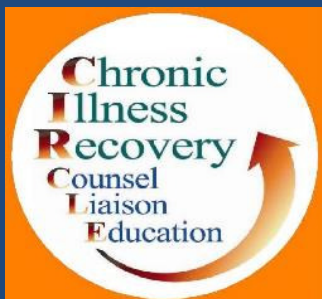


Clinical Evidence of Immune System Dysregulation Caused by Intracellular Infection



Meg Mangin, RN
Immunology Summit
September 30, 2014

Overactive Immune System

Sarcoidosis

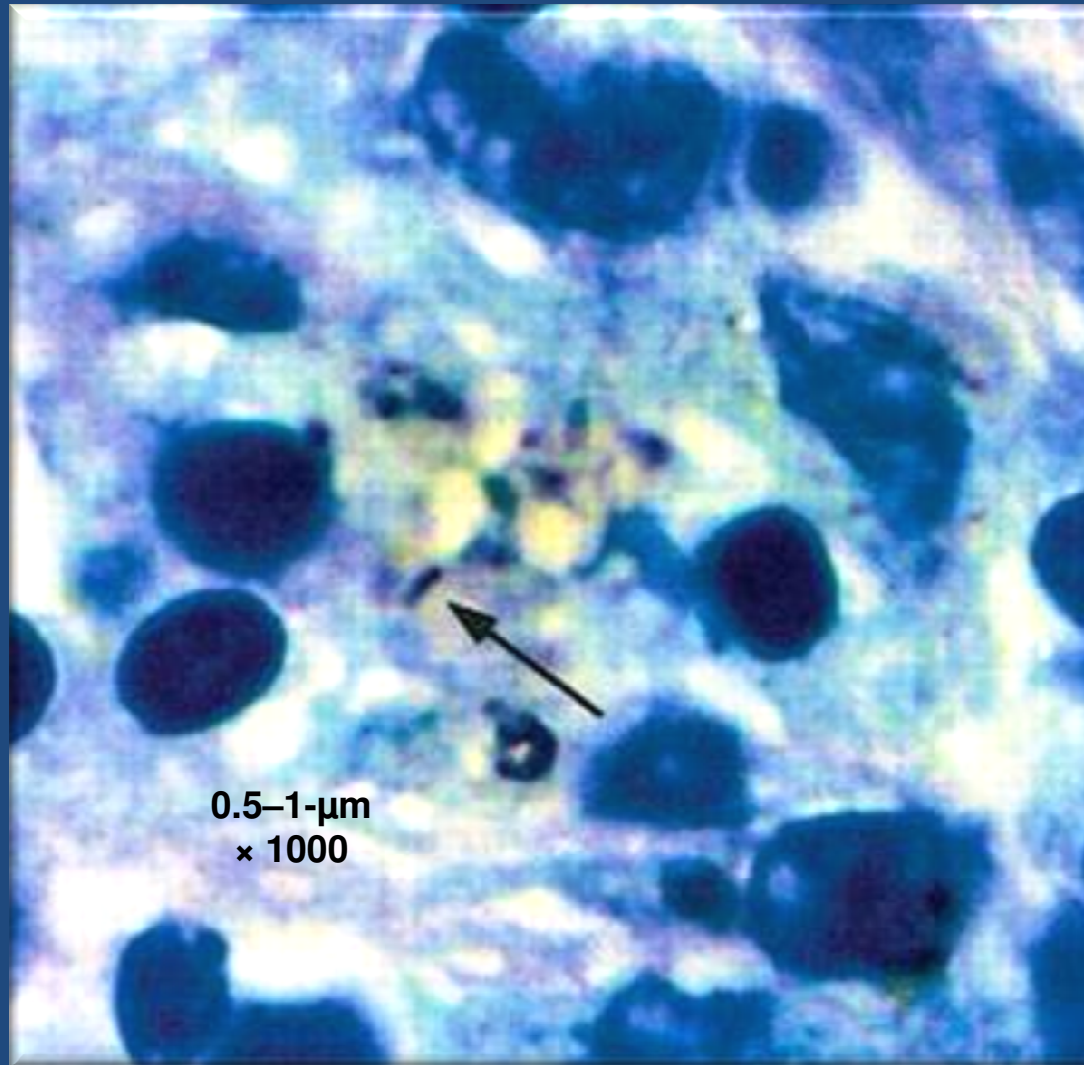
Granulomas



Light sensitive

Elevated calcitriol

Rickettsia-like Organisms in a Pulmonary Giant Cell Granuloma



Violet May-Grünwald-Giemsa-stained round cells

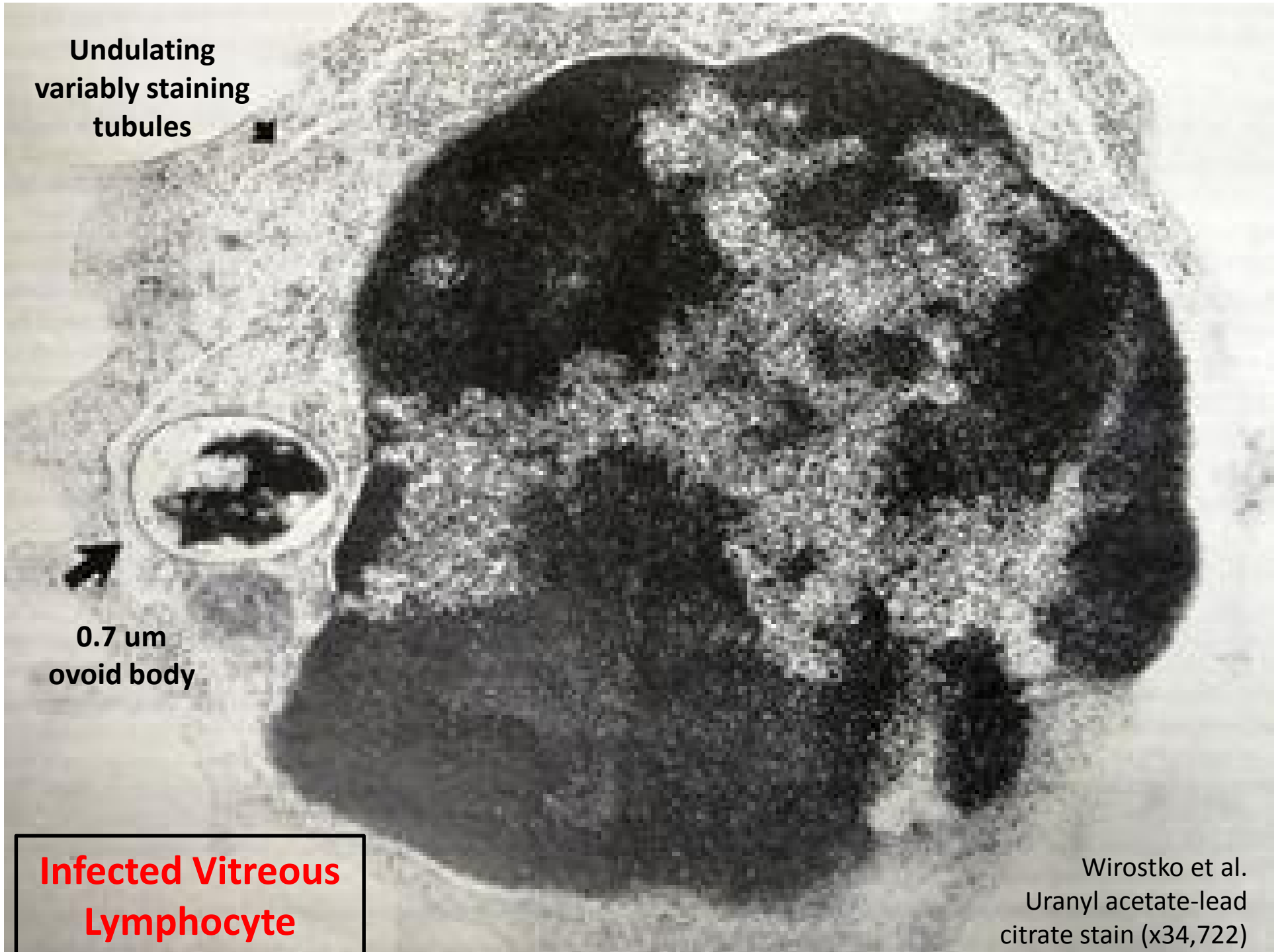
Nilsson K et al. J Infect Dis. 2002;185:1128-1138

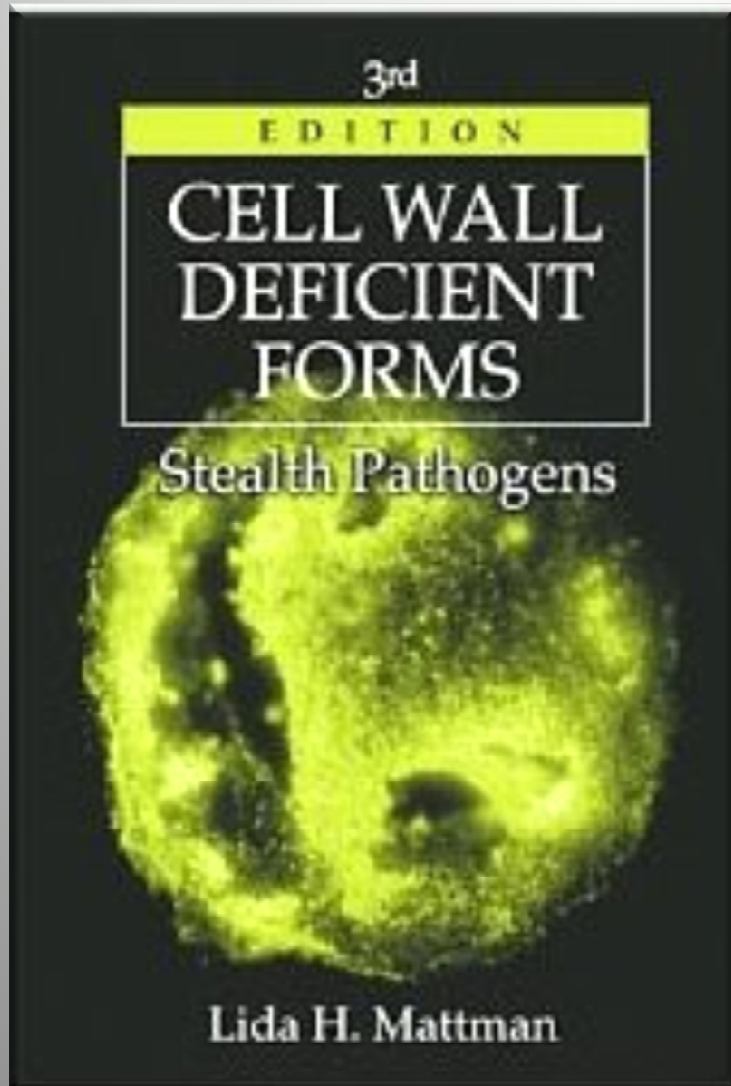
Undulating
variably staining
tubules

0.7 μ m
ovoid body

**Infected Vitreous
Lymphocyte**

Wirostko et al.
Uranyl acetate-lead
citrate stain (x34,722)

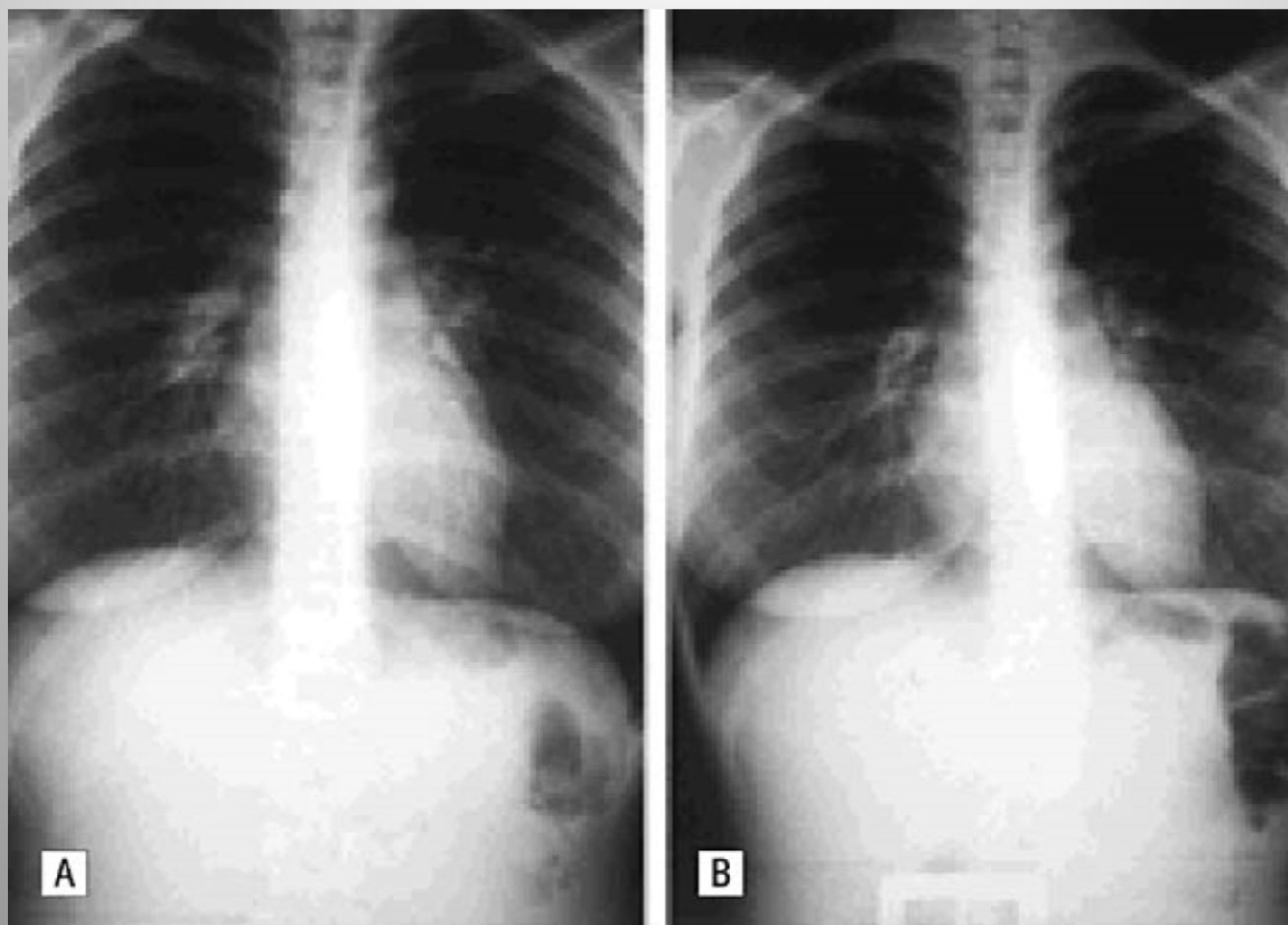




Lida Holmes Mattman, Ph.D.
(1912-2008)

The Use of Minocycline for the Treatment of Sarcoidosis

Bachelez et al. Arch Dermatol. 2001;137(1):69-73. doi:10.1001/archderm.137.1.69



A, Enlarged mediastinal lymph nodes in patient at the time of the onset of minocycline therapy.

B, Six months after the onset of the study, complete regression of mediastinal lymphadenopathy.



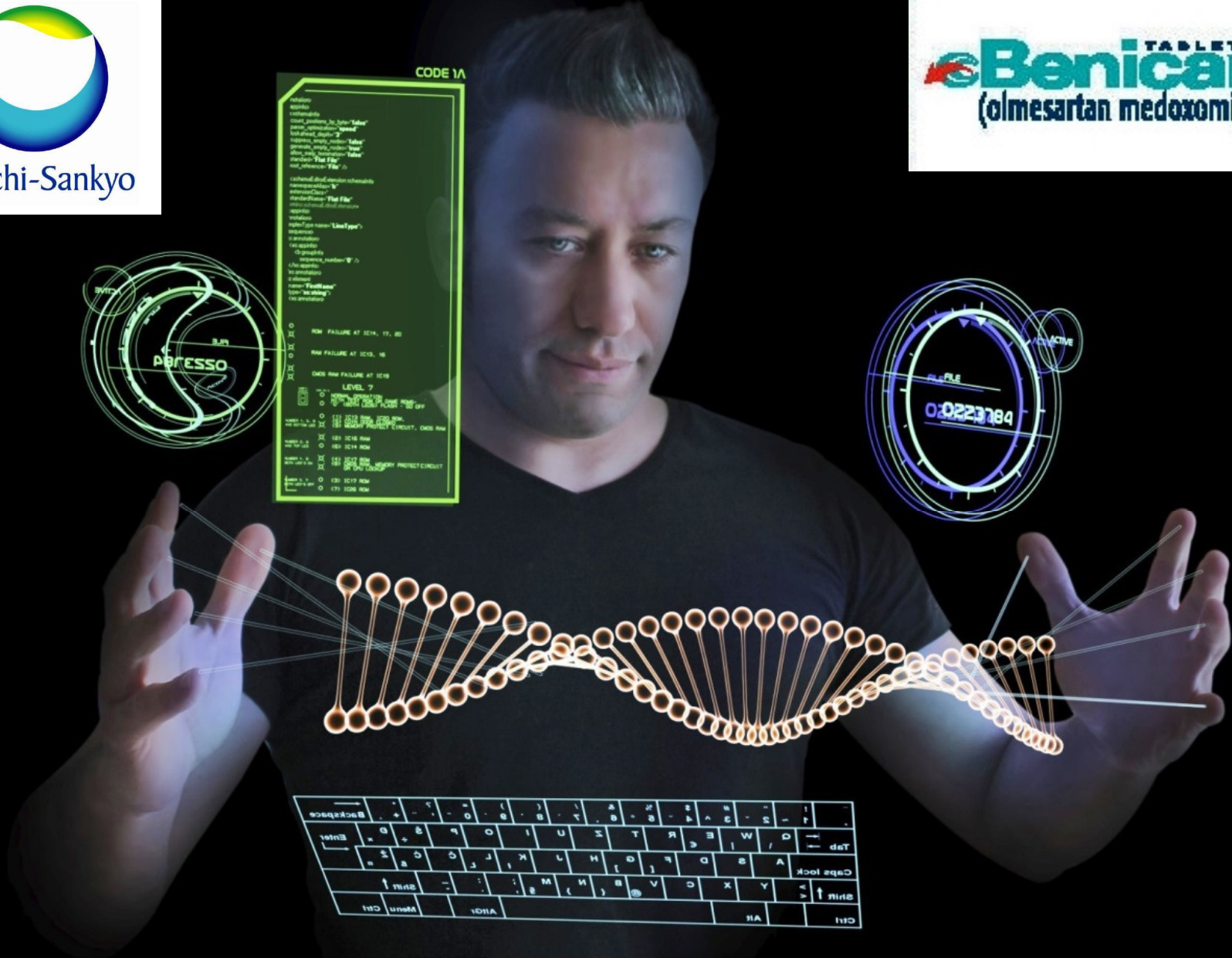
Ann Intern Med. 1995 Jan 15;122(2):81-9.

Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group.

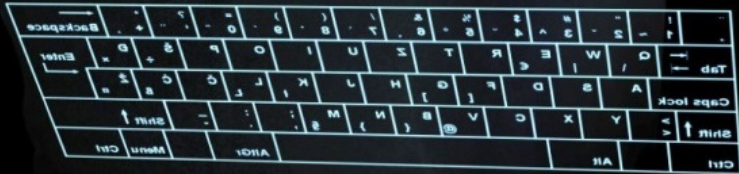
Tilley BC, Alarcón GS, Heyse SP, Trentham DE, Neuner R, Kaplan DA, Clegg DO, Leisen JC, Buckley L, Cooper SM, Duncan H, Pillemer SR, Tuttleman M, Fowler SE.

Pulsed antibiotic therapy (every other day)

- More effective
- Allows for tissue recovery
- No antibiotic resistance



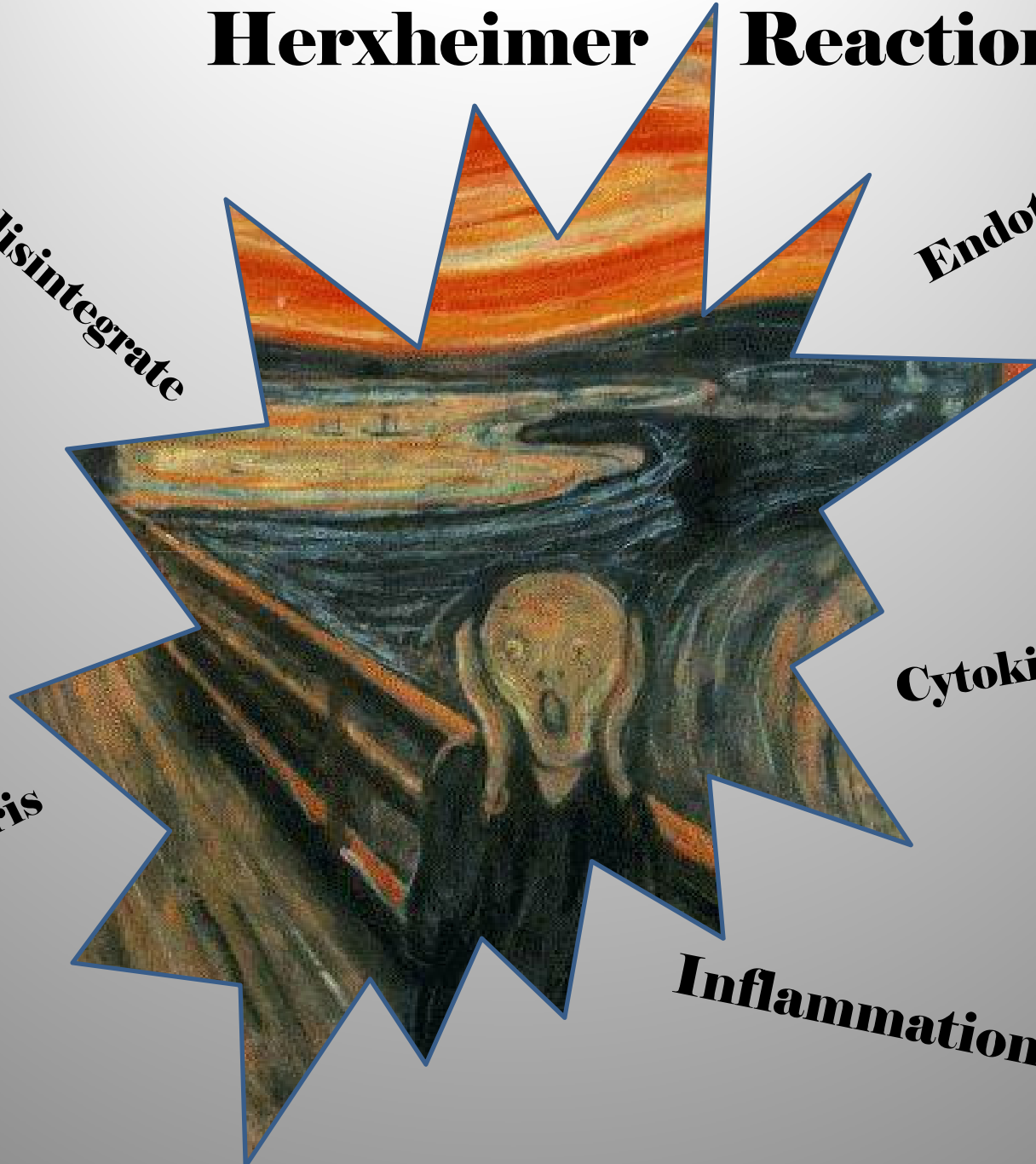
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CODE 1A
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Herxheimer Reaction

Infected cells disintegrate

Endotoxin release



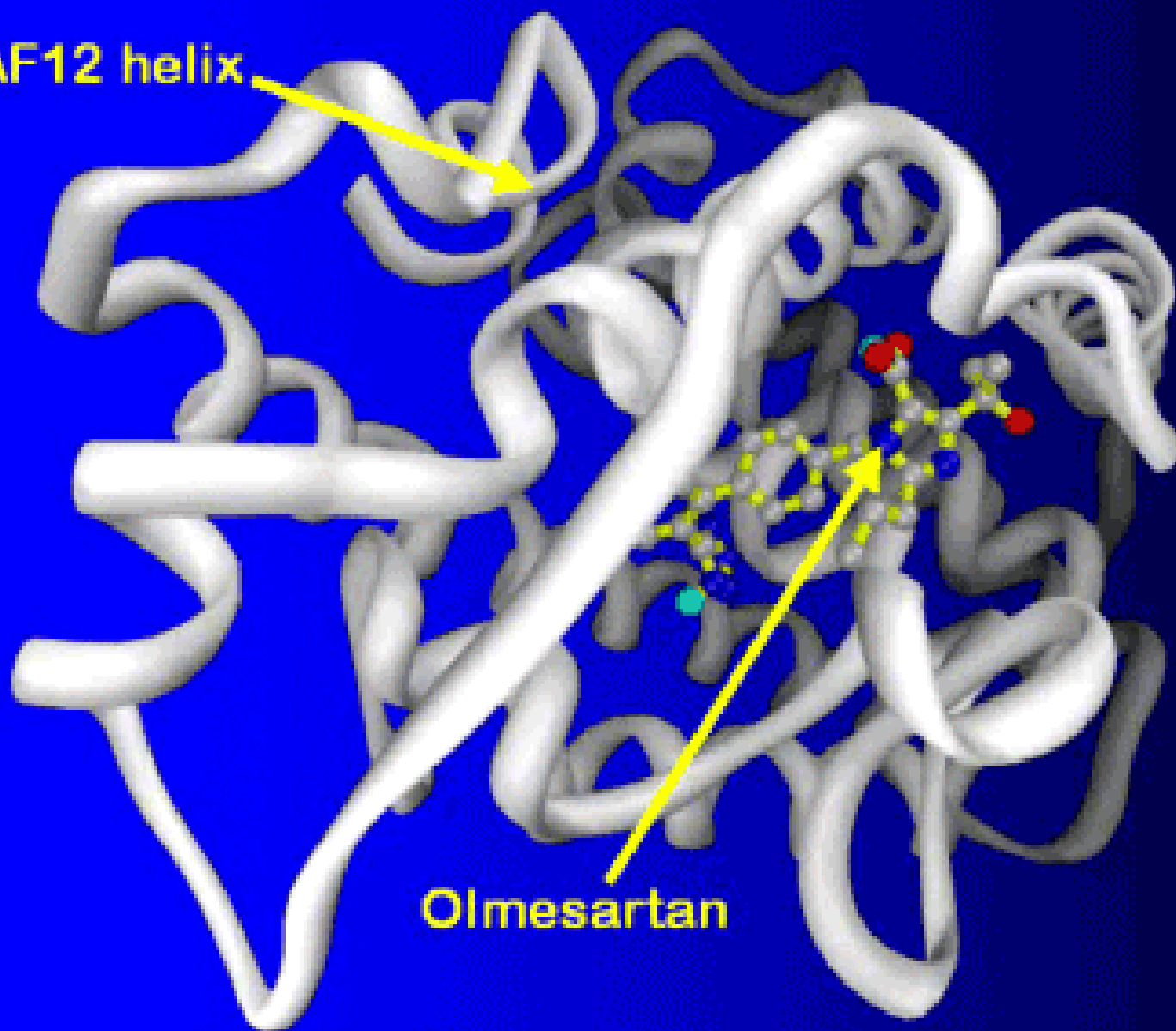
Cellular debris

Cytokine release

Inflammation

Olmesartan Medoxomil is VDR Agonist

AF12 helix



Olmesartan

Hydrogen
Bonds:

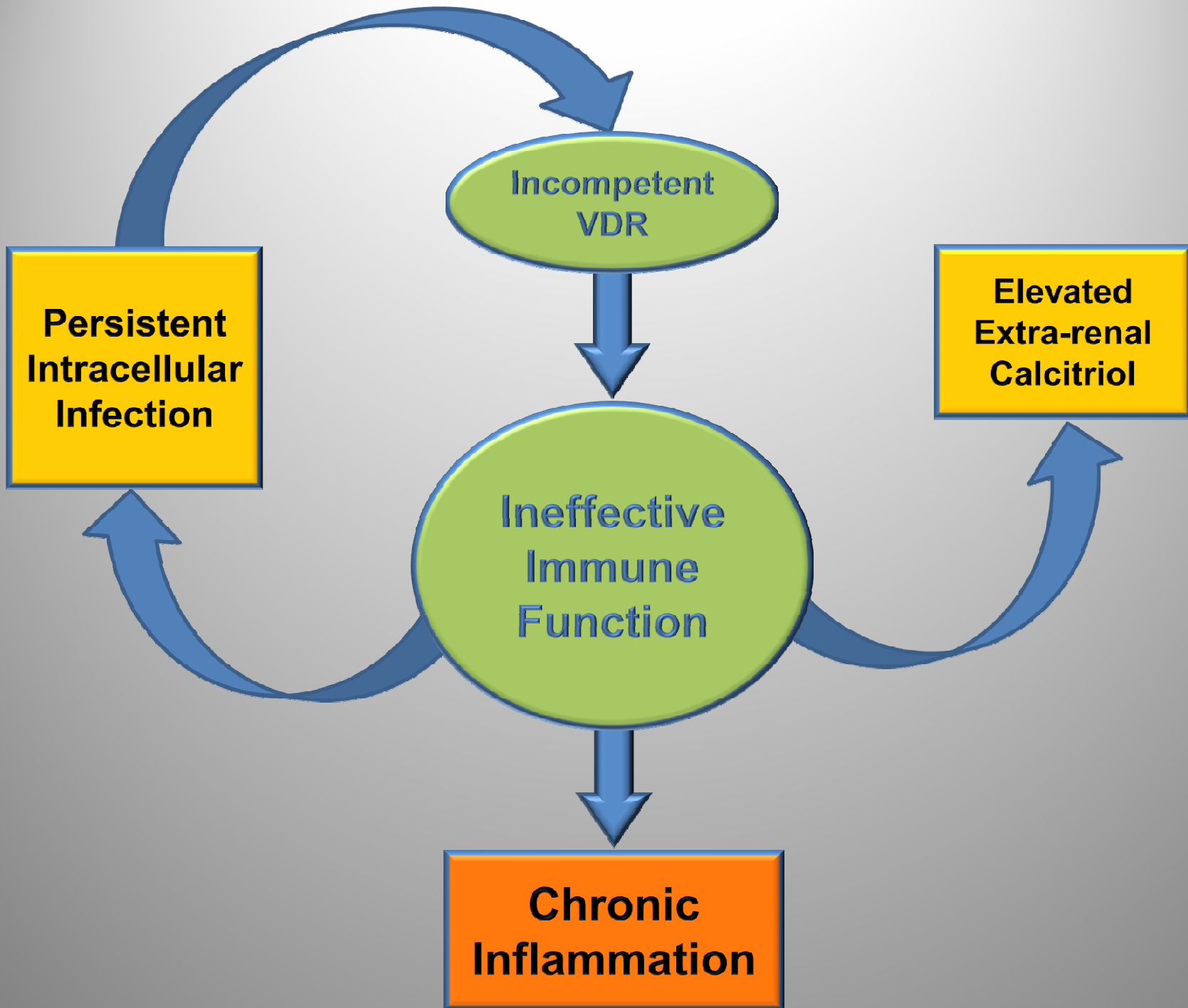
SER237

ARG274

SER278

LYS240

ASP144



85% of subjects had elevated calcitriol without hypercalcemia.

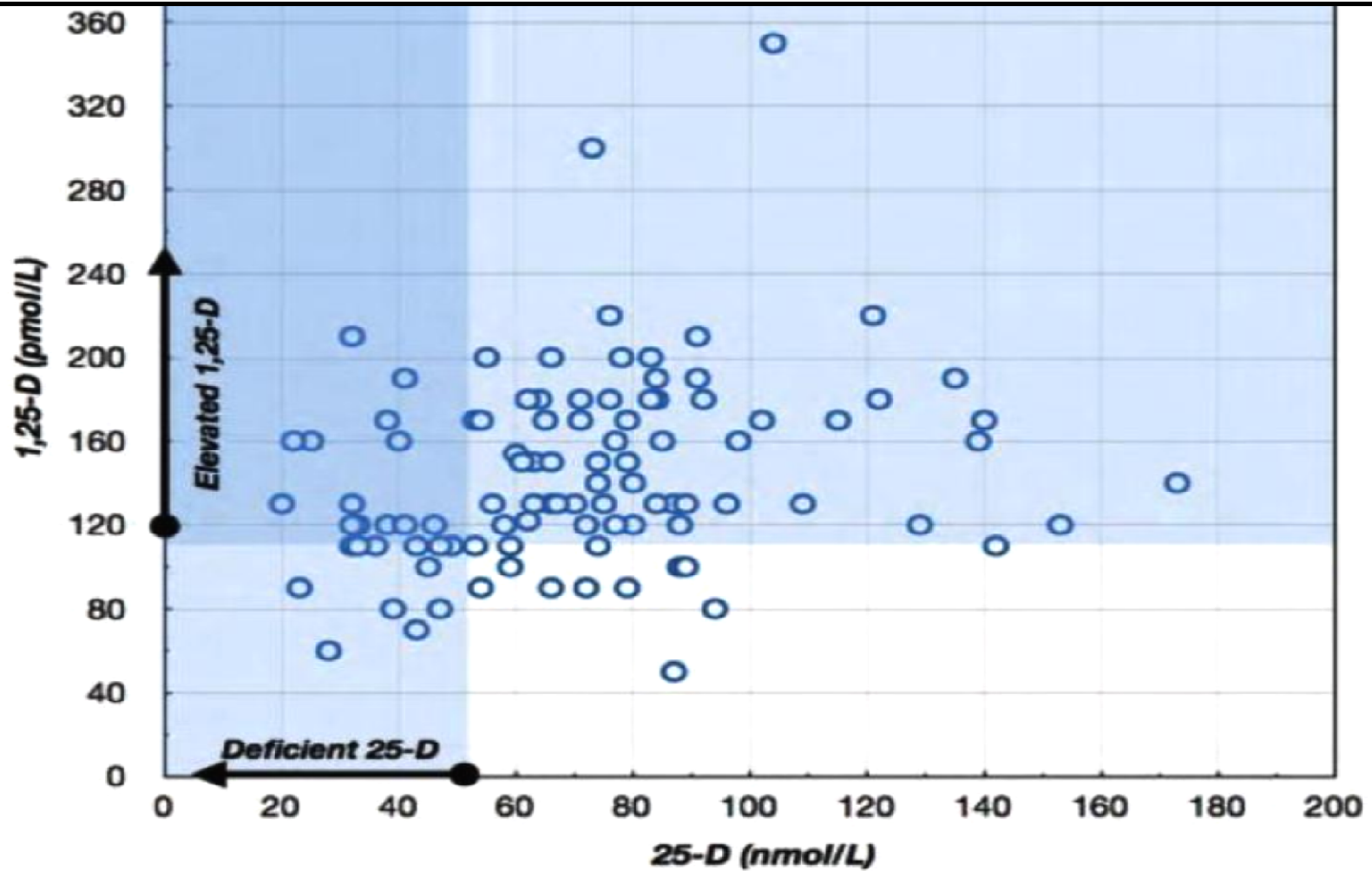
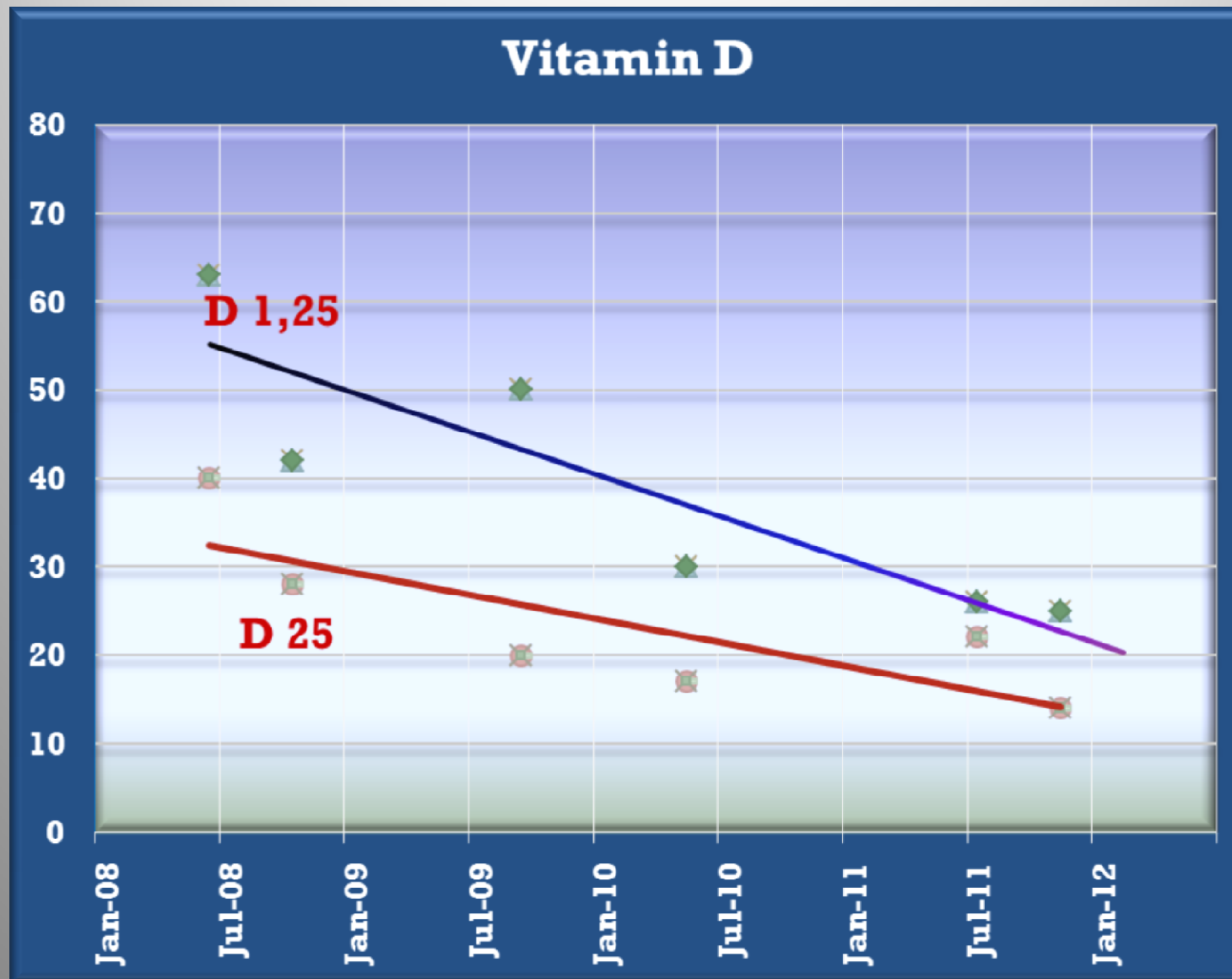


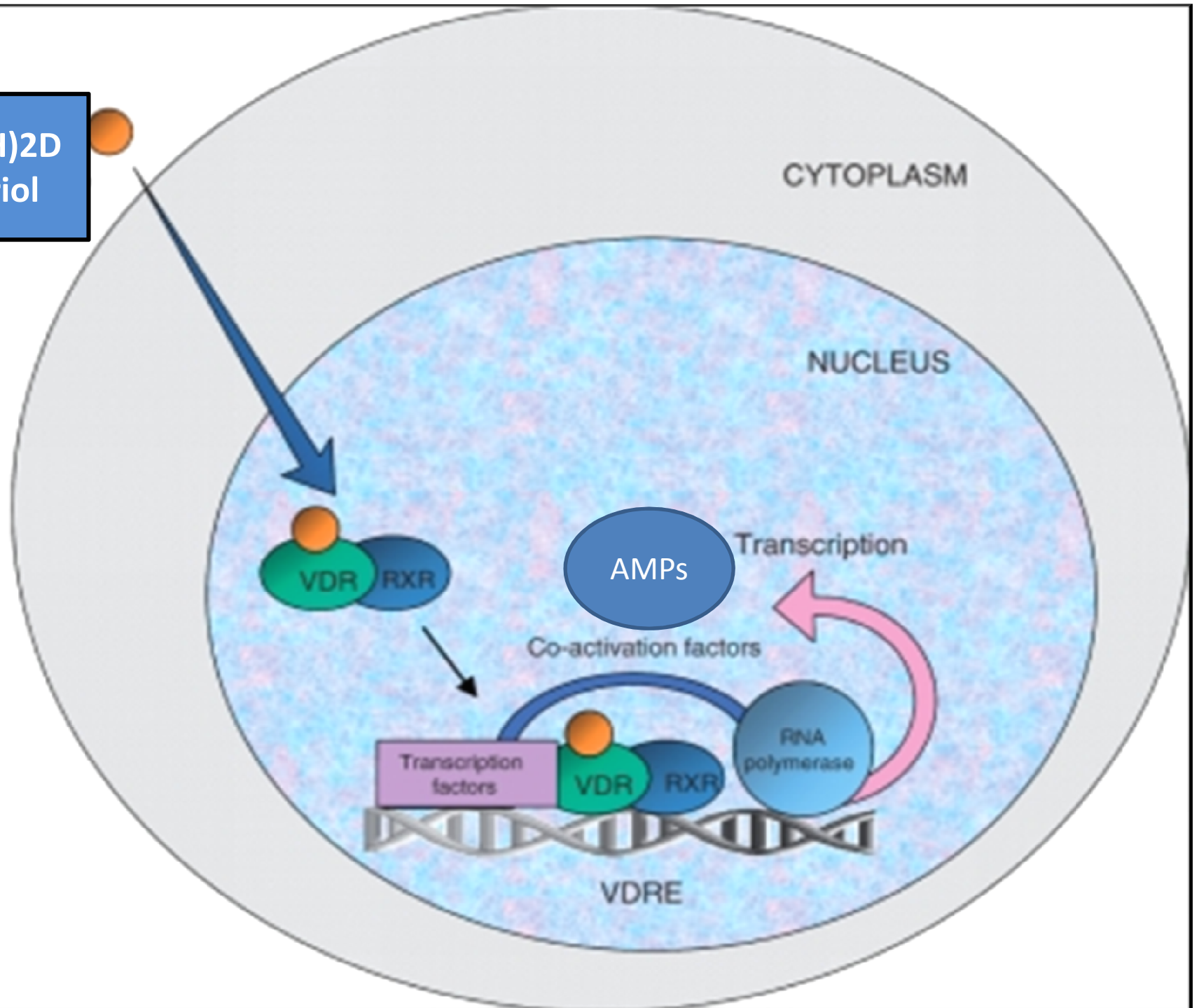
Figure 3. 25-D vs. 1,25-D in a cohort of 100 autoimmune patients ⁶⁹

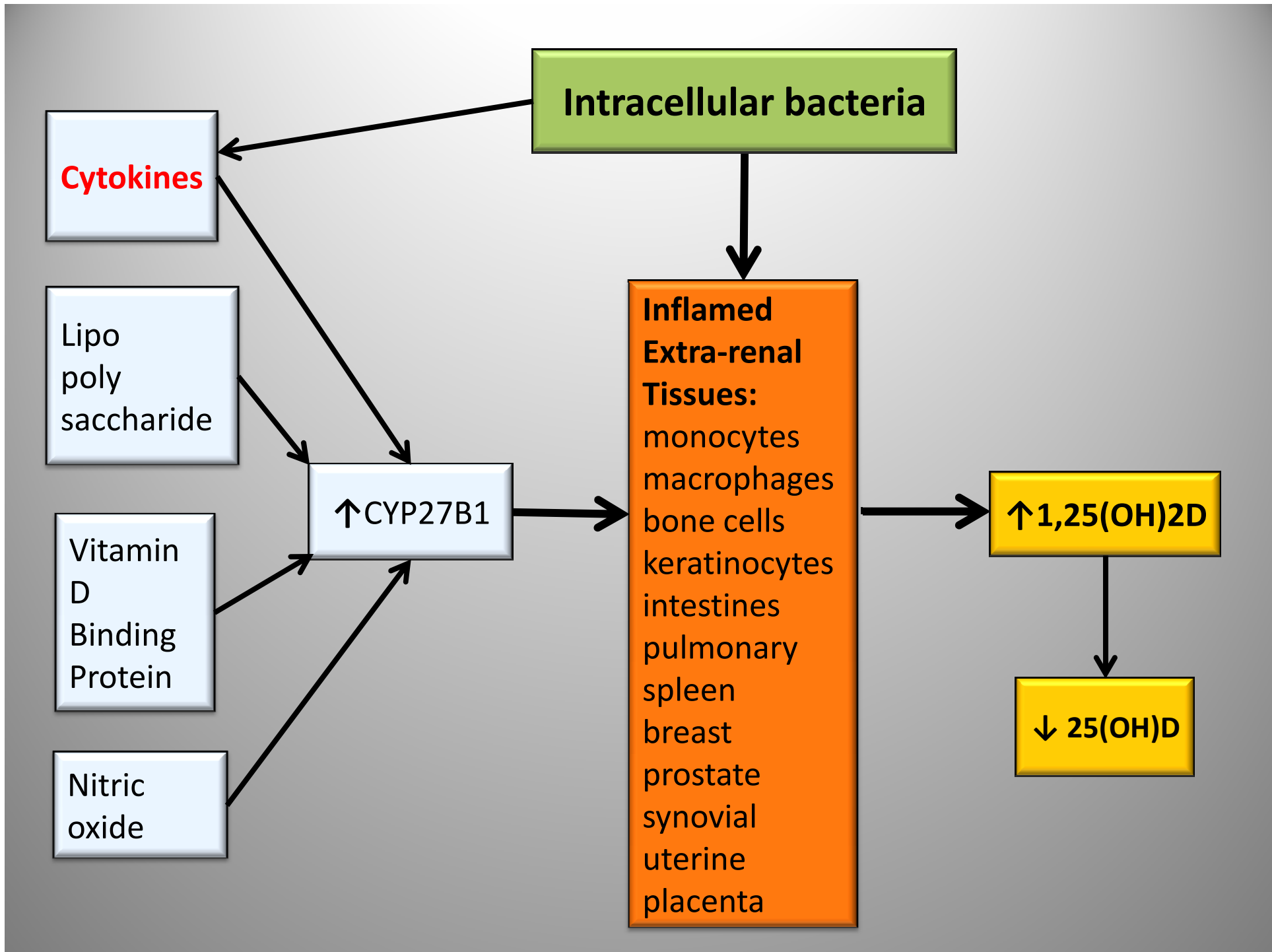
Blaney et al.

Effect of Olmesartan on Elevated Calcitriol



1,25(OH)₂D
Calcitriol





Olmesartan

Agonizes VDR

↑ CYP24A1
↑ CYP3a4

↓ Elevated
Calcitriol

↓ CYP27B1

↓ Elevated
Calcitriol

Antimicrobial peptides
are transcribed

Intracellular bacteria are eliminated

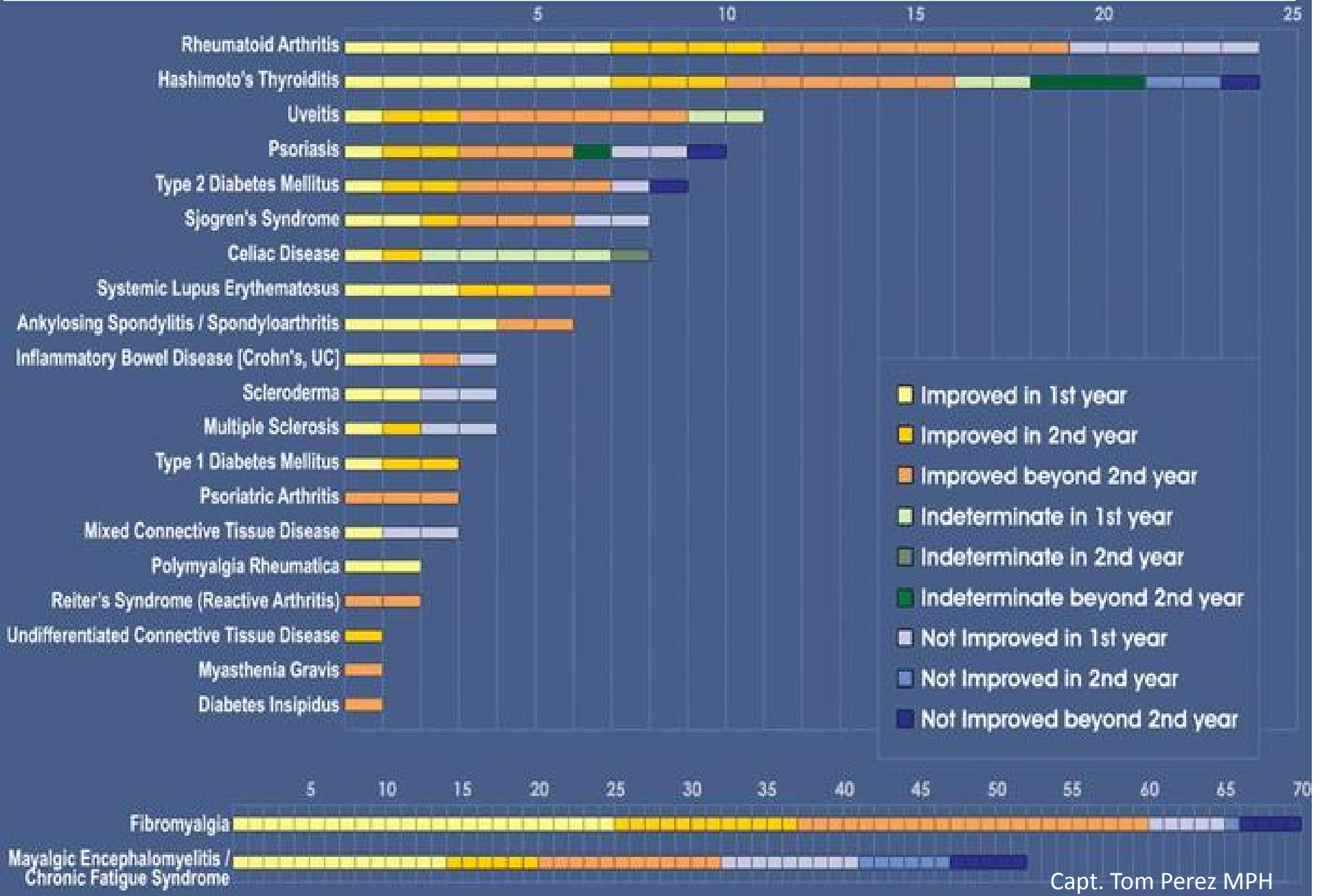
Clinical Response to Treatment



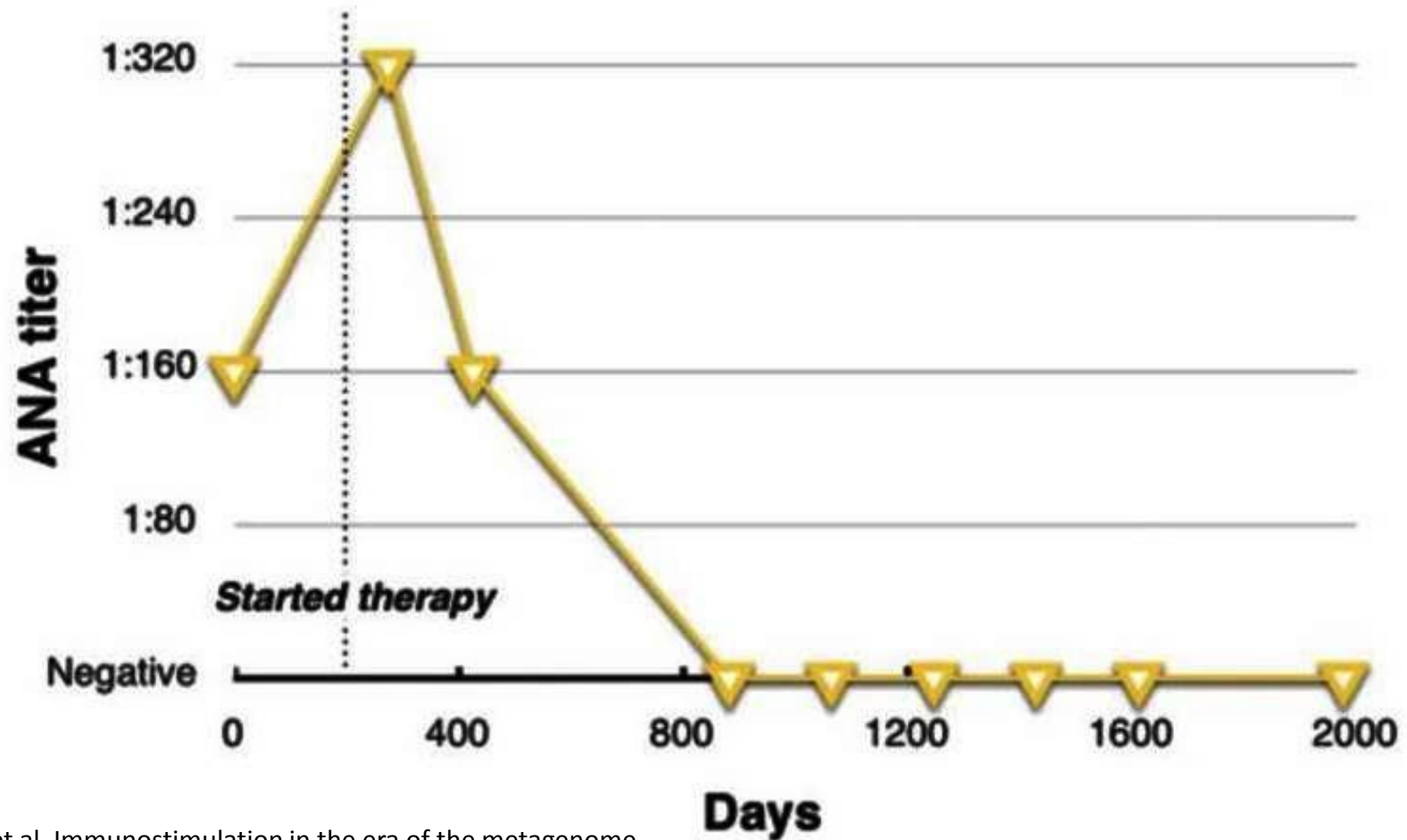
Category	10 Year		
	Goal	Average	Feb-12
HDL	↓ 39	→ 42	↑ 46
LDL	↑ 90	↓ 112	↑ 83
LDL/HDL	↓ 3.55	→ 2.64	↑ 1.80
Cholesterol	↑ 150	↓ 175	↑ 147
Triglycerides	↓ 150	↑ 107	↑ 91
Triglycerides/HDL	↓ 3.50	↑ 2.38	↑ 1.98
Homocysteine	↑ 10	↓ 16	→ 13
HS CRP	→ 0.30	↓ 0.39	↑ 0.20
Glucose	↓ 100	→ 93	↑ 85
Bun	↓ 25	→ 18	↑ 12
Creatinine	↓ 1.20	↓ 1.21	↑ 1.00
Better Than Goal		55%	91%
Improved			100%

Olmesartan
improved
100% of
laboratory
markers

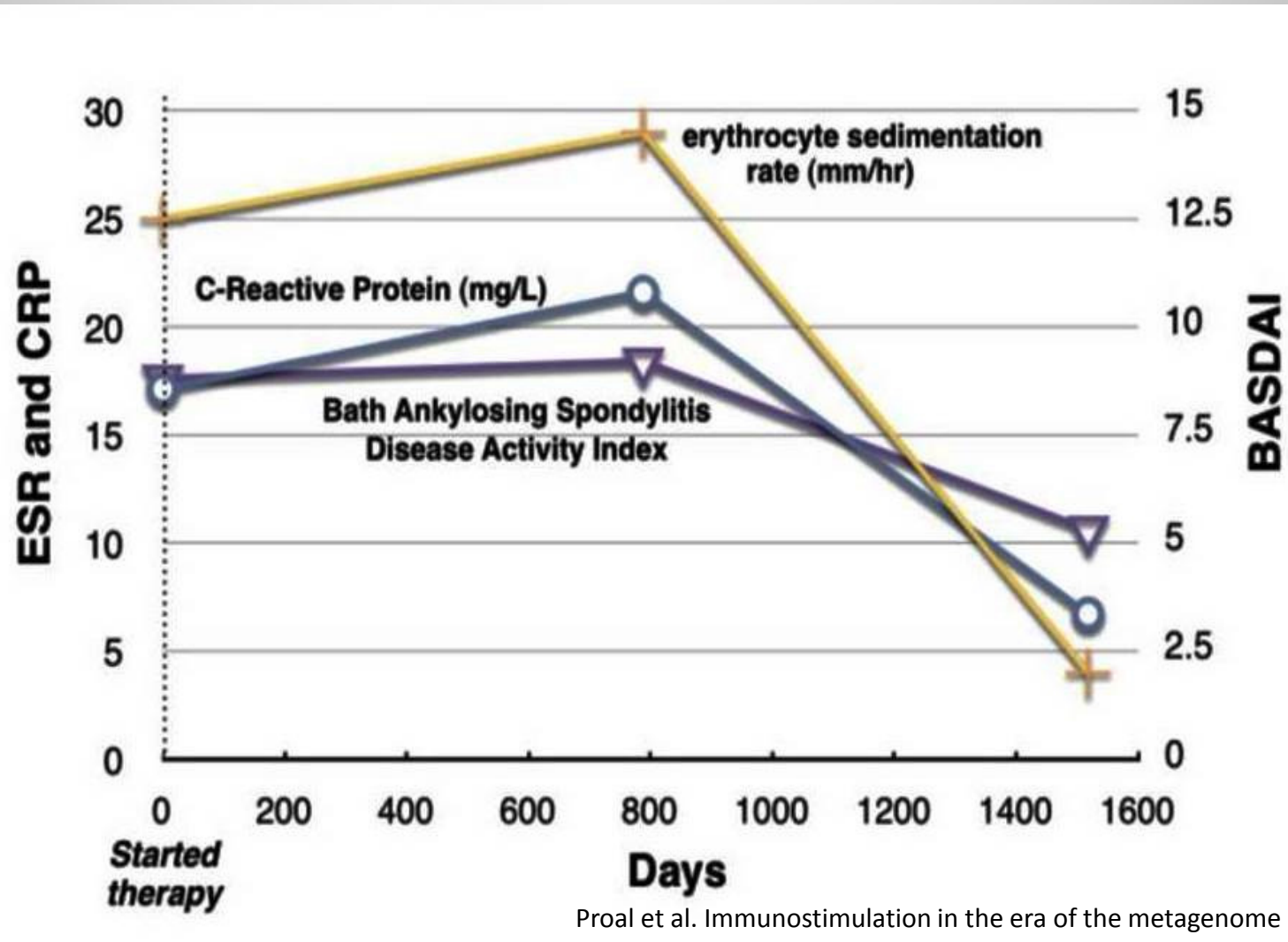
Timeline of Symptom Improvement in a Varied Cohort



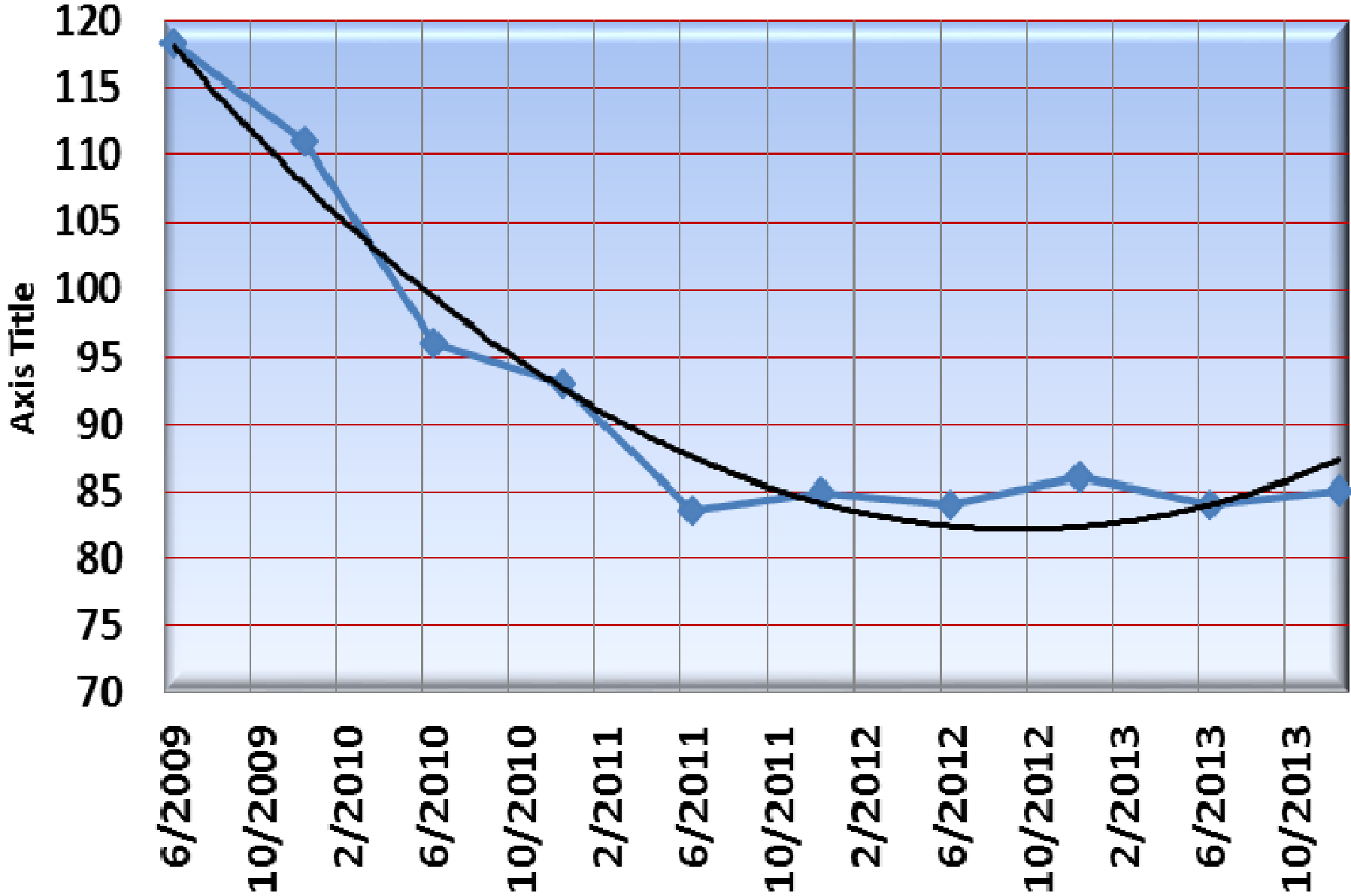
Antinuclear Antibodies in a 58yo Female with Rheumatoid Arthritis



BASDAI, ESR, and CRP in a 50yo Male with Ankylosing Spondylitis



Mean Aterial Pressure



“It is becoming increasingly clear that microbes slow down immune reactivity by dysregulating the VDR, ultimately to increase their chance of survival.”

“Immune modulatory therapies that enhance VDR expression and activity should, therefore, be considered in the clinical setting.”



Dr. Marina Rode von Essen
Senior Research
Copenhagen University Hospital