

Immunogenicity of anti TNF biopharmaceuticals in rheumatic diseases: the causes and the consequences



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Disclosures

- Grant for research: Abbott
- Consultancies: Schering Plough
- Payment for lectures: UCB, MSD, Amgen, Pfizer, Roche
- Co-investigator for clinical trials: Abbott, Roche, BMS, Pfizer, UCB, Schering-Plough

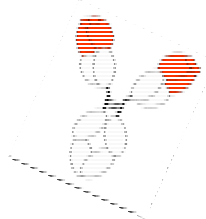
Agenda

1. Dose response relationship
2. Causes of immunisation
3. Immunisation to monoclonals clinical and pharmacological consequences & Factors that can help clinician to reduce immunisation: methotrexate and dosing regimen
4. Practical use of drug and ADA measurements.

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Even after careful drug development, an interindividual variability in response is observed



Drug
standard
dose



**Dose-
dependent
adverse
effects**

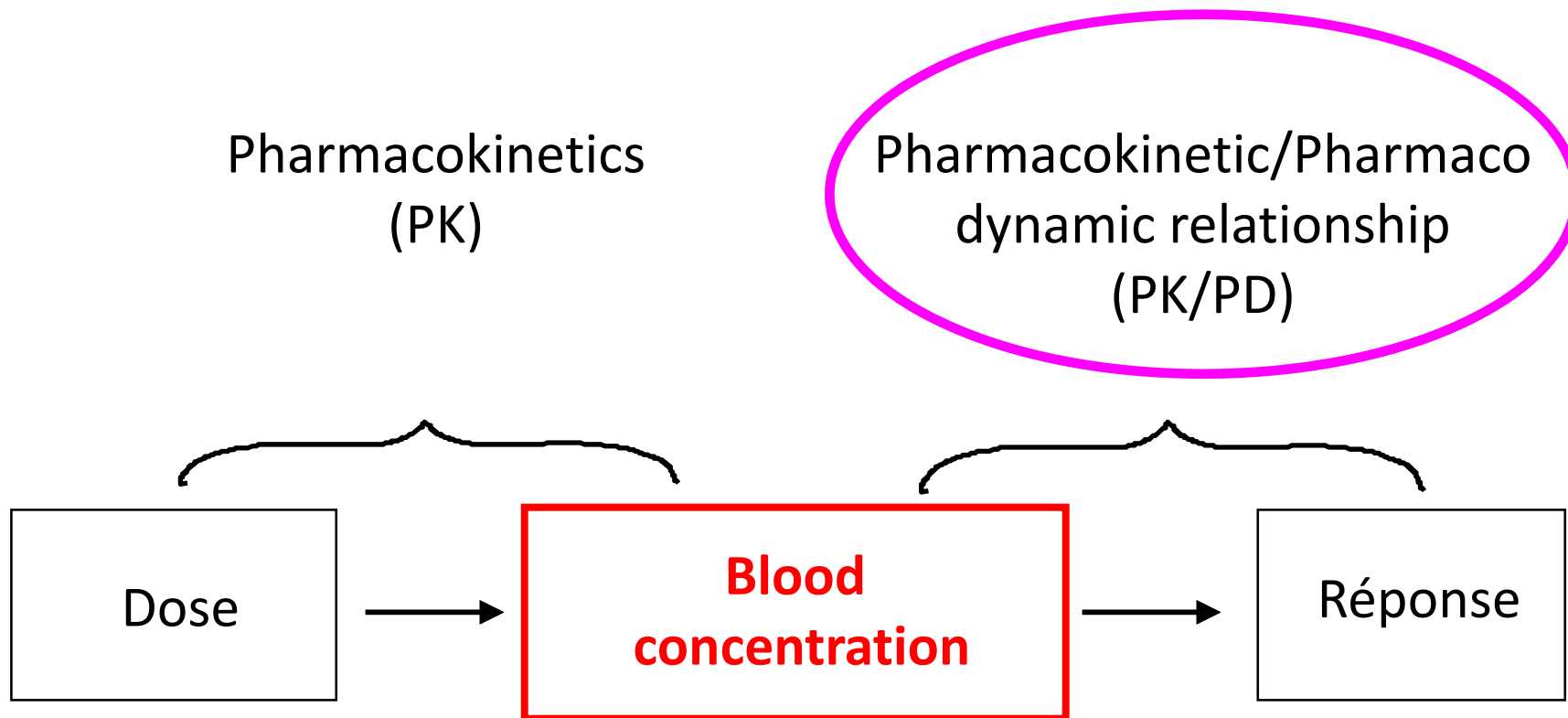


**Expected
response**

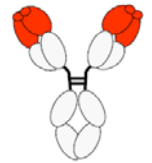
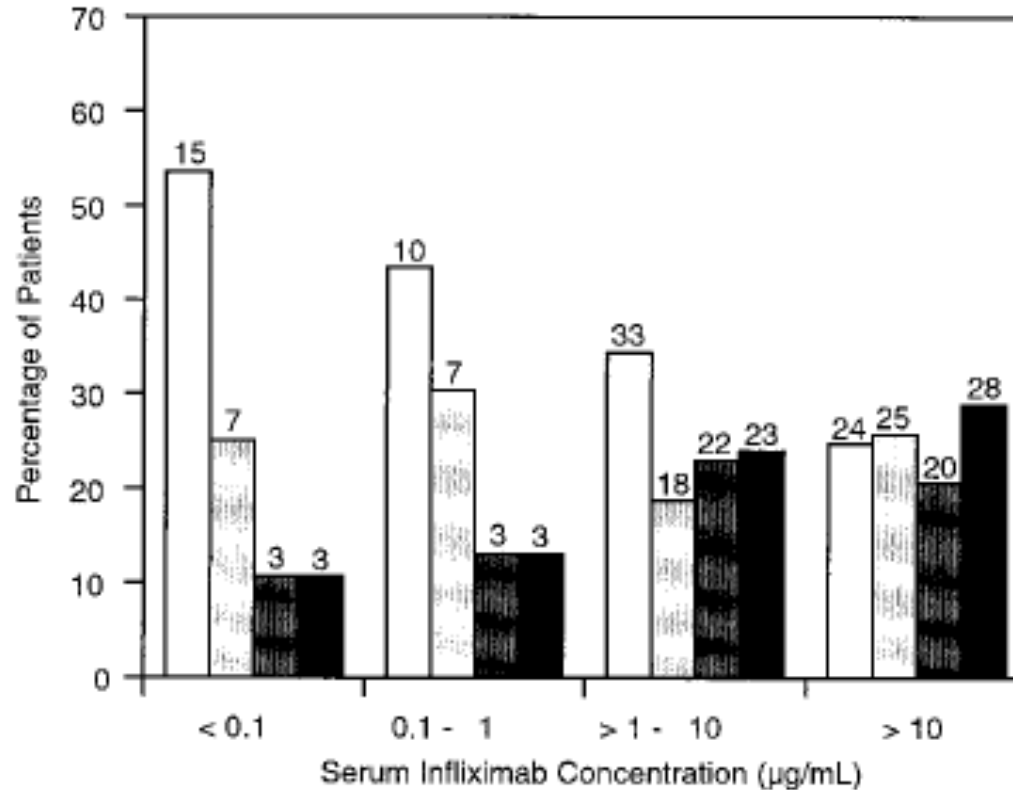


**Insufficient or
no response**

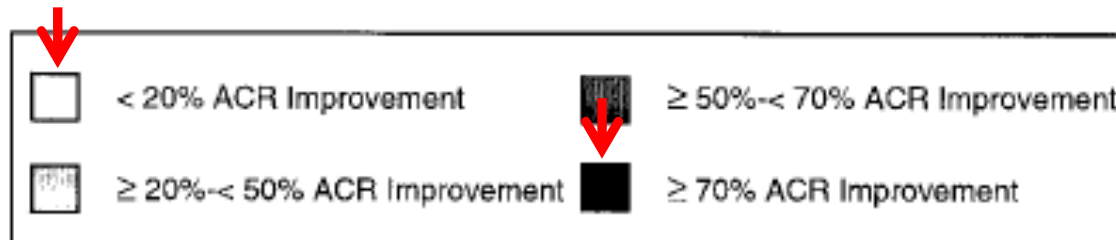
Dose-response relationship



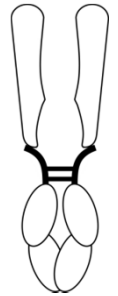
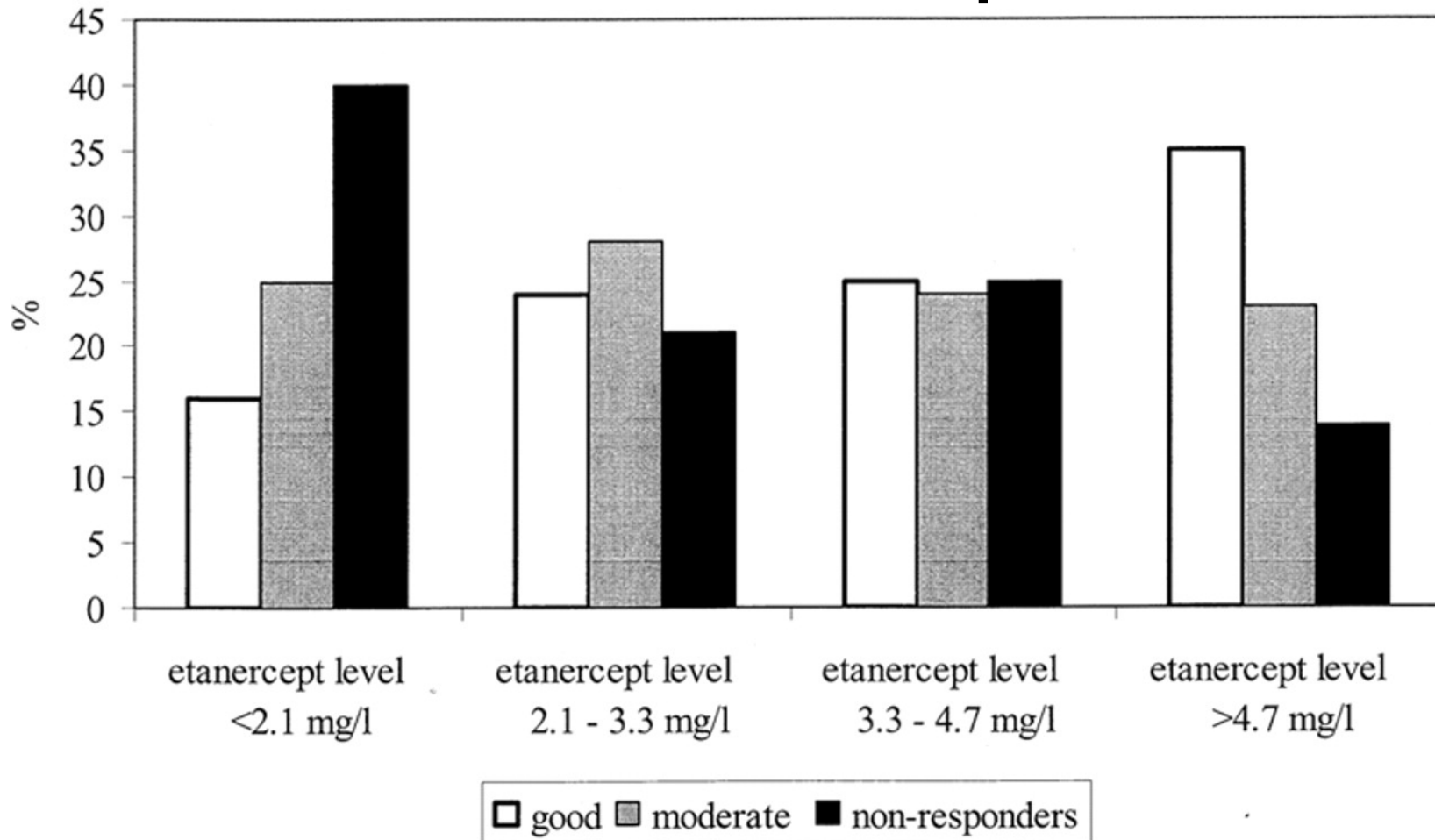
Concentration-response relationship



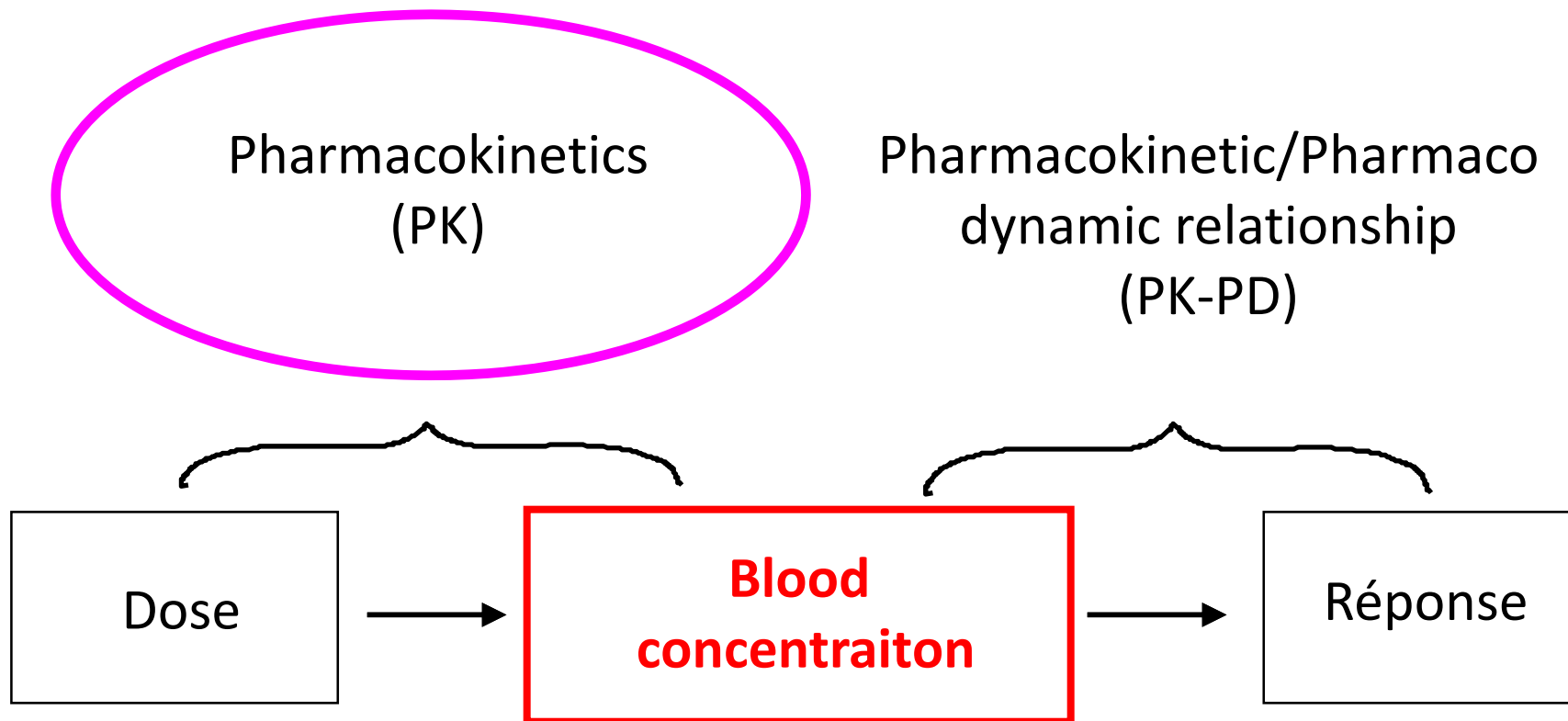
RA patients
Infliximab



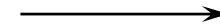
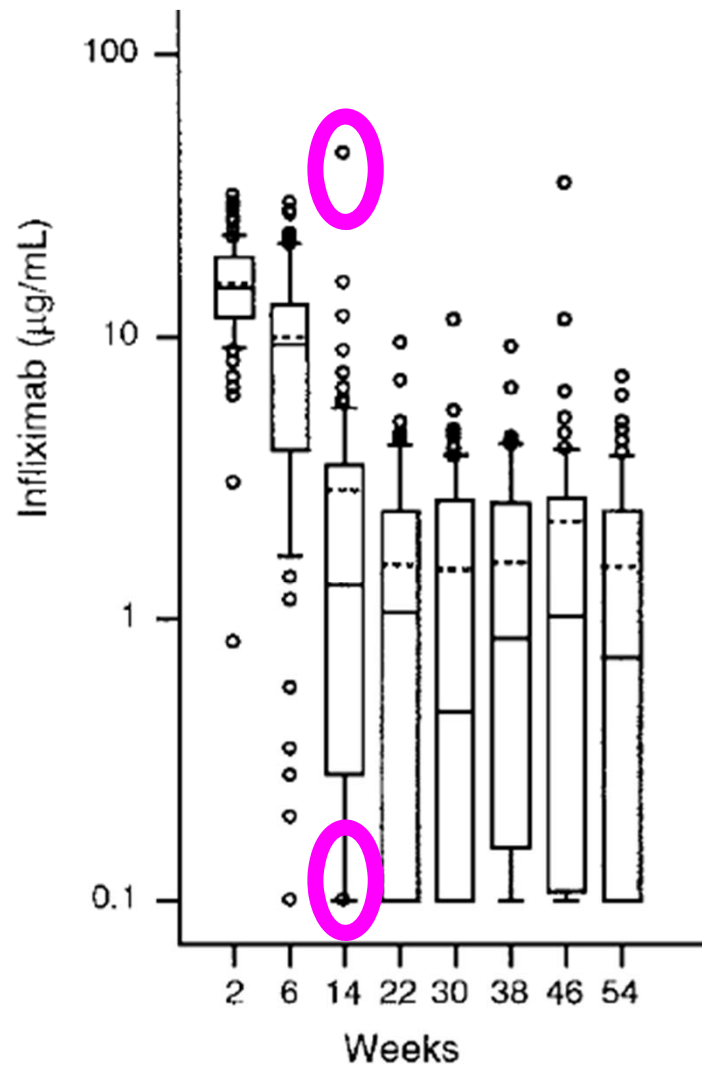
Concentration-response relationship



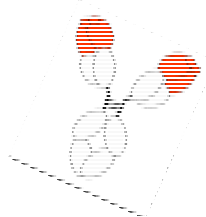
Dose-response relationship



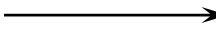
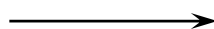
Pharmacokinetic variability



Even after careful drug development, an interindividual variability in response is observed



Drug
standard
dose



**Dose-
dependent
adverse
effects**

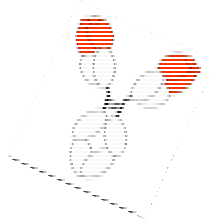


**Expected
response**

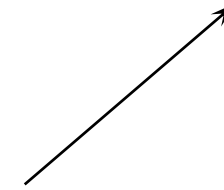
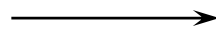


**Insufficient or
no response**

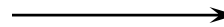
One of the tools of clinical pharmacology is the measurement of blood concentrations of treated patients



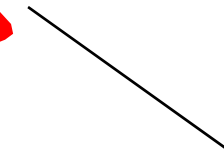
Drug
standard
dose



Dose-
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adverse
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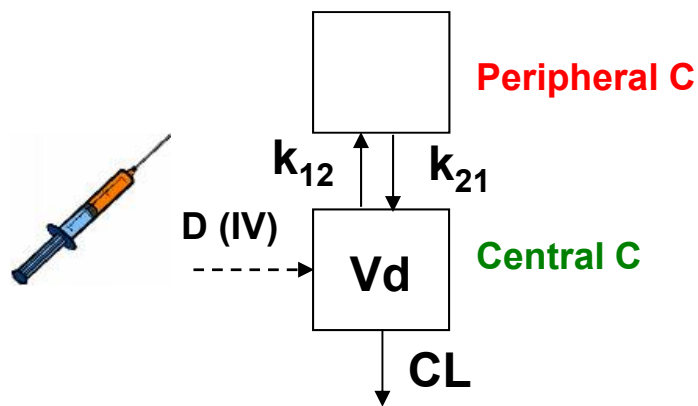
Expected
response



Insufficient or
no response

Pharmacokinetic Modelling

Two compartment model



V_d : Distribution volume

CL : clearance

k_{12}, k_{21} : distribution constants

$T_{1/2-\beta}$: Elimination half-life

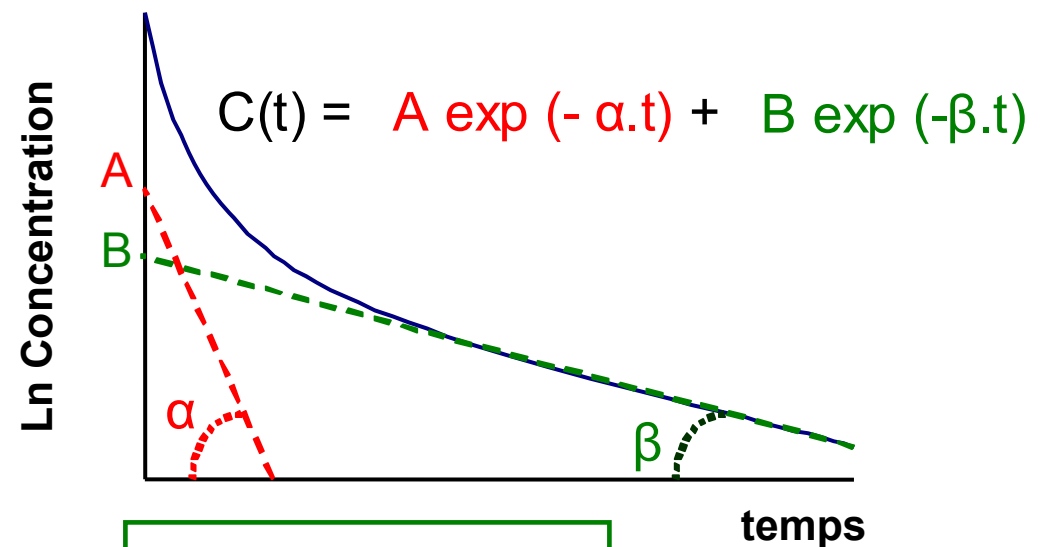
$$T_{1/2} \propto \frac{V_d}{CL}$$

$$dC_C/dt = -(CL/V_d) \cdot C_C - k_{12} \cdot C_C + k_{21} \cdot C_P$$

$$dC_P/dt = k_{12} \cdot C_C - k_{21} \cdot C_P$$

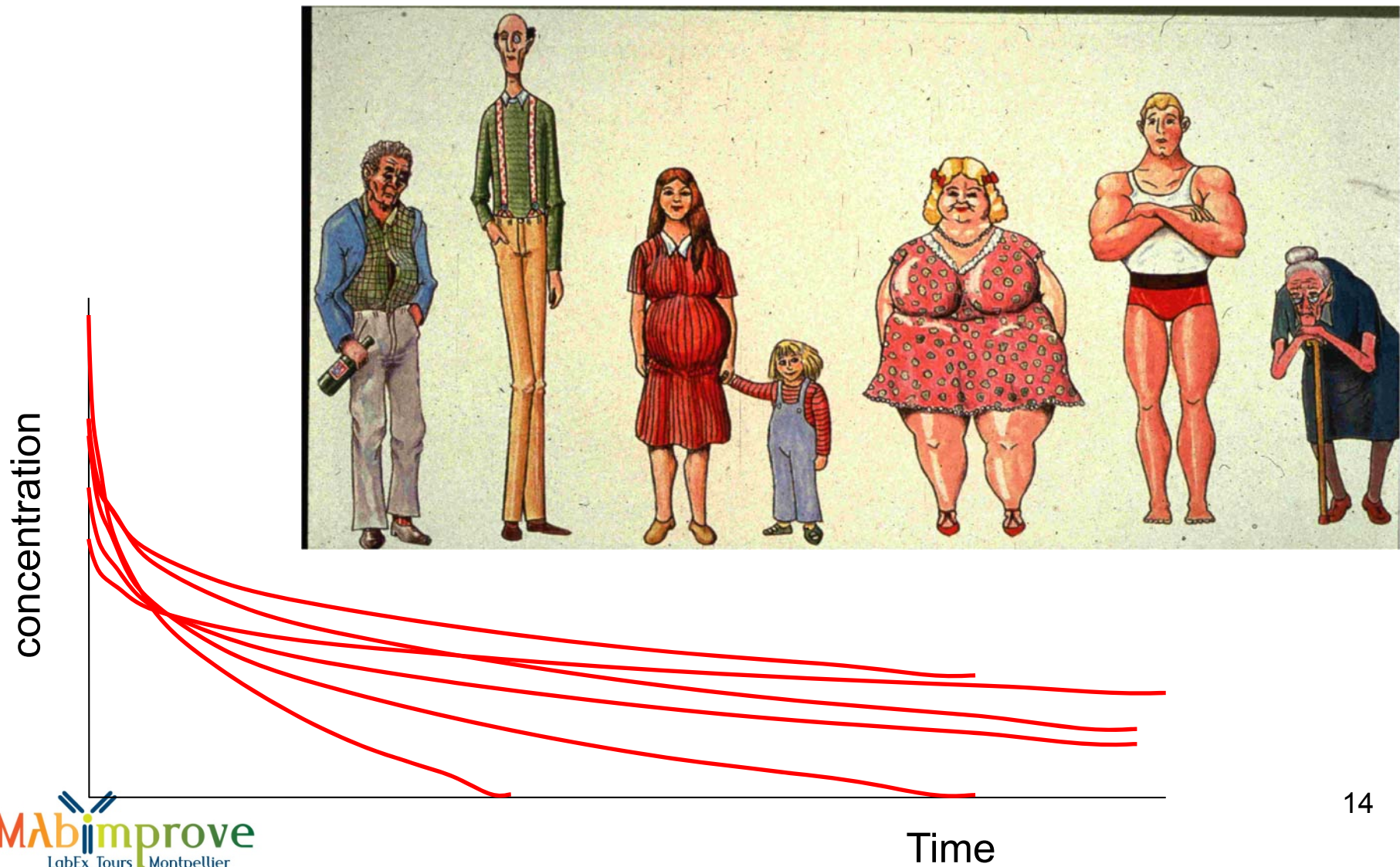
$$C_C(0) = D/V_d$$

$$C_P(0) = 0$$



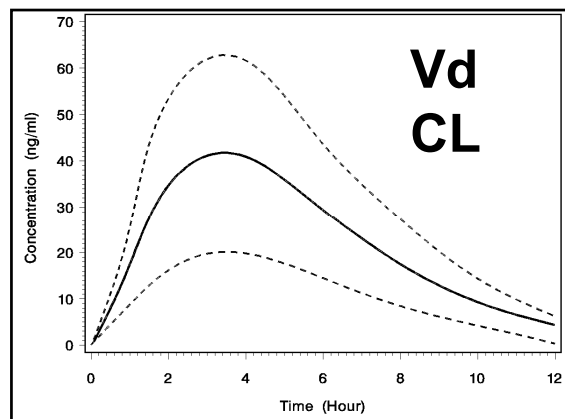
$$T_{1/2-\beta} = \ln(2) / \beta$$

Pharmacokinetic variability : population approach



Pharmacokinetic variability : population approach

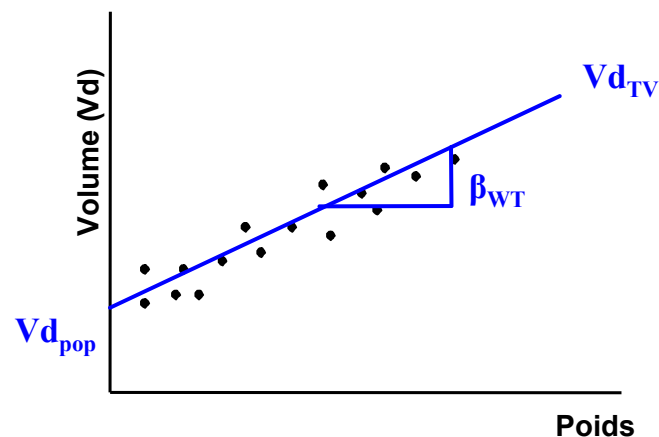
Structural model



$$C(t) = f(\theta, t)$$

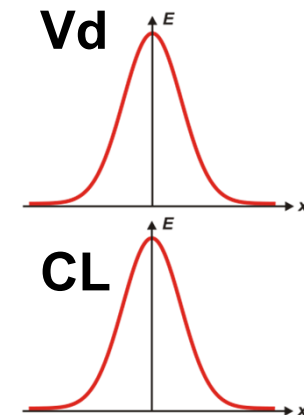
$$\theta = (Vd, CL)$$

Model with covariates



$$Vd_{TV} = Vd_{pop} + \beta_{WT} \cdot WT$$

interindividual model



$$\theta_i = \theta_{TV} + \eta_i$$

$$\eta_i \sim N(0, \omega^2)$$

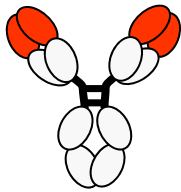
Individual parameters = typical parameters + covariate effect + random effect



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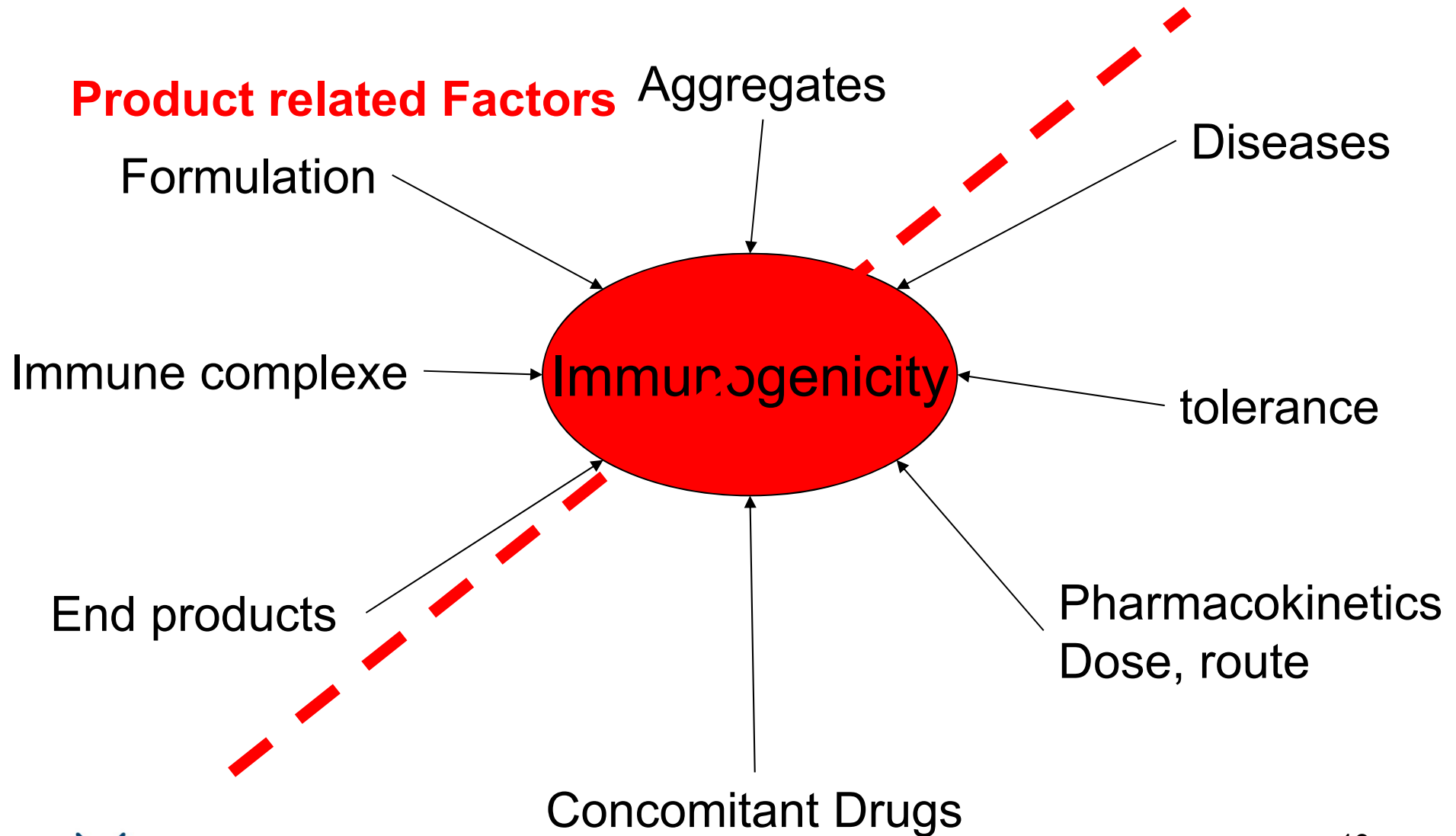
Causes of immunisation



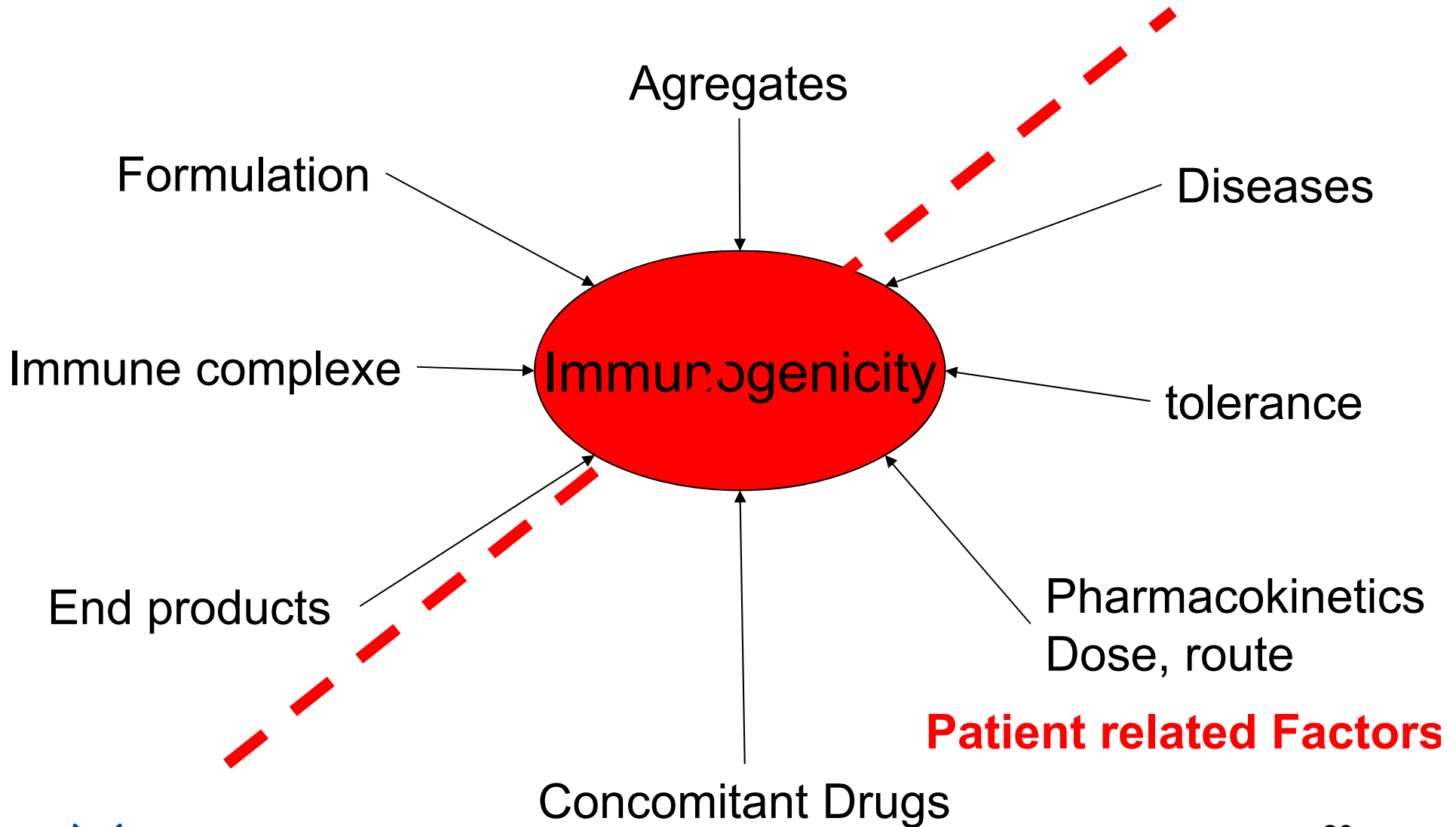
Causes of immunisation



Candidate factors of immunisation



Candidate factors of immunisation



Agenda

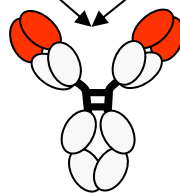
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Two conditions

- Rheumatoid Arthritis
 - Auto immune disease
 - Peripheral joints
 - Bone/destruction destruction
- Spondylarthropathies
 - Inflammatory disease
 - Axial>> peripheral joints
 - Ankylosing (axial)

– DMARDS +++++
(methotrexate)

DMARDS + (peripheral)
(Methotrexate)



Anti TNF-alpha

« ATI* » cohort

Ducourau *et al. Arthritis Research & Therapy* 2011, **13**:R105
<http://arthritis-research.com/content/13/3/R105>



RESEARCH ARTICLE

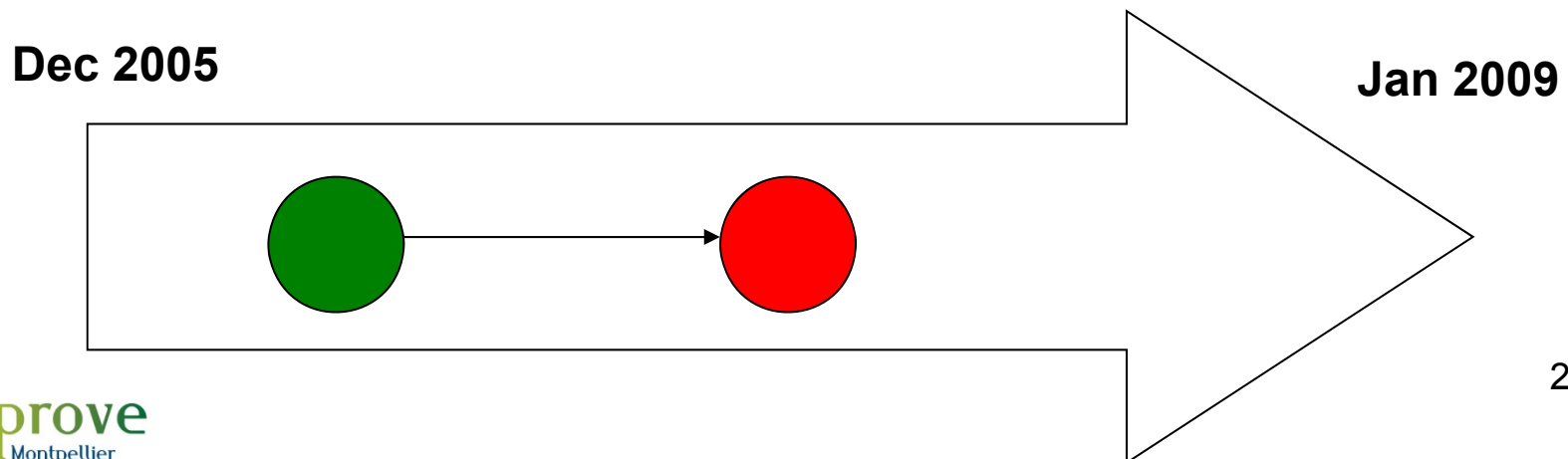
Open Access

Antibodies toward infliximab are associated with low infliximab concentration at treatment initiation and poor infliximab maintenance in rheumatic diseases

Emilie Ducourau^{1,2†}, Denis Mulleman^{1,2*†}, Gilles Paintaud^{1,3}, Delphine Chu Miow Lin^{1,2}, Francine Lauféron^{1,2}, David Ternant^{1,3}, Hervé Watier^{1,4} and Philippe Goupille^{1,2}

ATI cohort

- Retrospective analysis (december 2005-january 2009)
- RA and SpA
- Trough serum infliximab concentration and ATI at each visit

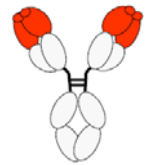


Results

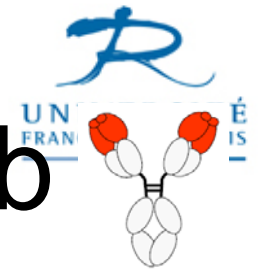
- 108 patients: 17 RA and 91 SpA
- ATI detectable in **21** patients during follow-up
 - 7 (**41%**) with RA,
 - 14 (15%) with SpA
- Median time for ATI detection was **3.7** months

Infusion reaction to infliximab

- 12 patients
 - Rashes
 - Hyperthermia
 - Chills
 - Angio-oedema
 - Tachycardia
- 11/12 ATI positive
 - 4 required IV corticosteroids and antihistamine
 - 2 required antihistamine
 - 4 no treatment required
 - 1 Guillain-Barré syndrome

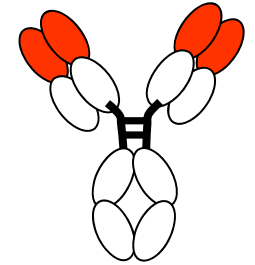


Infusion reaction to infliximab



Cause of discontinuation	ATI _{pos} (n = 18)	ATI _{neg} (n = 41)
Treatment failure		
Primary failure	2 (11%)	23 (56%)
Secondary failure	3 (17%)	8 (20%)
Infusion reactions	9 (50%)	1 (2%)
Adverse events	1 (5.5%)	6 (15%)
Other	1 (5.5%)	2 (5%)
Lost to follow-up	2 (11%)	1 (2%)

Immunogenicity of infliximab in Spondylarthropathies



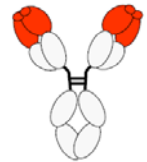
- **Low risk of immunisation in patient with concomitant Methotrexate**

MTX treatment	SpA (n = 91)		
	ATI _{pos}	ATI _{neg}	P value
MTX+	0	25	0.03
MTX-	14	52	

Methotrexate in Rheumatoid Arthritis

THERAPEUTIC EFFICACY OF MULTIPLE INTRAVENOUS INFUSIONS
OF ANTI-TUMOR NECROSIS FACTOR α MONOCLONAL ANTIBODY
COMBINED WITH LOW-DOSE WEEKLY METHOTREXATE IN
RHEUMATOID ARTHRITIS

RAVINDER N. MAINI, FERDINAND C. BREEDVELD, JOACHIM R. KALDEN, JOSEF S. SMOLEN,
DIANA DAVIS, JOHN D. MACFARLANE, CHRISTIAN ANTONI, BURKHARD LEEB,
MICHAEL J. ELLIOTT, JAMES N. WOODY, THOMAS F. SCHAIBLE, and MARC FELDMANN



ATI In RA patients receiving infliximab at 3 mg/Kg

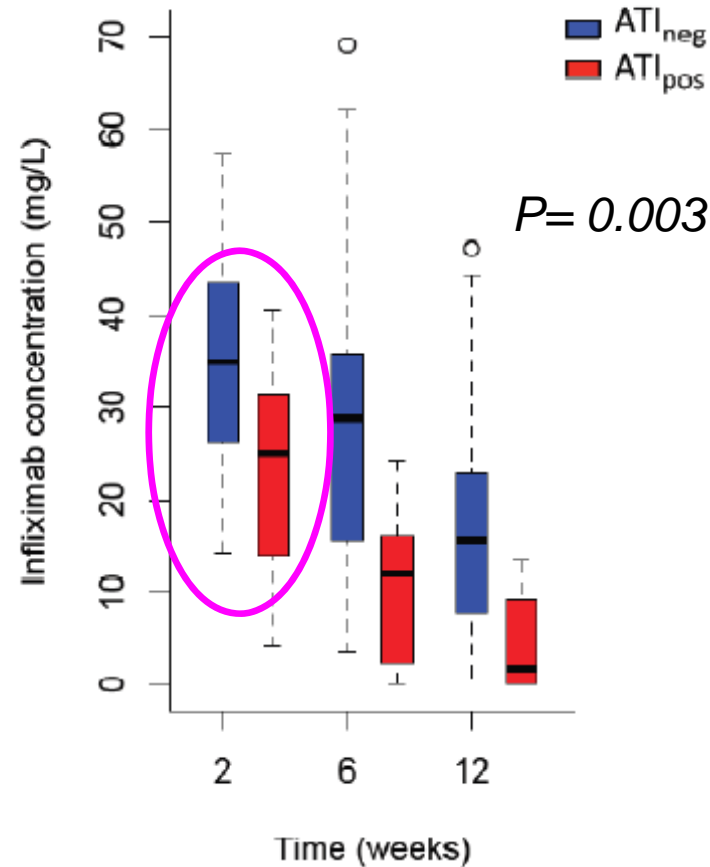
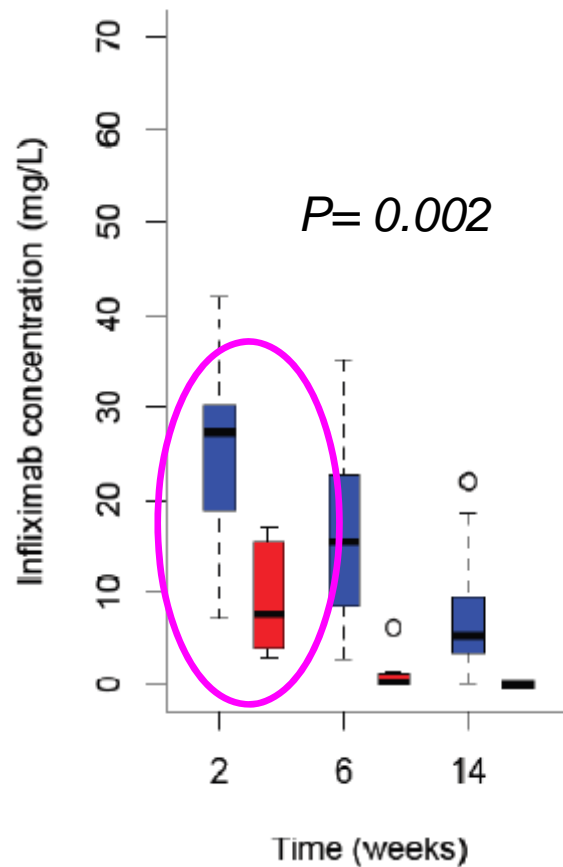
MTX -
21,0%

MTX +
7,0%

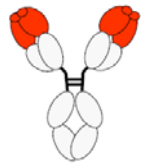
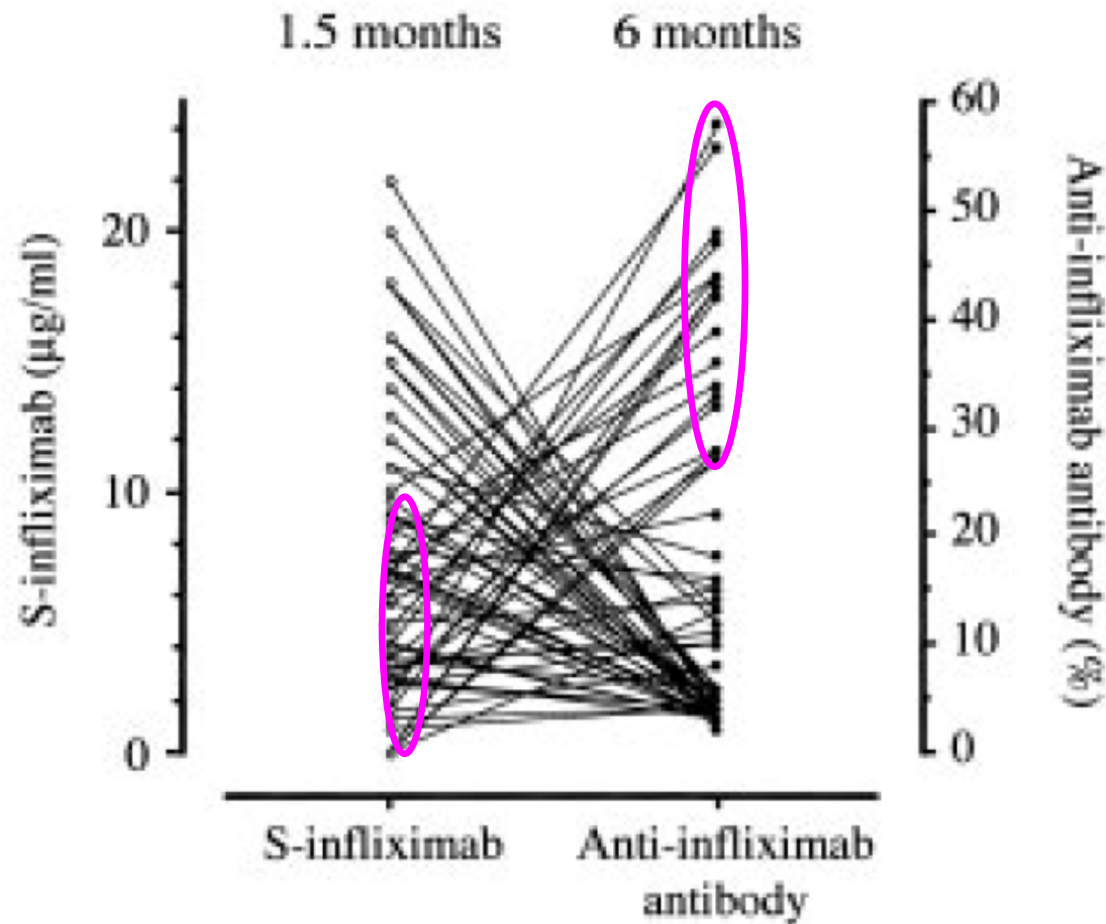
Immunogenic concentration threshold

RA (n=17)

SpA (n=91)



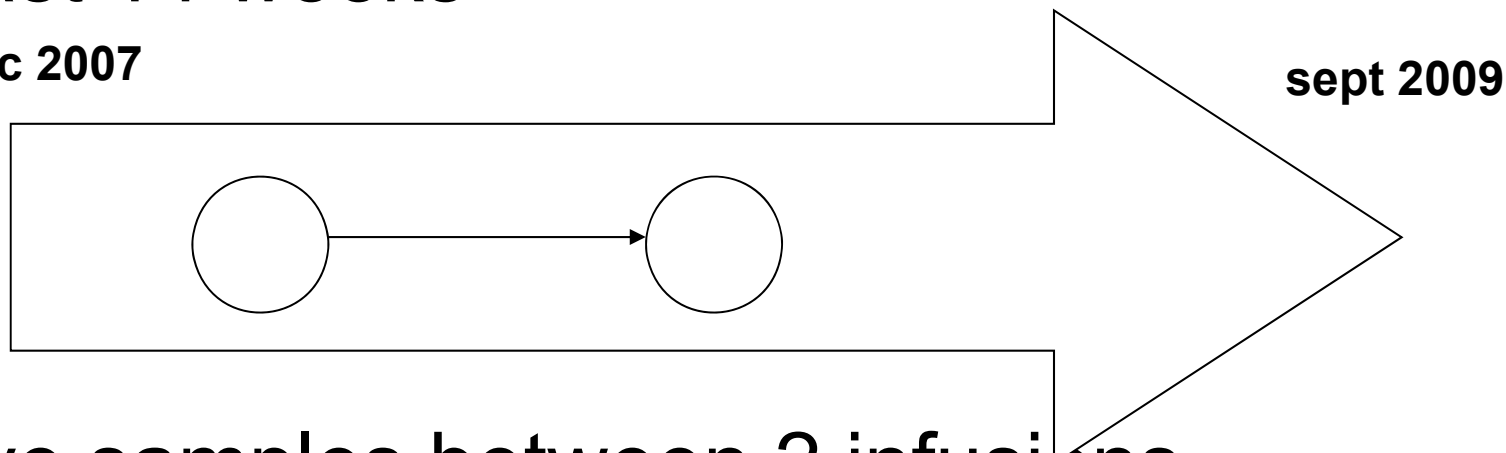
Immunogenic concentration threshold



FAKIR* study

- Prospective study (Western France University Hospitals Network)
- RA patients treated with infliximab for at least 14 weeks

Dec 2007

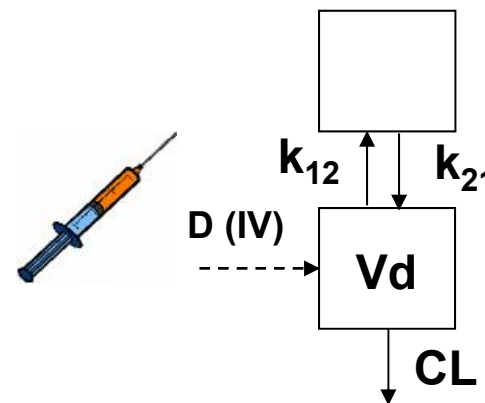


sept 2009

- Five samples between 2 infusions

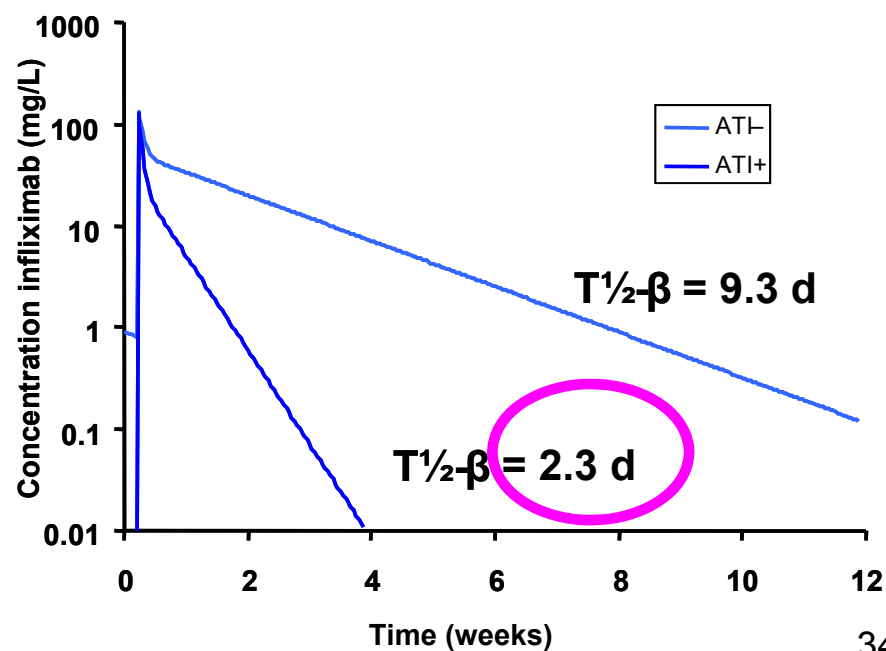
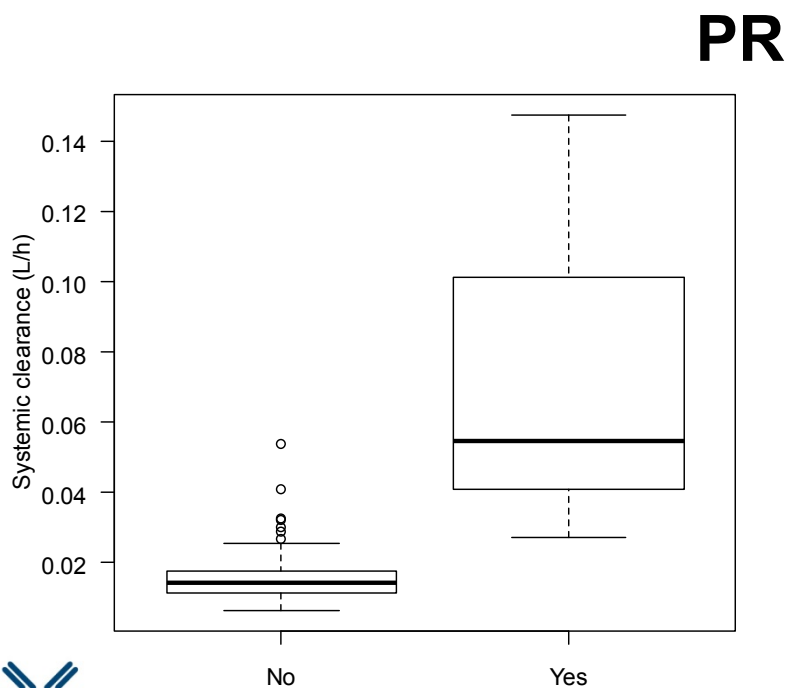
Results

- 84 patients
- 412 sera available.
- ATI were detected in the pre-infusion serum of 3 patients
- Two-compartment model



Results

- CL was dramatically increased (5 fold) in ATI+ patients as compared to ATI- patients



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Situation 1

Inadequate disease control

- No initial treatment response, secondary loss of effectiveness, or inadequate effectiveness: switch to another biologic agent or increase the dosage?



SWITCH TO ANOTHER
BIOPHARMACEUTICAL ?

INCREASE
THE
DOSAGE?

Disease control

	Optimal	Acceptable	Inadequate
High	Dose reduction	Dose unchanged [*]	Switch
Target range	Dose unchanged	Consider increasing the dose ^{#*}	
Low	Dose unchanged [§]	Increase the dose [#]	

Fig. 1. Decision algorithm for therapeutic drug monitoring in patients receiving TNF- α antagonist therapy.

Disease control

		Optimal	Acceptable	Inadequate
Serum level	High	Dose reduction	Dose unchanged [*]	Switch
	Target range	Dose unchanged	Consider increasing the dose [#]	
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Fig. 1. Decision algorithm for therapeutic drug monitoring in patients receiving TNF- α antagonist therapy.

Disease control

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Serum level	High	Dose reduction	Dose unchanged [*]	Switch
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Situation 2

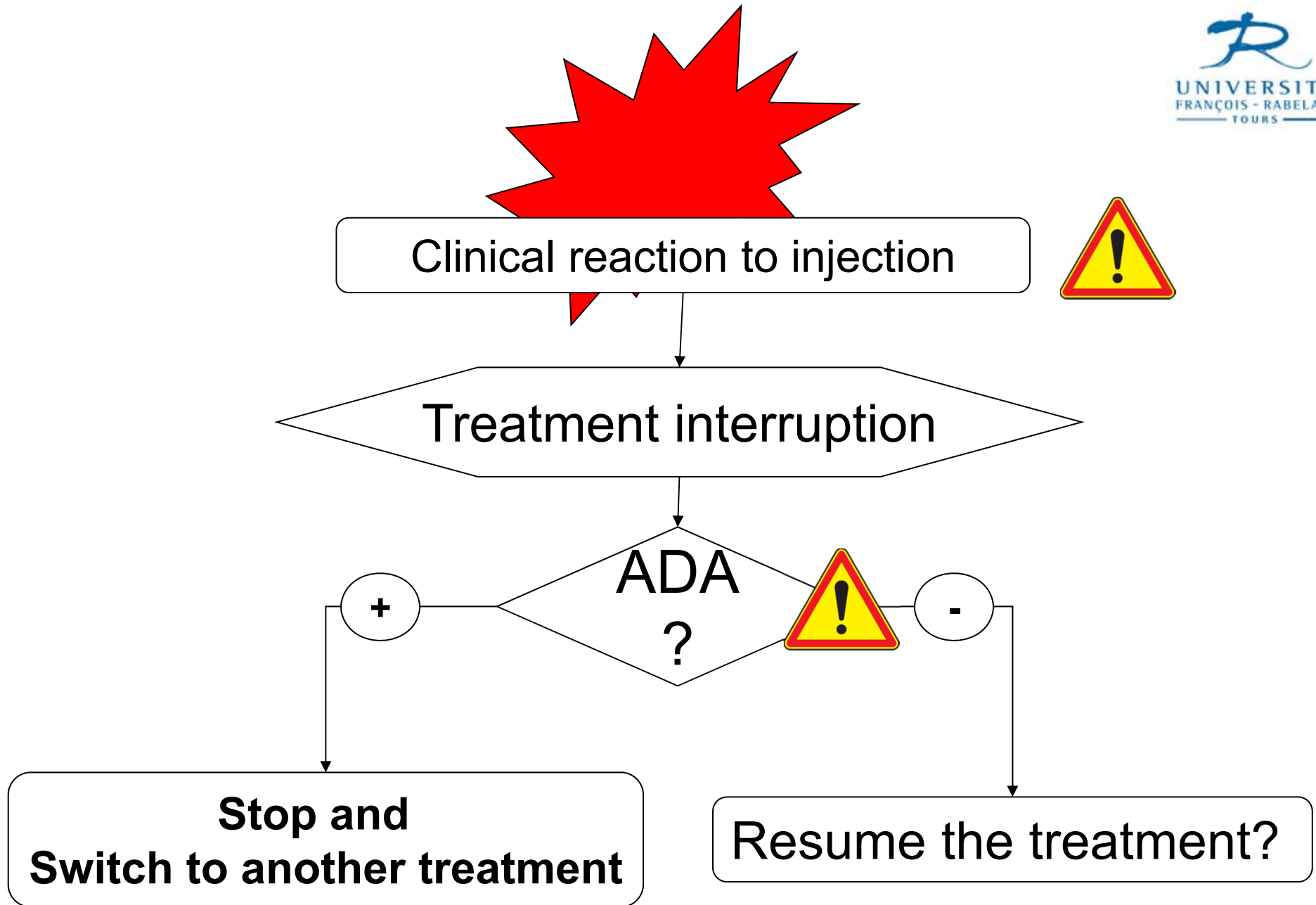
Clinical adverse drug reaction

- Continue the same drug or switch to another TNF- α antagonist?



SWITCH?

CONTINUE THE
SAME DRUG?



Situation 3

Optimal disease control

- Good treatment response: should the dosage be decreased??



DECREASE
THE
DOSAGE?

		Disease control		
		Optimal	Acceptable	Inadequate
Serum level	High	Dose reduction	Dose unchanged [*]	Switch
	Target range	Dose unchanged	Consider increasing the dose ^{##}	
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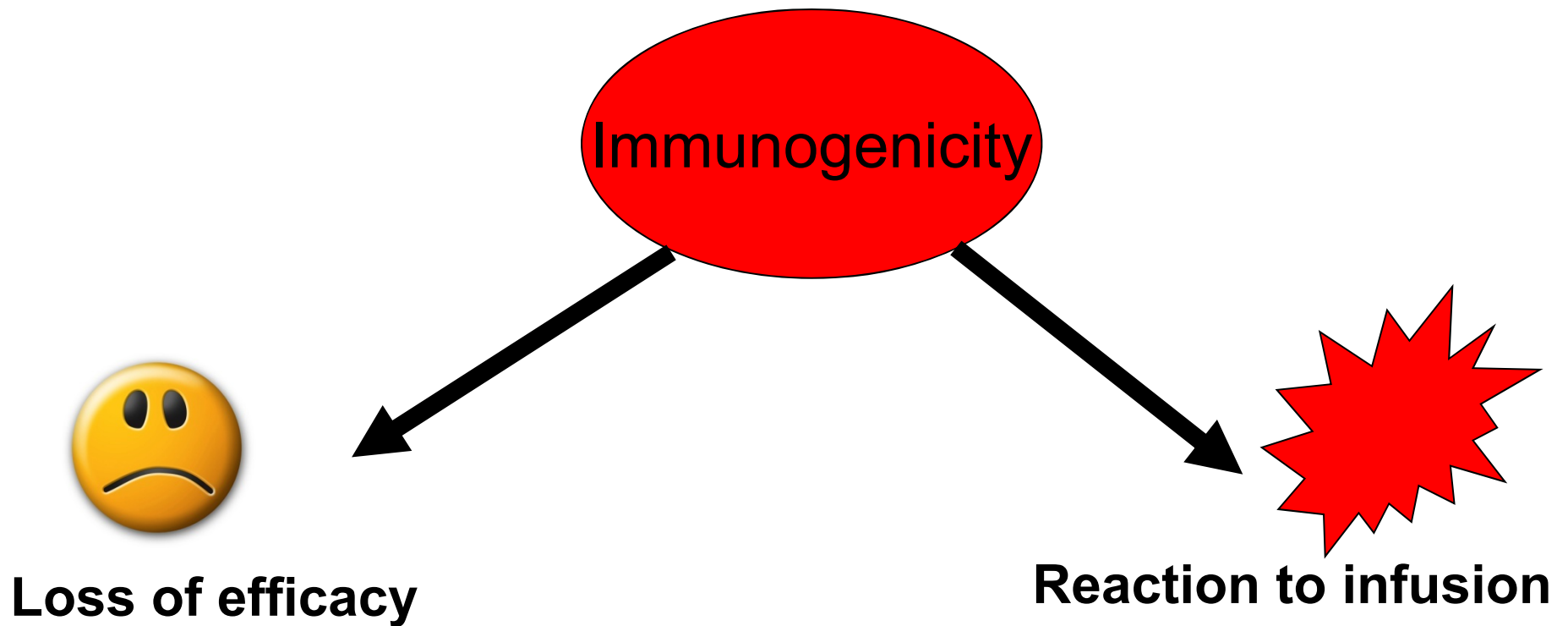
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Disease control

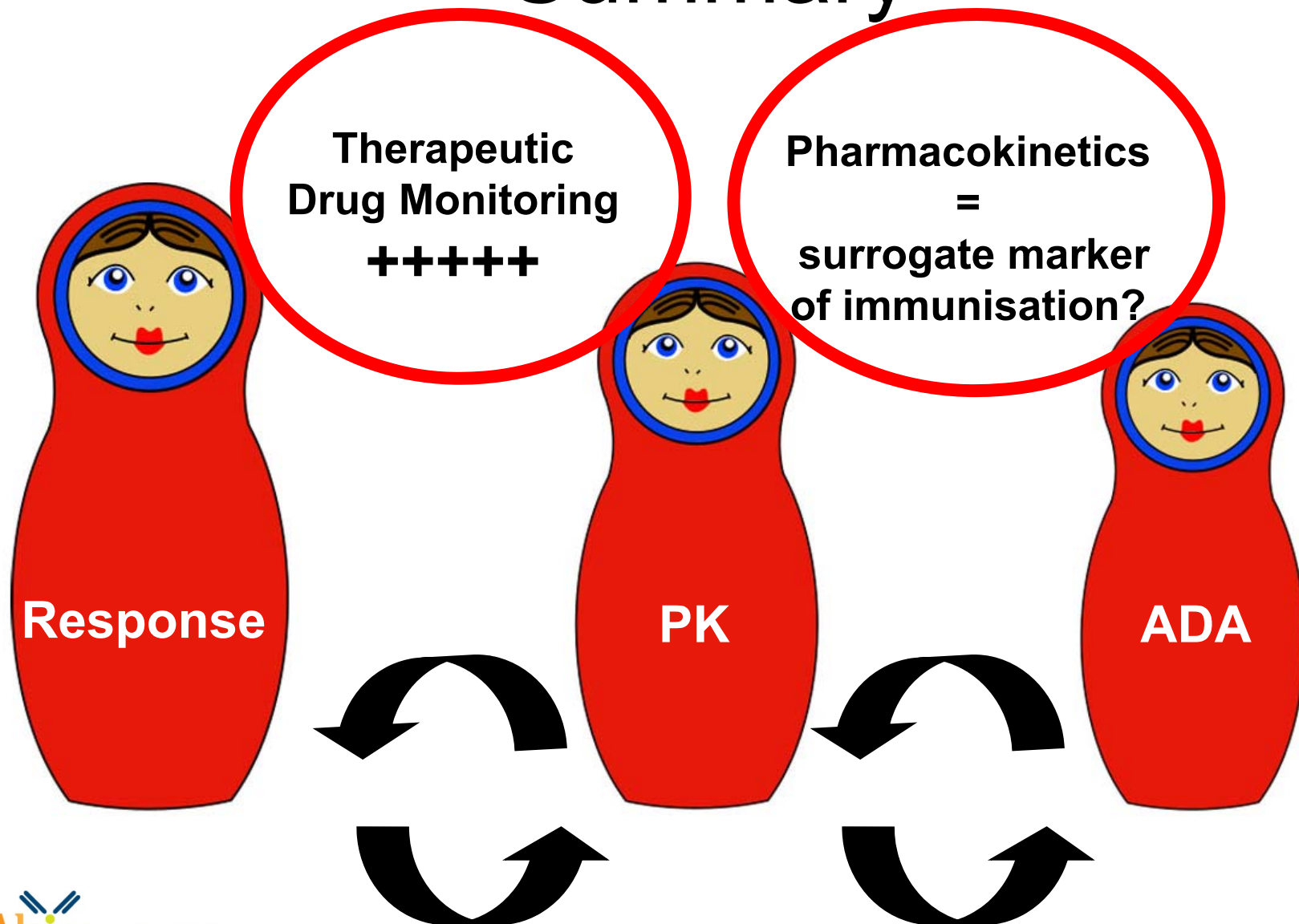
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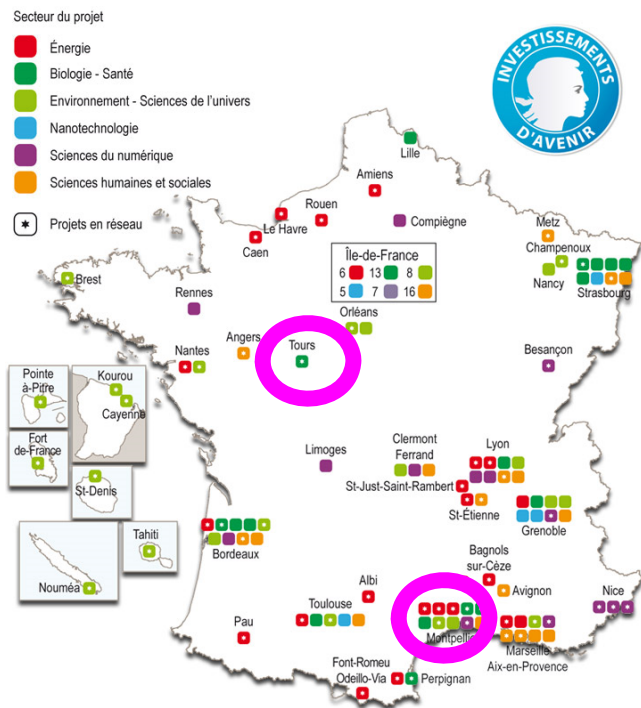
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Summary



Summary





Gilles Paintaud



Philippe Goupille



Hervé Watier



David Ternant



Denis Mulleman



Emilie Ducourau

Thank you for your attention!