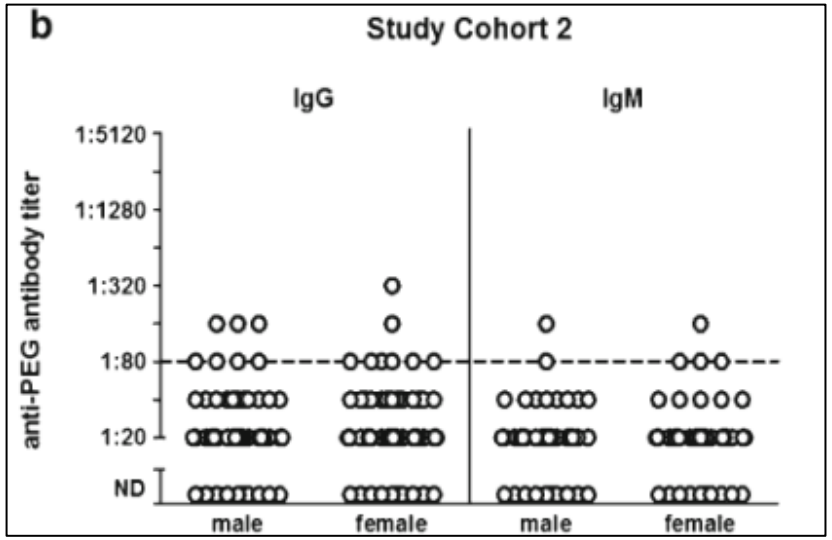
Fig. 2. Specificity of pre-existing antibodies identified in clinical samples

The AAPS Journal, 2013

examples

Example: Anti-PEG in healthy population





- Pre-existing ADA present in healthy populations
- Prevalence of preexisting ADA in different regions

Lubich et al 2016; Pharm Res

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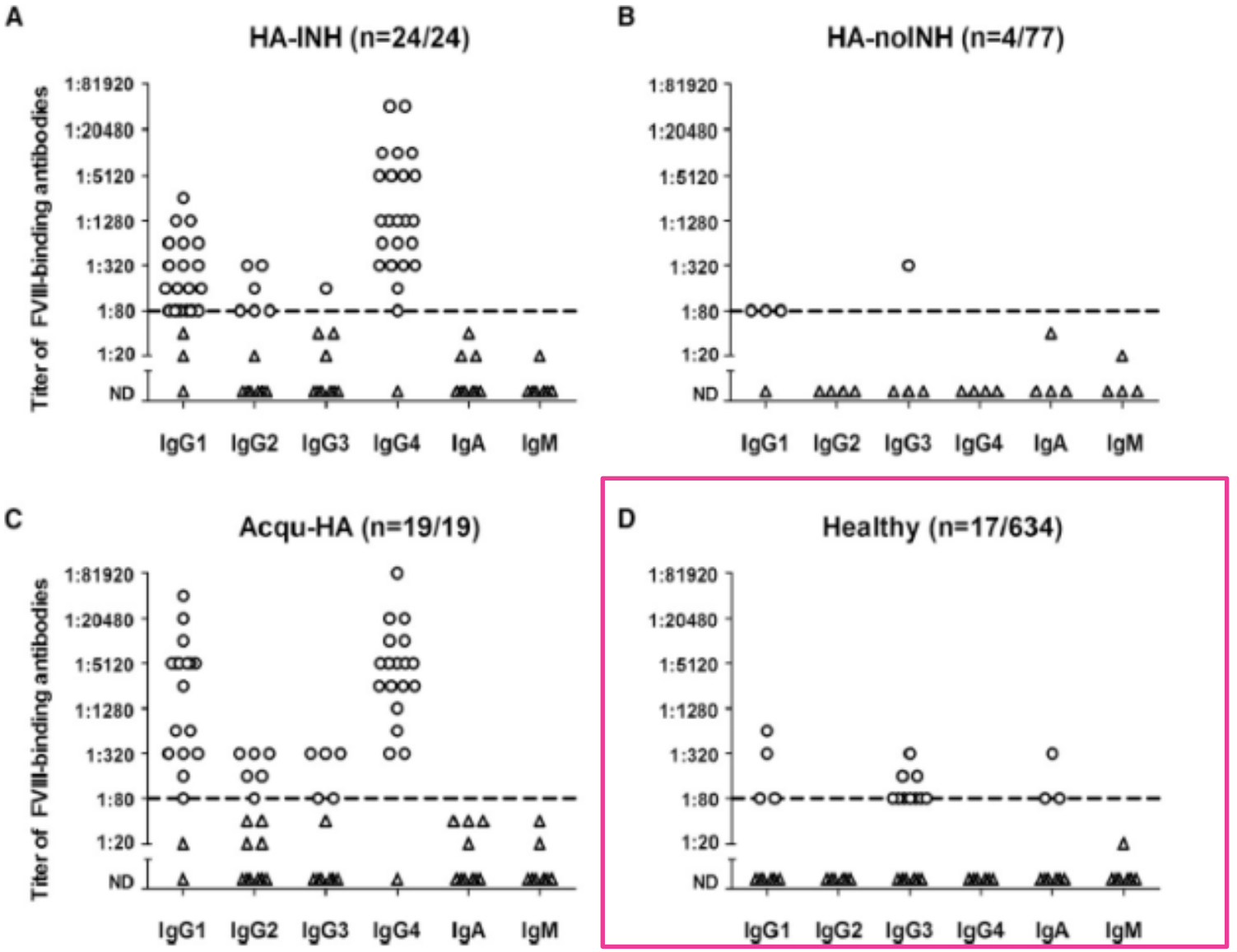
Example: Anti-FVIII in healthy and hemophilia patients



- Pre-existing ADA in HV and treatment induced have different Ig populations
- Differences in magnitude and type of response
- Epitopes of pre-existing ADA in healthy volunteers may differ from the target patient population

Hofbauer et al 2015; Blood

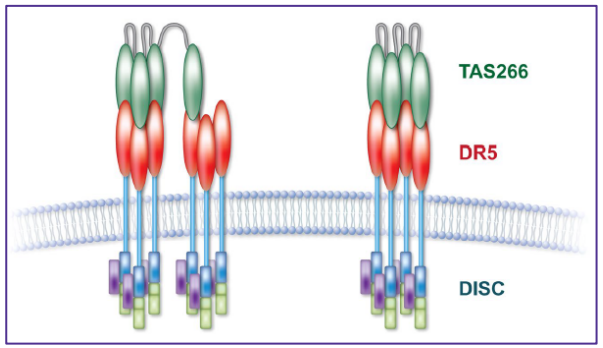
Example: anti-TAS266 and adverse event

TAS266:

Tetravalent anti-DR5 VHH

MoA:

Mulimerization and superclustering of DR5, initiating DISC formation and downstream apoptotic signaling



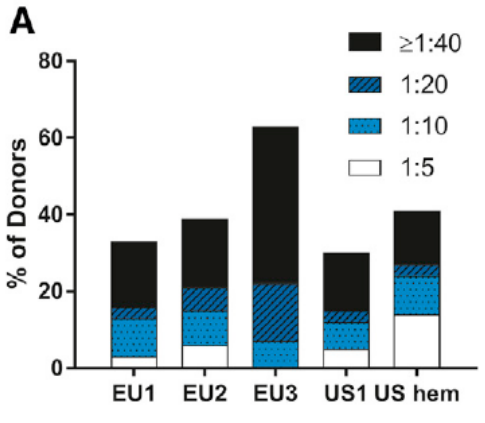
Papadopoulos KP, et al. Cancer Chemother Pharmacol. 2015

Table 3 TAS266 Immunogenicity

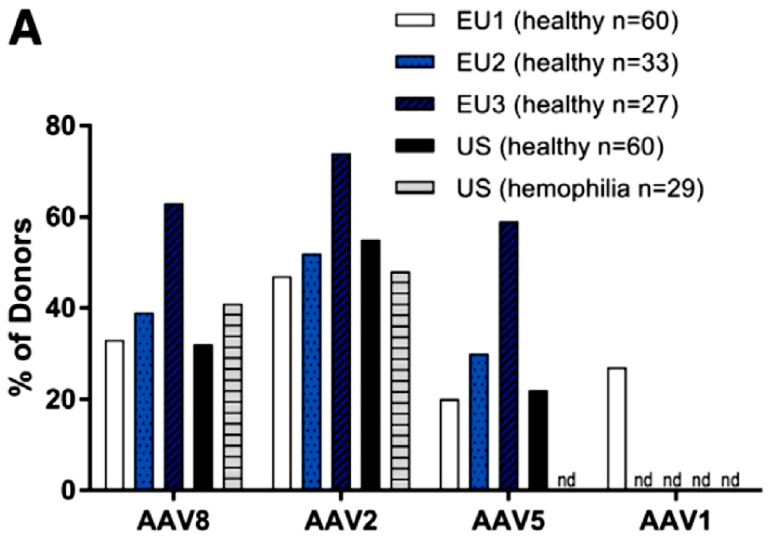
Patient	Study day	Anti-TAS266 antibody presence	Optical density (OD)
1	1	Yes	0.68
	10	Yes	1.94
	15	Yes	2.03
2	1	No	
	8	No	
	14	No	
	21	No	
	29	Yes	0.41
3	1	Yes	0.24
	9	Yes	1.05
	15	Yes	1.64
4	1	Yes	1.00
	5	Yes	0.81
	8	Yes	1.610
	15	Yes	2.06

Positive: OD >0.16. Patients 1, 3, and 4 experienced liver enzyme adverse events

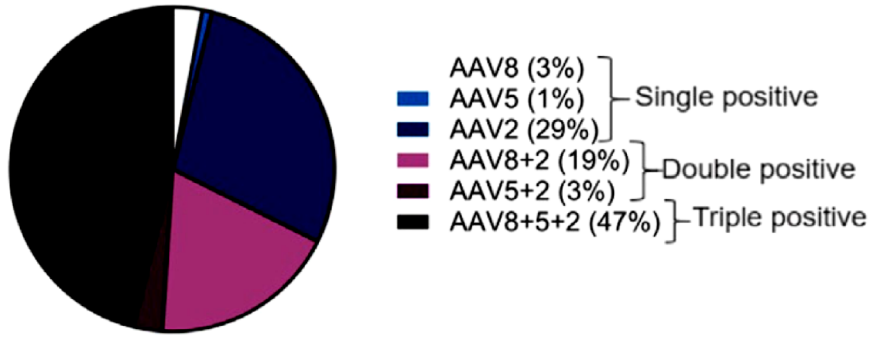
Example: Gene therapy anti-viral capsid pre-ADA



Ab prevalence against AAV8



Prevalence of NAbs against AAV8, AAV2, AAV5, and AAV1 in healthy donors and patients with hemophilia B.



Co-prevalence of NAbs against AAV8, AAV2,and AAV5.

Kruzik et al Molecular Therapy: Methods & Clinical Development 2019

Why do I care?

A look beyond ADA assays

Why do I care?
A look beyond ADA assays

1. Pre-ADA evaluation early in the project helps to avoid costly setbacks

2. Pre-ADA as potential biomarker for patient stratification

3. Pre-ADA data useful when evaluating potential impact of ADA on safety and efficacy

anti-TAS266 and adverse event
Evaluation early in the project helps to avoid costly setbacks

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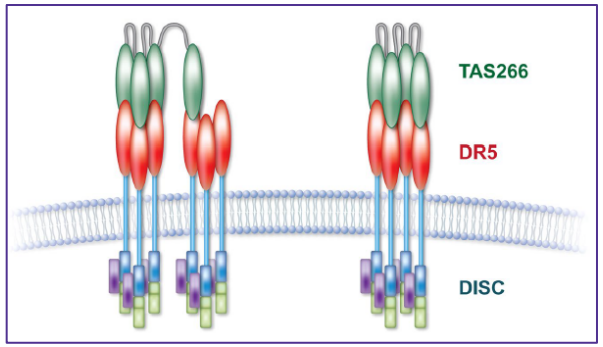

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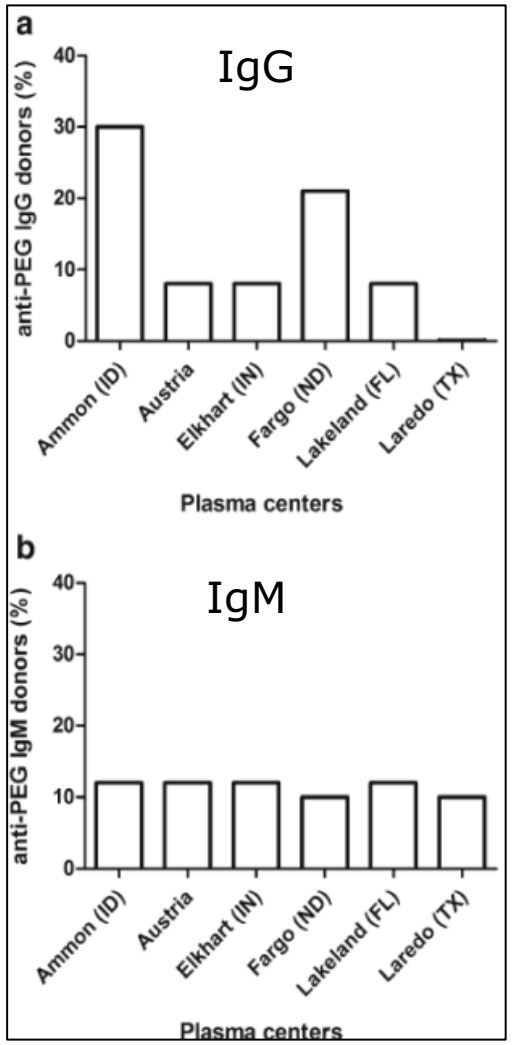
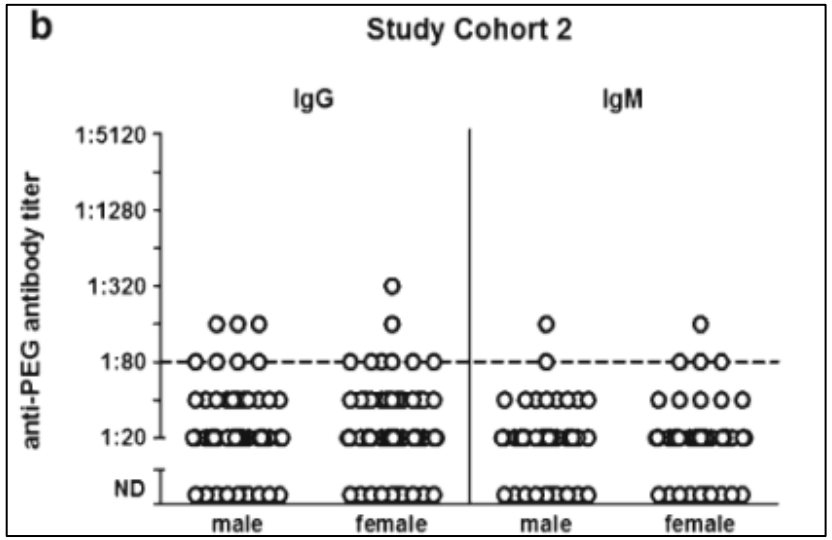
Positive: OD >0.16. Patients 1, 3, and 4 experienced liver enzyme adverse events

What do I do to mitigate such risks?
Evaluation early in the project helps to avoid costly setbacks

- Theoretical immunogenicity risk assessment of new modalities and constructs
- Pre-ADA screening for of healthy population
- Pre-ADA screening in target disease populations performed before introducing new molecular formats into the pipeline
- Pre-ADA testing and De-immunization if pre-ADA have shown to have impact on early PK

Anti-PEG in healthy population
Interesting but is it relevant?





- Pre-existing ADA present in healthy populations
- Prevalence of preexisting ADA in different regions

Lubich et al 2016; Pharm Res

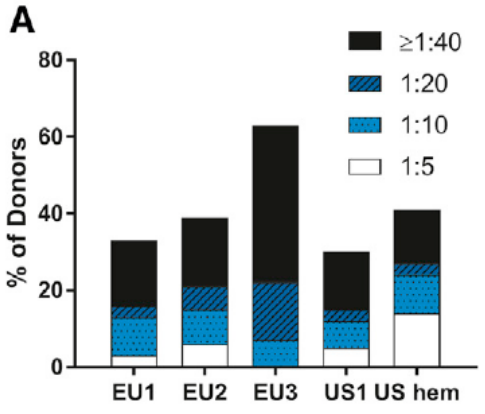
How do I use such data?
Evaluating potential impact on safety and efficacy

- There are different views about how impactful or relevant anti-PEG pre-ADA are

- If I’m working with the pegylated biologic I would like to know if pre-existing anti-PEG ADA have impact on a drug exposure

- Data on pre-existing anti-PEG ADA is helpful when evaluating safety impact of anti-PEG antibodies observed in clinical studies.

Gene therapy anti-viral capsid pre-ADA
Pre-ADA as potential biomarker for patient stratification



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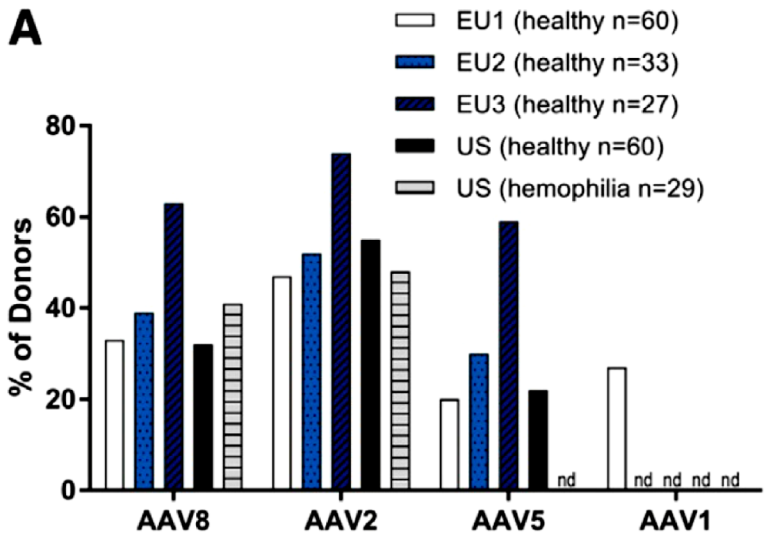

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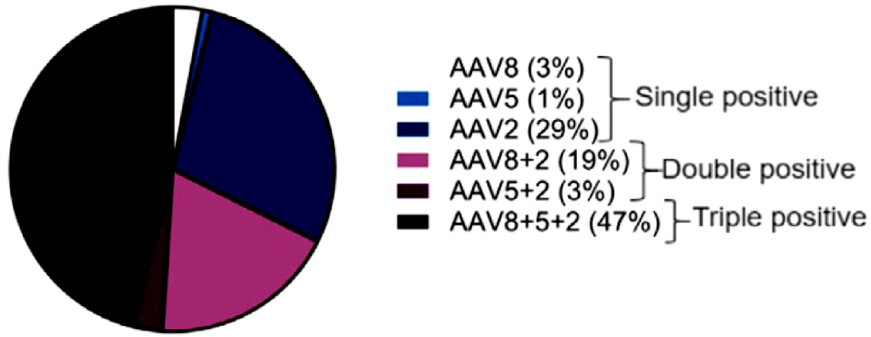

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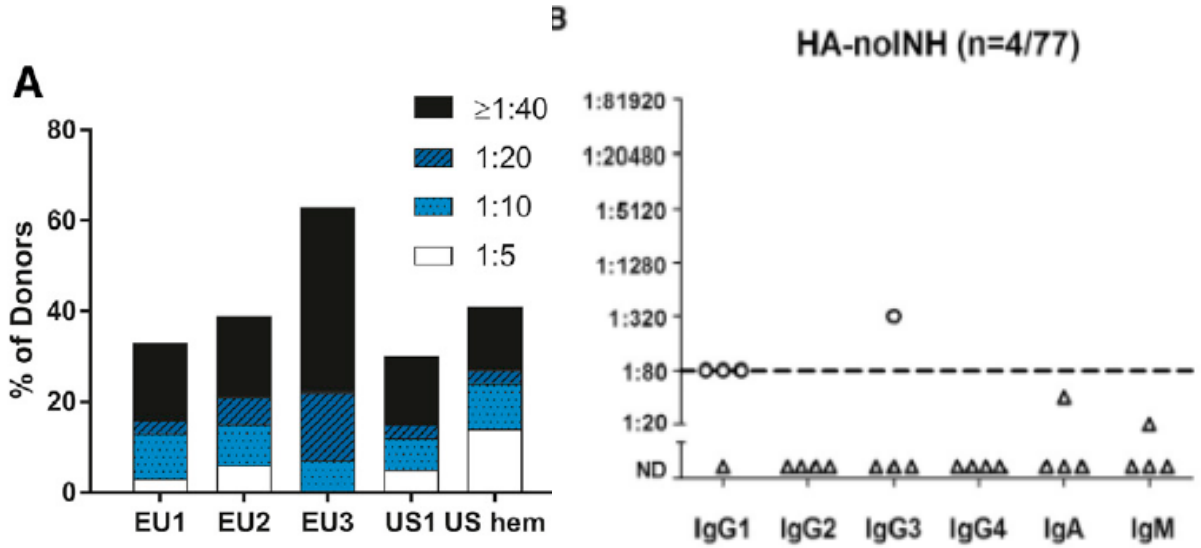
Kruzik et al Molecular Therapy: Methods & Clinical Development 2019

How do I use such data?
Pre-ADA as potential biomarker for patient stratification

- Serve as base for further assessments into which pre-ADA levels may impact the efficacy of a gene therapy (GT) drug
- Cornerstone data in designing the strategies to overcome pre-ADA impact on GT
- Key data for the personalized medicine – identify patients where GT has highest probability of success
- Pre-ADA data from other antigens (e.g. FVIII) might be needed for decision making



Summary

- Pre-existing ADAs are common and reported against a variety of antigens
- Early information about pre-ADA against your new modality/ framework will help you to design better molecules and minimize risk of costly setbacks
- People from around the world may have different prevalence and titers of pre-ADA: testing 50 healthy volunteer samples collected in one county will no provide global overview
- Pre-ADA data may help you to develop patient stratification strategy and path towards personalized medicine
- Pre-ADA data helps you to put clinical ADA findings into the perspective: how to evaluate immunogenicity related risks

Thank you !