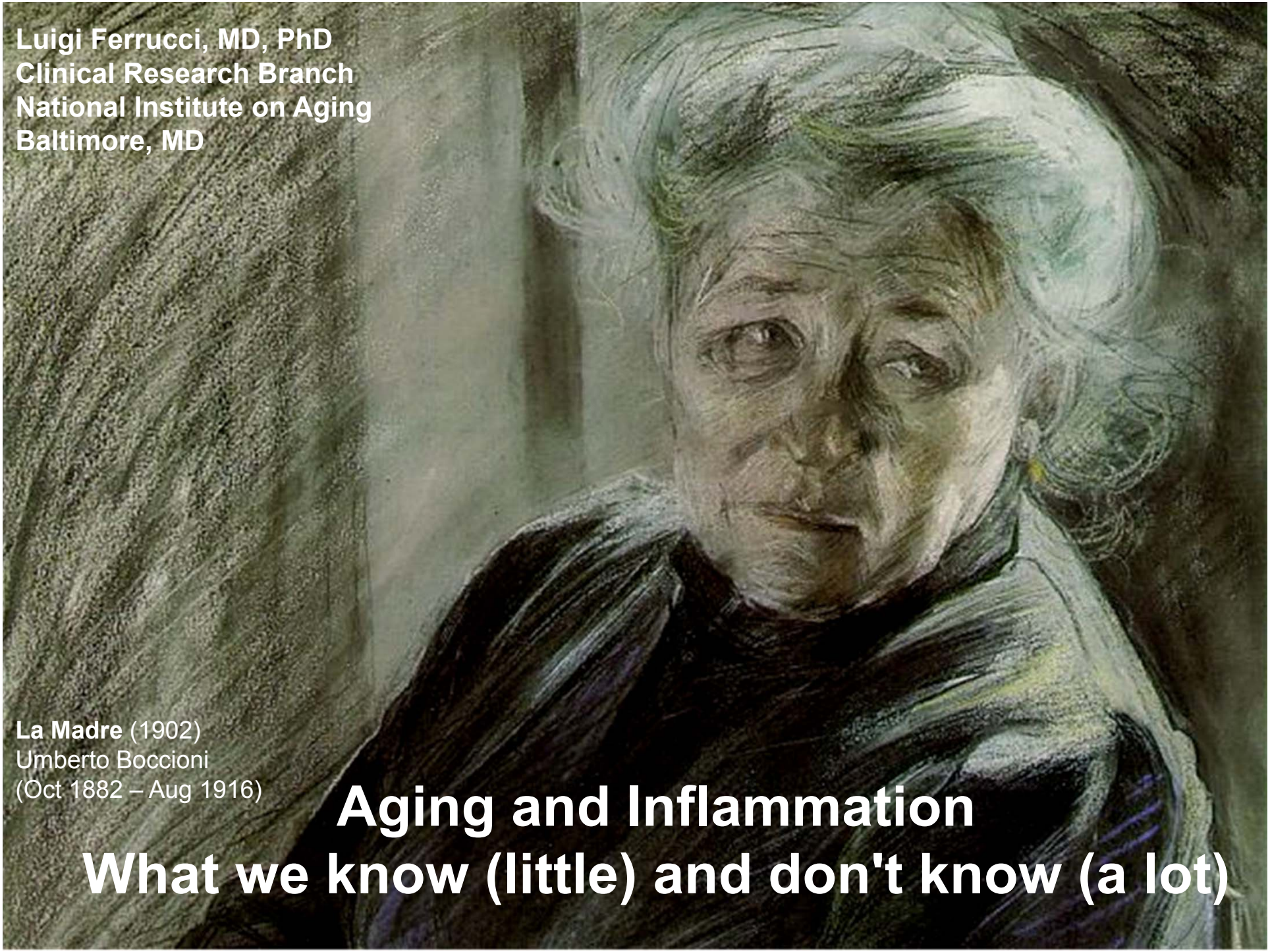
Luigi Ferrucci, MD, PhD
Clinical Research Branch
National Institute on Aging
Baltimore, MD



La Madre (1902)
Umberto Boccioni
(Oct 1882 – Aug 1916)

Aging and Inflammation
What we know (little) and don't know (a lot)

Meta-analysis of age-related gene expression profiles identifies common signatures of aging

João Pedro de Magalhães[1,*,†], João Curado[2] and George M. Church[1]

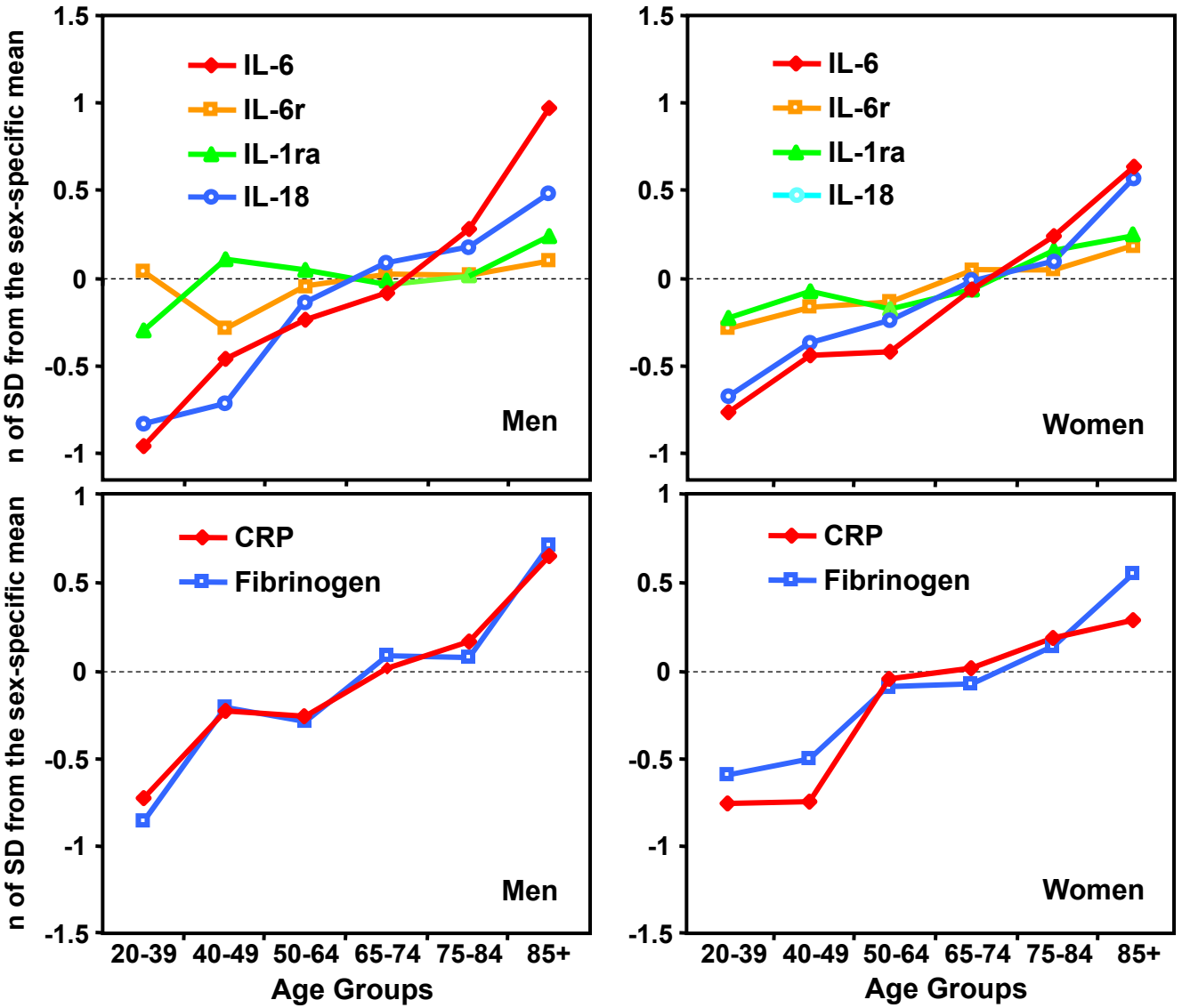
Table 1. Top functional annotation clusters of significant differentially expressed genes

Cluster	Enrich. score	No. of annot.	No. of genes
Overexpressed genes ($n = 236$ with $Q < 0.5$)			
Immune response, complement activation	6.88	41	86
Lysosome	6.48	7	16
Plasma, extracellular region	5.41	5	37
Signal, glycoprotein	4.55	6	80
Negative regulation of apoptosis	2.75	16	53
Underexpressed genes ($n = 141$ with $Q < 0.5$)			
Mitochondrion	5.49	52	70
Oxidative phosphorylation	3.57	79	82
Cytoplasm	3.19	5	108
Hydroxylysine, hydroxylation, collagen	2.83	43	47

Clusters from DAVID with an enrichment score above 2.5 are displayed. Cluster titles were selected based on the broadest of the top annotations in the cluster.

Bioinformatics *Vol. 25 no. 7 2009, pages 875–881*

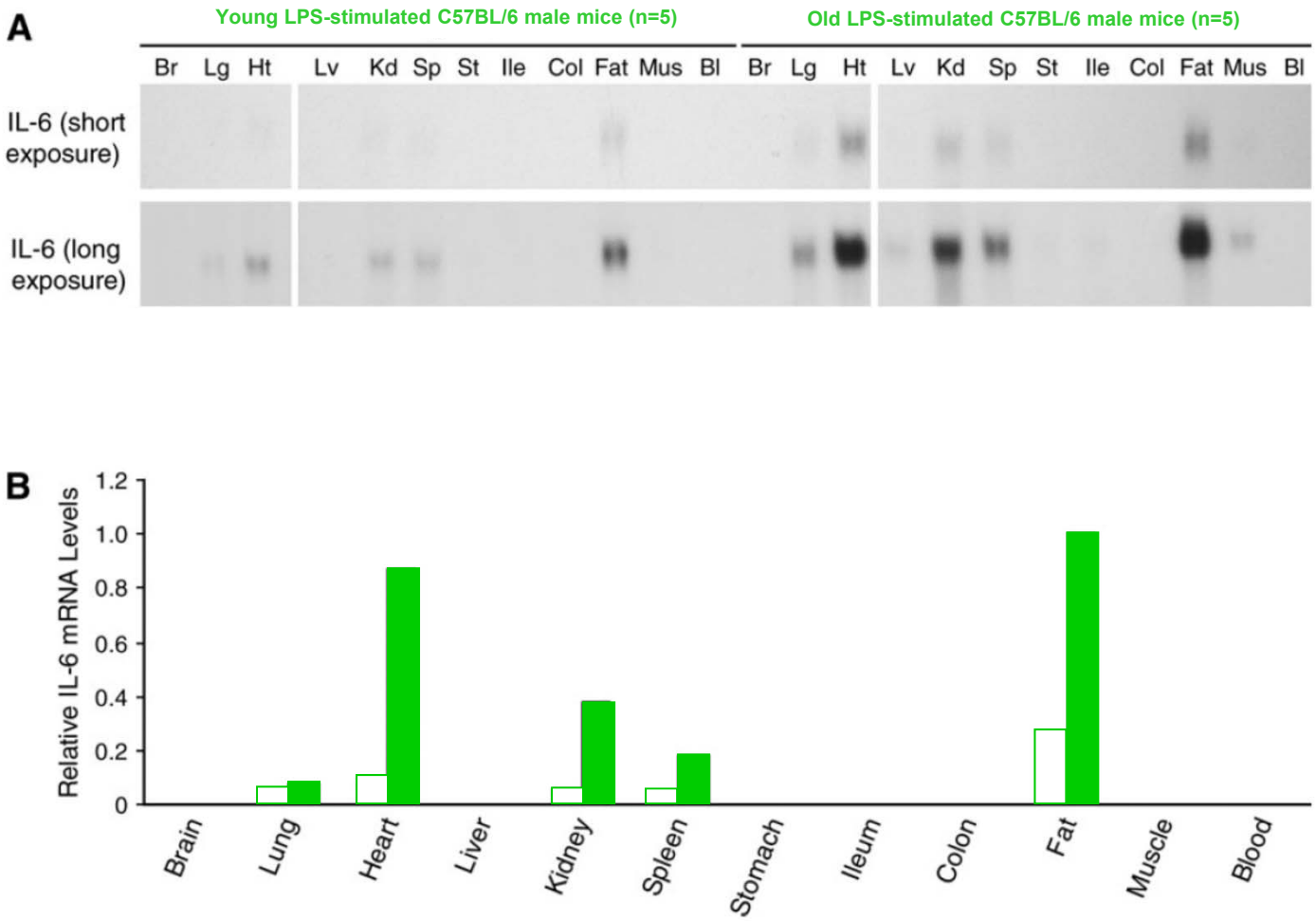
The Mild Pro-Inflammatory State of Aging



Ferrucci L et al. Blood. 2005;105:2294-9.

Age-Associated Increase in Cytokine Production During Systemic Inflammation: Adipose Tissue as a Major Source of IL-6

Marlene E. Starr,[1] B. Mark Evers,[1,2] and Hiroshi Saito[1,2]



Journal of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
2009. Vol. 64A, No. 7, 723–730

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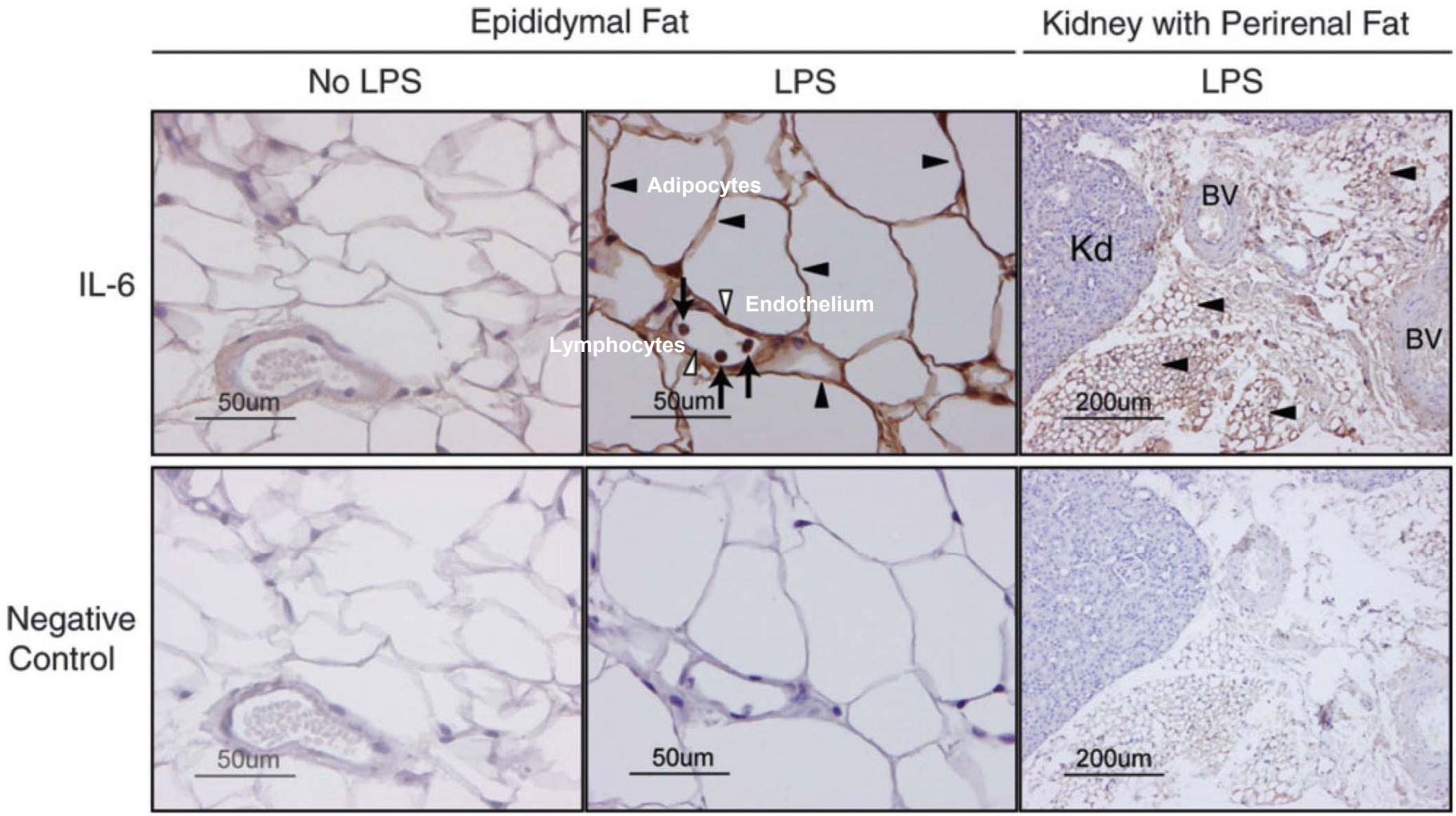
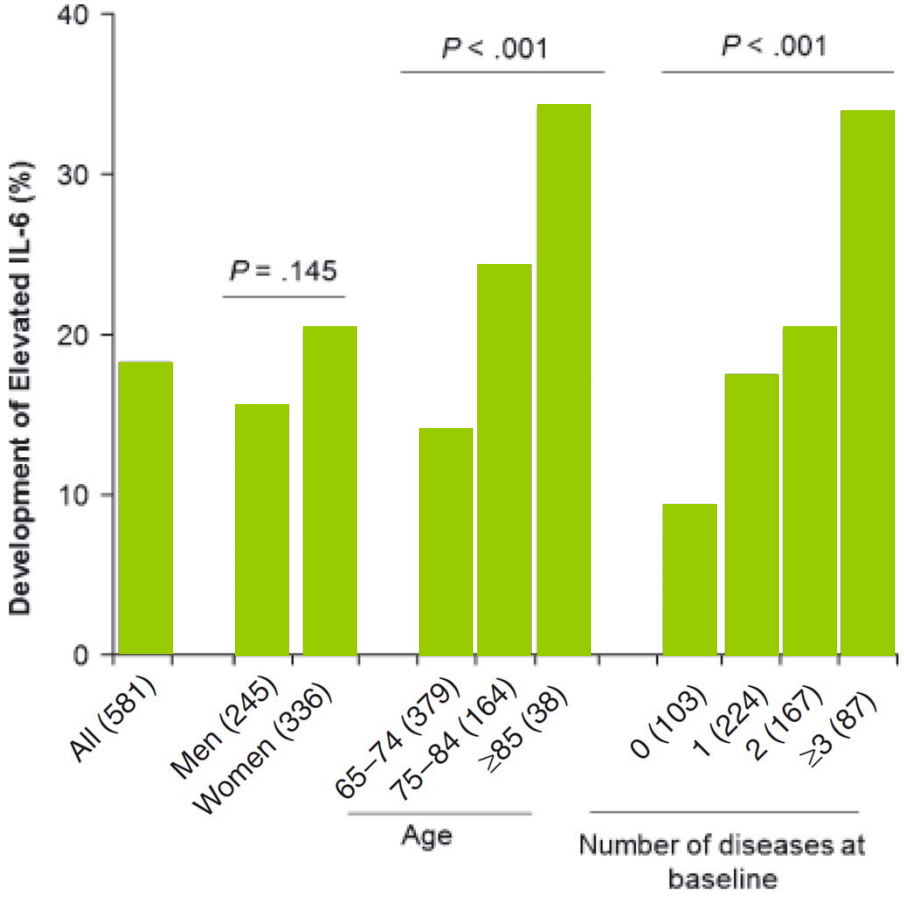
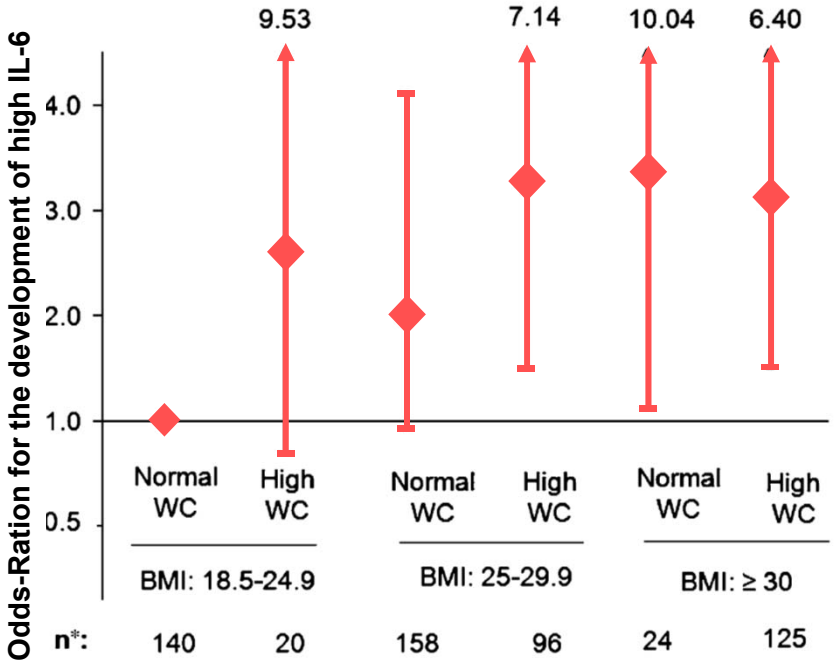


Journal of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
2009. Vol. 64A, No. 7, 723–730

Predictors of Interleukin-6 Elevation in Older Adults

Shuhan Zhu, BS,[*†] *Kushang V. Patel, PhD, MPH,*[†] *Stefania Bandinelli, MD,*[‡] *Luigi Ferrucci, MD, PhD,*[§] *and Jack M. Guralnik, MD, PhD*[†]

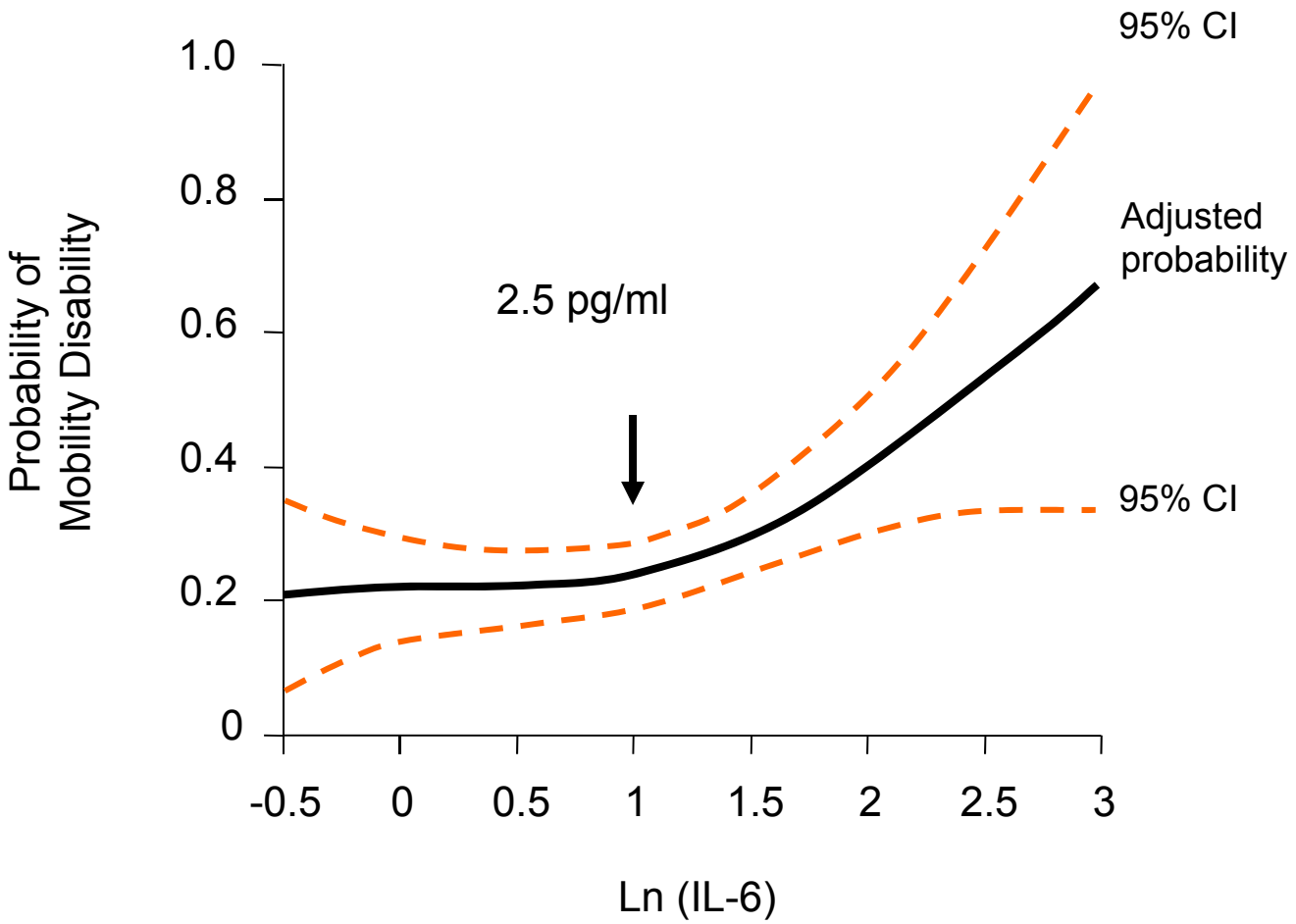




J Am Geriatr Soc 2009.

Interleukin-6 Serum Levels Predict Incident Disability

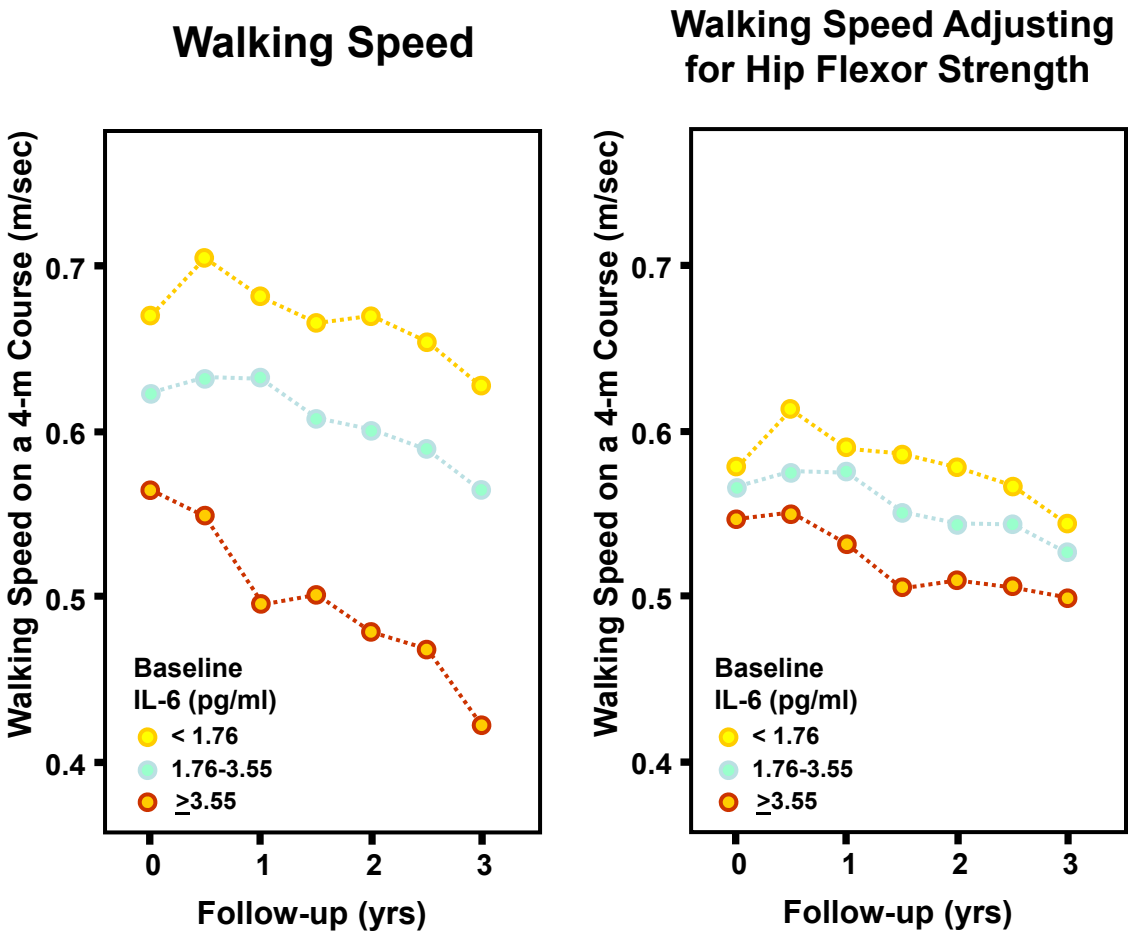
A Case Cohort Study Nested in the EPESE



Ferrucci et al. *JAGS 1999;47: 639-44*

Inflammation, Muscle Strength, and Physical Performance

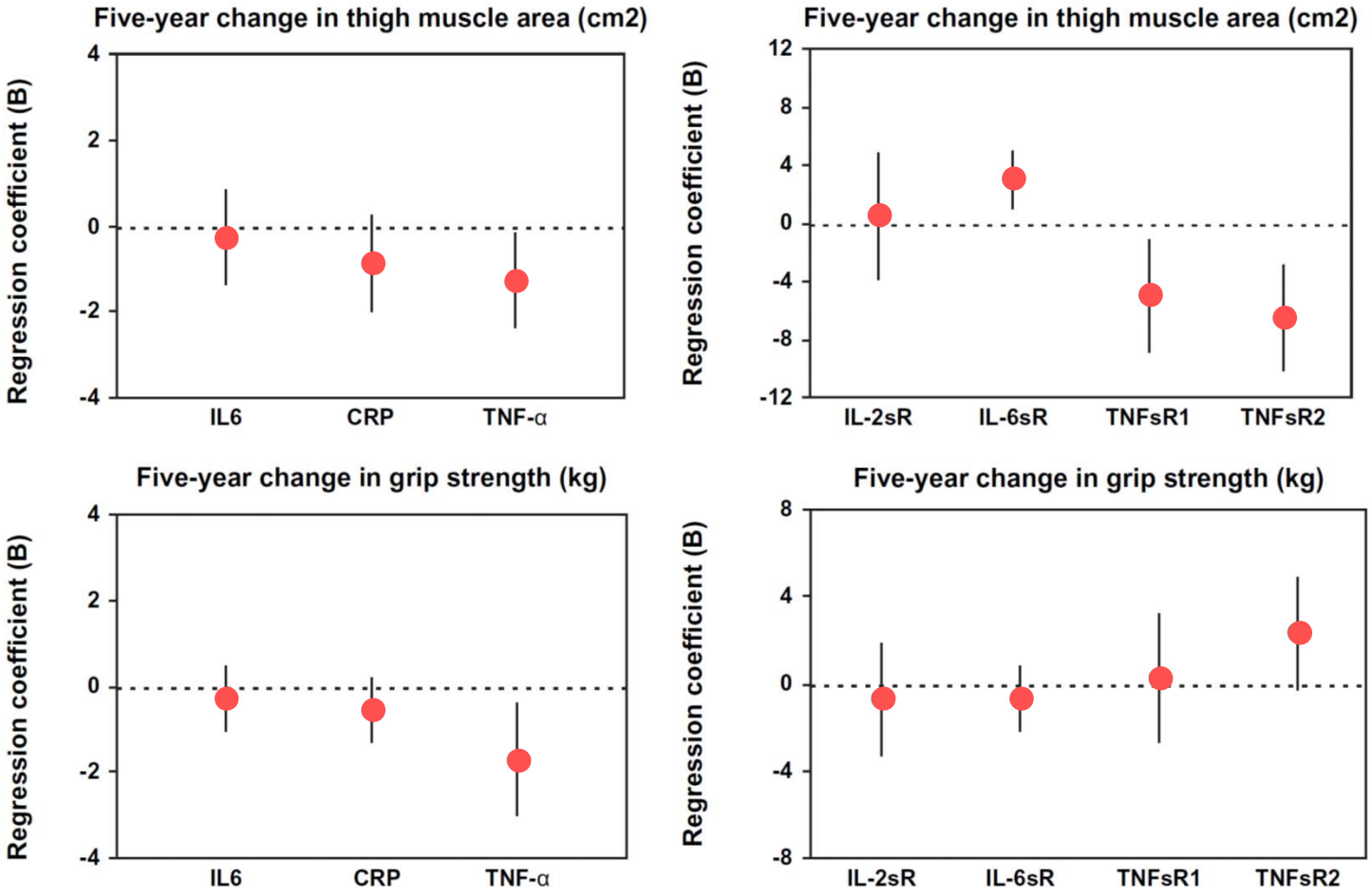
The Women's Health and Aging Study



Ferrucci L et al. J Am Geriatr Soc 2002; 50: 1947-54

Higher Inflammatory Marker Levels in Older Persons: Associations With 5-Year Change in Muscle Mass and Muscle Strength

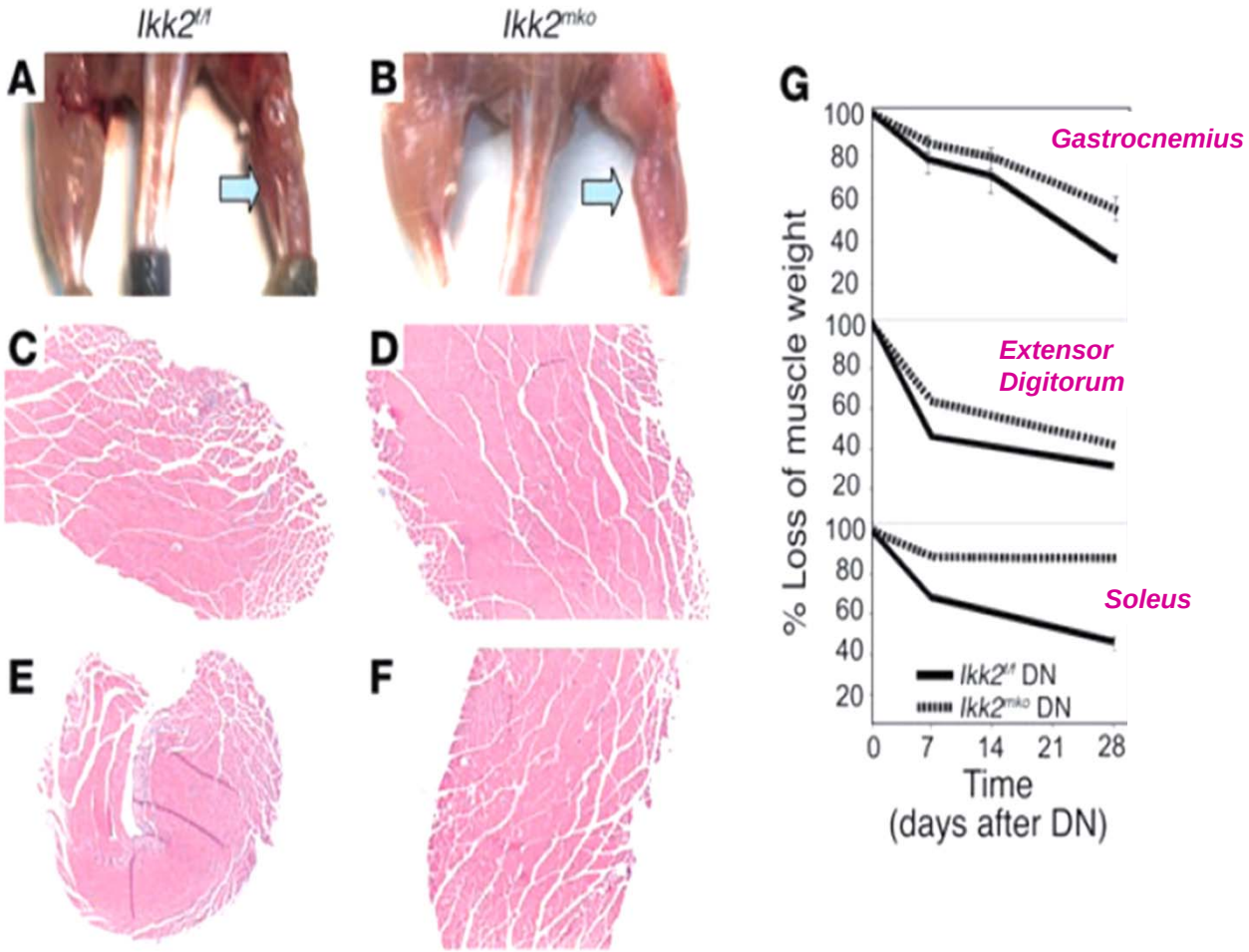
Laura A. Schaap,[1] Saskia M. F. Pluijm,[2] Dorly J. H. Deeg,[1] Tamara B. Harris,[3] Stephen B. Kritchevsky,[4] Anne B. Newman,[5] Lisa H. Colbert,[6] Marco Pahor,[7] Susan M. Rubin,[8] Frances A. Tylavsky,[9] Marjolein Visser,[1,10] for the Health ABC Study



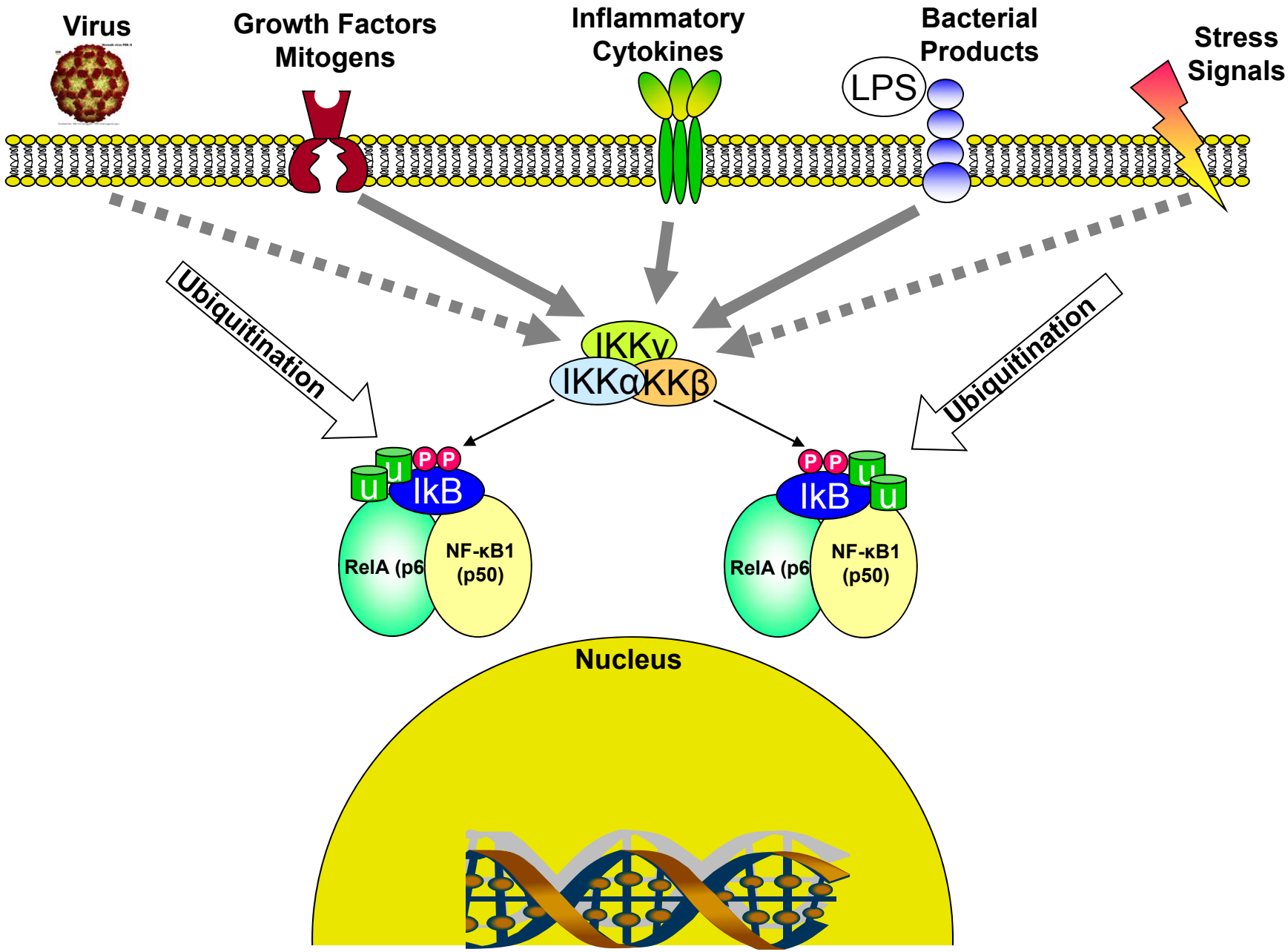
J Gerontol A Biol Sci Med Sci 2009

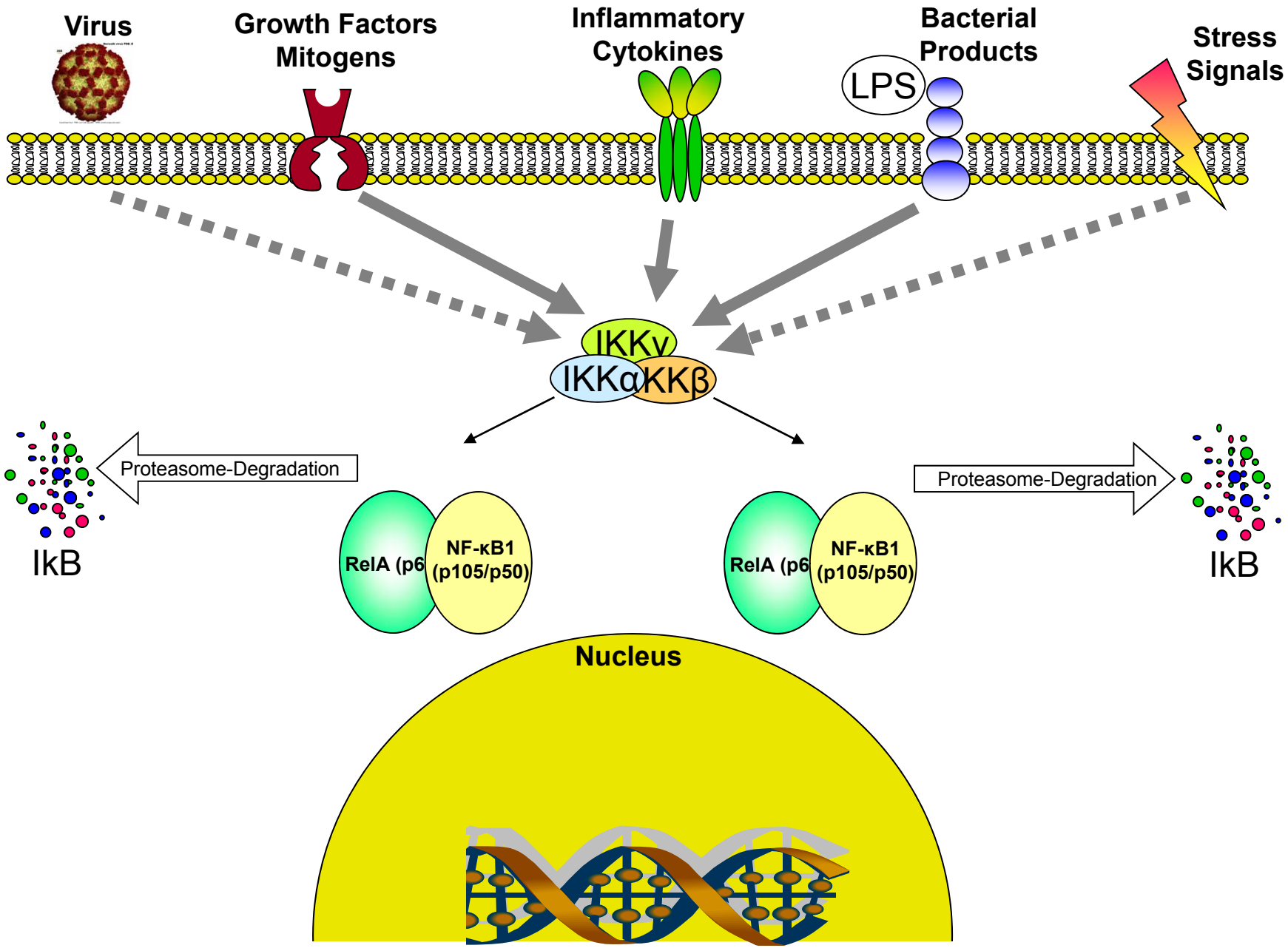
Targeted ablation of IKK2 improves skeletal muscle strength, maintains mass, and promotes regeneration

Foteini Mourkioti,[1] Paschalis Kratsios,[1] Tom Luedde,[1,2] Yao-Hua Song,[3] Patrick Delafontaine,[3] Raffaella Adami,[4] Valeria Parente,[4] Roberto Bottinelli,[4] Manolis Pasparakis,[1,2] and Nadia Rosenthal[1]



The Journal of Clinical Investigation http://www.jci.org Volume 116 Number 11 November 2006


Virus
Growth Factors
Mitogens
Inflammatory
Cytokines
Bacterial
Products
LPS
Stress
Signals
Ubiquitination
IKKγ
IKKαIKKβ
Ubiquitination
u
P P
IkB
RelA (p6
NF-κB1
(p50)
Nucleus


Virus
Growth Factors
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Inflammatory
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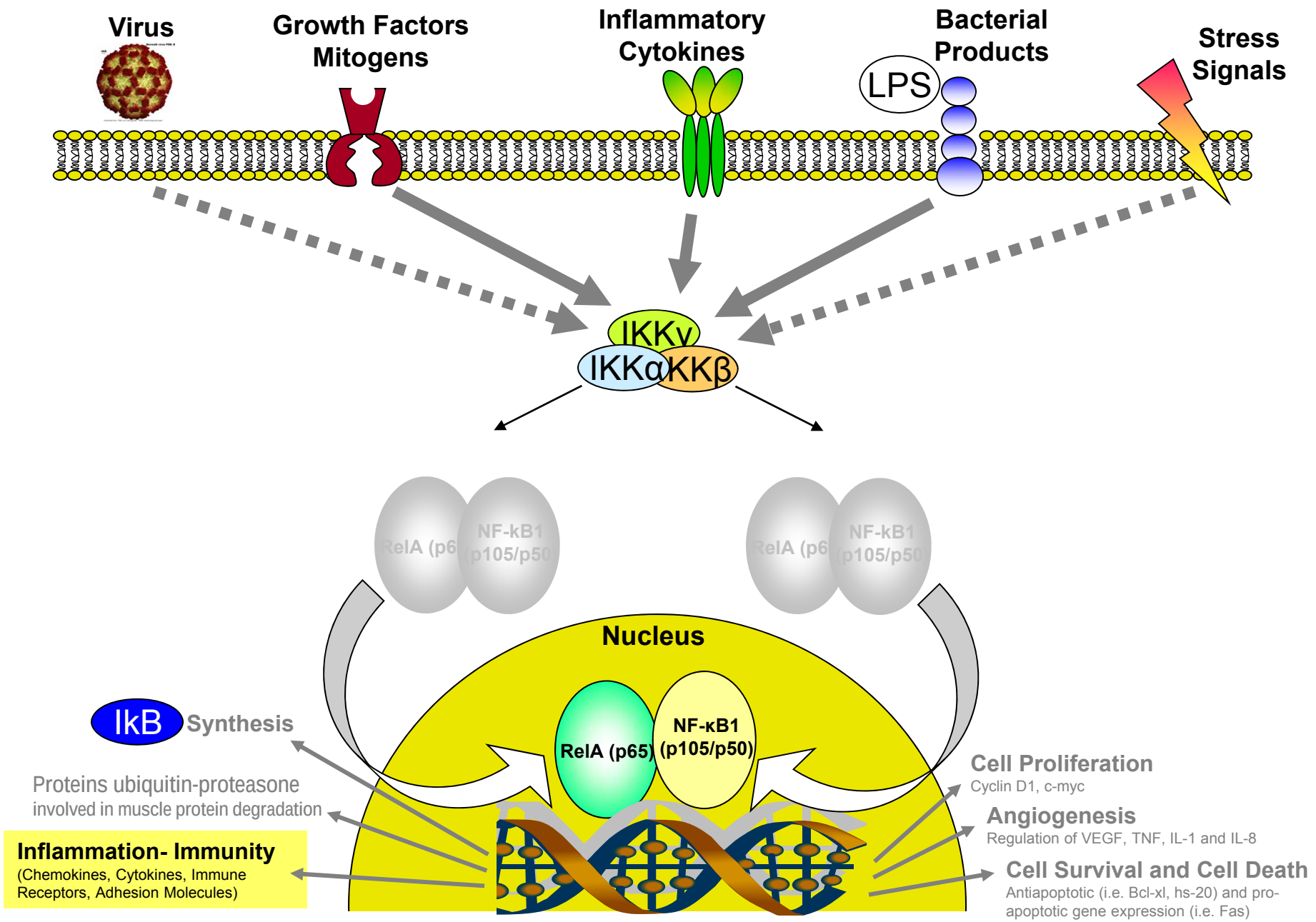
Bacterial
Products
LPS
Stress
Signals
IKKγ
IKKαIKKβ
Proteasome-Degradation
IkB
RelA (p6
NF-κB1
(p105/p50)
RelA (p6
NF-κB1
(p105/p50)
Proteasome-Degradation
IkB
Nucleus


Virus
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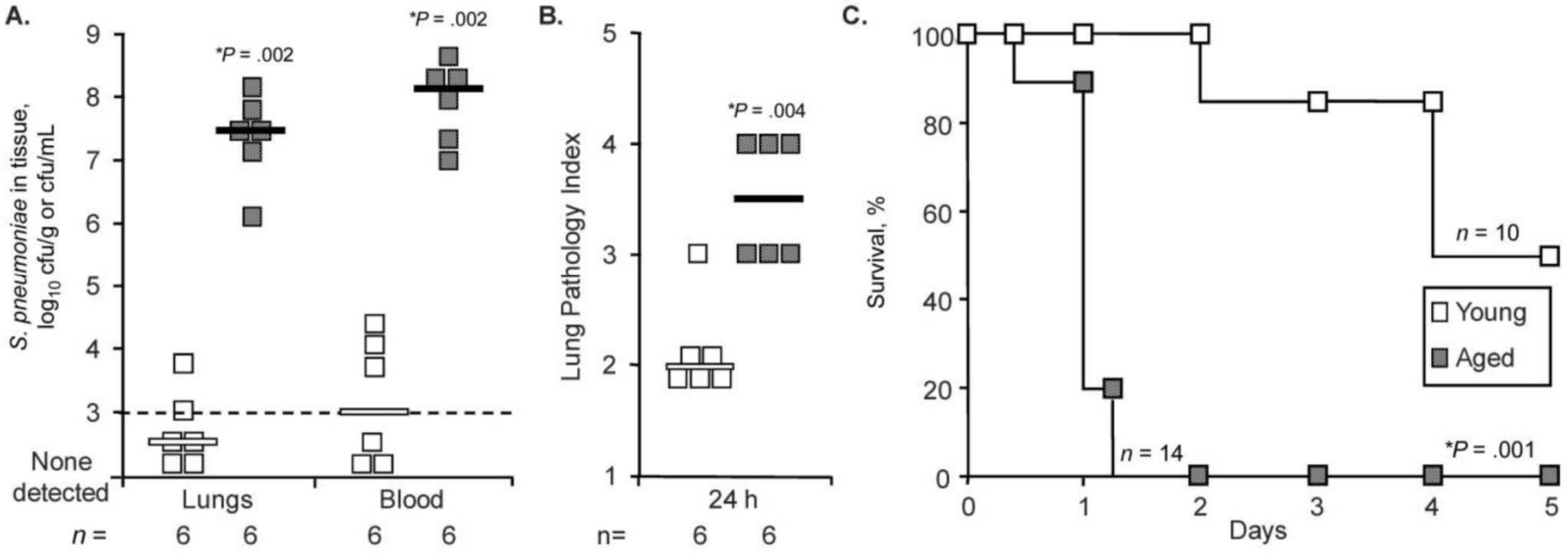
Products
LPS
Stress
Signals
IKKγ
IKKαKKβ
RelA (p6
NF-kB1
(p105/p50
RelA (p6
NF-kB1
(p105/p50
Nucleus
RelA (p65)
NF-κB1
(p105/p50)
IkB
Synthesis
Proteins ubiquitin-proteasone
involved in muscle protein degradation
Inflammation- Immunity
(Chemokines, Cytokines, Immune
Receptors, Adhesion Molecules)
Cell Proliferation
Cyclin D1, c-myc
Angiogenesis
Regulation of VEGF, TNF, IL-1 and IL-8
Cell Survival and Cell Death
Antiapoptotic (i.e. Bcl-xl, hs-20) and pro-
apoptotic gene expression (i.e. Fas)

Age-Associated Inflammation and Toll-Like Receptor Dysfunction Prime the Lungs for Pneumococcal Pneumonia

Ernesto Hinojosa,[a] Angela R. Boyd,[a] and Carlos J. Orihuela

Data collected 1day after intranasal challenge with 1 x 10^7 colony-forming units of S. pneumoniae.

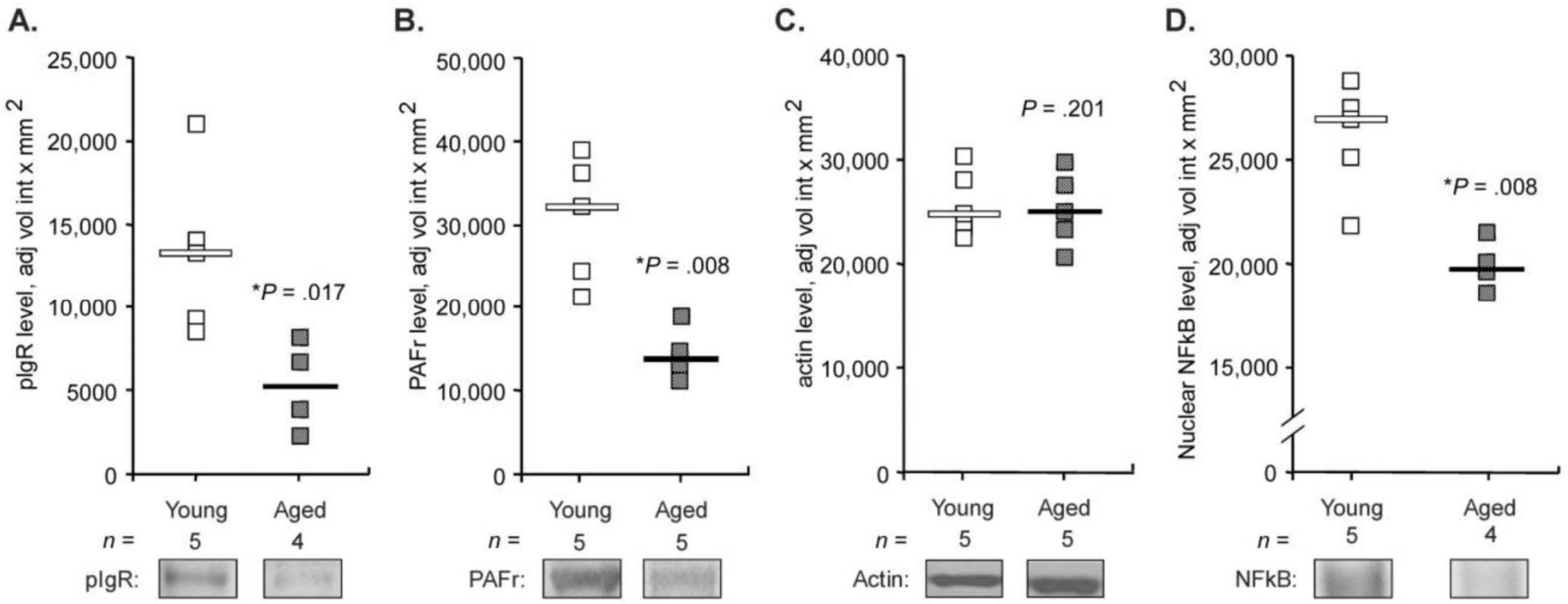


The Journal of Infectious Diseases 2009; 200:546–54

Age-Associated Inflammation and Toll-Like Receptor Dysfunction Prime the Lungs for Pneumococcal Pneumonia

Ernesto Hinojosa,[a] Angela R. Boyd,[a] and Carlos J. Orihuela

Data collected 2 days after intranasal challenge with 1 x 10^7 colony-forming units of S. pneumoniae.



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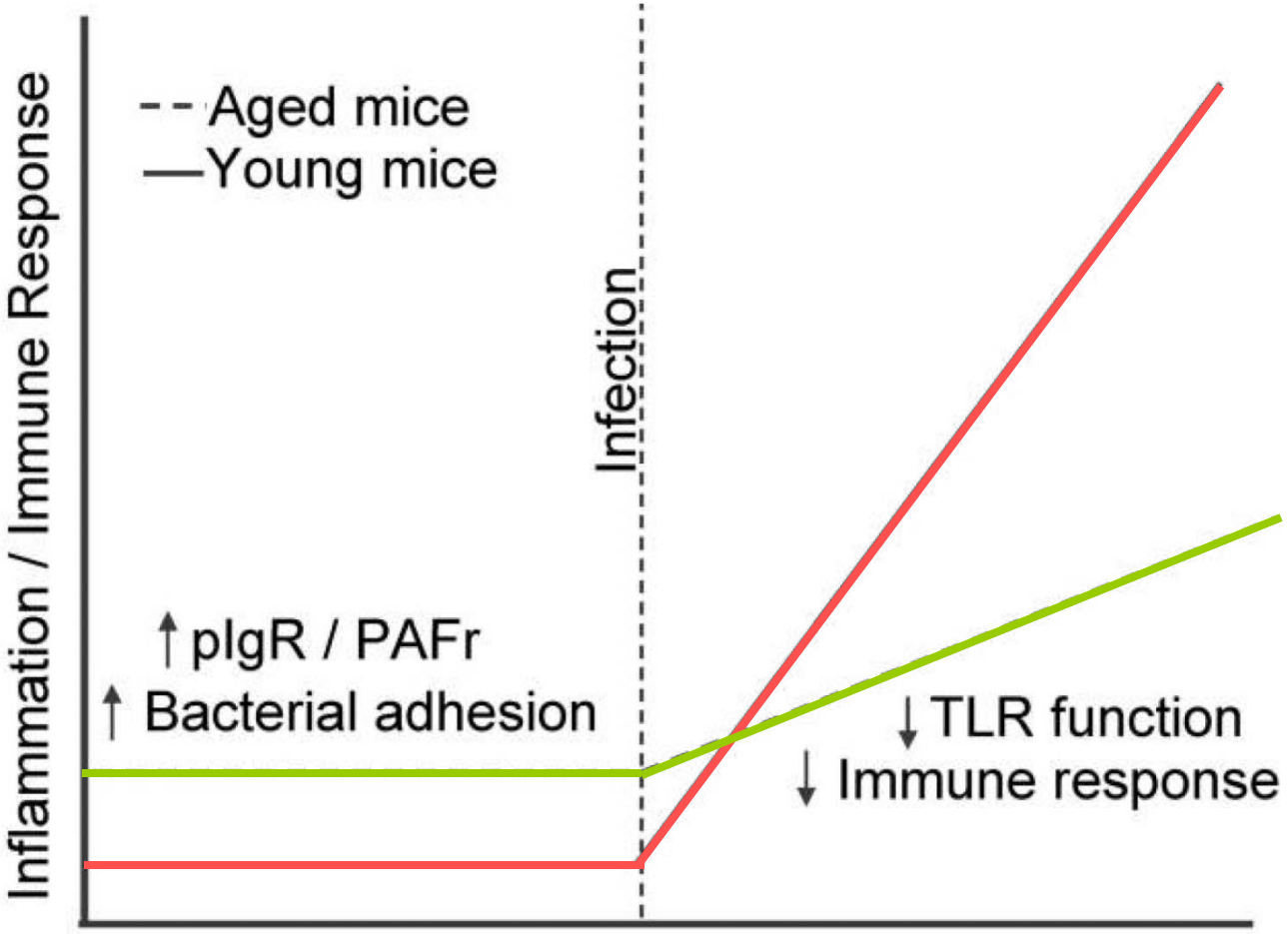

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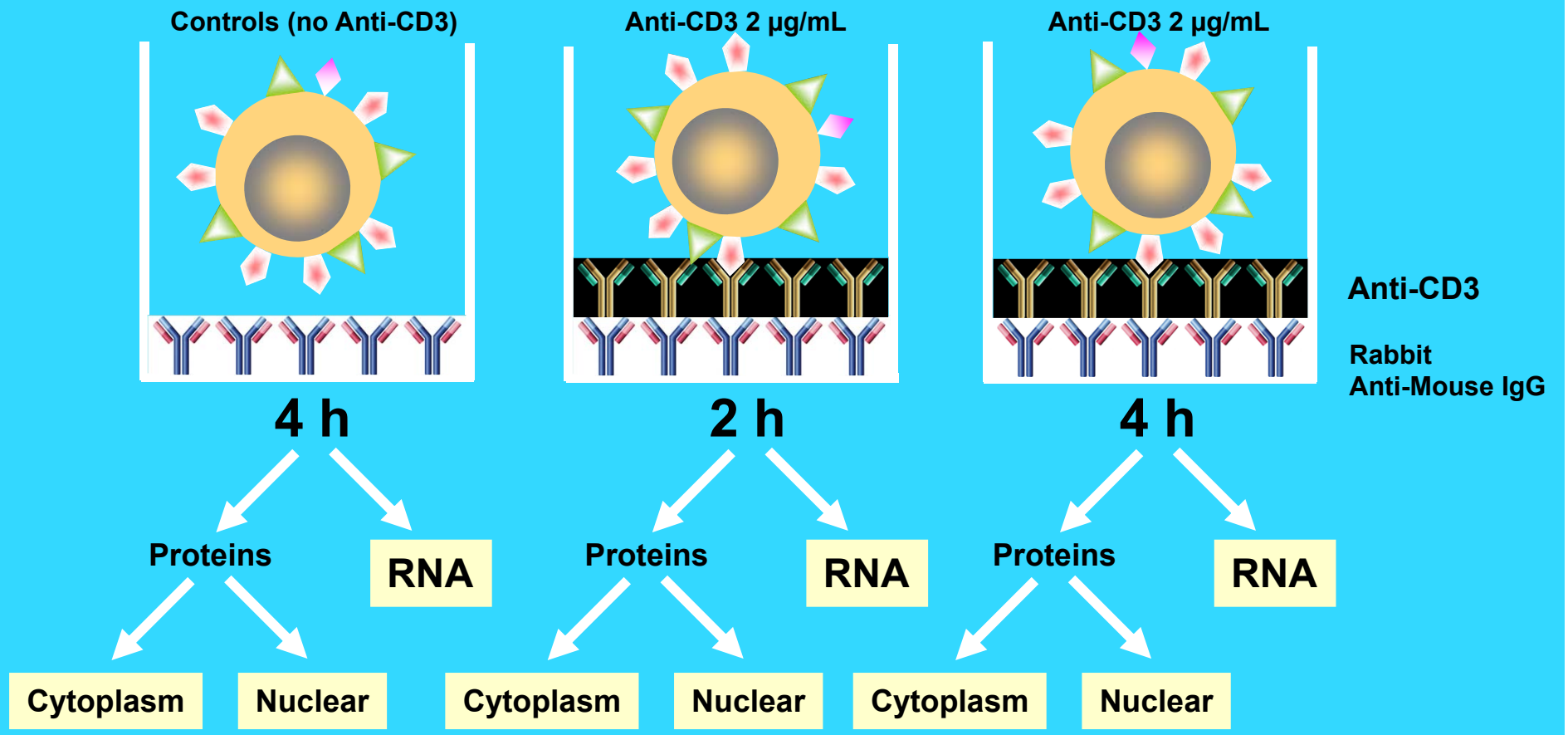
COBE Spectra

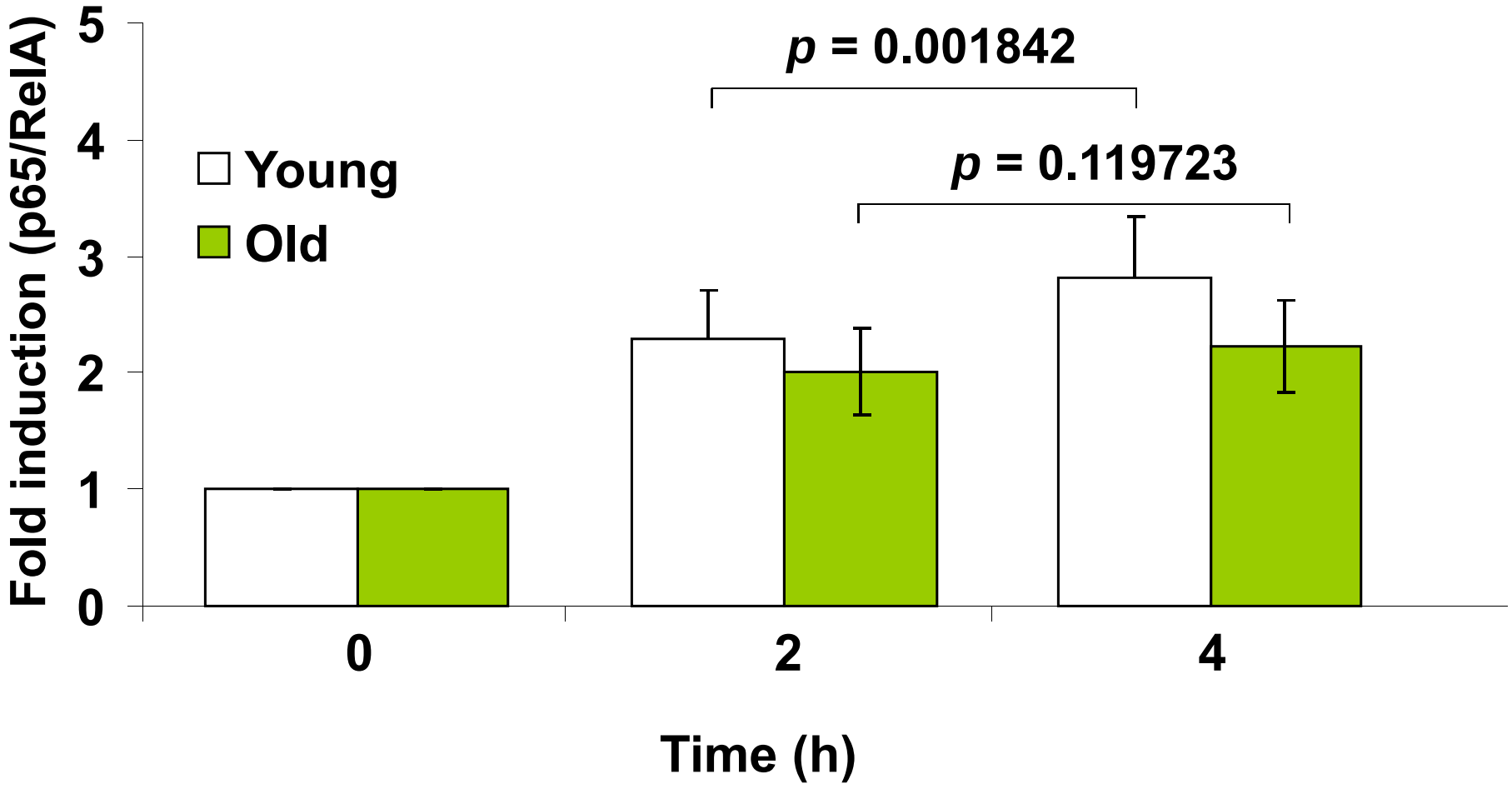
Cytapheresis
$5*10^9$ WBC → Ficoll Separation → PBMC → Magnetic Bead Cell Sorting (CD4+) → Lymphocytes CD4+ → Overnight Rest

Study of the early, effects of NF-κB induction



Age-associated dysregulation of NF-κB function in human CD4+ T Lymphocytes

Arsun Bektas, Yongqing Zhang, Gertrude C. Kokkonen, William H. Wood.
Kevin G. Becker, Karen Madara, Luigi Ferrucci and Ranjan Sen



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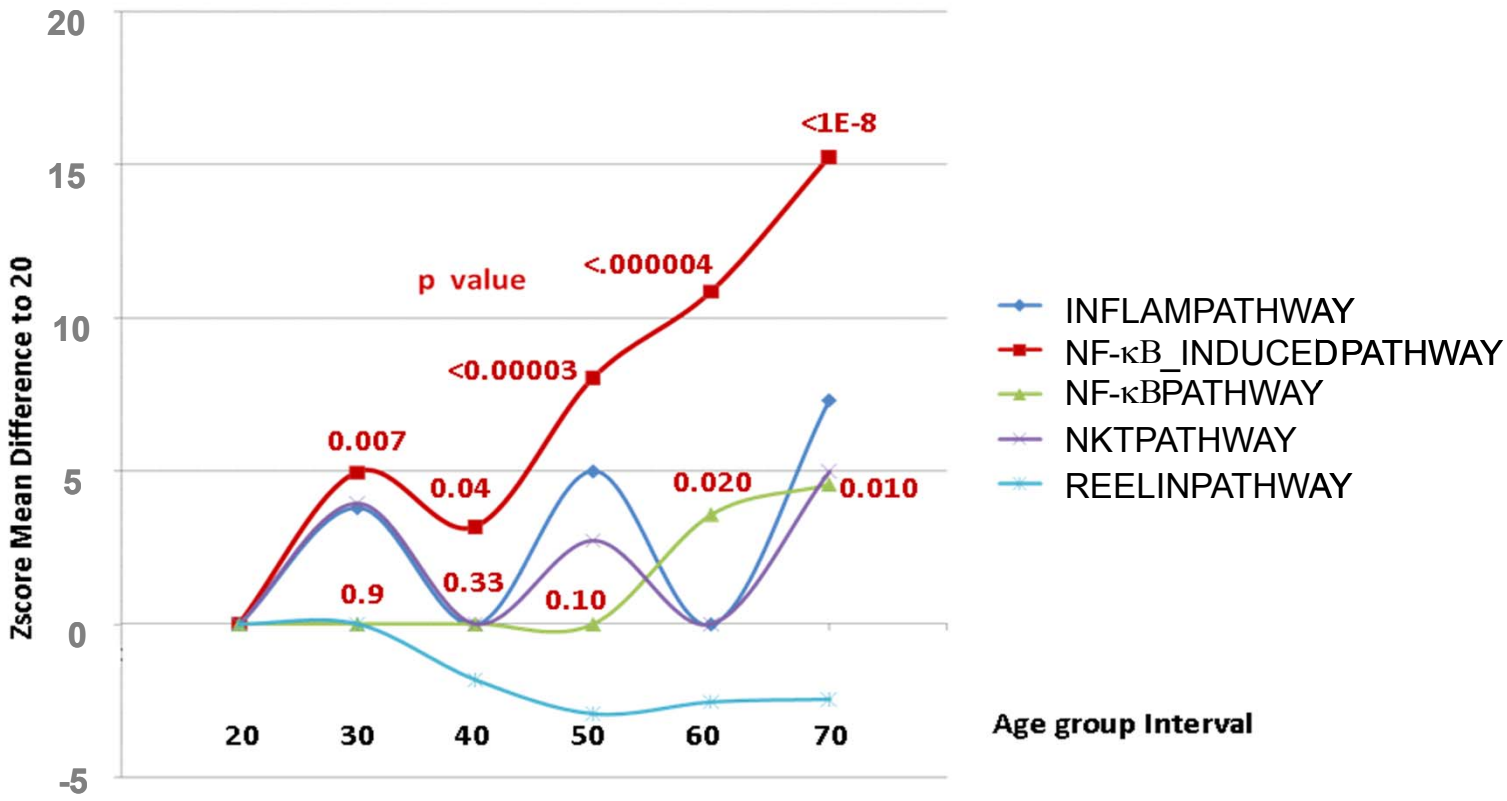

Unpublished (please , do not cite)

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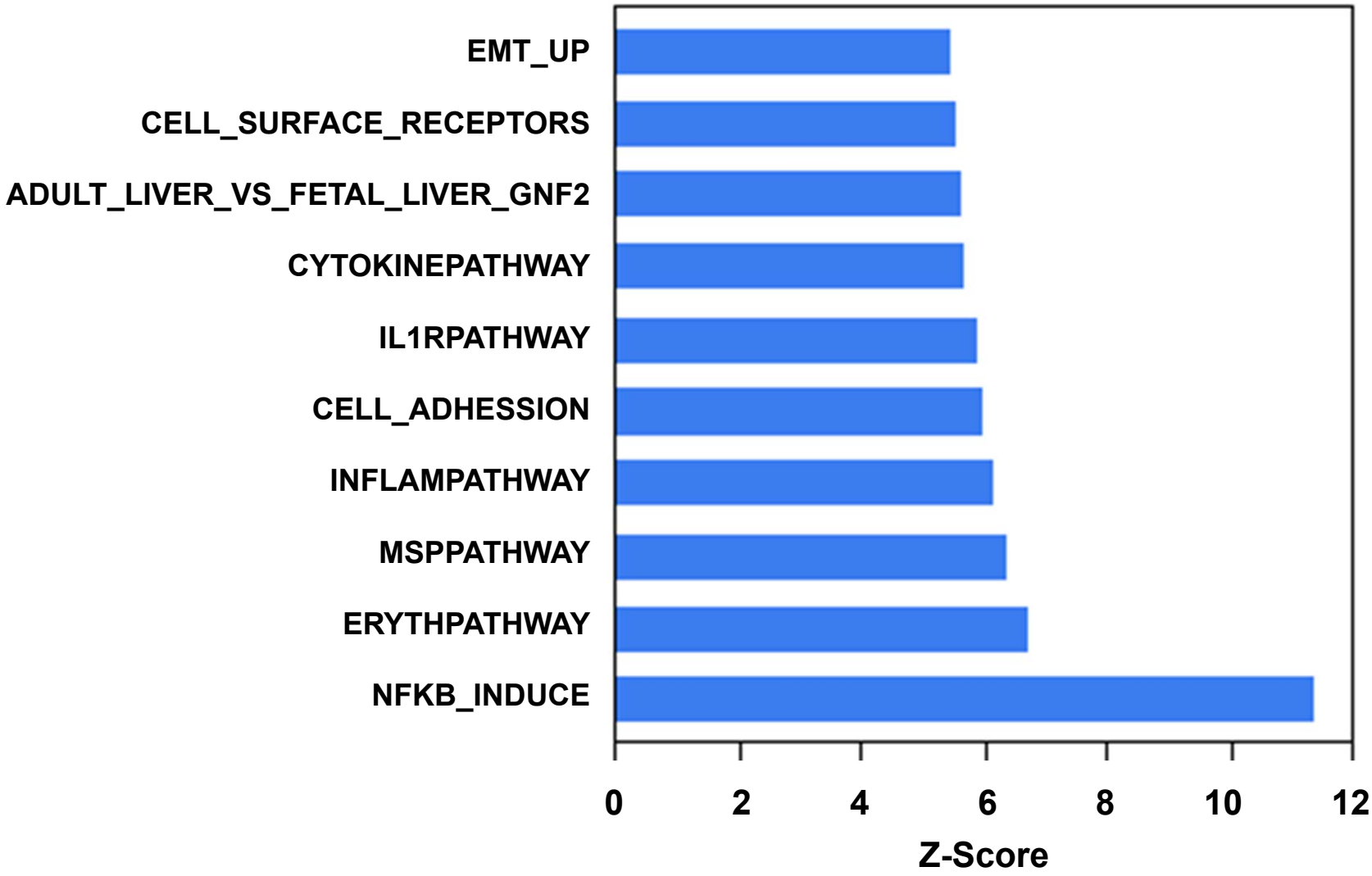

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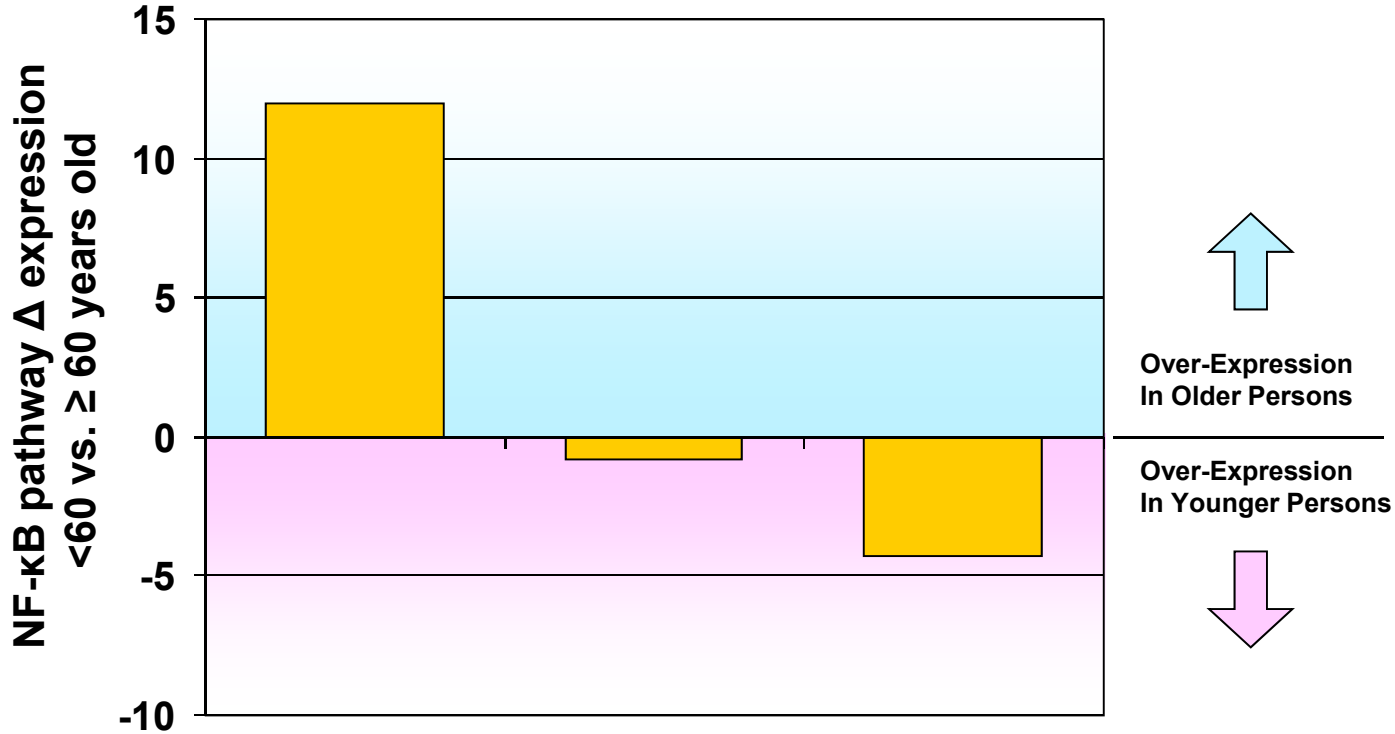
Kevin G. Becker, Karen Madara, Luigi Ferrucci and Ranjan Sen

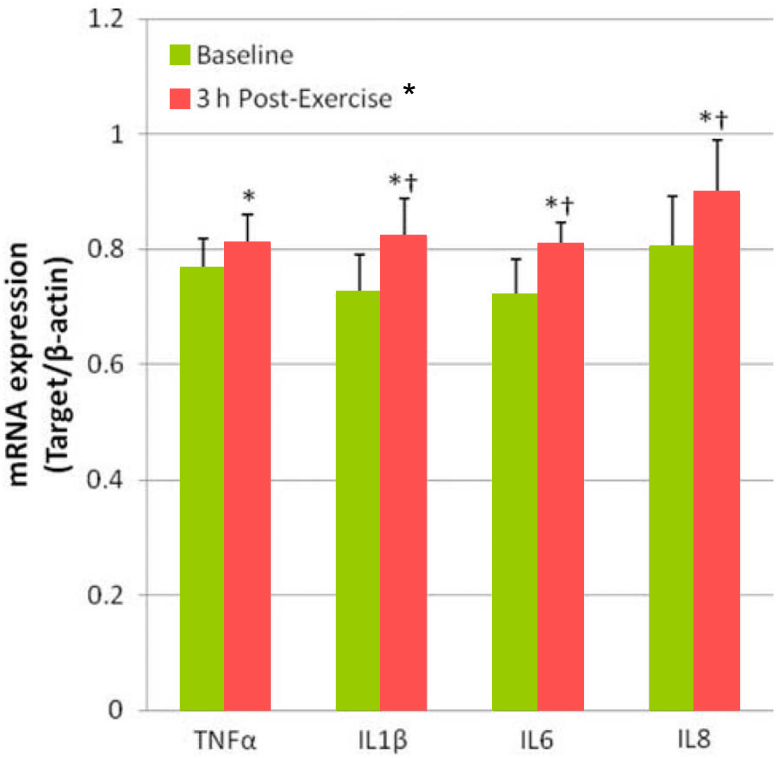
RNA Pathway Analysis (microarray for 22K genes)

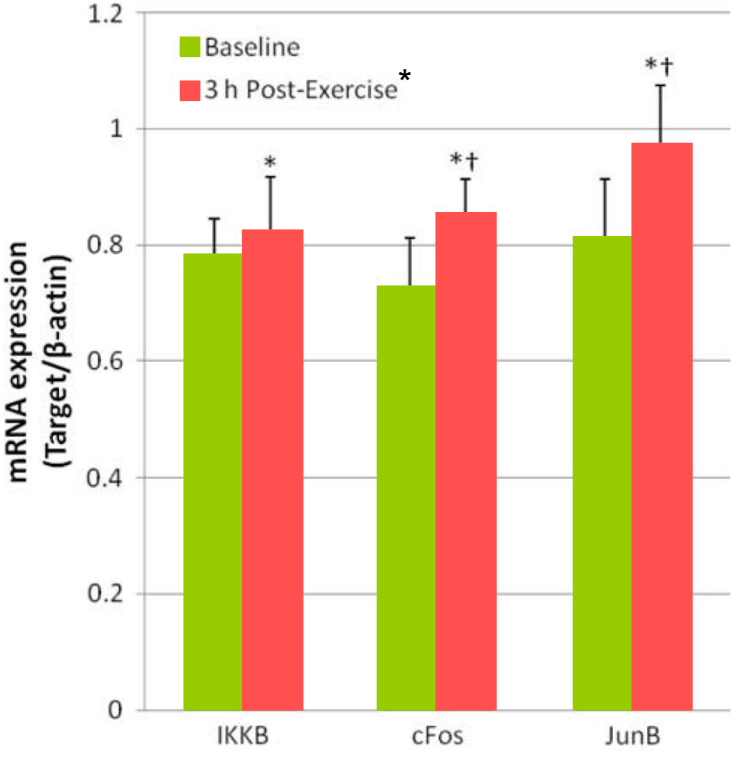


	Controls	2-h Activation	4-h activation
IL-6	3.17	1.61	-1.07
IL-8	4.32	-0.87	-0.83
MMP9	3.20	-0.73	-0.41
TNF	3.53	1.79	1.63
Colony stimulator factor 2	0.4	-1.62	-10.27
Macrophage Inflamm. Protein-3	1.85	-3.65	-7.65

Resistance exercise-induced changes of inflammatory gene expression within human skeletal muscle

Thomas W. Buford · Matthew B. Cooke
Darryn S. Willoughby

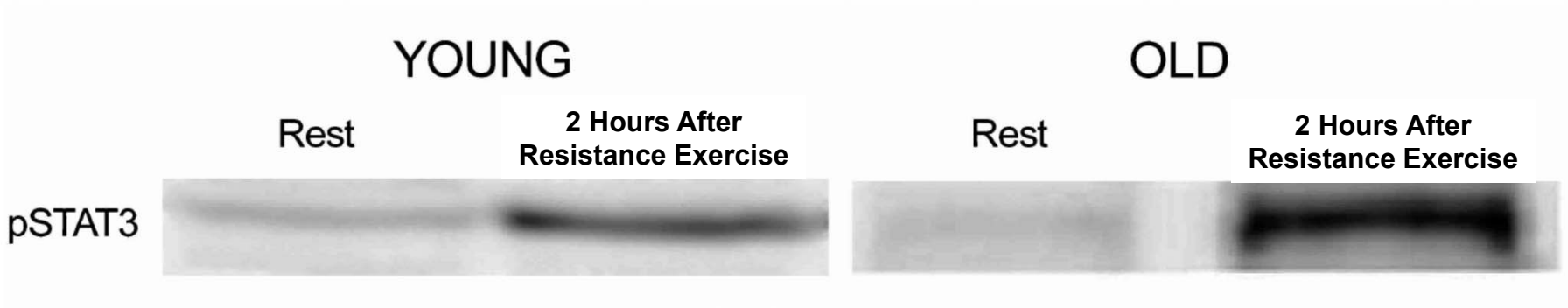


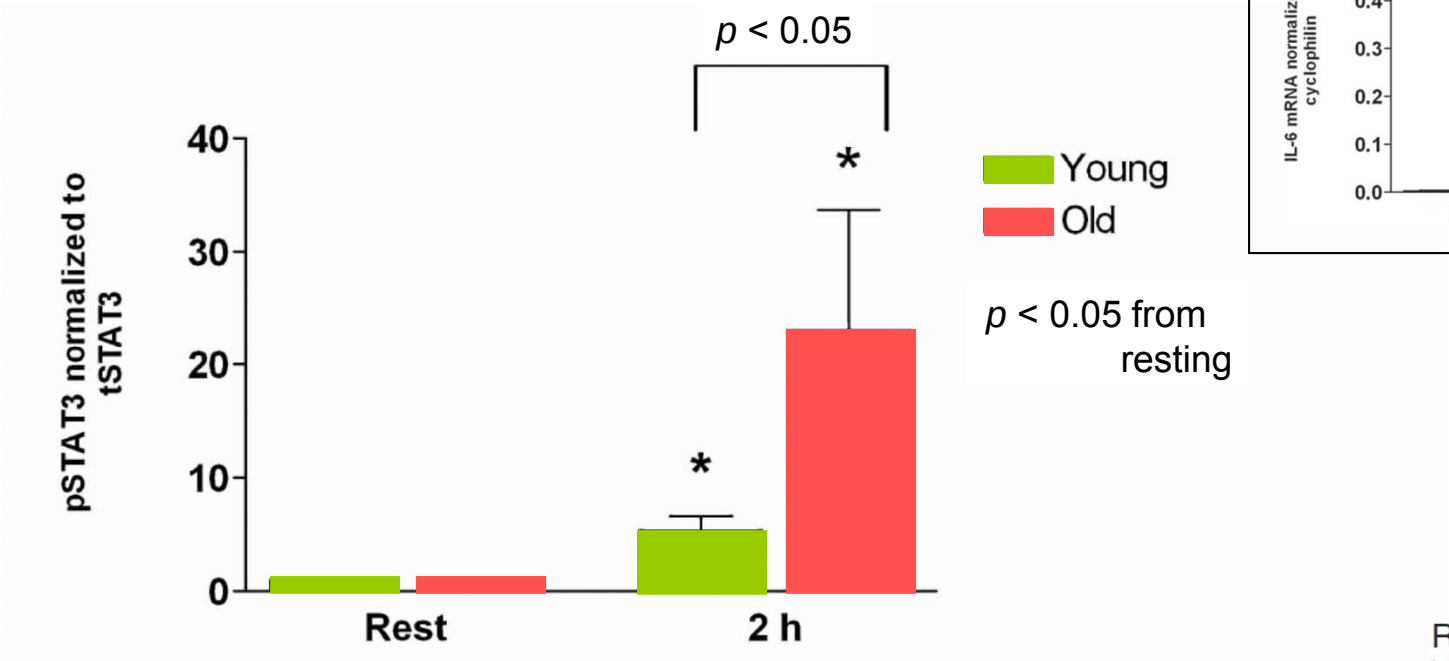


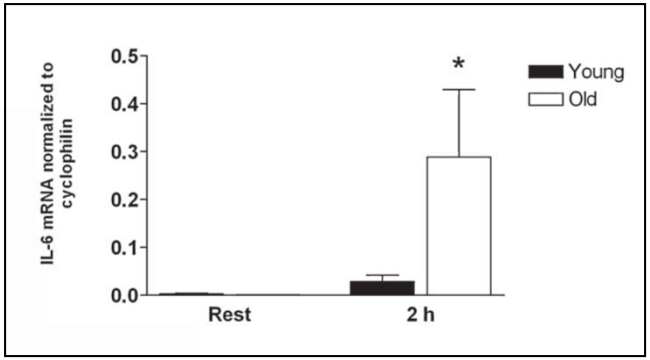
* 3 sets of 10 repetitions at 80% of 1RM on each of the three exercises (24 women).

Eur J Appl Physiol 2009

Exercise-Induced Activation of STAT3 Signaling Is Increased with Age

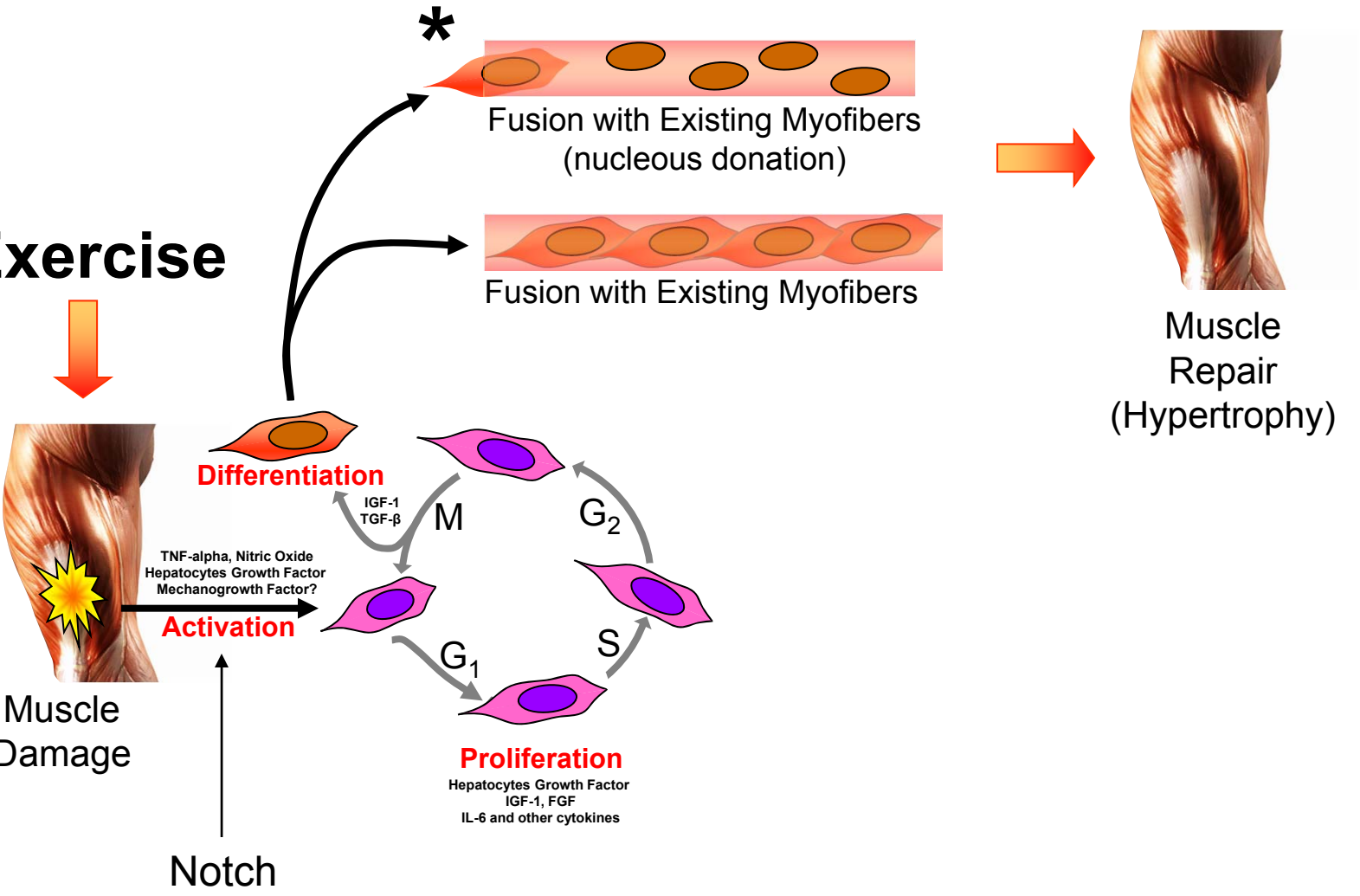






REJUVENATION RESEARCH
Volume 11, Number 4, 2008

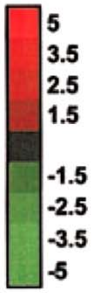
Muscle Stem Cells and Exercise



Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression

STEWART H. LECKER,[1] R. THOMAS JAGOE,*,[1] ALEXANDER GILBERT, MARCELO GOMES,†† VICKIE BARACOS,† JAMES BAILEY,‡ S. RUSS PRICE,‡ WILLIAM E. MITCH,§ AND ALFRED L. GOLDBERG††,[2]

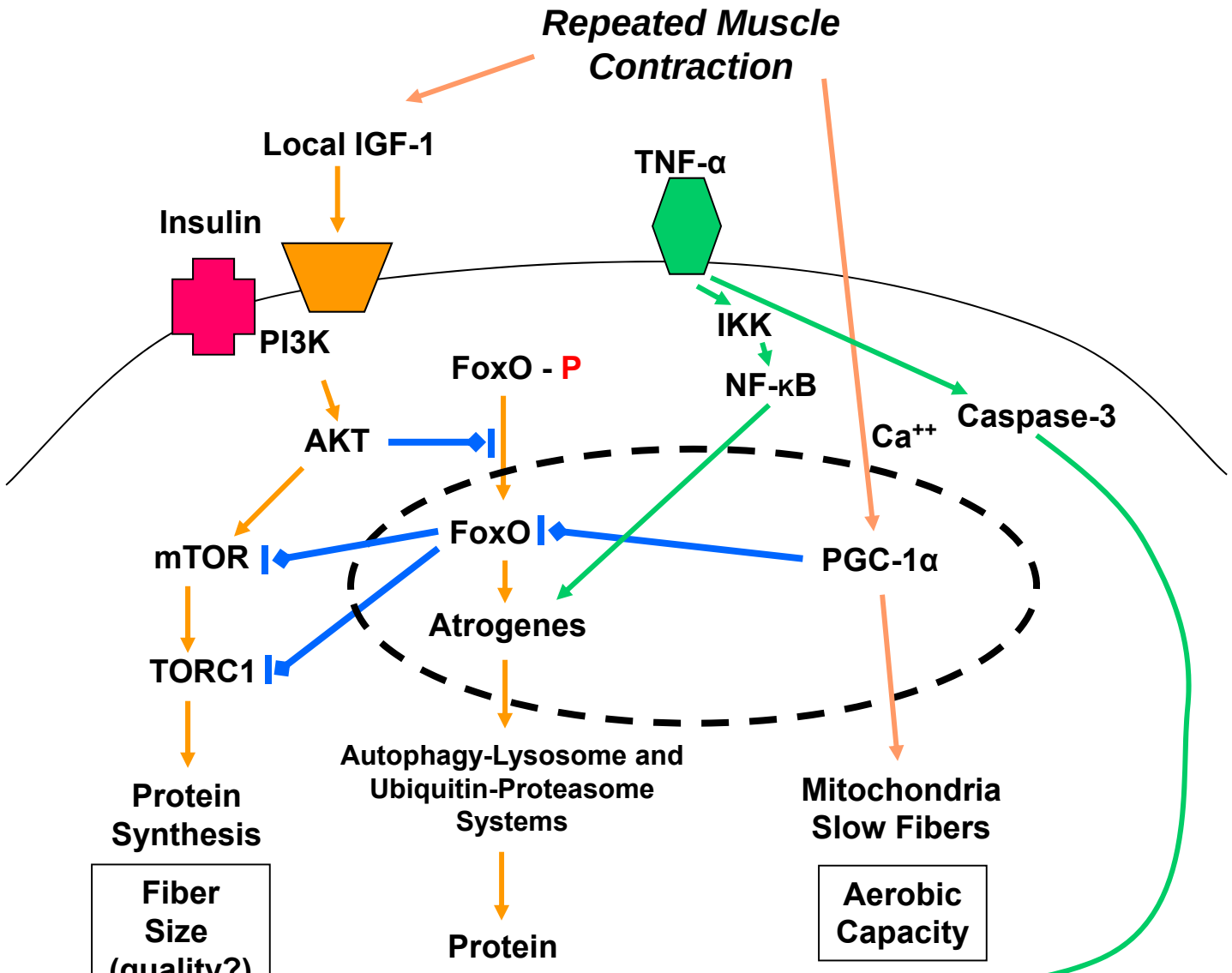
Clone	Unigene	Primary Sequence Name		F T U D
3137251	Hs.183842	UBB	ubiquitin B	
2730250	Hs.183704	UBC	ubiquitin C	
2132619	Hs.3297	RPS27A	ribosomal protein S27a	
4157922	Hs.5308	UBA52	ubiquitin A-ribosomal protein fusion product	
1723142	Hs.61661	FBXO32	Atrogin-1/MAFbx	
751477	Mm.32920	Ncube1	non-canonical Ub-conjugating enzyme 1	
747318	Mm.21634	Ube4b	ubiquitination factor E4B	
2195309	Hs.82159	PSMA1	proteasome 20S subunit, alpha 1	
723267	Mm.30097	Psma1		
466041	Mm.30097			
572285	Mm.2287	Psma5	proteasome 20S subunit, alpha 5	
1737833	Hs.82793	PSMB3	proteasome 20S subunit, beta 3	
571569	Mm.21874	Psmb3		
901317	Hs.89545	PSMB4	proteasome 20S subunit, beta 4	
466254	Mm.29582	Psmc4	proteasome 19S subunit, ATPase, 4	
2123183	Hs.78466	PSMD8	proteasome 19S subunit, non-ATPase, 8	
113452	Hs.90744	PSMD11	proteasome 19S subunit, non-ATPase, 11	
833508	Mm.28571	Psmd11		
448976	Hs.112396	PA200	KIAA0077 protein	
1707220	Hs.75981	USP14	Ub-specific protease 14	
315082	Mm.930	Ctsl	cathepsin L	
2935790	Hs.87417	CTSL2		



sed expression of mRNAs involved in protein degradation. Fold increase is graded by intensity of red
ing to the key. **F**, Fasting; **T**, tumor bearing; **U**, uremia; **D**, diabetes mellitus.

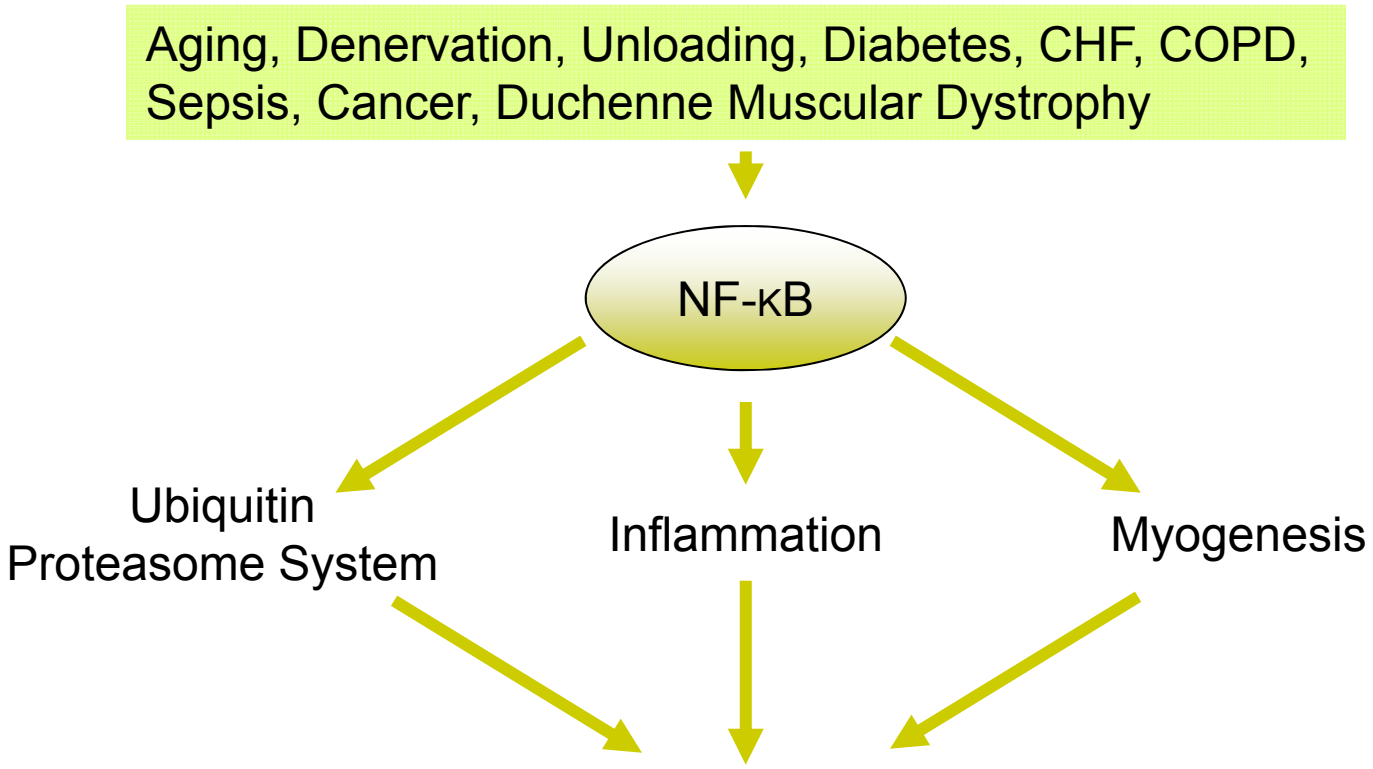
ri M et al.

anisms for Inhibition of Atrophy and Growth Promotion by Muscle Activity



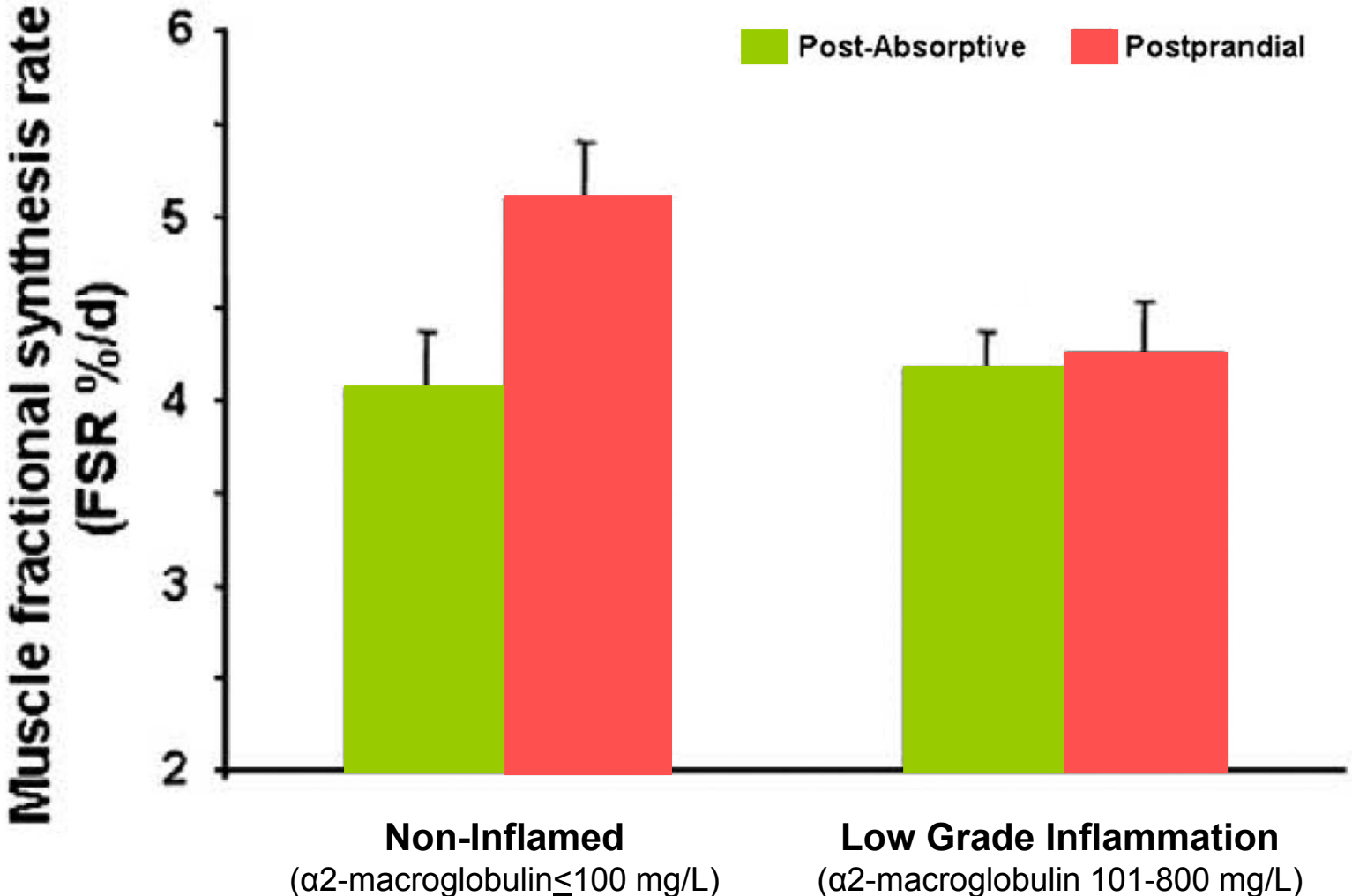
uclear factor-kappa B signaling in skeletal muscle atrophy

Hong Li · Shweta Malhotra · Ashok Kumar



...ce of low-grade inflammation impaired postprandial stimulation of muscle protein synthesis in old rats☆

...e Balage[a,b], Julien Averous[a,b], Didier Rémond[a,b], Cécile Bos[c], Estelle Pujos-Guillot[a,b], Isabelle Papet[a,b], Laurent Mosoni[a,b], Lydie Combaret[a,b], Dominique Dardevet[a,b,*]



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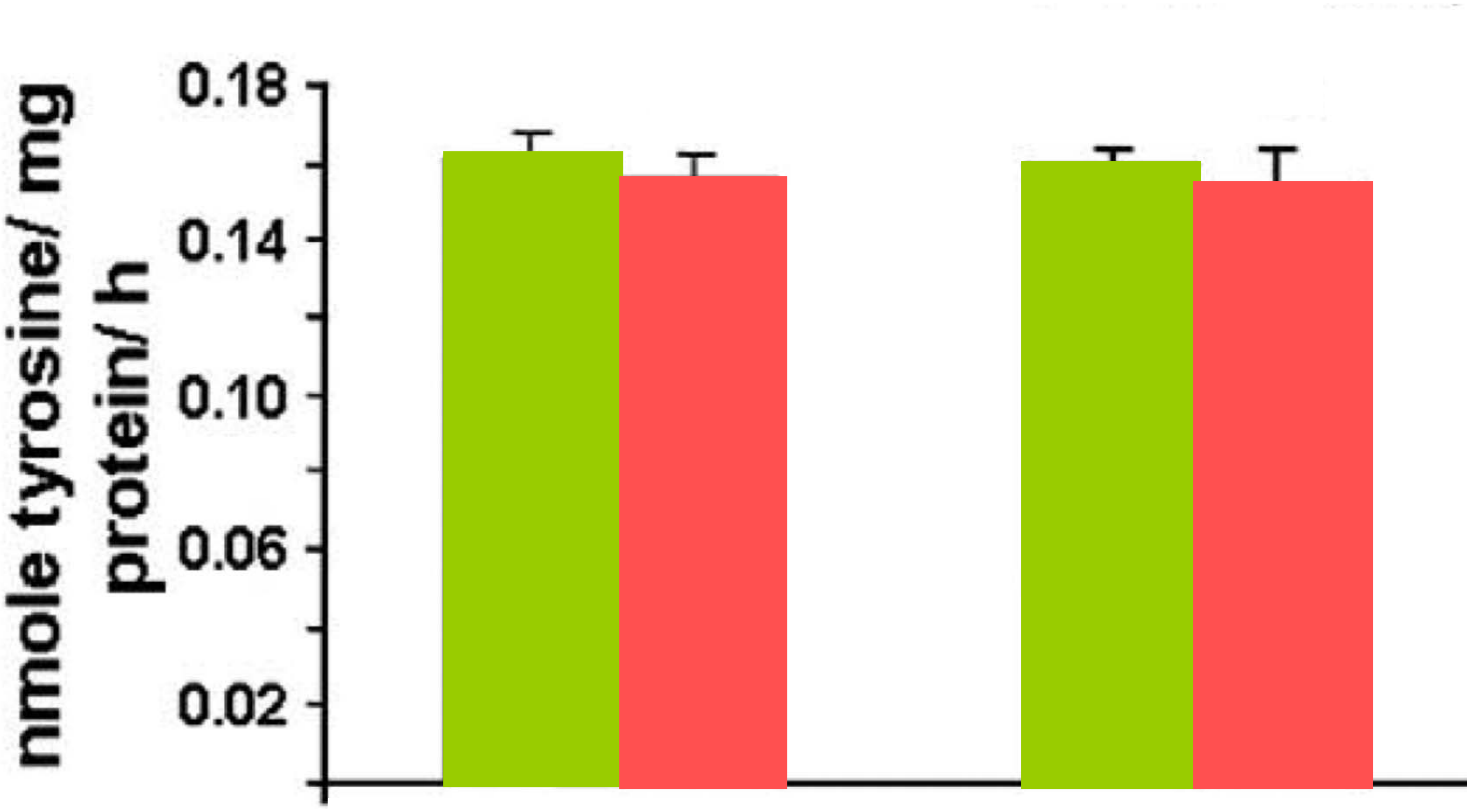
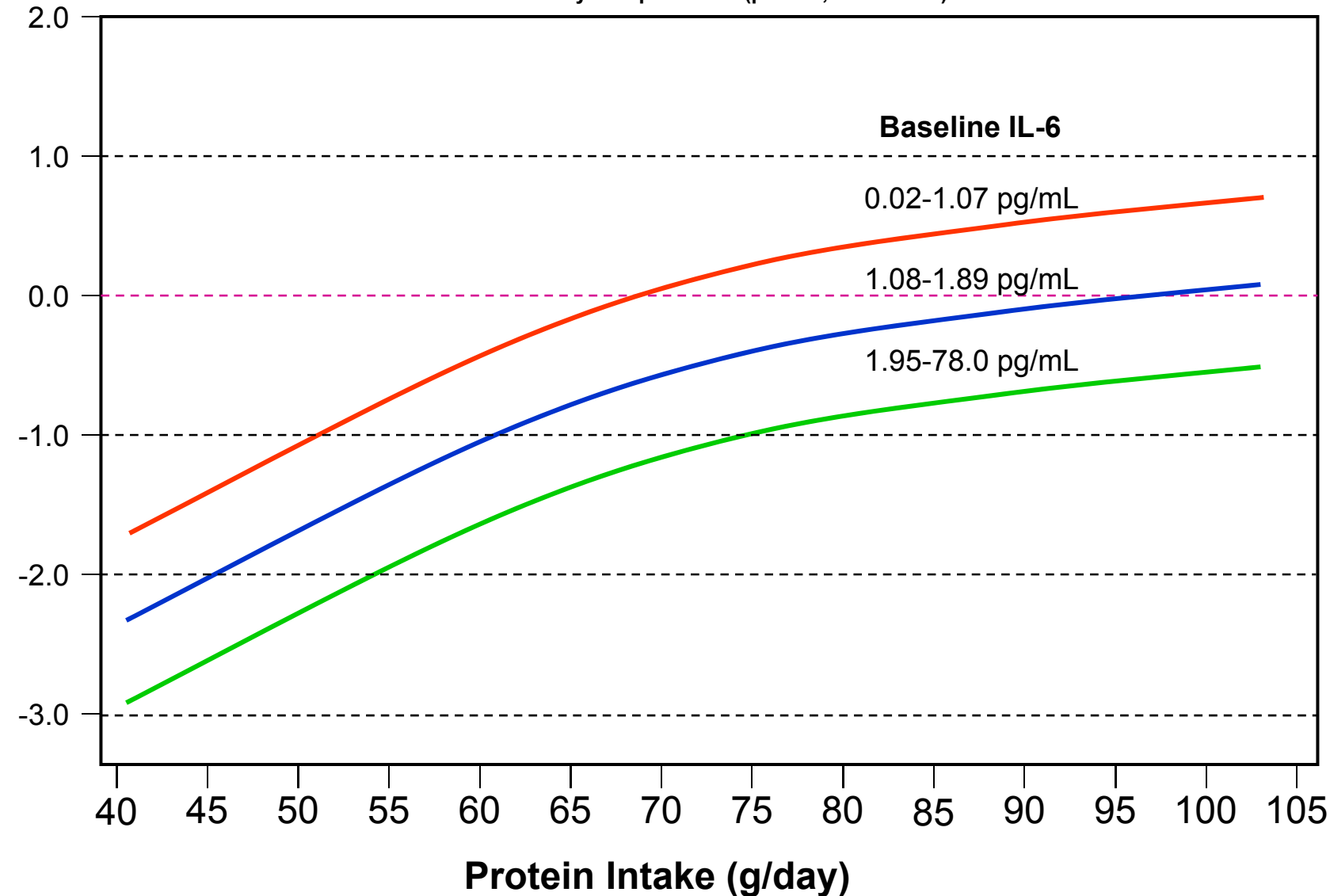
Muscle Total Proteolysis



Effect of Protein Intake on Change in Muscle Strength in Older Persons: Does Inflammation Matter?

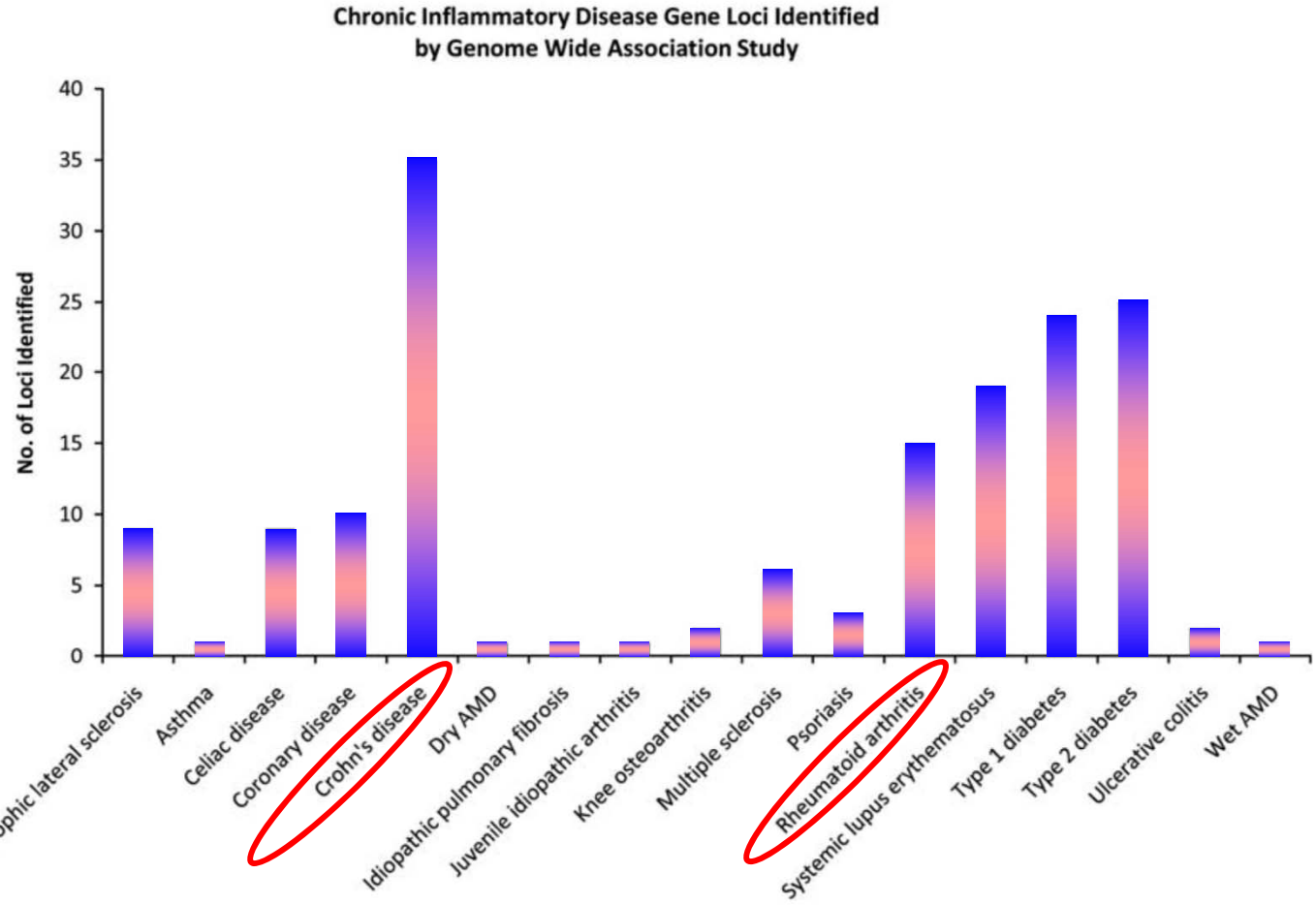
Bartali B. et al. InCHIANTI Study – Unpublished (please , do not cite)



The genetics of chronic inflammatory diseases

Graham A. Heap and David A. van Heel*

Centre for Gastroenterology, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Whitechapel, London E1 2AT, UK



1. Number of loci identified for chronic inflammatory diseases (2008). The sum of the number of loci identified from individual GWAS. Data was ed from The National Human Genome Research Initiative Catalogue of Genome Wide Association Study Variants, available at http://www.genome.

The genetics of chronic inflammatory diseases

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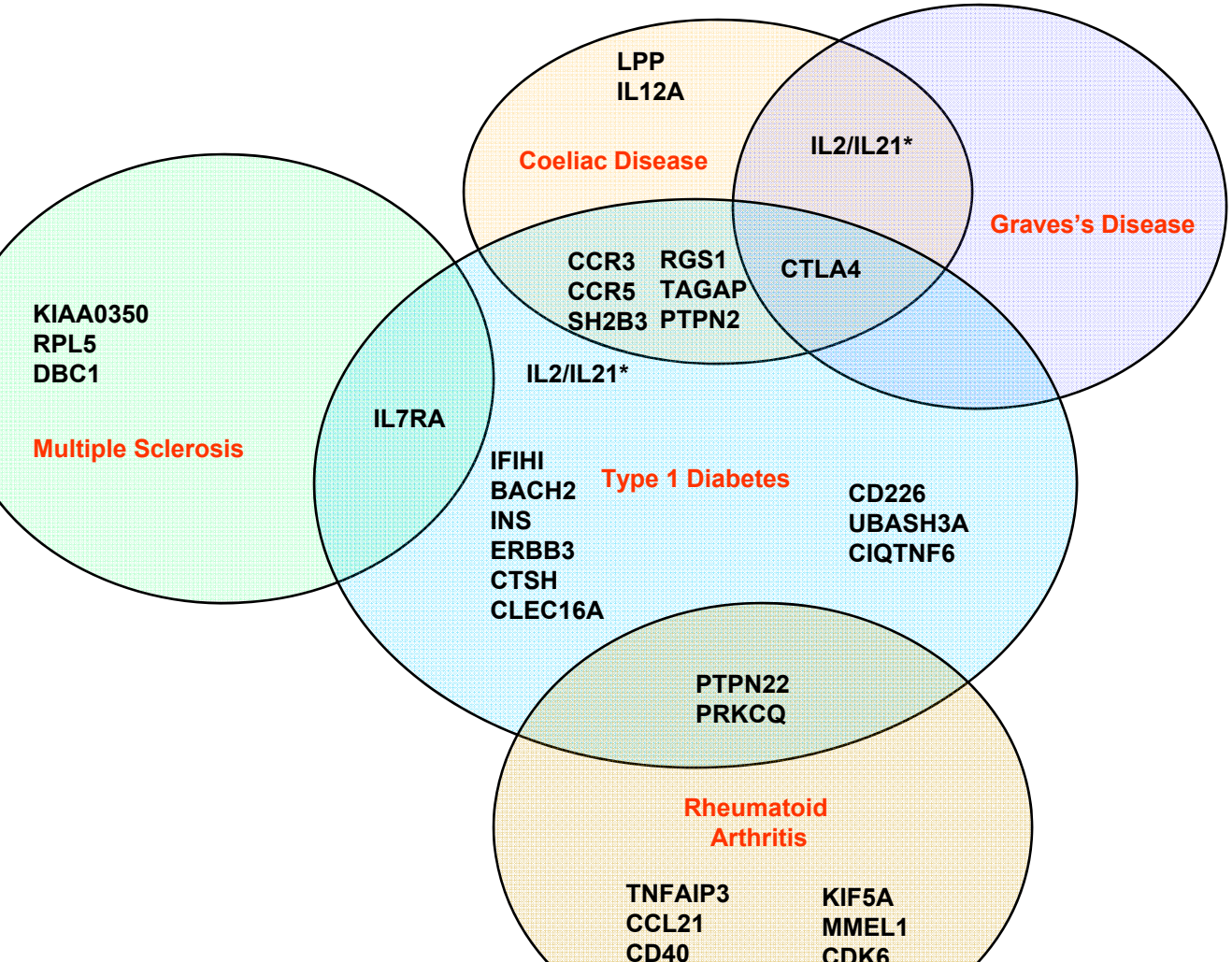
Centre for Gastroenterology, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Whitechapel, London E1 2AT, UK



Abnormal Body Composition Phenotypes in Older Rheumatoid Arthritis Patients: Association With Disease Characteristics and Pharmacotherapies

JON T. GILES,[1] SHARI M. LING,[2] LUIGI FERRUCCI,[2] SUSAN J. BARTLETT,[1] ROSS E. ANDERSEN,[1] MARILYN TOWNS,[1] DENIS MULLER,[2] KEVIN R. FONTAINE,[1] AND JOAN M. BATHON[1]

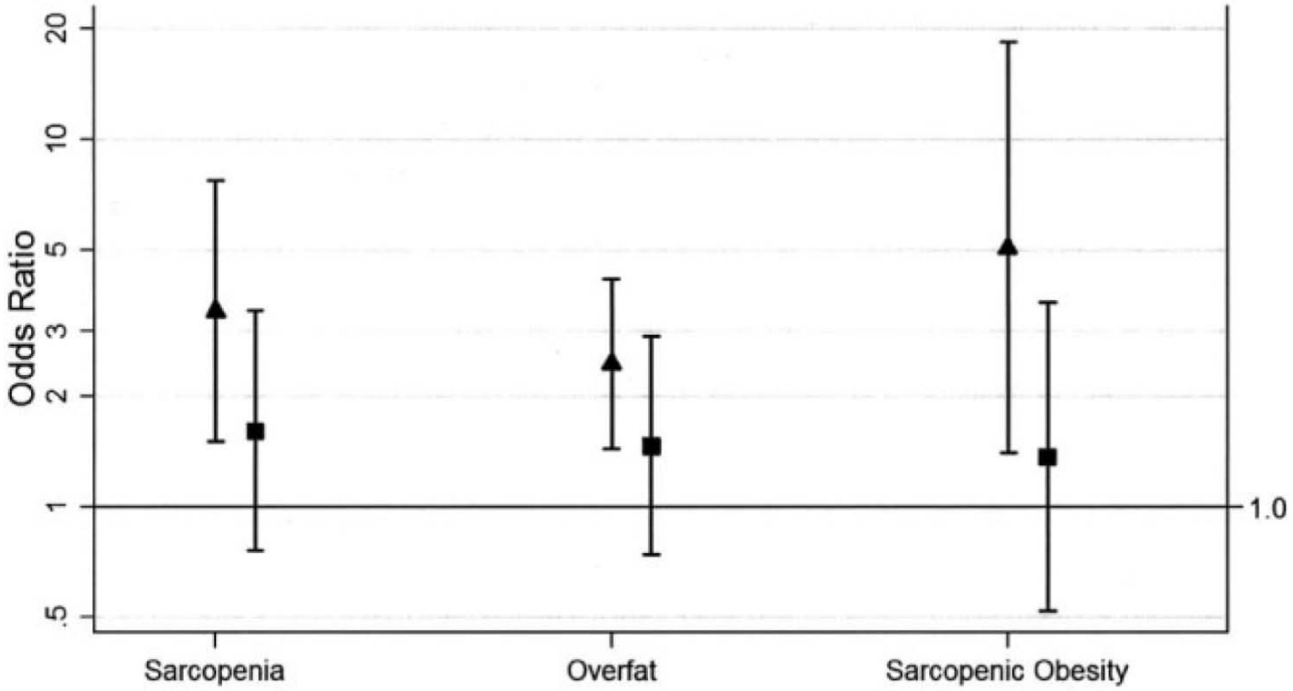
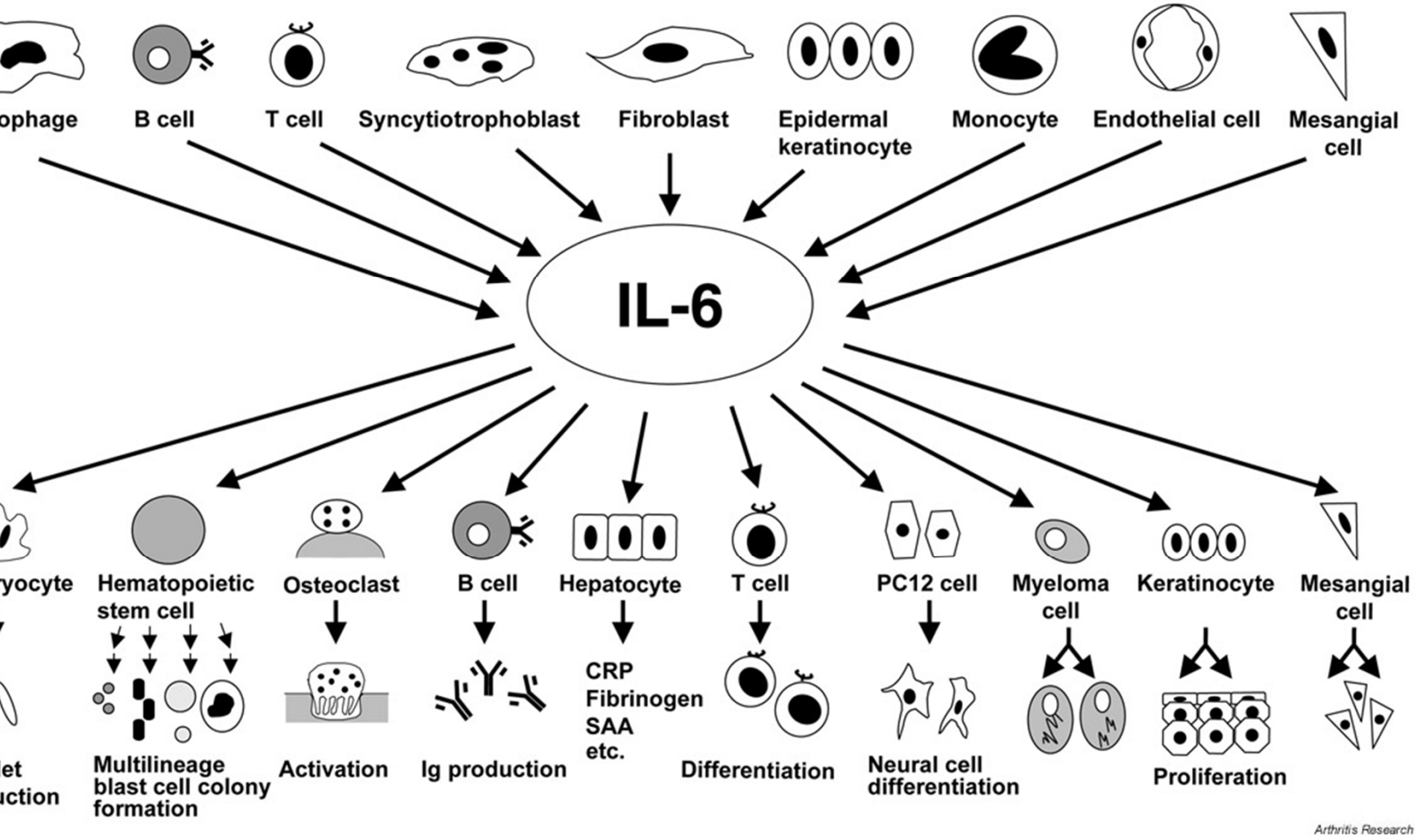


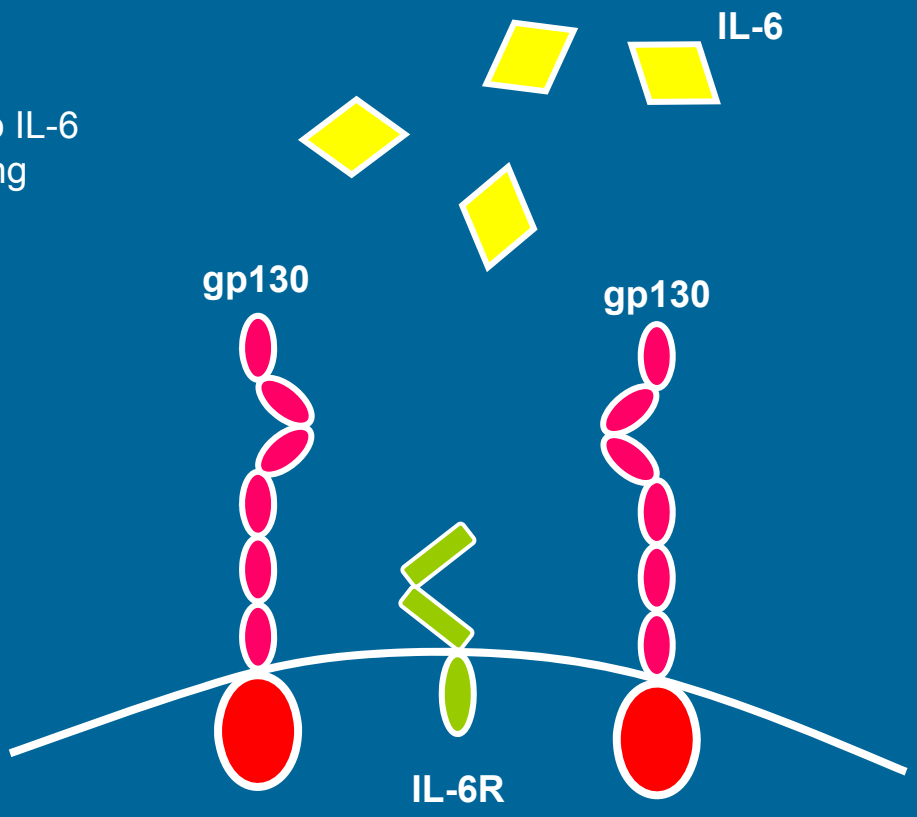
Figure 1. Adjusted odds of sarcopenia, overfat, and sarcopenic obesity for rheumatoid arthritis (RA) subjects compared with non-RA controls, by sex. Adjusted for current smokers and menopausal women. Values are shown as the odds ratio (95% confidence interval). Solid triangles = female; solid squares = male.

-producing cells and biological activities of IL-6.



IL-6 Signaling

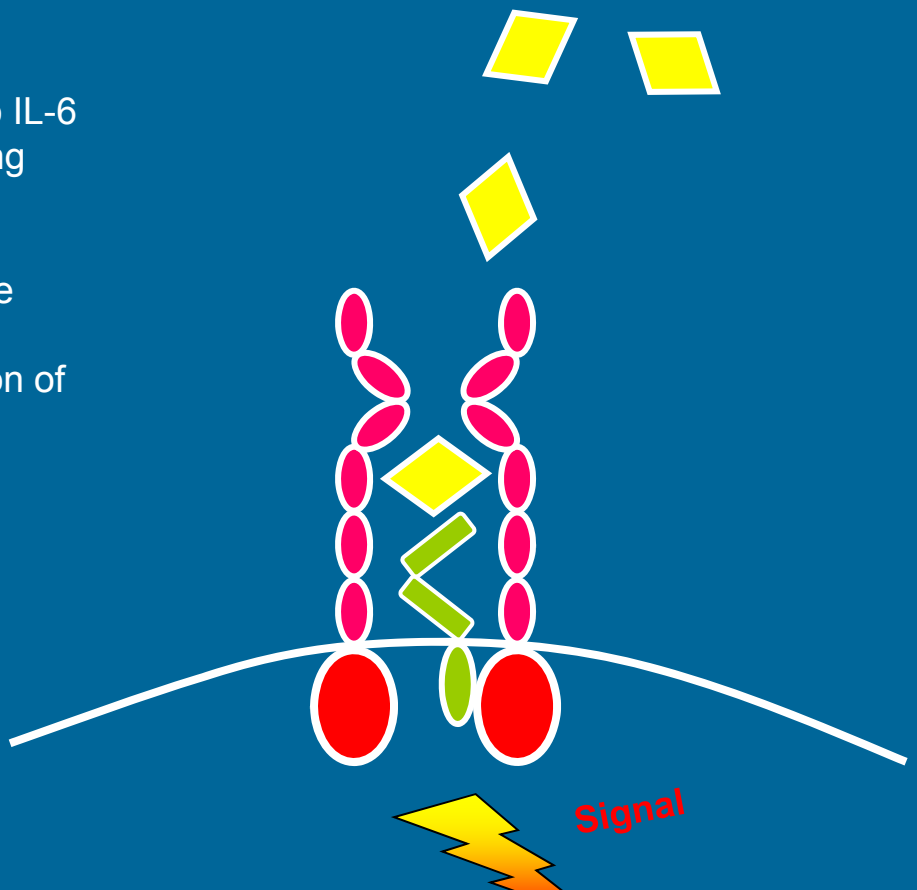
-6R is present in cells sensible to IL-6
sociated with a signal-transducing
embrane protein gp130



IL-6 Signaling

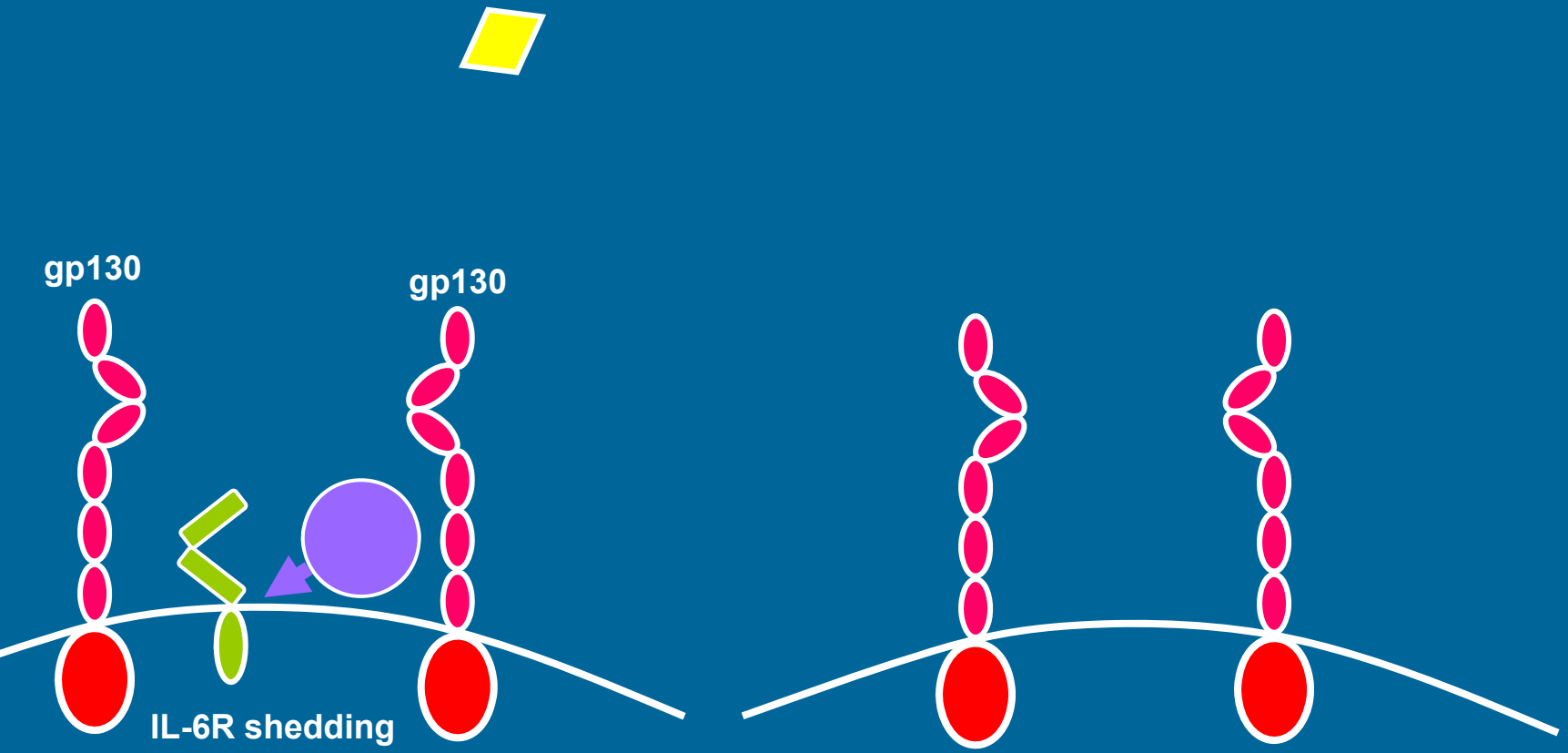
-6R is present in cells sensible to IL-6
sociated with a signal-transducing
embrane protein gp130

e complex IL-6/IL-6R induces the
merization of the gp130 signal-
nsducing membrane and initiation of
gnaling



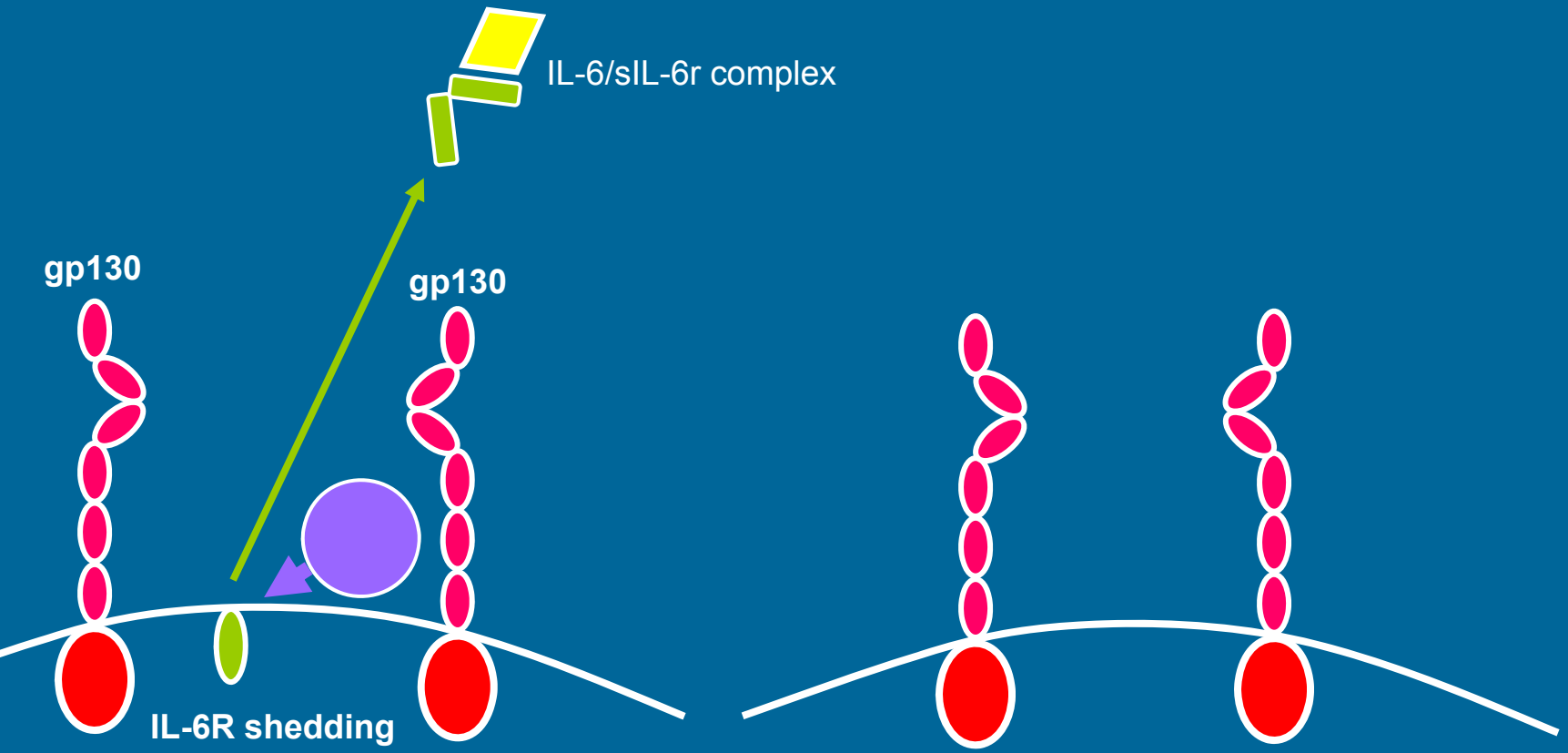
e IL-6r is shedded from the membrane of
e IL-6 sensible cell and becomes sIL-6r

IL-6 Transsignaling



e IL-6r is shedded from the membrane of
e IL-6 sensible cell and becomes sIL-6r
soluble IL-6/sIL-6r complex is created

IL-6 Transsignaling

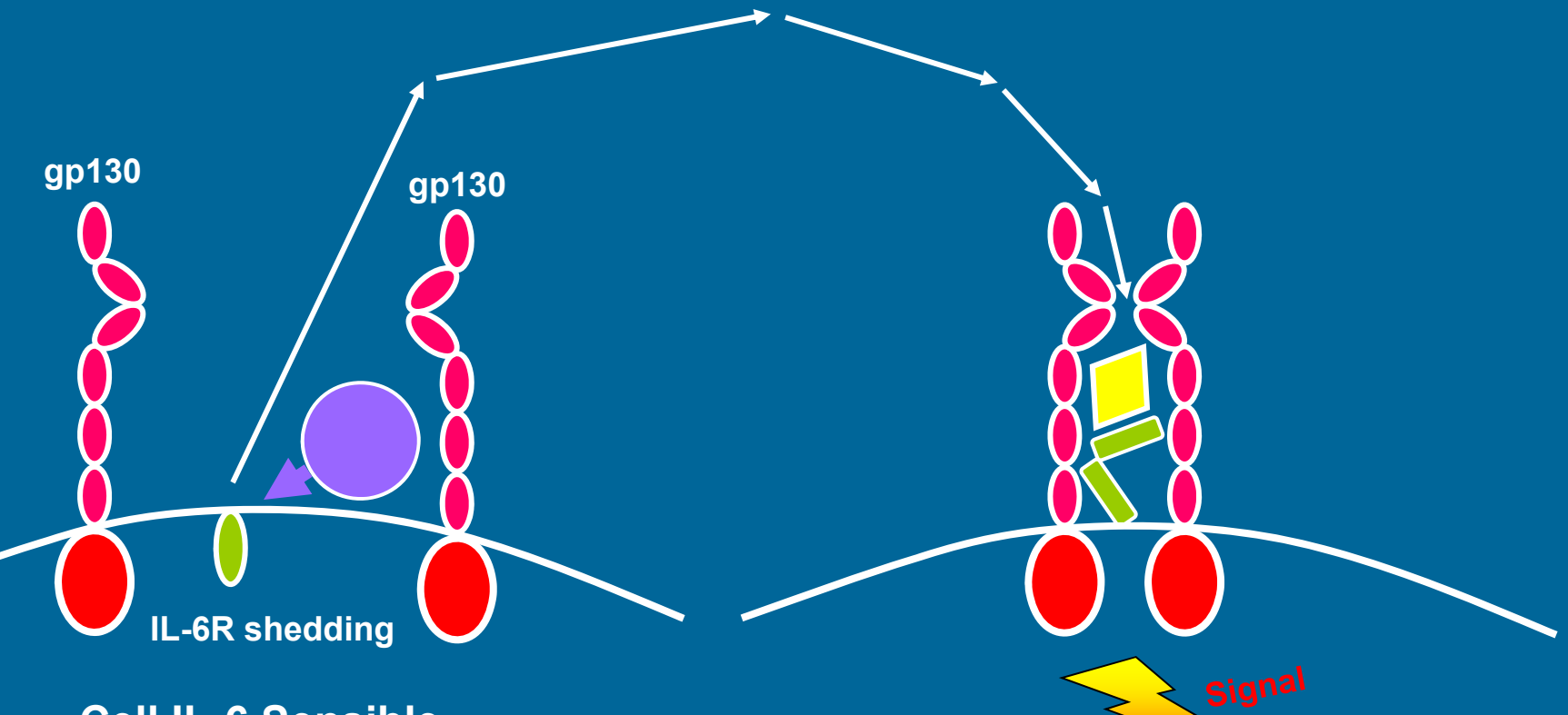


IL-6 Transsignaling

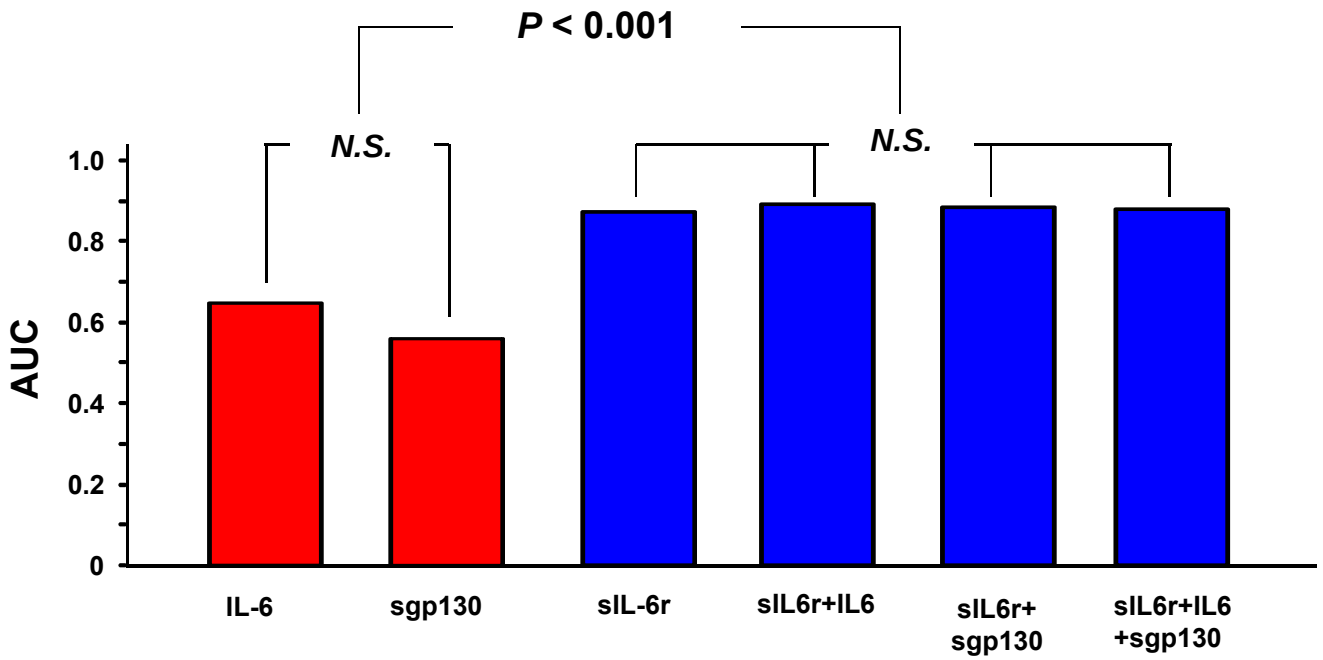
e IL-6r is shedded from the membrane of
e IL-6 sensible cell and becomes sIL-6r

soluble IL-6/sIL-6r complex is created

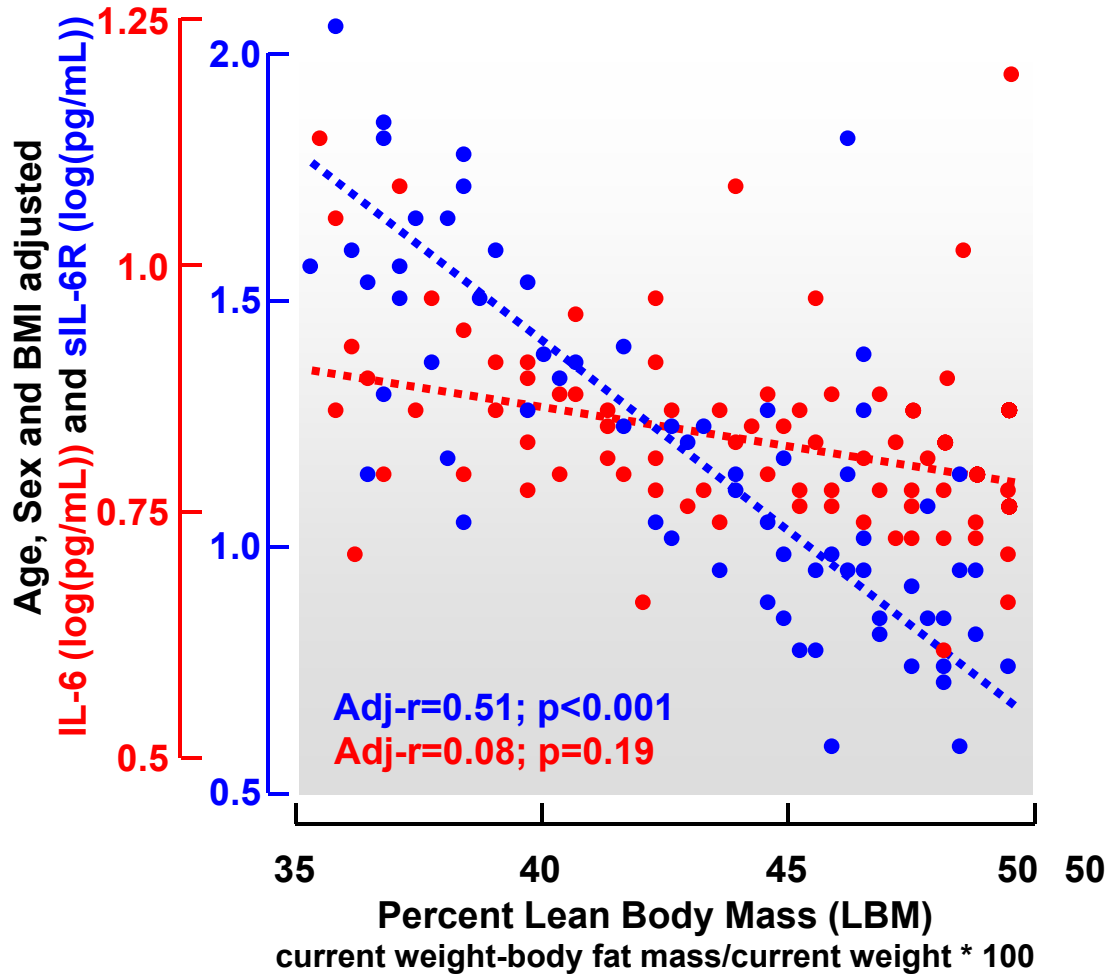
e IL-6/sIL-6r complex initiates gp130
merization of a cell type lacking IL-6R
pression and triggers cellular activation.



Discriminative Power for RA (n=136) vs. Age- and BMI-atched Controls (BLSA) for Different Inflammatory Markers The IL-6 Pathway



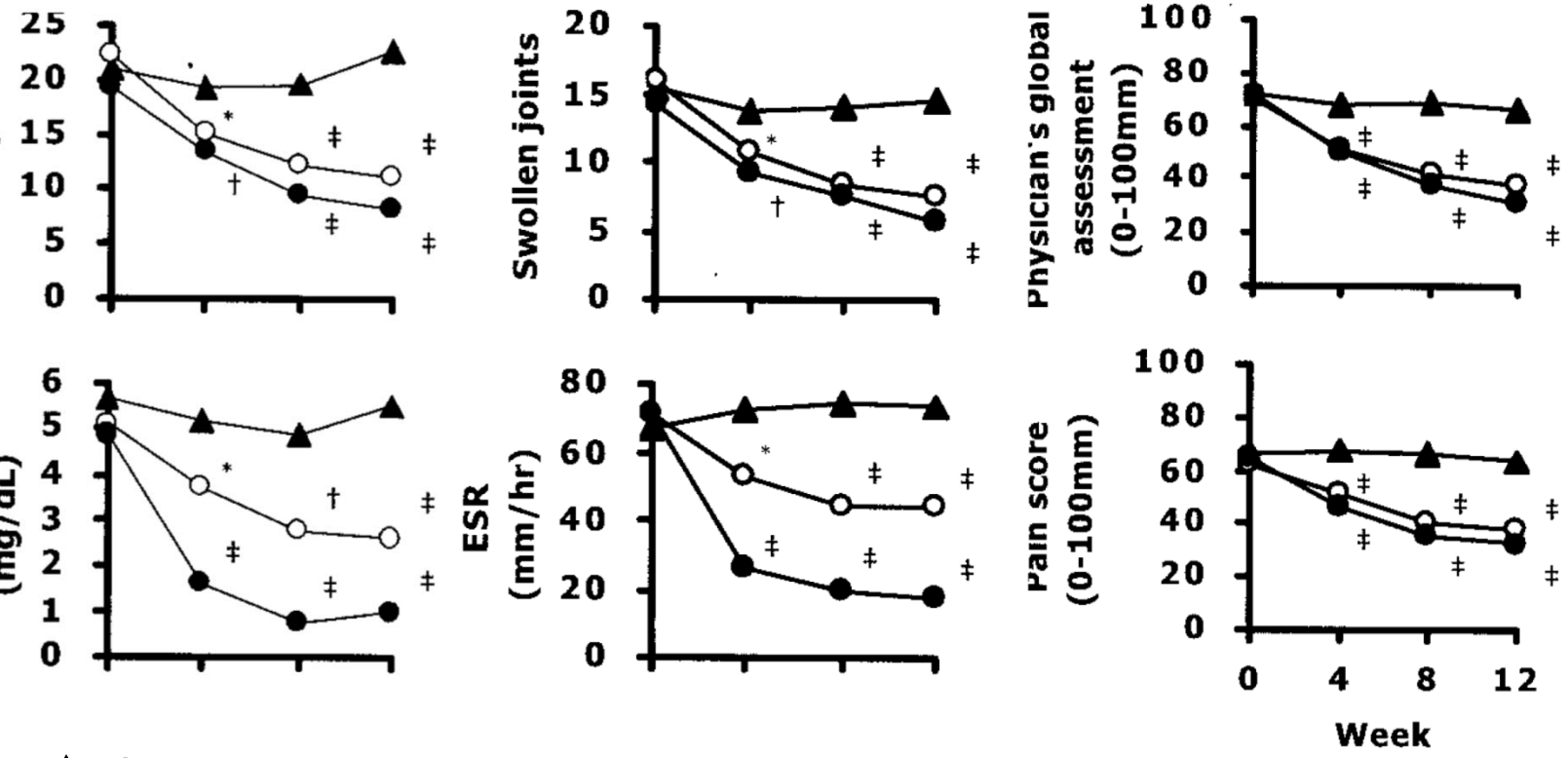
IL-6, sIL6r and Parameters of Body Composition in 136 RA Patients



Treatment of Rheumatoid Arthritis With Humanized Anti–Interleukin-6 Receptor Antibody

A Multicenter, Double-Blind, Placebo-Controlled Trial

Norihiro Nishimoto,[1] Kazuyuki Yoshizaki,[1] Nobuyuki Miyasaka,[2] Kazuhiko Yamamoto,[3] Shinichi Kawai,[4] Tsutomu Takeuchi,[5] Jun Hashimoto,[1] Junichi Azuma,[1] and Tadamitsu Kishimoto[1]



▲ Controls

○ 4 mg/kg humanized anti–interleukin-6 receptor antibody (MRA)

● 8 mg/kg humanized anti–interleukin-6 receptor antibody (MRA)

Serum Interleukin-6 Receptor in Polymyalgia Rheumatica: A Potential Marker of Relapse/Recurrence Risk

LIA PULSATELLI,[1] LUIGI BOIARDI,[2] ELETTRA PIGNOTTI,[1] PAOLO DOLZANI,[1] TANIA SILVESTRI,[1] PIERLUIGI MACCHIONI,[2] FABRIZIO CANTINI,[3] CARLO SALVARANI,[2] ANDREA FACCHINI,[4] AND RICCARDO MELICONI[4]

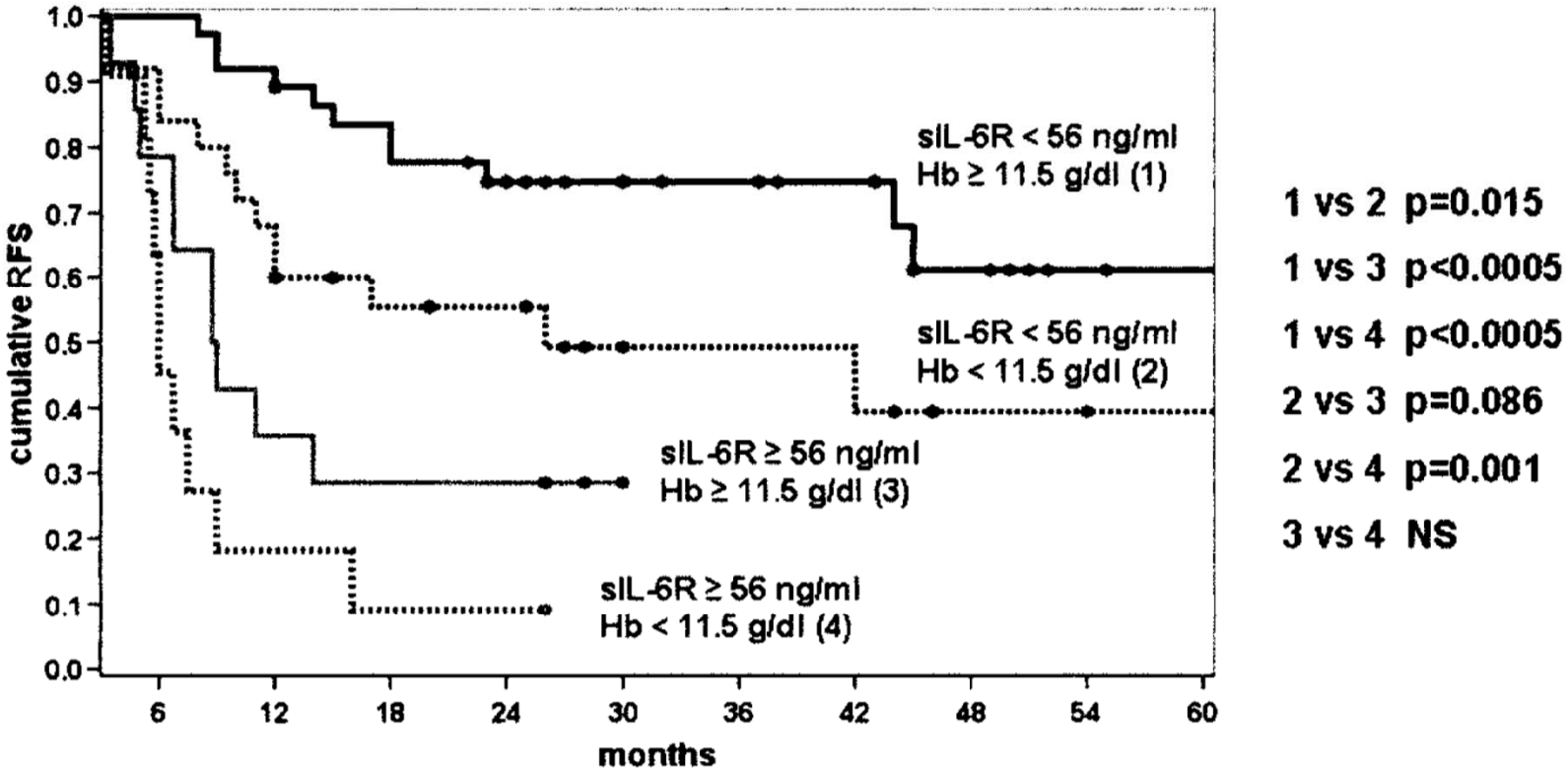


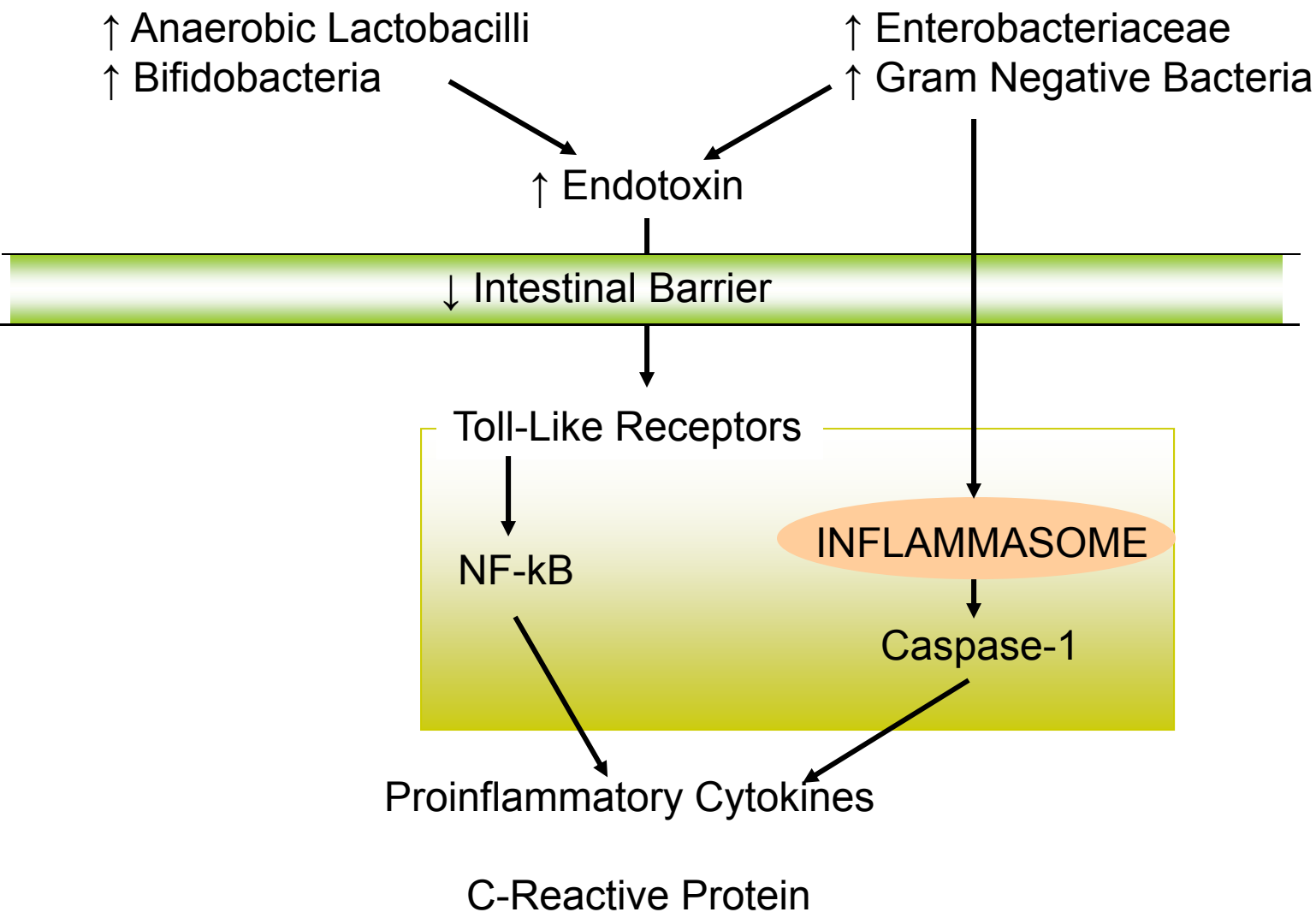
Figure 3. Kaplan-Meier curve. Cumulative rate of relapse-free survival (RFS) for the different subsets of patients with polymyalgia rheumatica divided according to both soluble interleukin-6 receptor (sIL-6R) levels and hemoglobin (Hb) values at diagnosis.


THE
NOT SO SECRET
KILLER
The surprising link between INFLAMMATION and
HEART ATTACKS, CANCER, ALZHEIMER'S and other diseases

The following only used eventually to address questions.

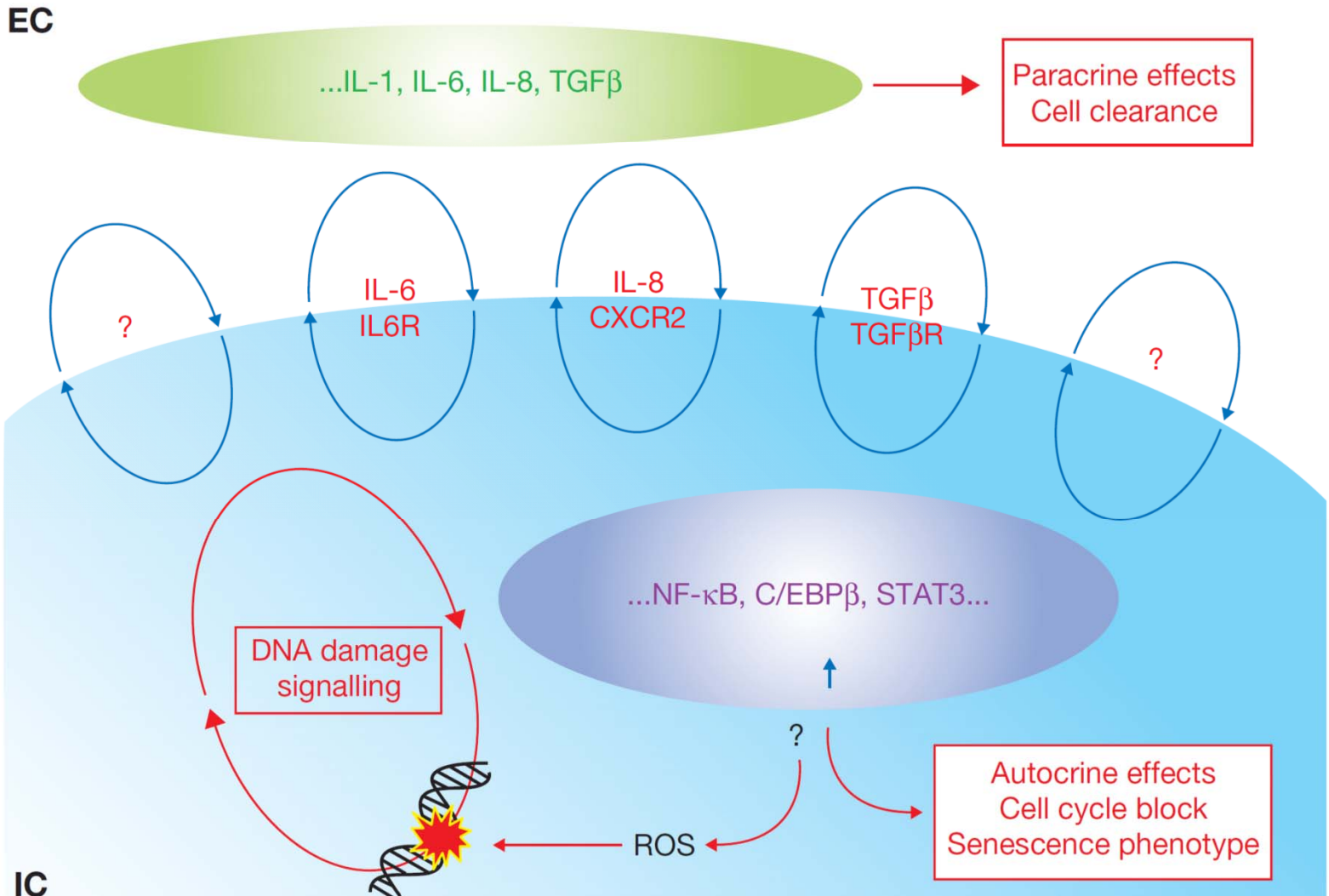
inflammatory status of the elderly: The intestinal contribution

Eduardo J. Schiffrin [a], John E. Morley [b], Anne Donnet-Hughes [a], Yves Guigoz [a,*]



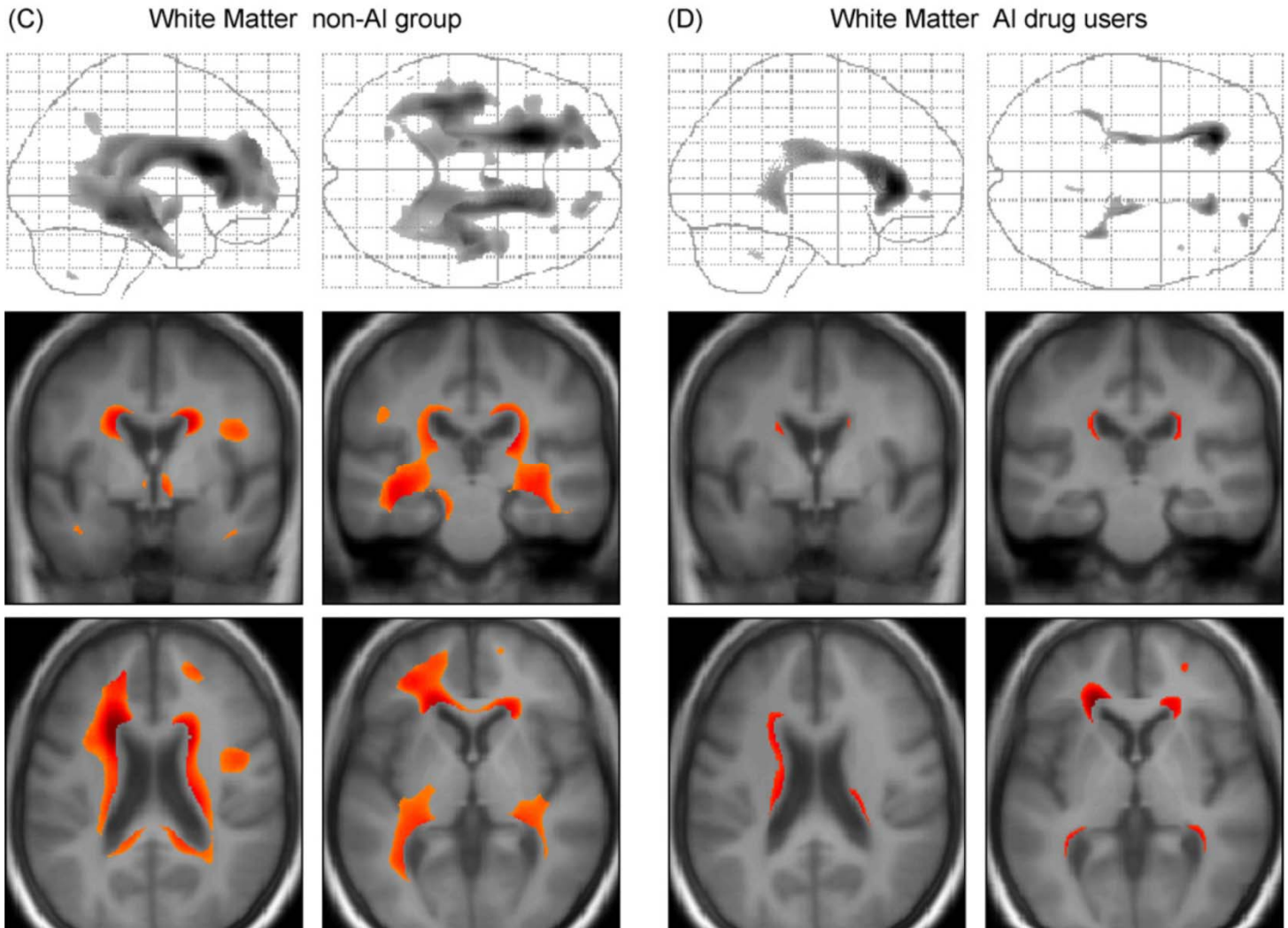
Cytokine loops driving senescence

iri Bartek, Zdenek Hodny and Jiri Lukas



Anti-inflammatory drugs reduce age-related decreases in brain volume in cognitively normal older adults

K. Walther[a], B.B. Bendlin[b,c], E.L. Glisky[a], T.P. Trouard[d], J.R. Lisse[e], J.O. Posever[f], L. Ryan[a,*]



Cytokines sing the blues: inflammation and the pathogenesis of depression

Charles L. Raison, Lucile Capuron and Andrew H. Miller