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Oct 29th 09

“The biology and clinical application of Lymphoid Stress-Surveillance”

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Immunity
Perspective

Cell
PRESS

$\gamma\delta$ T Cells and the Lymphoid Stress-Surveillance Response

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Guy's Hospital, London SE1 9RT, UK

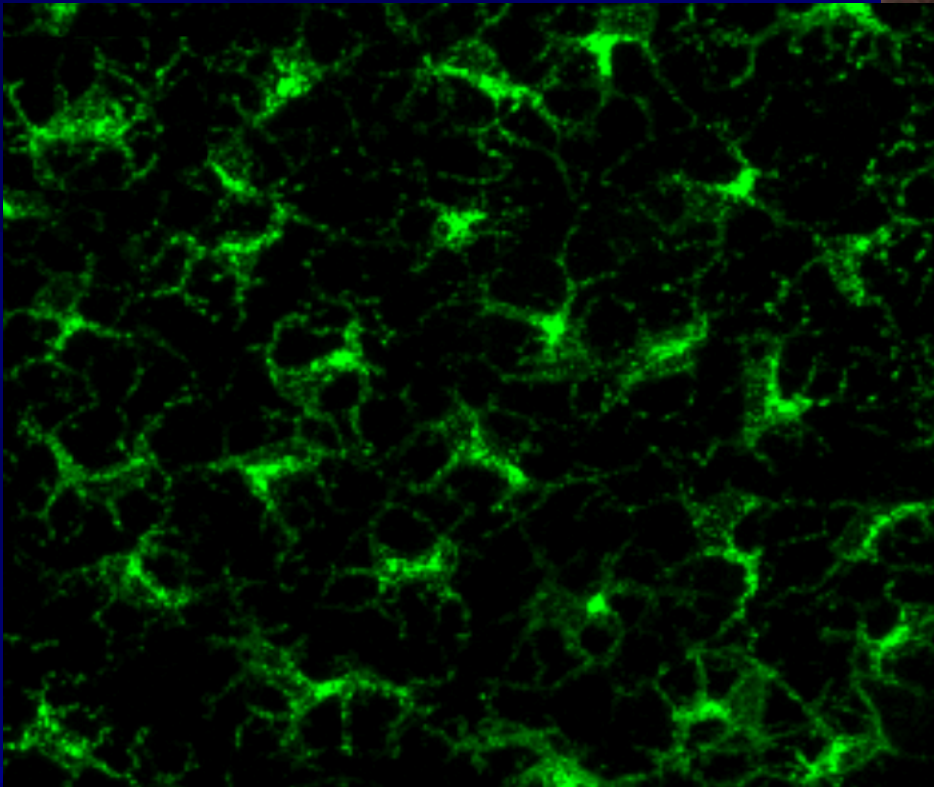
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DOI 10.1016/j.immuni.2009.08.006

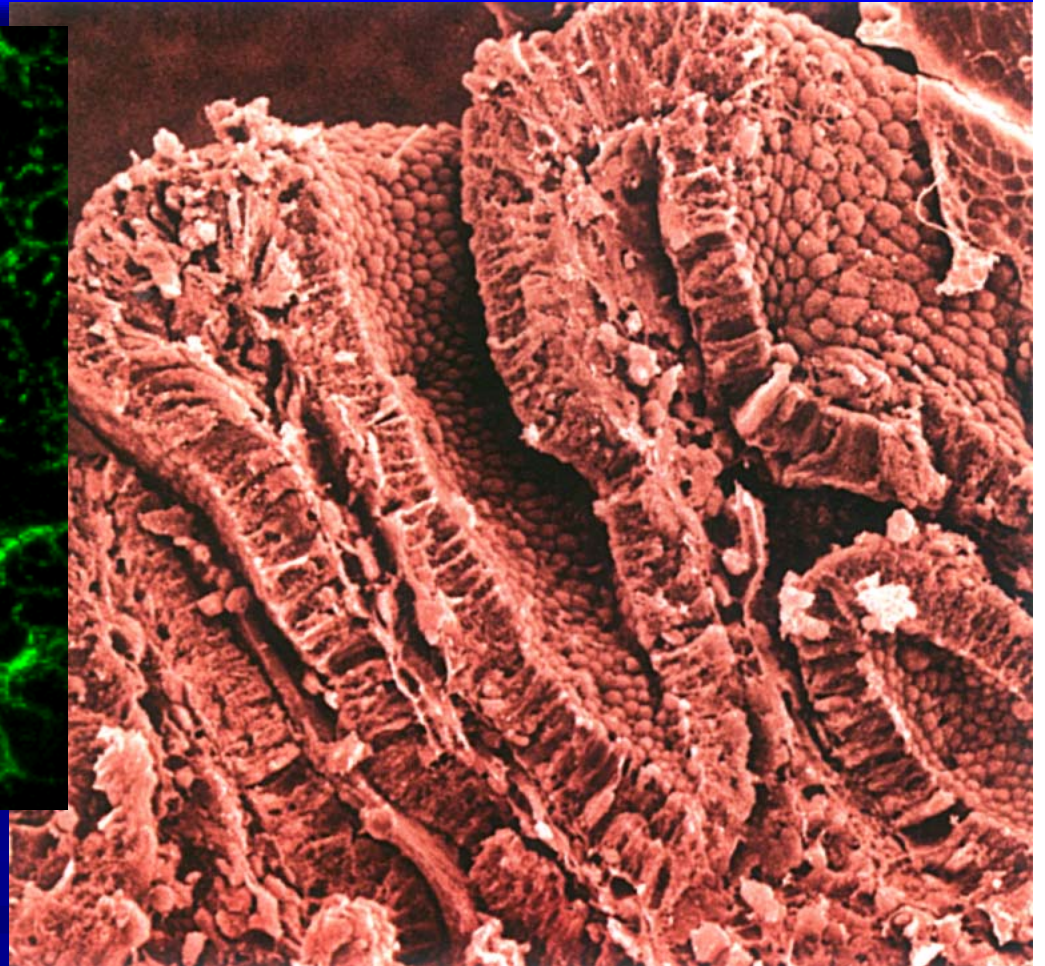
Important note -

For the benefit of the most effective dissemination of knowledge and its discussion, this presentation includes unpublished data relating to the effect of lymphoid stress-surveillance on immunoglobulin production, and on the effects of gamma delta T cell re-activation in patients with advanced breast cancer. These data cannot be cited or reproduced for any purpose without the authors' written and specific permission

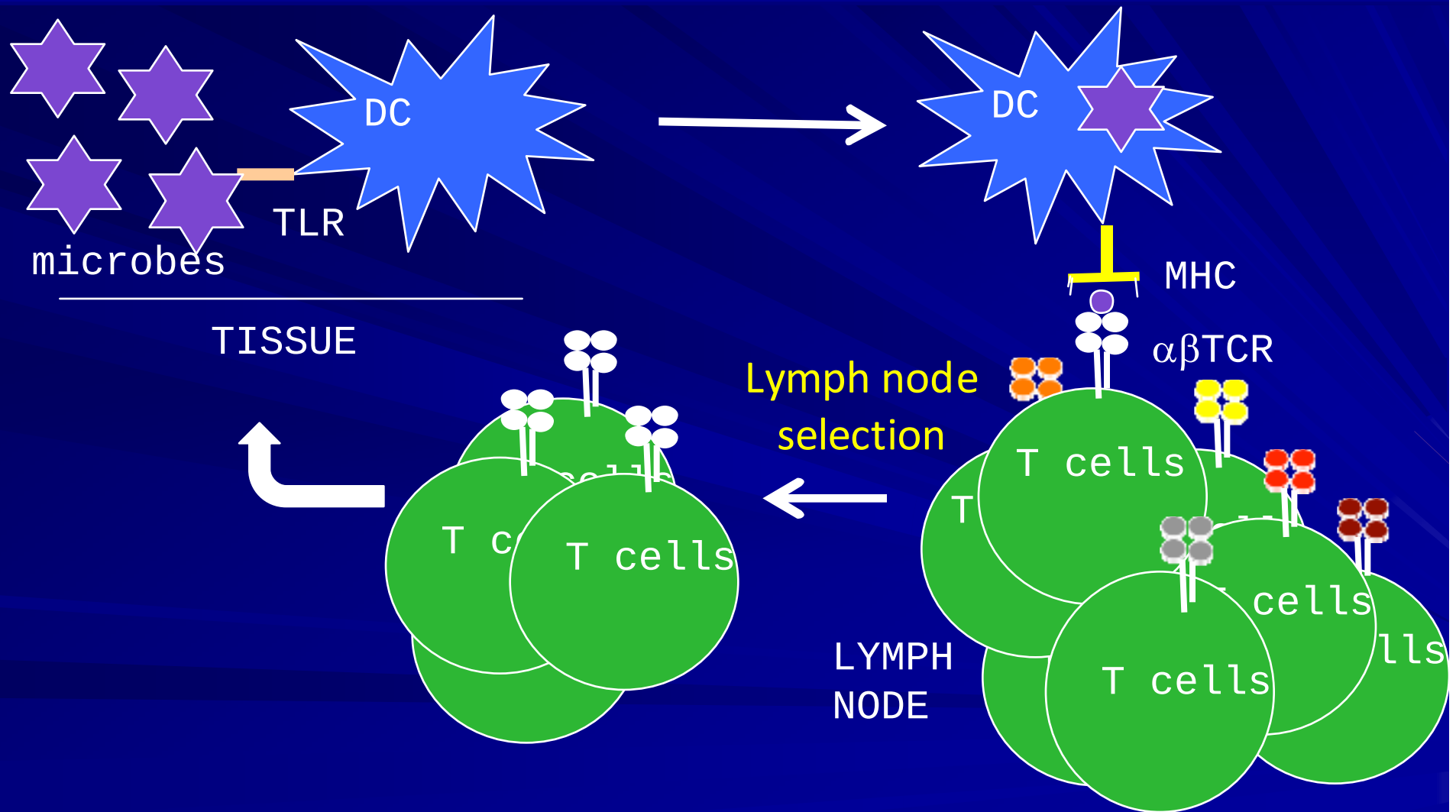
Immunology and body surfaces



Langerhans
Cells



Conventional lymphocyte surveillance





Immune surveillance of epithelial tissues - gap 1

- The epithelial cell itself

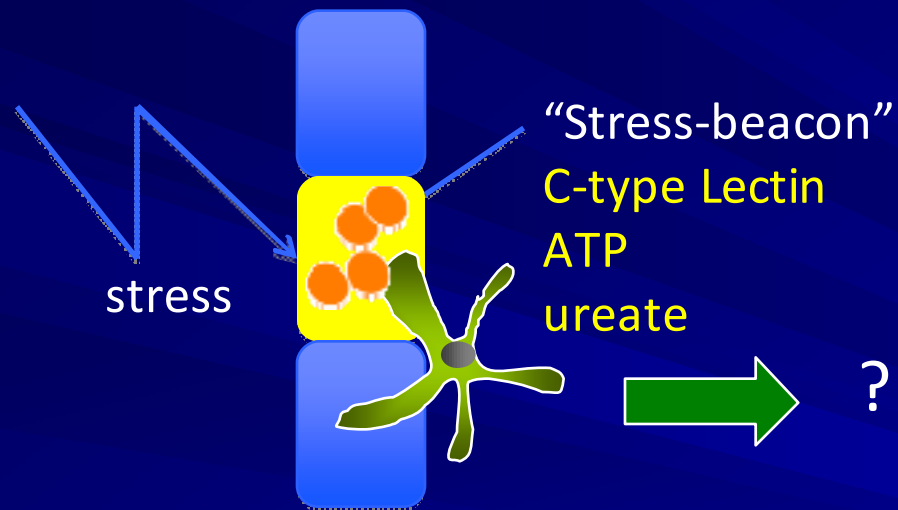


gap 2-

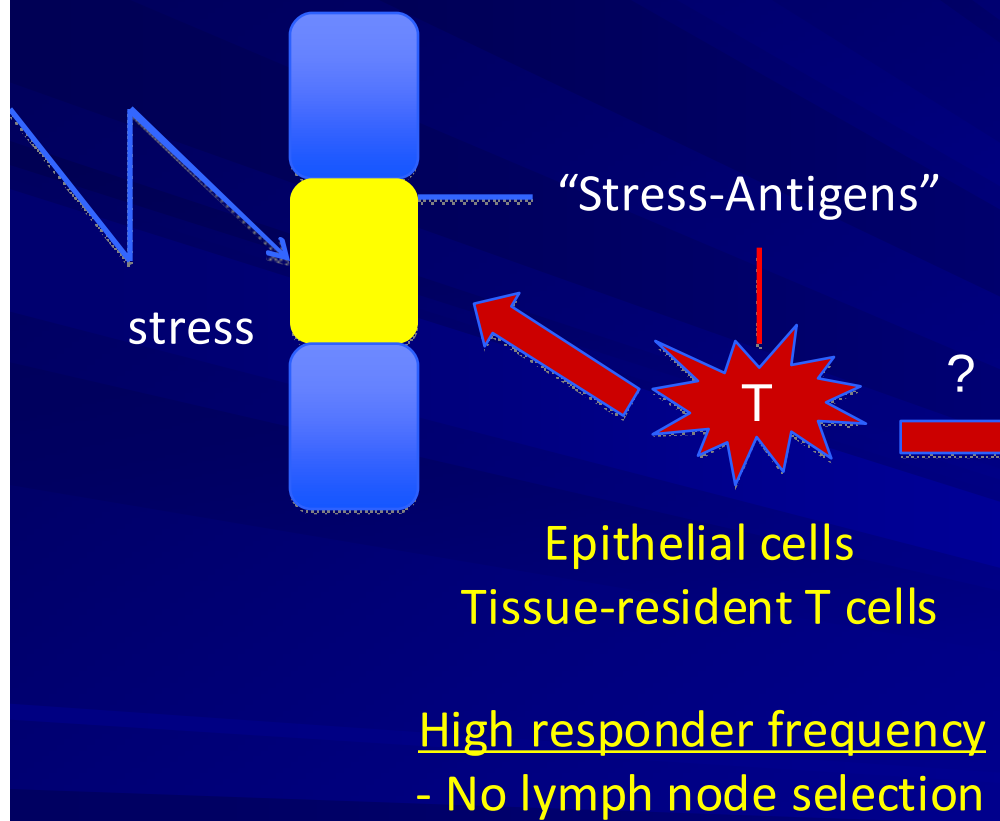
Non microbial stress



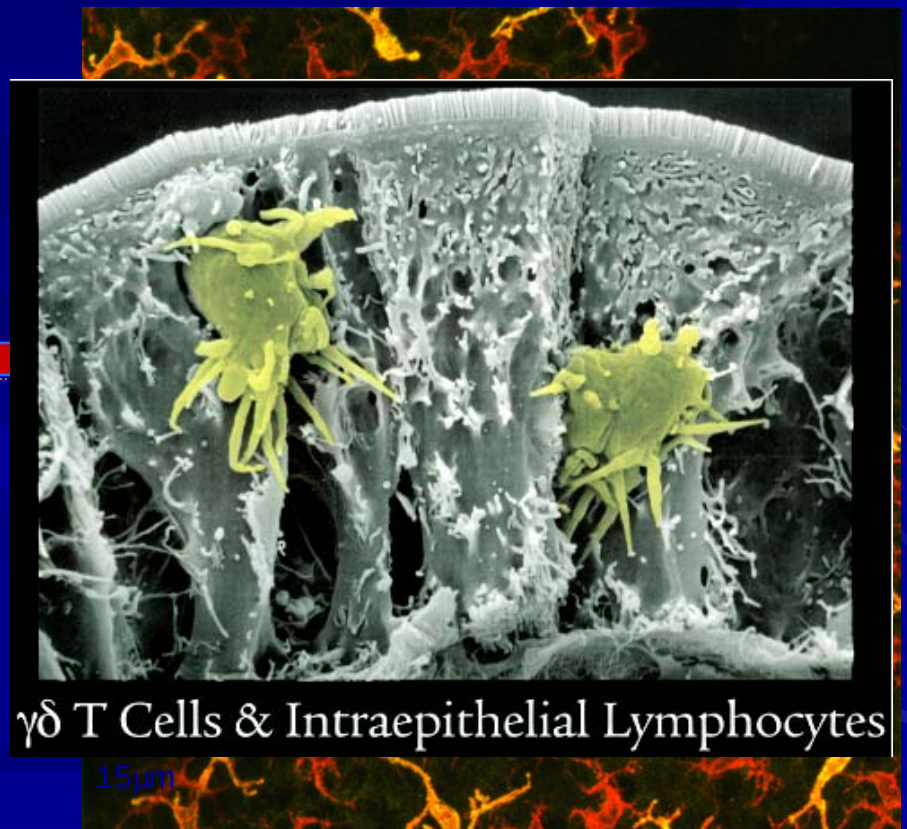
Immune surveillance of stressed tissues



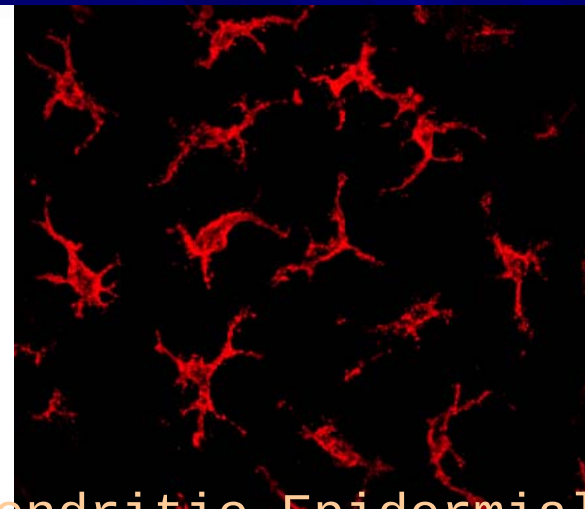
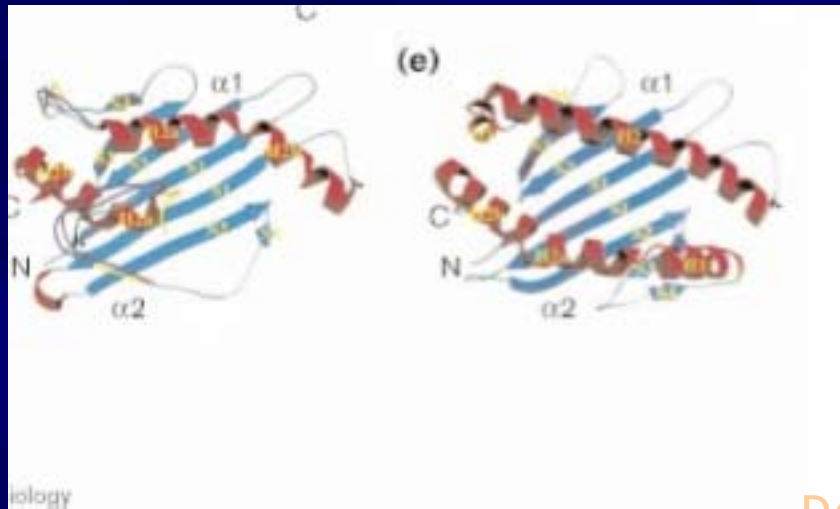
Lymphoid stress-surveillance



gap 3- "unconventional T



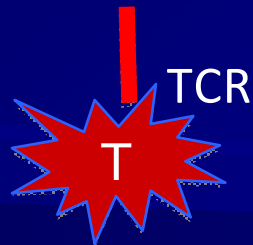
Lymphoid stress-surveillance: evidence for high frequency responses



Dendritic Epidermal T
cells

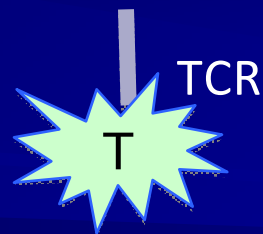
(DETC) $V\gamma 5$ $V\delta 1$

T10/T22



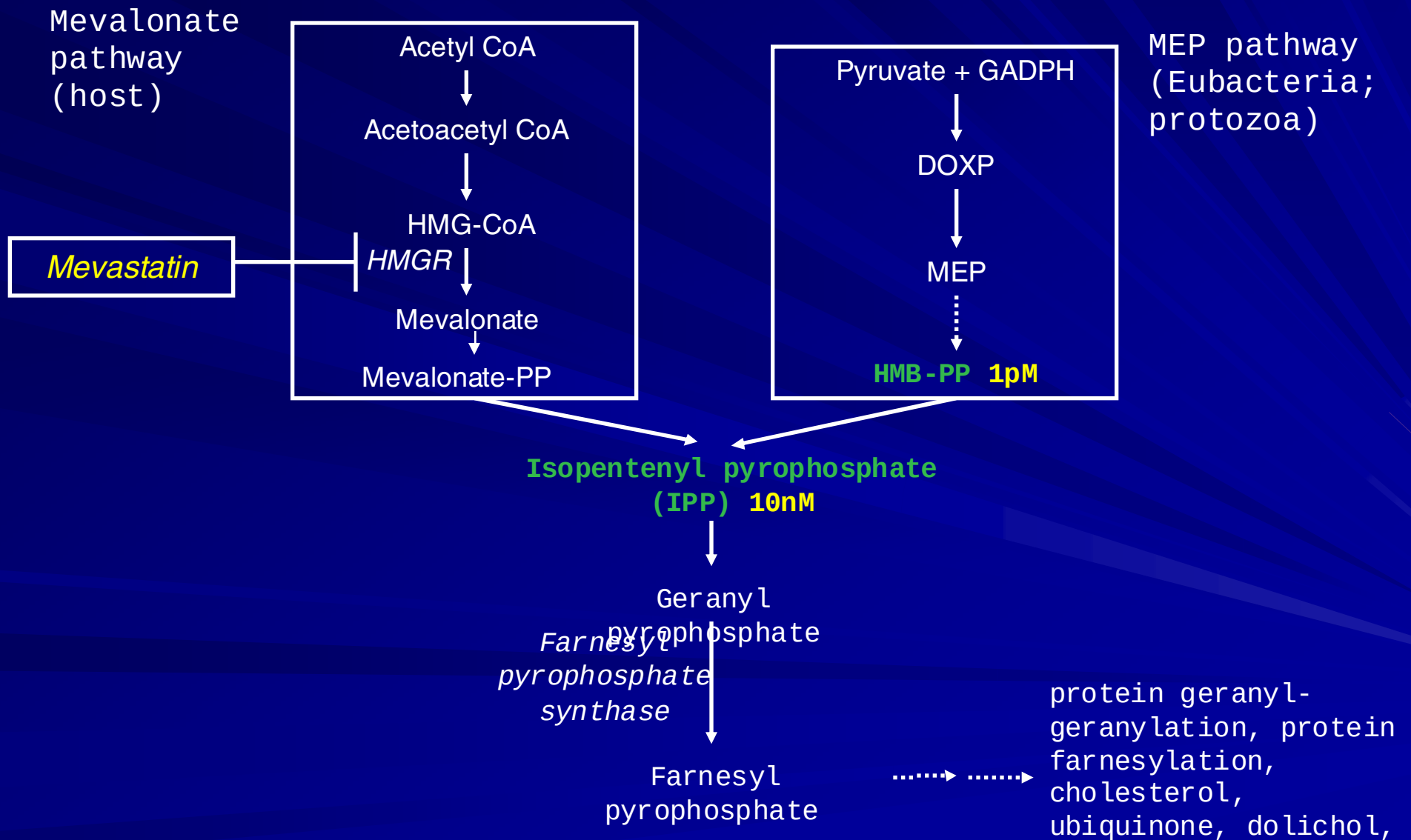
1 in 200

Peptide-MHC

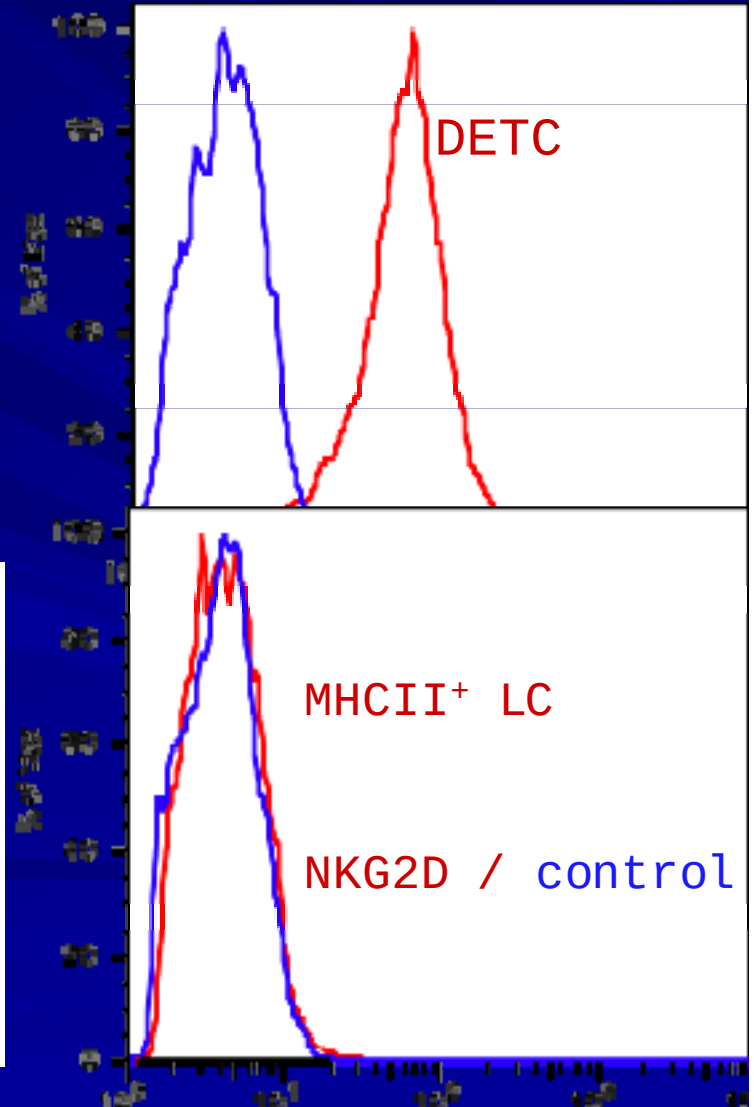
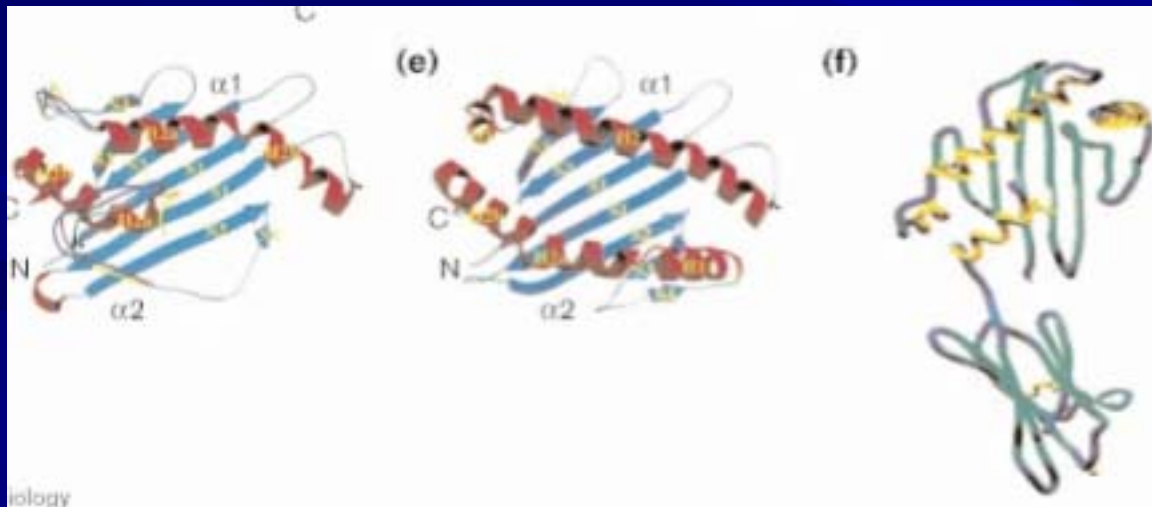
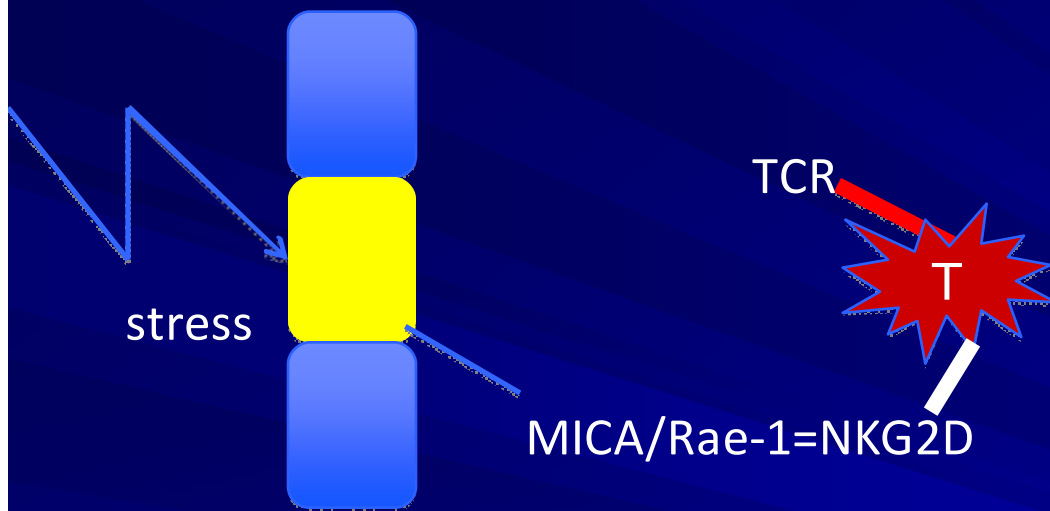


1 in 10^6

High Frequency Response of Human $\gamma\delta$ cells to common microbial metabolite or "self stress signal"



Lymphoid stress-surveillance: another route to obtaining high frequency responses

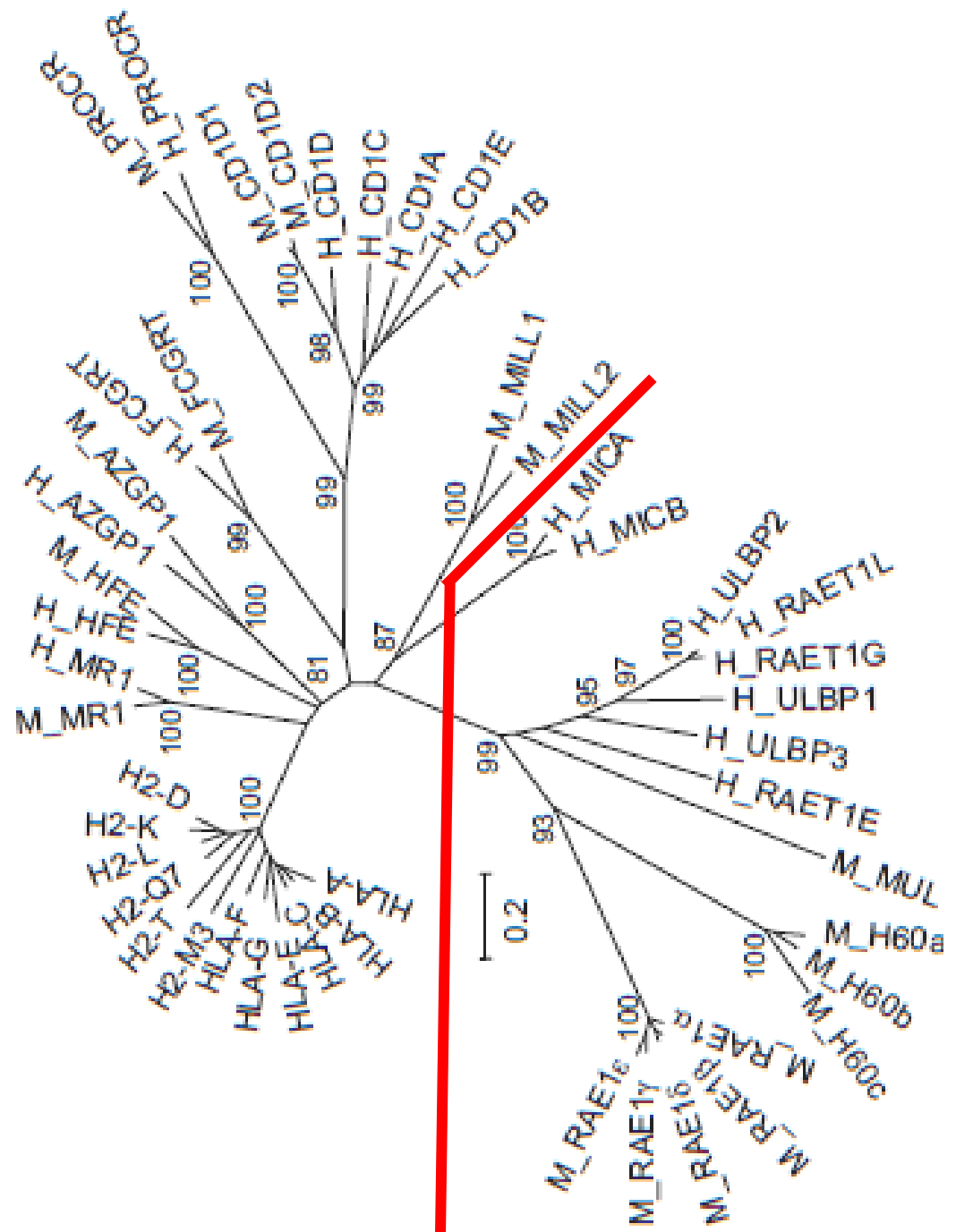


MHC versus NKG2D lig

Many NKG2D ligands
are stress-regulated
e.g. genotoxic shock

Many are expressed by tumours

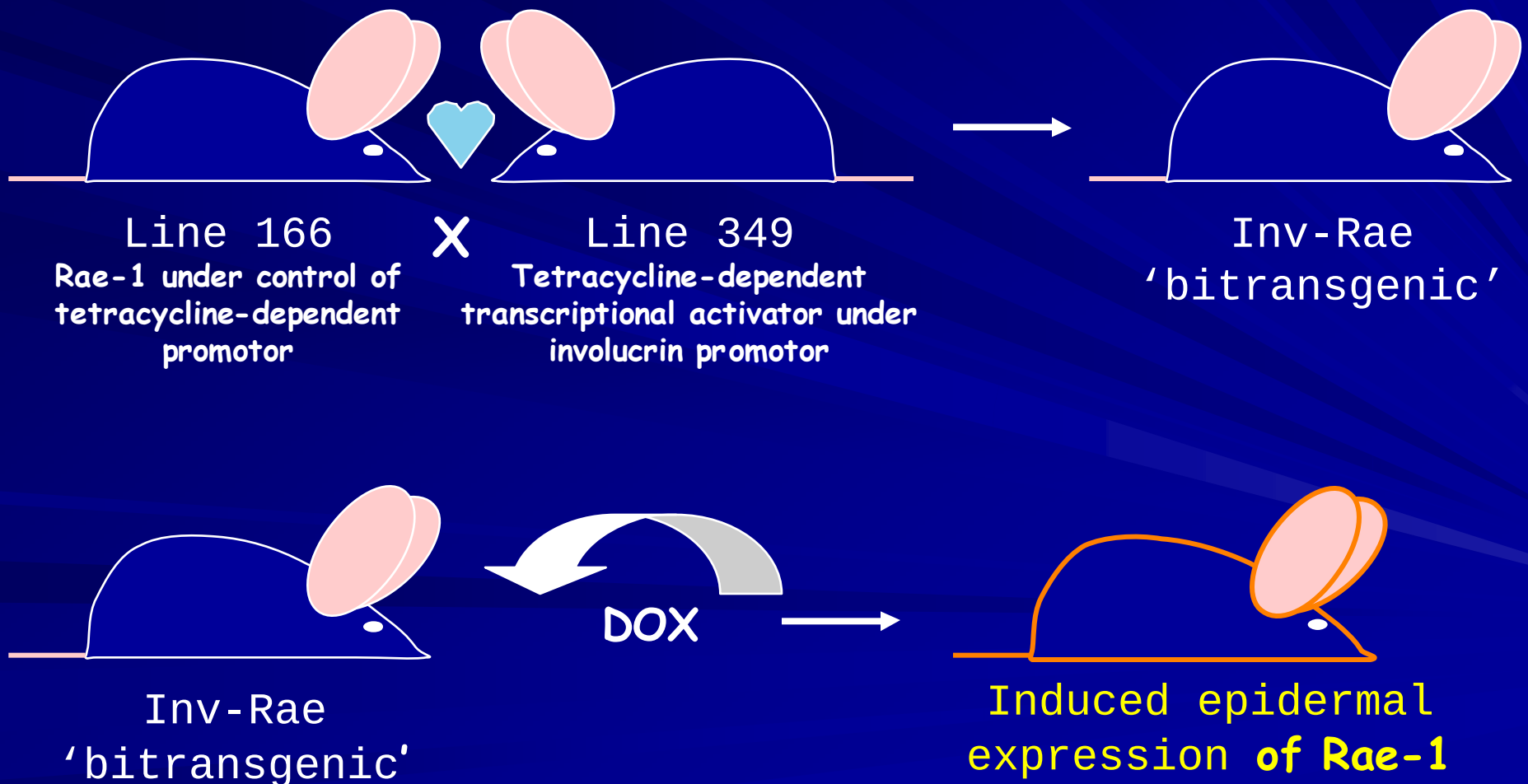
Tumours (and viruses) often
display immune evasion strategies



Is NKG2D-ligand upregulation on normal cells an immune activator?

Jessica Strid (Nature Immunology, 2008)

Transgenic mice induced to express Rae-1:



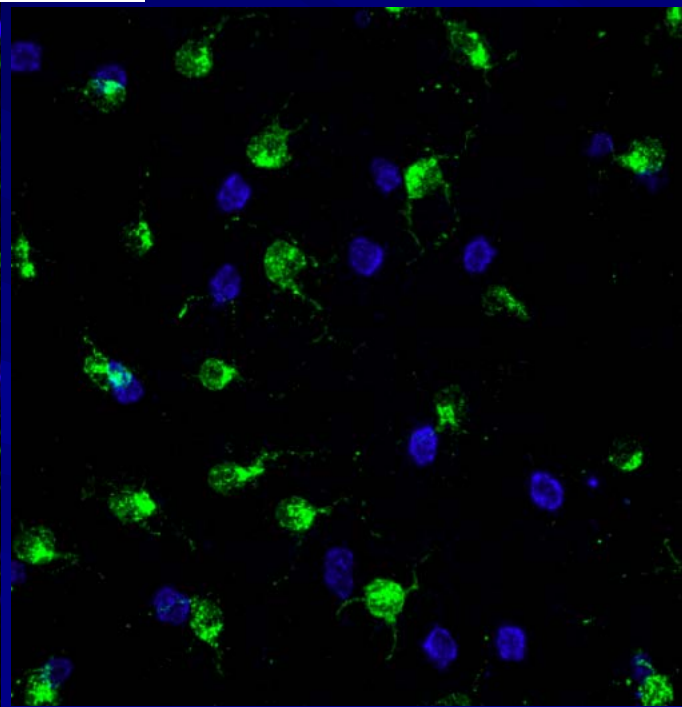
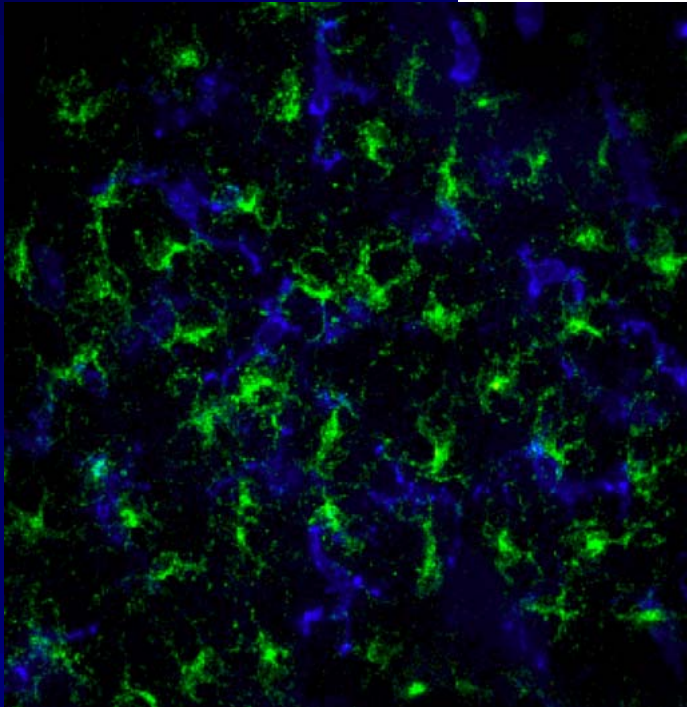
Effects of Inducing Rae-1 β

Inv-rtTA siTg

$\gamma\delta$ TCR (GL3)

MHCII (2G9)

Inv-Rae-1 biTg



DETC (NKG2D⁺)
round-up
(DAP10 → vav
upregulate CD69
downregulate TC

LC (NKG2D⁽⁻⁾)
round-up;
upregulate
CD86 etc.

Conclude : resident tissue-associated immune compartments are highly dynamic in response to altered expression of self "stress-antigen"

Effects of Inducing Rae-1 β

$\gamma\delta$ TCR (GL3)

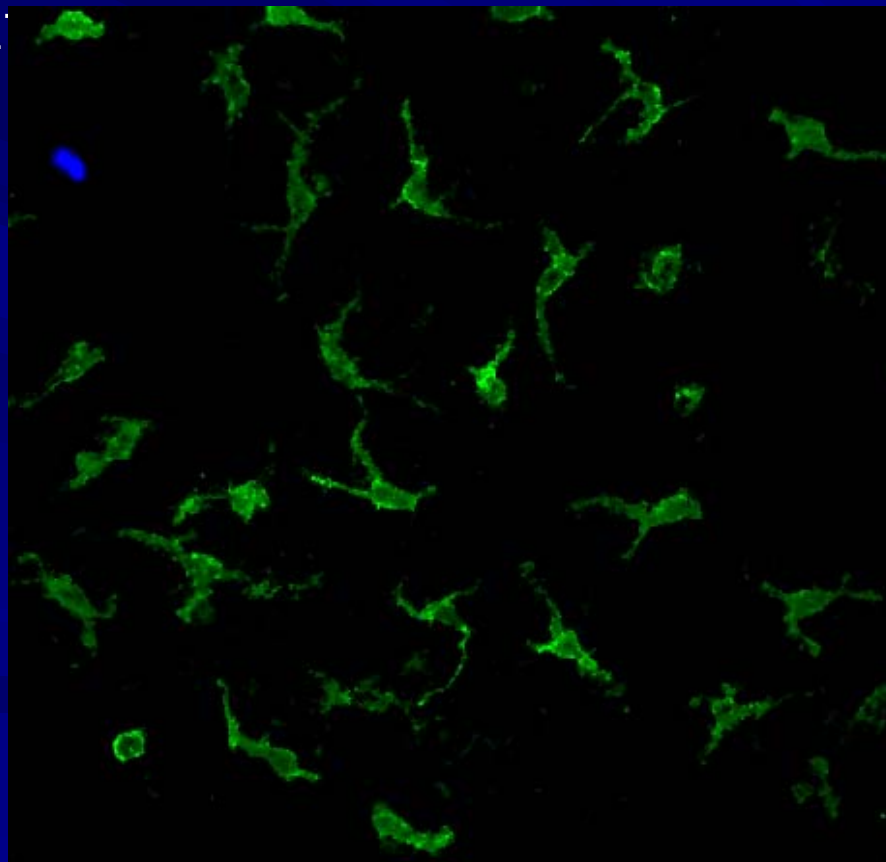
Rae-1 (186107)

$\alpha\beta$ TCR (H57)

Inv-rtTA bi

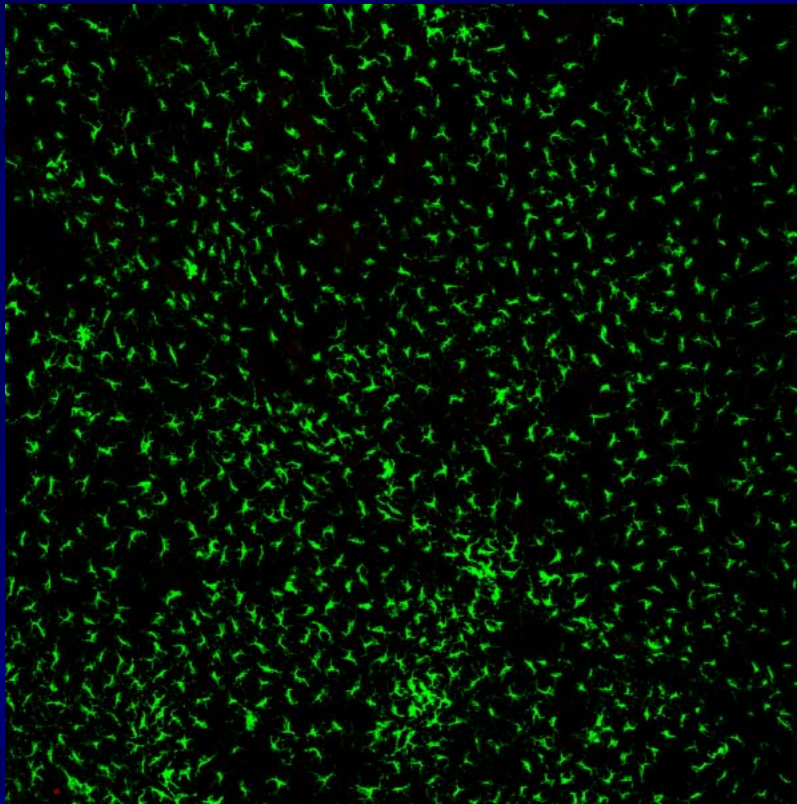
cal microscopy of epidermal sheets (120h)

Conspicuous
 $\alpha\beta$ T cell
infiltration

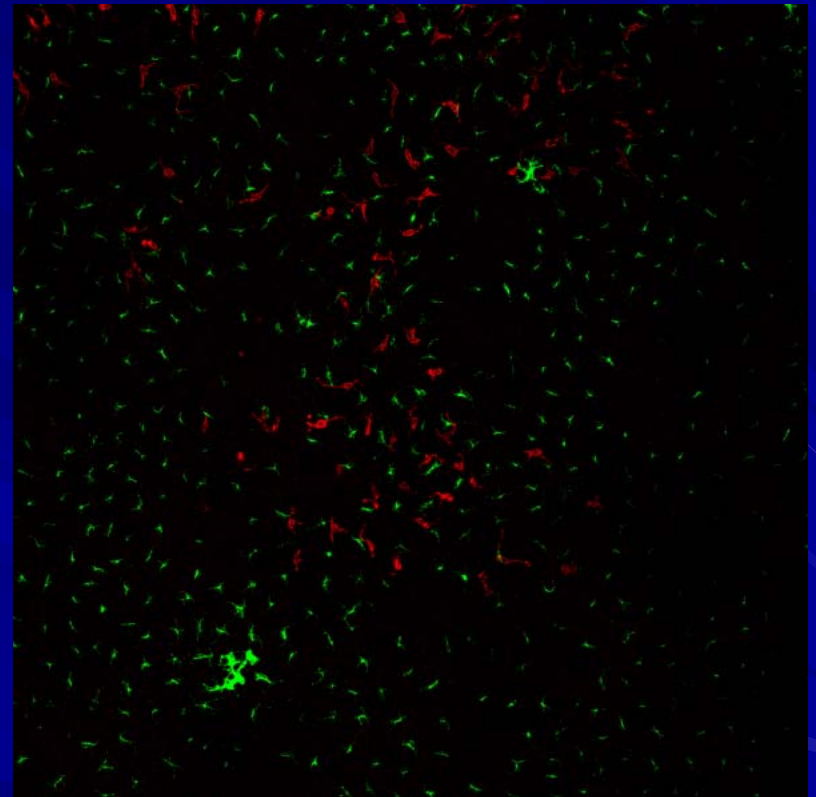


72 post-induction (founder 16)

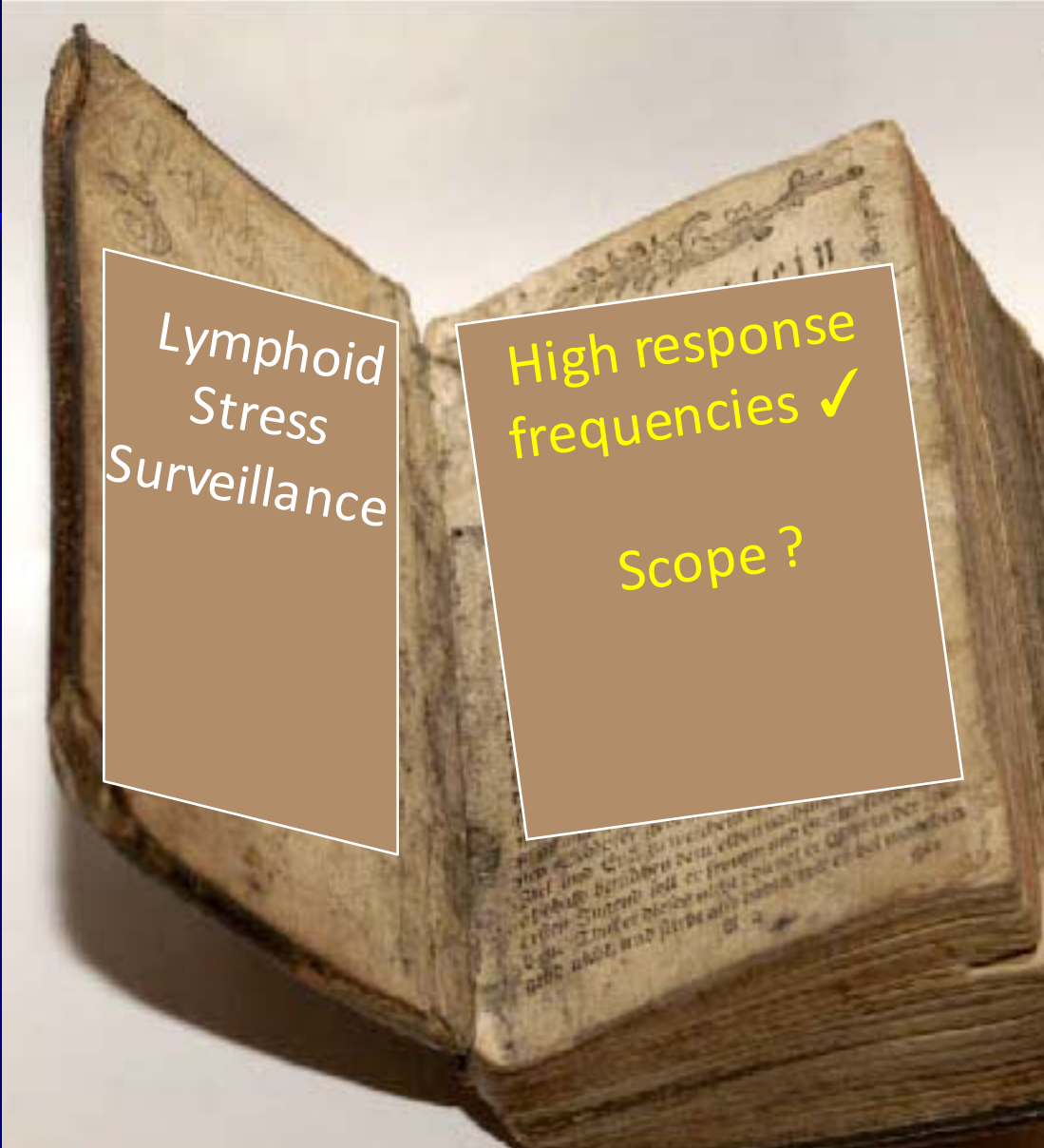
Single tg



bi-tg



MHCII
TCR $\alpha\beta$

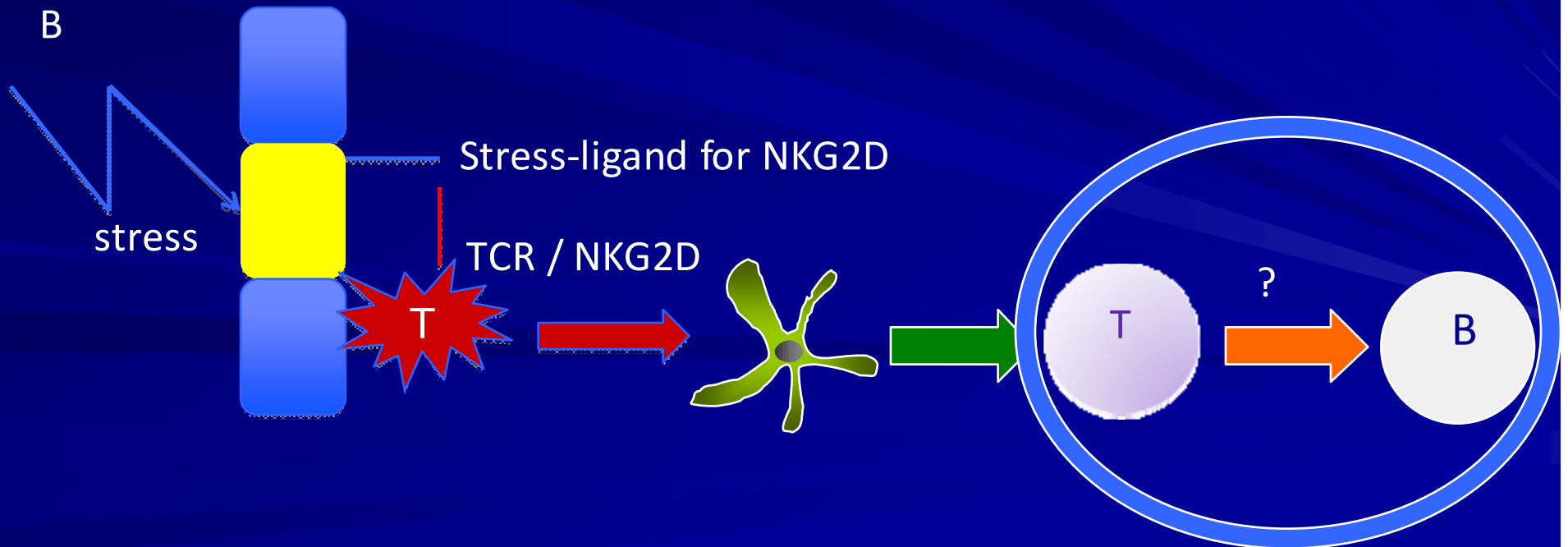
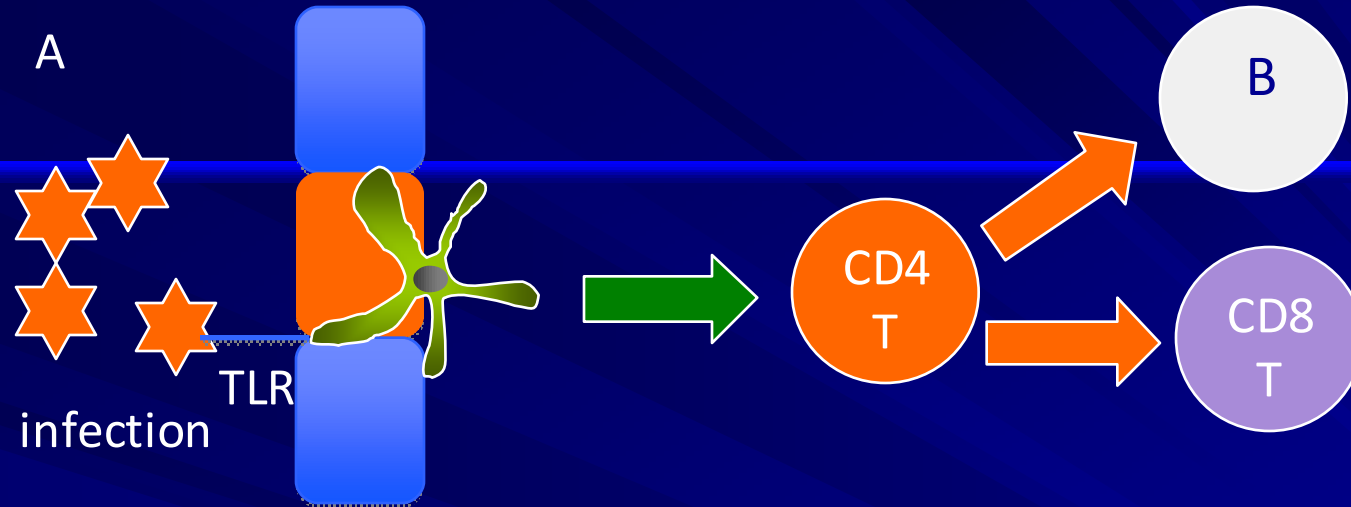


Lymphoid
Stress
Surveillance

High response
frequencies ✓

Scope ?

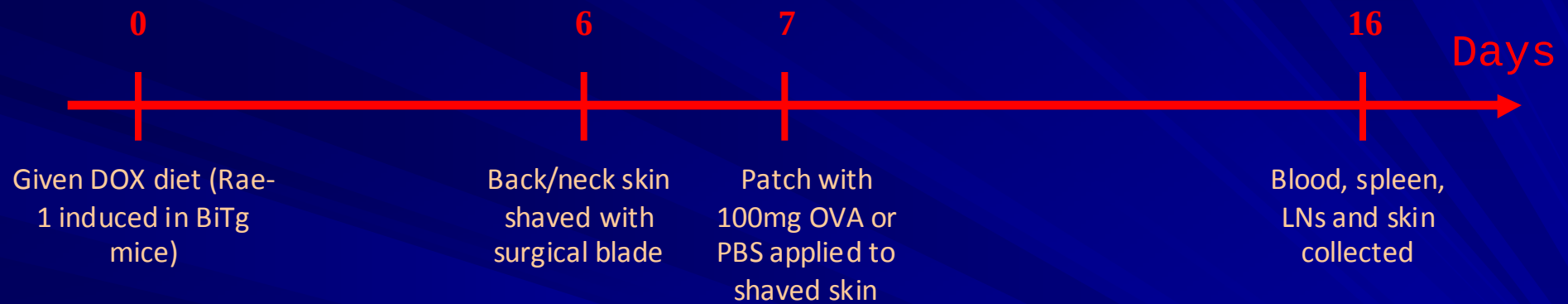
The scope of lymphoid stress-surveillance



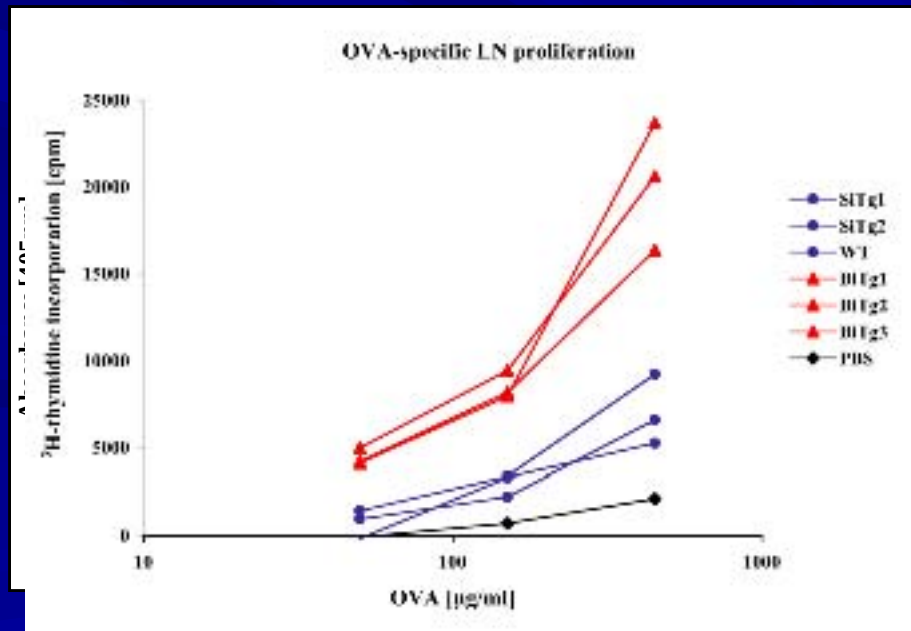
OVA skin-patch experiment following induction of Rae-1 - primary response to OVA

Jessica Strid; Olga Sobolev - unpublished

Experimental time-line:



Adjuvant activity of acute stress – *Tumour immunogenicity*



The value of the $\gamma\delta$ cell stress-surveillance system

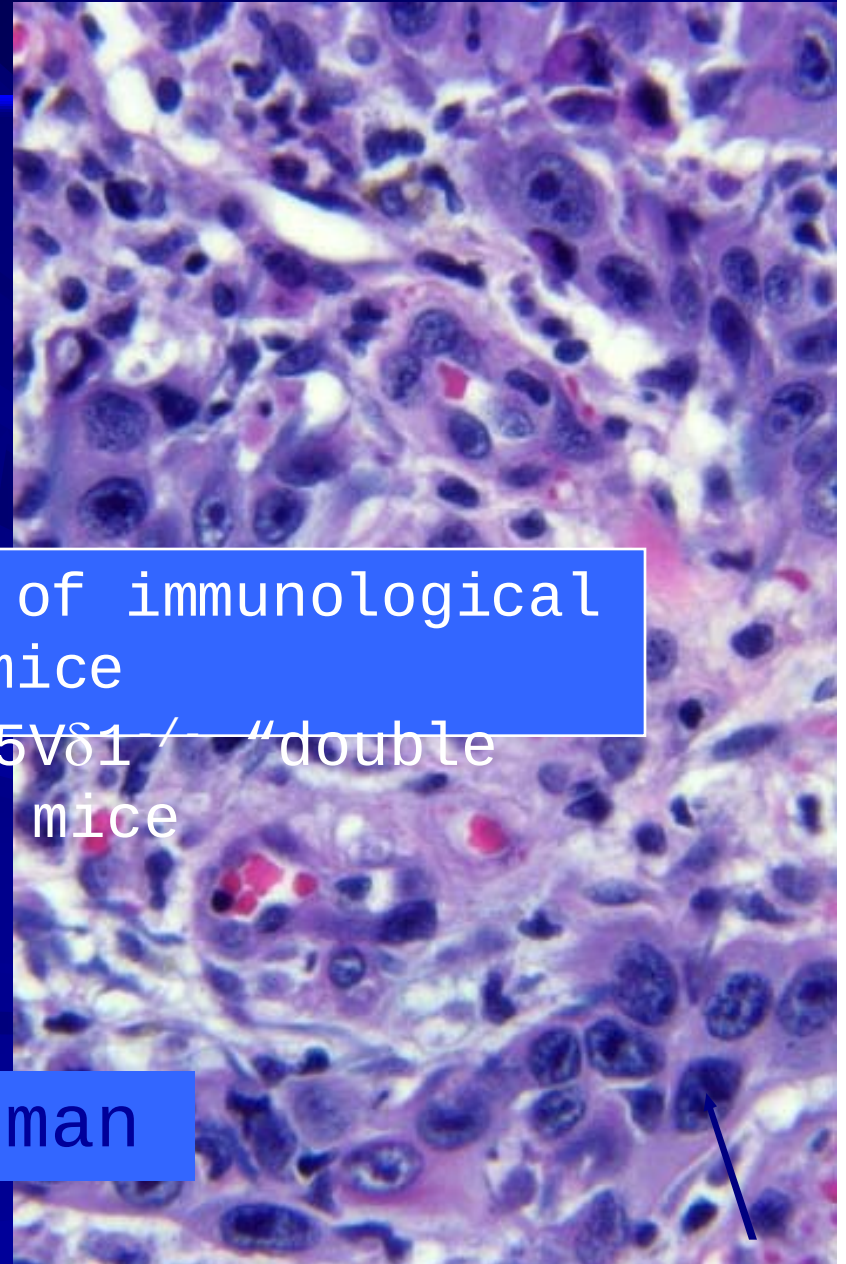
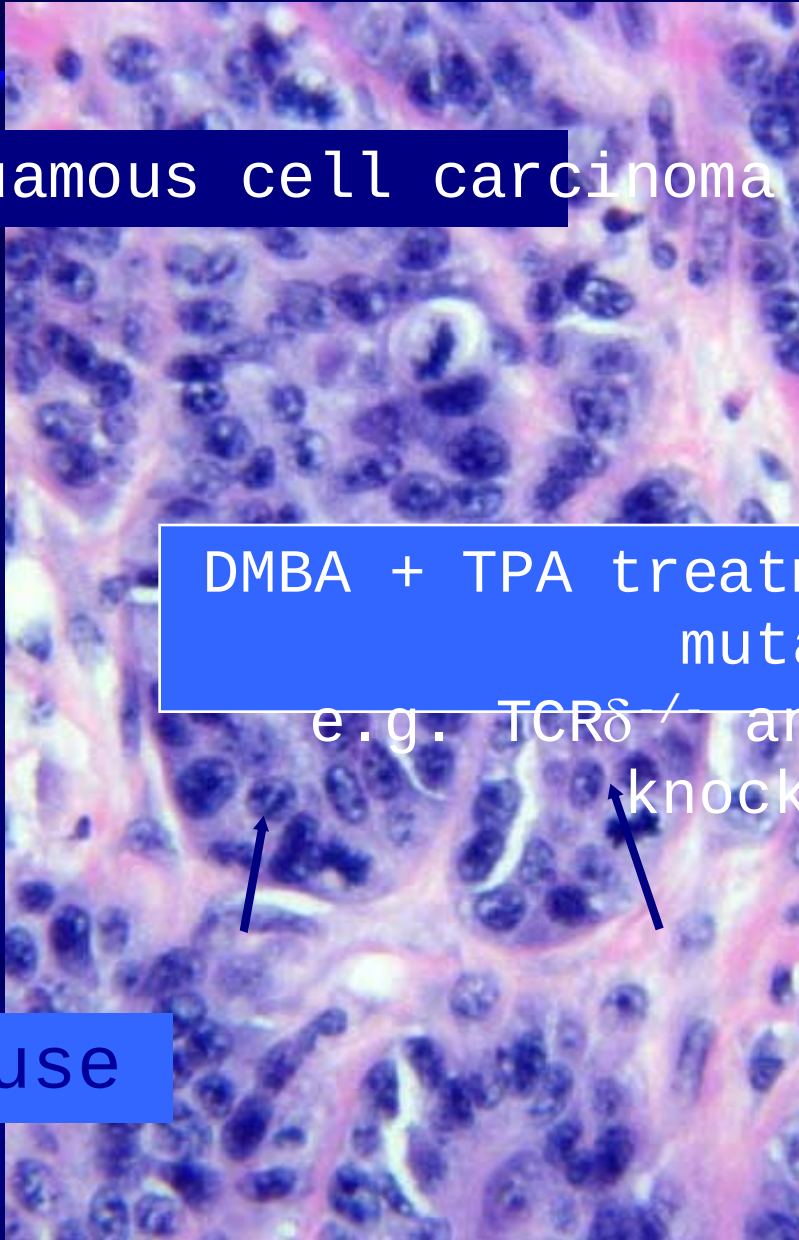
Squamous cell carcinoma

DMBA + TPA treatment of immunological mutant mice

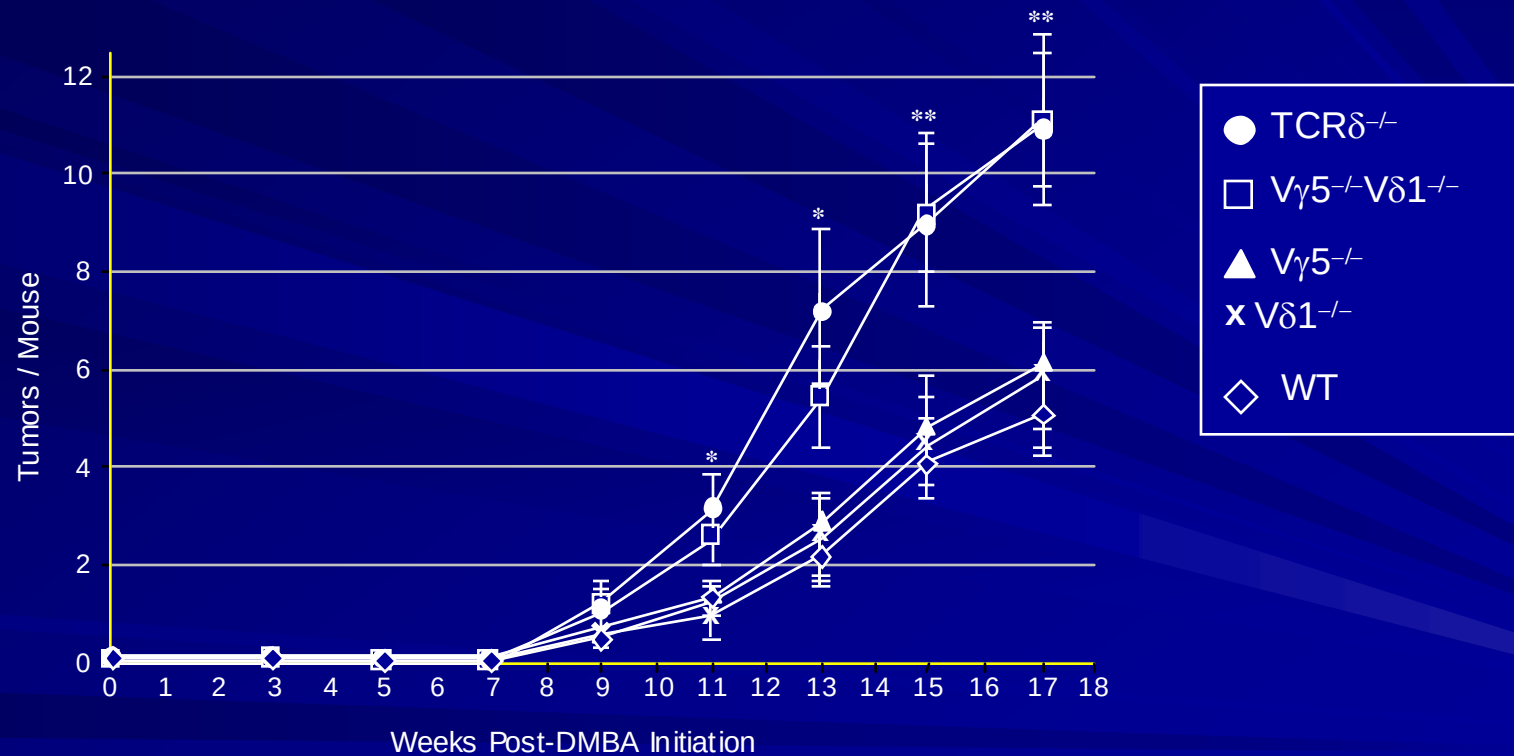
e.g. $\text{TCR}\delta^-/-$ and $\text{V}\gamma 5\text{V}\delta 1^-/-$ “double knockout” mice

Mouse

Human

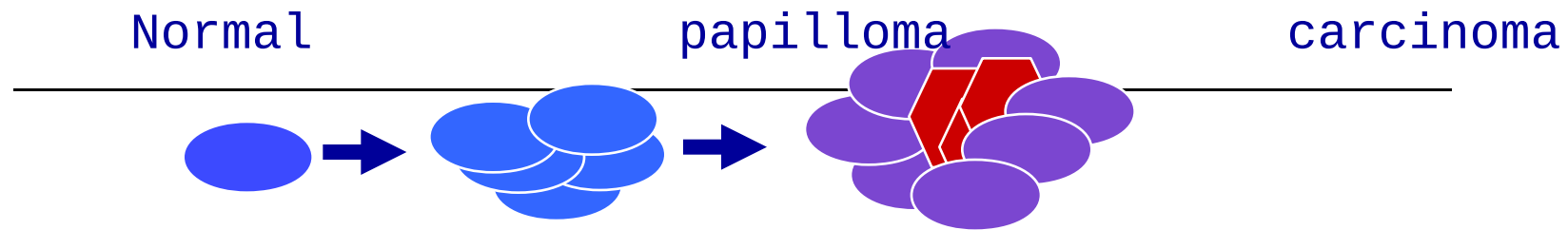


Reduced susceptibility to inflammatory chemical carcinogenesis of mice lacking $V\gamma 5V\delta 1^+$ DETC



1⁺ DETC act early, consistent with stress-surveillance

Irardi et al., Science, 2001; Strid et al., Nat Immunol 2008



Mouse Strain	Tumors / Mouse ¹	P-value ²	Carcinomas / Mouse ¹	P-value ²
TCR $\delta^{-/-}$	11.08 $\pm$ 1.74	≤ 0.002	5.46 $\pm$ 1.24	≤ 0.05
V $\gamma 5^{-/-}$	5.83 $\pm$ 1.09	N.S.	3.58 $\pm$ 0.99	N.S.
V $\delta 1^{-/-}$	6.07 $\pm$ 0.95	N.S.	3.79 $\pm$ 0.73	N.S.
V $\gamma 5^{-/-}$ V $\delta 1^{-/-}$	11.17 $\pm$ 1.36	≤ 0.0004	7.08 $\pm$ 1.05	≤ 0.01
WT	5.08 $\pm$ 0.84	-	3.38 $\pm$ 0.75	-

¹Mean values at week 17 post-DMBA initiation.

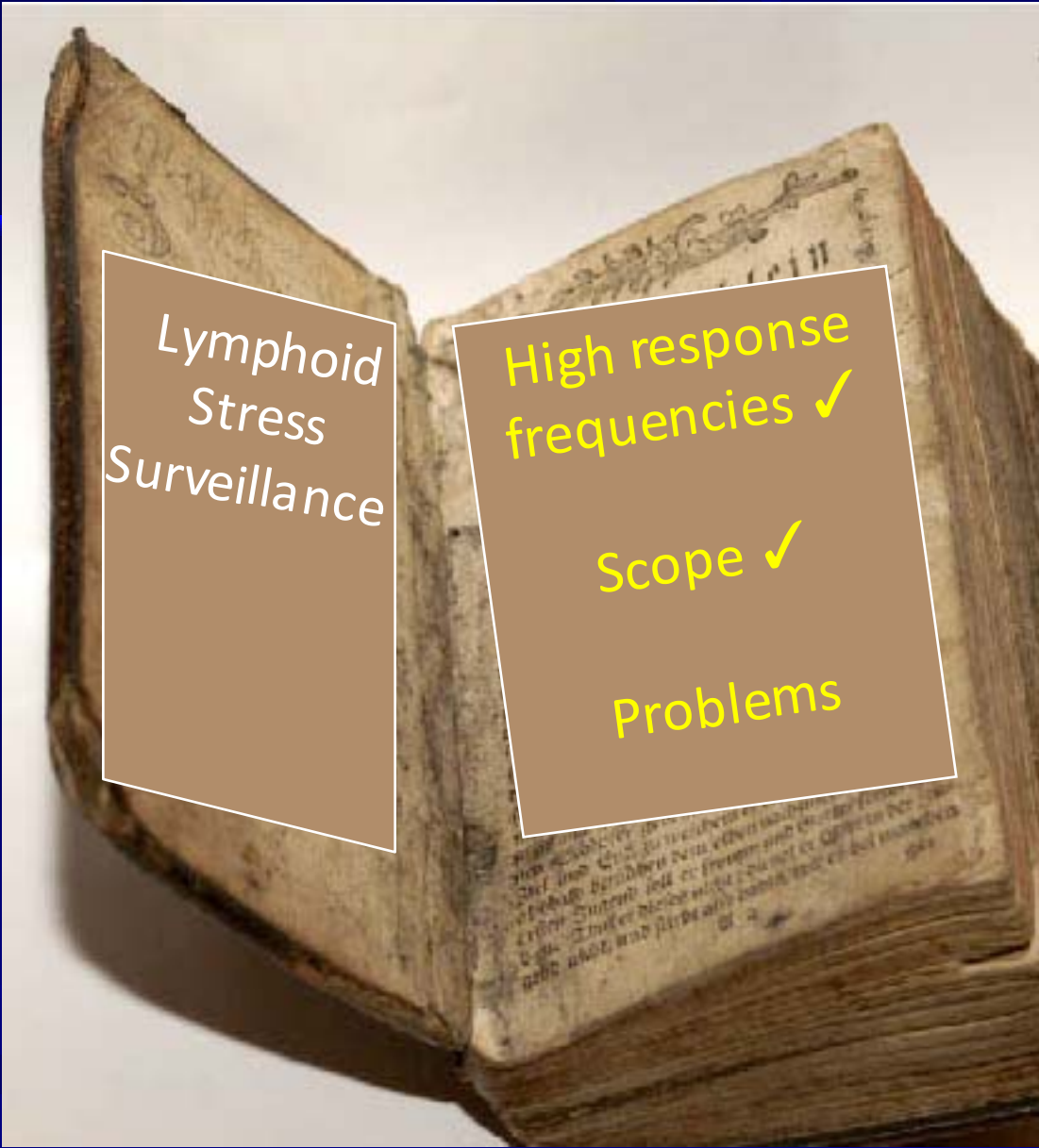
²P-values versus WT ; N.S., not significant.

Progression ratio

w.t .665

sko .614

dko .634



Lymphoid
Stress
Surveillance

High response
frequencies ✓

Scope ✓

Problems

The UN model of immune function - *Lederberg*

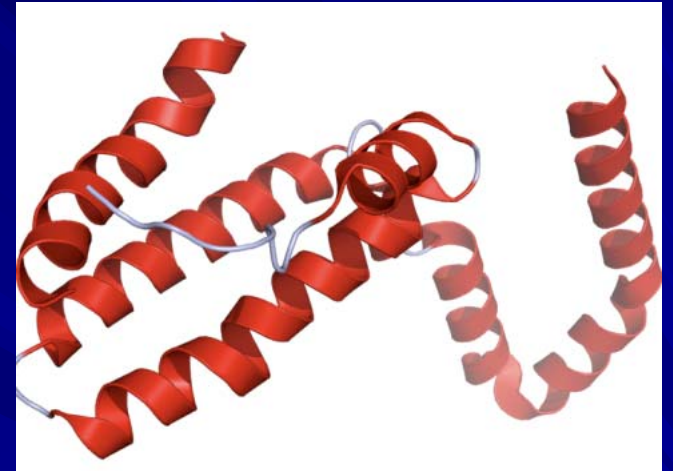
There maybe a limited capacity to eradicate chronic infections, related to which is our struggle to make vaccines against them



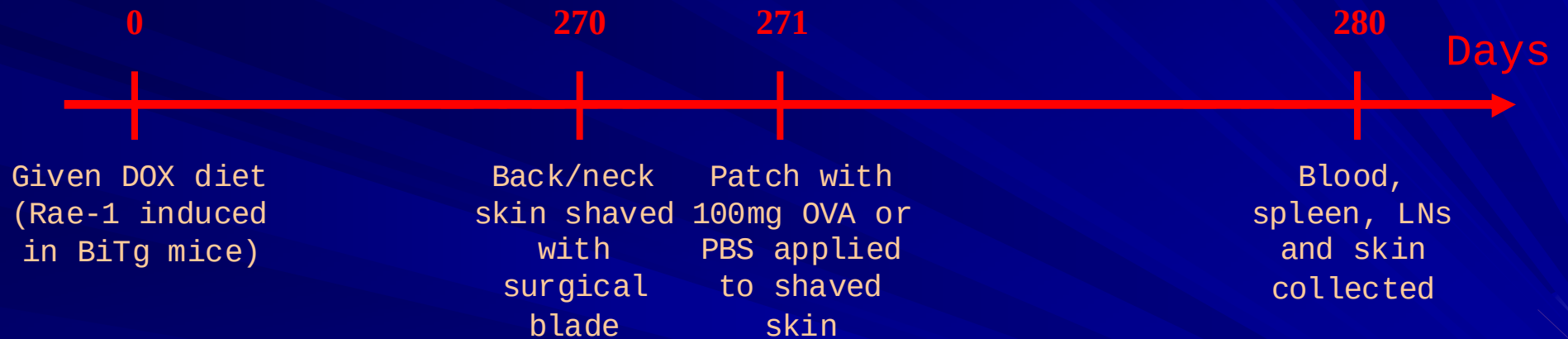
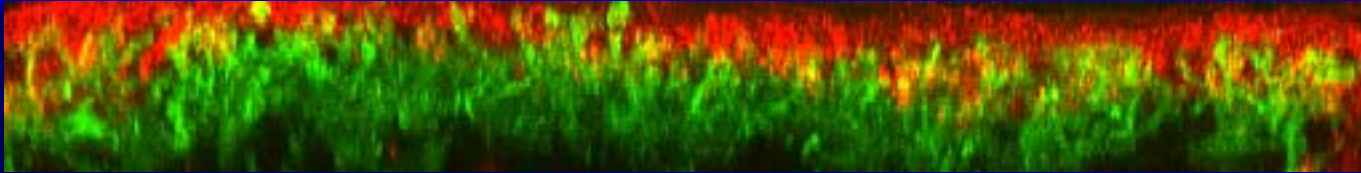
Surprising partners in chronic infections



Parasitic worms and IL10



Does chronic stress-surveillance immune sup



Chronic “stress-surveillance” reverts to an immuno-suppressive state

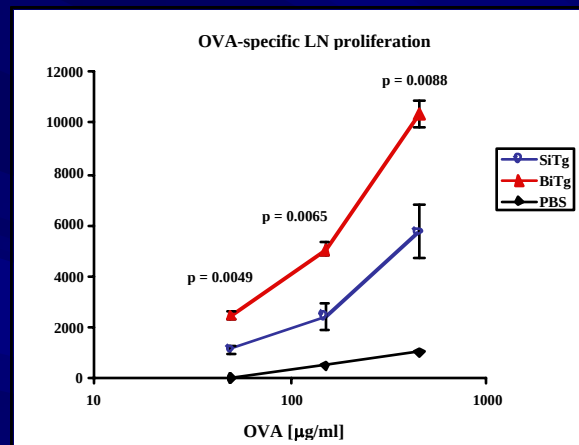
OVA-specific
proliferatio

n:

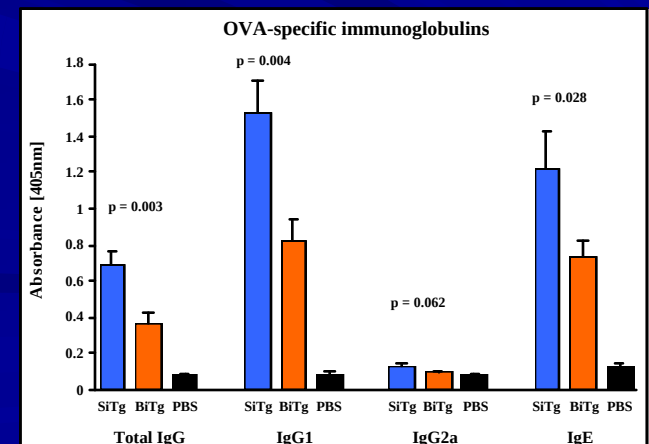
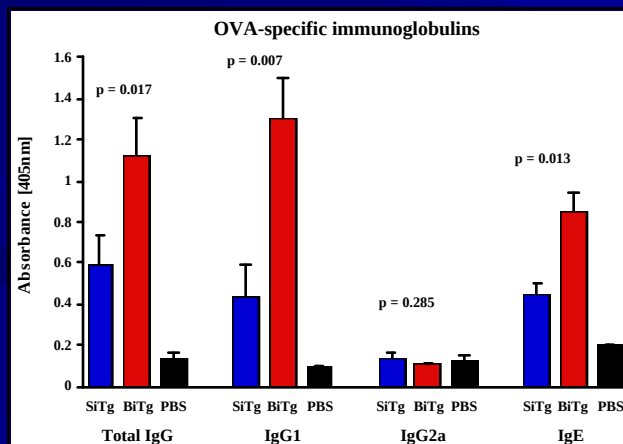
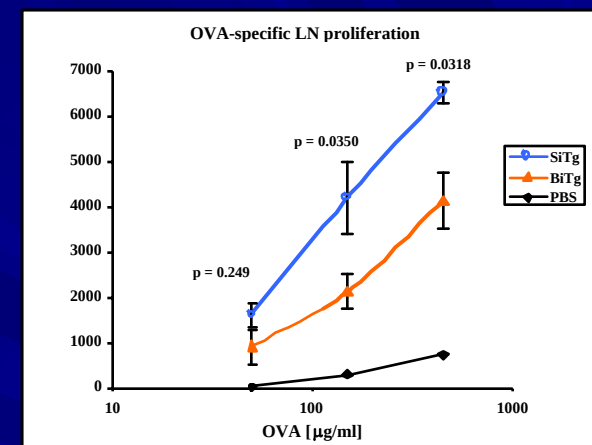
OVA-specific
immunoglobul

ins:

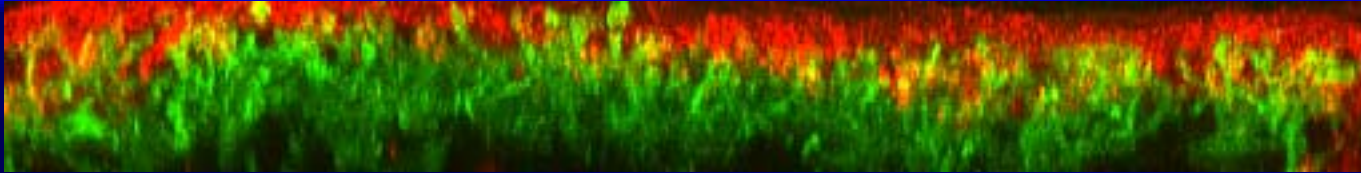
Acute Rae-1
(5 days)



Long-term Rae-1
(9 months)

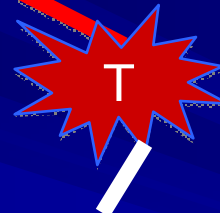


“stress-surveillance” reverts to an immuno-suppress



MICA/Rae-1=NKG2D

TCR

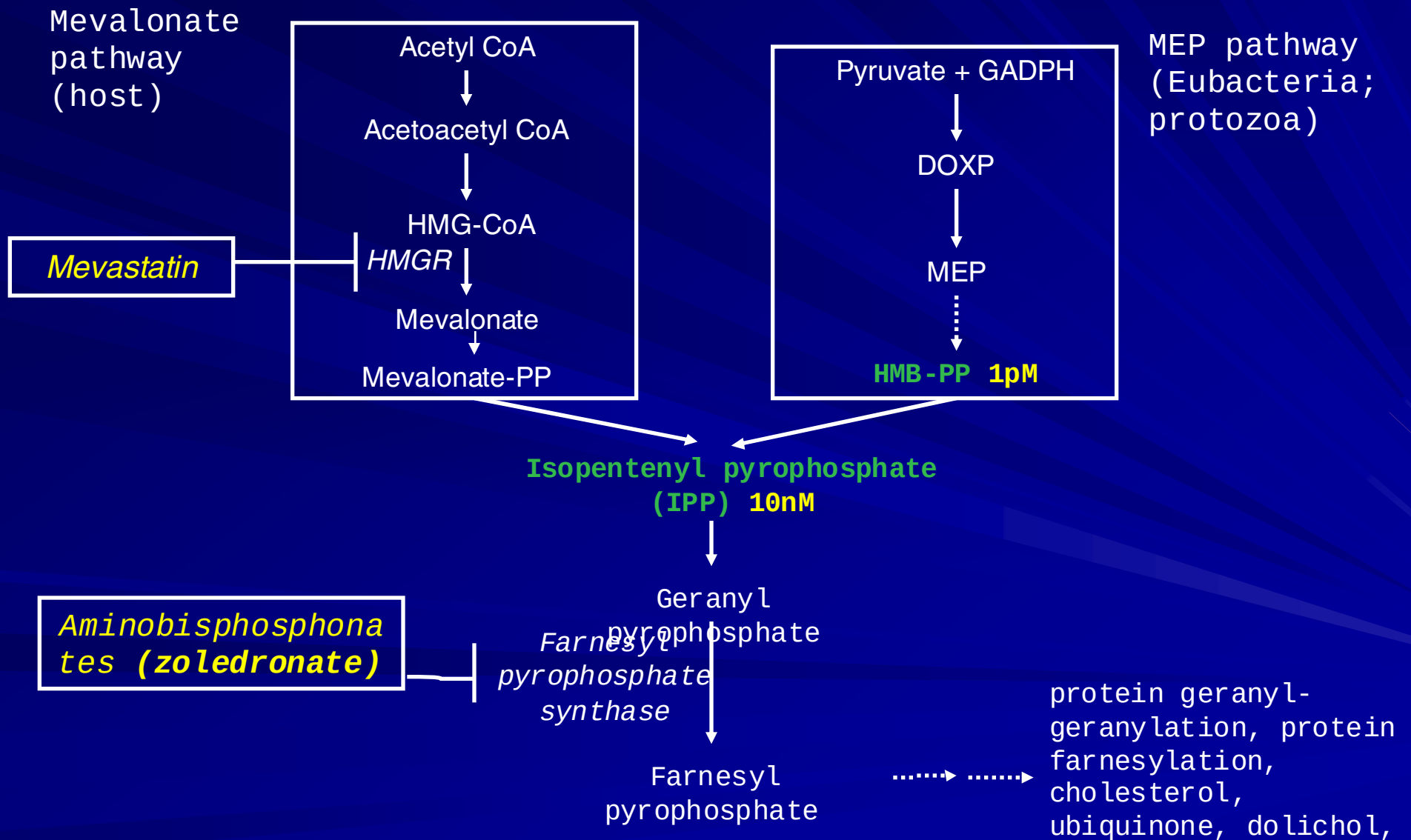


NKG2D downregulation
Loss of activity of $\gamma\delta$ cells
and NK cells

Rejuvenating Stress-Surveillance



Rejuvenating T cells Responses in the Clinic



Clinical Trial

Francesco Dieli - Palermo

Research Article

Targeting Human $\gamma\delta$ T Cells with Zoledronate and Interleukin-2 for Immunotherapy of Hormone-Refractory Prostate Cancer

Francesco Dieli,¹ David Vermijlen,³ Fabio Fulfaro,² Nadia Caccamo,¹ Serena Meraviglia,¹ Giuseppe Cicero,² Andrew Roberts,³ Simona Buccheri,¹ Matilde D'Asaro,¹ Nicola Gebbia,² Alfredo Salerno,¹ Matthias Eberl,^{4,5} and Adrian C. Hayday³

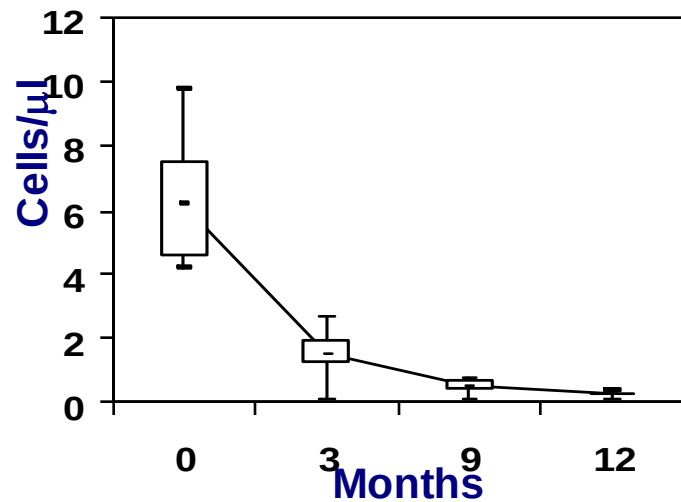
... (1 mg
i.v.) - *low m.w. activator of*
V γ 9⁺ T cells; safe; used in metastasis

+/- a low dose of IL-2 (0.6 million U IL-2 s.c.) (Francesco Dieli, University of Palermo) - *safe;*

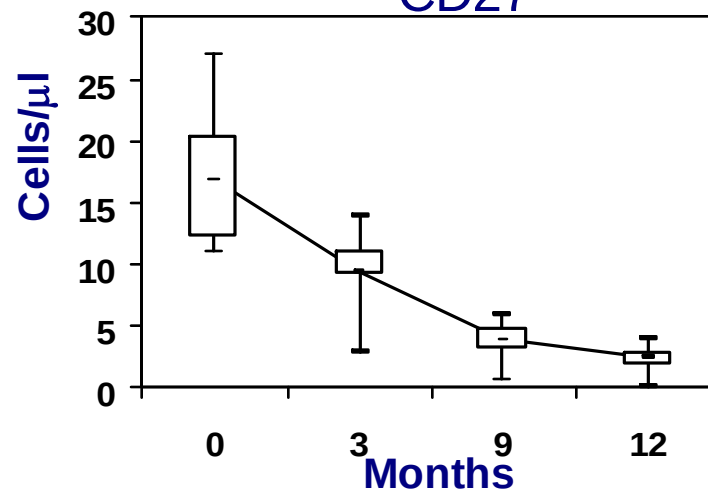
effects on $\gamma\delta$ cells are the only ones

$\gamma\delta$ cell subsets

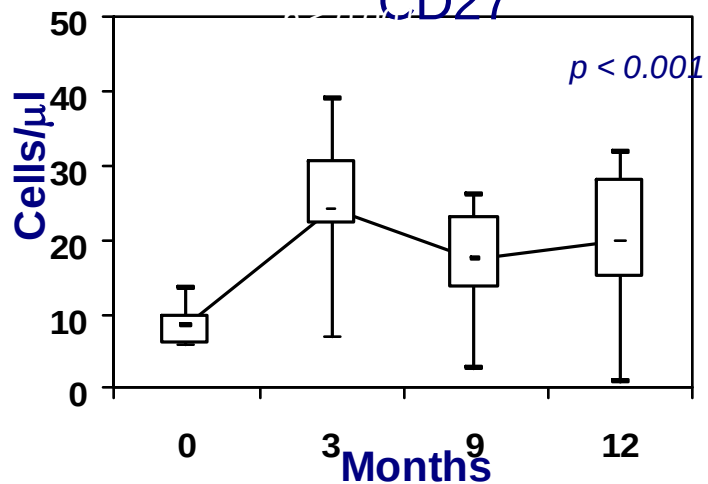
T_{naive} CD45RA⁺CD27⁺



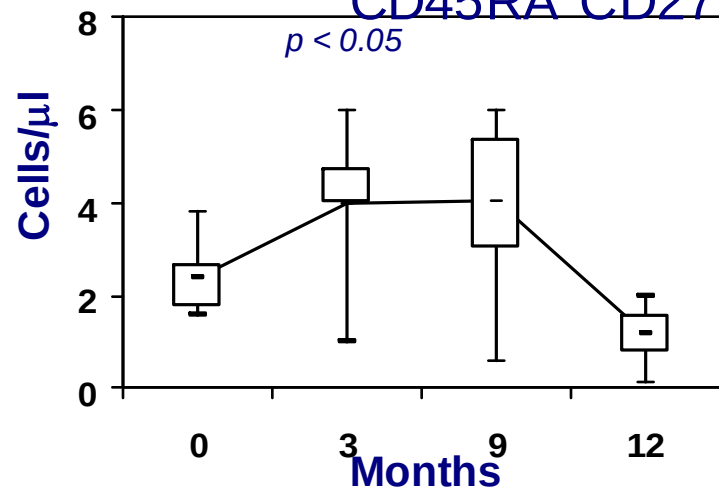
T_{CM} CD45RA⁻CD27⁺



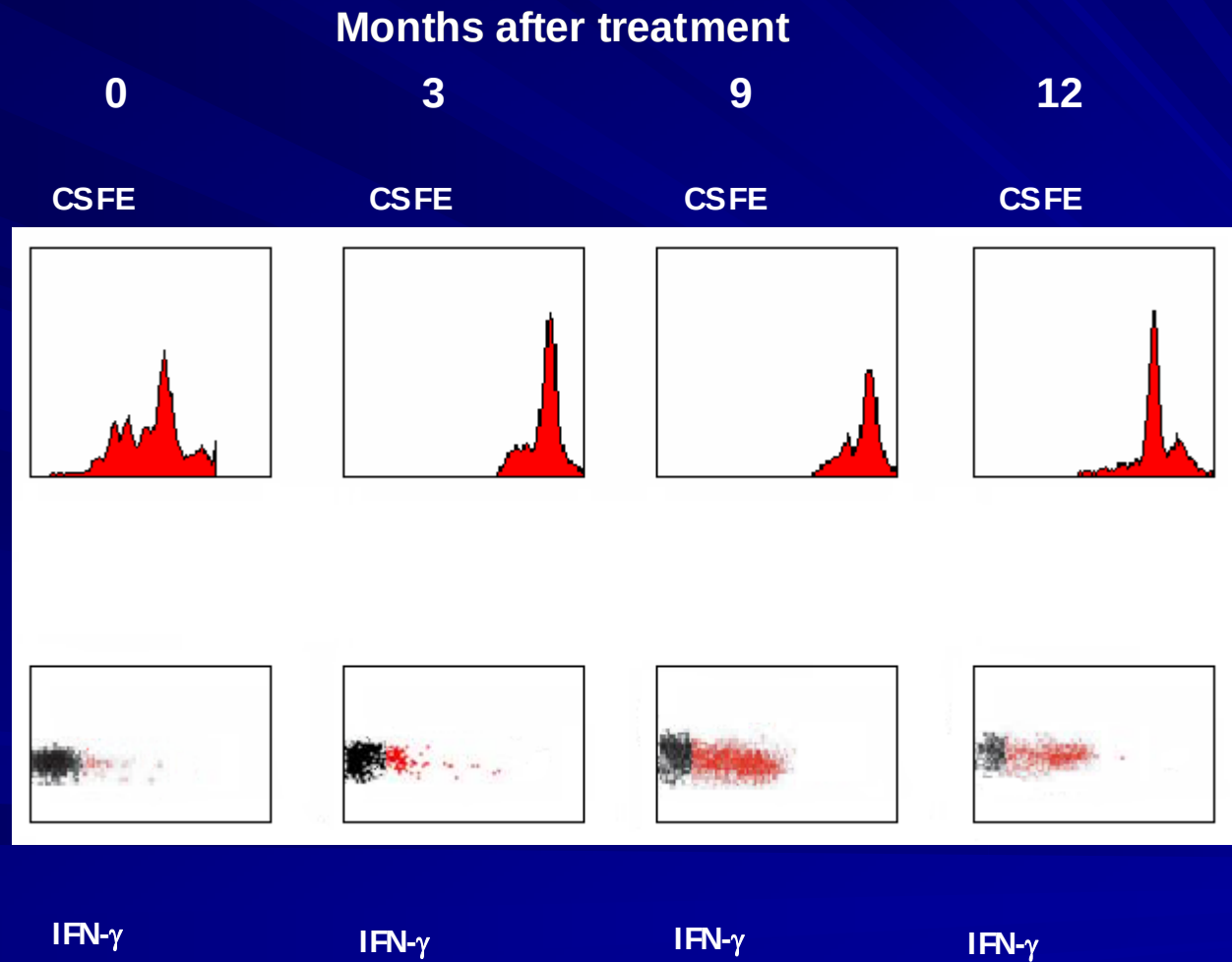
T_{EM} CD45RA⁻CD27⁻



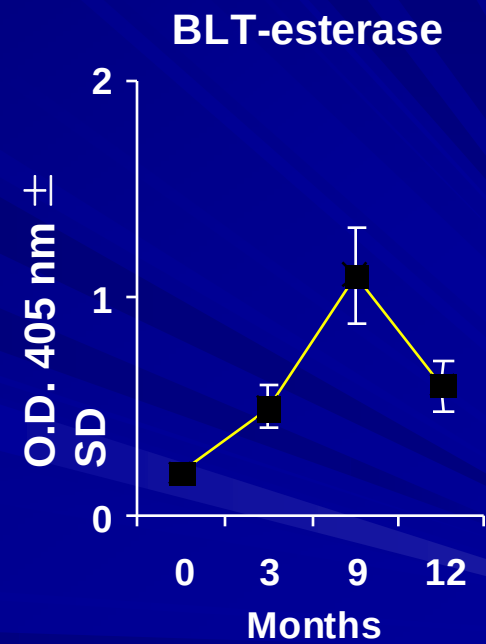
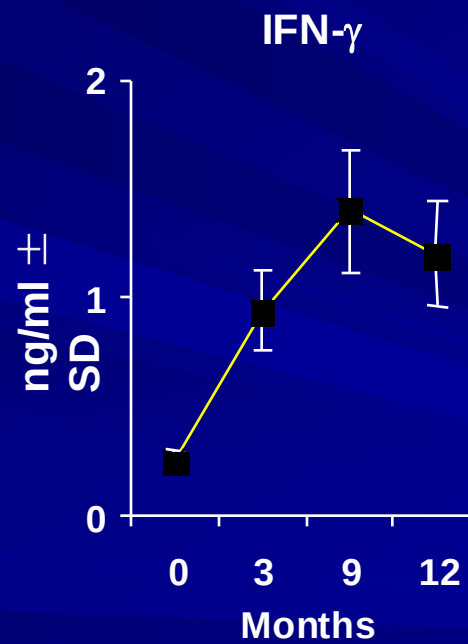
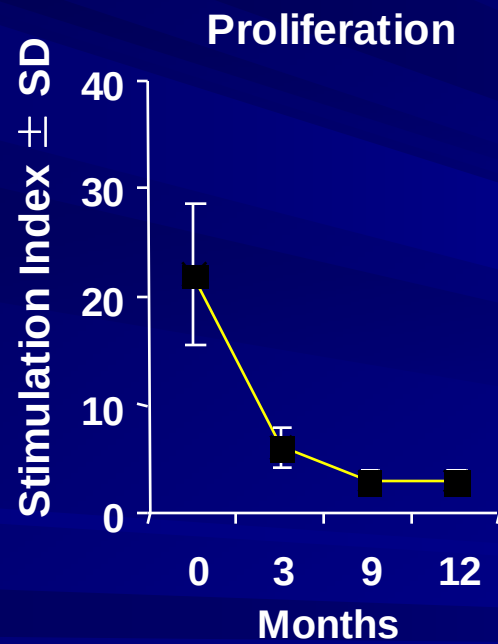
T_{EMRA} CD45RA⁺CD27⁻



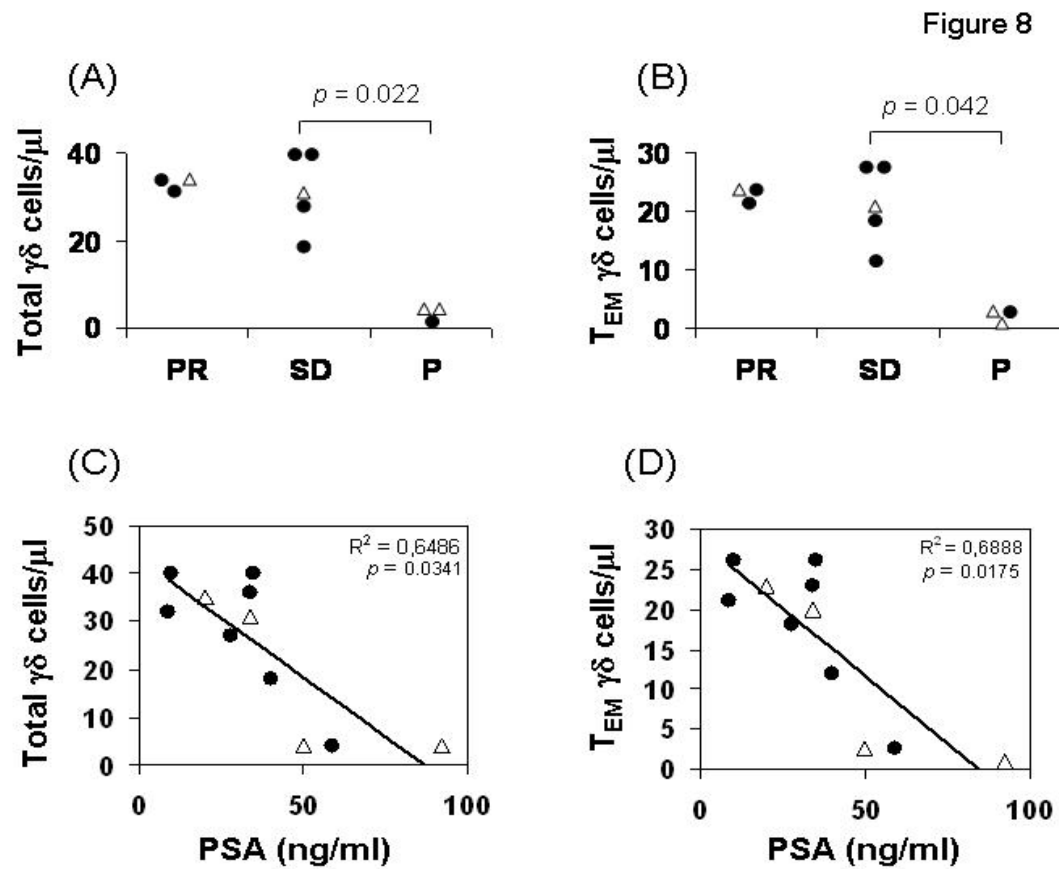
$\gamma\delta$ cell responses



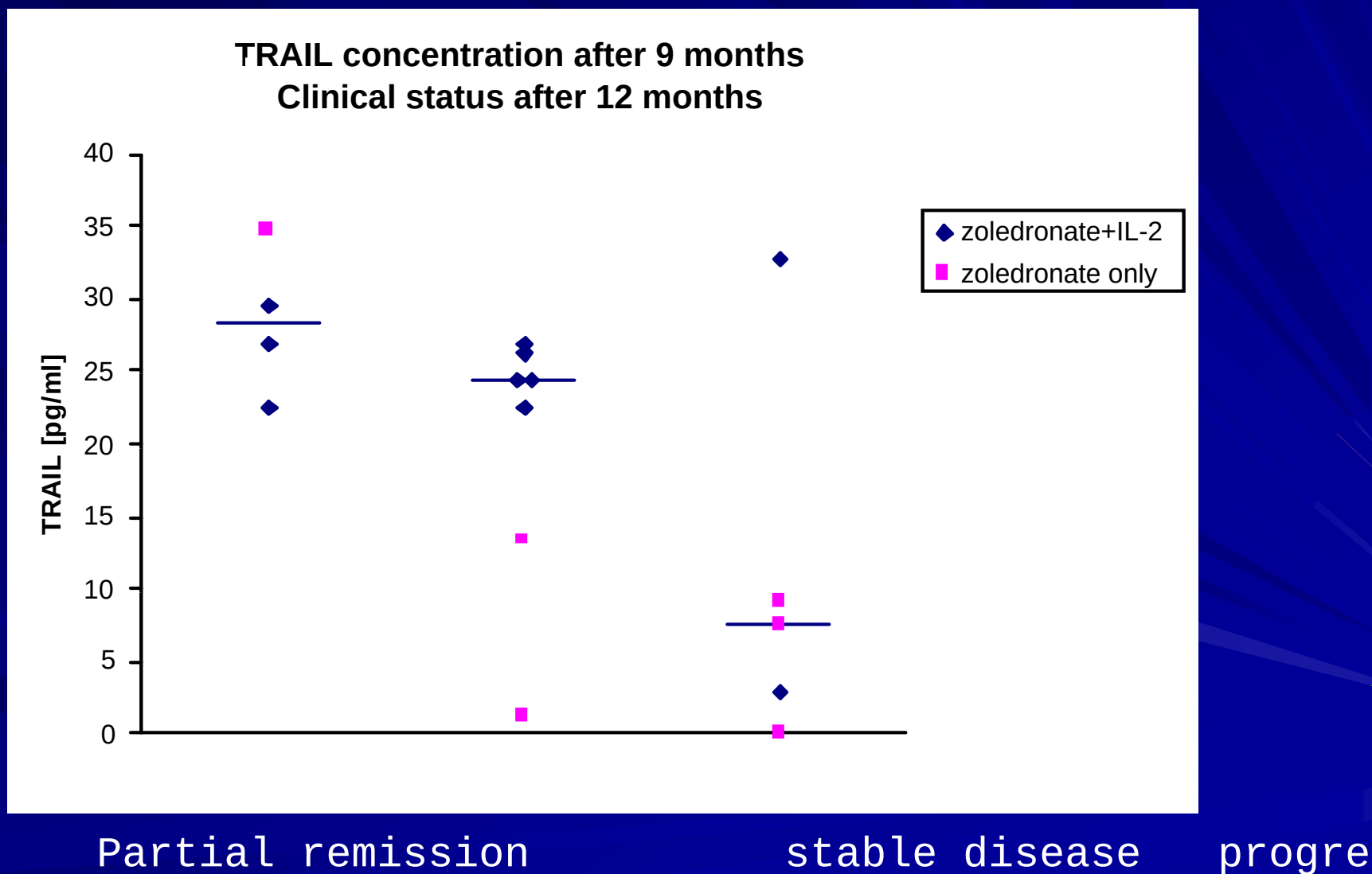
$\gamma\delta$ cell responses



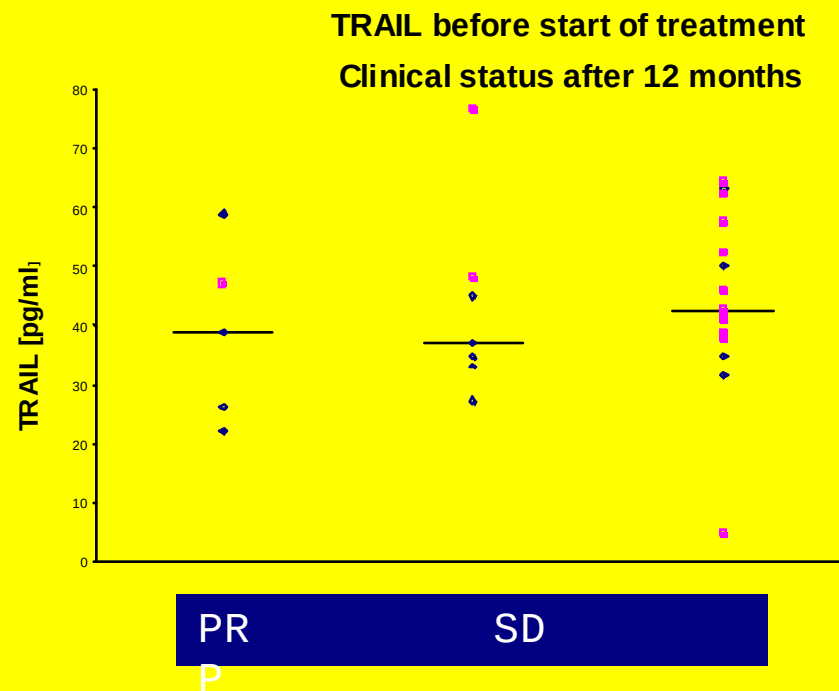
clinical outcome



correlations of T cell activity and outcome



Data so far.....TRAIL vs outcome.....



TRAIL: before start of treatment

Achieving High Frequency Responses in the Clinic

In vivo manipulation of V γ 9V δ 2 T cells with zoledronate and low dose interleukin-2 for immunotherapy of advanced breast cancer patients.

Serena Meraviglia¹, Matthias Eberl², David Vermijlen³, Matilde Todaro⁴, Simona Buccheri⁵, Giuseppe Cicero⁴, Carmela La Mendola¹, Giuliana Guggino¹, Matilde D'Asaro¹, Valentina Orlando¹, Francesco Scarpa¹, Andrew Roberts⁶, Nadia Caccamo¹, Francesco Dieli^{1*}, Giorgio Stassi⁴, and Adrian C. Hayday^{6*}.

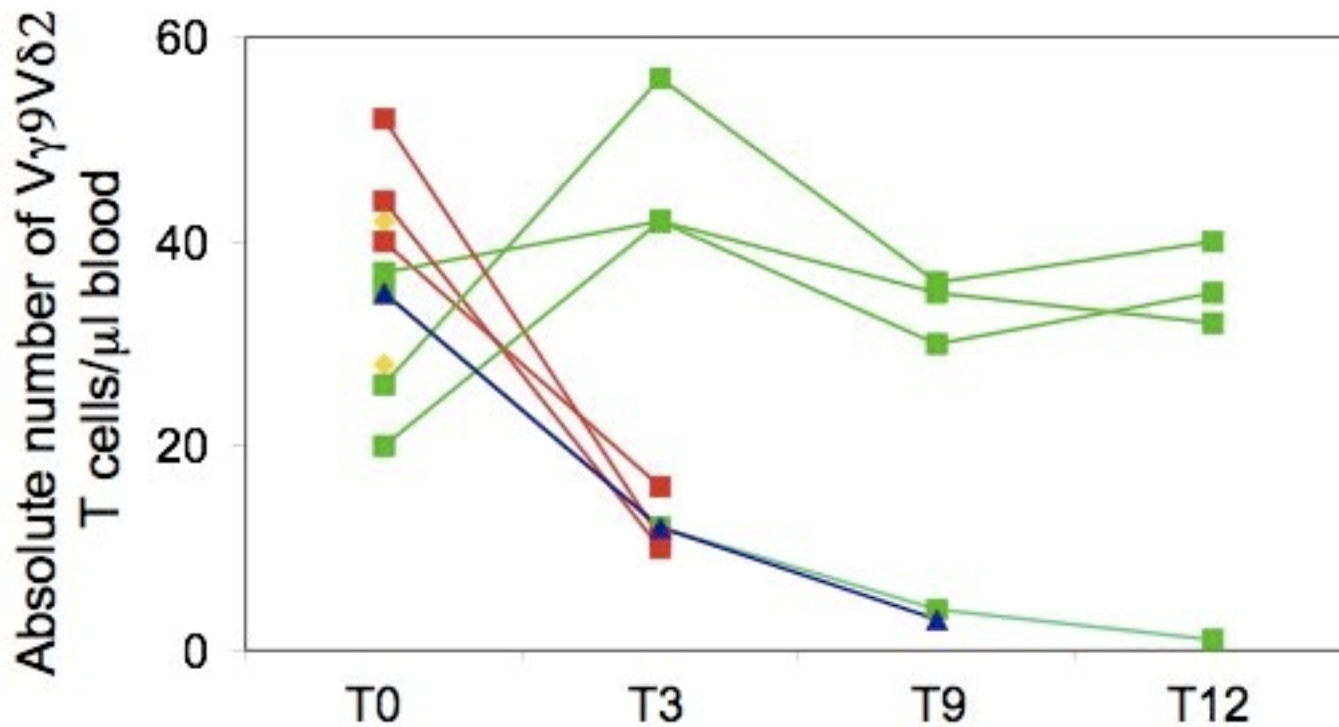
Mevalonate pathway (host)

MEP pathway (Eubacteria; protozoa)

Mevast

Amino
tes (

IL2



farnesyl
pyrophosphate

cholesterol,
ubiquinone, dolichol,

Acknowledgements

Jessica Strid
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Susannah
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Martin
Woodward
Lucie Dorner
Mahima Swamy
Deena Gibbons
Yasmin Haque
Andy Roberts

Marie-Laure
Michel

