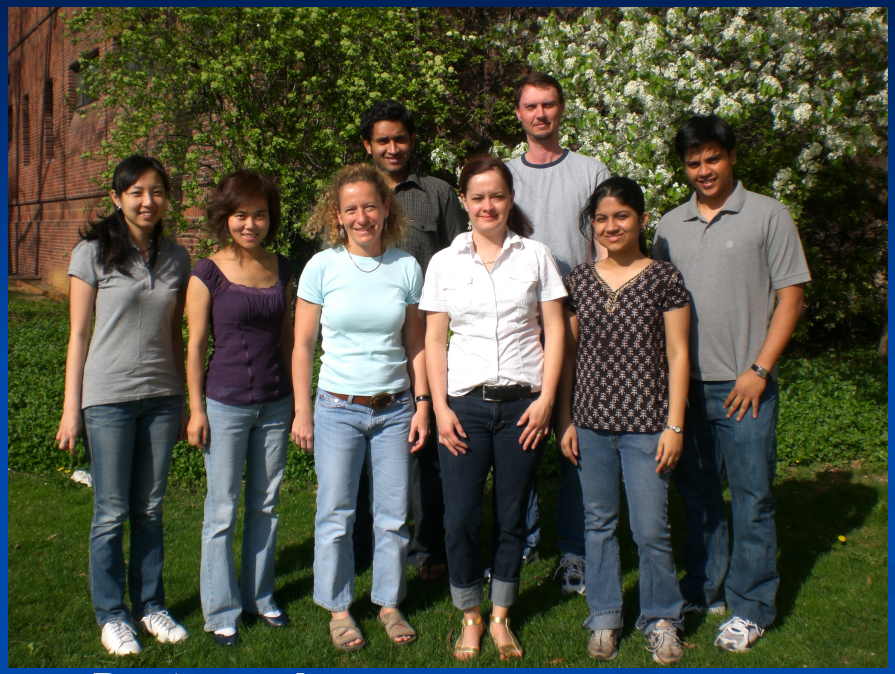
# Vitamin D and autoimmunity.



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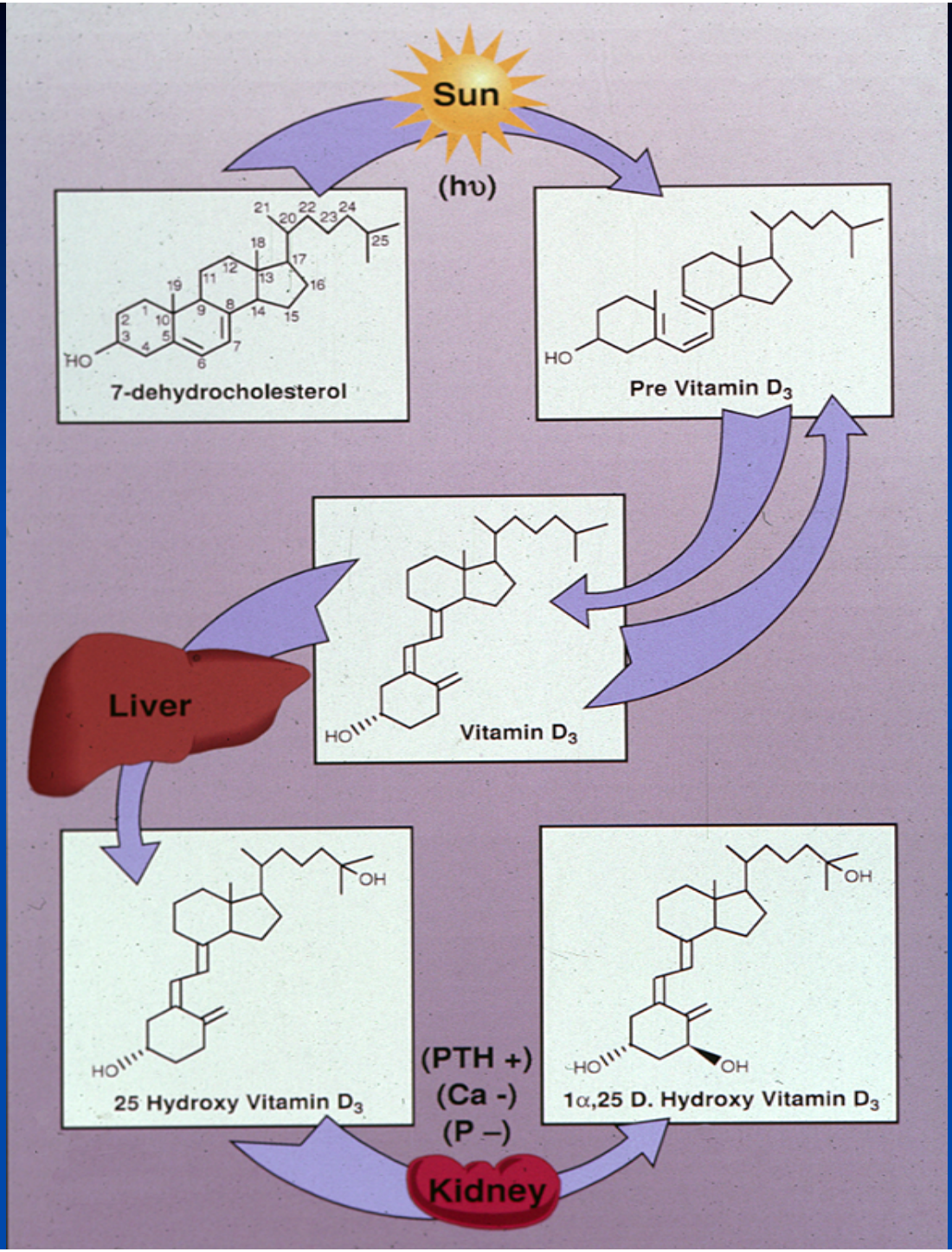
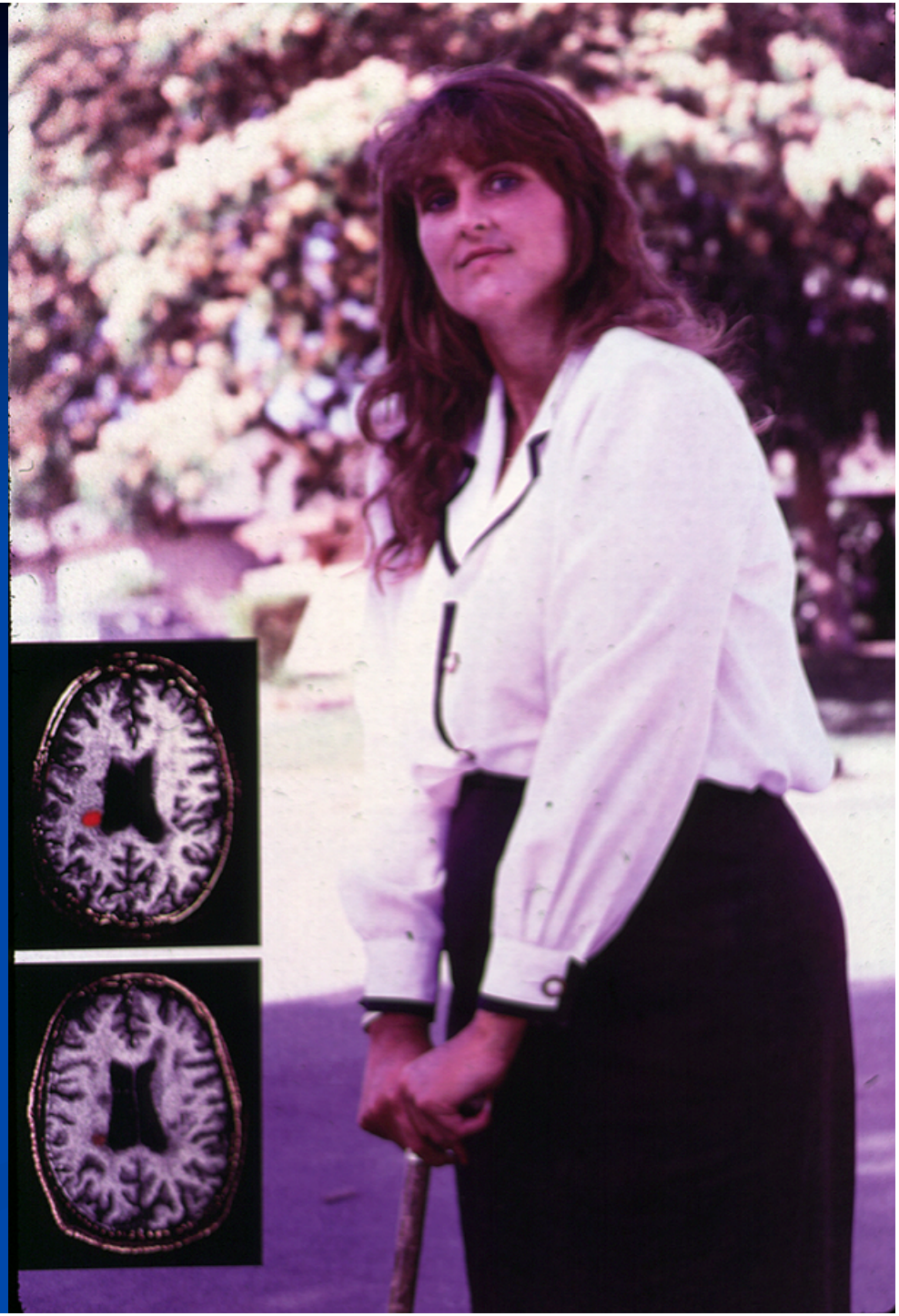

Sun
(hυ)
7-dehydrocholesterol
Pre Vitamin D3
Liver
Vitamin D3
25 Hydroxy Vitamin D3
1α,25 D. Hydroxy Vitamin D3
(PTH +)
(Ca -)
(P –)
Kidney

# Autoimmunity

Multiple sclerosis
Lupus
Arthritis
Type I Diabetes
Inflammatory Bowel Disease



# Genes and Environment

**Biological relatives of IBD patients show 10 fold increased risk.**

**Sisters/brothers show a 30 fold increased risk.**

**However, monozygotic twins show a 18% (ulcerative colitis) and 50% (Crohn's) concordance rate.**

# Inflammatory Bowel Disease

**Environment:**
**Higher: urban than rural**
**northern than southern**
**(Europe and North America)**
**developed than underdeveloped**

**Sunlight?**
**Bacterial flora**

**When measured vitamin D status low/bone diseases!**

Does vitamin D status affect the development of autoimmune diseases?

# Experimental Inflammatory Bowel Disease

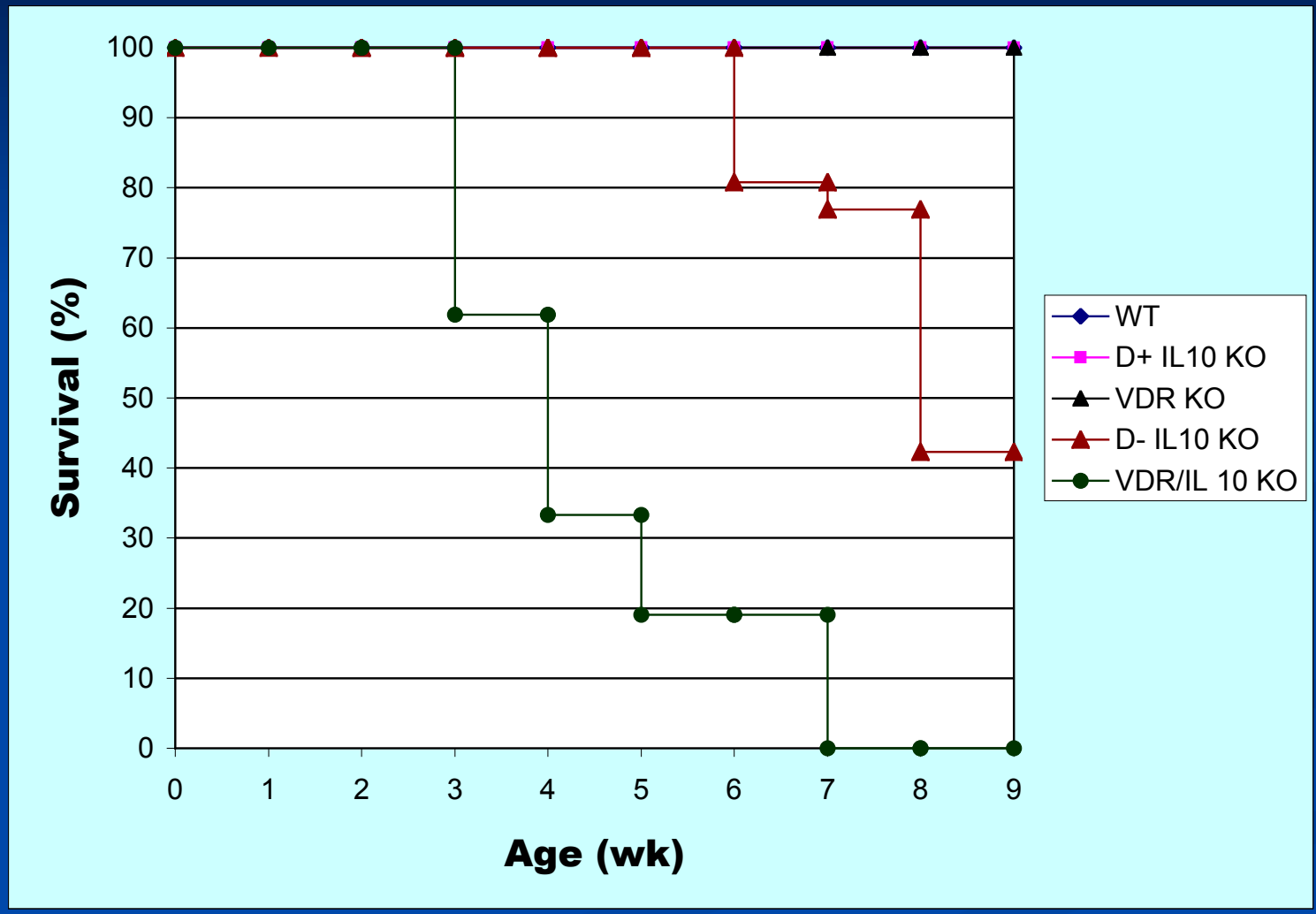
## Spontaneous colitis - as a consequence of targeted mutations

**IL-10 KO mice spontaneously develop IBD symptoms in the ileum and colon because of a defect in regulatory T cells.**

**Disease develops sporadically beginning at 9-10 weeks of age. Some mice may not show symptoms after much longer.**

**Wasting, diarrhea, rectal prolapse and bleeding which can lead to premature mortality.**

# Vitamin D and VDR deficiency exacerbates Inflammatory Bowel Disease




Cantorna et. al 2000 Journal of Nutrition, Froicu et. al 2003 Molecular Endocrinology

# Dextran sodium sulfate induced colitis

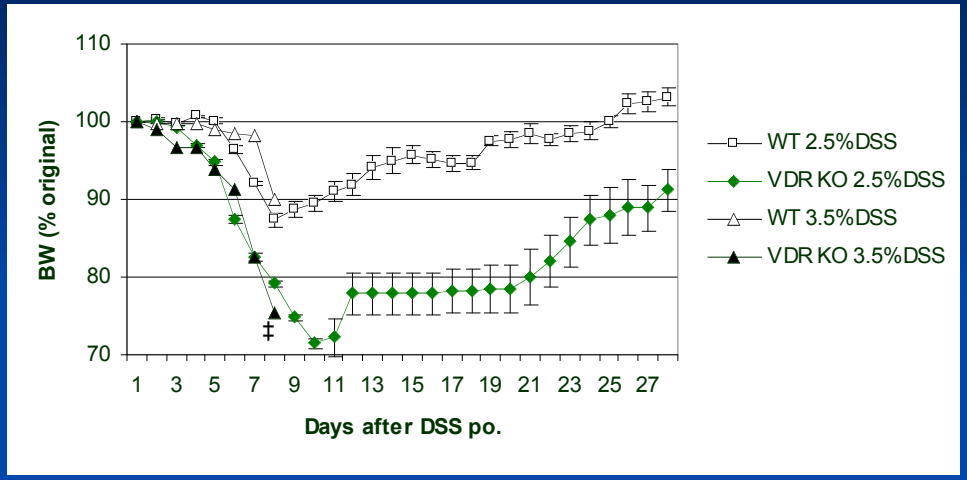
DSS in drinking water
5 days/ 5 days regular drinking water

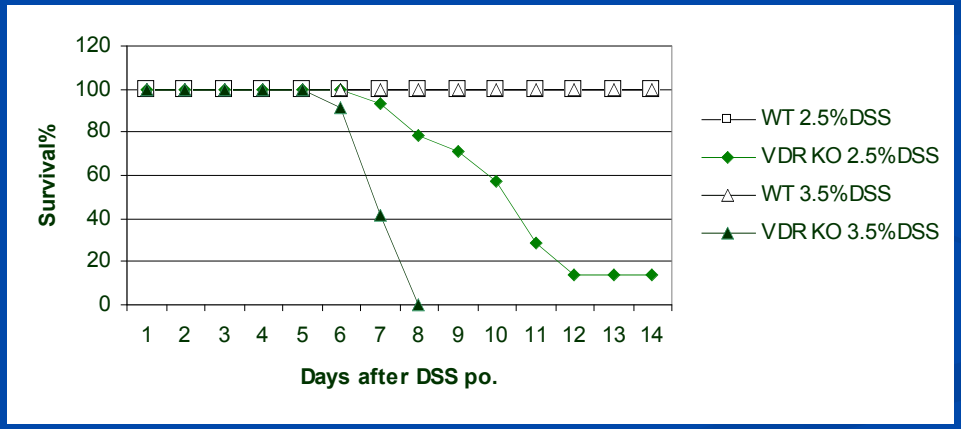
WT

VDR KO

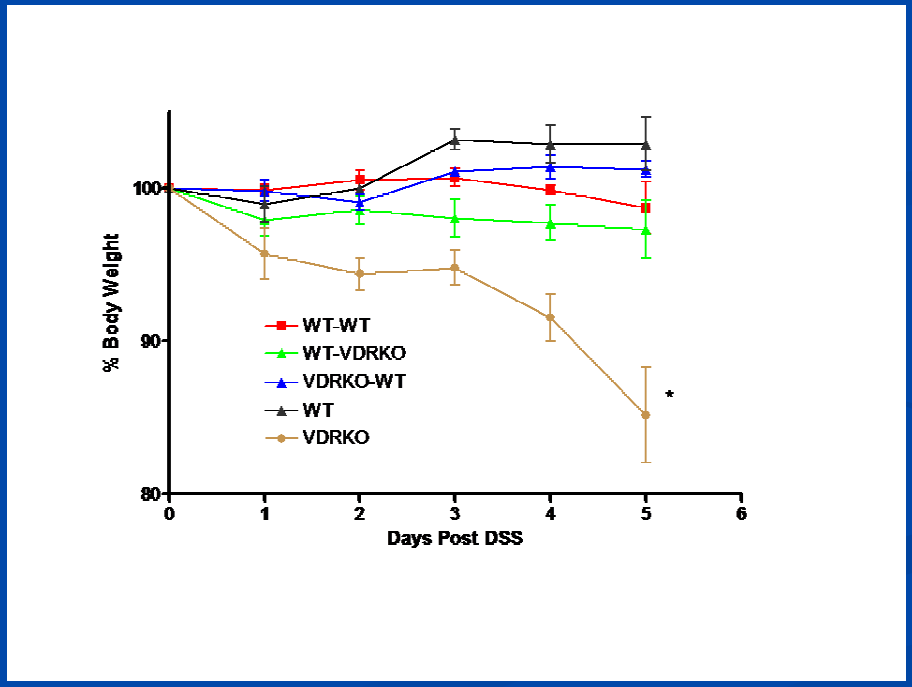
-colonic length
-Histopathology colon
-body weight changes

# VDR KO mice are highly susceptible to dextran sulfate induced colitis



# Wild type bone marrow transplantation rescues VDR KO mice from DSS colitis.



# CONCLUSIONS

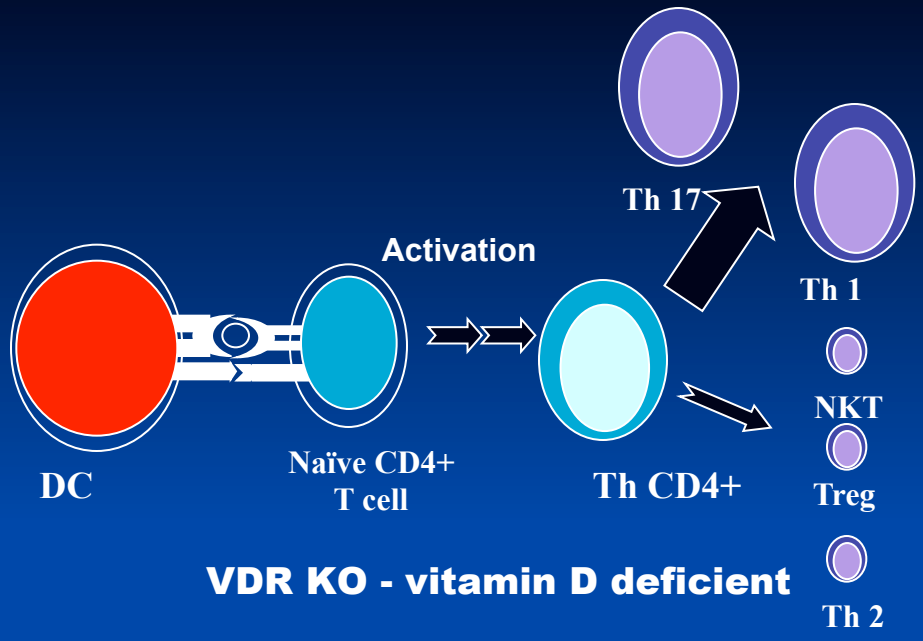
Vitamin D or VDR deficiency increased the mortality rate in IBD susceptible strains of mice.

$1,25(OH)_2D_3$ reduced inflammation in IL10 KO mice. The reduction in inflammation correlated with the decreased expression of TNF$\alpha$ related genes.

VDR/IL10 double KO mice develop a fulminating form of IBD. IBD transferred via splenocytes.

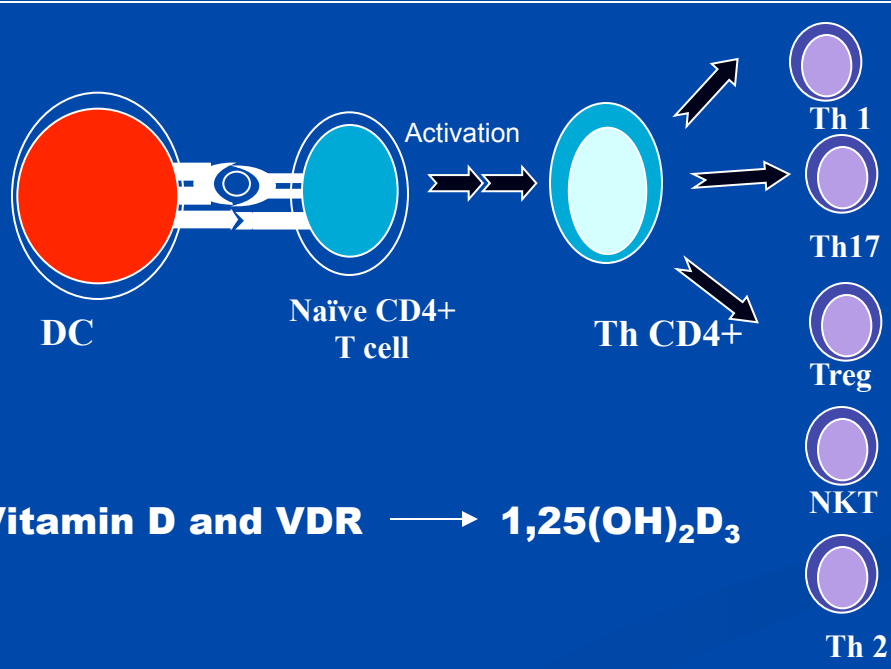
VDR KO mice are highly susceptible to DSS colitis. WT bone marrow protects VDR KO mice from DSS. $1,25(OH)_2D_3$ treatment reduced symptoms of colitis.

Model of defect in VDR KO CD4+ T cells increase IBD




IBD

**VDR KO - vitamin D deficient**




**Normal T cell function**

**Less IBD**

**Vitamin D and VDR → $1,25(OH)_2D_3$**

## IBD: Following CD4/CD45RB$^{high}$ T Cell Transfer into RAG KO mice.

**CD4 naive (CD25-)** →  → **IBD**

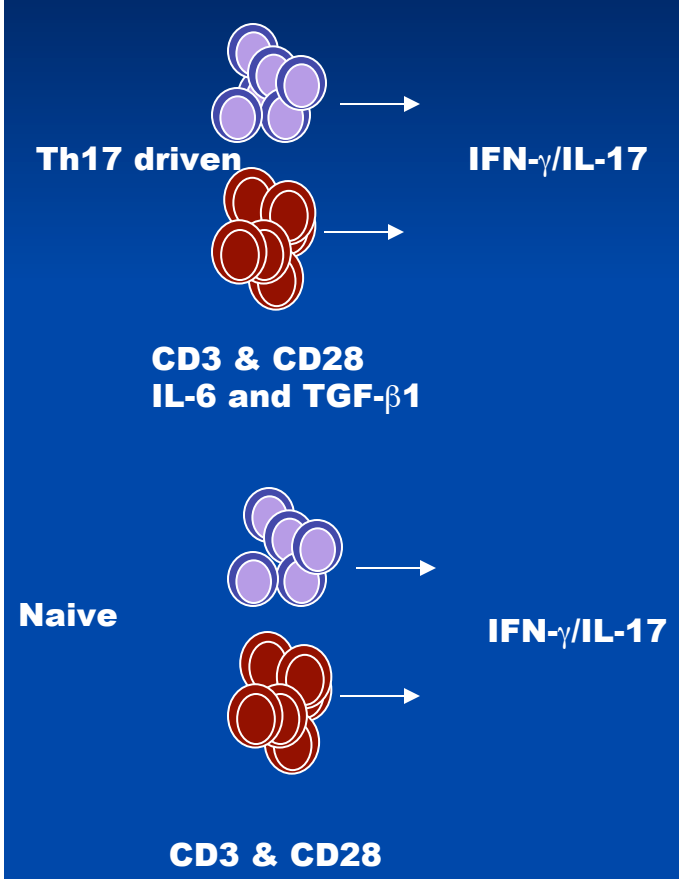
**C57BL/6 Rag KO mice**

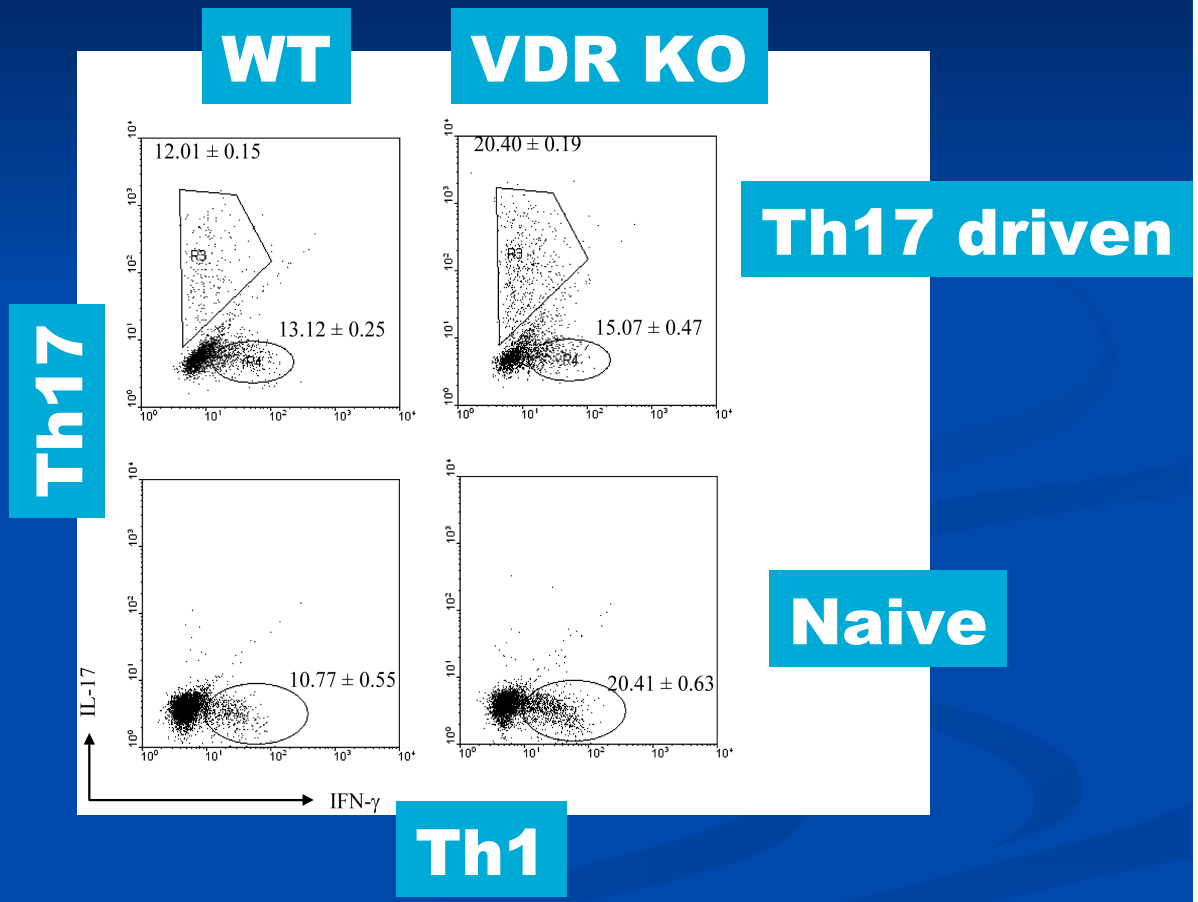
| Donor Cells | Body Weight (g) | SI/BW (%) | LI/BW (%) | Colitis | |
|---|---|---|---|---|---|
| WT naive | 18.8 ± 0.8$^{a}$ | 6.8 ± 0.4$^{b}$ | 3.6 ± 0.6$^{a}$ | 2.9 ± 0.3$^{b}$ | IBD |
| VDR KO naive | 17.4 ± 0.6$^{a}$ | 11.0 ± 0.9$^{d}$ | 6.4 ± 1.0$^{b}$ | 5.8 ± 0.5$^{c}$ | more severe IBD |

**VDR KO CD4+ T cells contain highly pathogenic T cells**

Froicu et. al 2003 Molecular Endocrinology

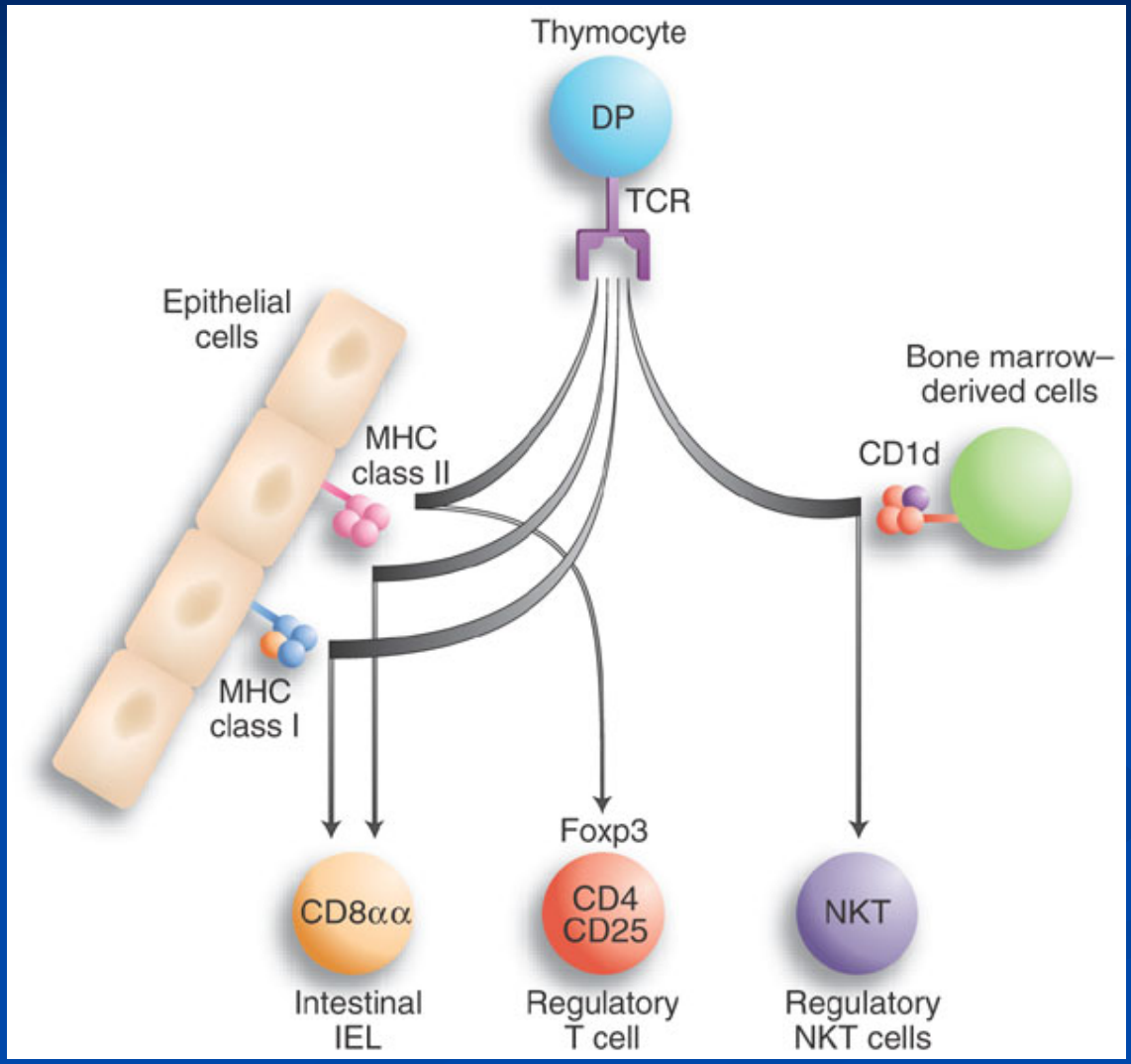
# More Th17 and Th1 cells in VDR KO mice.



# Unconventional T cells as regulatory cells

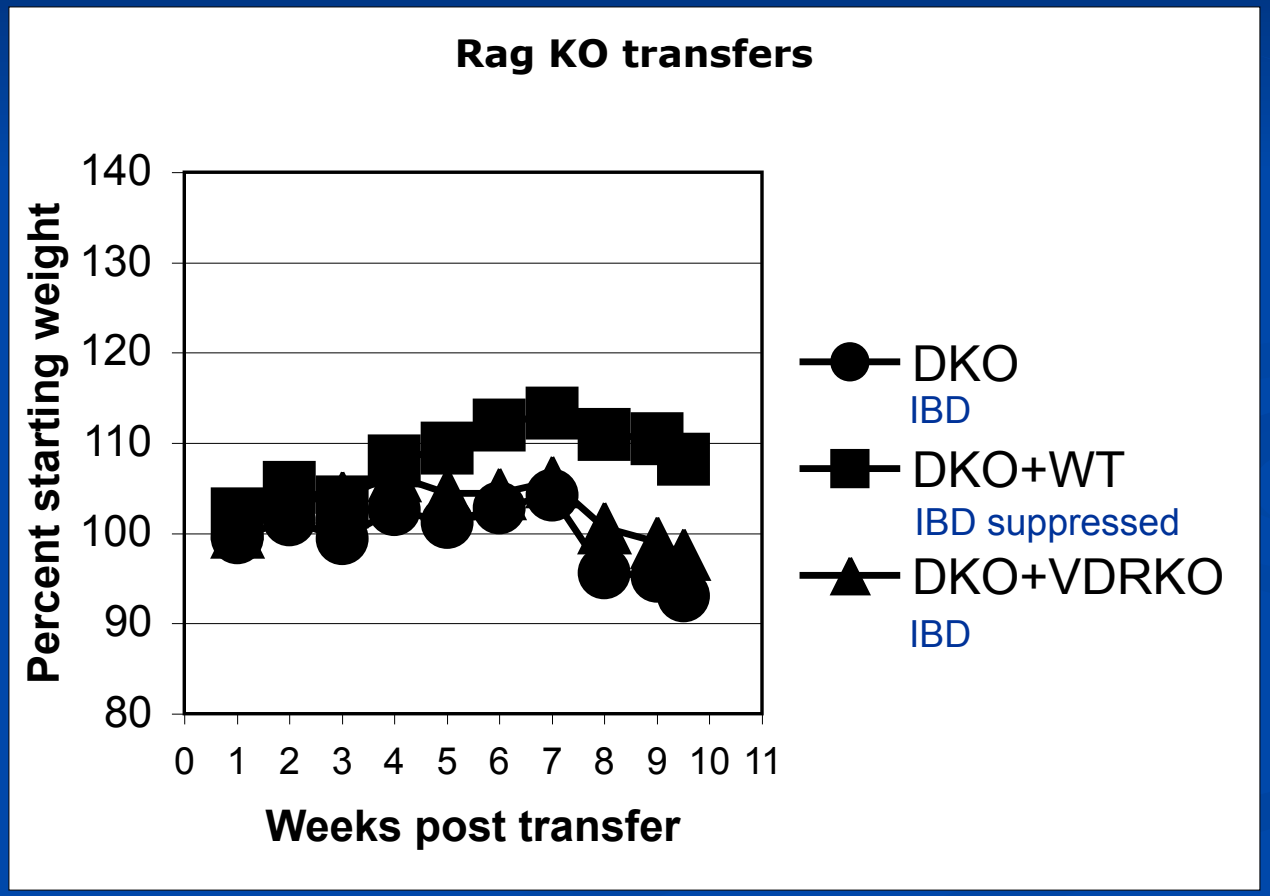
Classical T cells CD4+, CD8+ etc. are present in normal numbers in the VDR KO mice.



# VDR KO CD4+ FAIL TO SUPPRESS WEIGHT LOSS

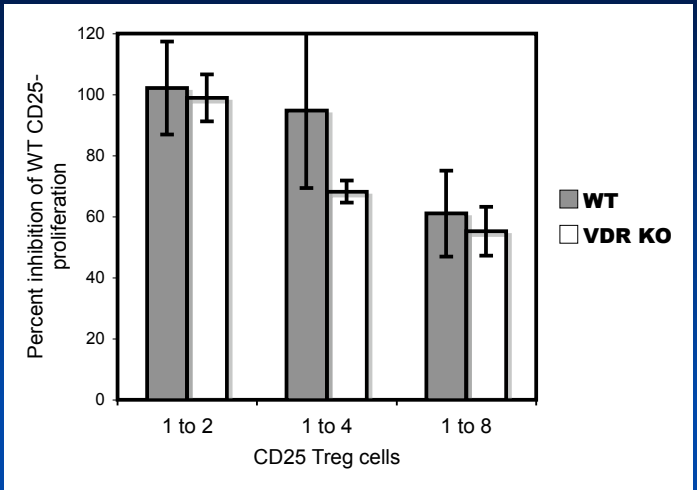
IL10/VDR KO spleen → IBD

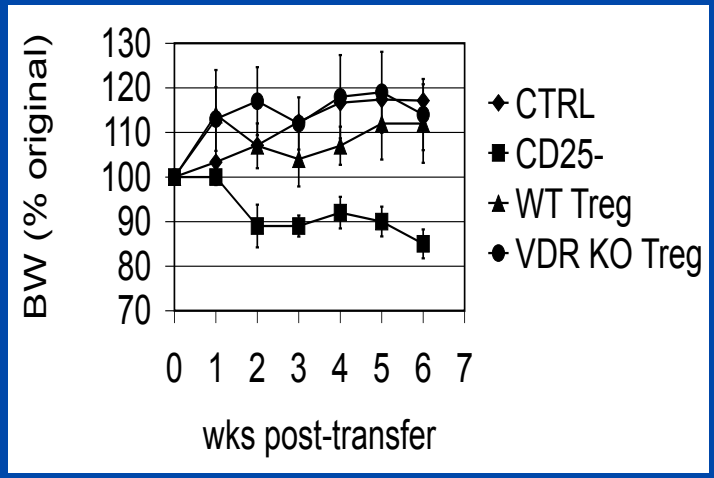
CD4+ IL10/VDR KO spleen → no disease

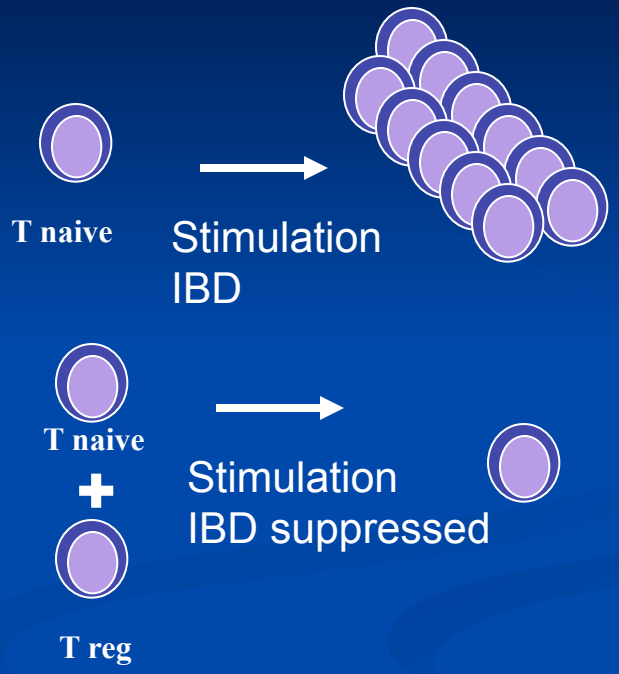



Yu & Bruce et. al 2008 PNAS

# In vitro and in vivo T reg function



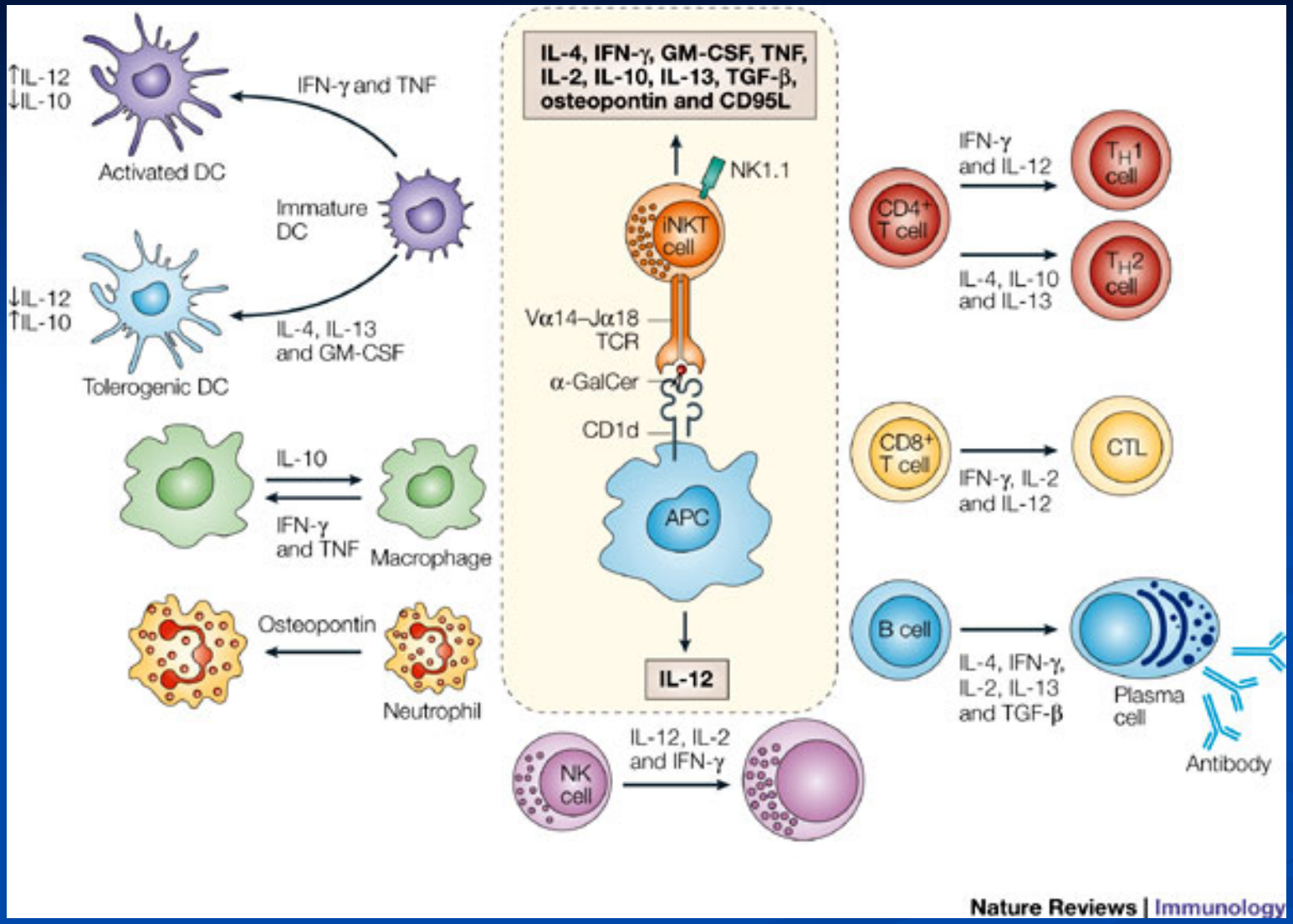



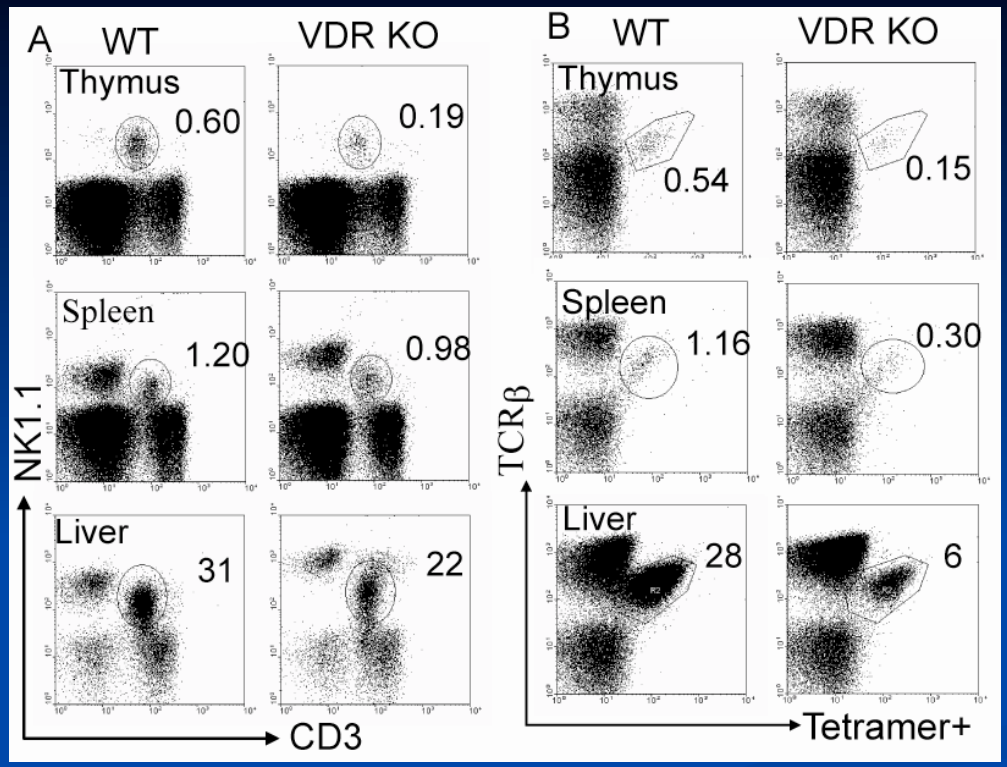

Numbers of T reg (FoxP3+) cells are not different in VDR KO and WT mice.

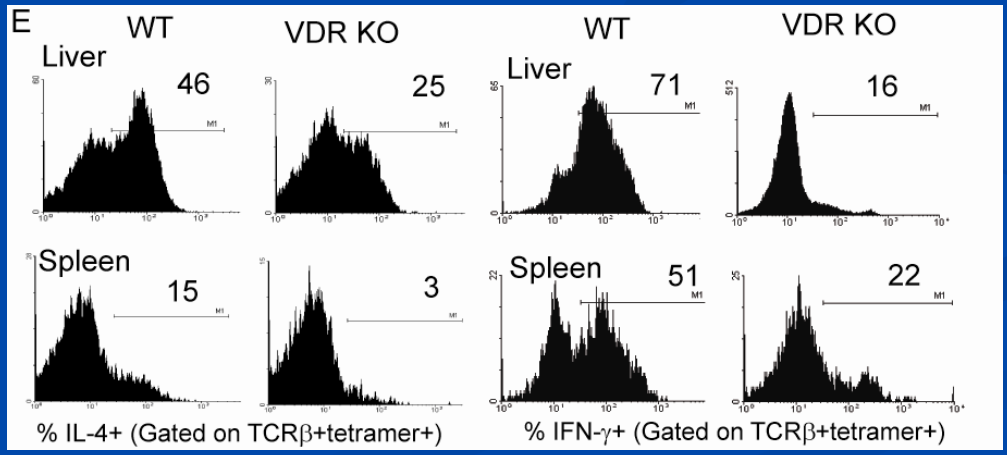
**T reg from VDR KO mice are functionally normal.**

**Yu & Bruce et. al 2008 PNAS**




**NKT cells are regulatory cells providing early cytokine secretion.**



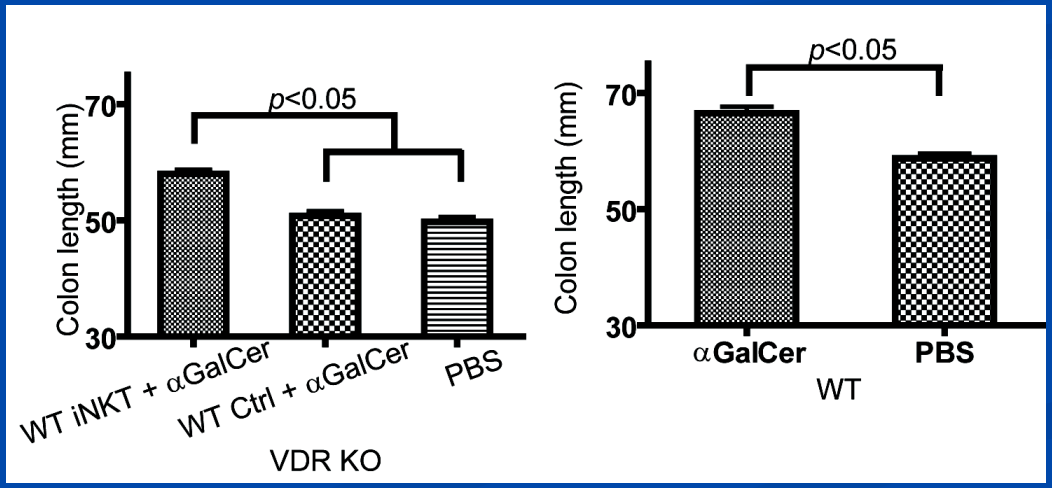




Yu et. al 2008 PNAS

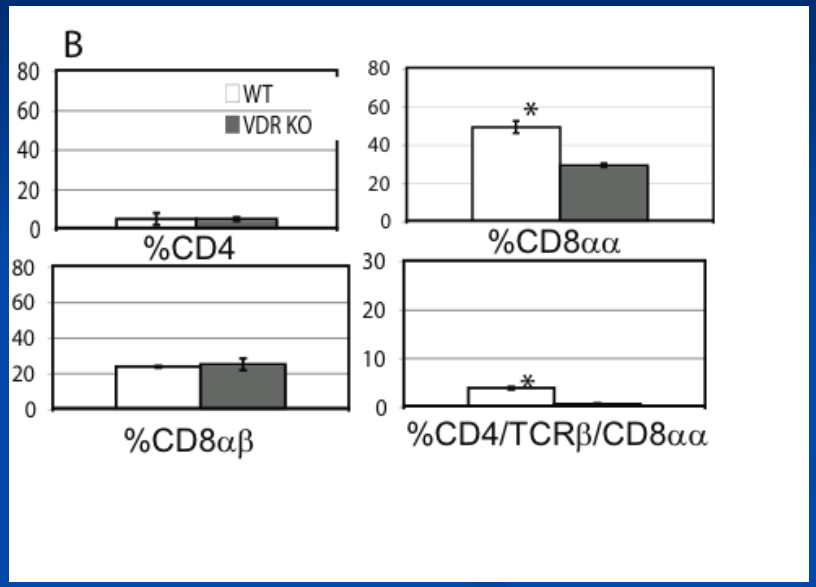
# Activated WT iNKT cells protect VDR KO mice from DSS colitis.

## DSS colitis





## CD8αα T cells are missing in VDR KO mice.



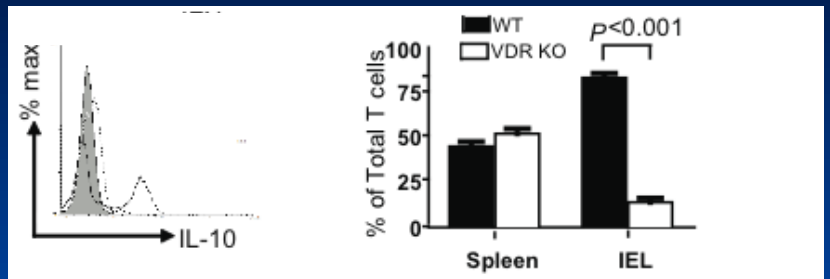

**CD8αα T cells are significantly reduced in the intestine of VDR KO mice.**

**CD8αα T cells suppress inflammation and proliferation in the intestine.**

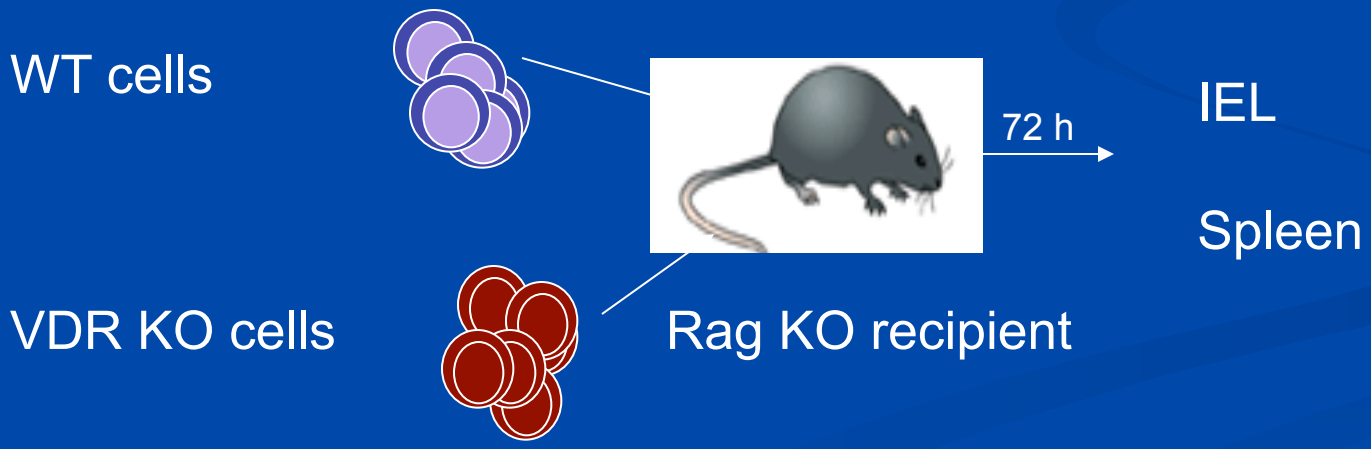
**CD8αα T cells secrete IL-10 and TGF-β1 in the intestine.**

**Yu & Bruce et. al 2008 PNAS**

# Homing and IL-10 secretion of VDR KO T cells




| IL-10 | | |
|---|---|---|
| | % IEL | % CD8αα |
| WT | 13.6 ± 2.1 | 10.8 ± 1.7 |
| VDR KO | 0.8 ± 0.4* | 0.7 ± 0.3 * |

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# IBD targets

CD4+CD45RB$^{high}$ T cells from VDR KO mice induce greater pathology than WT counterparts.

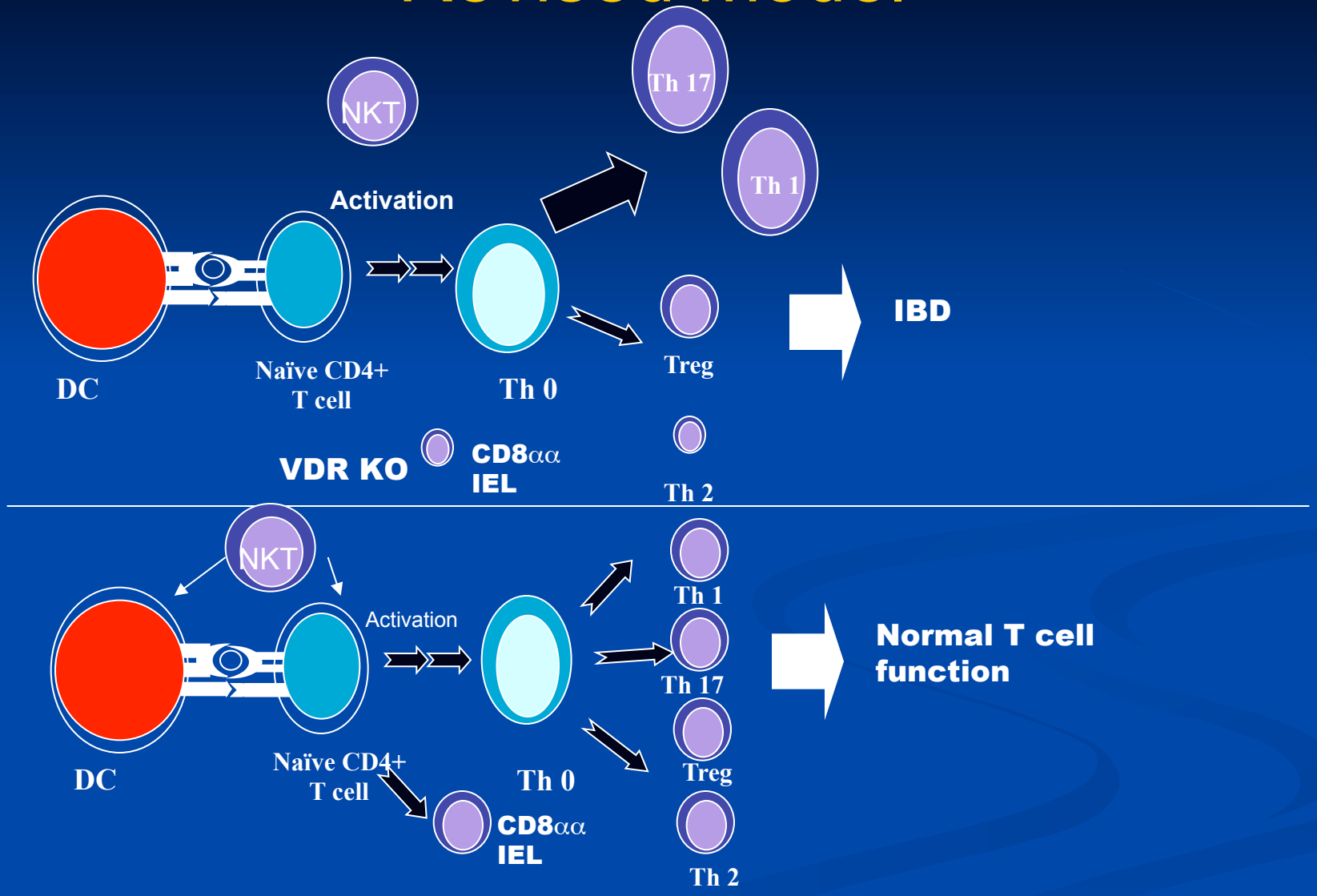
More IL-17, and IFN-$\gamma$ less IL-10 in the VDR KO host.

Expression of the VDR is not required for T reg cell development or function.

NKT cell development and function require the VDR.

T cell homing and expression of CD8$\alpha\alpha$ in the IEL require the VDR.

# Revised model




**Vitamin D and VDR ⟶ $1,25(OH)_2D_3$**

## Conclusions

Vitamin D is required for NKT cell development and function. Protective T cells in the gut require vitamin D and the VDR.

One consequence of reduced levels of vitamin D is increased inflammation in the gastrointestinal tract.