Vitamin D and autoimmune disease

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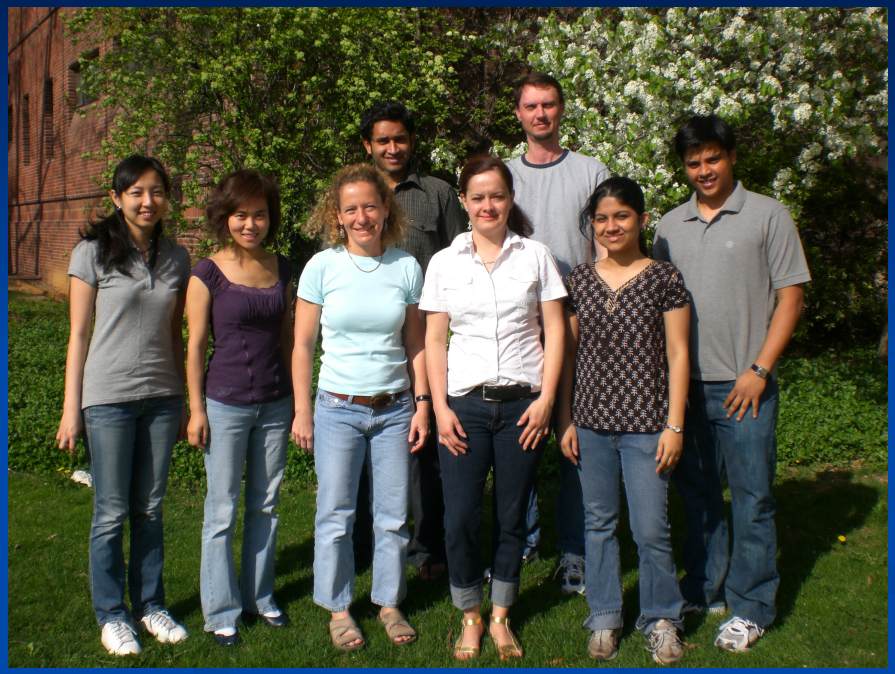

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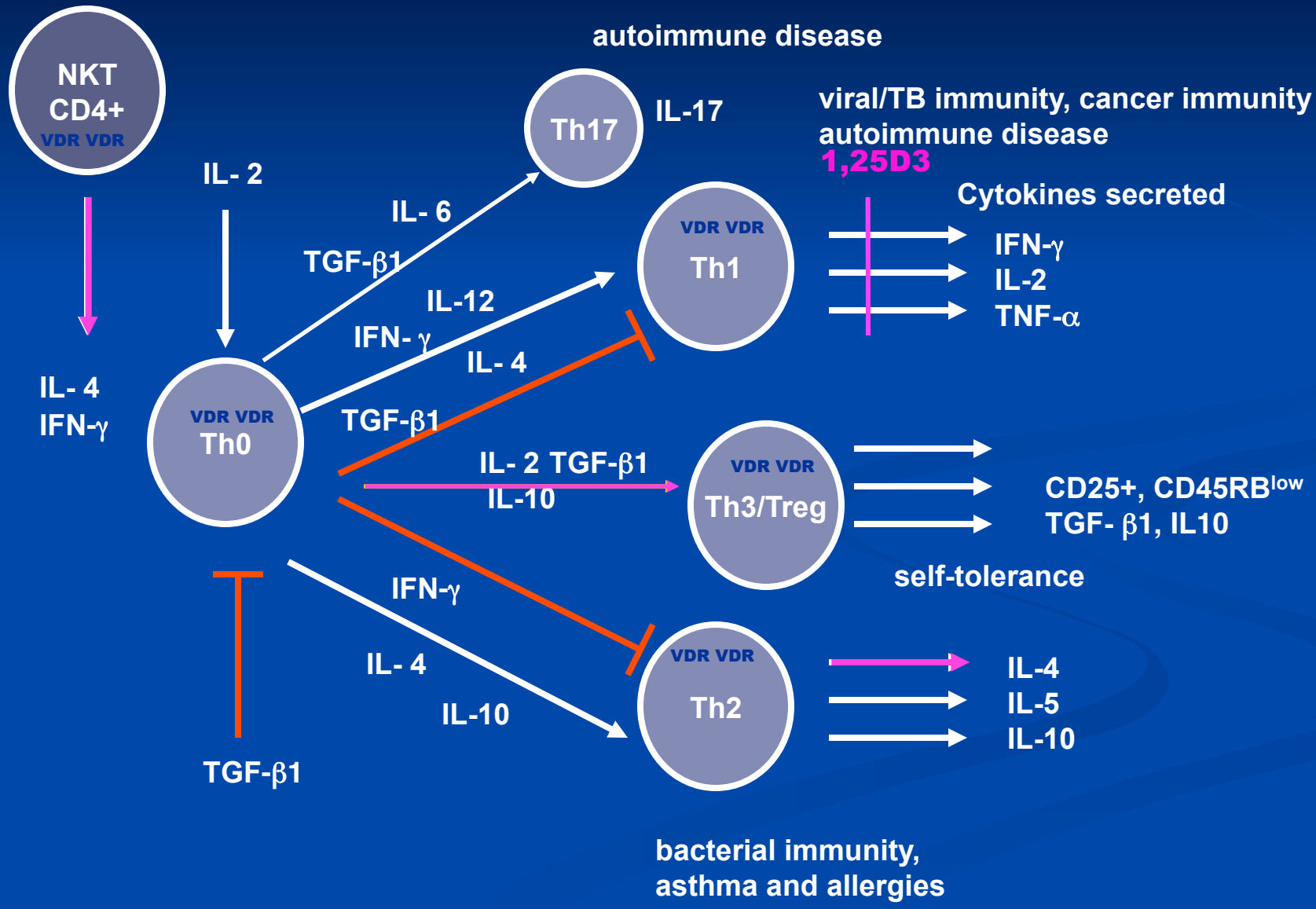
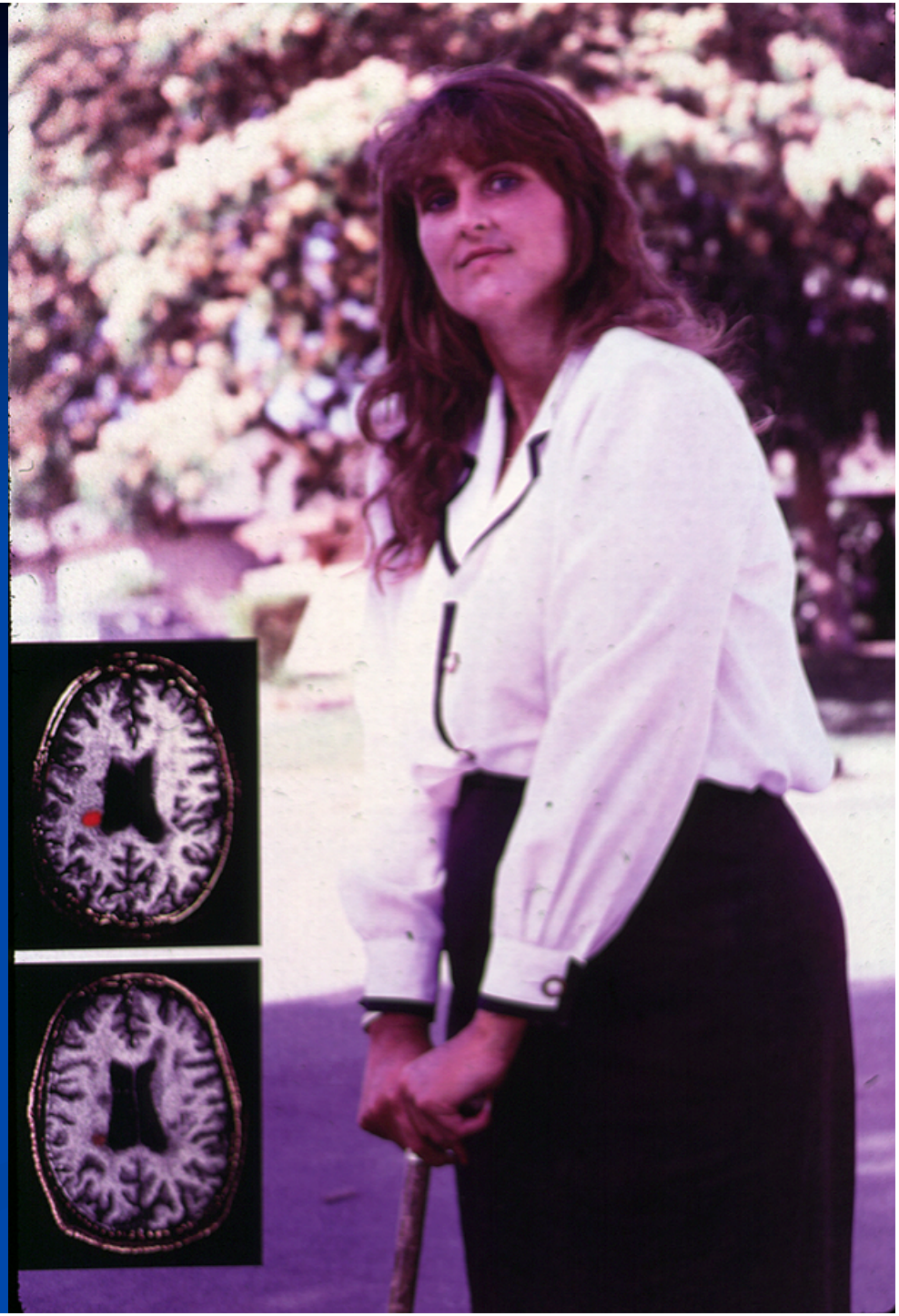
Cytokines that regulate Th cell differentiation.



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

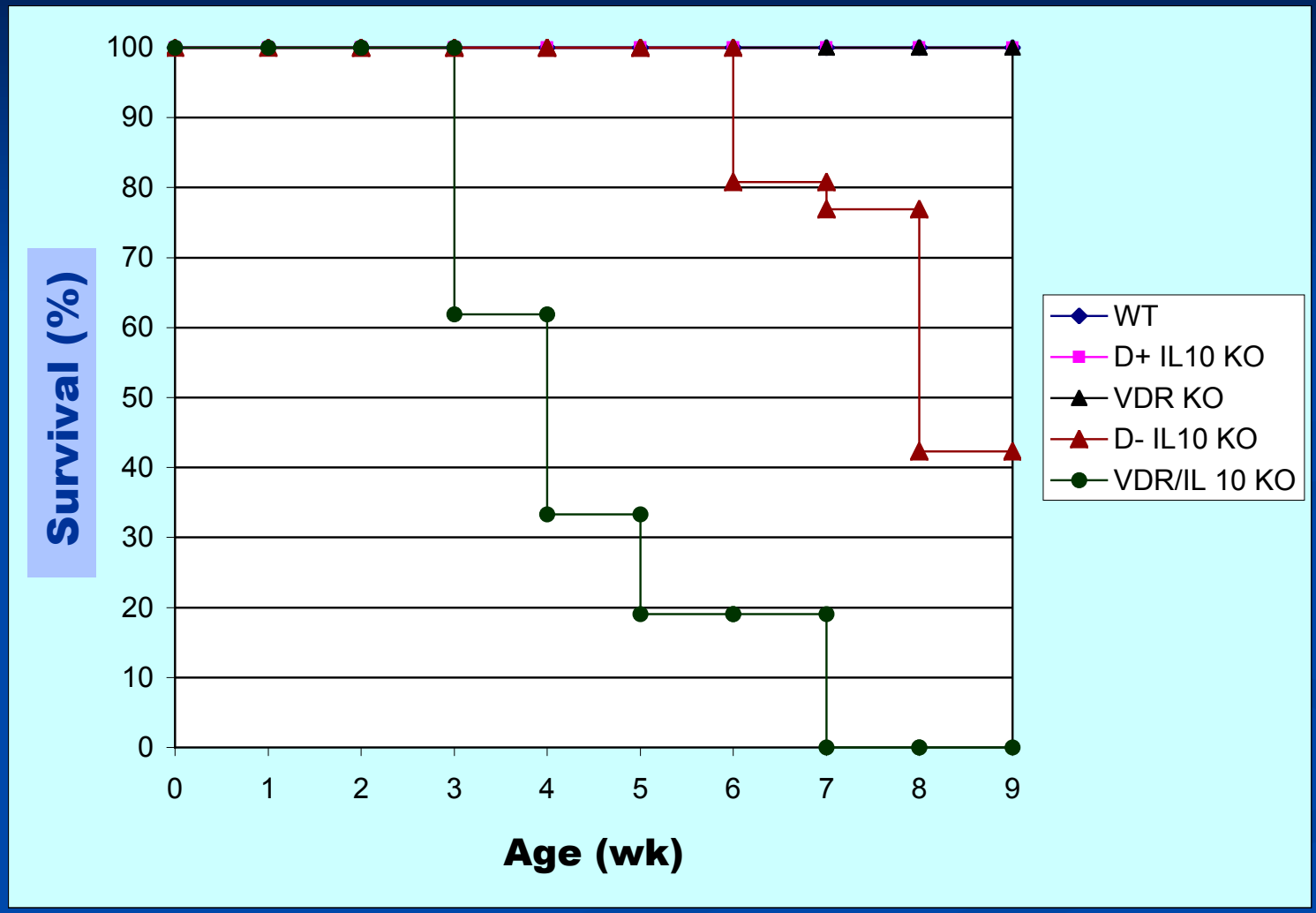
Spontaneous colitis - as a consequence of targeted mutations

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

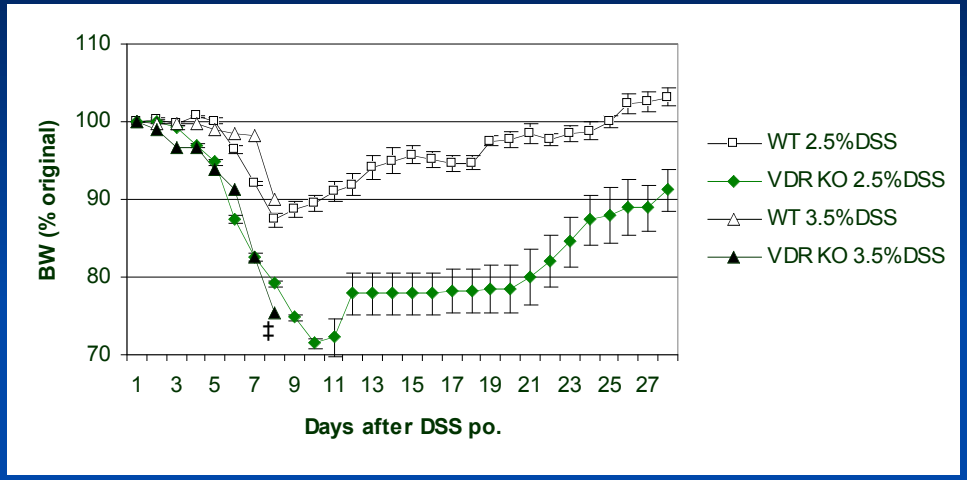
DSS in drinking water
5 days/ 5 days regular drinking water

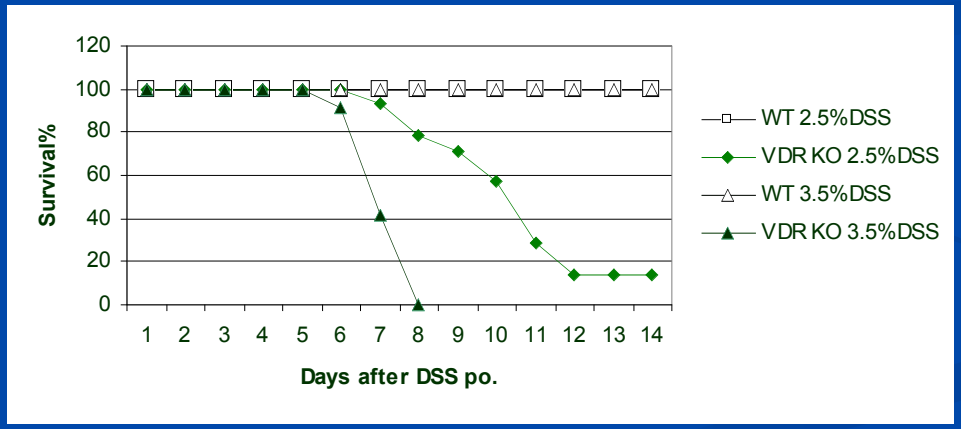
WT

VDR KO

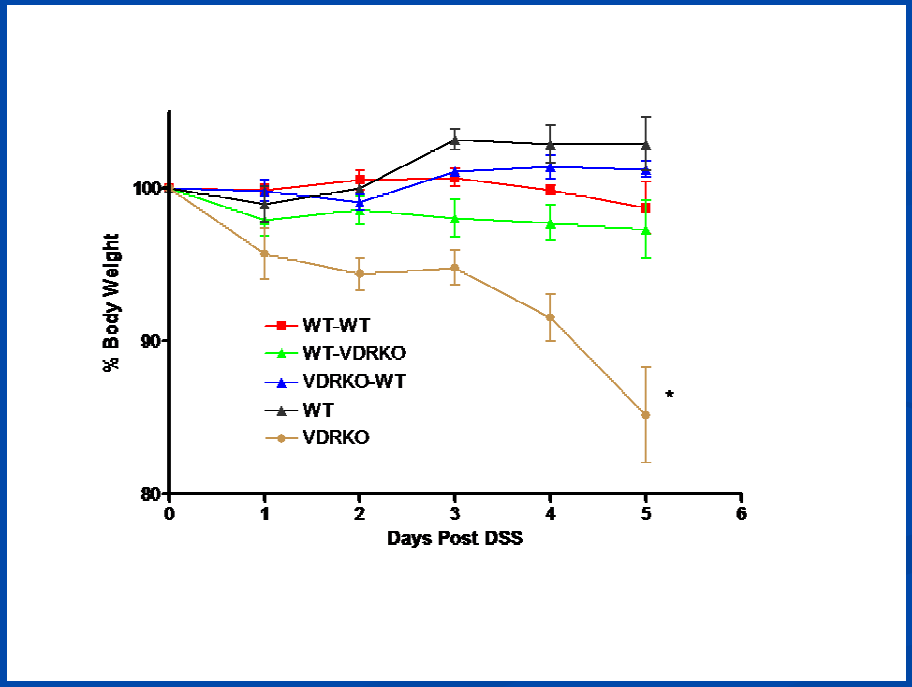
-colonic length
-Histopathology colon
-body weight changes

VDR KO mice are highly susceptible to dextran sulfate induced colitis





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



CONCLUSIONS

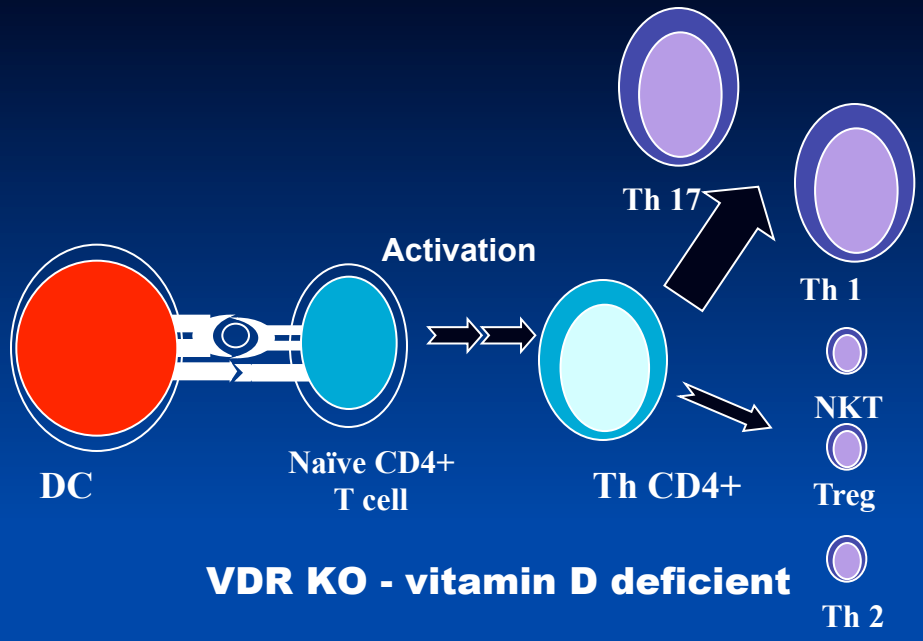
Vitamin D or VDR deficiency increased the mortality rate in IBD susceptible strains of mice.

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

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

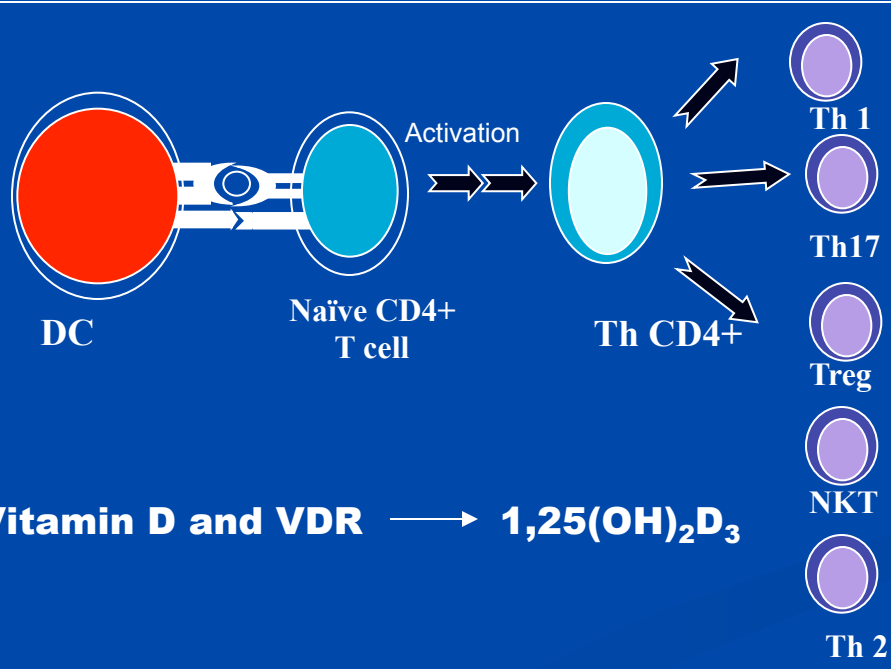
VDR KO mice are highly susceptible to DSS colitis. WT bone marrow protects VDR KO mice from DSS. $1,25(OH)_2D_3$ treatment reduced symptoms of colitis.

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**

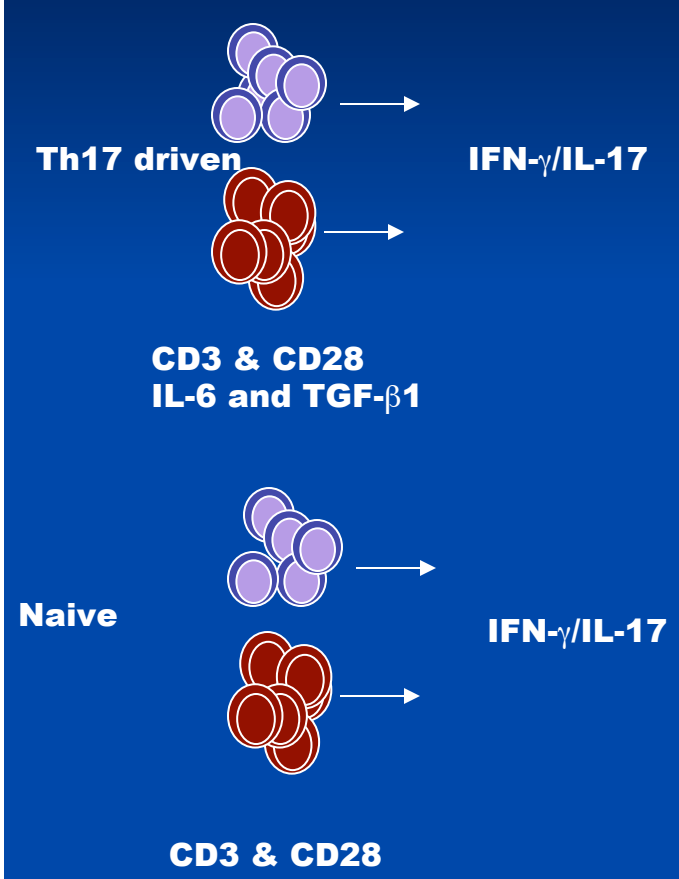
C57BL/6 Rag KO mice

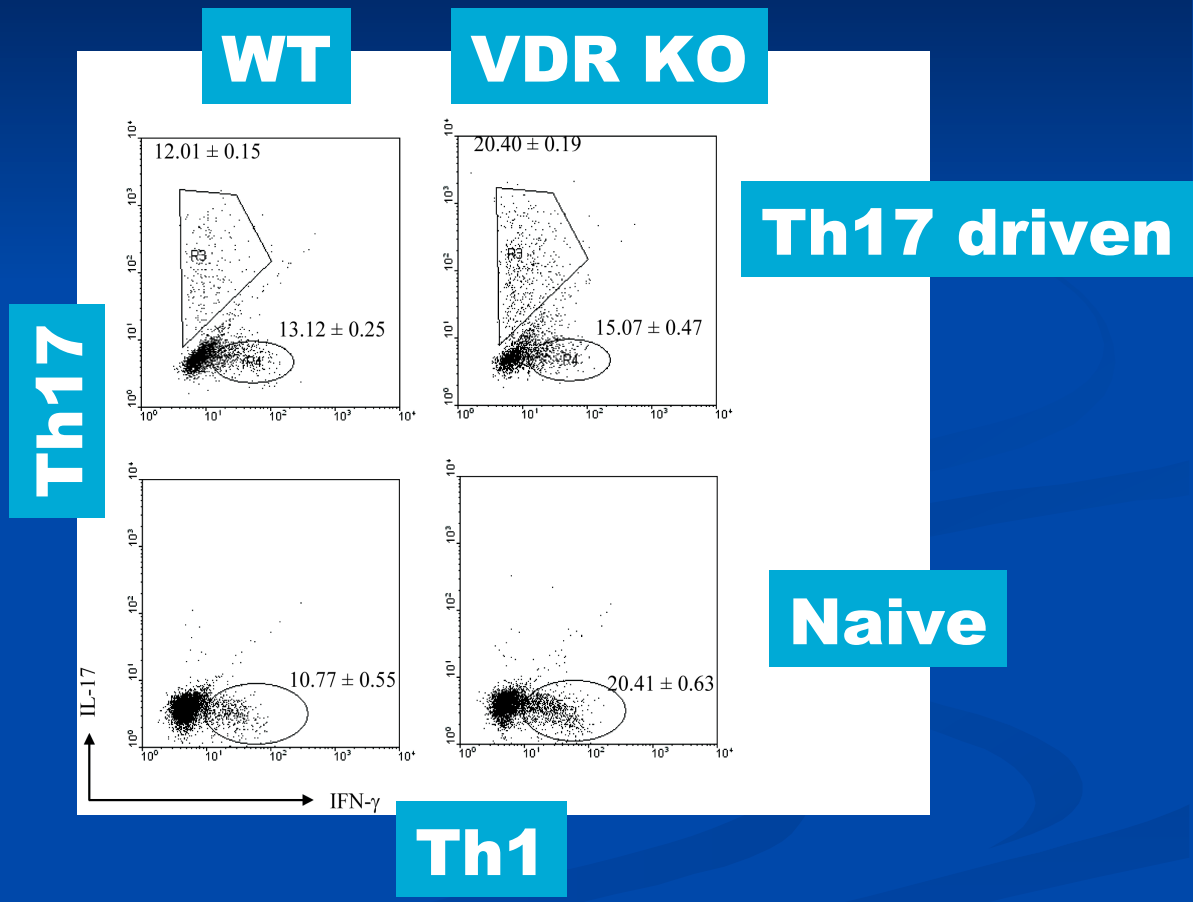
Donor Cells	Body Weight (g)	SI/BW (%)	LI/BW (%)	Colitis	
WT naive	18.8 ± 0.8^{a}	6.8 ± 0.4^{b}	3.6 ± 0.6^{a}	2.9 ± 0.3^{b}	IBD
VDR KO naive	17.4 ± 0.6^{a}	11.0 ± 0.9^{d}	6.4 ± 1.0^{b}	5.8 ± 0.5^{c}	more severe IBD

VDR KO CD4+ T cells contain highly pathogenic T cells

Froicu et. al 2003 Molecular Endocrinology

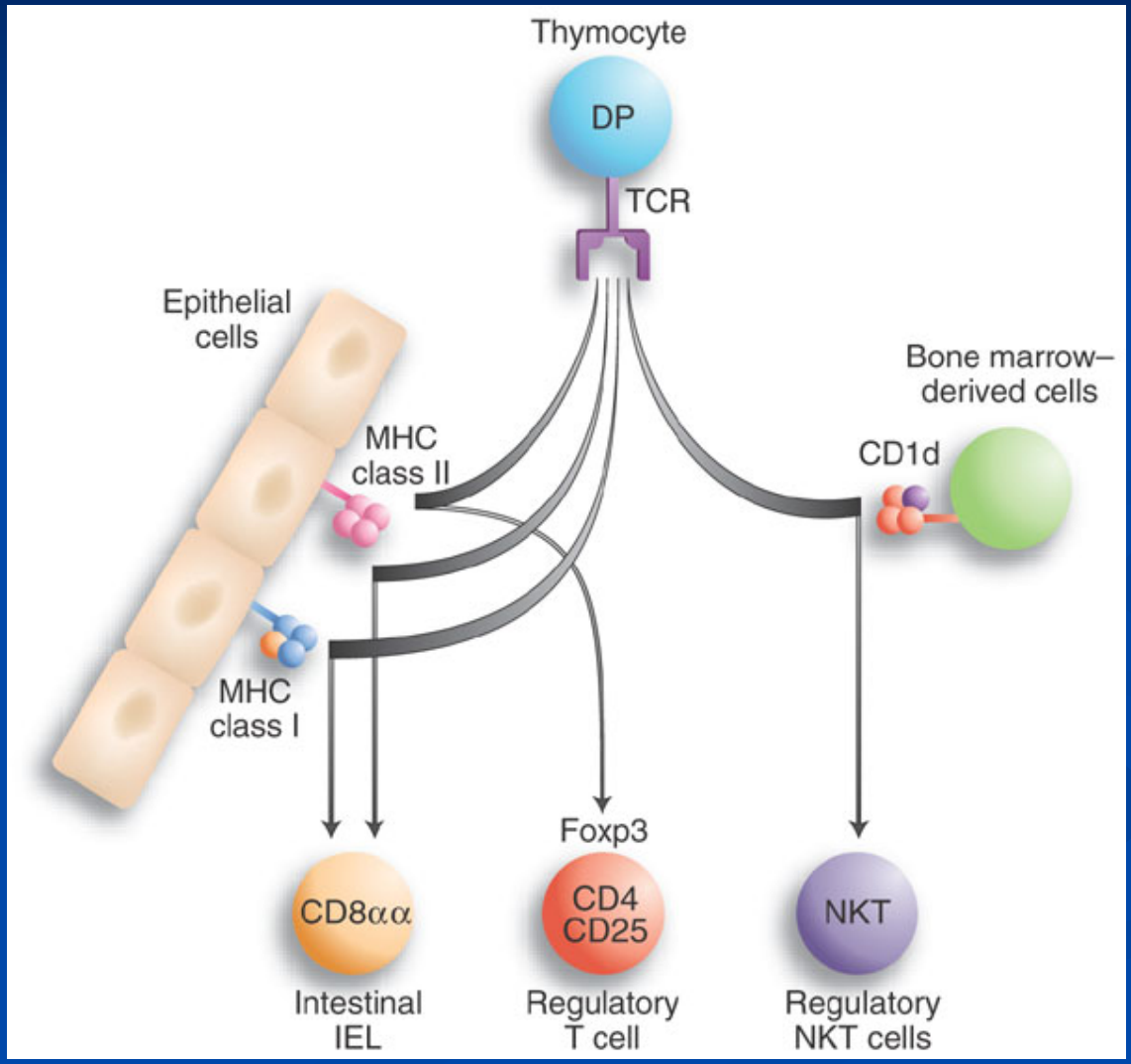
More Th17 and Th1 cells in VDR KO mice.



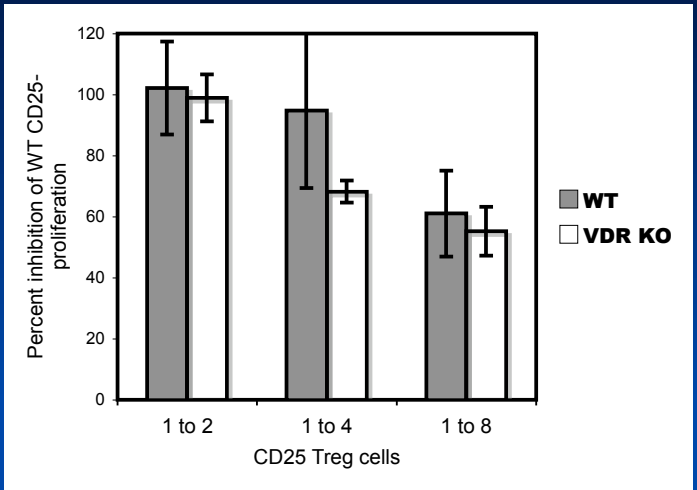


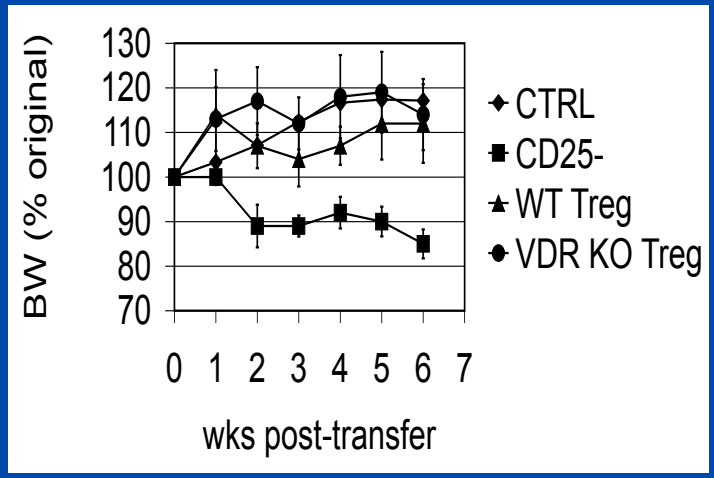
Unconventional T cells as regulatory cells

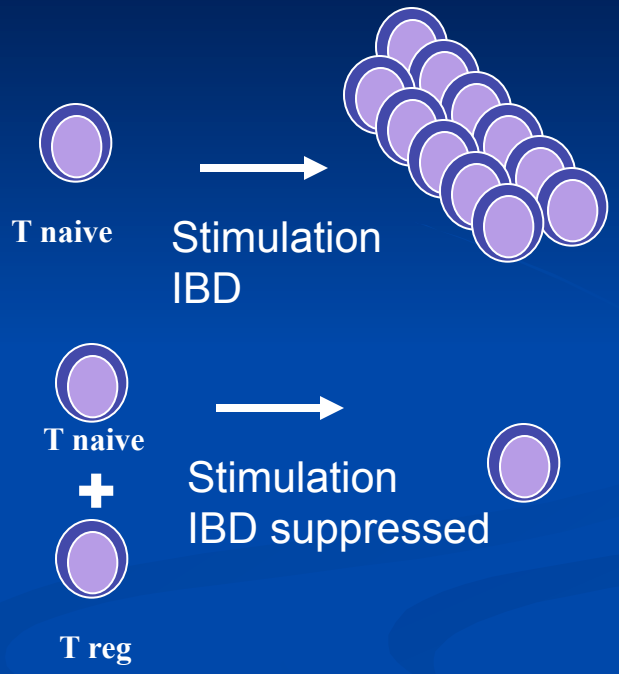
Classical T cells CD4+, CD8+ etc. are present in normal numbers in the VDR KO mice.



In vitro and in vivo T reg function



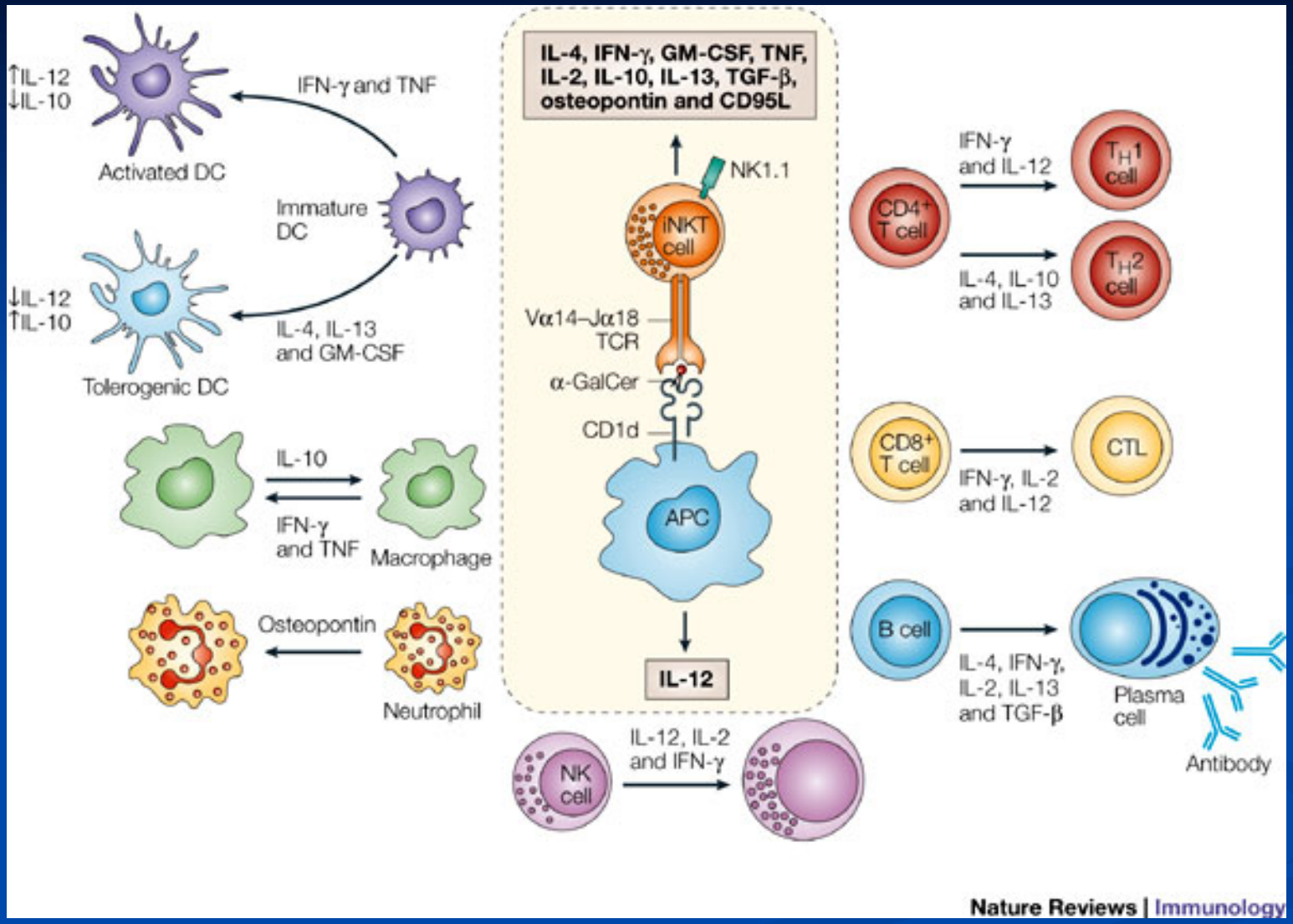




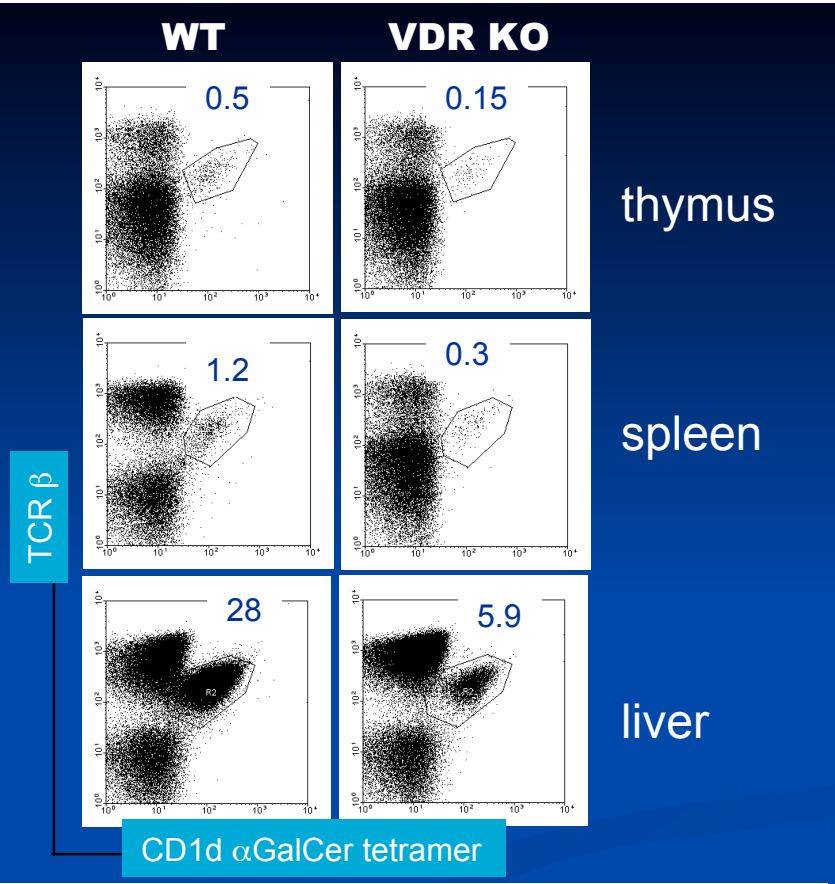
Numbers of T reg (FoxP3+) cells are not different in VDR KO and WT mice.

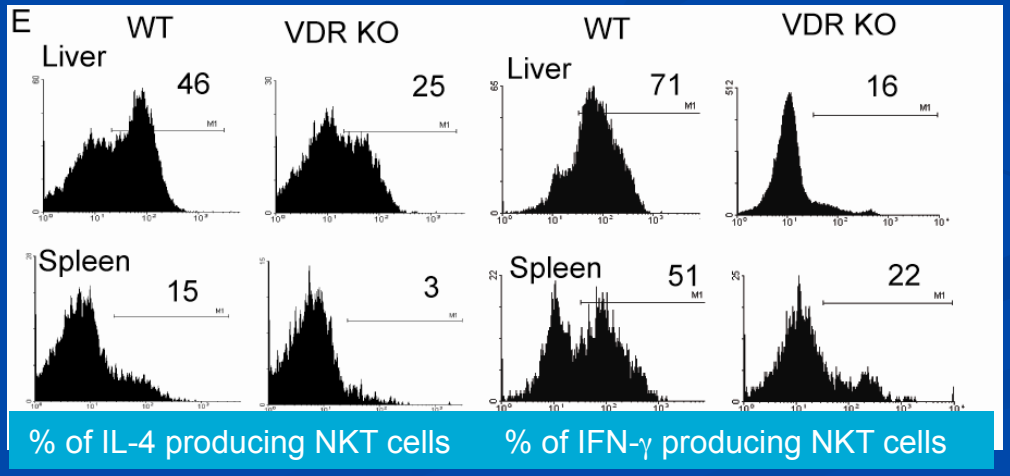
T reg from VDR KO mice are functionally normal.

Yu & Bruce et. al 2008 PNAS

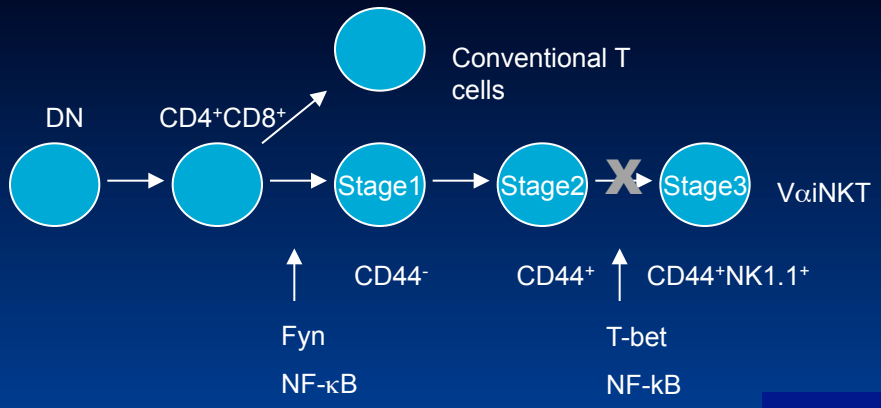


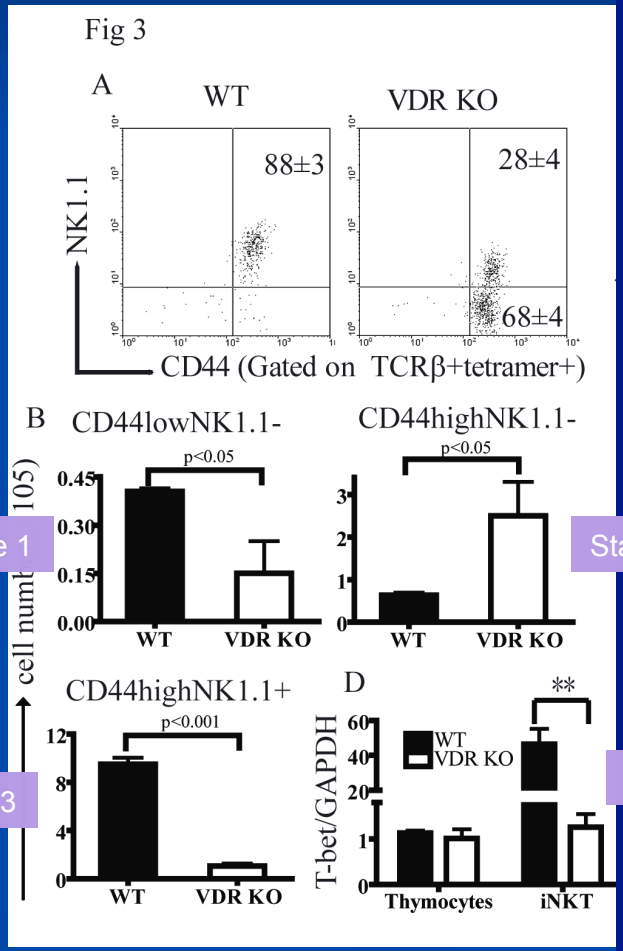
NKT cells are regulatory cells providing early cytokine secretion.





Yu et. al 2008 PNAS





Stage 1

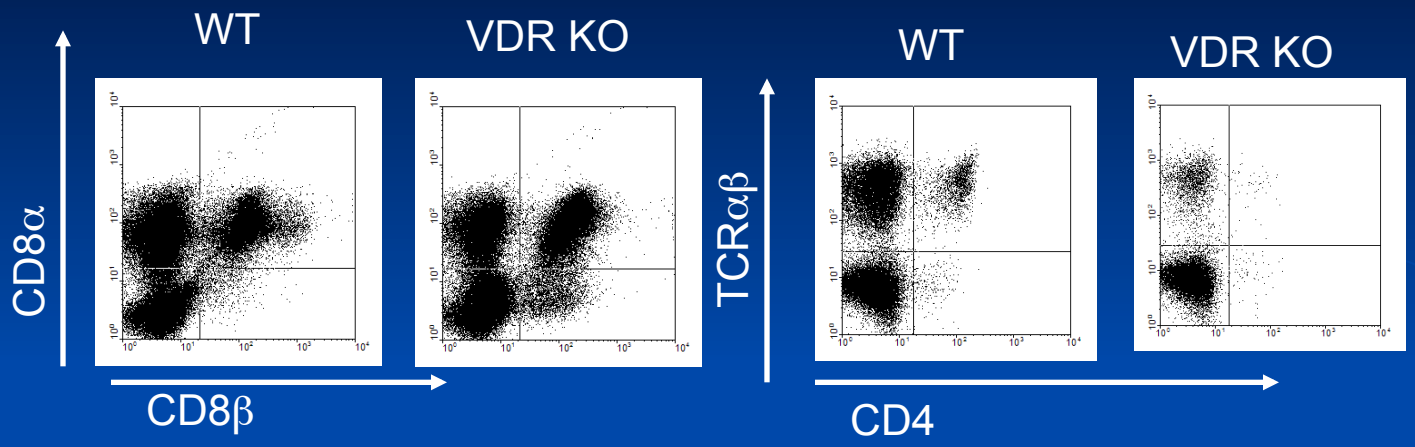
Stage 2

Stage 3

T bet

Yu et. al 2008 PNAS

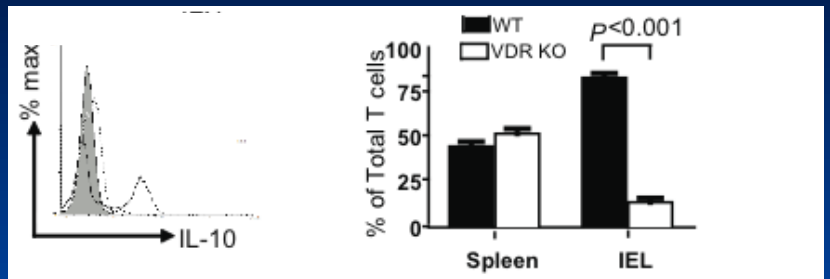
Gated on CD8αα



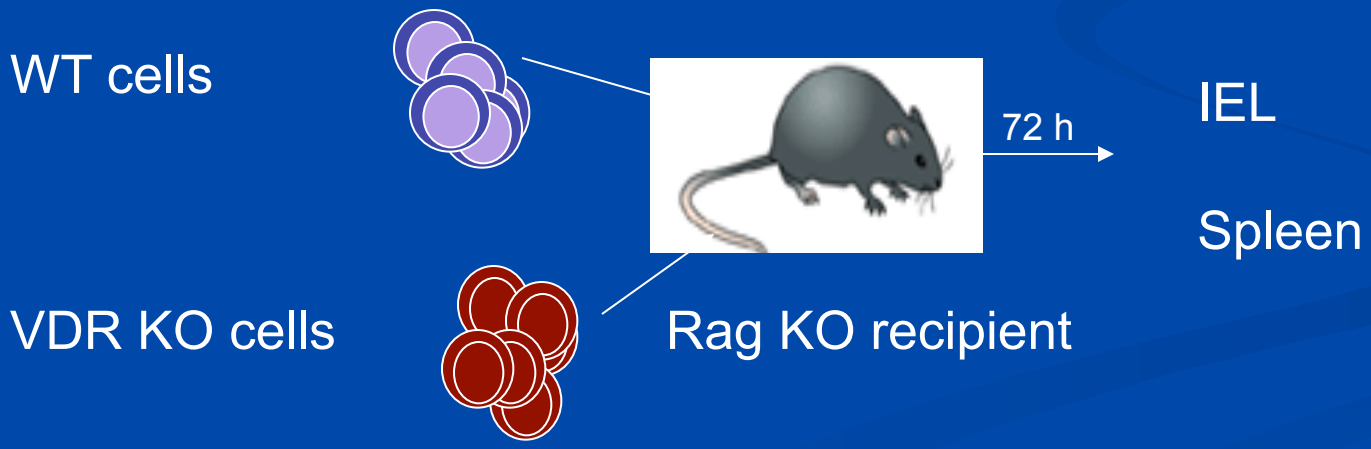
CD8αα VDR KO IEL					
	Total CD4	Total CD8αβ	Total CD8αα	CD8αα TCRαβ	CD4+/CD8αα TCRαβ
WT	4.64 ± 0.22	23.44 ± 0.56	49.03 ± 3.09	36.73 ± 4.16	3.7 ± 0.28
VDR KO	4.49 ± 1.01	24.67 ± 3.3	29.01 ± 1.05	16.86 ± 1.39	0.47 ± 0.096
p value	0.89 not sig.	0.7 not sig.	0.0036 **	0.0106 *	0.0004 ***

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.

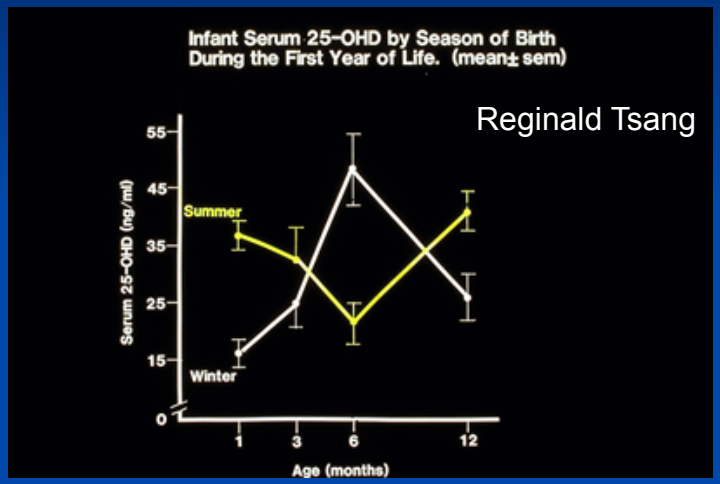
More IL-17, and IFN-γ less IL-10 in the VDR KO host.

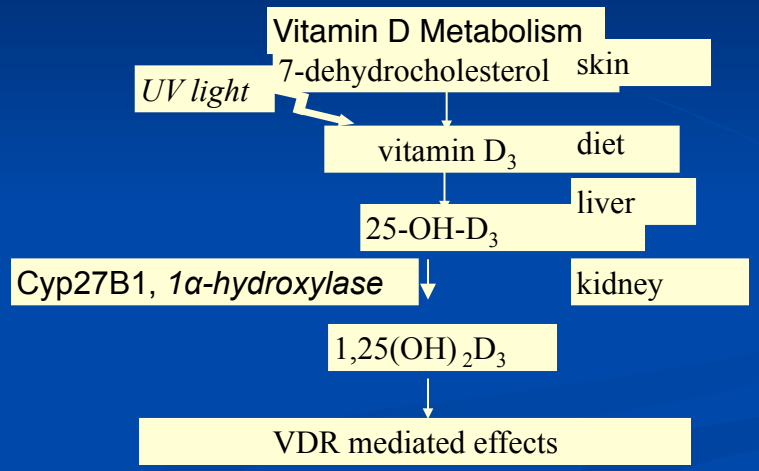
Expression of the VDR is not required for T reg cell development or function.

NKT cell development and function require the VDR.

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

What is the effect of changing levels of vitamin D on immunity?





Cyp27B1 KO mice: unable to use the vitamin D in the diet to make 1,25(OH)2D3.

Cyp27B1 ko/+ breeders: compare WT and KO fed the same diets.

Vitamin D deficient Cyp27B1 KO and WT mice : VERY FEW iNKT cells.

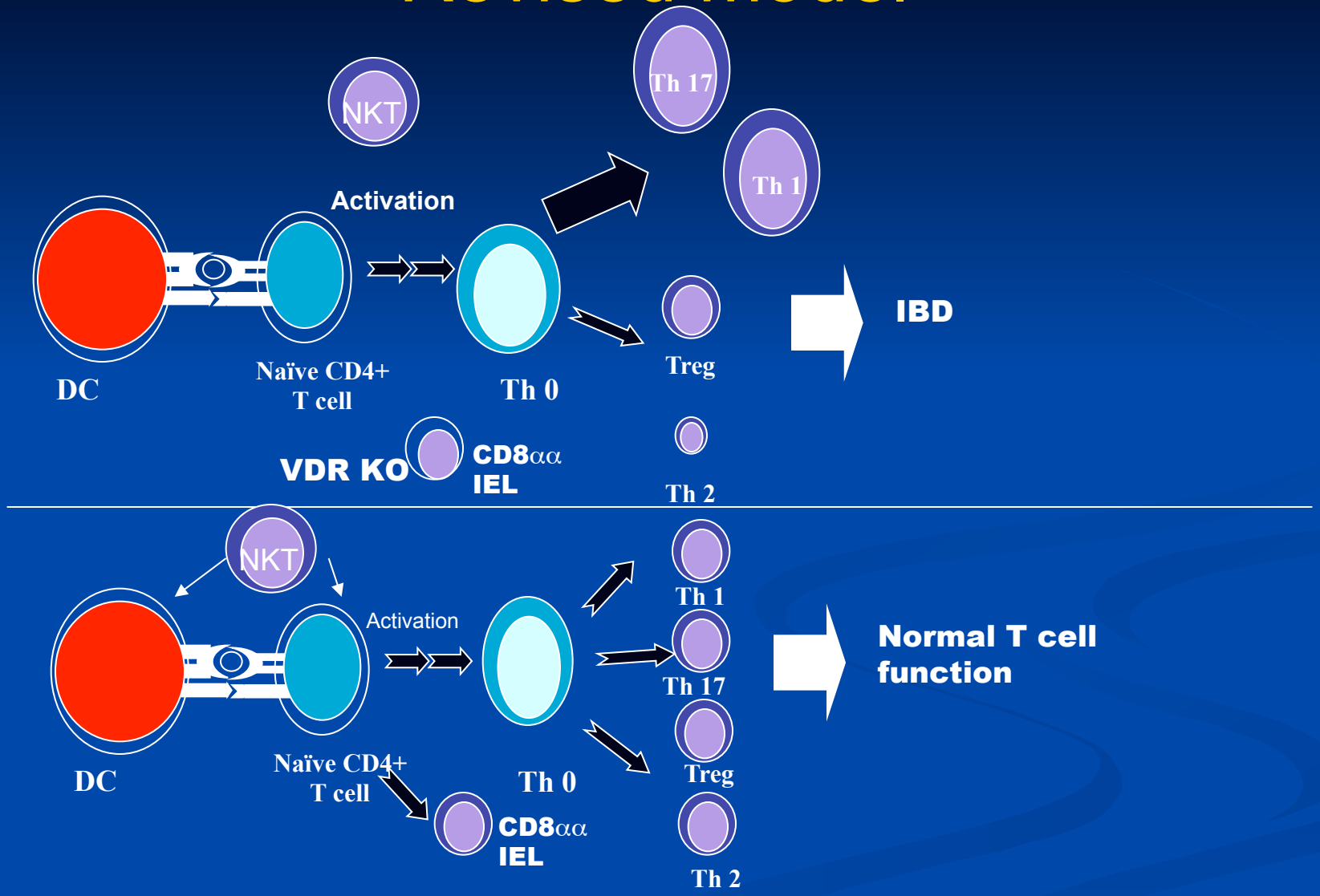
Conclusions

There is a block in the development of iNKT cells following vitamin D deficiency in utero.

D- iNKT cells fail to increase to +D WT levels with either vitamin D supplementation or 1,25(OH)2D3 treatment beginning at the day of birth.

Epigenetic changes in iNKT cells following in utero vitamin D deficiency.

Revised model



Vitamin D and VDR ⟶ $1,25(OH)_2D_3$