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Clinical relevance of (unwanted drug-induced) immune responses

EIP working group on Clinical Relevance

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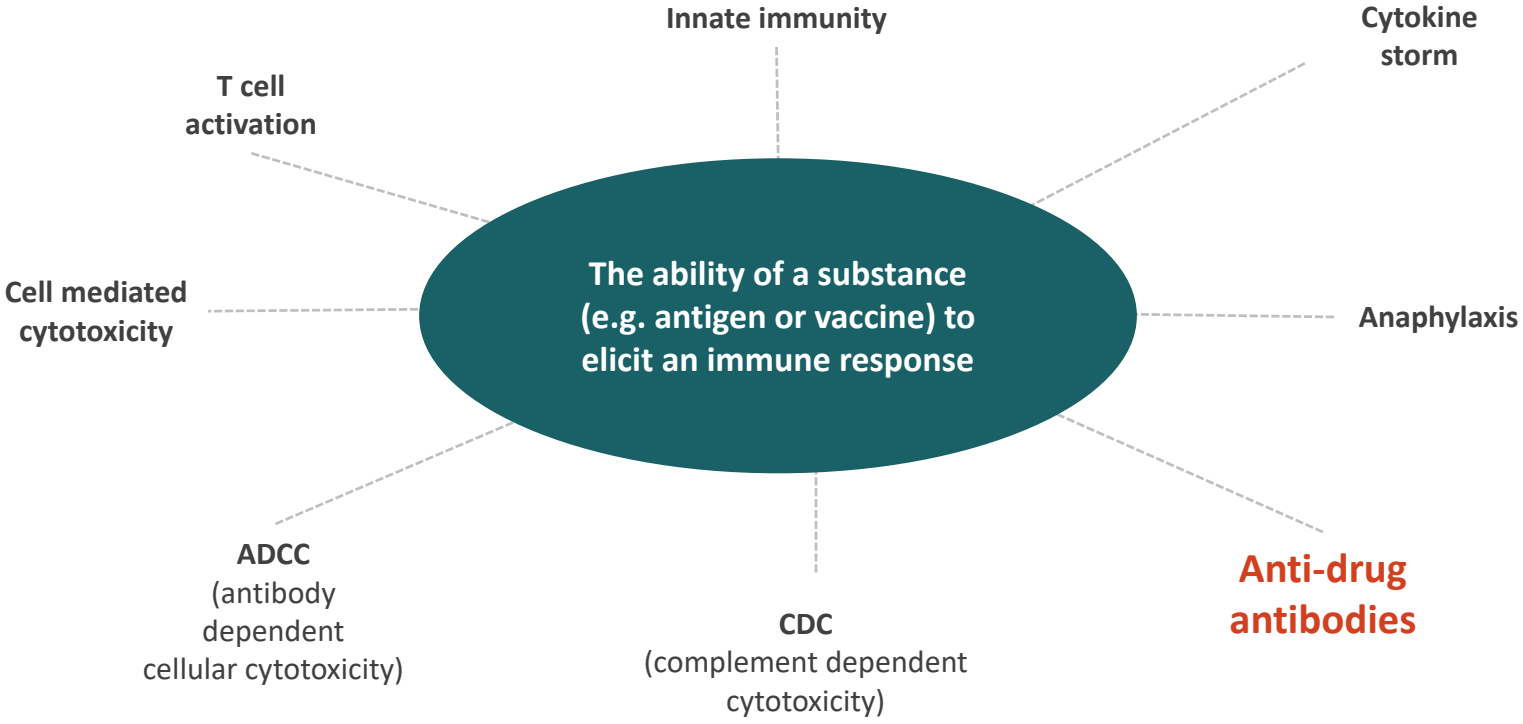
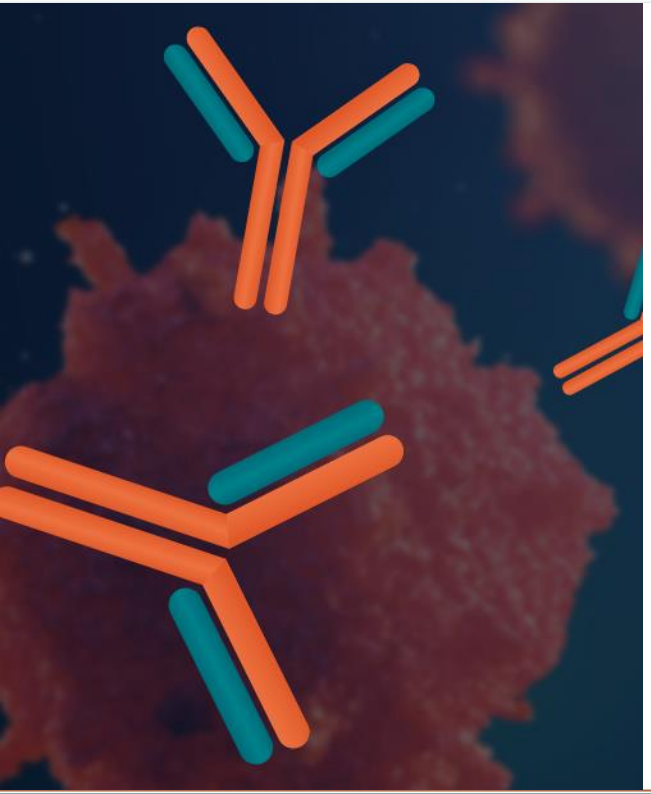
February 27th, 2019

What is **Immunogenicity?**



Consequences of Immunogenicity



Immunogenicity

1. SAFETY
2. EFFICACY

- ✓ Pivotal clinical trials
- ✓ Long-term treatment of the patients with a marketted drug

Incidence vs. Prevalence

Prevalence

Proportion of a population with baseline (pre-existing) ADA to a particular biologic drug. **Prevalence is a measurement of *all* individuals affected by a phenomenon before an administration.**

VS.

Incidence

Proportion of the study population found to have seroconverted, or boosted their pre-existing ADA, during the study period. **Incidence is the sum of both treatment-induced and treatment-boosted ADA positive subjects.**

Incidence of ADAs

Class	Drug	Indication	Incidence
Interferons	Interferon α (non-PEG)	HCV	hi
	Interferon β	Multiple Sclerosis	hi
Receptors	TNF Receptor	RA	lo
Enzymes	Factor VIII	Hemophilia	mod
	Cerebrosidase	Gaucher disease	mod
	DNase	Cystic Fibrosis	mod
Hormone	Insulin	Diabetes mellitus	hi
	HGH	Growth retardation	mod
	Erythropoietin	Anemia	lo
mAb	Infliximab	RA, IBD	mod
	Adalimumab	RA, IBD	mod
	Certolizumab	RA, IBD	mod
	Rituximab	NHL, RA, SLE	lo/mod

FDA Immunogenicity Guidance, 2019

The assays should have sufficient sensitivity to enable detection of ADA before they reach levels that can be associated with altered pharmacokinetic (PK), pharmacodynamic (PD), safety, or efficacy profiles.

FDA recommends that screening and confirmatory IgG and IgM ADA assays achieve a sensitivity of **at least 100 nanograms per milliliter (ng/mL) …**

Traditionally, FDA has recommended sensitivity of at least 250 to 500 ng/mL. However, recent data suggest that **concentrations as low as 100 ng/mL may be associated with clinical events** (Plotkin 2010; Zhou et al., 2013).

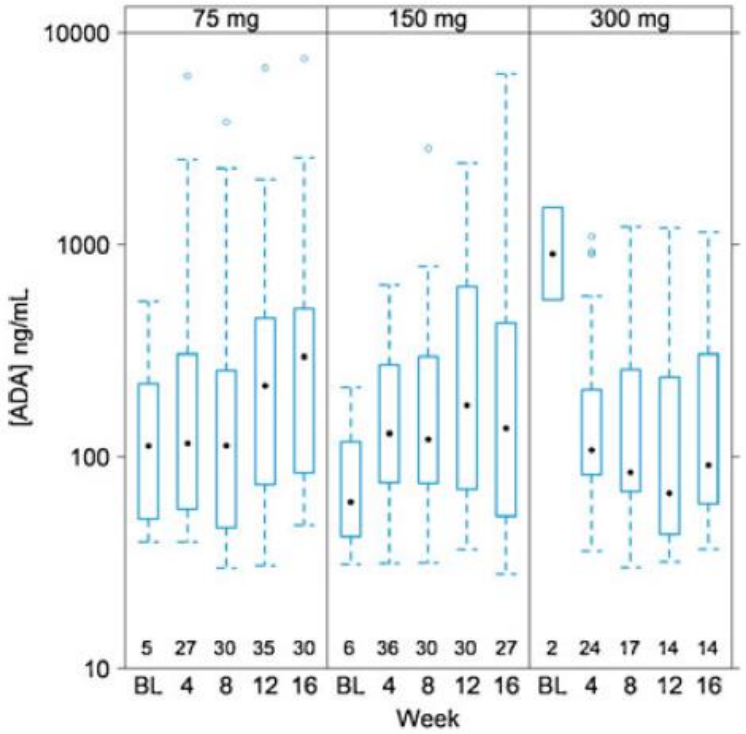
Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection
Guidance for Industry, FDA, January 2019

ADA Kinetics and Characteristics

Concentration and characteristics of the ADA response observed following weekly administration of a fully human mAb therapeutic

- ✓ Phase 2 clinical trial: 45% of subjects developed ADAs.
- ✓ Relative ADA concentration detected in antibody-positive samples during the course of the study:
- ✓ Wide range of relative concentrations of the antibody responses: 30 ng/mL to >13 µg/mL.
- ✓ Highest median and individual antibody levels detected in the lowest (75 mg) dose group at week 16.

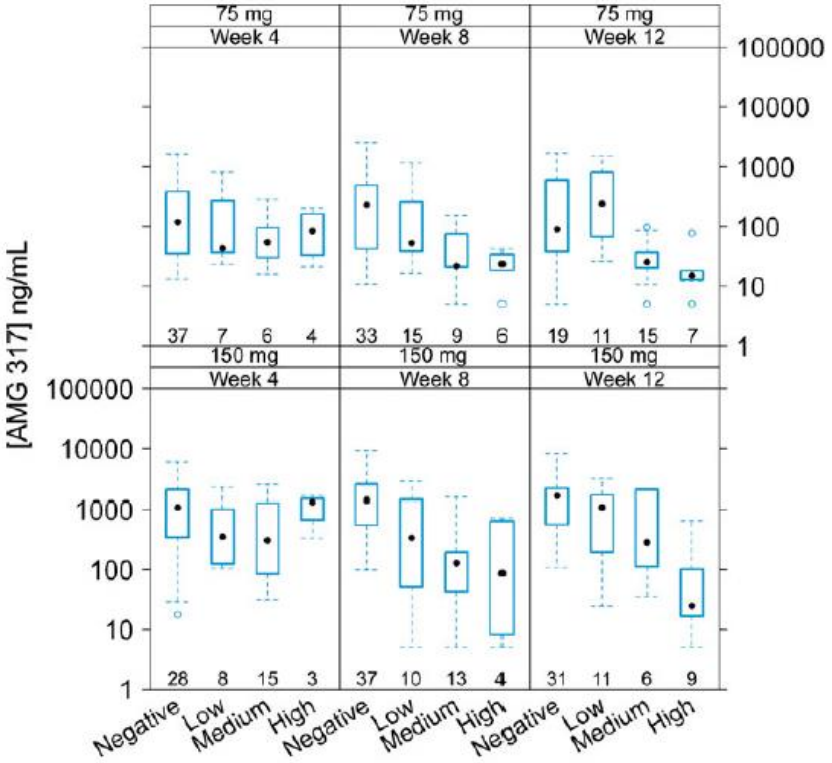
Zhou et al, AAPSJ, 2013



ADA Kinetics and Characteristics

Analysis of the impact of antibody status on drug pharmacokinetics (PK)

Stratifying variables: both time point and antibody level
=> significant reduction in drug levels revealed



Zhou et al, AAPSJ, 2013

Determination of the sensitivity of an ADA assay

Assay Run	Linear Fit	Sigmoidal Fit	Asymmetric Sigmoidal Fit
#1	0,933	0,922	0,960
	0,761	0,615	0,615
#2	1,126	1,172	1,212
	1,048	0,980	0,998
#3	1,146	1,118	1,166
	0,942	0,756	0,759
#4	1,065	1,069	1,127
	0,997	0,891	0,938
Mean	1,002	0,940	0,972
SD	0,125	0,187	0,205
Sensitivity: mean + (t0,05df*SD) in ng/mL	**1,3**	**1,4**	**1,6**
LPC1: mean + (t0,01df*SD) in ng/mL	1,4	1,8	2,4

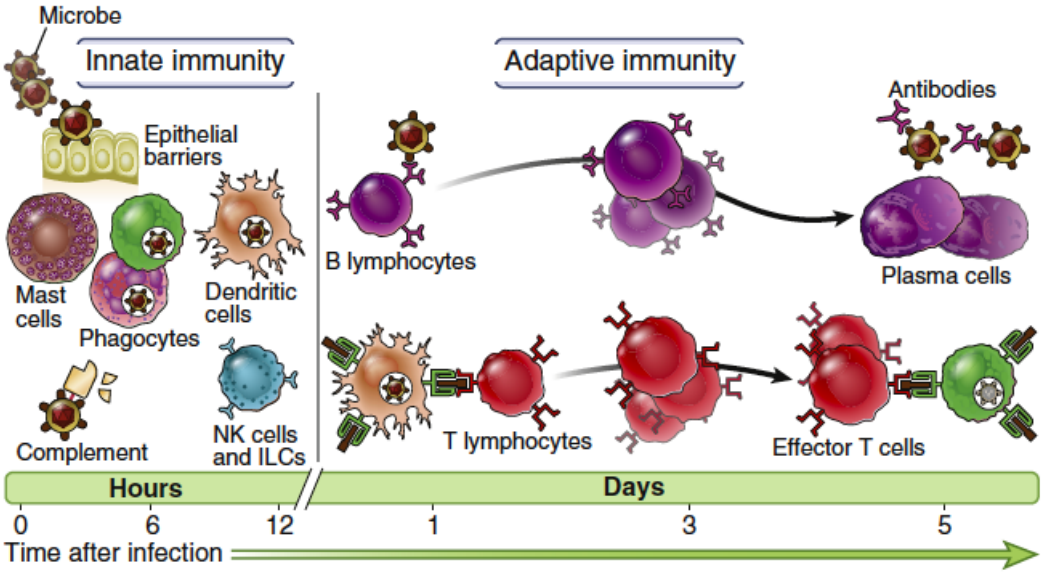
ADA sensitivity as low as low ng or even sub-ng range can be achieved with a given positive control.

Are these high analytical sensitivities needed or clinically relevant?

Induction of **Immune Responses**

The induction of immune response is **cascade of multiple steps and ultimately leads to highly specific antibodies and T cells.**

Abbas, Lichtman and Pillai, 2016



Natural **Antibodies**

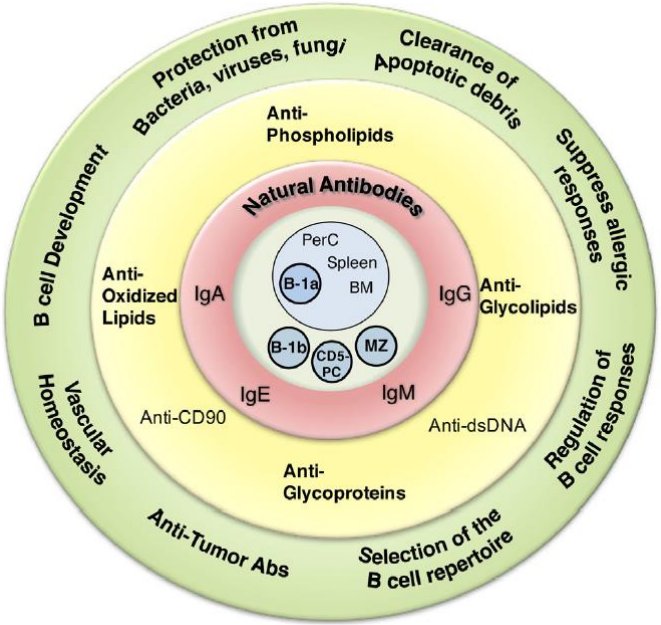
Natural antibodies are pre-immune antibodies generated in the absence of exogenous antigenic stimulation.

Natural antibodies

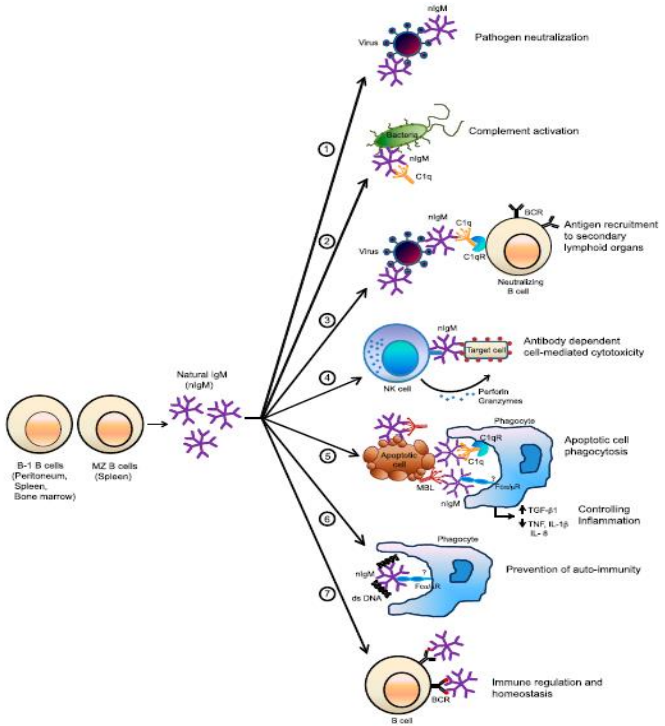
- ✓ have the ability to exert a protective or regulatory function
- ✓ show a pre-existing/immediate immune responsiveness.

Green: various functions	**Red:** isotype
Yellow: epitope recognition	**Blue:** cells

Holodick NE et al, Front Immunol, 2017



Diverse Roles of Natural IgM Antibodies

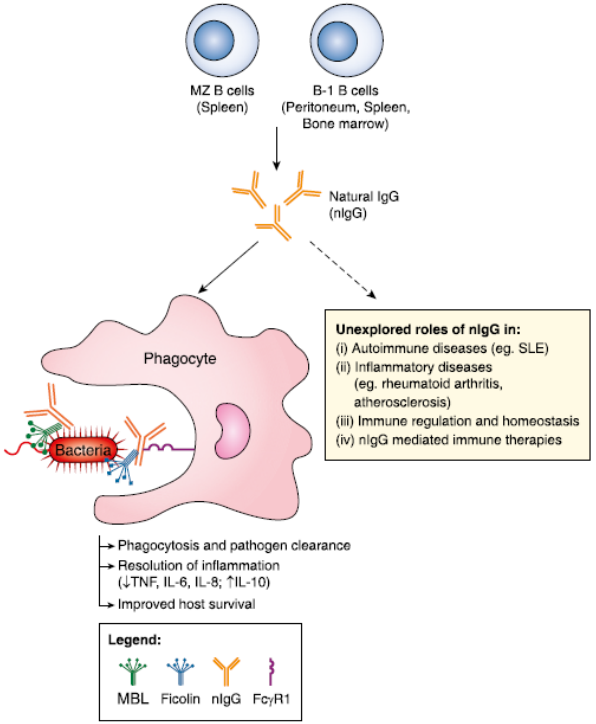


Natural IgM plays a role in:

- ✓ Direct pathogen neutralization
- ✓ Classical complement activation
- ✓ Ag recruitment and priming of subsequent TI adaptive immunity
- ✓ Ab-dependent cell-mediated cytotoxicity
- ✓ Apoptotic cell phagocytosis
- ✓ Clearance of DAMPs
- ✓ B cell homeostasis

Panda S & Ding JL, J Immunol, 2015

(Possible) Roles of Natural IgG Antibodies



a. **Pathogen recognition and clearance,** thus controlling inflammation by regulating the production of cytokines

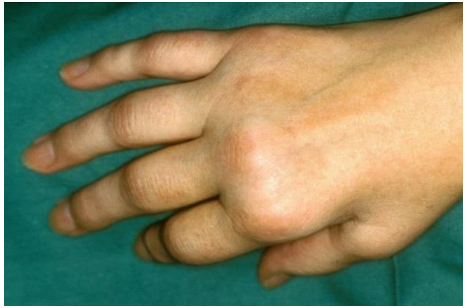
b. **Role in Health and Disease:**

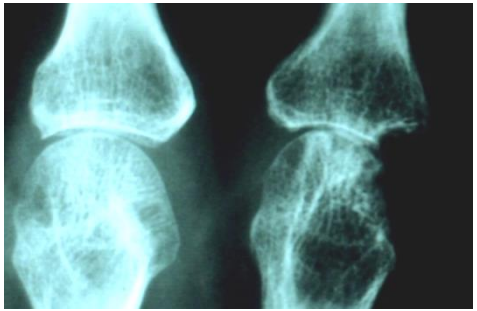
- ✓ Controlling or exacerbating autoimmune diseases,
- ✓ Ameliorating inflammation,
- ✓ Immune regulation and homeostasis,
- ✓ Development of safer and more effective immunomodulators.

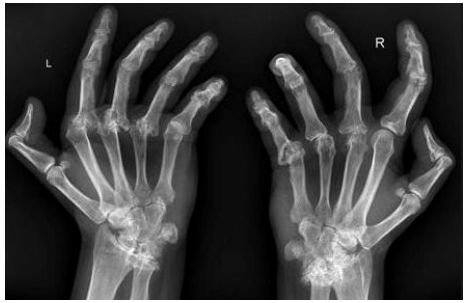
Panda S & Ding JL, J Immunol, 2015

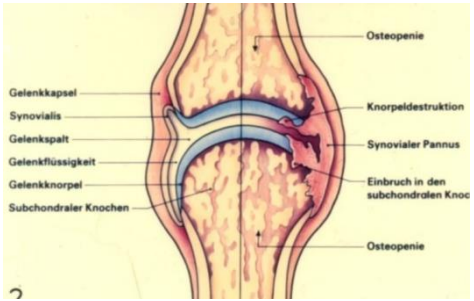
Rheumatoid Arthritis

- ✓ Prevalence: 1.0%
- ✓ f/m: 2.5/1
- ✓ Age: 43 (± 40)
- ✓ Chronic synovitis
- ✓ Anti-CCP antibodies (cyclic citrullinated peptide)

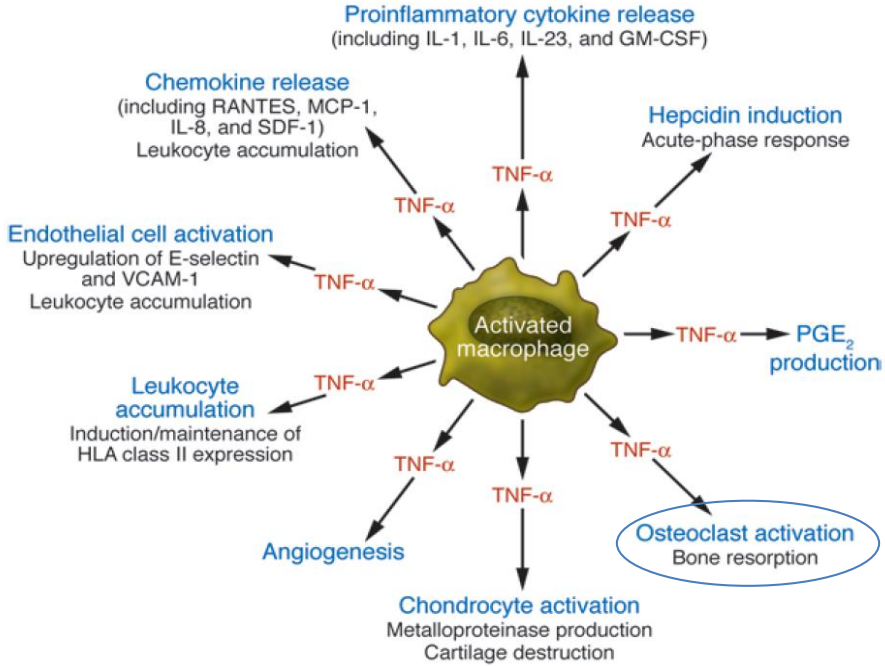




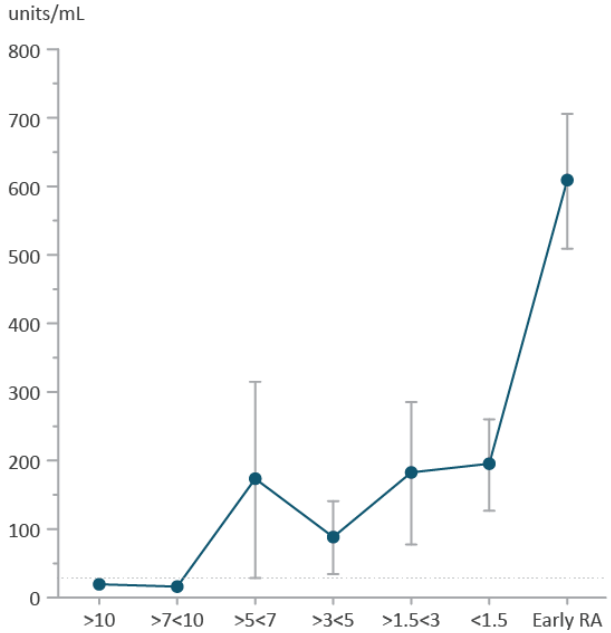




TNF-α as a Target in RA



Anti-CCP Ab Detection Prior to the Disease Onset

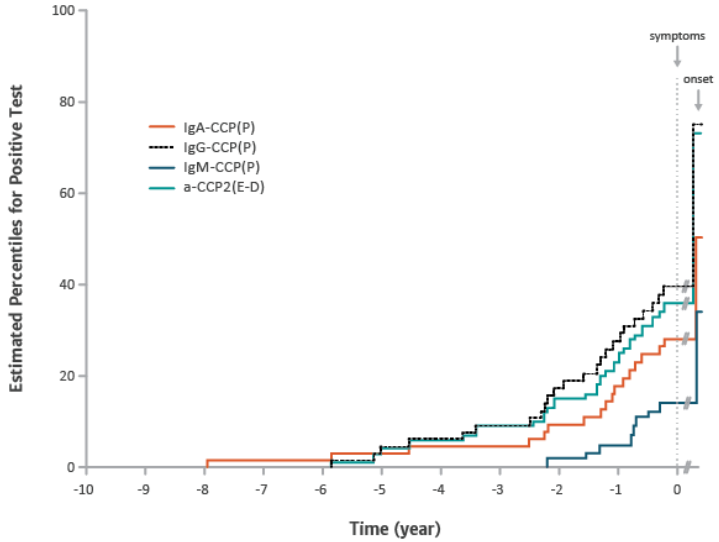


	Sens (%)	Spec (%)	PPV (%)	NPV (%)
RA Patients	34	98	82	86
>1.5 years before symptoms	25	98	80	84
<1.5 years before symptoms	52	98	85	89
Early RA	70	98	91	93

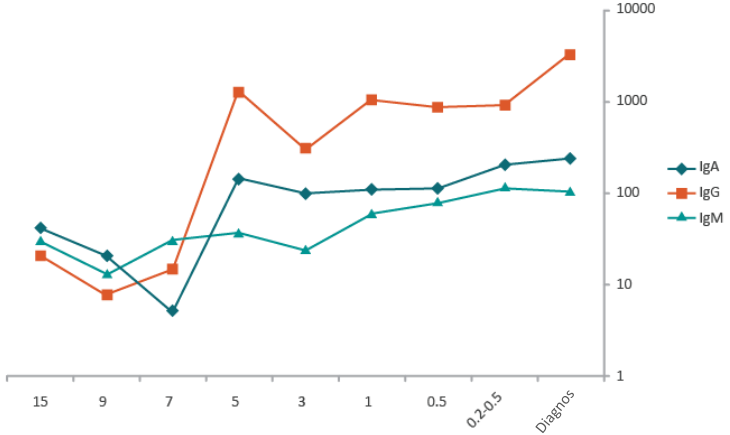
Rantapää-Dahlqvist S et al., Arthritis Rheum, 2003

PPV: Positive predictive value
NPV: Negative predictive value

Time Course of anti-CCP Antibodies (in RA)



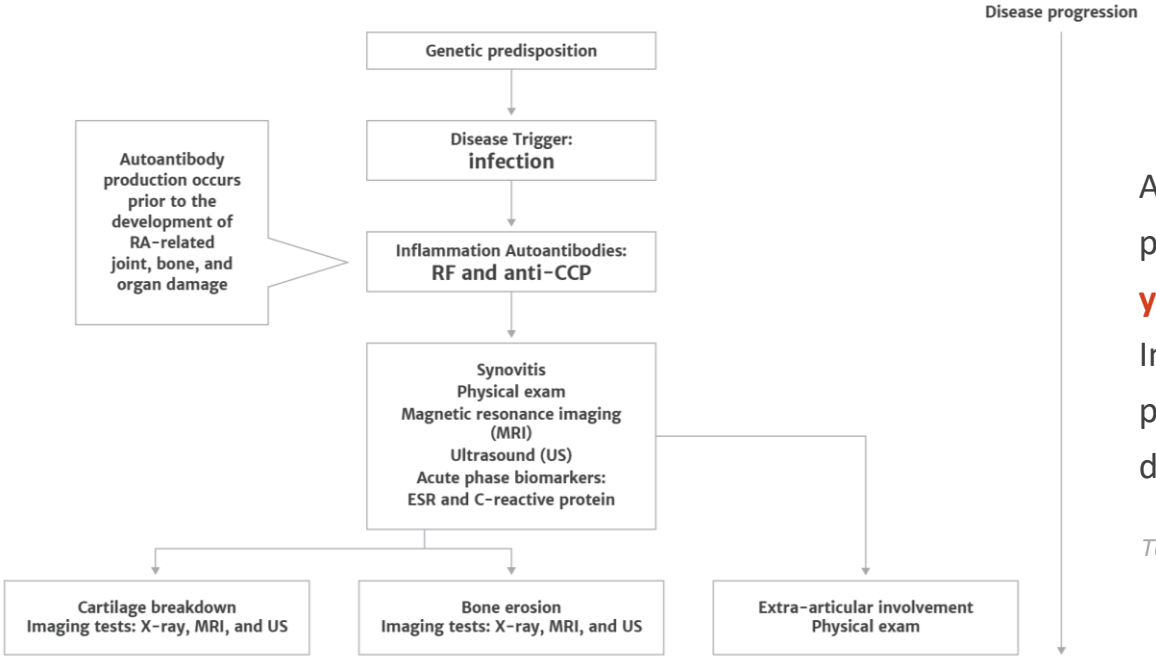
Accumulated **percentage positive samples** analyzed before onset of symptoms and at diagnosis.



Antibody levels, as **percentage of cut-off values** before and at disease onset

Kokkonen et al. Arth Res & Ther, 2011

Time Course of **Clinical RA Onset**



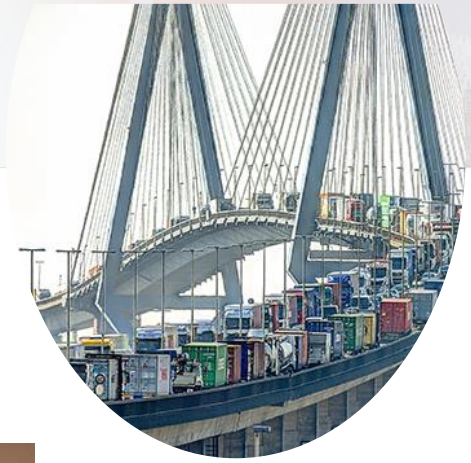
Anti-CCP antibodies in the serum of patients are present as early **as 12 to 14 years** prior to the development of RA. In these studies, **34%–40%** of the RA patients had anti-CCP+ results prior to disease onset

Taylor P et al. Autoimmune Dis, 2011

Concluding remarks

- ✓ Clinical Immunology:
  - ✓ Antibody formation **often precedes the clinical onset** of immune-mediated diseases.
  - ✓ Antibody assays **cannot be too sensitive.**
- ✓ **Translation to the clinical immunogenicity field:**
  - ✓ Ultrasensitive IG assays => a **careful and thorough data interpretation is needed** which takes into account the drug levels, the clinical manifestations and clinically relevant biomarkers.
  - ✓ Mention of ADA incidence on **drug label**: the sole percentage value is not sufficient.
- ✓ **Post-approval immunogenicity monitoring** of patients on long-term treatment:
  - ✓ The kinetics and type of antibody responses should be monitored to **assess the risk of developing a treatment-emergent immune response.**
  - ✓ Easy and sensitive method for early detection of loss of efficacy.
  - ✓ «Assessment of immunogenicity does not end at drug approval».

Outlook



Köhlbrand Brücke crossing the Elb River in Hamburg

Clinical relevance - Working group charter

Problem statement:

1. Lack of understanding of the disease activity and characterization
2. Correlation of ADA with clinical parameters (PK, efficacy and safety e.g. injection site reaction, infusion reaction, hypersensitivity)

In scope: Clinical relevance of ADA assays in the context of PK, BM, clinical signs and symptoms

Out of scope: Clinical trial design, non-clinical ADA data

Key Deliverables:

Re. 1) To collect examples for PK impact by ADA and its implication on clinical efficacy and safety readout

Re. 2) To collect examples for ADA-sensitive BM and its implication on clinical efficacy and safety readout

Re. 3) To discuss clinical disease activity scores with ADA/PK/BM

Re. 4) To discuss clinical impact of NAb assays versus ADA assays

Meetings schedule:

TC once per month and at least one F2F meeting per year.

The companies will take turns hosting the F2F meetings. Travel expenses should be covered by the individual companies.

What success looks like:

Publication/communication reflecting the principles to consider when interpreting clinical context of immunogenicity data

Project Leads:

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Thank you