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Cloning of the mycobacterial epitc recognized by T lymphocytes in adjuvant arthritis

Willem van Eden*, Jelle E. R. Thole†, Ruurd van der Zee‡, Alie Noordzij*, Jan D. A. van Embden†, Evert J. Hensen* & Irun R. Cohen§

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Adjuvant arthritis (AA) is a chronic disease inducible in rats by immunization with an antigen of *Mycobacterium tuberculosis*[1]. After the isolation of arthritogenic T-cell lines[2] and clones[3], it became possible to demonstrate that the critical *M. tuberculosis* antigen contained an epitope cross-reactive with a self-antigen in joint cartilage[4–6]. Like AA rats, patients suffering from rheumatoid arthritis demonstrated specific T-lymphocyte reactivity to the *M. tuberculosis* fraction containing the cross-reactive epitope[7]. To characterize the critical *M. tuberculosis* epitope we used AA T-cell clones to screen mycobacterial antigens expressed in *Escherichia coli* and genetically engineered truncated proteins and synthetic peptides. The AA T-cell clones recognized an epitope formed by the amino acids at positions 180–188 in the sequence of a *Mycobacterium bovis* BCG antigen[8]. Administration of this antigen to rats induced resistance to subsequent attempts to produce AA.

Top 100 most cited in life sciences

Why often cited:

Immune recognition of stress proteins with extensive sequence conservation (HSP) may inhibit autoimmune diseases?

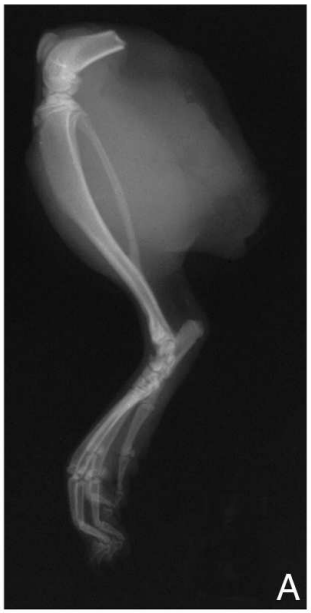
A conserved HSP60 T cell epitope induced self cross-reactive regulatory T cells

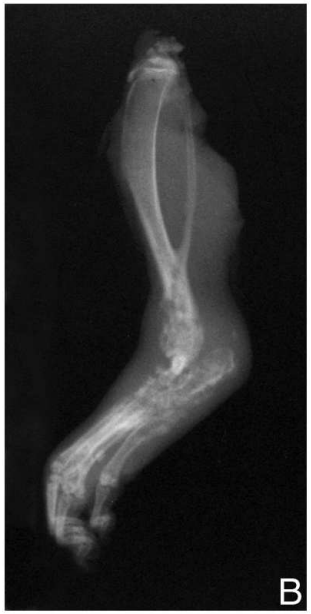
Epitope	Sequence	T-cell line	Response to rat hsp
91 – 100	**DGTTTATVLA**QALVR	H.18	-
176 – 190	EESN**T**FGLQ**LE**LT**EG**	H.36	-
216 – 225	AVLE**D**P**Y**I**LL**VSS**K**V	H.43	-
226 – 235	**S**TVKDLL**P**L**LE**KVIG	H.46	-
256 – 265	**ALSTLVVNK**IRGTFK	**H.52**	**+**
386 – 400	**E**LK**ER**K**H**R**I**E**DA**VRN	-	-
396 – 405	**DA**VRNAK**AAVEEGIV**	H.80	-
446 – 455	A**P**LKQ**IA**F**N**S**G**L**E**PG	H.90	-
511 – 520	FL**TTEAVV**ADK**P**EK**E**	H.103	-

Only H. 52 prevented arthritis

X-ray analysis day 35 after HSP treatment of experimental arthritis

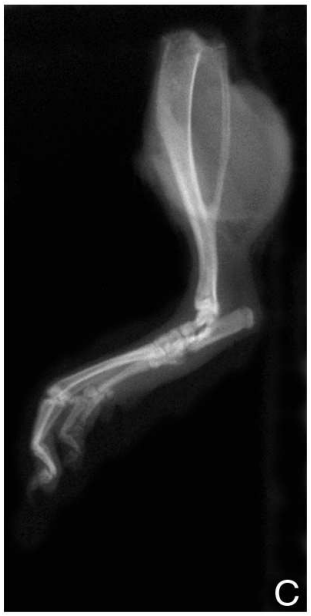
Naive





Arthritis: no treatment

HSP treatment

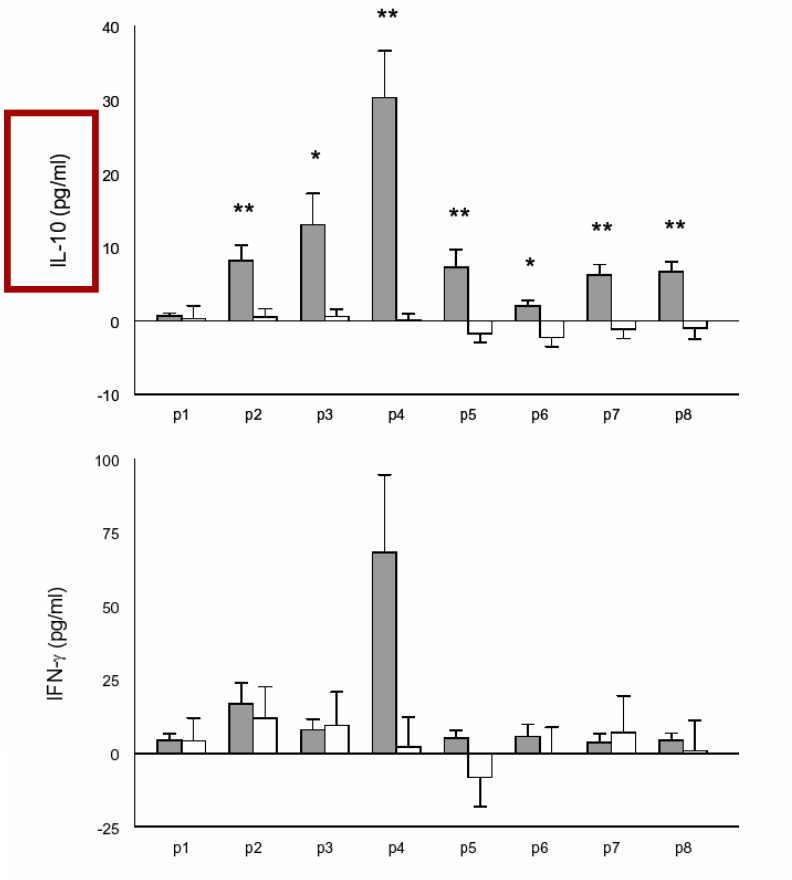


D

Tolerogenic immune responses to novel T-cell epitopes from heat-shock protein 60 in juvenile idiopathic arthritis

Sylvia Kamphuis, Wietse Kuis, Wilco de Jager, Gijs Teklenburg, Margherita Massa, Grace Gordon, Marjolein Boerhof, Ger T Rijkers, Cuno S Uiterwaal, Henny G Otten, Alessandro Sette, Salvatore Albani, Berent J Prakken

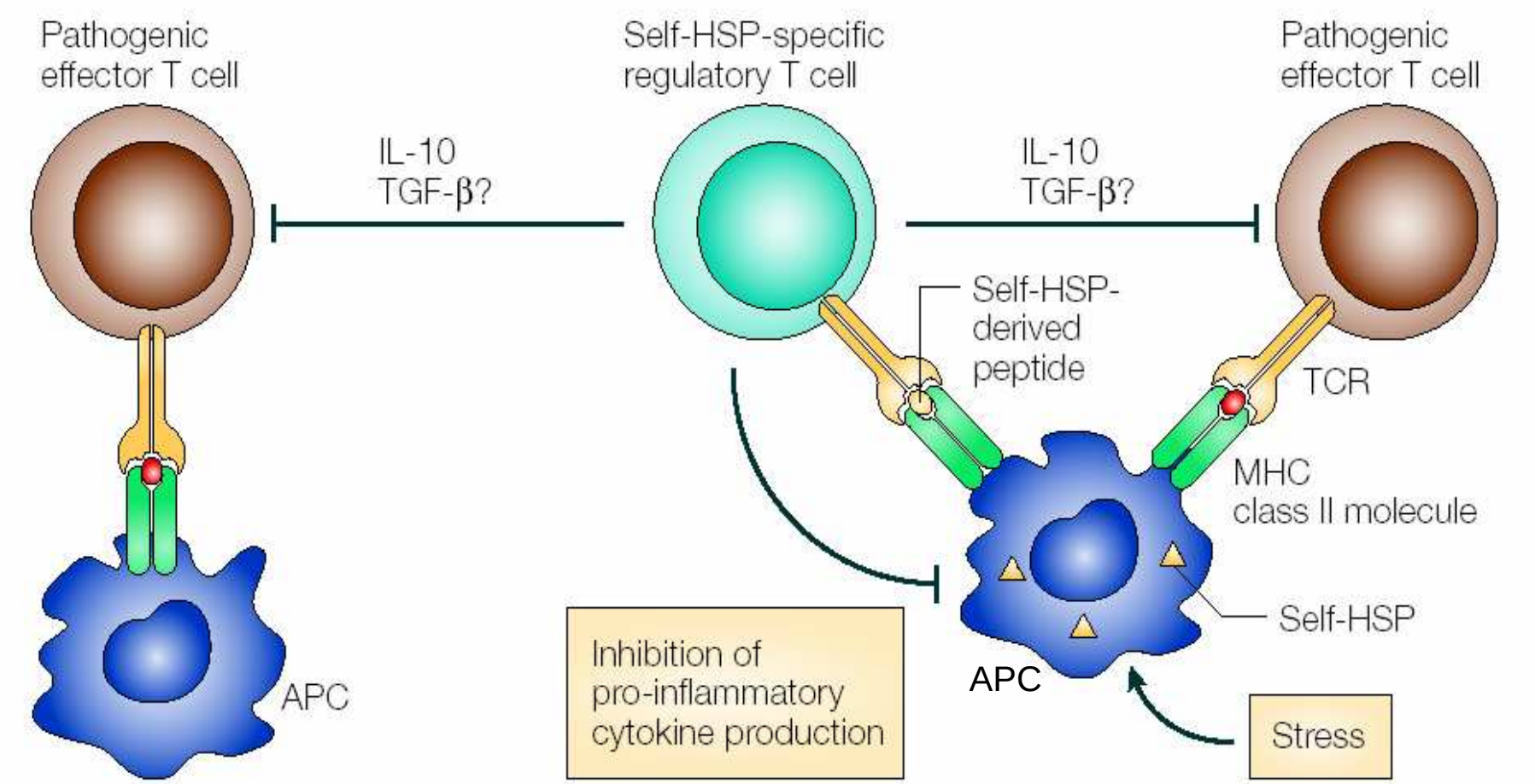
Lancet 366: 50-56; 2005



The pattern of T cell responses induced by these HSP60 peptides in JIA patients and controls supports their potential use as target epitopes for HSP60 immunotherapy in JIA.

Results suggest the induction of T cells with a regulatory phenotype that in oligoarticular JIA patients may contribute to disease remission.

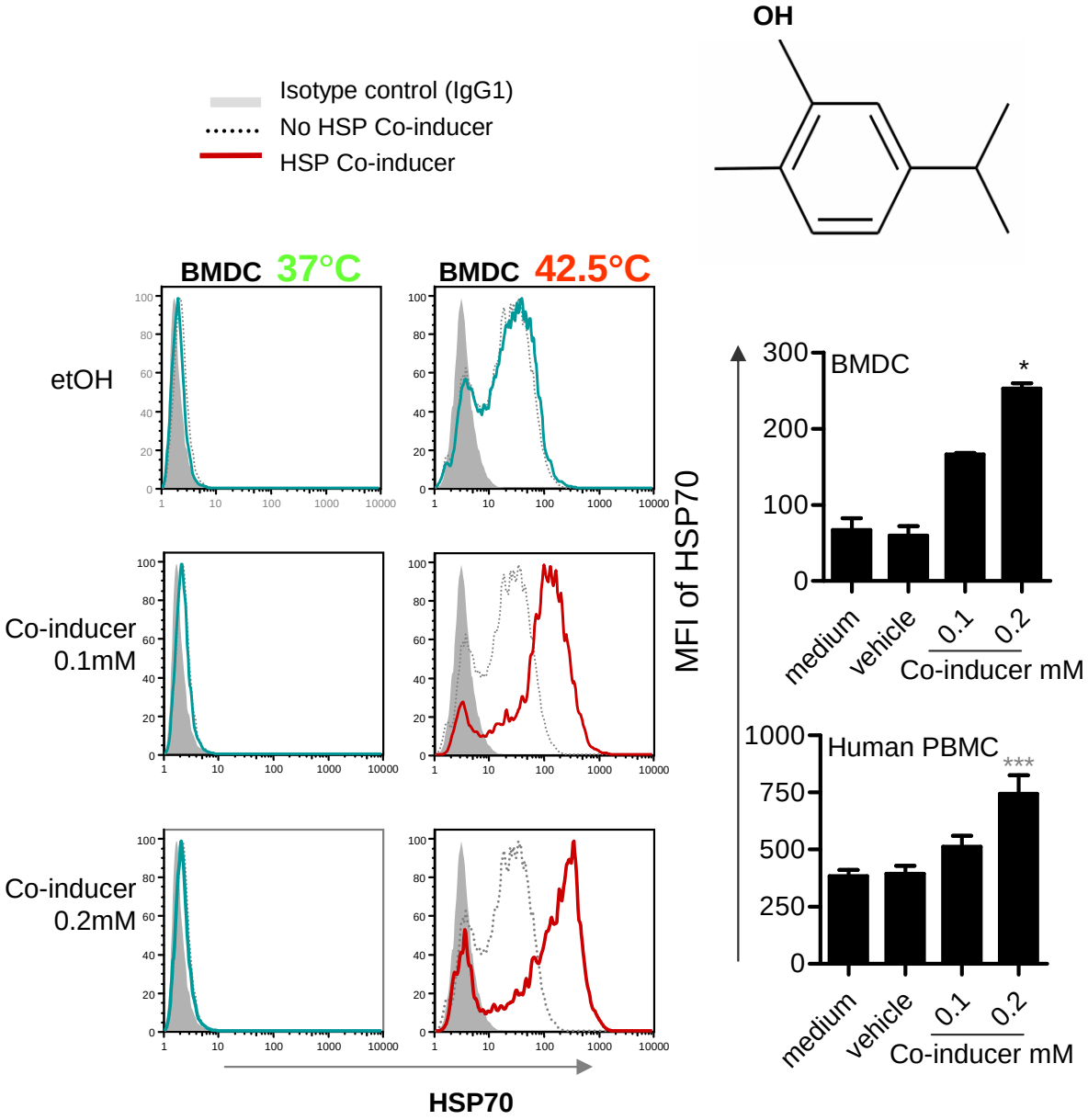
Regulation by self-Hsp specific T-cells



Regulation through self-heat-shock-protein-specific T cell

Van Eden et al., Nat Rev Imm 2005

HSP up-regulated by HSP co-inducer (carvacrol)

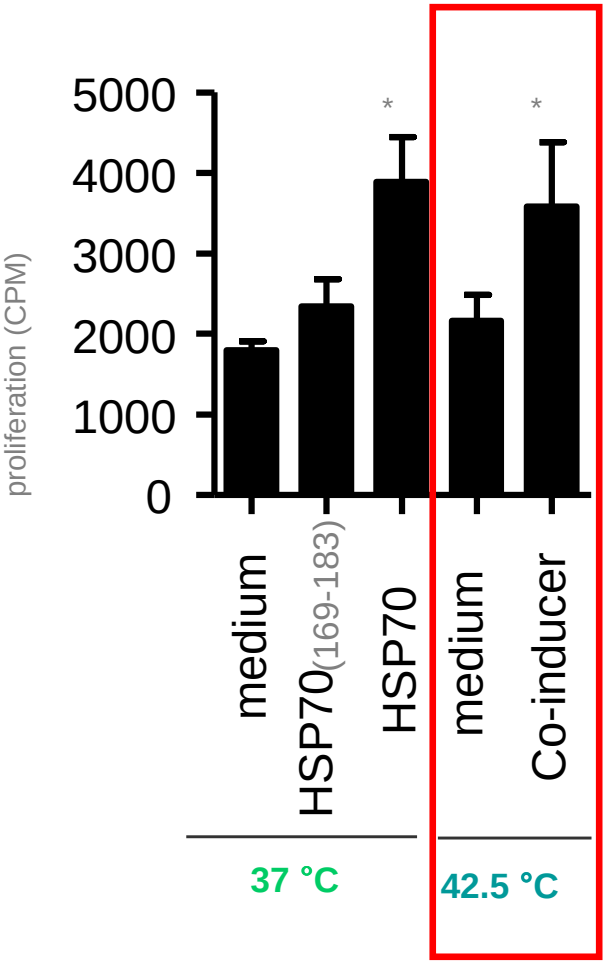


HSP spec. T cell response

Carvacrol

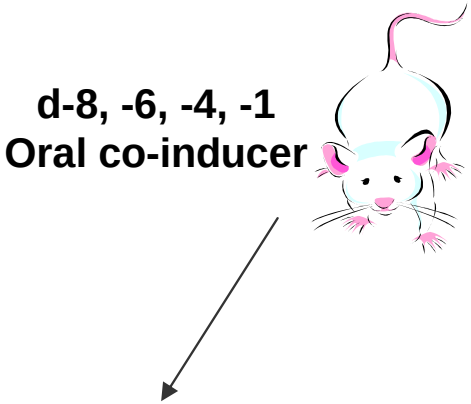
mouse

human

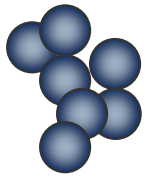


Wieten et al. , A&R in press

Oregano derived carvacrol: a novel HSP co-inducer triggering HSP specific T reg

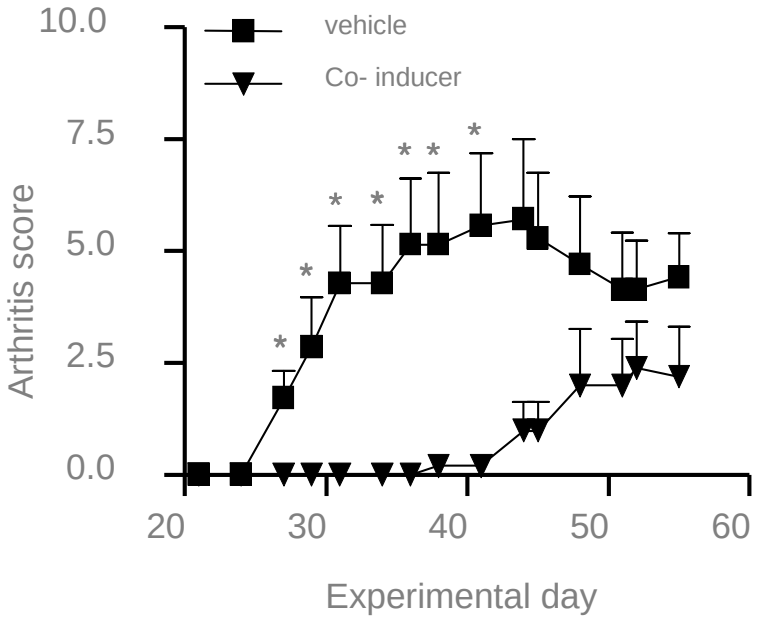


d-8, -6, -4, -1
Oral co-inducer

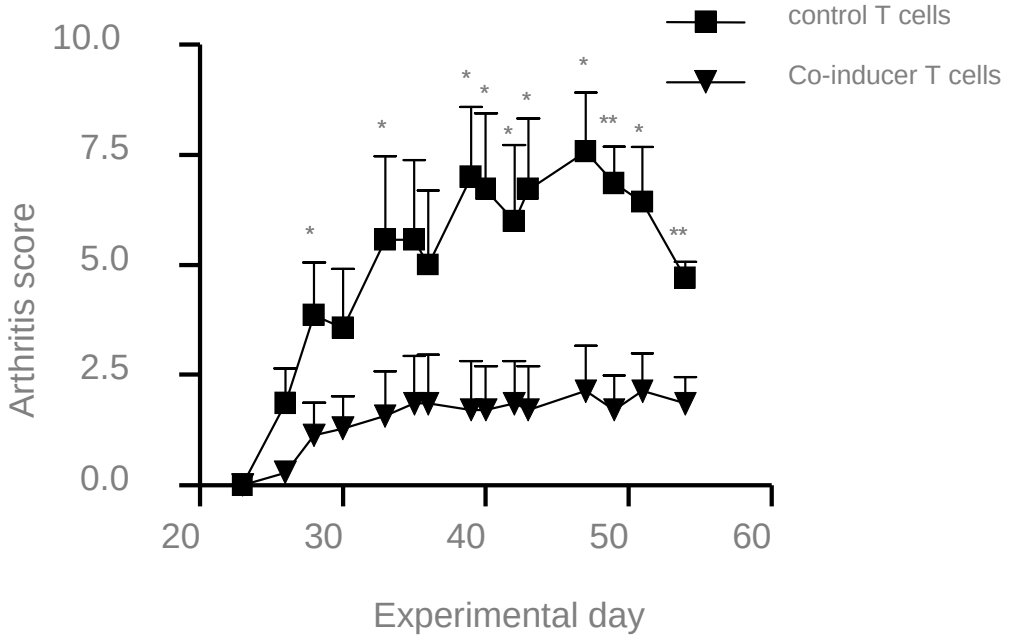


d7: Transfer of T cells

Induction of PGIA



Induction of PGIA



Wieten et al. , A&R in press

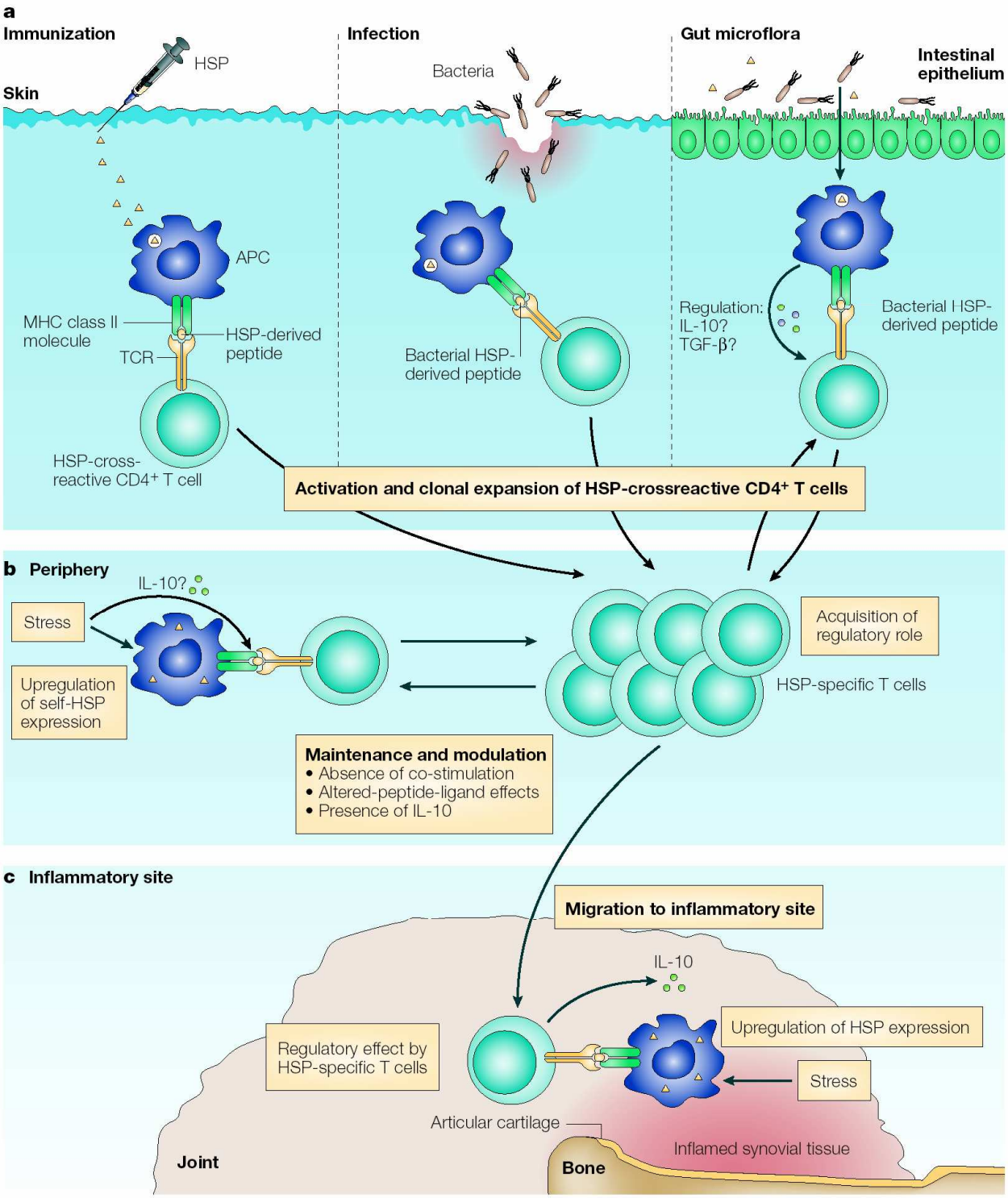


Figure 1 | **Cellular interactions that induce a regulatory mode in heat-shock-protein-specific T cells.**

Van Eden et al.
Nat Rev Imm,
2005

Reduced plaque formation in HSP60 (peptide) treated atherosclerotic mice

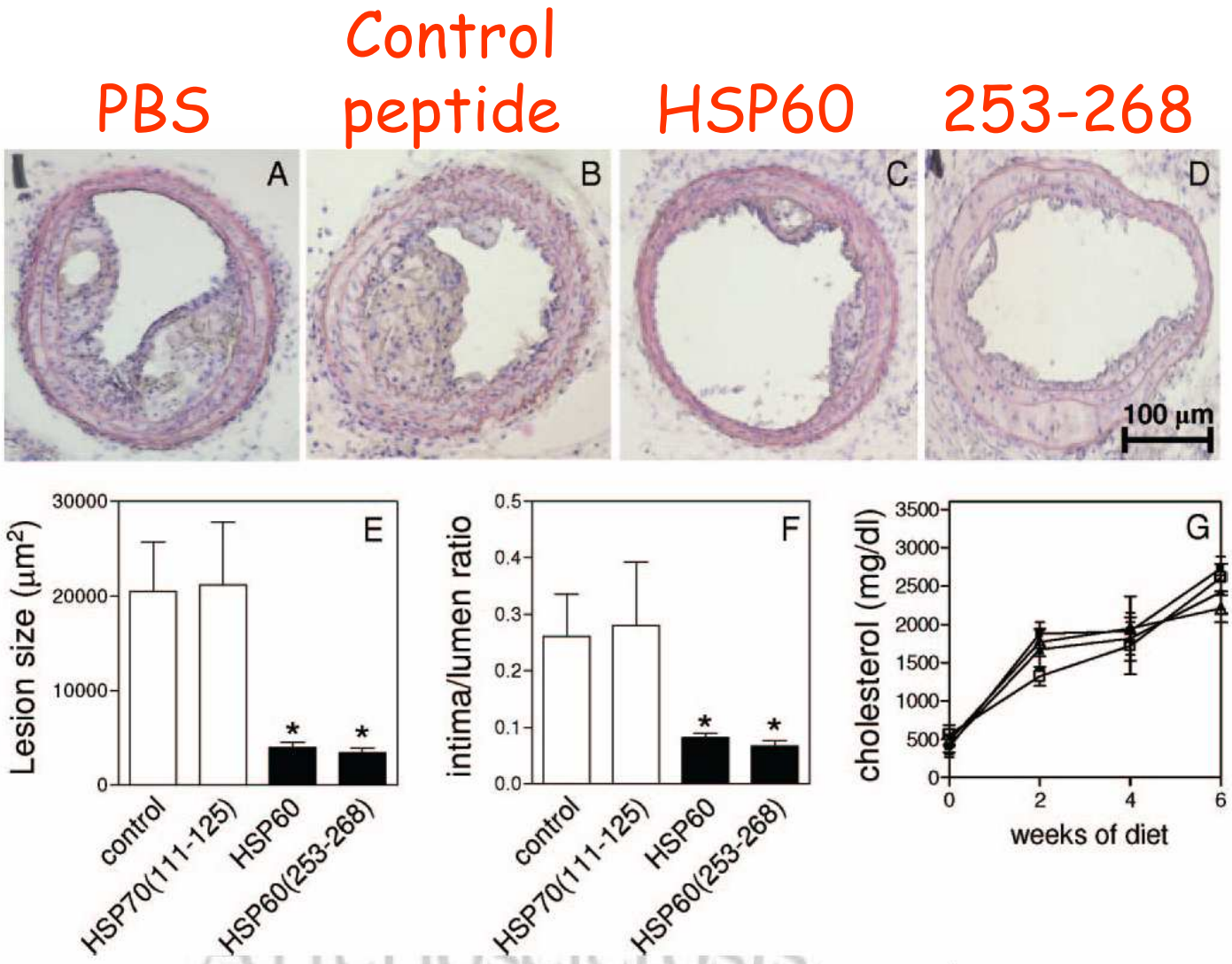


Figure 2. Oral tolerance induction to HSP60 and HSP60 (253 to 268) attenuates plaque formation. LDLr$^{-/-}$ mice were treated intragastrically with PBS (A), HSP70 (111 to 125) (B), HSP60 (C), or HSP60 (253 to 268) (D), and 6 weeks thereafter the carotid arteries were sectioned and lesions were quantified (E and F). During the experiment cholesterol levels were monitored (G). *$P<0.05$.

Van Puijvelde et al., 2007

HSP are immuno-modulatory stress proteins : human

- Rheumatoid arthritis, IBD: trajectum Pharma diabetes, atherosclerosis, allergy

- Paratb vaccine in cattle [Intervet Merck &Co]
- Phytochemicals with immuno-stimulating, antimicrobial activity: carvacrol in chickens [ALTANT]
- HSP in canine atopic dermatitis [Pfizer Animal Health Ltd.]

- Biomarkers of disease…..

OPINION

Real and artificial immune systems: computing the state of the body

Irun R. Cohen

Abstract | Here I present the idea that the immune system uses a computational strategy to carry out its many functions in protecting and maintaining the body. Along the way, I define the concepts of computation, Turing machines and system states. I attempt to show that reframing our view of the immune system in computational terms is worth our while.

The field of artificial immune systems (AIS) was developed by a group of computer and informatic scientists and mathematicians

The question for us as immunologists, however, is not what we can do for AIS scientists, but what AIS scientists can do for

How might immunologists consider immune computation? First, note that the concept of computation takes us beyond particular molecules, cells and interactions. When referring to immune computation the view is synthetic rather than analytical; we look to the end behaviour of the system and not at its component parts. The computational question is not which cellular and molecular interactions comprise the immune system, but, what, if anything, might the immune system be computing. Moreover, reframing the immune system in computational terms shifts our attention from the proposed goals of immunity (defence against pathogens, self versus non-self or danger discrimination and so forth) to the 'state of the immune system'.

What is meant by the state of the

Nature Rev Imm, July 2007

Autophagy promotes MHC class II presentation of peptides from intracellular source proteins

Jörn Dengjel[†‡], Oliver Schoor[†‡], Rainer Fischer[§], Michael Reich[¶], Marianne Kraus[¶], Margret Müller[†], Katharina Kreymborg[†], Florian Altenberend[†], Jens Brandenburg[‖], Hubert Kalbacher[‖], Roland Brock[§], Christoph Driessen[¶], Hans-Georg Rammensee[†], and Stefan Stevanovic[†,††]

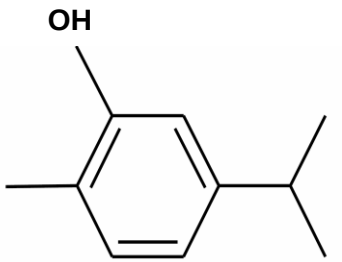
Table 1. Differential presentation of peptides on HLA-DR molecules and corresponding mRNA data

Source protein	Entrez gene ID	Peptide sequence	6 h of starvation		24 h of starvation	
			Peptide ratio	mRNA ratio	Peptide ratio	mRNA ratio
Membrane proteins						
					1.53	NC
					1.30	NC
					0.36	NC
					0.82	NC
					1.23	NC
					0.95	NC
					0.42	NC
					1.07	NC
					0.50	NC
					—	NC
					0.61	NC
					1.12	NC
					0.70	2.46
					—	NC
					—	0.54
					0.97	0.54
					1.33	
					—	
					1.45	
B-lymphocyte antigen CD 20	931	INIYNCEPANPSEK	1.16	NC	1.53	NC
Class I cytokine receptor	9466	VGVPYRITVTAVSASG	1.20	NC	—	NC
Transferrin receptor protein 1	7037	FTYINLDKAVLGTSN	1.18	NC	0.85	NC
Carboxypeptidase D	1362	VPGTYKITASARGYNPV	1.27	1.23	1.37	1.52
	1362	VPGTYKITASARGYN	1.13	1.23	—	1.52
Extracellular proteins						
Serotransferrin (bovine)		FVKDQTVIQNTD	0.66	—	1.37	—
		DVAFVKDQTVIQNTD	1.13	—	—	—
		DVAFVKDQTVIQ	1.24	—	—	—
Serum albumin (bovine)		SPDLPKLKPDPNTLCDEF	1.24	—	1.01	—
Apolipoprot B-100 (bovine)		SASYKADTVAKVQGT	1.08	—	1.02	—
		SASYKADTVAKVQGTE	0.98	—	0.44	—
Intracellular proteins						
Heat shock 70-kDa protein 1	3303	NVLRIINEPTAAAIAYG	1.50	3.48	1.48	NC
	3303	VLRIINEPTAAAIAY	1.03	3.48	1.24	NC
	3303	RIINEPTAAAIA	1.49	3.48	2.25	NC
	3303	VLRIINEPTAAAIAYG	1.12	3.48	1.30	NC
Heat shock cognate 71-kDa protein	3312	GILNVSAVDKSTGKE	1.67	NC	1.51	NC
	3312	ERAMTKDNNLLGKFE	1.19	NC	1.50	NC
	3312	GERAMTKDNNLLGKFE	1.48	NC	1.30	NC
Elongation factor 1-α 1	1917	IEKFEKEAAEMGKGSF	1.49	NC	2.87	NC
TNF, α-induced protein 3	7128	EIIHKALIDRNIQ	1.32	2.14	—	2.64
RAD23 homolog B	5887	LLQQISQHQEHF	1.88	NC	1.79	NC
Actin, cytoplasmic 2	71	TDYLMKILTERGYS	1.30	NC	1.09	NC
NEDD4La	23327	DGRTFYIDHNSKITQ	1.26	NC	1.51	NC
T complex protein 1, β subunit	10576	SLMVTNDGATILKN	1.15	NC	—	NC
Ubiquitin	7311	SDYNIQKESTLHLV	1.05	—	1.42	—
α enolase	2023	VPLYRHIADLAGNSEV	1.50	NC	1.14	NC
syntaxin 6	10228	NPRKFNLDATELSIRK	1.60	NC	—	NC
tubulin β-5 chain	10382	EPYNATLSVHQL	1.50	NC	1.23	NC
Lysosomal proteins						
Cathepsin C	1075	YDHNFVKAINAIQKSWT	1.31	NC	1.28	NC
	1075	YDHNFVKAINAIQKSW	1.28	NC	1.27	NC
	1075	YDHNFVKAINAIQKS	1.56	NC	1.40	NC
Cathepsin D	1509	LSRDPDAQPGGE	0.83	NC	2.30	NC
Cathepsin S	1520	TTAFQYIIDNKGIDSD	1.61	2.30	—	4.92
	1520	TTAFQYIIDNKGID	1.90	2.30	1.56	4.92
Lysosomal α-mannosidase	4125	VDYFLNVATAQGRYY	1.64	NC	—	NC

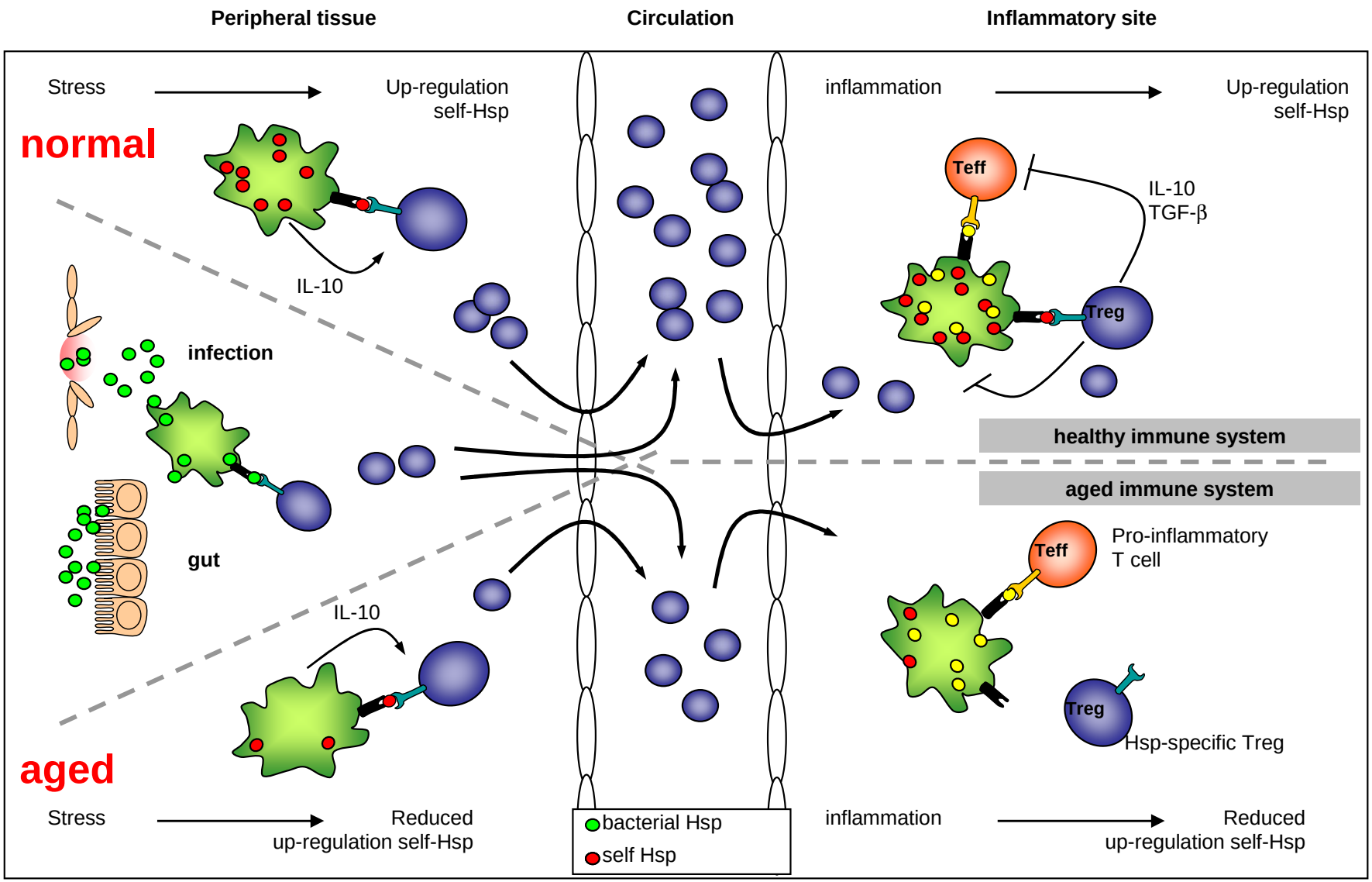
The given peptide and mRNA ratios refer to the comparison of cells grown under starvation with control cells. For peptides, ratios were calculated from the signal intensities in LC-MS experiments. mRNA ratios were calculated from the signal log ratios given by the microarray analysis. No change (NC) is displayed if no significant change in the expression level was observed according to the change algorithm.

Intracellular proteins		
Heat shock 70-kDa protein 1	3303	VLRIINEPTAAAIAY
	3303	RIINEPTAAAIA
	3303	VLRIINEPTAAAIAYG
Heat shock cognate 71-kDa protein	3312	GILNVSAVDKSTGKE
	3312	ERAMTKDNNLLGKFE
	3312	GERAMTKDNNLLGKFE

Hsc70, Hsp70 and GAPDH are the three most frequent cytosolic/nuclear MHC class II natural ligand sources: Paludan, et al. Science 307, 593 (2005)



Stress proteins as functional biomarkers of immune regulation



Thesis Wieten 2009

SenterNovem IOP

Mission 2007-2010

Re-inforce economic spin-off for Noord-Holland, Utrecht and Flevoland related to knowledge on infectious diseases of animal and man

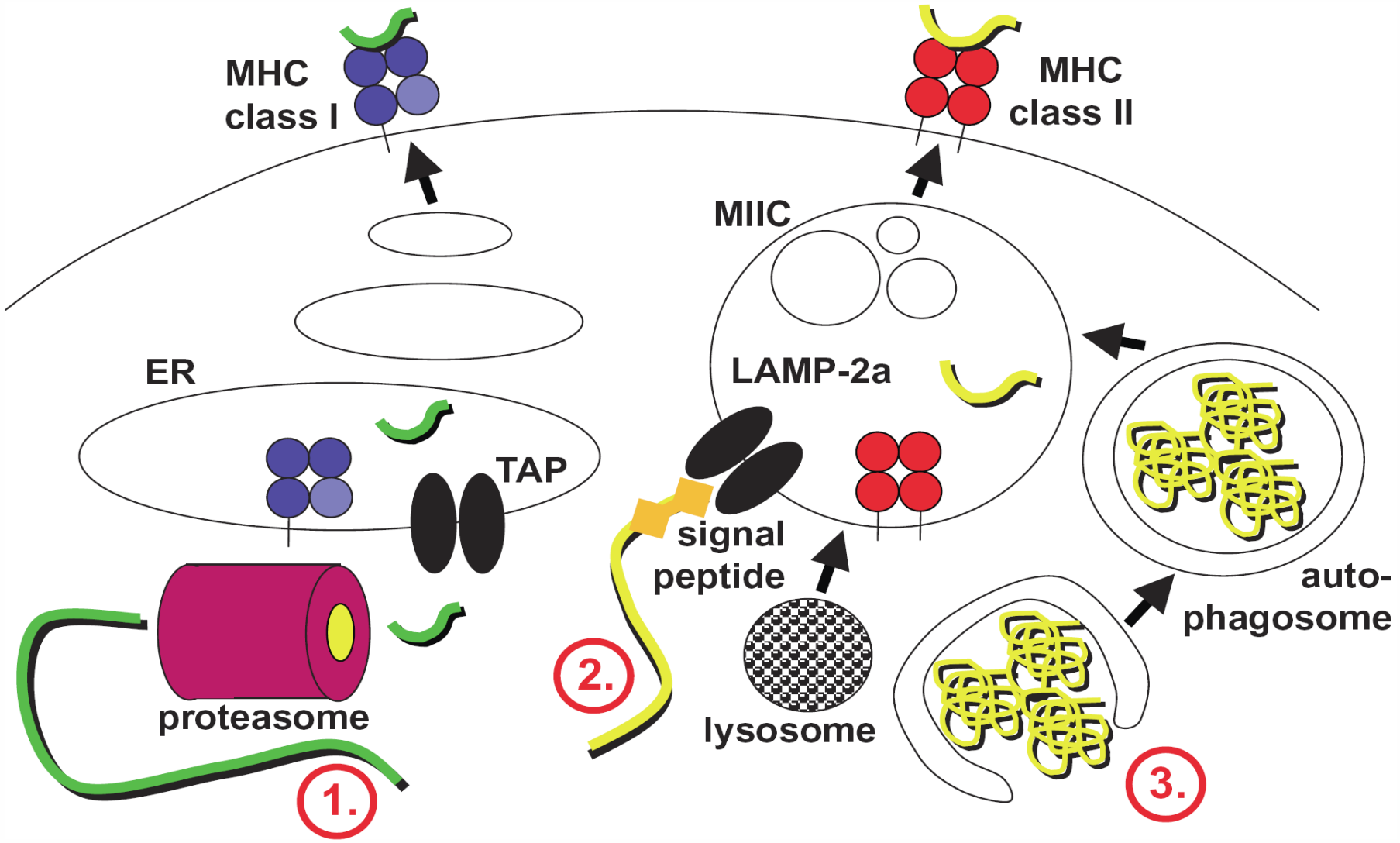
“Network of Excellence”

- Big pharma /Biotech R&D
  Intervet Merck&Co, Pfizer Animal Health Ltd., Eli Lilly-Elanco, GSK

- Specialized SME’s
  diagnostics, drug delivery, immunomodulation and immunotherapeutics

- Knowledge institutes (unique facilities) >1000fte
  - Utrecht Veterinary Research top 5 of world
  - Utrecht University Life Sciences top 10 of Europe
  - Cluster Randstad NL top 3 of all life sciences clusters in EU.
  - Strong integration between clusters Lelystad CVI, Wageningen UR, Utrecht/ RIVM/NVI, Amsterdam LS.

MHC Presentation of stress protein fragments by cells under stress



From Münz, Cell. Microbiol., (2006) 8:891-898

Epitope-specific immunotherapy induces immune deviation of proinflammatory T cells in rheumatoid arthritis

Berent J. Prakken[†‡], Rodrigo Samodal[†], Tho D. Le[†], Francesca Giannoni[†], Gisella Puga Yung[†], John Scavulli[†], Diane Amox[†], Sarah Roord[†‡], Isme de Kleer[†‡], Dustan Bonnin[†], Paola Lanza[§], Charles Berry[†], Margherita Massa[†¶], Rosario Billetta[§], and Salvatore Albani[†§‖]

4228–4233 | PNAS | March 23, 2004 | vol. 101 | no. 12

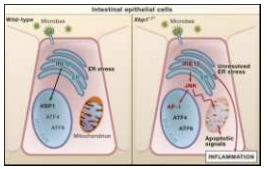
Cell

Leading Edge
Previews

Unresolved ER Stress Inflames the Intestine

Averil Ma[1,*]
[1]Department of Medicine, University of California at San Francisco, San Francisco, CA 94143-0451, USA
*Correspondence: averil.ma@ucsf.edu
DOI 10.1016/j.cell.2008.08.023

Cell *134*, September 5, 2008 ©2008 Elsevier Inc.

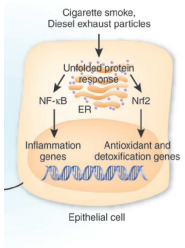


BENCH TO BEDSIDE

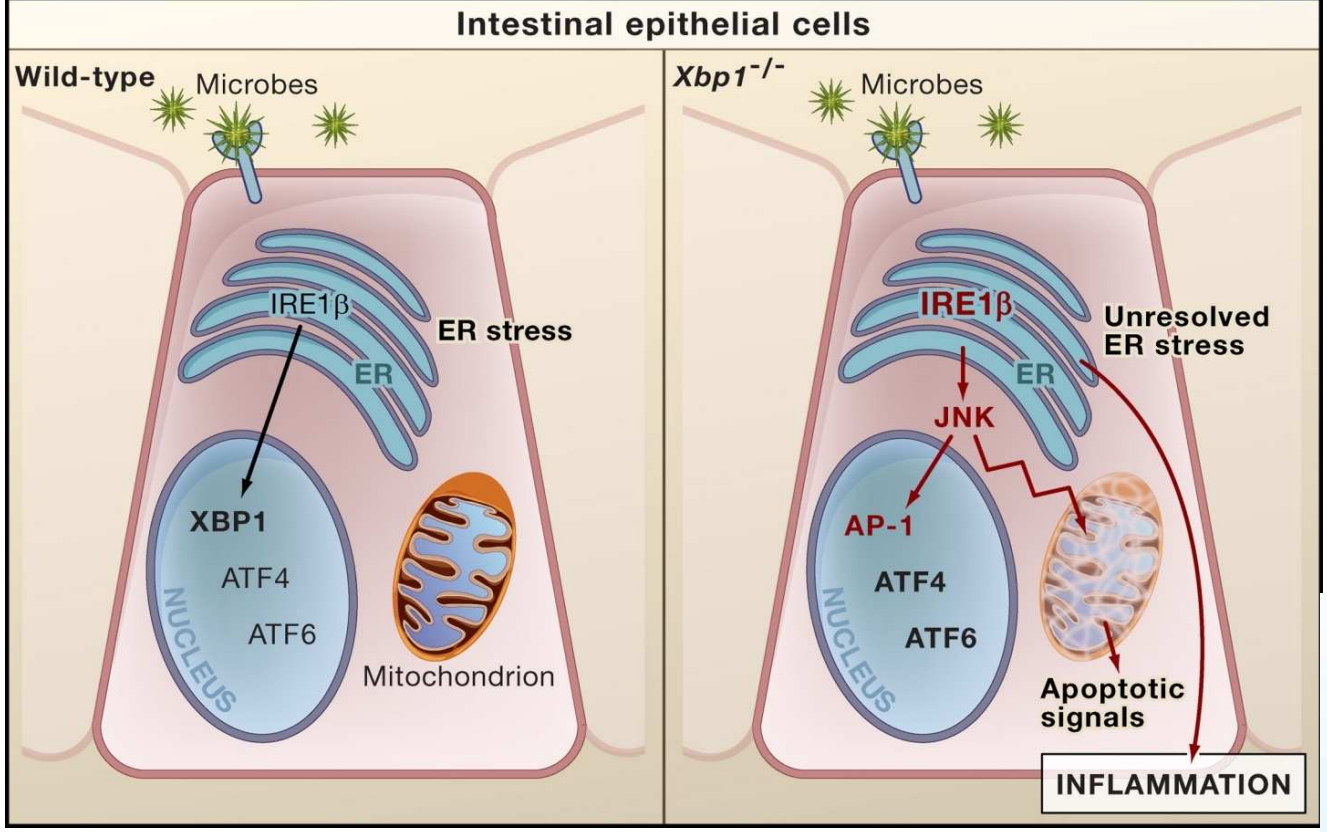
Smoke particulates stress lung cells

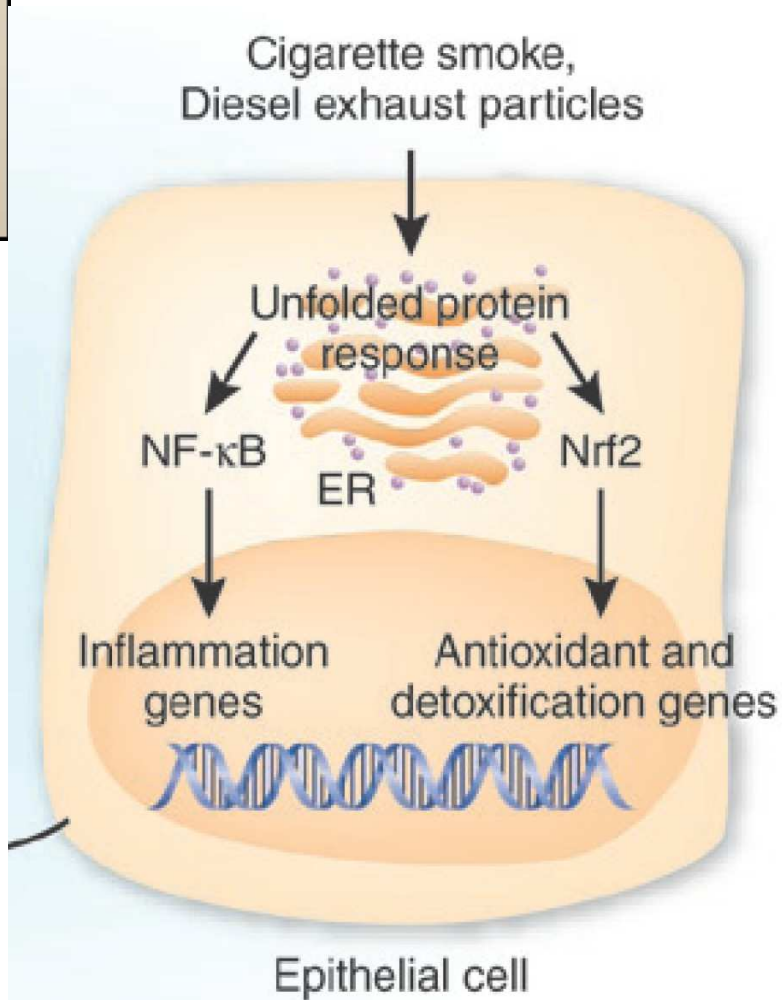
Tracy L Adair-Kirk, Jeffrey J Atkinson & Robert M Senior

VOLUME 14 | NUMBER 10 | OCTOBER 2008 NATURE MEDICINE

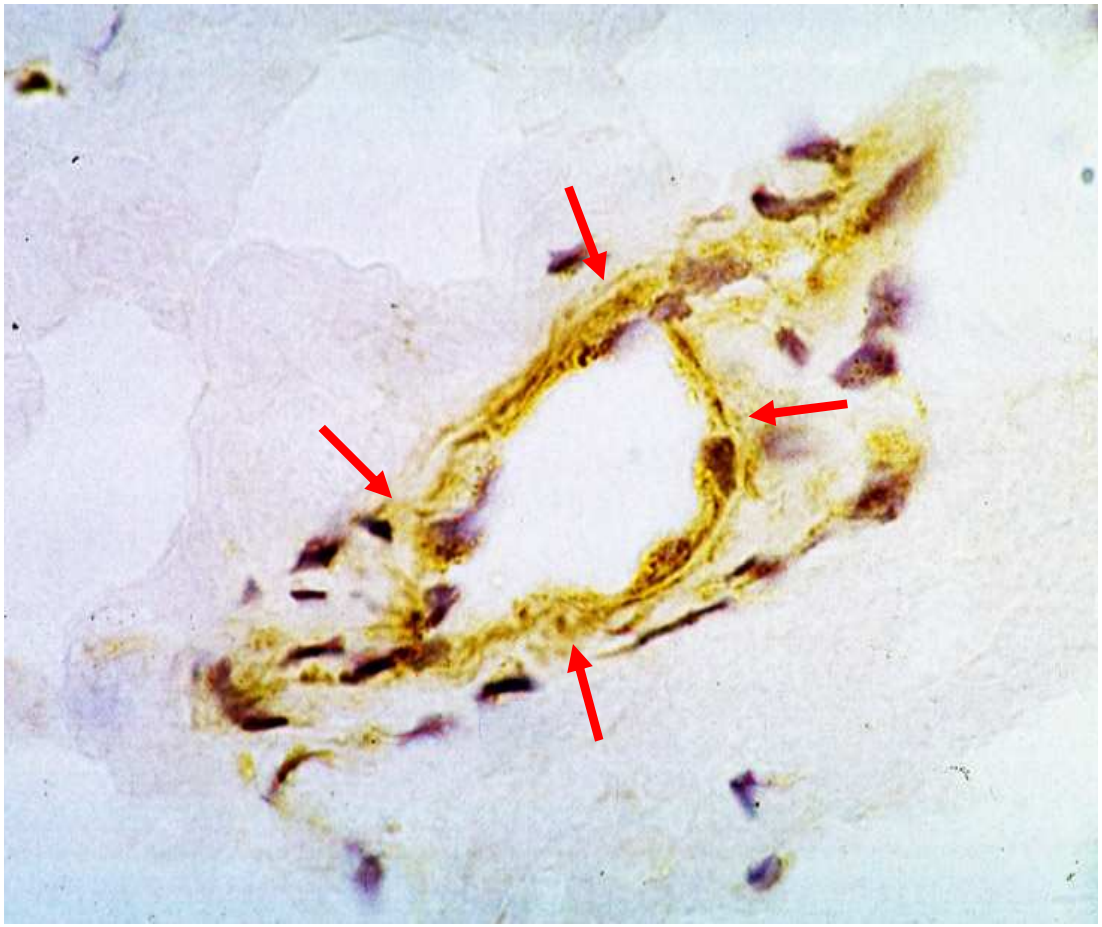


Andromeda Biotech Announces Successful Phase III Interim Results Of Its Lead Product, DiaPep277 For Type 1 Diabetes
02 Jan 2009


Intestinal epithelial cells
Wild-type
Microbes
IRE1β
ER stress
ER
XBP1
ATF4
ATF6
NUCLEUS
Mitochondrion
Xbp1-/-
Microbes
IRE1β
Unresolved
ER stress
ER
JNK
AP-1
ATF4
ATF6
NUCLEUS
Apoptotic
signals
INFLAMMATION


Cigarette smoke,
Diesel exhaust particles
Unfolded protein
response
NF-κB
ER
Nrf2
Inflammation
genes
Antioxidant and
detoxification genes
Epithelial cell

HSP60 in Juvenile Idiopathic Arthritis

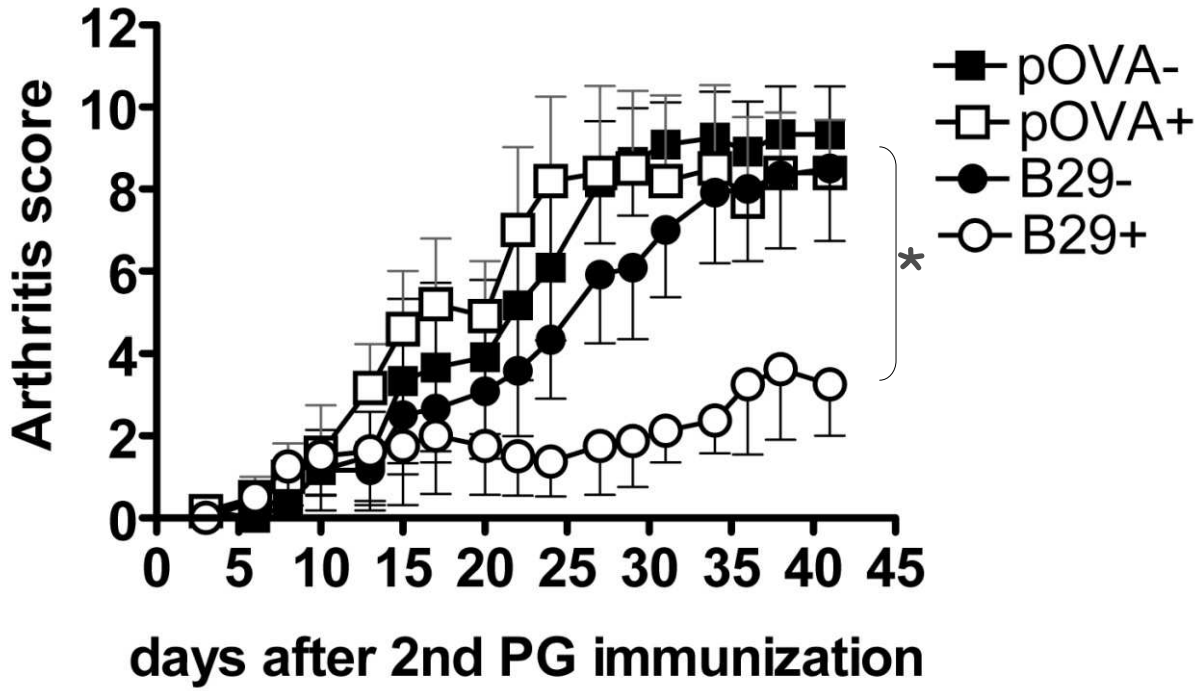


- **Raised expression in inflamed synovium**
- **T cell responses to HSP60 in remitting disease**
- **Disease remission preceded by HSP60 responses**
- **Especially T reg respond**

(Lancet 1991, JCI 1995, Nature Rev Immunol 2005, Arthritis and Rheumatism 2006, Drug Discovery Today 2009)

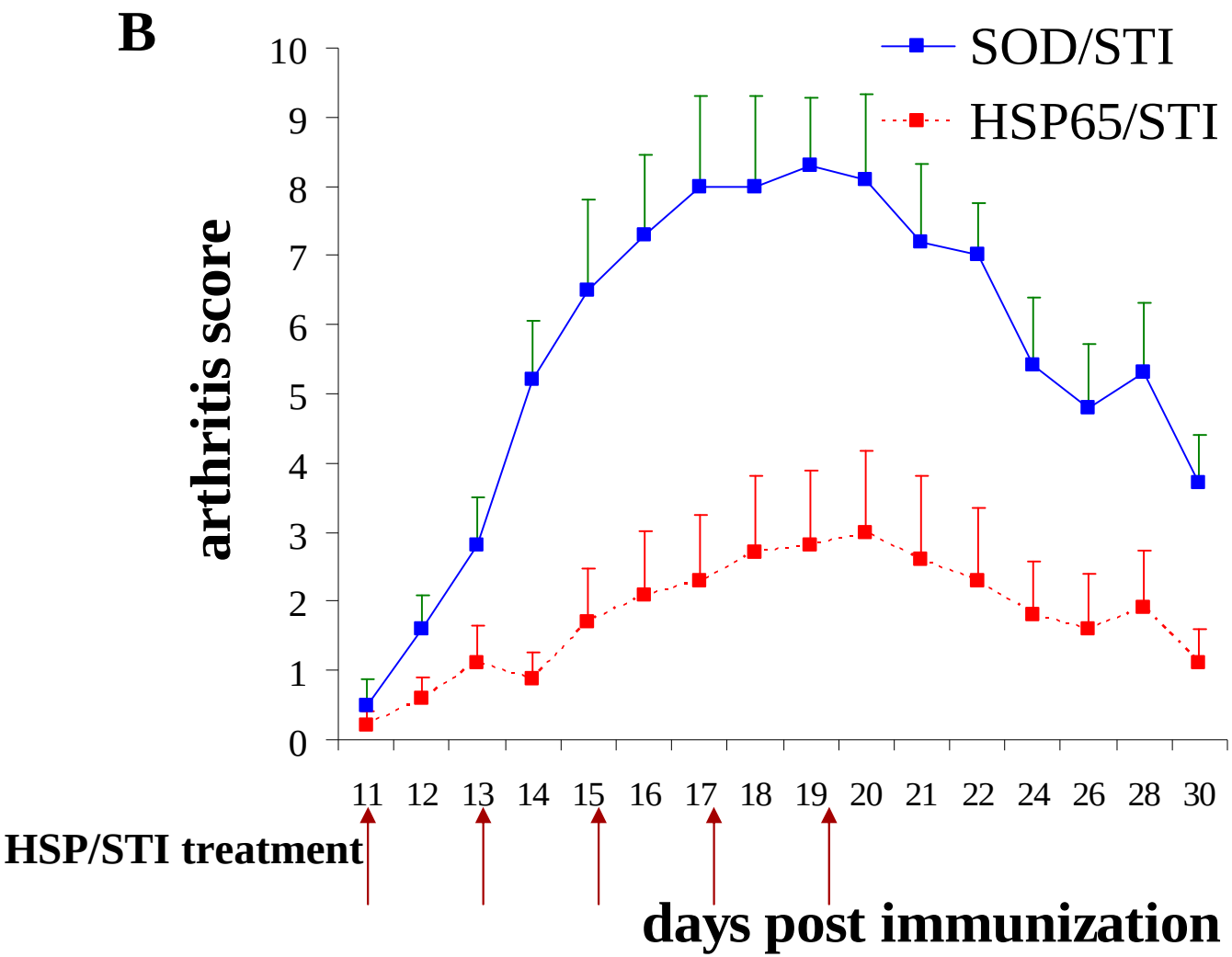
HSP-specific regulatory T cells

Mean arthritis score recipient mice



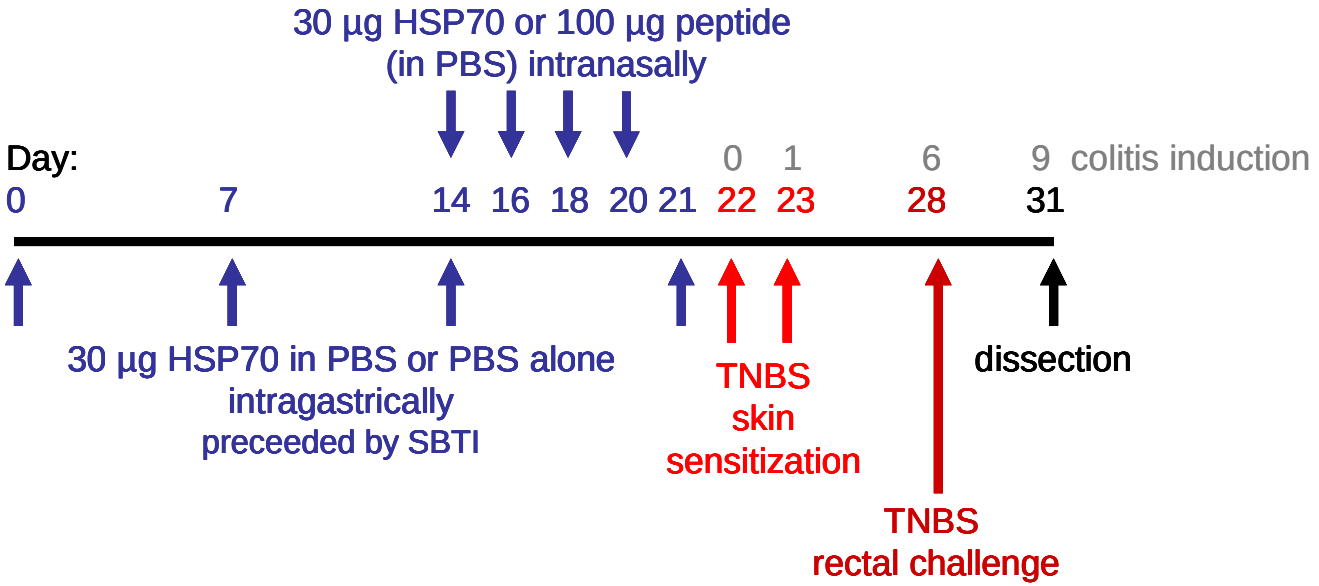
Van Herwijnen et al., in prep.

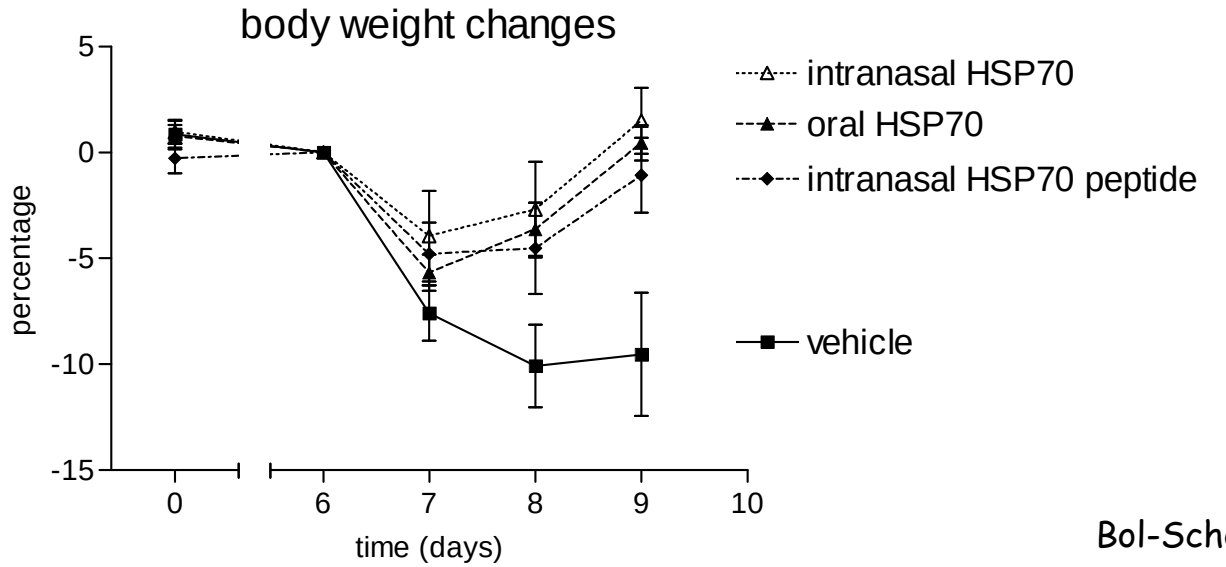
Effect of oral Mt-Hsp60 (30μ) on Adjuvant Arthritis



Cobelens et al., A&R, 2001

Suppressive effect of intranasally given Hsp70 peptide in TNBS-colitis





Bol-Schoenmakers et al., in prep.

Editorial

Vaccination Against Atherosclerosis
Science or Fiction?

Göran K. Hansson, MD, PhD

Atherosclerosis bears many similarities to inflammatory/autoimmune diseases like rheumatoid arthritis and multiple sclerosis (MS).[1,2] Compelling data from experimental models show that such diseases may be treated by vaccination. Will it be possible to attack atherosclerotic cardiovascular disease with the same approach? Several studies have shown positive effects of immunization with antigenic LDL preparations.[3–6] and a report in this issue of *Circulation* demonstrates a protective effect of oral and nasal immunization with another antigen, heat shock protein 65 (HSP65).[7]

See p 1708

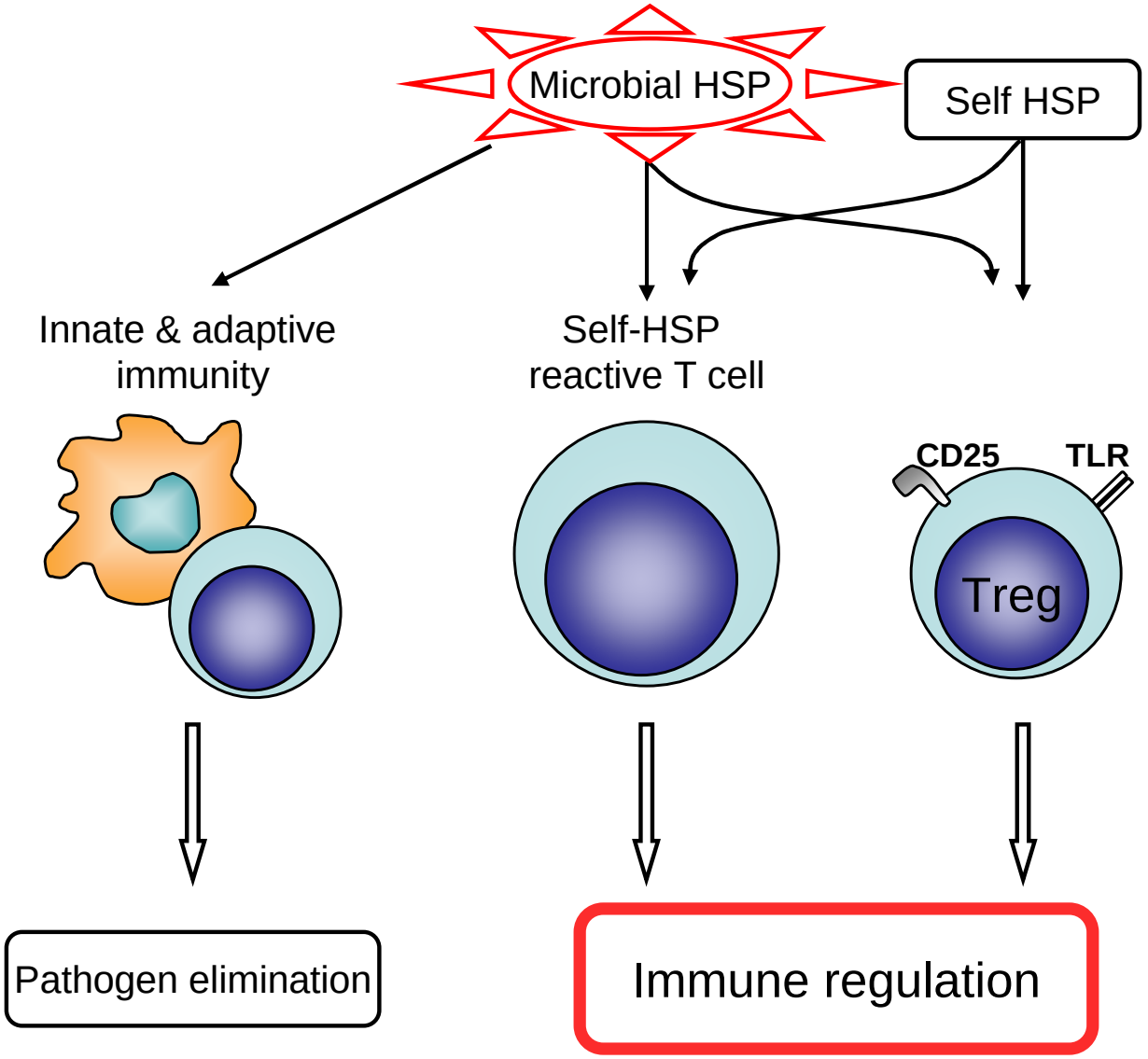
interleukin-4, interleukin-10 (IL-10), and transforming growth factor-β.

Interestingly, Th2 activation can be induced by oral or nasal administration of antigens.[10] In experimental autoimmune conditions, such as experimental autoimmune encephalomyelitis and collagen-induced arthritis, the administration of myelin and cartilage proteins, respectively, can be used to successfully prevent development of disease.[11] A similar mucosal vaccination is presently being tested in the human counterparts, MS and rheumatoid arthritis.

The key to inhibiting inflammation by mucosal vaccination is obviously to use the right antigen. In atherosclerosis, 2 major autoantigens are implicated: oxidized LDL (oxLDL)

Circulation 2002.

Microbial HSP are immuno-dominant and promote immune regulation



Oral HSP60 induces Foxp3+ T reg

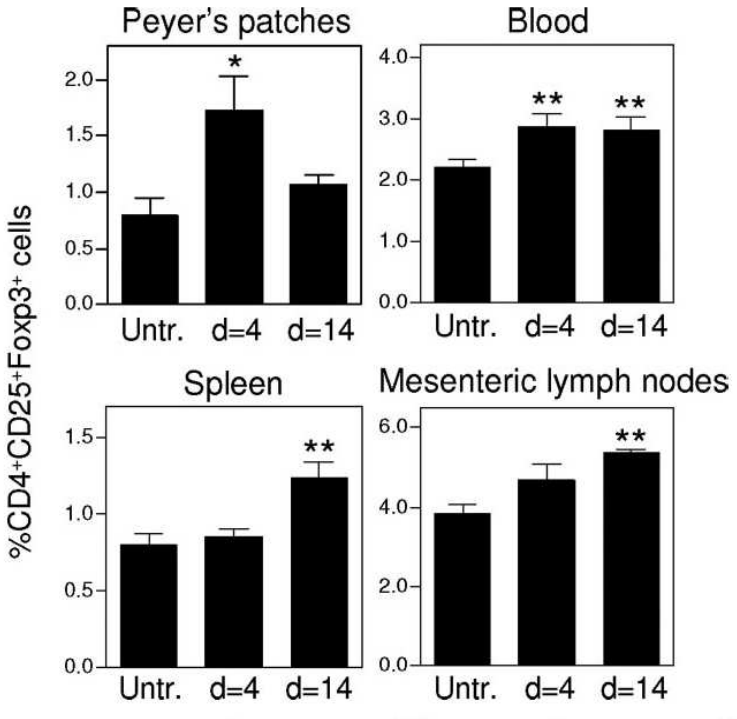


Figure 3. Oral tolerance induction to HSP60 leads to an increased amount of $CD4^+CD25^+$ $Foxp3^+$ cells. $LDLr^{-/-}$ mice were treated intragastrically with HSP60 and killed 4 and 14 days after the last treatment. As a control, untreated animals were used. The graphs represent the amount of $CD4^+CD25^+Foxp3^+$ cells in different organs (mean±SEM). $^*P<0.05$, $^{**}P<0.01$.

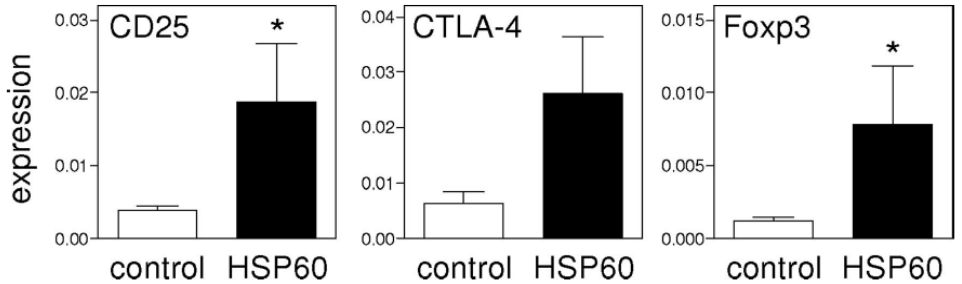
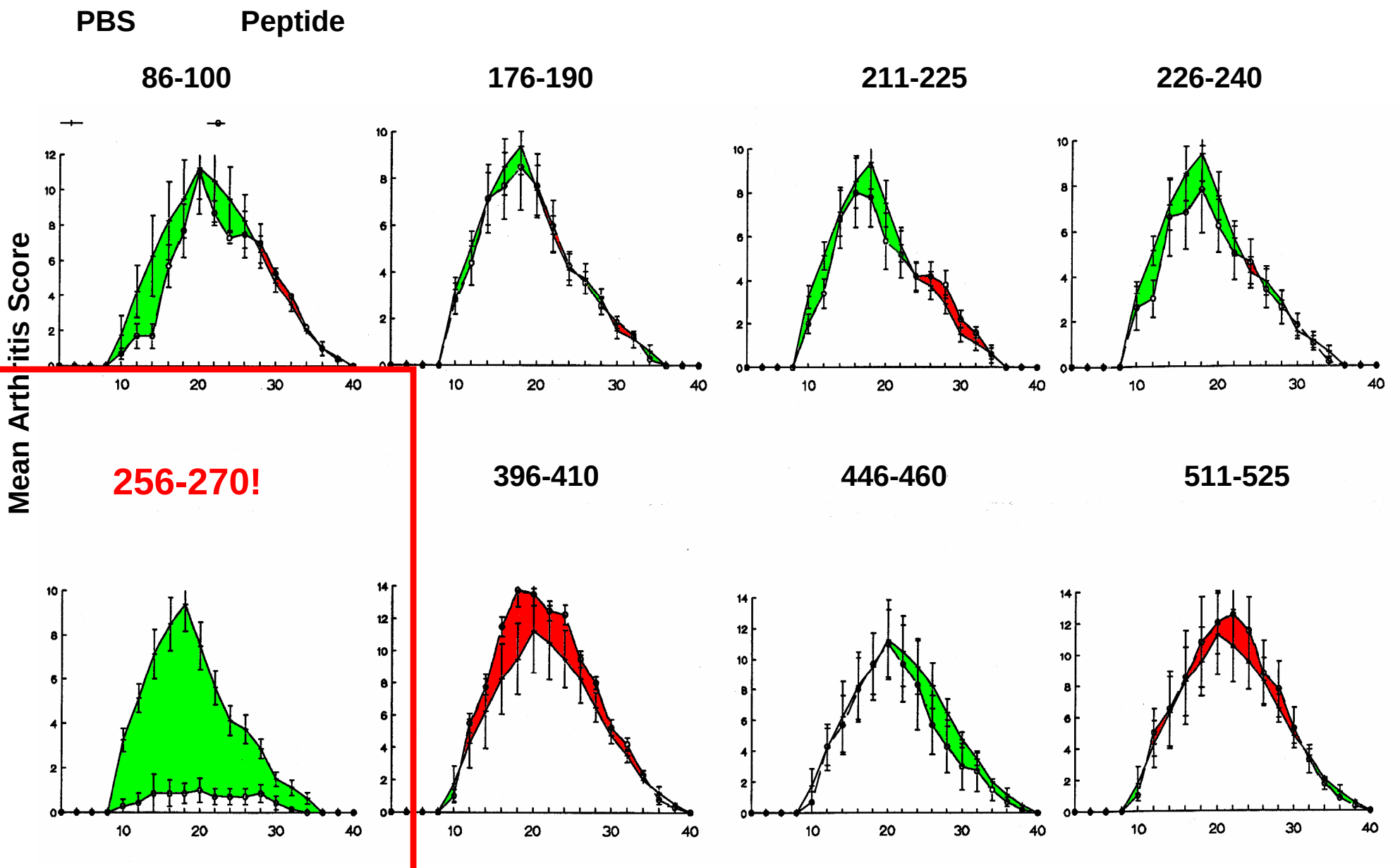


Figure 4. Increased expression of Treg markers is observed within lesions of HSP60-treated $LDLr^{-/-}$ mice. To investigate the presence of Tregs within atherosclerotic lesions, mRNA was isolated from carotid arteries of PBS (n=9) and HSP60-treated (n=5) mice and the expression of CD25, CTLA-4, and Foxp3 was quantitatively determined. $^*P<0.05$.

Van Puijvelde et al., 2007

Modulation of arthritis by pre-immunization with hsp60 peptides



Anderton et al. JEM 1995