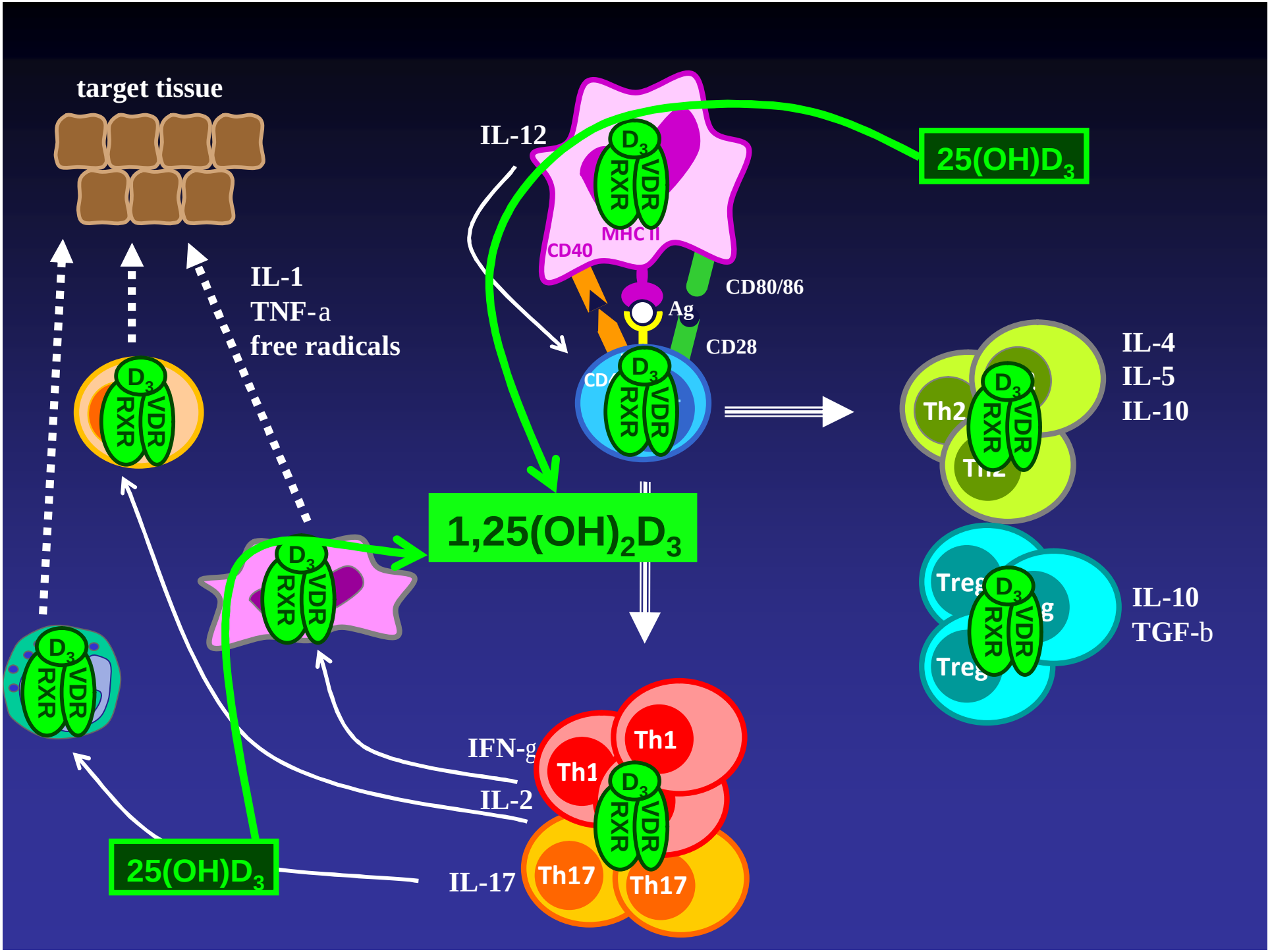
Vitamin D
and
its role in the immune system

Roger Bouillon

Clinic and Laboratory of
Endocrinology
University Leuven, Belgium


target tissue
IL-12
25(OH)D3
MHC II
CD40
CD80/86
Ag
CD28
IL-1
TNF-a
free radicals
1,25(OH)2D3
IL-4
IL-5
IL-10
Th2
IL-10
TGF-b
Treg
IFN-g
IL-2
IL-17
Th1
Th17
25(OH)D3
D3
VDR
RXR

The immune system

Natural immunity

- rapid
- little specificity
- modest efficacy

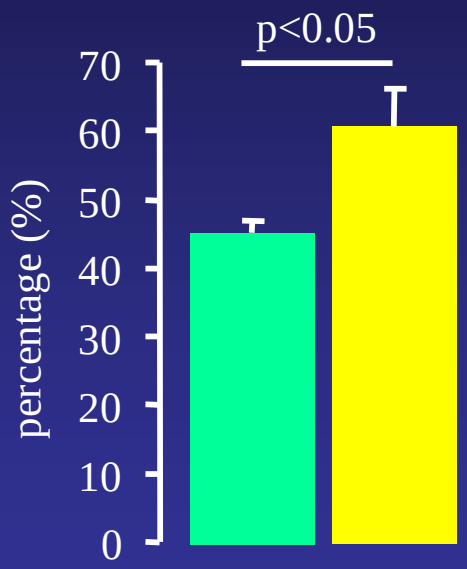
= macrophages

Acquired immune system

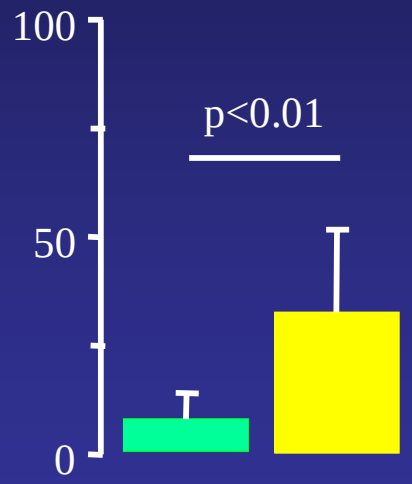
Vitamin D deficiency
VDR KO

Abnormal macrophage behaviour in vitamin D-deficient mice

Burst Capacity

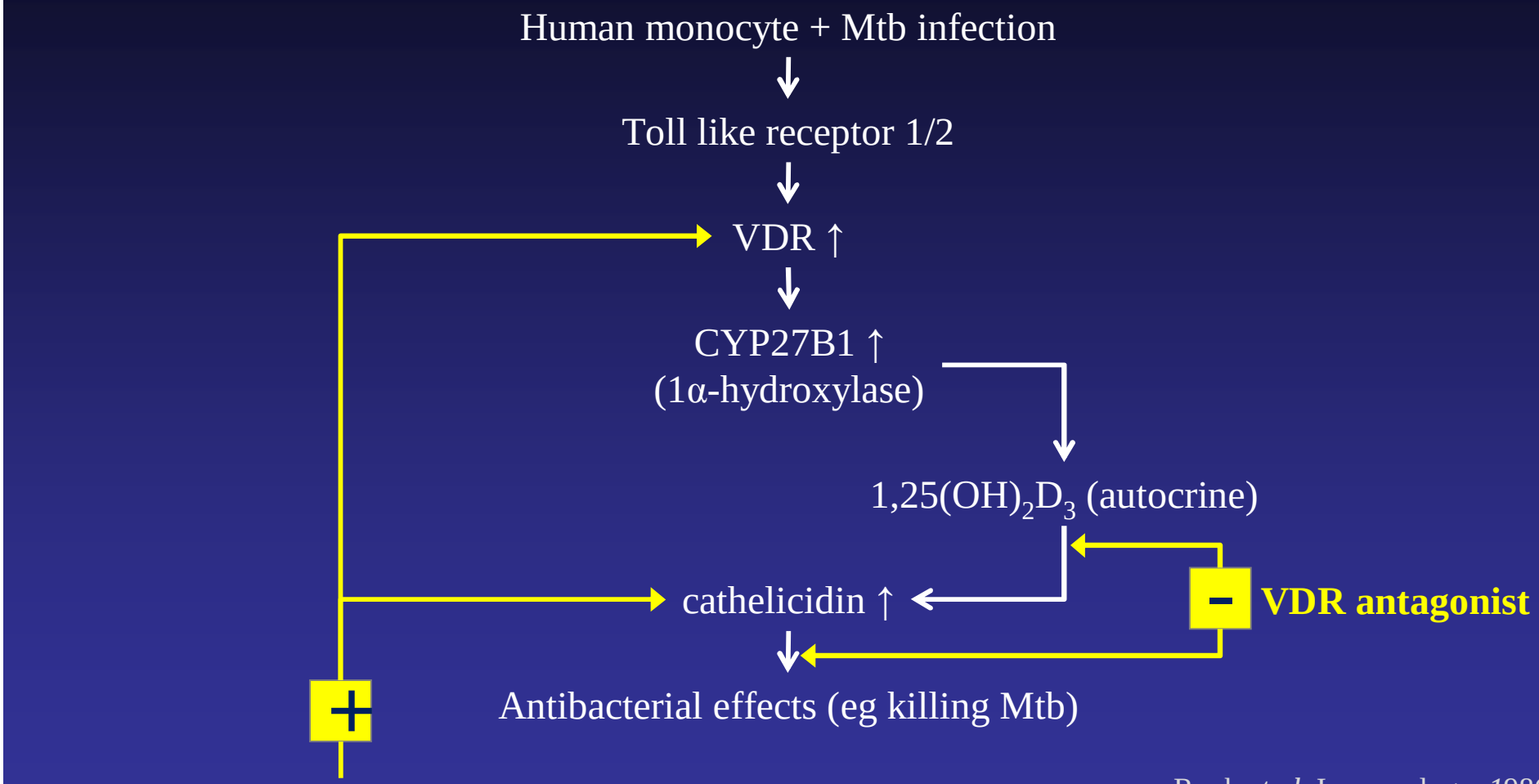


Chemotaxis Casein



male C57Bl/6
vitamin D deficient
control

Vitamin D & innate immune system



Rook *et al*, Immunology, *1*986
Crowle *et al*, Infect and Immun, 1987
Lin *et al*, Science, 2006
Wang *et al*, J Immun, 2005
Gombart *et al*, Faseb J, 2004

Vitamin D and the immune system
Infections

Association rickets and (respiratory) infections:

- historic records
- recent studies in Middle East/Africa

Association 25OHD levels and infections:

- tuberculosis
- respiratory infections:

Finnish soldiers: + 63% ; if 25OHD < 16 ng/ml

(Laaksi *et al*, Am J Clin Nutr, 2007)

NHANES III: OR of 1.36 if 25OHD < 10 versus > 30 ng/ml

(Ginde *et al*, Arch Intern Med, 2009)

especially in patients with asthma or COPD

No association of serum 25OHD and mortality due to infections

(NHANES, Melamed *et al*, Arch Intern Med, 2007)

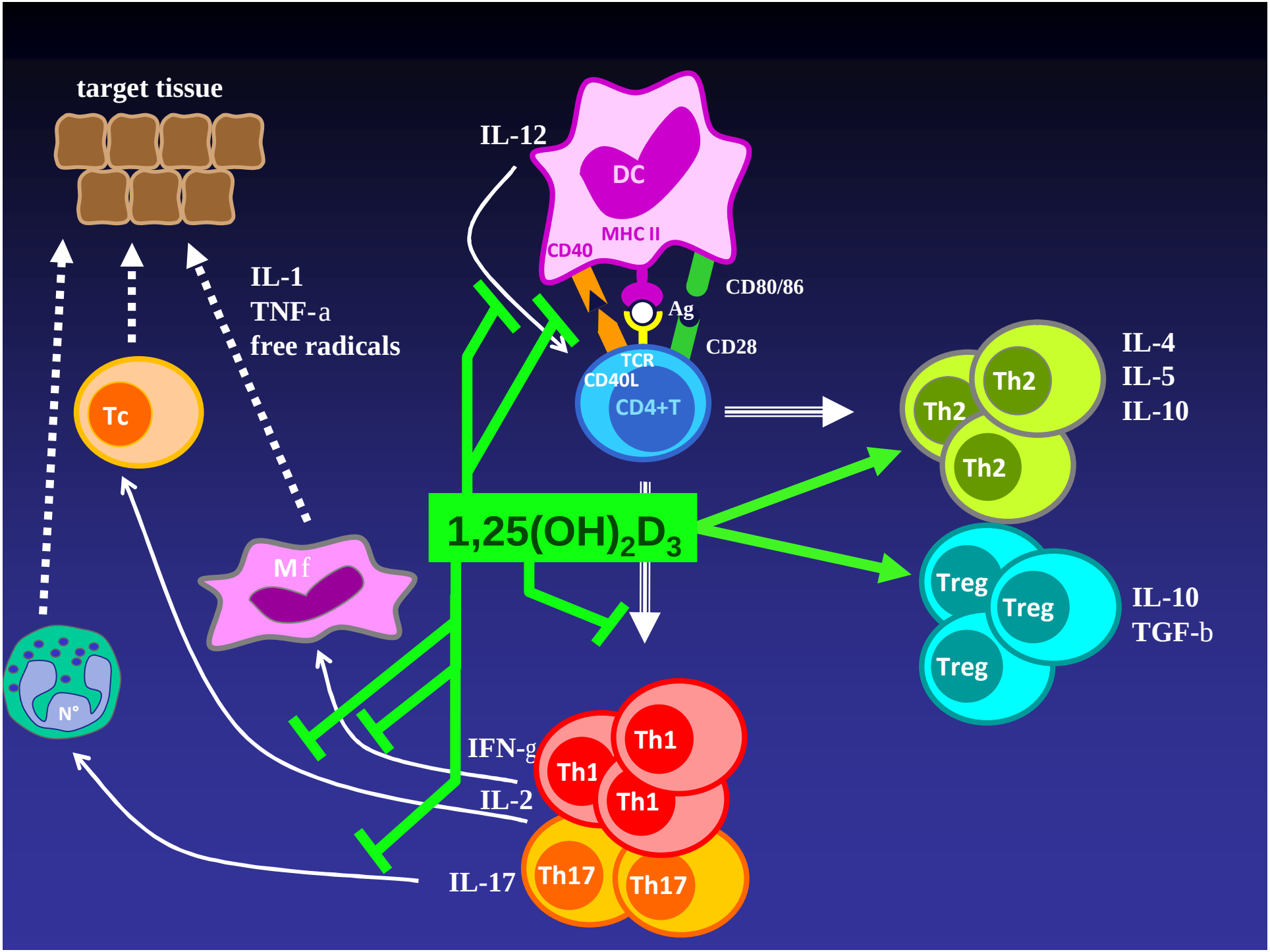
No published RCT but several ongoing studies

The immune system

Acquired immunity

- slow
- highly specific
- highly effective
- memory
- tolerance to self

= DC, T cells, B cells


target tissue
IL-12
DC
MHC II
CD40
CD80/86
Ag
CD28
TCR
CD40L
CD4+T
IL-1
TNF-a
free radicals
Tc
Mf
N°
1,25(OH)2D3
Th2
Th2
Th2
IL-4
IL-5
IL-10
Treg
Treg
Treg
IL-10
TGF-b
IFN-g
IL-2
IL-17
Th1
Th1
Th1
Th17
Th17

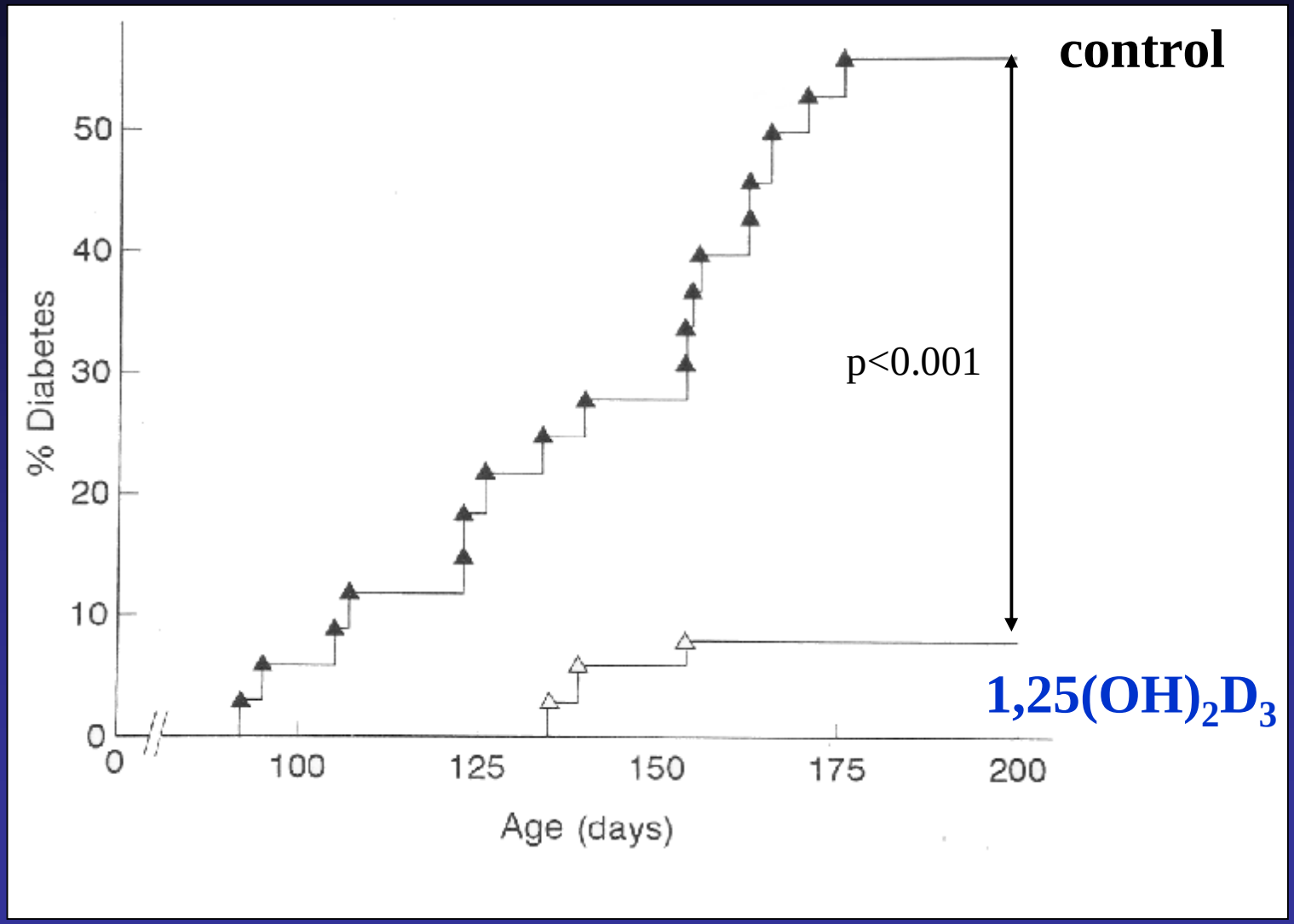
Vitamin D & acquired immune system

Prevention of autoimmune diseases:

- ***Type 1 diabetes***
- EAE
- reumatoid arthritis
- allergic nephritis
- inflammatory bowel disease
- thyroiditis
- autoimmune prostatitis
- autoimmune uveitis

Prolongation of graft survival

$1,25(OH)_2D_3$ prevents insulitis and diabetes in NOD mice



Mathieu *et al*, Diabetologia, 1994

$1,25(OH)_2D_3$ analogs prevent insulitis and diabetes in NOD mice

- in primary prevention (start R/ from weaning) *

- in secondary prevention
  (start R/ after biopsy-proven onset of insulitis) **

- in tertiary prevention
  (syngeneic islet transplantation) **

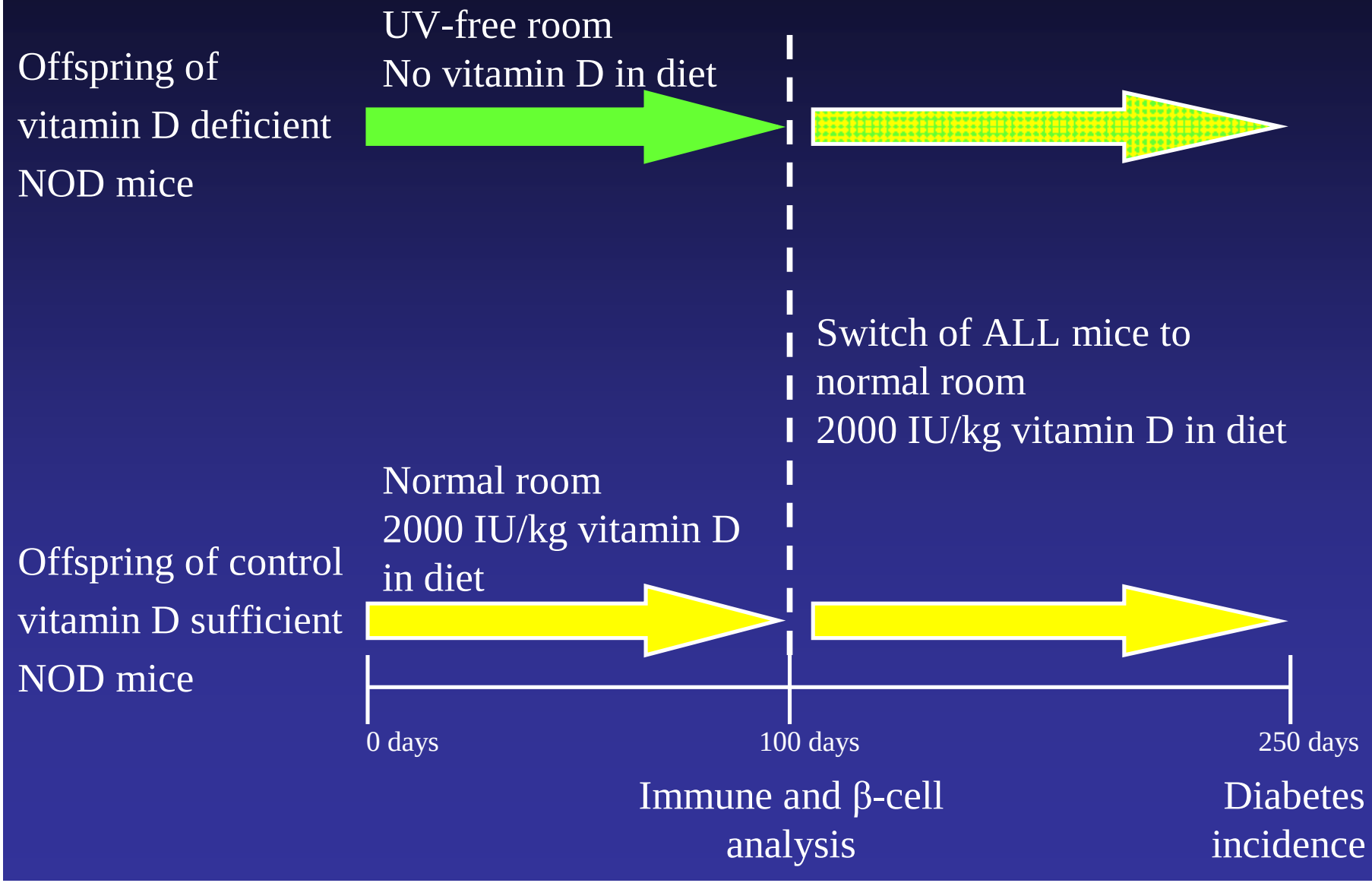
* idem for low dose streptozotocin induced and other models of autoimmune diabetes
** higher efficacy and synergy when transiently combined with other immunosuppressive agent

Mathieu *et al*, Diabetologia, 2004

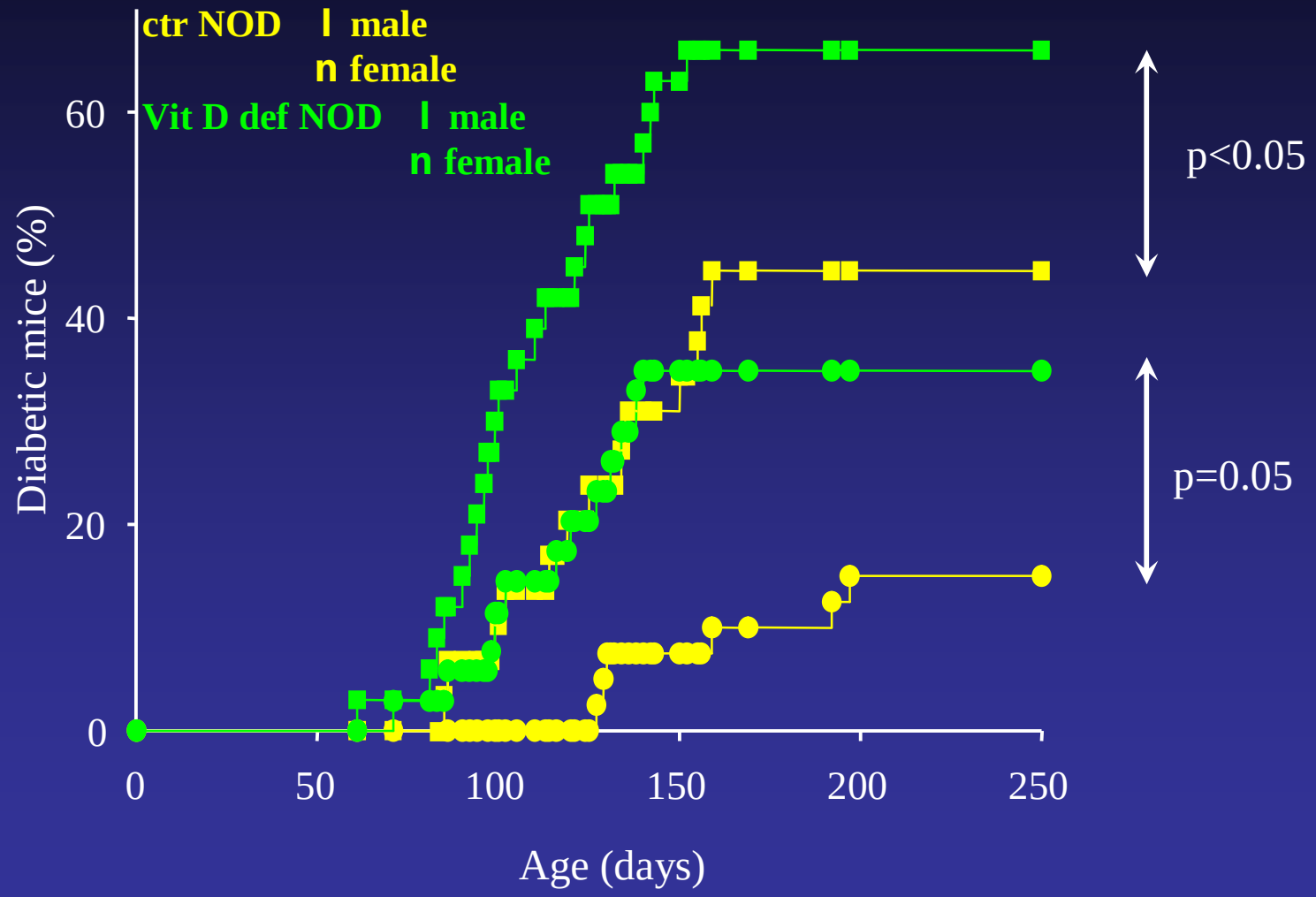
Vitamin D and type 1 diabetes: Case-control studies in humans

	Parameter	Subjects	OR
EURODIAB [Diabetologia, 1999]	Vitamin D intake via supplementation during 1st yr of life	<5 yrs 5-9 yrs 10-14 yrs	0.83 0.81 0.47
Stene *et al* [Am J Nutr Sci, 2003]	Vitamin D intake via cod liver oil 10µg for ≥5x/wk during 1st yr of life	<15 yrs	0.74
Hypponen [Lancet, 2001]	Vitamin D intake via supplementation 2000IU/d during 1st yr of life	1-31 yrs	0.12
	Rickets during 1st yr of life	1-31 yrs	2.60
Fronczak *et al* [Diabetes Care, 2003]	Vitamin D intake via food variable IU during pregnancy	<5 yrs	0.49
Tenconi *et al* [Acta Diabetol, 2007]	Vitamin D intake during lactation	<14 yrs	0.31

Experimental design



Diabetes incidence



Giulietti *et al*, Diabetologia, 2004

Vitamin D & acquired immune system Preclinical models

1. Vitamin D deficiency: predisposes to a large number of autoimmune diseases
   - type 1 diabetes (NOD and other models)
   - EAE/ multiple sclerosis
   - Inflammatory bowel disease
2. VDR and/or CYP27B1 KO: more prone to autoimmune diseases
   - EAE/MS
   - IBD
   - prostatitis
3. Vitamin D analogs: reduce disease severity in several models of autoimmune diseases
   - type 1 diabetes (NOD and other models)
   - MS/EAE
   - IBD
   - uveitis
   - prostatitis
   - nephritis
   - thyroiditis

Vitamin D & acquired immune system Clinical observations

Observational Studies

low vitamin D status associated with autoimmune diseases:

- MS: increased prevalence and recurrence
- Type 1 diabetes
- Inflammatory bowel disease

with higher prevalence of allergy

Interventional Studies

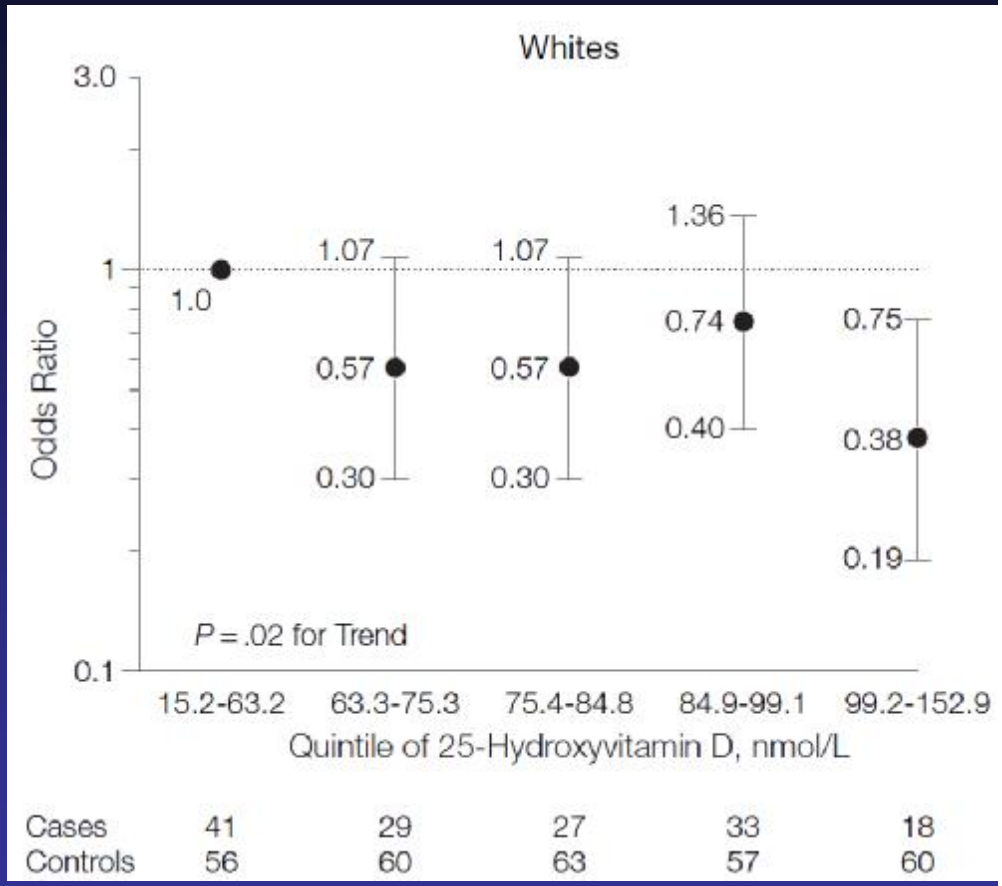
25OHD and multiple sclerosis

USA study:

- Prospective nested case control study
- >7 million US military personel
- 257 cases of MS vs 2x controls

Dutch studies:

- Similar results
- Low 250HD levels linked to more severe recurrence of MS disease



Munger *et al*, JAMA, 2006
Kragt *et al*, Multiple Sclerosis, 2009
Smolders *et al*, Multiple Sclerosis, 2008

Vitamin D and the immune system
Allergy

Maternal vitamin D status and allergy in offspring:

If maternal 25OHD > 75 nmol/l (> 30 ng/ml)
OR in offspring
–for atopic eczema at 9 m = 3.26 (CL 1.15-9.29)
–for asthma at 9 yrs = 5.40 (CL 1.09-26.65)

Gale *et al*, Eur J Clin Nutr, 2008

(Similar results in Finnish birth cohort study, 2004)

Vitamin D & acquired immune system Clinical observations

Observational Studies

Interventional Studies

- Retrospective analysis: type 1 diabetes
- True RCT missing but ongoing studies (ClinTrial)

Vitamin D and the immune system
Conclusions

The vitamin D endocrine system has well documented effects on many immune genes and all immune cells (in vitro and animal models)

Observational studies link poor vitamin D status with

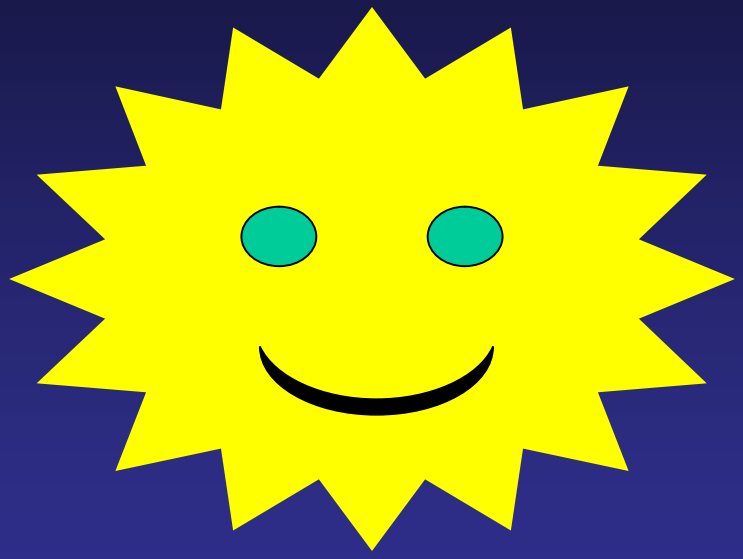
- some infections
- all major human autoimmune diseases

Highest risk if 25OHD < 20 ng/ml

Trend for still lower risk with 25OHD > 20 ng/ml

True RCT are missing but needed

Bright sunny future for vitamin D



Thank you!!!

MARK YOUR CALENDARS

14th Vitamin D Workshop
October 4-8, 2009
Brugge, Belgium

Monday, June 1, 2009: Abstract deadline
Monday, June 29, 2009: Early bird registration deadline
Tuesday, August 4, 2009: Hotel registration deadline
Sunday, October 4, 2009: Arrival and Welcoming Reception
Wednesday, October 7, 2009: Grand Banquet

Information on meeting Registration and Hotel Housing will be available soon.

http://vitamind.ucr.edu/workshop.html

! There will be no printed announcements
Only electronic announcements will be sent.