Clinical Evidence of Immune System Dysregulation Caused by Intracellular Infection

Meg Mangin, RN
Immunology Summit
September 30, 2014

Sarcoidosis

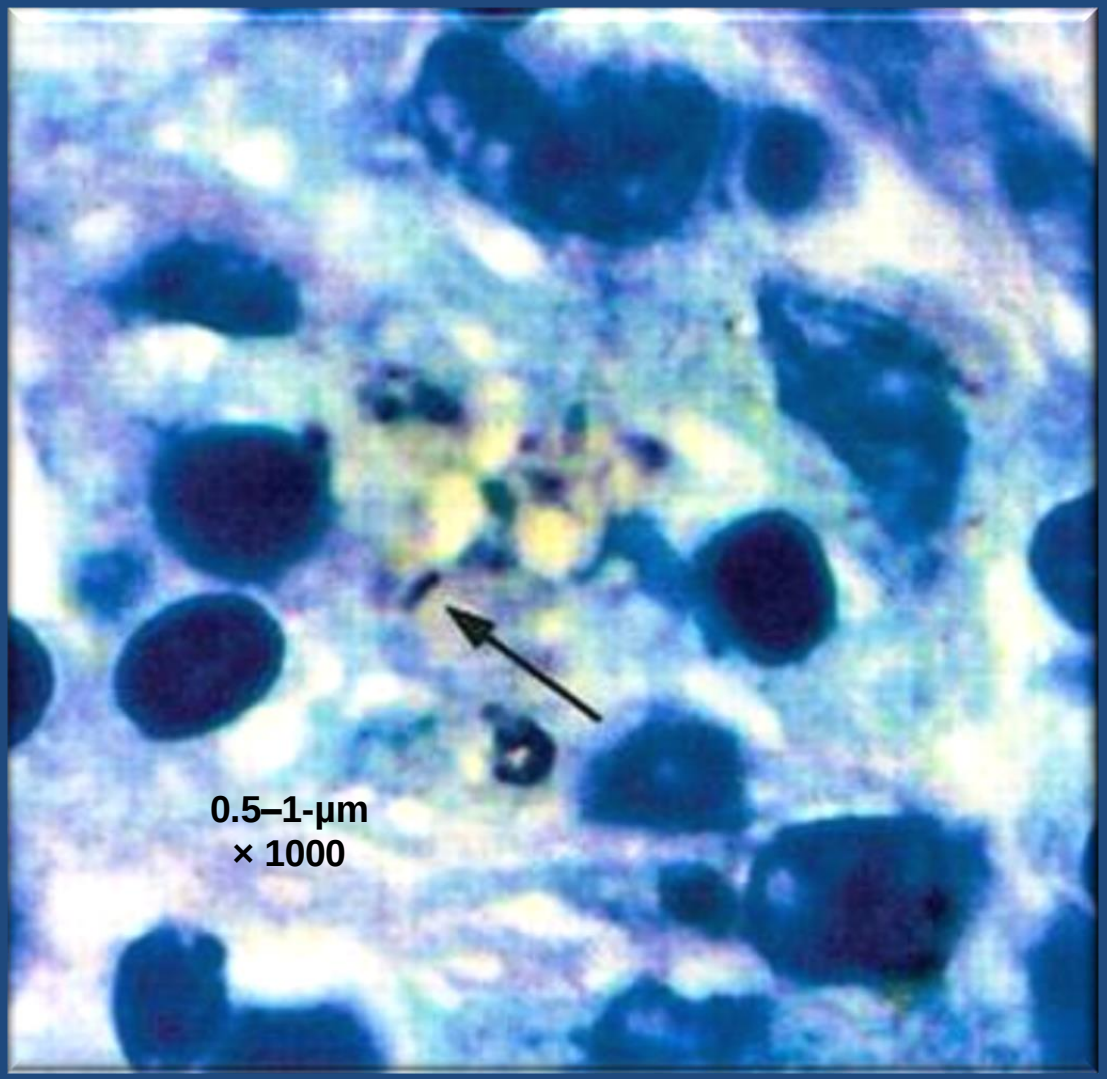
Granulomas



Elevated calcitriol

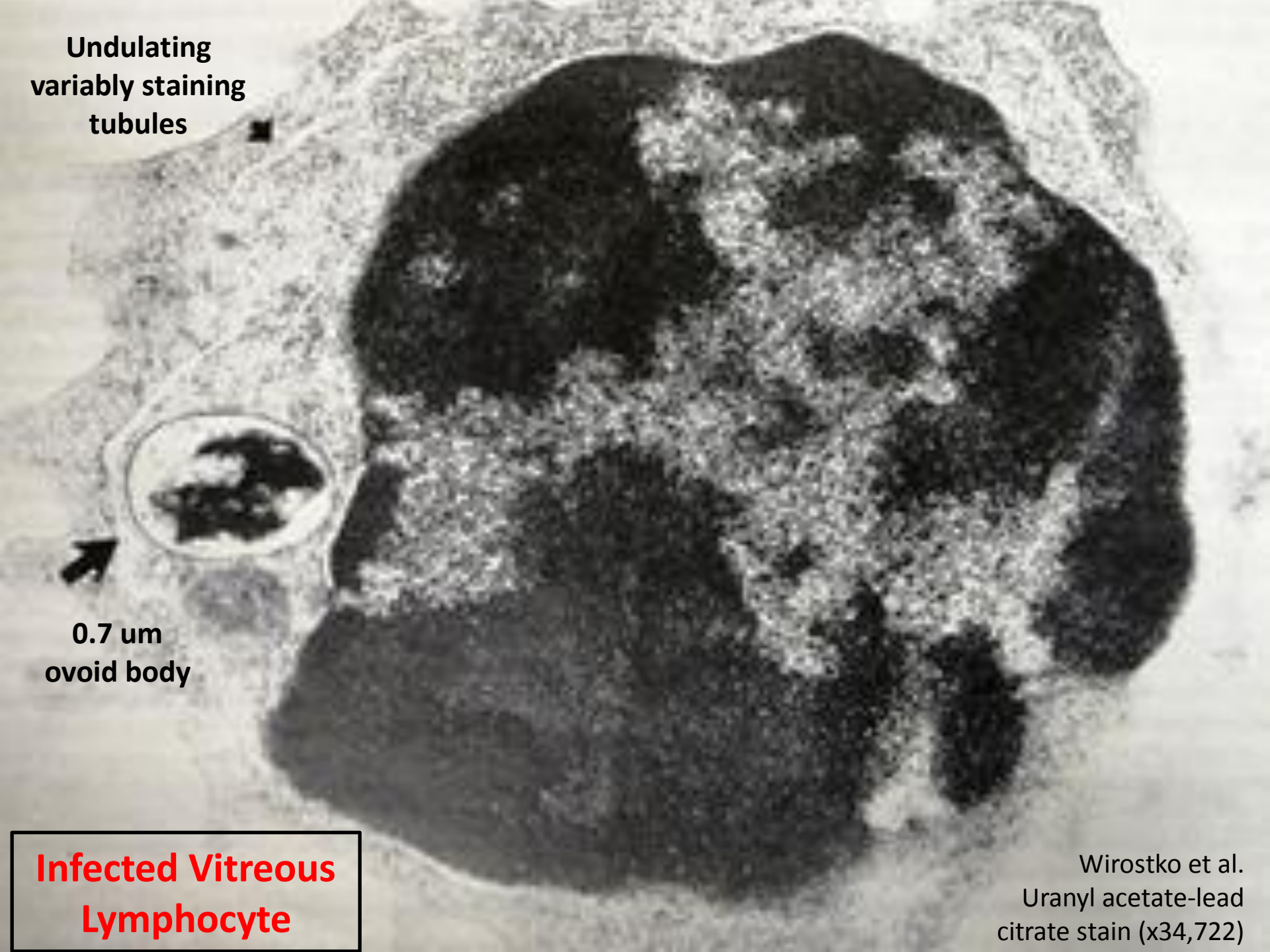
Light sensitive

Rickettsia-like Organisms in a Pulmonary Giant Cell Granuloma



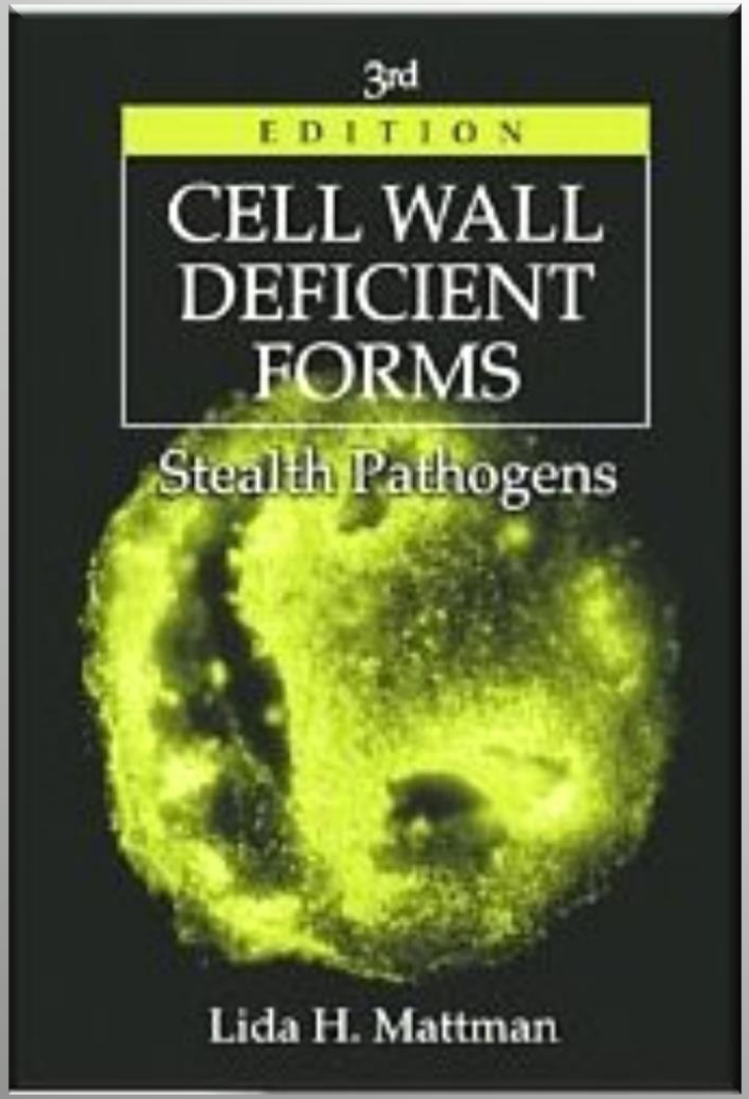
Violet May-Grünwald-Giemsa-stained round cells

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



Infected Vitreous Lymphocyte

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

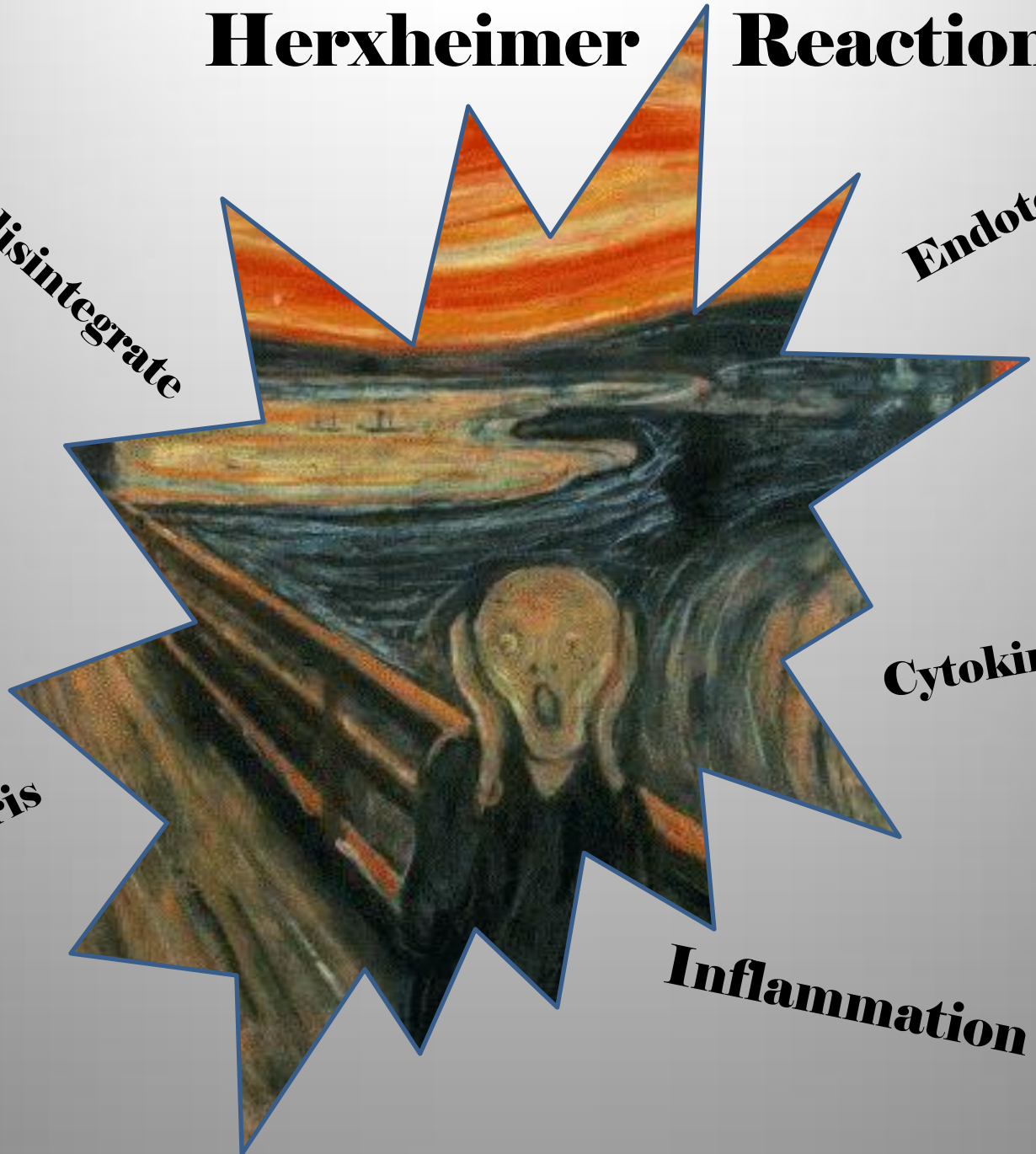




Lida Holmes Mattman, Ph.D.
(1912-2008)


Daiichi-Sankyo
30 TABLETS
40
Benicar
RIGHT ARM

Herxheimer Reaction



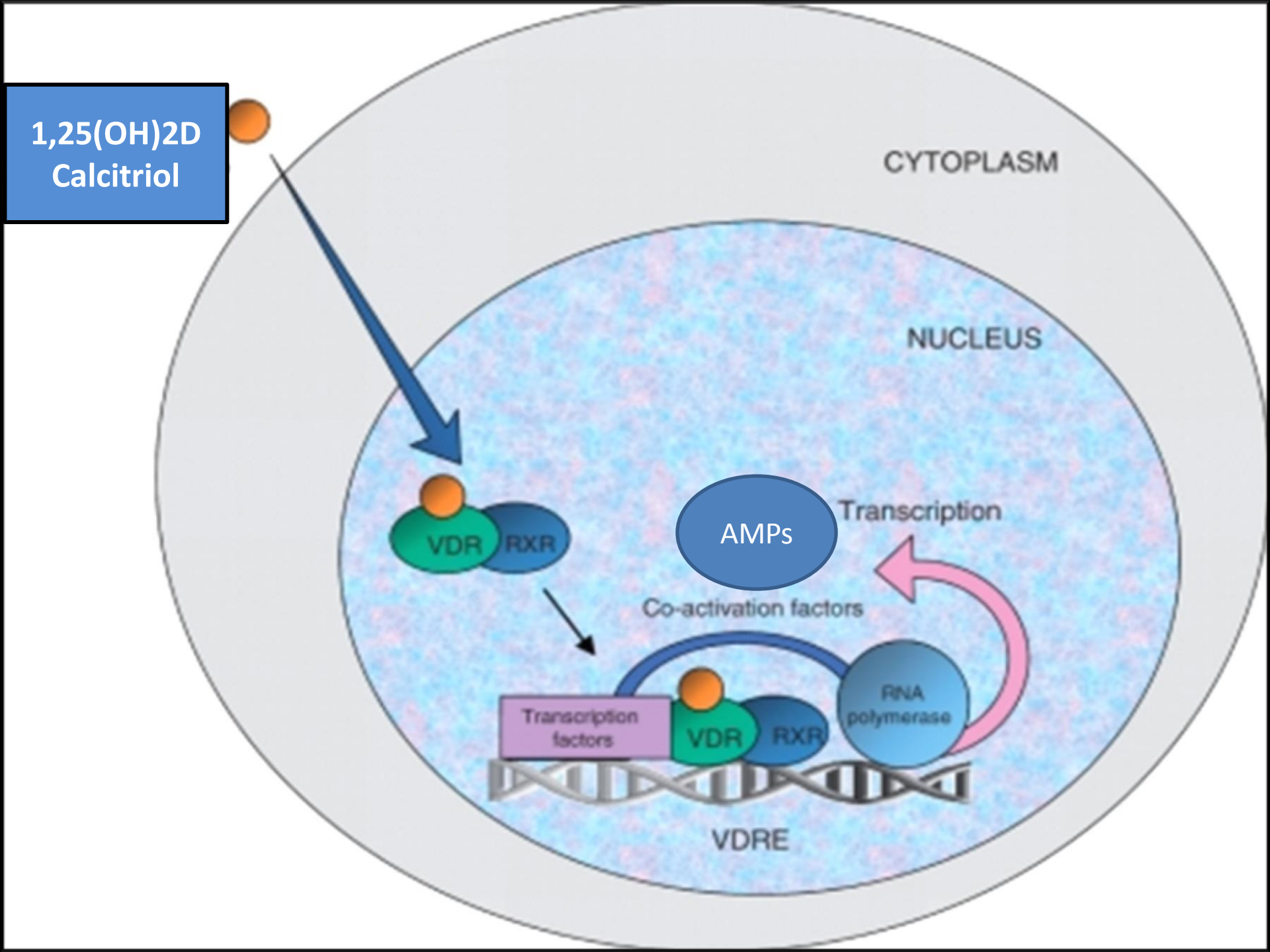
Infected cells disintegrate

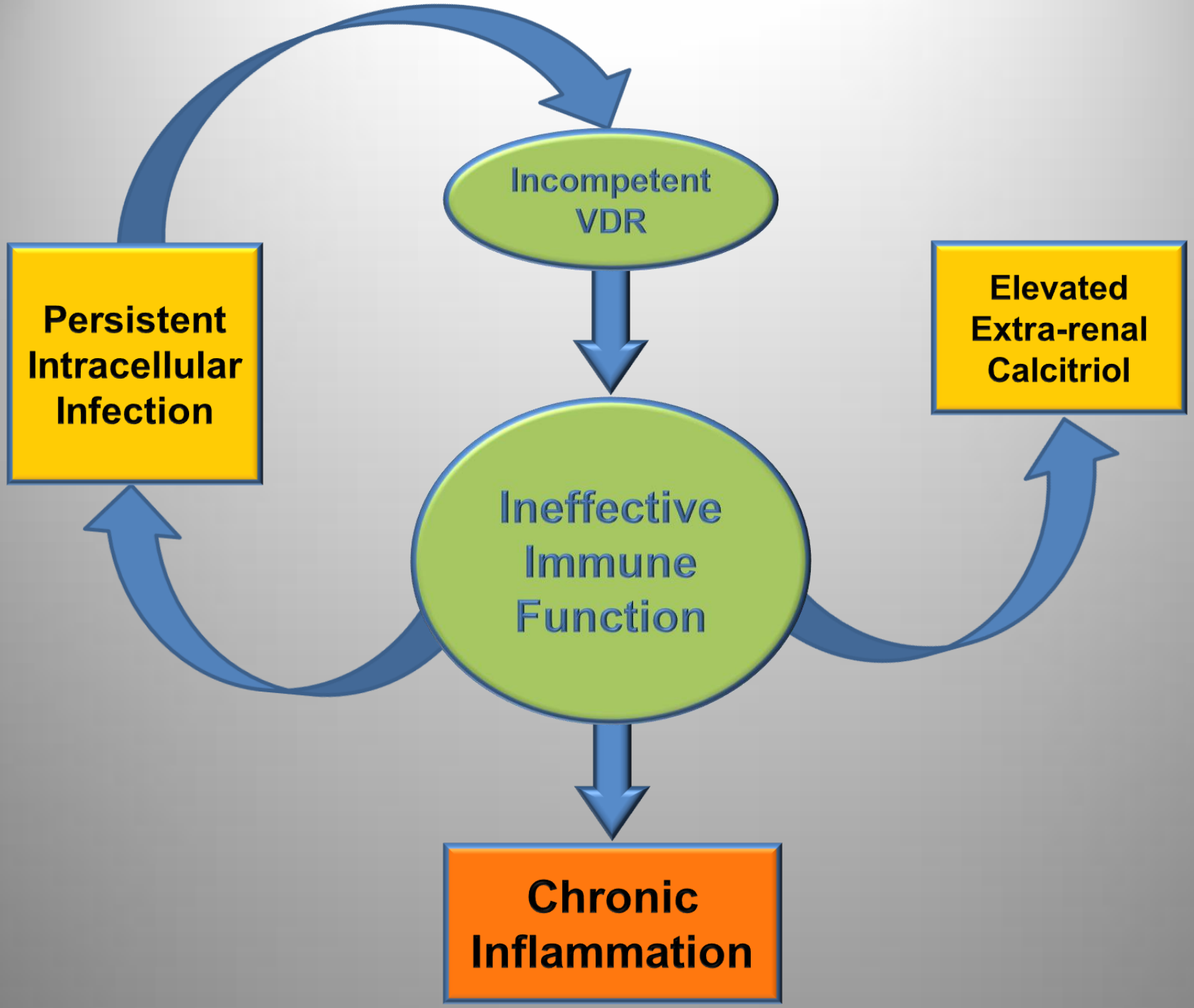
Endotoxin release

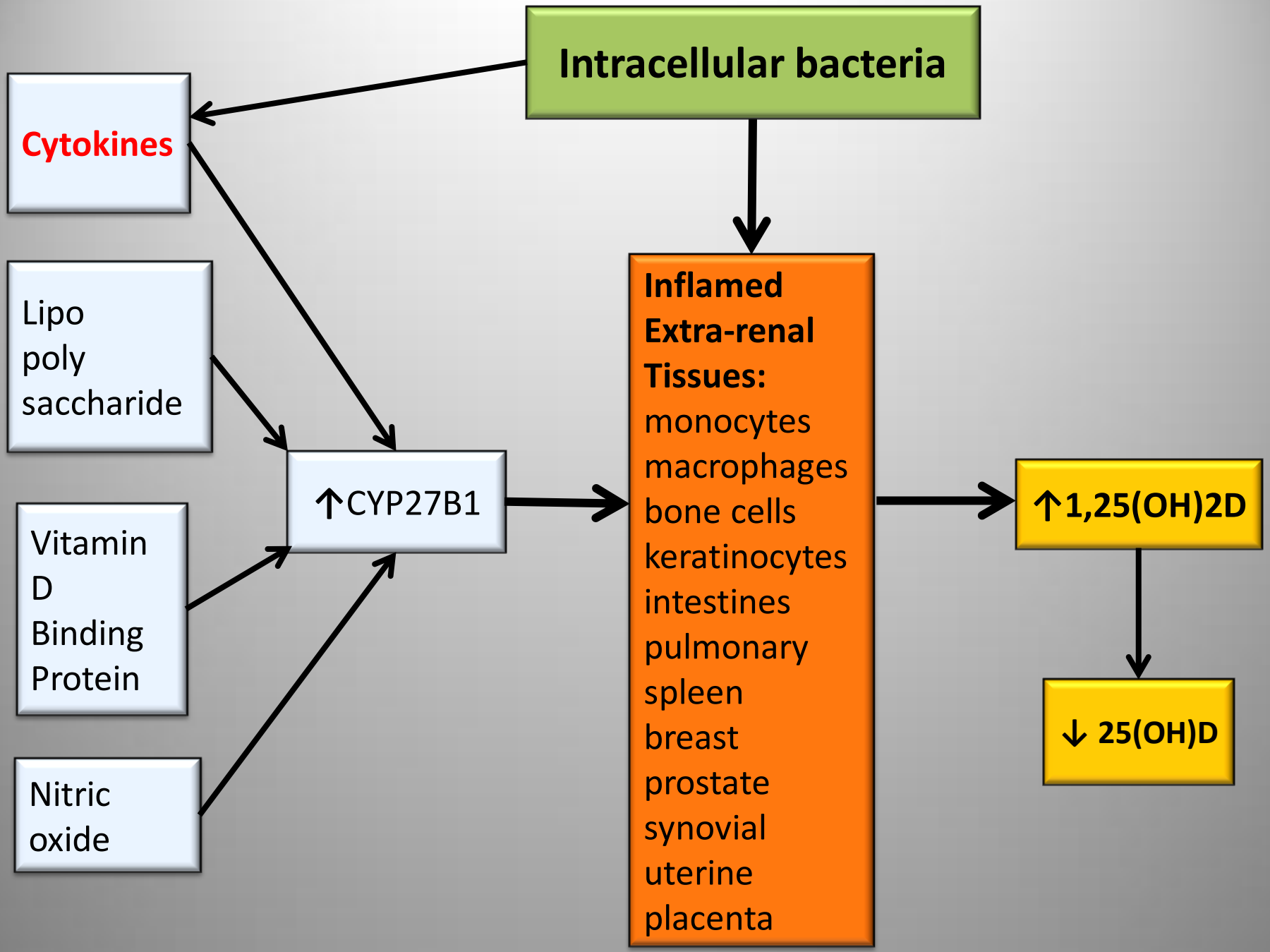
Cytokine release

Inflammation

Cellular debris

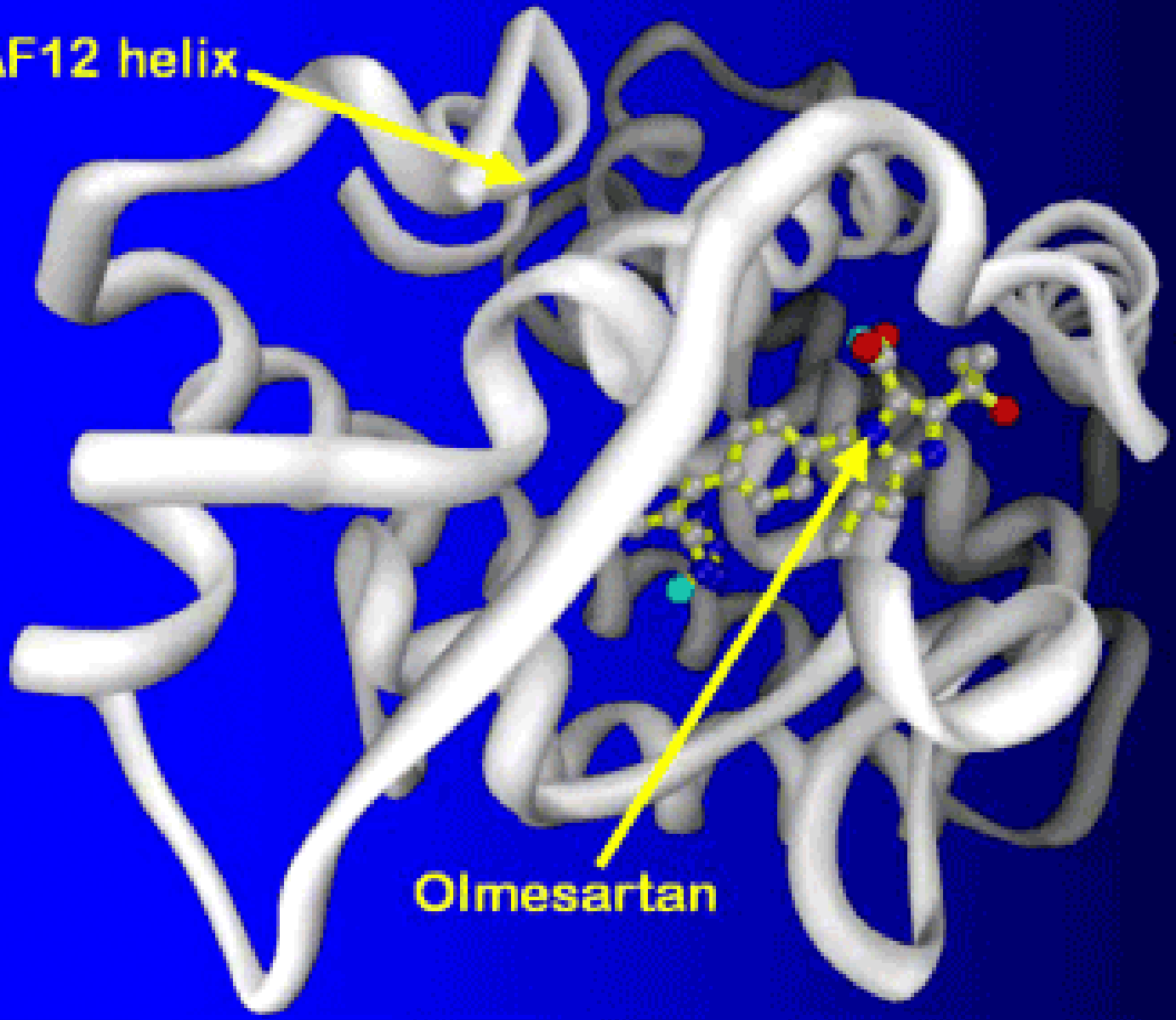

1,25(OH)2D
Calcitriol
CYTOPLASM
NUCLEUS
VDR
RXR
AMPs
Transcription
Co-activation factors
Transcription factors
VDR
RXR
RNA polymerase
VDRE


Incompetent VDR
Persistent Intracellular Infection
Elevated Extra-renal Calcitriol
Ineffective Immune Function
Chronic Inflammation


Intracellular bacteria
Cytokines
Lipo poly saccharide
Vitamin D Binding Protein
Nitric oxide
↑CYP27B1
Inflamed Extra-renal Tissues:
monocytes
macrophages
bone cells
keratinocytes
intestines
pulmonary
spleen
breast
prostate
synovial
uterine
placenta
↑1,25(OH)2D
↓ 25(OH)D


CODE 1A
LEVEL 7

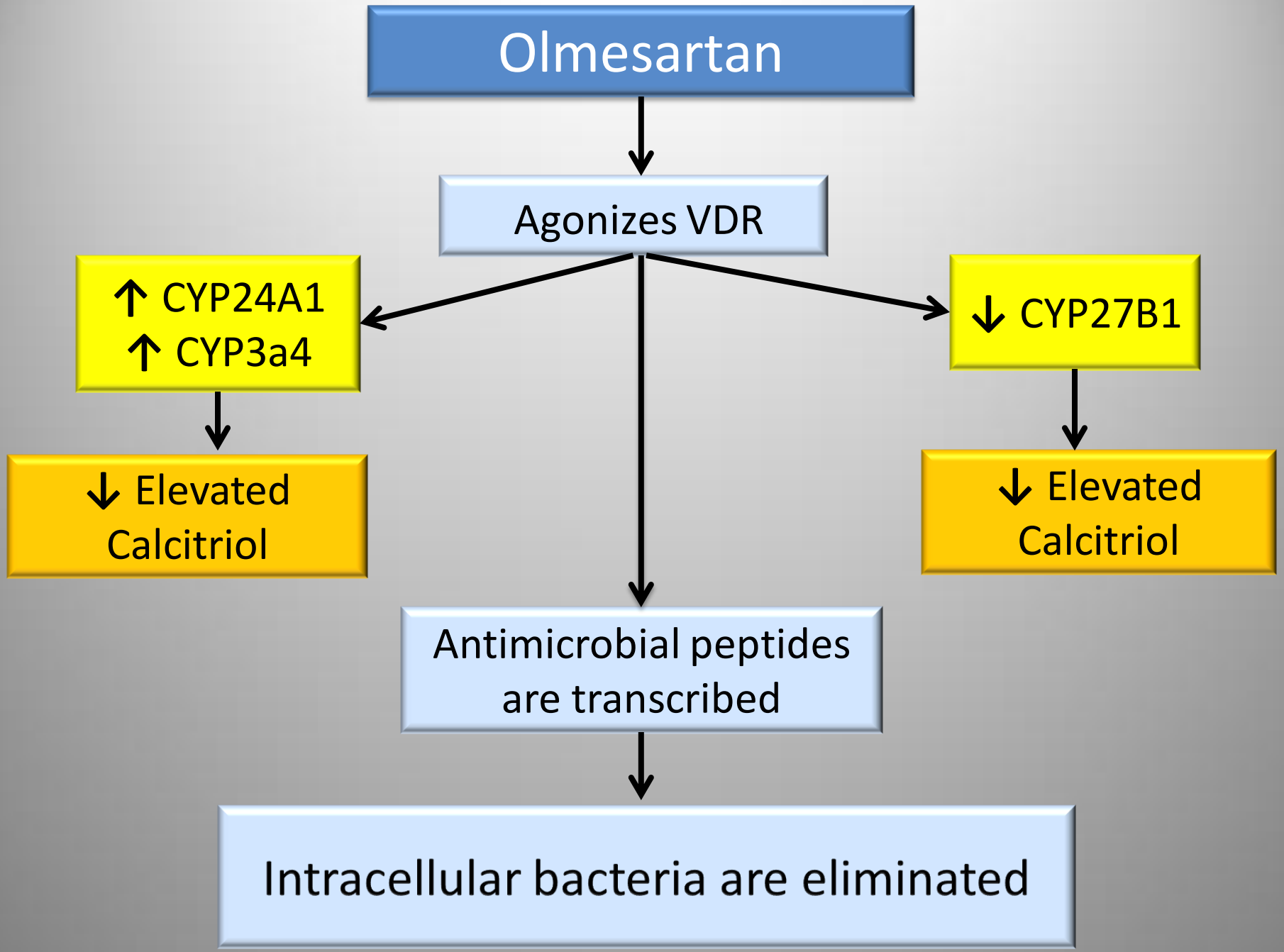
Olmesartan Medoxomil is VDR Agonist



Hydrogen Bonds:

SER237
ARG274
SER278
LYS240
ASP144

TG Marshall slide


Olmesartan
Agonizes VDR
↑ CYP24A1
↑ CYP3a4
↓ CYP27B1
↓ Elevated Calcitriol
↓ Elevated Calcitriol
Antimicrobial peptides are transcribed
Intracellular bacteria are eliminated

Recovery from Sarcoidosis





85% of subjects had elevated calcitriol without hypercalcemia.

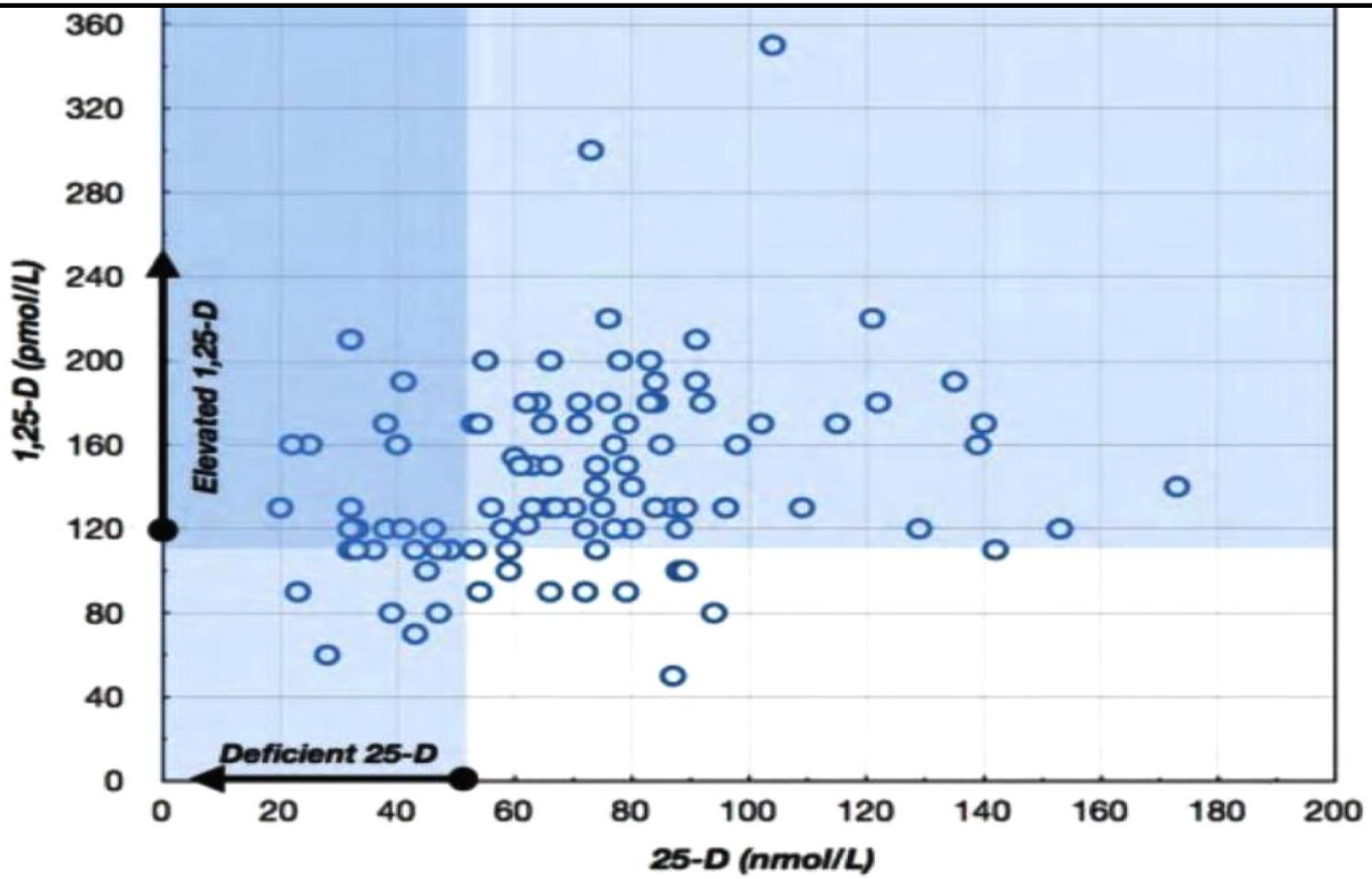
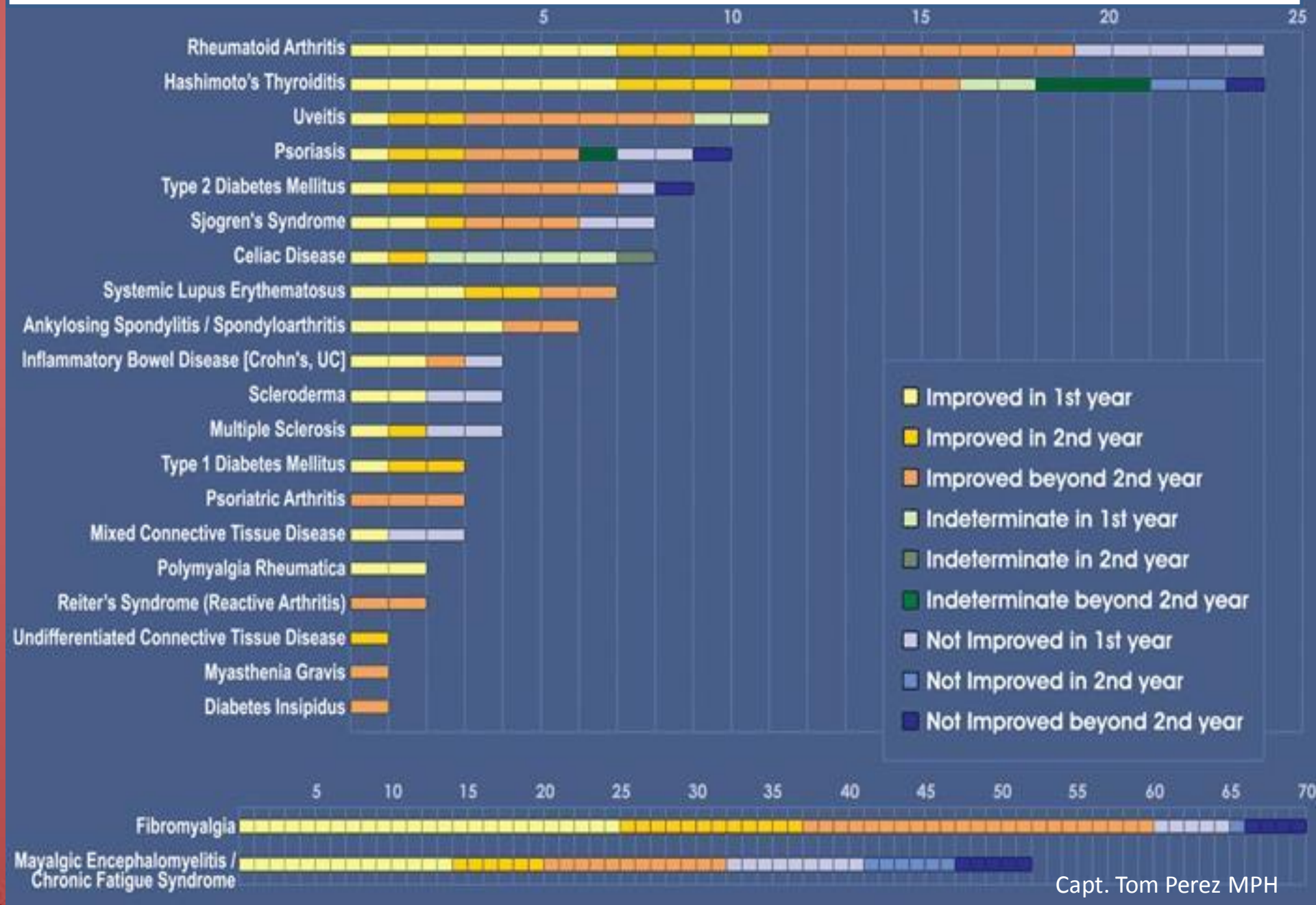


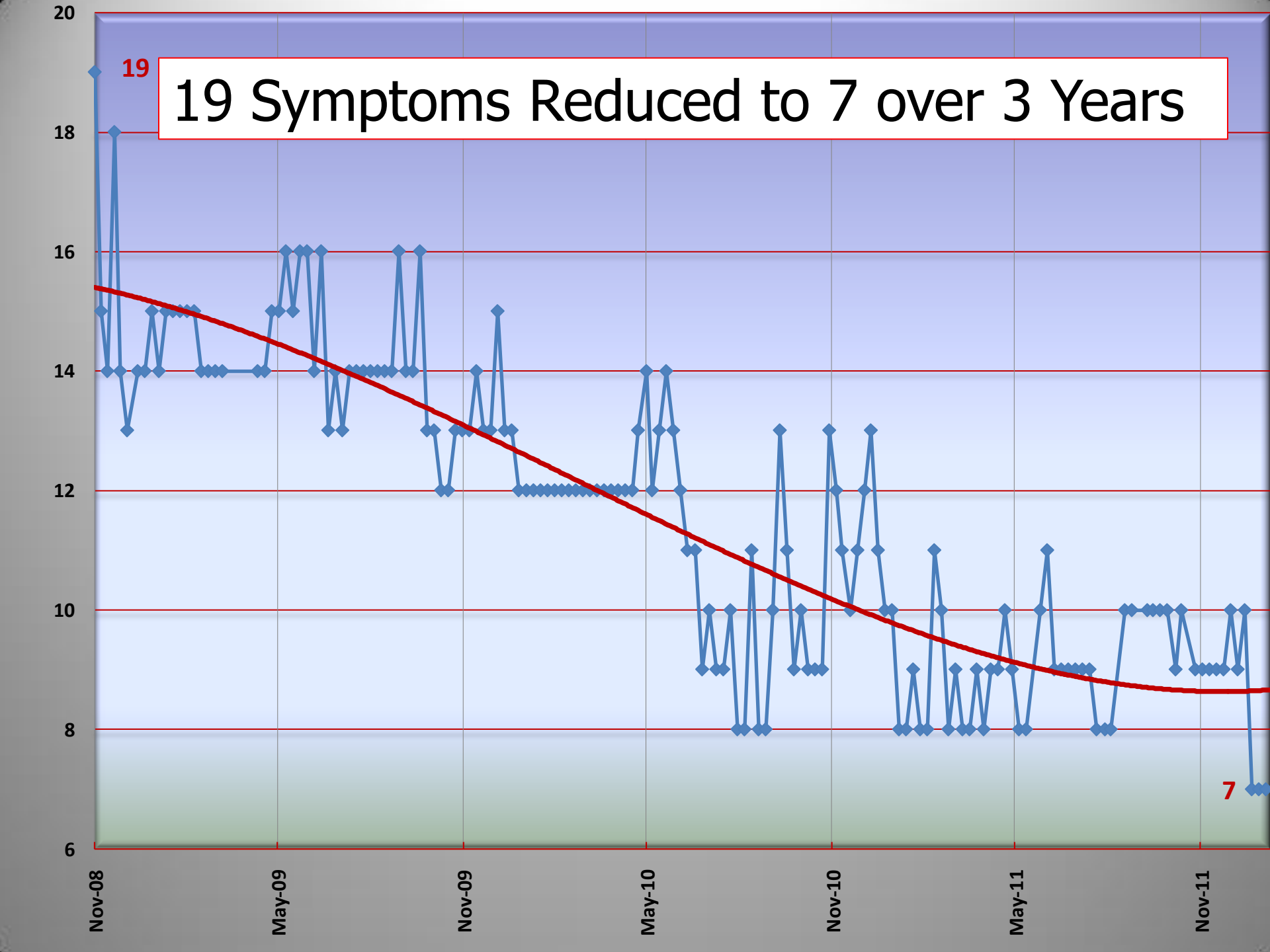
Figure 3. 25-D vs. 1,25-D in a cohort of 100 autoimmune patients [69]

Blaney et al.

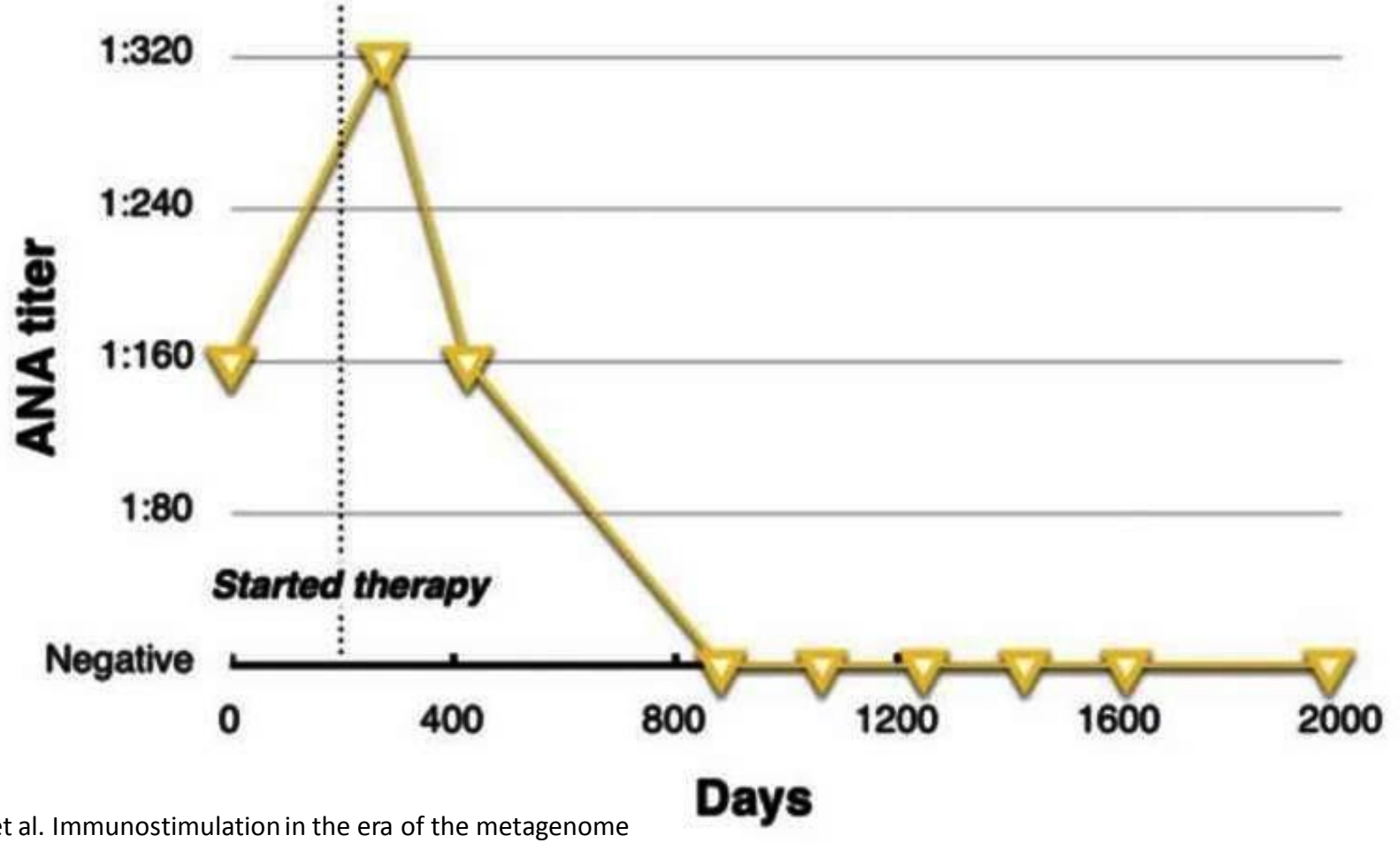
Timeline of Symptom Improvement in a Varied Cohort



Capt. Tom Perez MPH

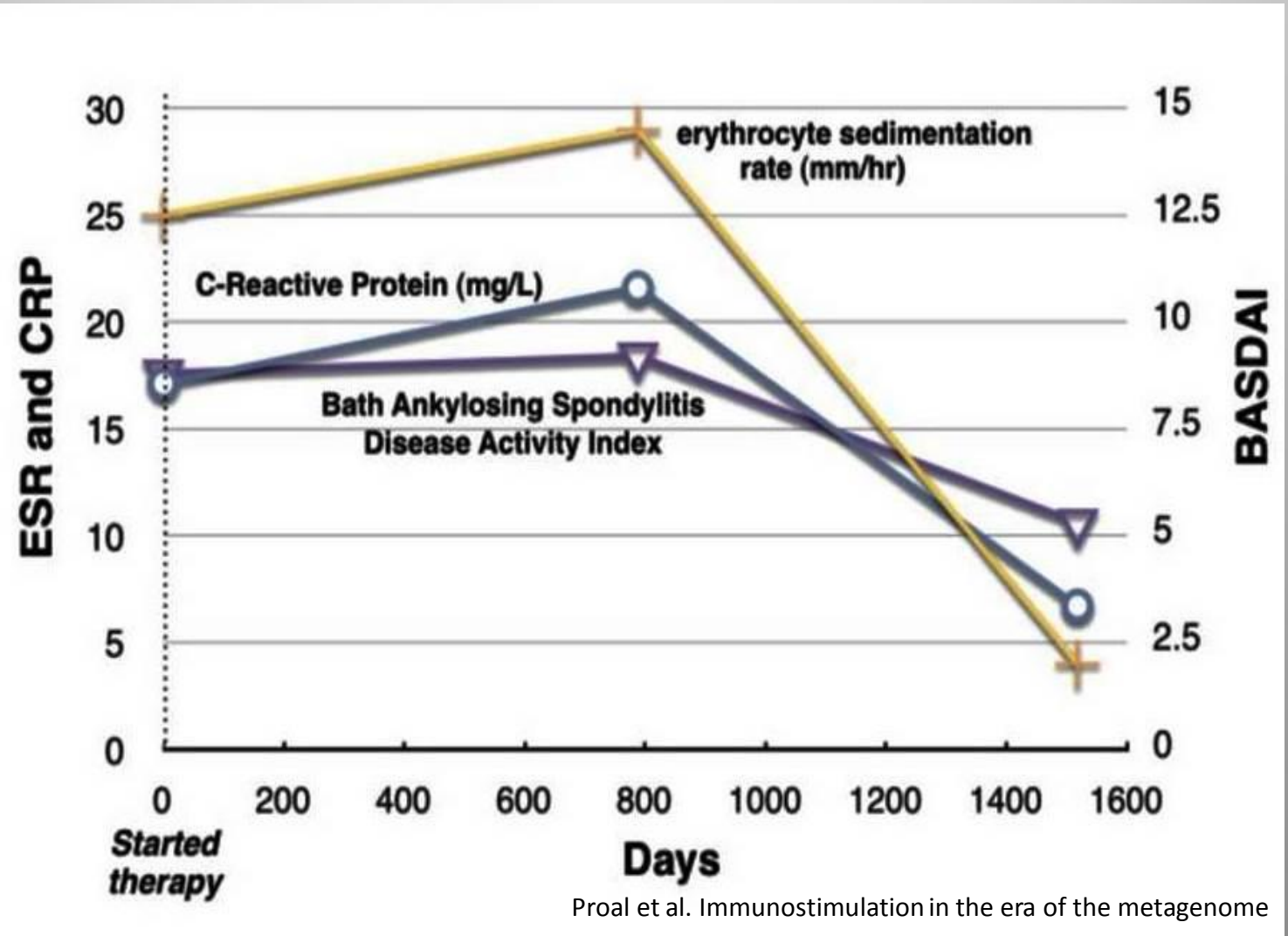

19 Symptoms Reduced to 7 over 3 Years
19
7
20
18
16
14
12
10
8
6
Nov-08
May-09
Nov-09
May-10
Nov-10
May-11
Nov-11

Antinuclear Antibodies in a 58yo Female with Rheumatoid Arthritis



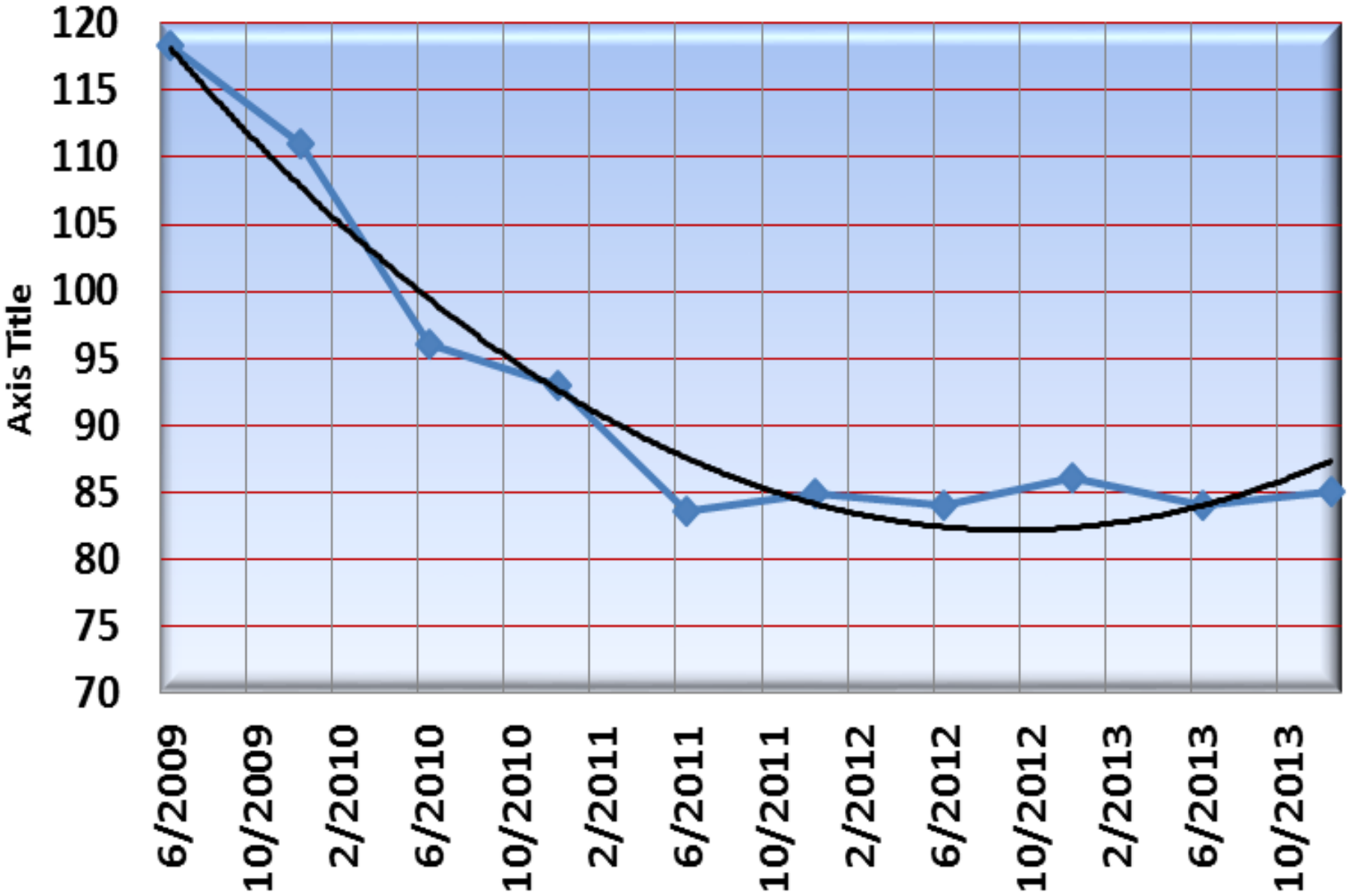
Proal et al. Immunostimulation in the era of the metagenome

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



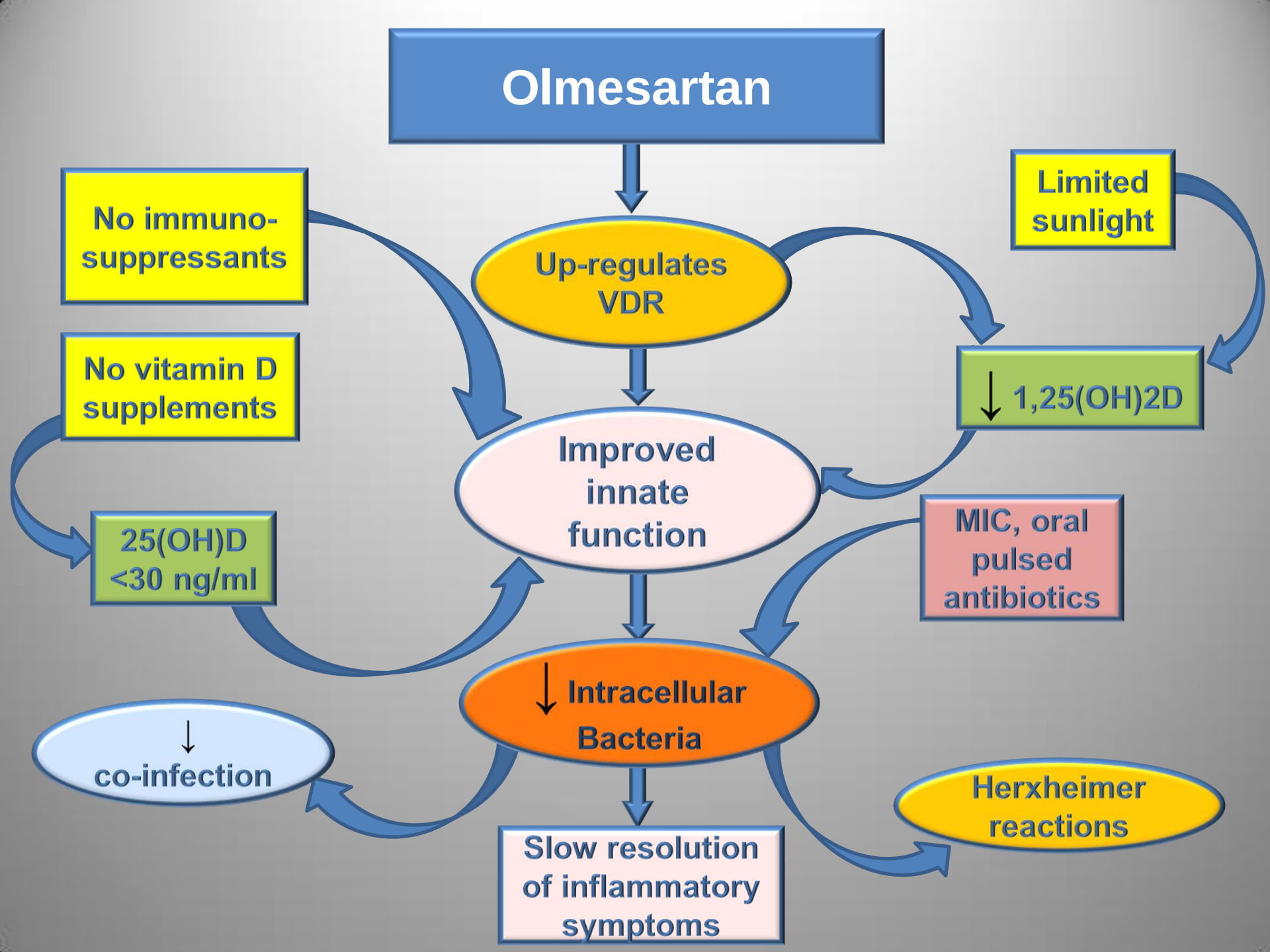
Proal et al. Immunostimulation in the era of the metagenome

Mean Aterial Pressure



Category	Goal	10 Year 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


Olmesartan
No immuno-suppressants
Limited sunlight
Up-regulates VDR
No vitamin D supplements
↓ 1,25(OH)2D
Improved innate function
25(OH)D <30 ng/ml
MIC, oral pulsed antibiotics
↓ Intracellular Bacteria
↓ co-infection
Herxheimer reactions
Slow resolution of inflammatory symptoms

Research Needed

- In vitro study of olmesartan VDR agonist hypothesis.
- Calcitriol range of a healthy population.
- Calcitriol levels in autoimmune patients.
- Effect of higher dose olmesartan on elevated calcitriol level.
- Long-term clinical trial of high-dose olmesartan & low-dose antibiotics.

“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