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Scientific update WP1

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Anti-Biopharmaceutical Immunization:
Prediction and analysis of clinical relevance to minimize the risk

Dan Sikkema, GSK: Overall Project Coordinator

Marc Pallardy, INSERM UMR 996, France: IMI JU managing entity

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Biological treatments for chronic inflammatory diseases given parenterally can stimulate the immune system and give rise to anti-drug antibodies

Haemophilia A (HA)

Multiple Sclerosis (MS)

Rheumatoid Arthritis (RA)

Juvenile Idiopathic Arthritis (JIA)

Inflammatory Bowel disease (IBD)

Systemic Lupus Erythematosus (SLE)

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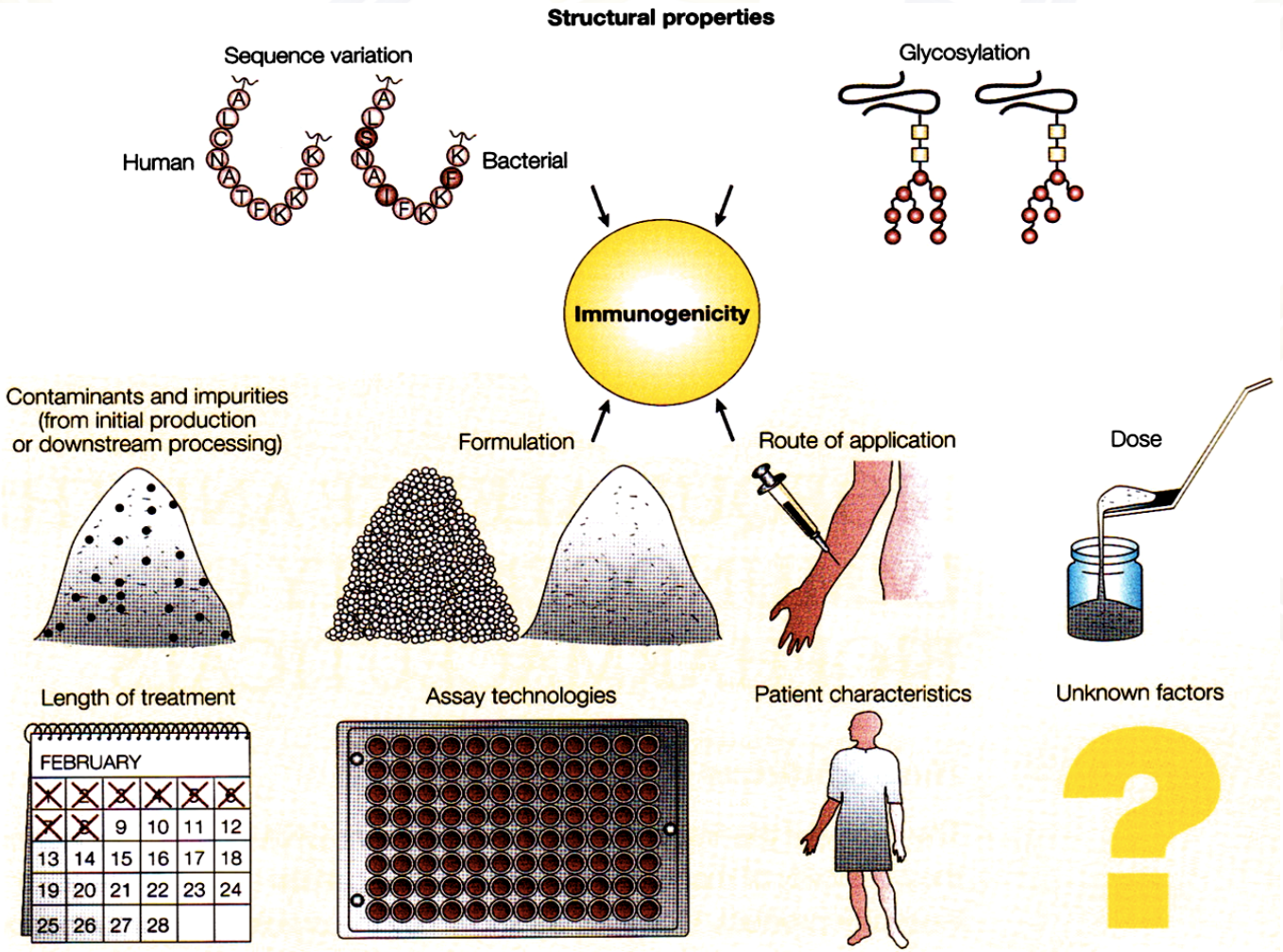

From Schellekens NEUROLOGY 61(Suppl 5) 2003

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ADA may differ depending on disease population

Differences in:

- immune status,
- underlying disease
- prior or concomitant treatments (e.g. immunosuppressive drugs)

Example ADA against rituximab

- non-Hodgkins lymphoma patients (11%),
- RA with methotrexate-treated (11%)
- Wegener's granulomatosist treated in combination with glucocorticoids (23%)

Rup et al. (2015) Clin Exp Imm

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Task WP1.1

Standardization of definitions and terminology related to immunogenicity, its prediction and associated clinical events.

Task WP1.2

Development and Validation of Standardized Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Assays

Task WP1.3

Cohorts management

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Accomplishment Task WP1.1

ABIRISK Consortium Recommendations for Terms and Definitions for Describing and Interpreting Unwanted Immunogenicity of Biopharmaceuticals

Rup et al.

Clinical and Experimental Immunology 2015 Sep;181:385-400

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Assay Development and Validation

IFNβ	Tociluzumab	Natalizumab	Anti-TNFs	Rituximab	Factor VIII

- New Natalizumab assay validation data is available
  - Assay protocols are available, reports need to be written
- Tocilizumab validation delayed
- IRB has produced human ADA
  - infliximab, natalizumab, rituximab and are in the process of producing human ADA for adalimumab.

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Assay Development and Validation

Assay	Status	Comments	Industry Contact	Affiliation	Sample sent to IRB	mAbs provided by IRB
IFNβ	Complete	Report complete	Elisa Bertotti	MERCK	Y	Y
Anti-TNFs	Complete	Labs selected, SOPs available	Mary Birchler	GSK	Y	Y/in progress
Rituxan	Complete	Report available, ready for testing	Amy Loercher	GSK	Y	Y
Factor VIII	Complete	Report available, ready for testing	Diana Martik	Pfizer	Y	Y
Tociluzumab	Ongoing	Protocols available	Keguan Chen	GSK	No	No
New Natalizumab	Ongoing	Protocols available	Keguan Chen	GSK	Y	Y

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Central Labs

Drug	PK	BAB	NAB
IFNb	n.a.	UDUS (Kathleen Wolfram)	Region H (Poul Eric Jensen)
Anti-TNFs	CRNS (Denis Mulleman)	INSERM (Salima Hacein-Bey)	BM
Anti FVIII*			
Natalizumab	IMU validation ongoing	BM/ED (Anna Lauren)	BM/ED
Rituximab	CRNS	GSK (Amy Loercher)	GSK
Tocilizumab	Not planned	BM	Not planned

*No central lab, assays have been cross-validated

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Interferon beta products used in MS

- IFNβ-1b

  E. coli produced
  non-glycosylated
  Cys17Ser, des-Met-1
  Betaferon, Extavia **250 µg SC every other day**

- IFNβ-1a

  Eukaryotic cell produced
  natural amino acid sequence
  glycosylated
  Avonex **30 µg IM 1 time/week**
  Plegridy (Pegylated Avonex) **125 µg SC 1 every other week**
  Rebif **22 or 44 µg SC 3 times/week**

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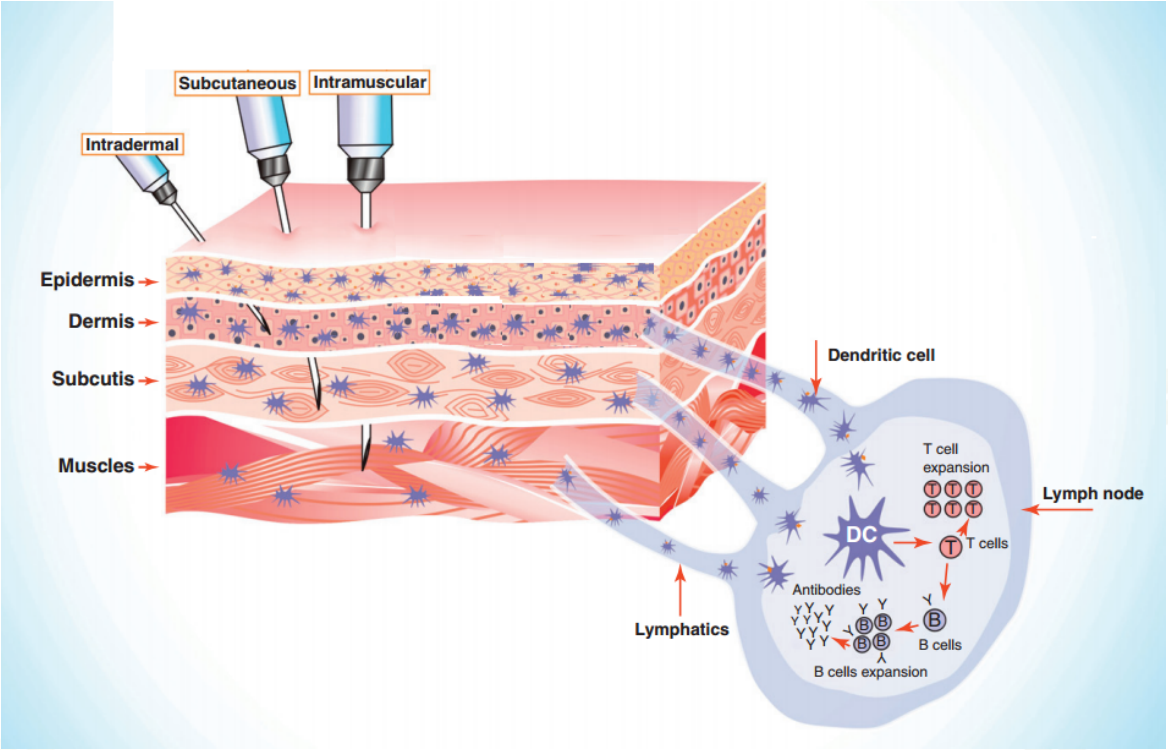
Neutralizing ADA (NAb) against IFNβ

- IFNβ-**1a** (s.c. Rebif®): 27-35%
- IFNβ-**1b** (s.c. Betafeson/Betaseron®): 27-53%
- IFNβ-**1a** (i.m. Avonex®): 2-19%



Govindappa K et al. Euro J Clin Pharmacol. 2015, Hegde NR et al. Drug discovery today. 2011

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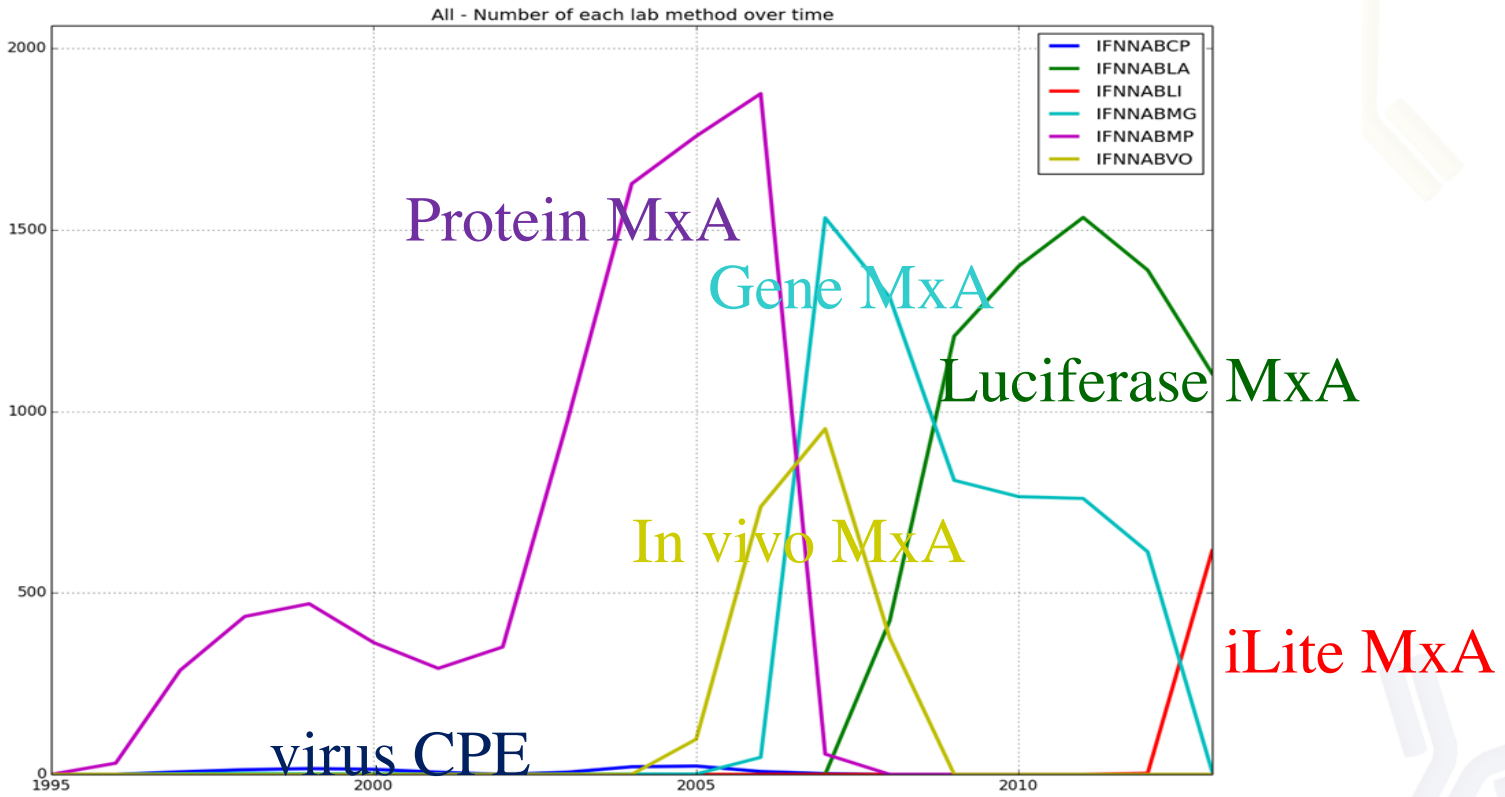
Anti-IFNβ ADA bioassays used in Europe over time



Data collected from Austria, Denmark, Germany, Spain, Sweden, Switzerland

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Redevelopment and revalidation of Luciferase based bioassays to measure nADA against IFNbeta

- Matrix effect: enhances IFNbeta activity
- Large variations between laboratories despite extensive efforts to harmonize the procedure (SOP, reagents, cells etc)
- Batch to batch variation in commercial growth arrested cell line

Hermanrud et al, manuscript in revision

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Assay validation parameters.

		LUC_{IMU}	LUC_{RH}	iLite
Cut-point type		Floating	Floating	Floating
Normalization factor (RLU)		557	4,532	35,014
Specificity cut-point		1.32	1.30	1.23
Sensitivity (LOD)	**ng/mL**	1520	814	320
Recovery (%)	**HPC**	80-116	81-124	87-113
	LPC	87-108	85-116	86-109
Inter-assay precision (CV %)	**HPC**	48	59	19
	LPC	50	57	25
	NC	21	29	35
Upper and lower acceptance criteria (RLU)	**HPC**	0-304	0-16,577	16,618-56,192
	LPC	0-967	0-27,158	17,690-102,357
	NC	853-3,501	5,898-44,833	17,013-229,200
Drug tolerance (IU/mL)	**HPC**	>1000	>1000	not determined
	LPC	100	500	

LOD = Lower Limit of Detection; HPC = high positive control; LPC = low positive control; NC = negative control; IU = international unit, IMU = Innsbruck Medical University, RH = Rigshospitalet, RLU = Relative Luminescence Units.

Corresponding drug tolerance concentration was for 100 IU/mL = 0.5 ng/mL, 500 IU/mL = 2.5 ng/mL, and > 1000 IU/mL > 5.0 ng/mL.

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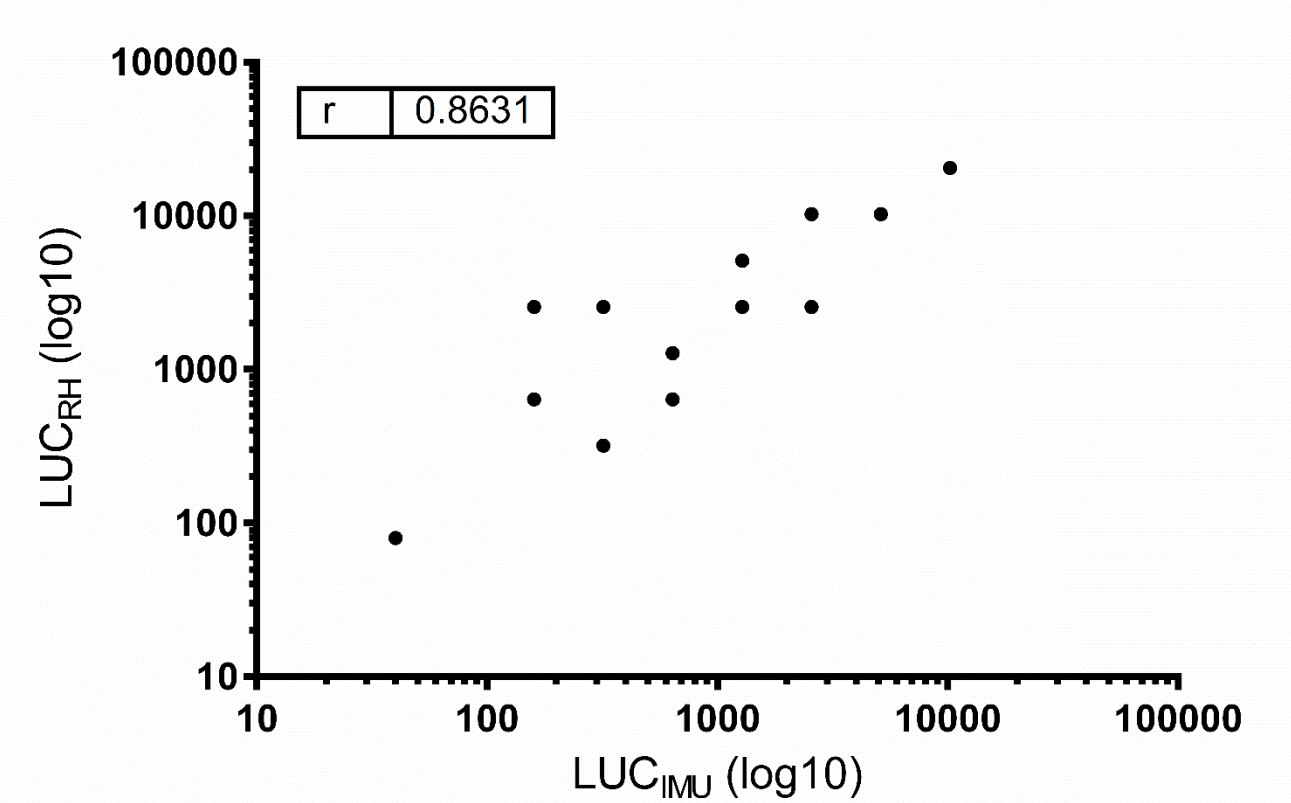
Correlation between sites



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Cut point or Kawade?

Cut point

- Established by test of baseline with at least 50 untreated patients sera or 50 sera from healthy controls

Kawade

- standard curve on all plates and results are adjusted to stimulation of the cells for each plate

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Kawade versus cut-point

a

Kawade	Cut-point		
	positive	negative	
	n		
positive	18	0	18
negative	7	5	12
	25	5	30

LUC_{RH}

b

Kawade	Cut-point		
	positive	negative	
	n		
positive	18	0	18
negative	2	10	12
	20	10	30

LUC_{IMU}

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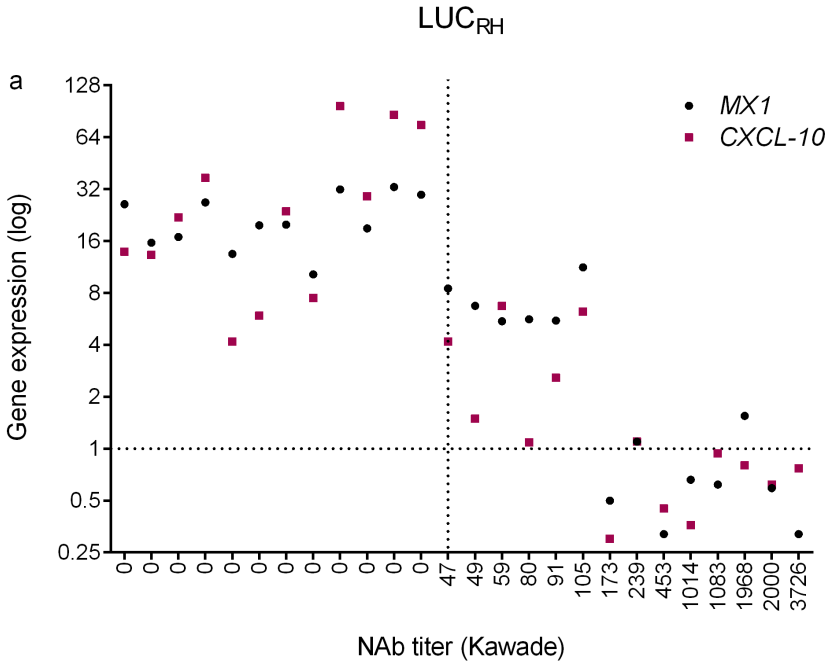
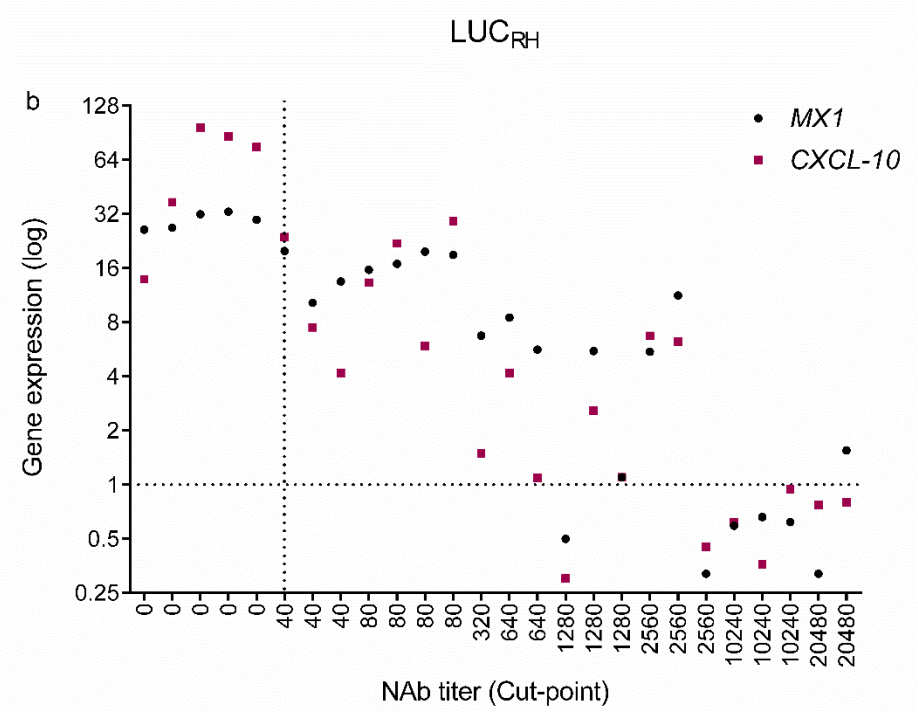
Kawade and Cut-point versus clinically relevant threshold





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Accomplishments Task 1.3

PROSPECTIVE COHORTS

RETROSPECTIVE COHORTS – WP4

CROSS SECTIONAL COHOHRTS – WP2

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Status 5 Jan 2016

Cohort/No patients	No centres	Active centres by eCRF	No included by report	% completed
MS (200)	16	12	149	75%
RA (250)	25	21	206	82%
IBD (200)	23	13	192	96%
JIA (200)	47	34	100	50%

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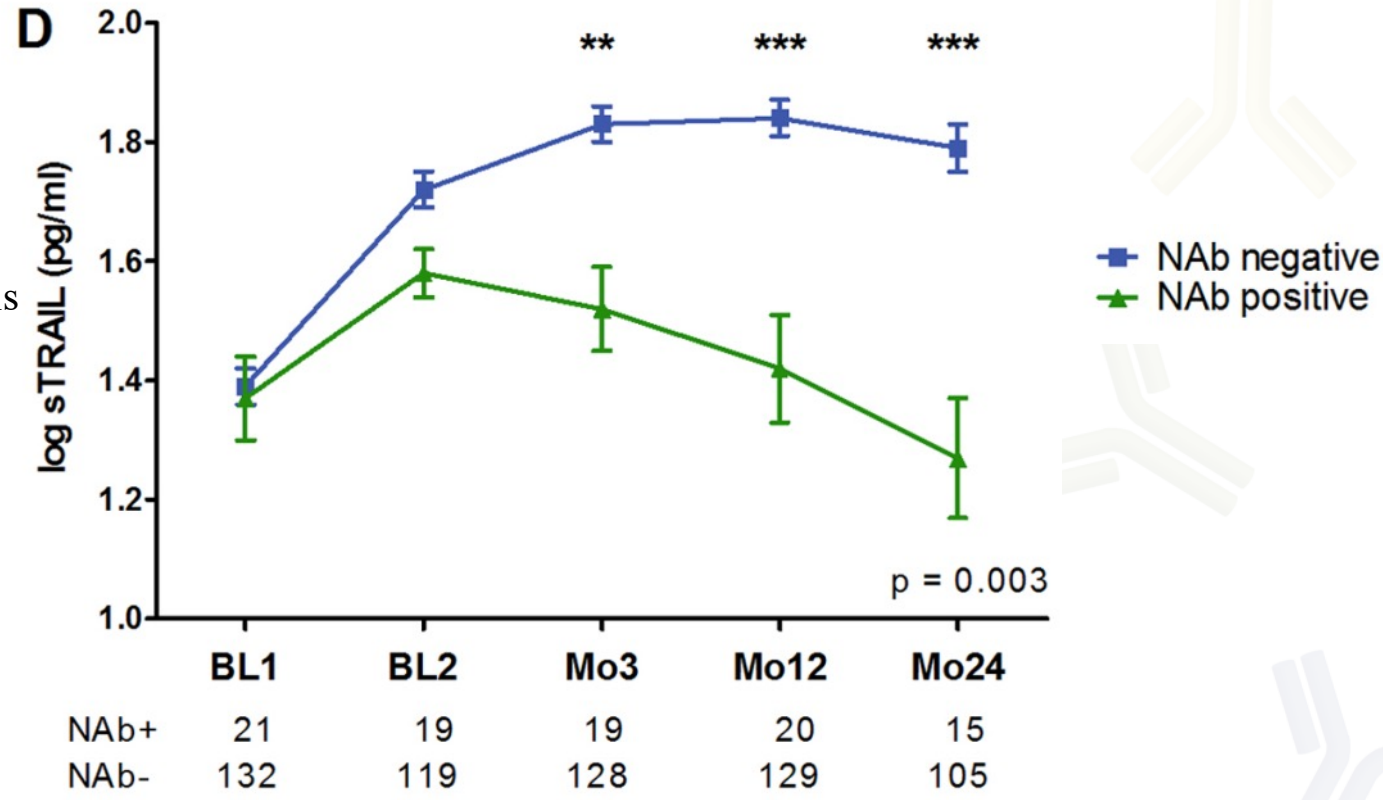
Early prediction

sTRAIL:
soluble tumor necrosis factor-related apoptosis-inducing ligand



Hegen (2013) MSJ

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WP4 Publications – MS Retrospective Data

Publication (Lead WP4 Partner)	KI (Sweden)	IMU (Austria)	Region H (Denmark)	TUM-Med (Germany – Mun)	UDUS (Germany-Duss)	UHBS (Switzerland)	VHIR (Spain)
Wave 1: Descriptive ADA testing (KI)	X	X	X	X	X	X	X
Wave 2: Factors associated with ADA incidence (restricted variable list) (INSERM)	X	X	X				
Wave 2: Factors associated with ADA incidence (extensive variable list) (INSERM)	X	X	X?				
Wave 2: Predictive model for ADA incidence (extensive variable list) (INSERM)	X	X	X?				
Wave 3: HLA associations with ADA status) (KI)	X			X			
Wave 4: Genetic association study (INSERM)	X			X			

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WP4 Publications – HA Retrospective Data

Publication (Lead WP4 Partner)	INSERM (France)	UKB (Germany – Bonn)	KGU (Germany-Frankfurt)	PEI (Germany)
Wave 1: Descriptive analysis of factors associated with ADA positivity **(INSERM)**	X	X	X?	X
Wave 2: Factors associated with ADA incidence (extensive variable list) **(INSERM)**		X	X?	X?
Wave 3: HLA association study?) **(INSERM)**		X?		
Wave 4: Genetic association study **(INSERM)**		X?		

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WP4 Publications – RA Retrospective Data

Publication (Lead WP4 Partner)	AMC (Netherlands)	APHP (France)	KI (Sweden)	LUMC (Netherlands)
Wave 1: Descriptive analysis of factors associated with ADA positivity **(INSERM)**				
Wave 2: Factors associated with ADA incidence (extensive variable list) **(INSERM)**				
Wave 3: HLA association study?) **(INSERM)**				
Wave 4: Genetic association study **(INSERM)**				

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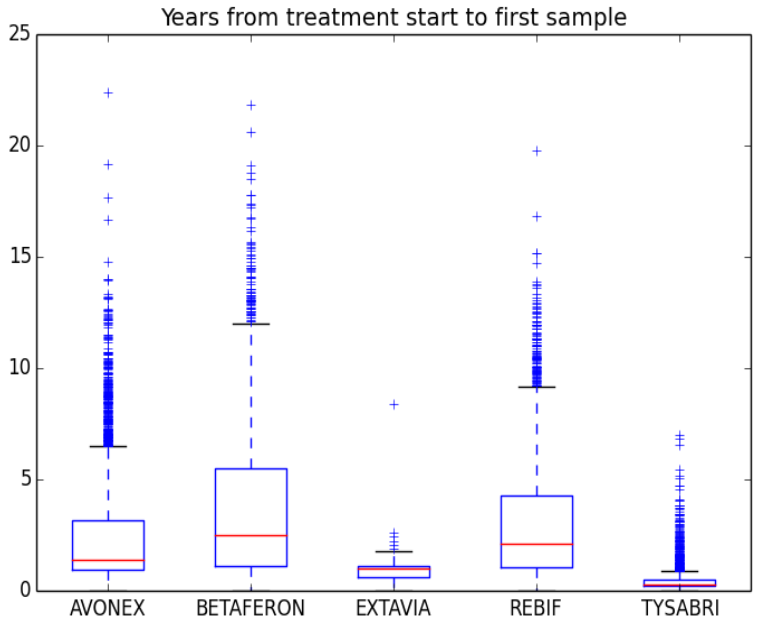
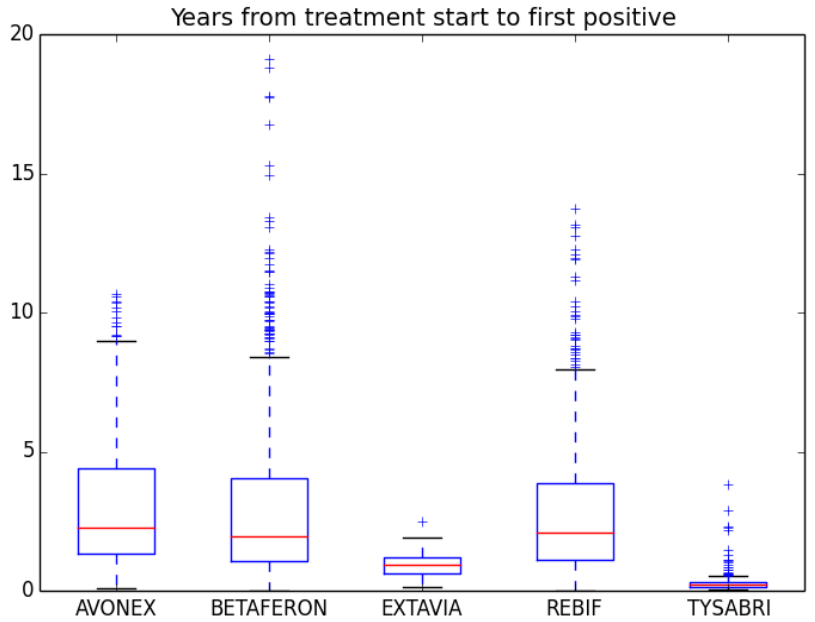
Time to detect first positive sample

patients (n=20,695), samples (n=42,555 samples)





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Potential harmfulness of ADA

- **Anti-Erythropoietin antibodies and Pure Red Cell Aplasia**
  (Rossert et al., 2004, J Am Soc Nephrol 15: 398)
- **Natalizumab ADA positive fatal case**

  (Svenningsson et al., 2013, Neurology)
- **IFNbeta nADA cross-react with endogenous IFNbeta**

  (Sominanda et al. (2010) Arch Neurol)
- **Important information for future B cell memory to know if ADA exist (similar to vaccination booster dose)?**

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Summary

- Terms and definition: published
- Validation and comparison of different IFNβ NAb assays: published
- Validation of assays for all other drugs near completion
- Human monoclonal ADA produced
- Retrospective and prospective samples started to be analyzed

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The EU/IMI consortium

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SME: SciCross

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