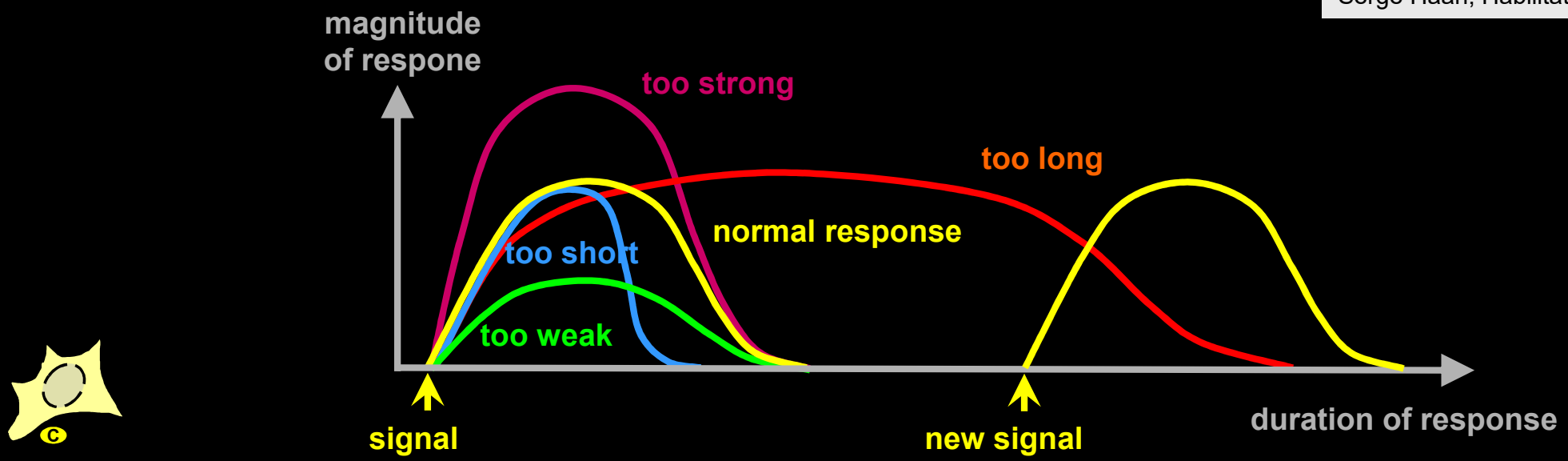
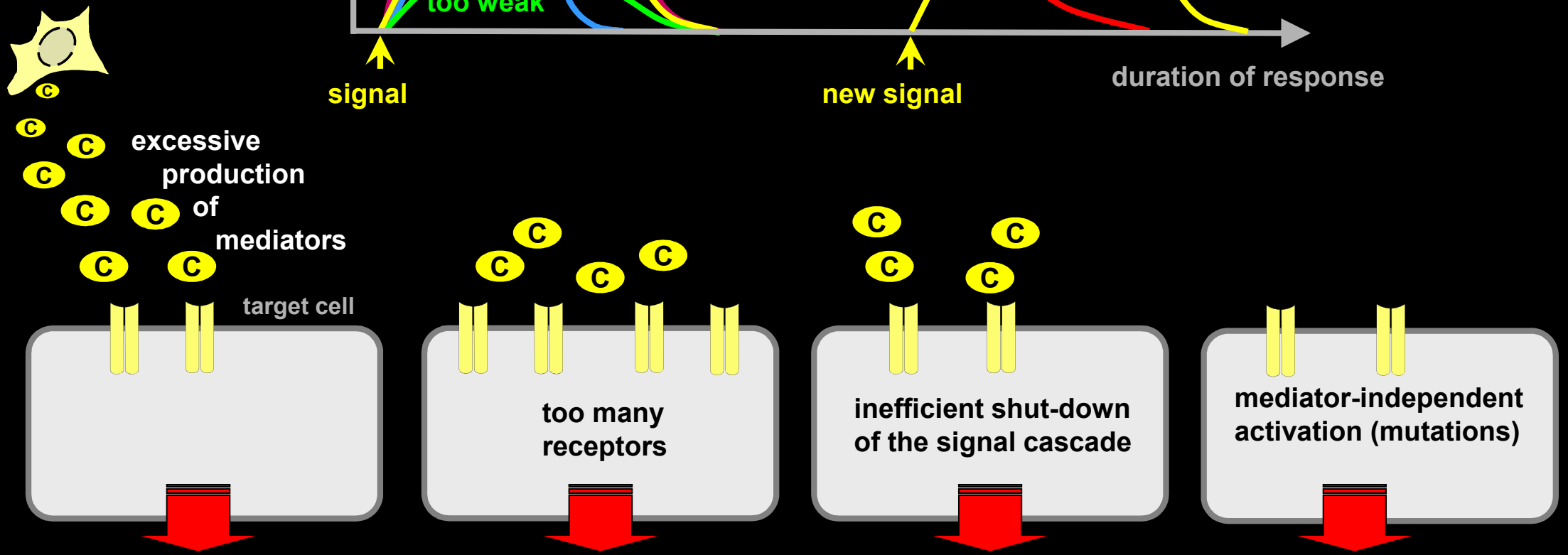
PART 2
Regulation of IL-6 Signaling

The correct response of the target cell to cytokines is crucial

Serge Haan, Habilitation 2005





overshooting response of the target cell

→ possible disease development

2003

REVIEW ARTICLE

Principles of interleukin (IL)-6-type cytokine signalling and its regulation[1]

Peter C. HEINRICH[2], Iris BEHRMANN, Serge HAAN, Heike M. HERMANNS, Gerhard MÜLLER-NEWEN and Fred SCHAPER

Institut für Biochemie, RWTH Aachen, Universitätsklinikum, Pauwelsstrasse 30, D-52074 Aachen, Germany

1756 citations (2018)

The IL (interleukin)-6-type cytokines IL-6, IL-11, LIF (leukaemia inhibitory factor), OSM (oncostatin M), ciliary neurotrophic factor, cardiotrophin-1 and cardiotrophin-like cytokine are an important family of mediators involved in the regulation of the acute-phase response to injury and infection. Besides their functions in inflammation and the immune response, these cytokines play also a crucial role in haematopoiesis, liver and neuronal regeneration, embryonal development and fertility. Dysregulation of IL-6-type cytokine signalling contributes to the onset and maintenance of several diseases, such as rheumatoid arthritis, inflammatory bowel disease, osteoporosis, multiple sclerosis and various types of cancer (e.g. multiple myeloma and prostate cancer). IL-6-type cytokines exert their action via the signal transducers gp (glycoprotein) 130, LIF receptor and OSM receptor leading to the activation of the JAK/STAT (Janus kinase/signal transducer and activator of transcription) and MAPK (mitogen-activated protein kinase) cascades. This review focuses on recent progress in the understanding of the molecular mechanisms of IL-6-type cytokine signal transduction. Emphasis is put on the termination and modulation of the JAK/STAT signalling pathway mediated by tyrosine phosphatases, the SOCS (suppressor of cytokine signalling) feedback inhibitors and PIAS (protein inhibitor of activated STAT) proteins. Also the cross-talk between the JAK/STAT pathway with other signalling cascades is discussed.

Key words: cytokine signalling, glycoprotein 130 (gp 130) interleukin-6 (IL-6), Janus kinase (JAK), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT).

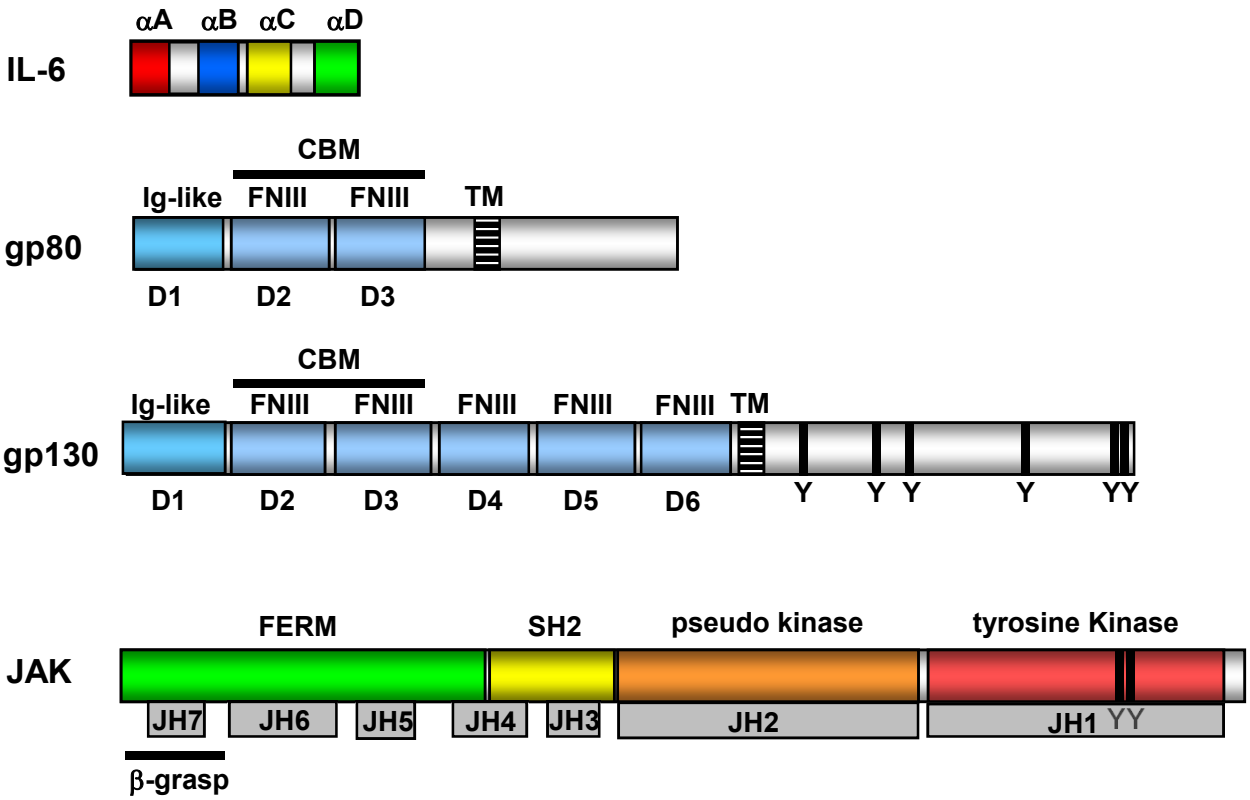
Outline: Interleukin-6 signal transduction and its regulation

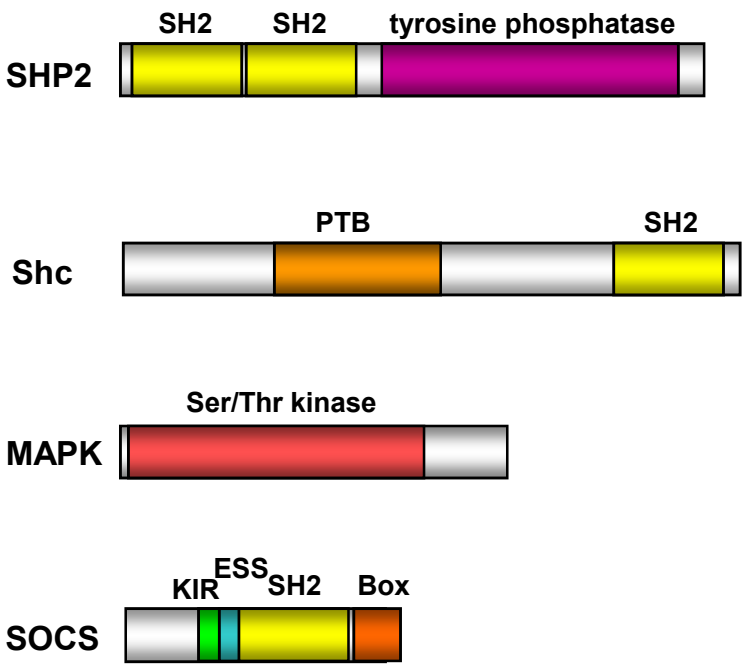
Part 1: **Molecular mechanisms of IL-6 signal transduction**

Part 2: **Regulation of IL-6 signal transduction**

- **Half-lifes of the signaling components**
- Polar expression of IL-6 receptor-α (gp80)
- IL-6 receptor-α shedding
- Internalization of the ligand/IL-6 receptor complex (desensitisation)
- Phosphotyrosine-phophatase SHP2 deactivates receptors, JAKs and STAT3
- SOCS proteins (suppressors of cytokine signaling) are feedback inhibitors
- Protein inhibitors of activated STATs (PIAS)
- Cross-talks between JAK/STAT signaling and proinflammatory cytokines (IL-1, TNFα)
  - STAT3 and NF- κB compete for an overlapping response element
  - IL-1 stabilizes SOCS3-mRNA
  - IL-1 accelerates the internalization of the signal transducer gp130

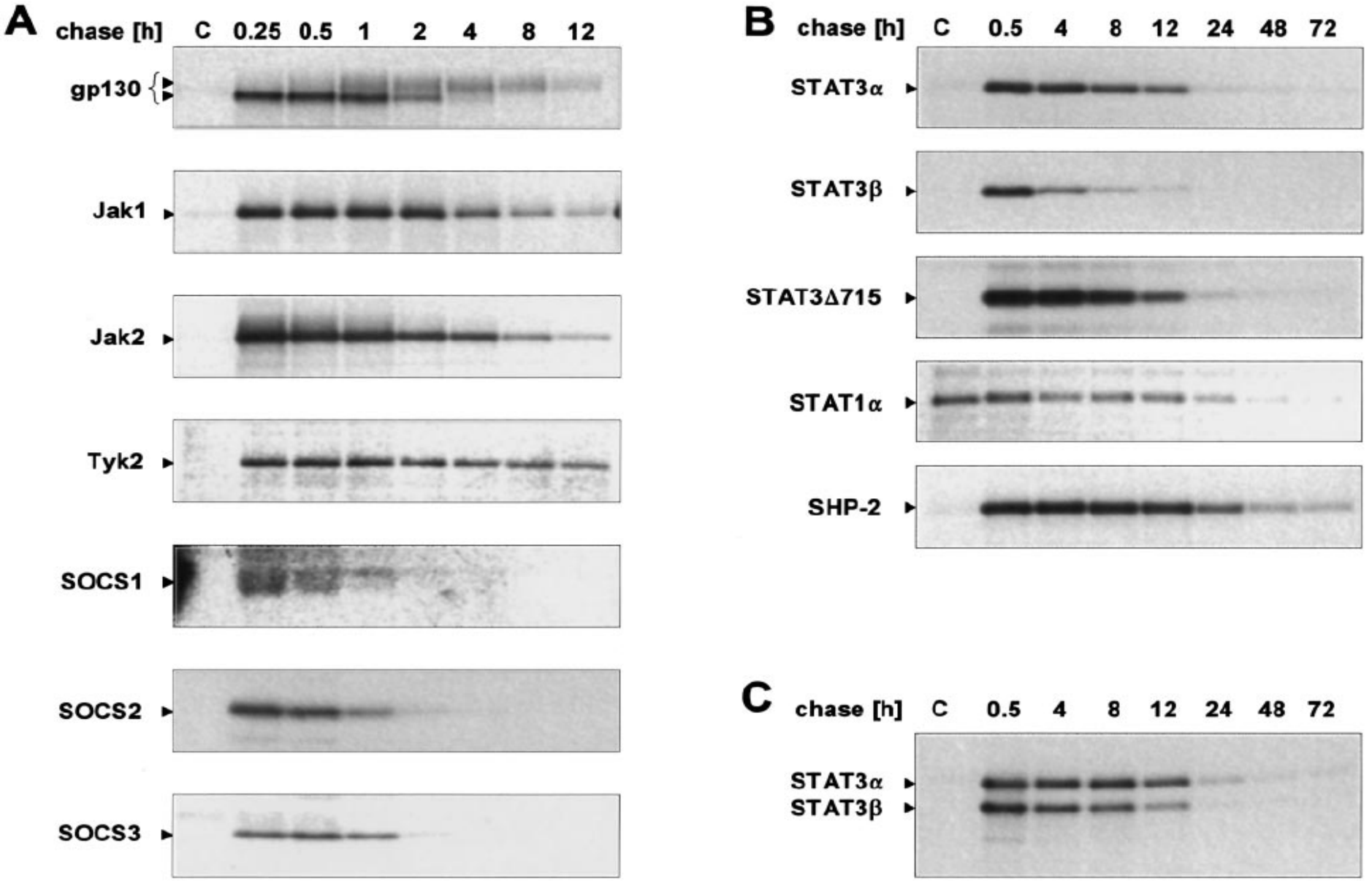
Structural organization of various IL-6-type cytokine signaling components





CBM	Cytokine Binding Module
ESS	Extended SH2 Subdomain
FERM	4.1/Ezrin/Radixin/Moesin
FNIII	Fibronectin type III
KIR	Kinase Inhibitory Region
PTB	Phosphotyrosine Binding
SH2	Src Homology 2
TM	Transmembrane

Half-lifes of proteins involved in IL-6-type cytokine signaling



COS-7 cells were pulse-labelled with [^{35}S]methionine/cysteine and chased for the times indicated (A, 0.25±12 h; B and C, 0.5±72 h).

Calculated half-lifes of IL-6 signaling components

Protein	Half-life [h]
gp80 (IL-6Rα)	2.5
gp130	2.5
Jak1	3.2
Jak2	1.9
Tyk2	2.0
SOCS1	1.5
SOCS2	1.0
SOCS3	1.6

Protein	Half-life [h]
STAT3α	8.5
STAT3β	4.5
STAT3 Δ715	8.5
STAT1	16.0
SHP2	18.0-20.0

STAT3β is a splice variant of STAT3α lacking the 55 C-terminal amino acids which are substituted by seven STAT3β-specific amino acids.

STAT3 Δ715 = STAT3 deletion mutant

Gerhartz et al. Eur. J. Biochem. 223, 265-274 (1994) **48 citations** (07/2022)

Siewert et al. Eur. J. Biochem. 265, 251-257 (1999) **93 citations** (07/2022)

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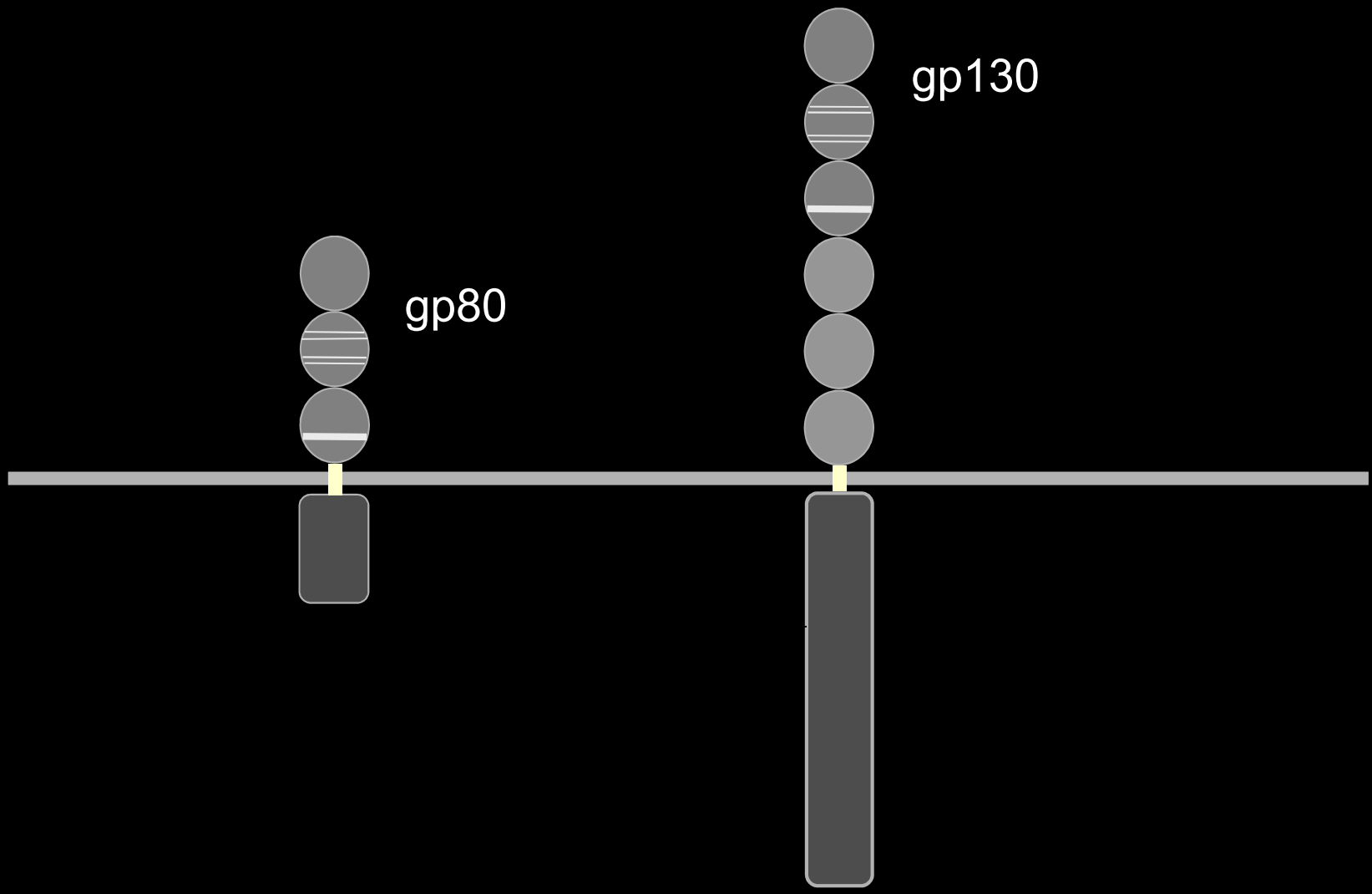
IL-6 receptor α chain:
What is the function of the cytoplasmic part?



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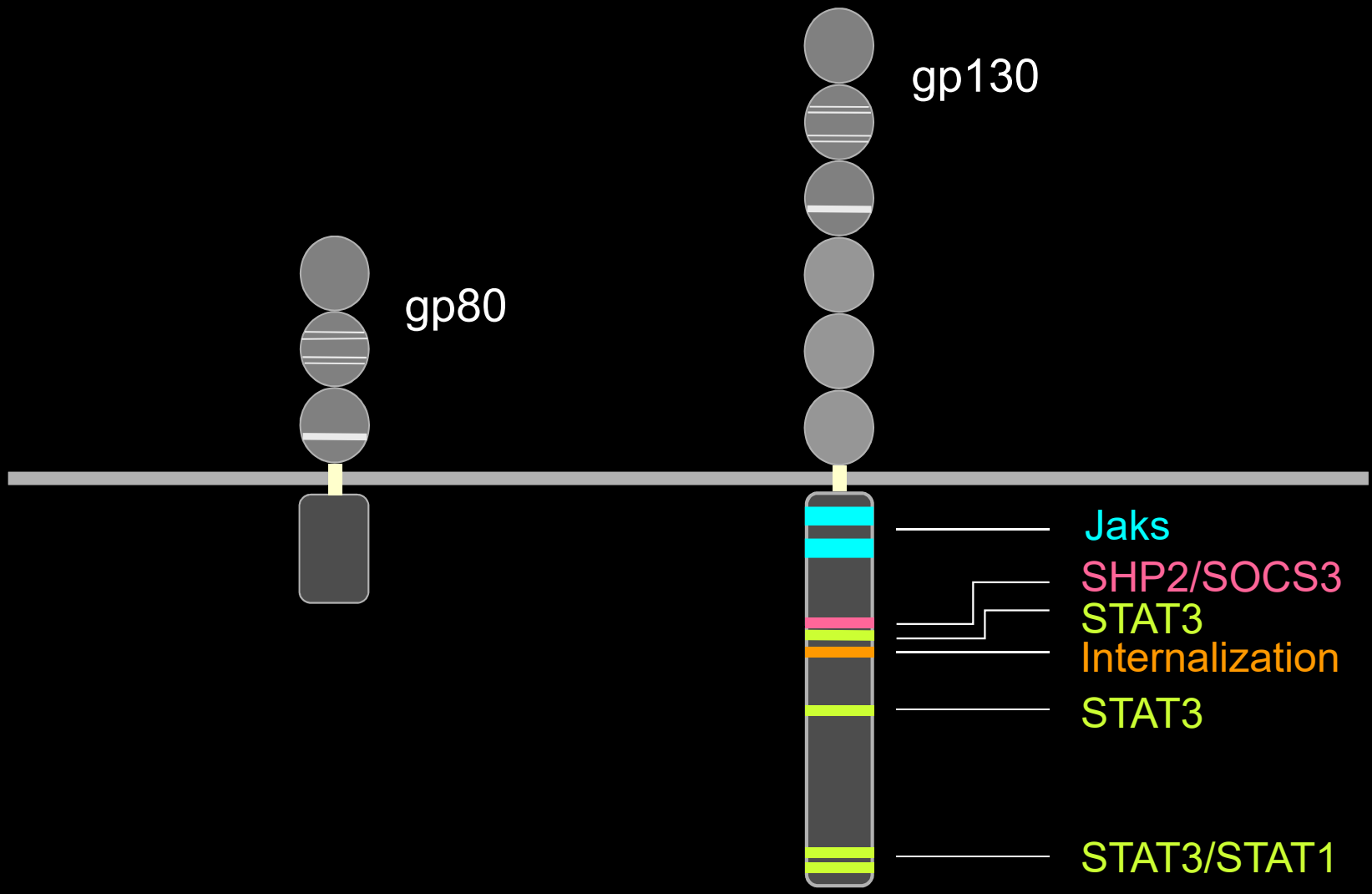

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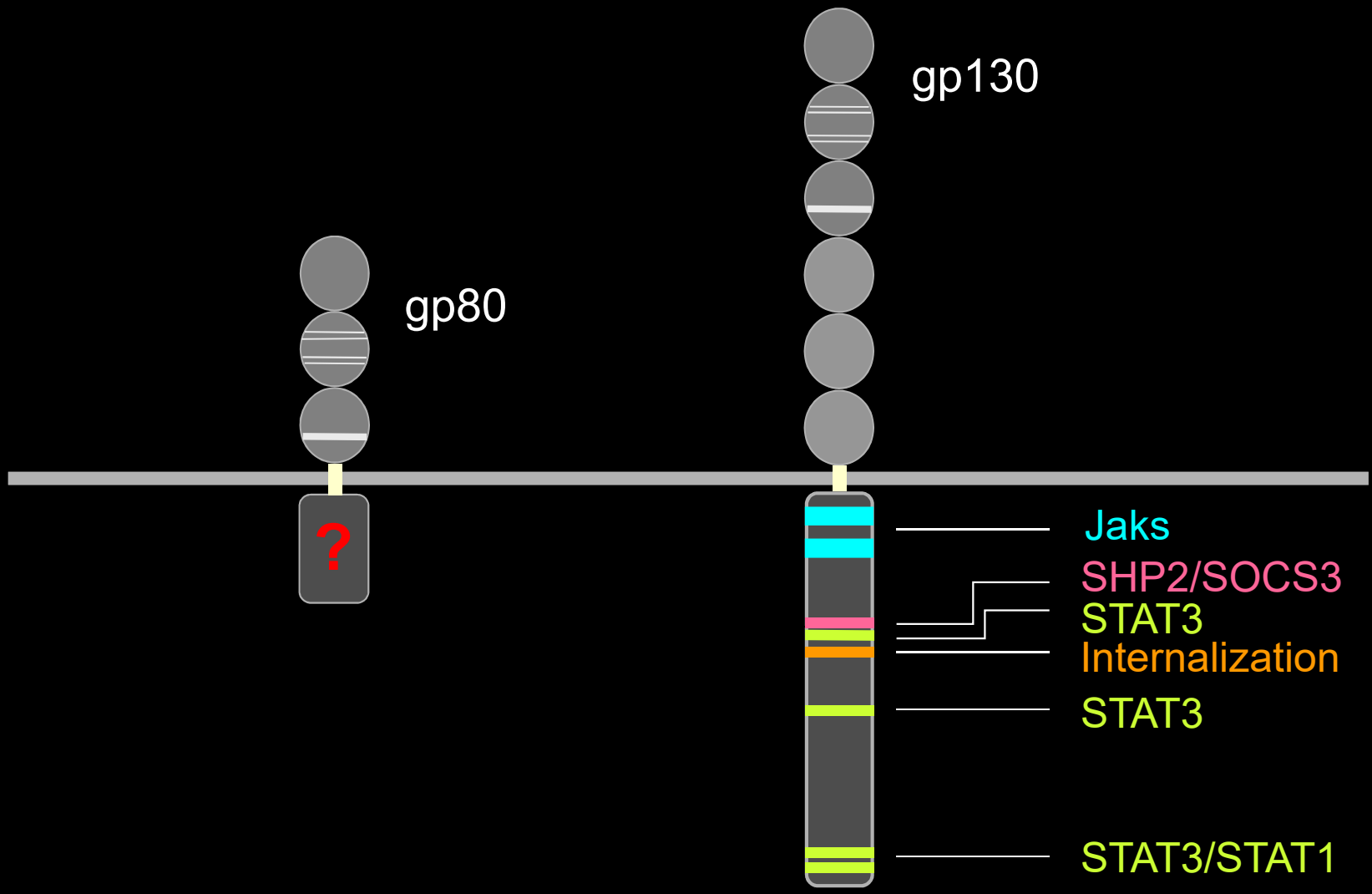


Journal of Cell Science 113, 3593-3602 (2000)
Printed in Great Britain © The Company of Biologists Limited 2000
JCS1532

The cytoplasmic domain of the interleukin-6 receptor gp80 mediates its basolateral sorting in polarized Madin-Darby canine kidney cells

Astrid S. Martens, Johannes G. Bode, Peter C. Heinrich and Lutz Graeve*

Institute of Biochemistry, Universitätsklinikum der Rheinisch-Westfälischen Technischen Hochschule, Pauwelsstrasse 30, 52074 Aachen, Germany

*Author for correspondence (e-mail: lutz.graeve@post.rwth-aachen.de)

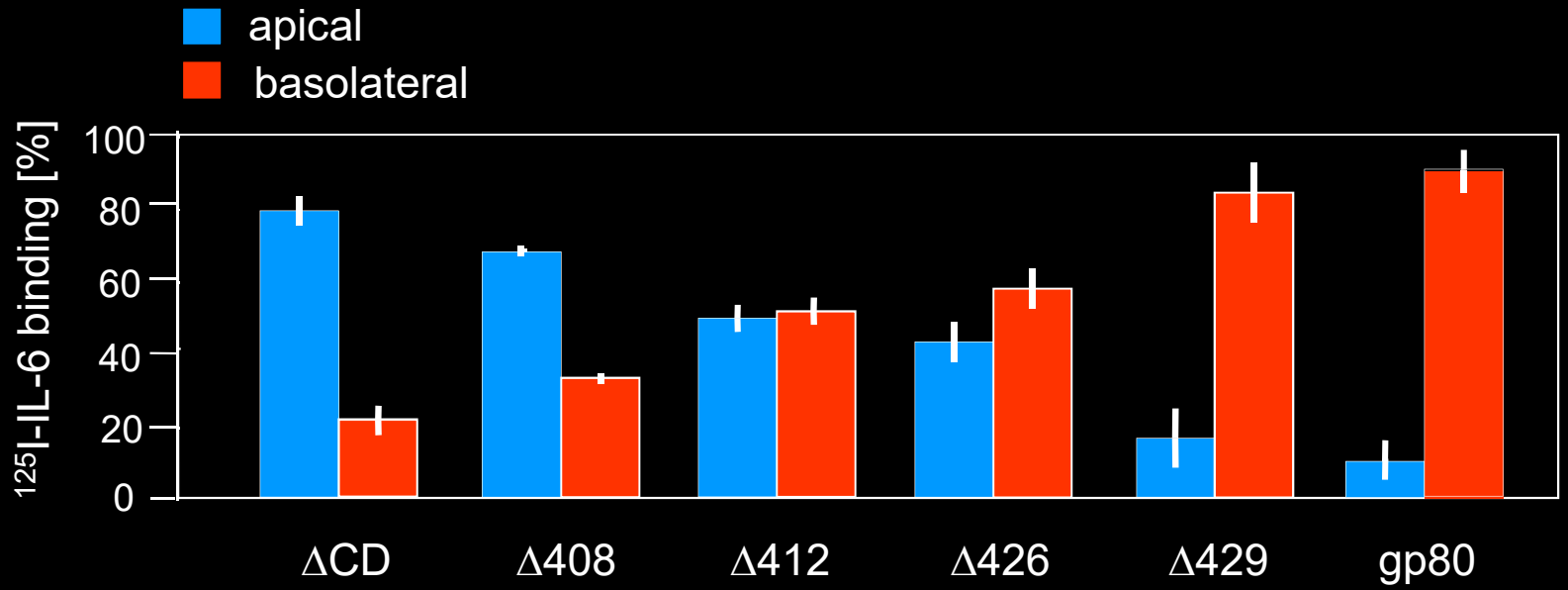
Accepted 1 August; published on WWW 4 October 2000


Astrid Martens


Johannes Bode

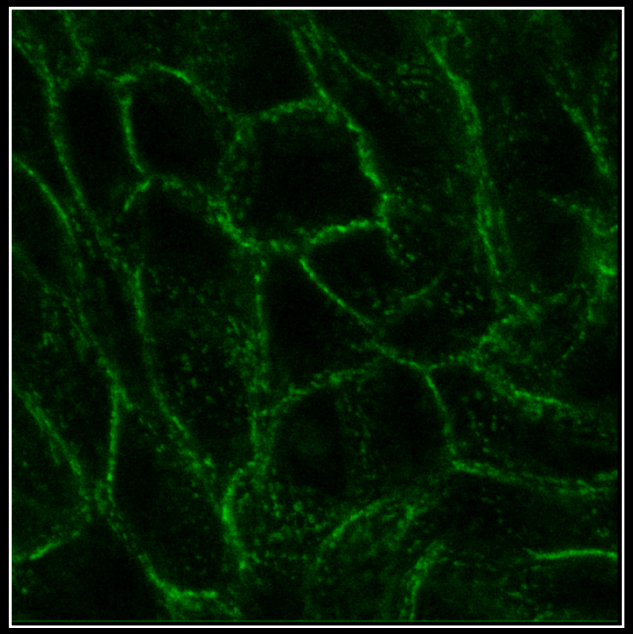

Lutz Graeve

Polar expression of gp80wt and deletion mutants in MDCK cells

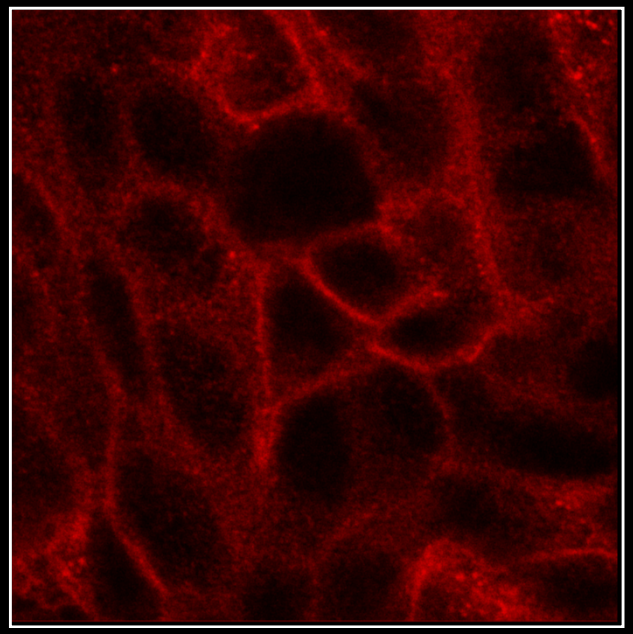


Basolateral expression of gp80wt in stably transfected MDCK cells

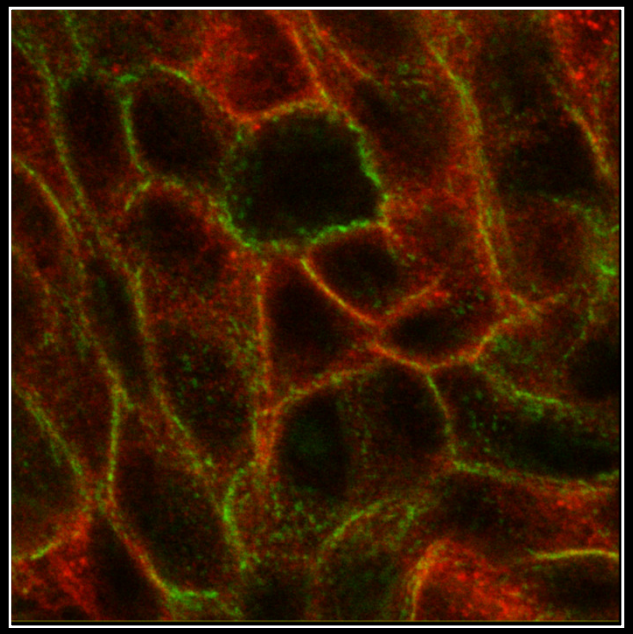
xy



basolateral marker



gp80wt



overlay

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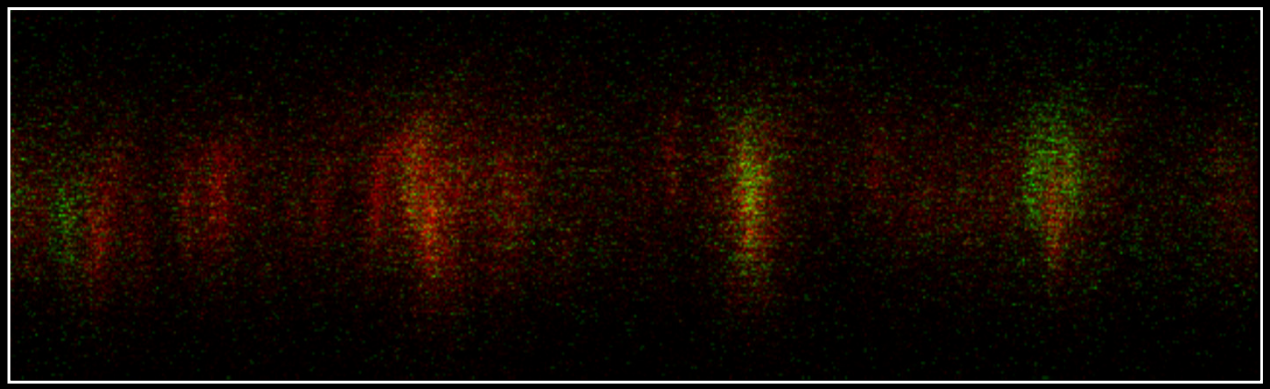
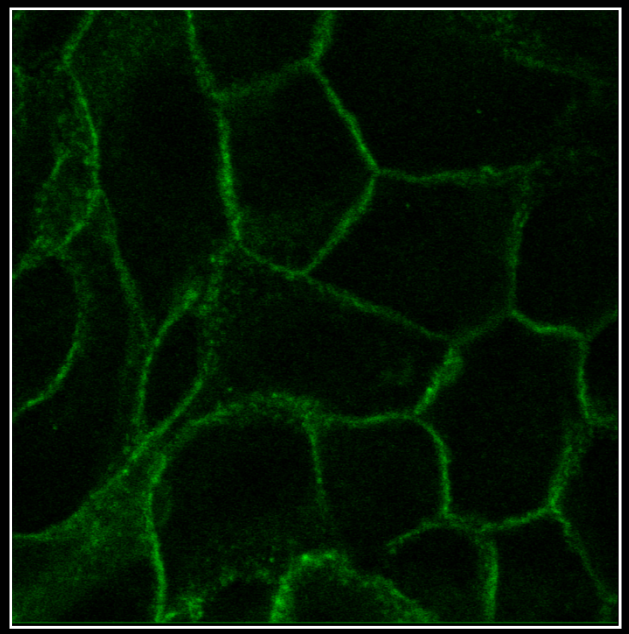
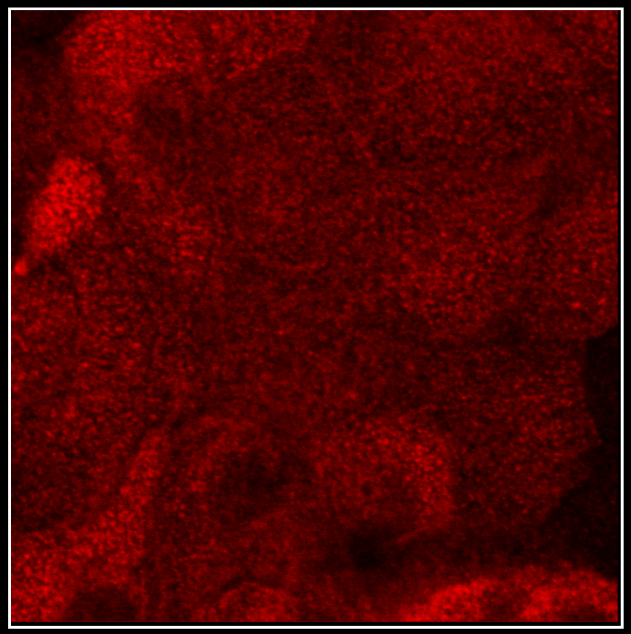


Apical expression of gp80ΔCD in stably transfected MDCK cells

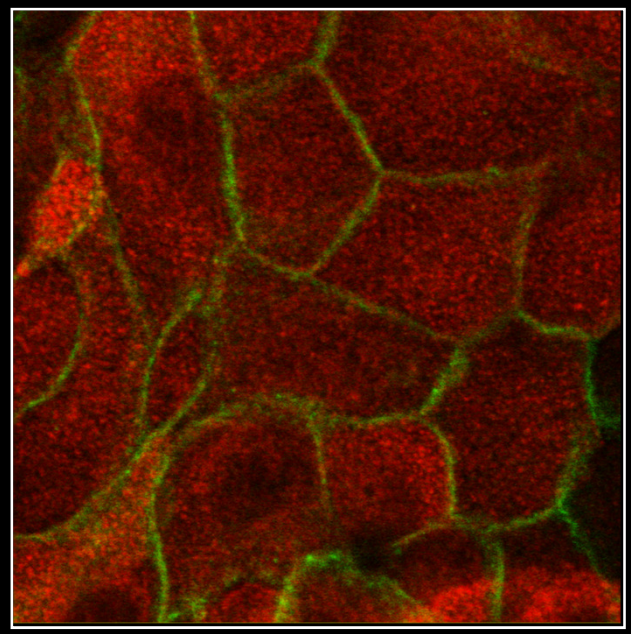
xy



basolateral marker



gp80ΔCD



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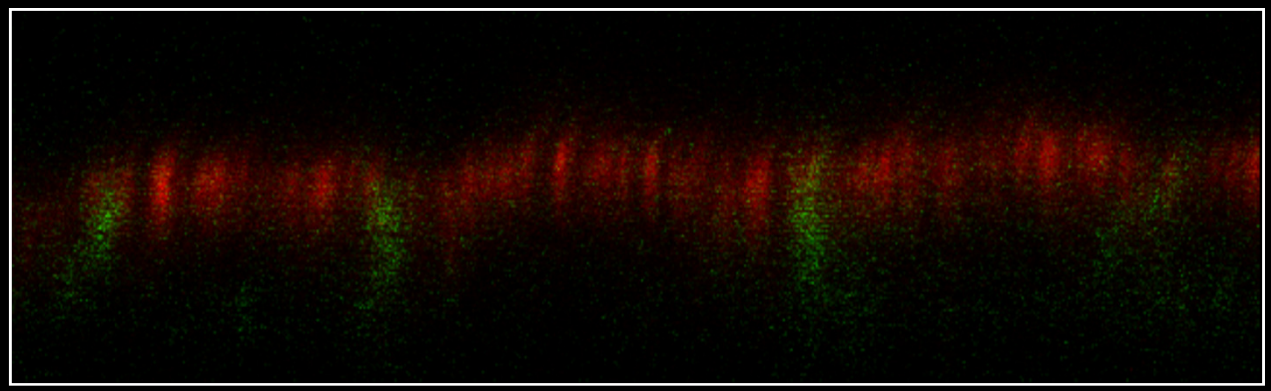

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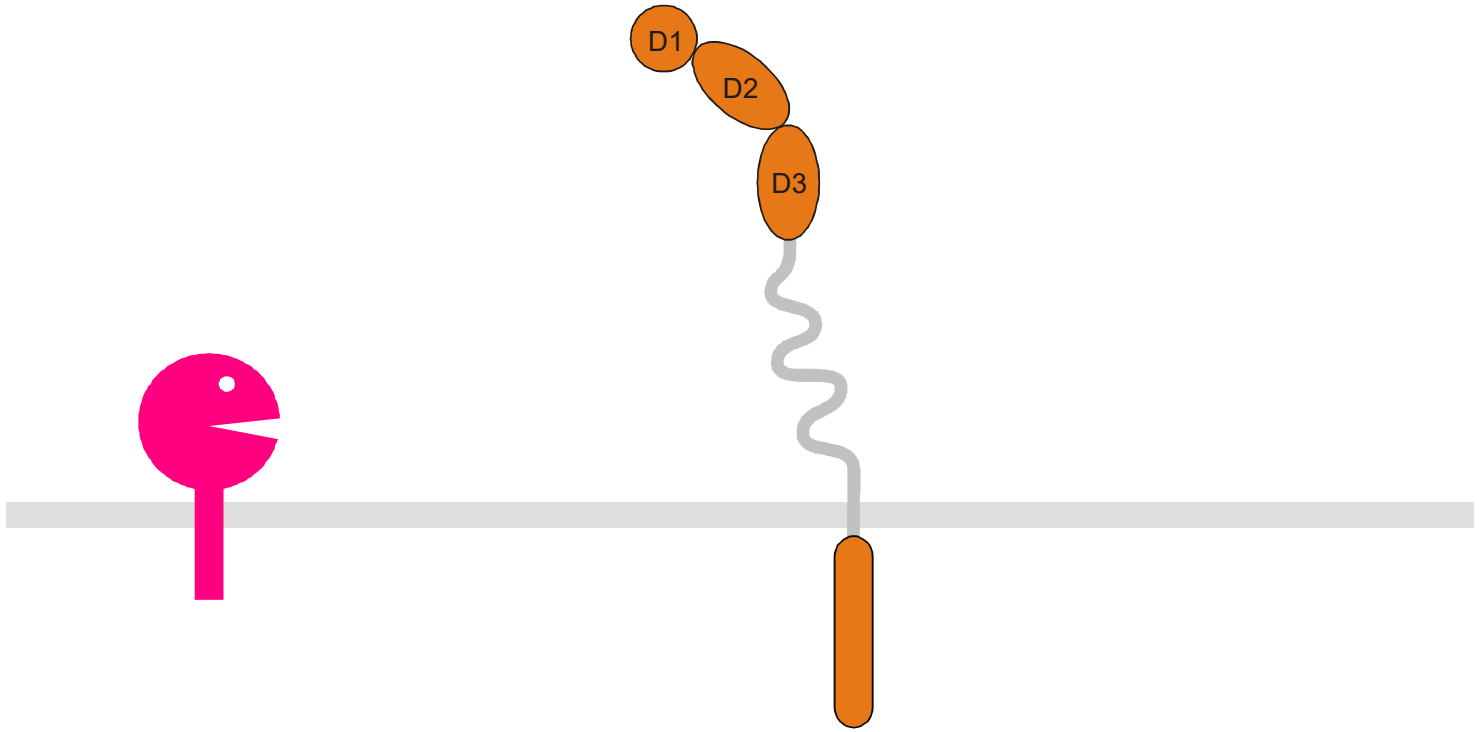
Regulation of IL-6 receptor-mediated signaling by limited proteolysis (shedding)



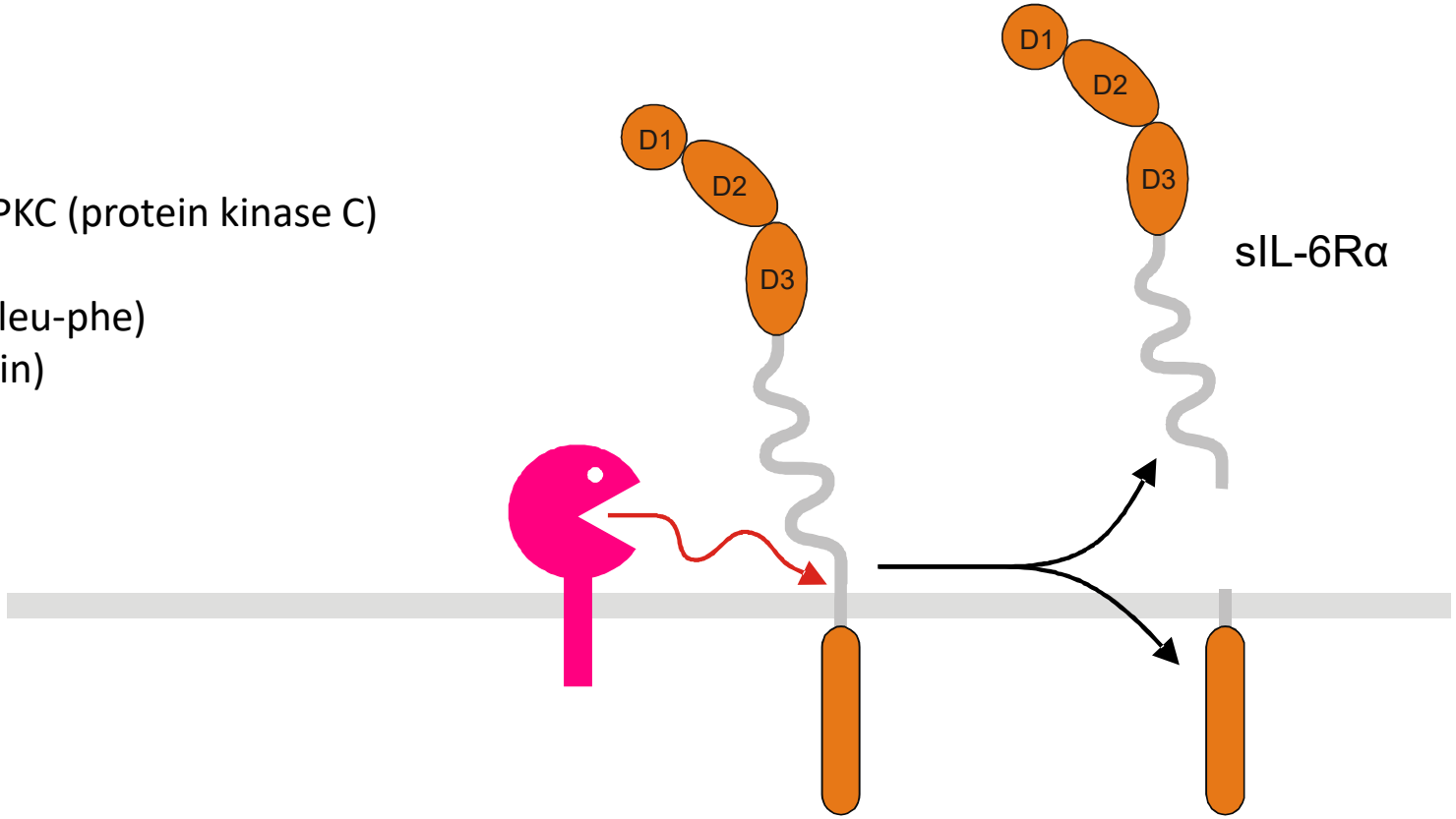
A membrane-bound protease:

ADAM17 (A Disintegrin and Metalloproteinase) ≡ TACE (TNFα converting enzyme) has been identified

Matthews et al. (2003), J Biol Chem 278, 38829-38839

Regulation of IL-6 receptor-mediated signaling by limited proteolysis (shedding)

- PMA (phorbolester)/PKC (protein kinase C)
- apoptosis
- FMLP (N-formyl-met-leu-phe)
- CRP (C-reactive protein)



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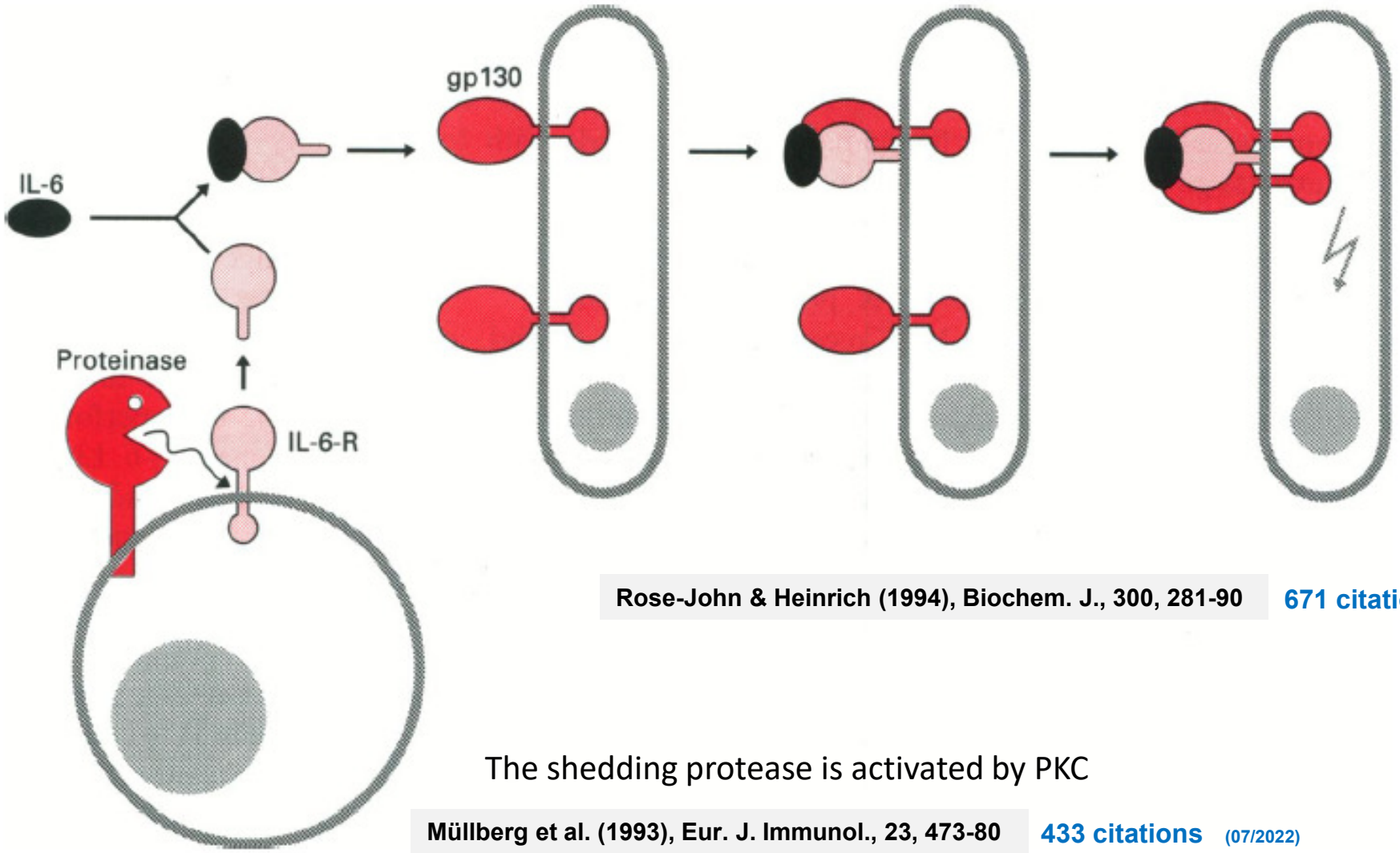
Agonistic action of the complex of IL-6/soluble-IL-6-receptor and trans-signaling between IL-6-responsive and non-responsive cells



Rose-John & Heinrich (1994), Biochem. J., 300, 281-90 671 citations (07/2022)

The shedding protease is activated by PKC

Müllberg et al. (1993), Eur. J. Immunol., 23, 473-80 433 citations (07/2022)

Müllberg et al. (1994), J. Immunol., 152, 4958-68 237 citations (07/2022)

cleavage site

Increased IL-6 and soluble IL-6 receptor-α levels are found in serum and synovial fluid from patients with rheumatoid arthritis (RA)

Serum				
	IL-6 (ng/ml)	sol IL-6Rα (ng/ml)	sol gp130 (ng/ml)	refs
Control	28	28	345	Keul et al. (1998)
RA	78 51	38 29	375 251	Keul et al. (1998) Richards et al. (2006)
Synovial fluid				
RA	6.4	15	250	Richards et al. (2006)

Keul et al. (1998), Cytokine 10, 729-734

61 citations (07/2022)

1998

Soluble IL-6 Receptor Potentiates the Antagonistic Activity of Soluble gp130 on IL-6 Responses[1]

130 citations (07/2022)

Gerhard Müller-Newen,* Andrea Küster,* Ulrike Hemmann,* Radovan Keul,* Ursula Horsten,* Astrid Martens,* Lutz Graeve,* John Wijdenes,† and Peter C. Heinrich[2]*

Soluble receptors for several cytokines have been detected in body fluids and are believed to modulate the cytokine response by binding the ligand and thereby reducing its bioavailability. In the case of IL-6, the situation is more complex. The receptor consists of two components, including a ligand-binding α-subunit (IL-6R, gp80, or CD126), which in its soluble (s) form (sIL-6R) acts agonistically by making the ligand accessible to the second subunit, the signal transducer gp130 (CD130). Soluble forms of both receptor subunits are present in human blood. Gel filtration of iodinated IL-6 that had been incubated with human serum revealed that IL-6 is partially trapped in IL-6/sIL-6R/sgp130 ternary complexes. sgp130 from human plasma was enriched by immunoaffinity chromatography and identified as a 100-kDa protein. Functionally equivalent rsgp130 was produced in baculovirus-infected insect cells to study its antagonistic potential on four different cell types. It was found that in situations in which cells lacking membrane-bound IL-6R were stimulated with IL-6/sIL-6R complexes, sgp130 was a much more potent antagonist than it was on IL-6R-positive cells stimulated with IL-6 alone. In the latter case, the neutralizing activity of sgp130 could be markedly enhanced by addition of sIL-6R. As a consequence of these findings, sIL-6R of human plasma must be regarded as an antagonistic molecule that enhances the inhibitory activity of sgp130. Furthermore, in combination with sIL-6R, sgp130 is a promising candidate for the development of IL-6 antagonists. *The Journal of Immunology,* 1998, 161: 6347–6355.

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THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 271, No. 10, Issue of March 8, pp. 5487–5494, 1996
Printed in U.S.A.

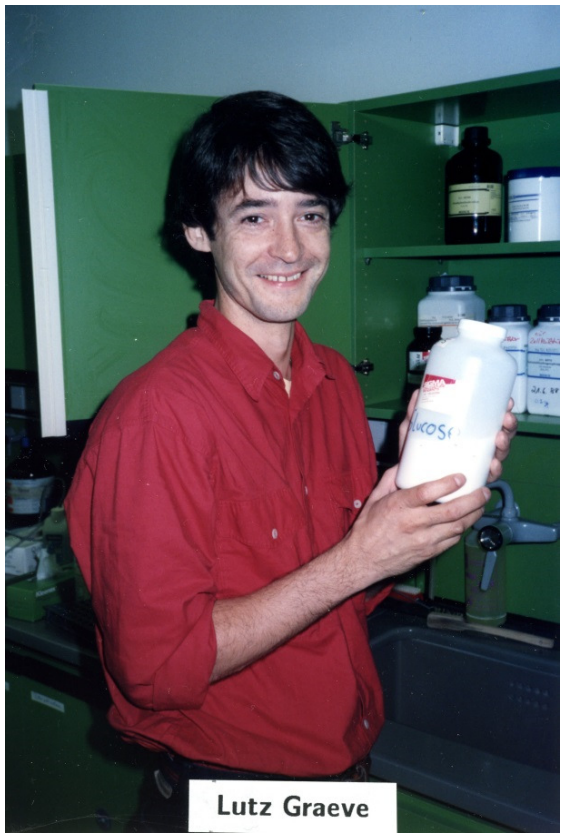
A Di-leucine Motif and an Upstream Serine in the Interleukin-6 (IL-6) Signal Transducer gp130 Mediate Ligand-induced Endocytosis and Down-regulation of the IL-6 Receptor*

145 citations (07/2022)

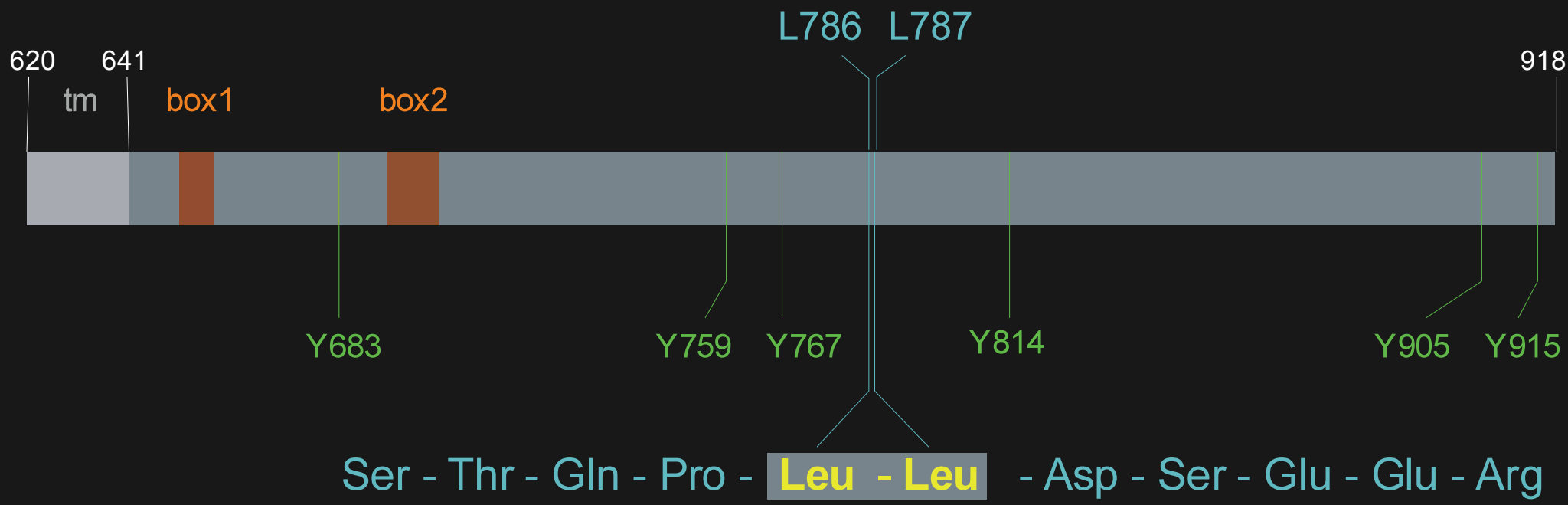
(Received for publication, August 31, 1995, and in revised form, December 4, 1995)

Elke Dittrich‡, Carol Renfrew Haft§, Leon Muys¶, Peter C. Heinrich‡, and Lutz Graeve‡‖

From the ‡Institute of Biochemistry, Rheinisch-Westfälische Technische Hochschule Aachen, 52057 Aachen, Germany, the §Diabetes Branch, NIDDKD, National Institutes of Health, Bethesda, Maryland 20892-1770, and the ¶Institute of Pathology, Rheinisch-Westfälische Technische Hochschule Aachen, 52057 Aachen, Germany

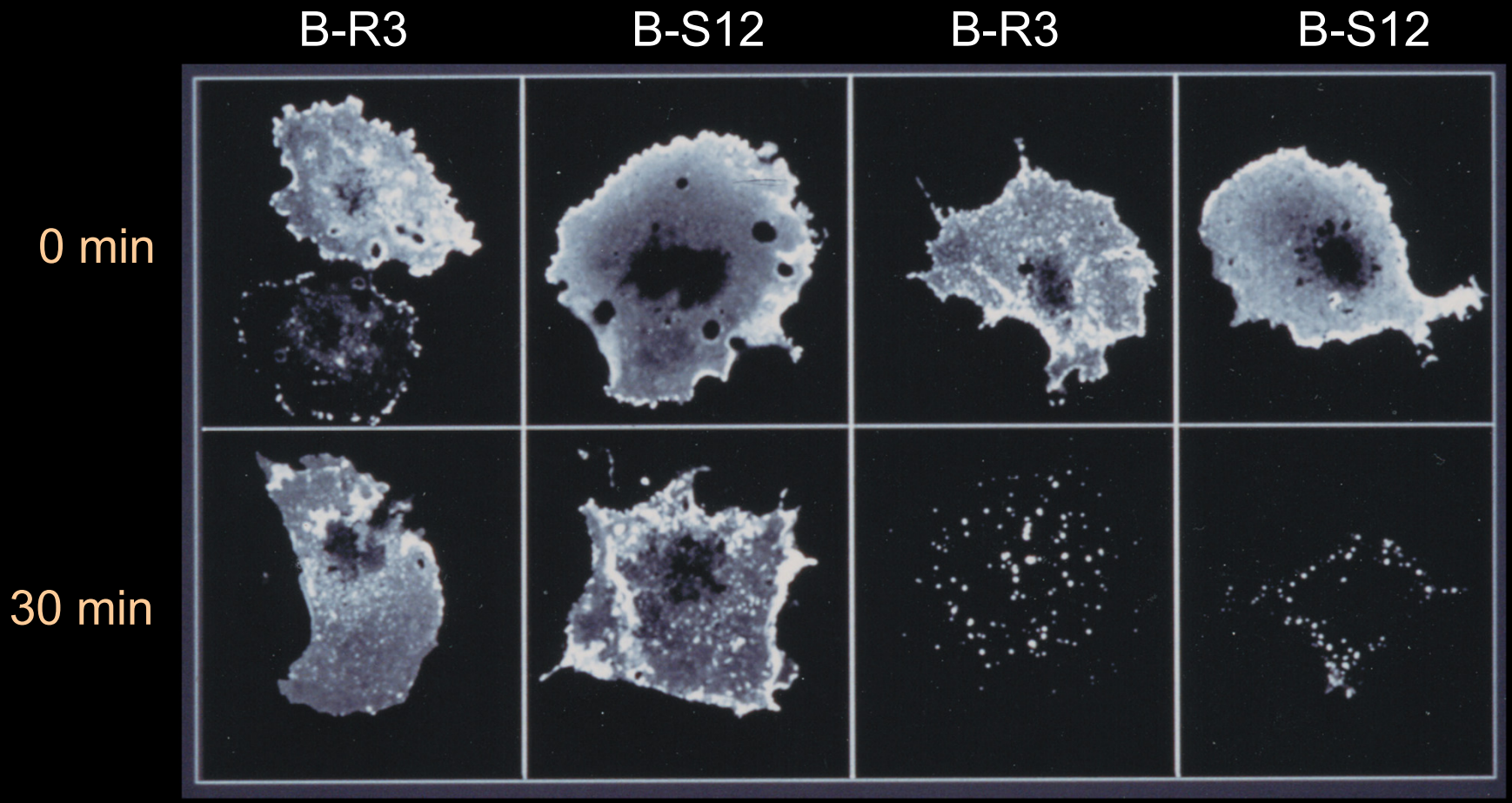


Intracellular domain of gp130



tm transmembrane domain

Internalization of monoclonal antibodies B-R3 and B-S12 by COS-7 cells expressing gp130AA or gp130



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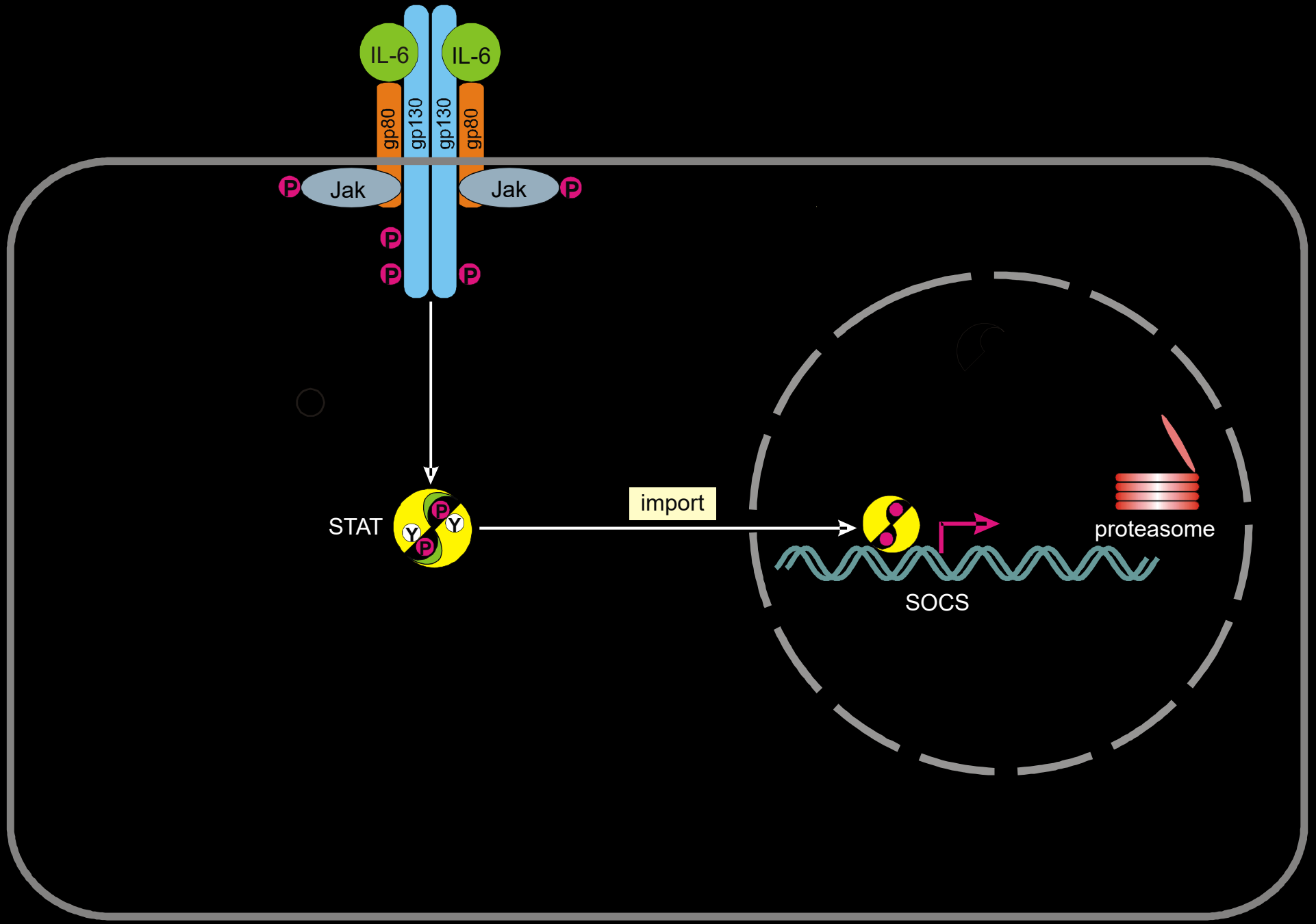
The IL-6 / JAK / STAT signaling cascade is well controlled



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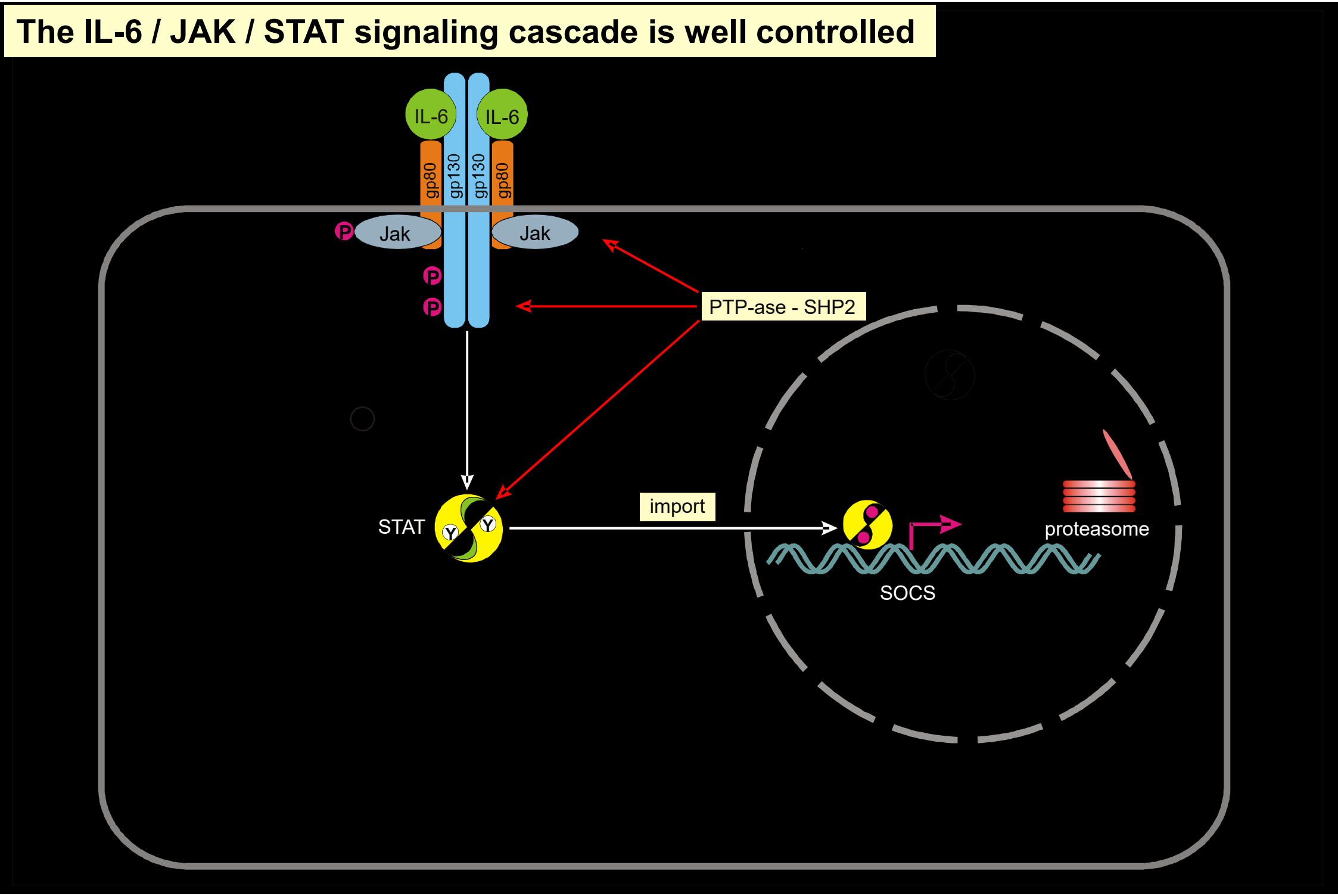

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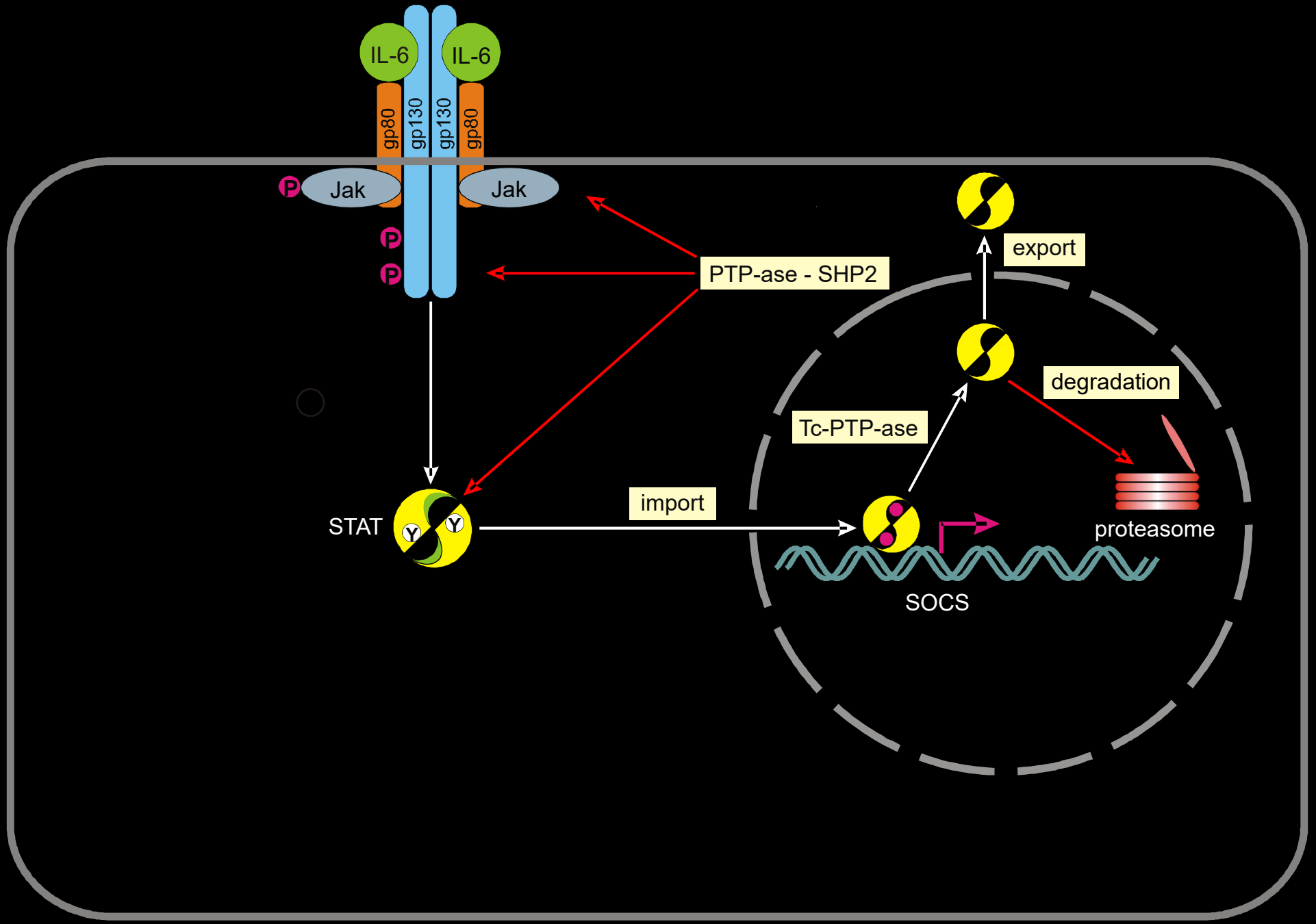
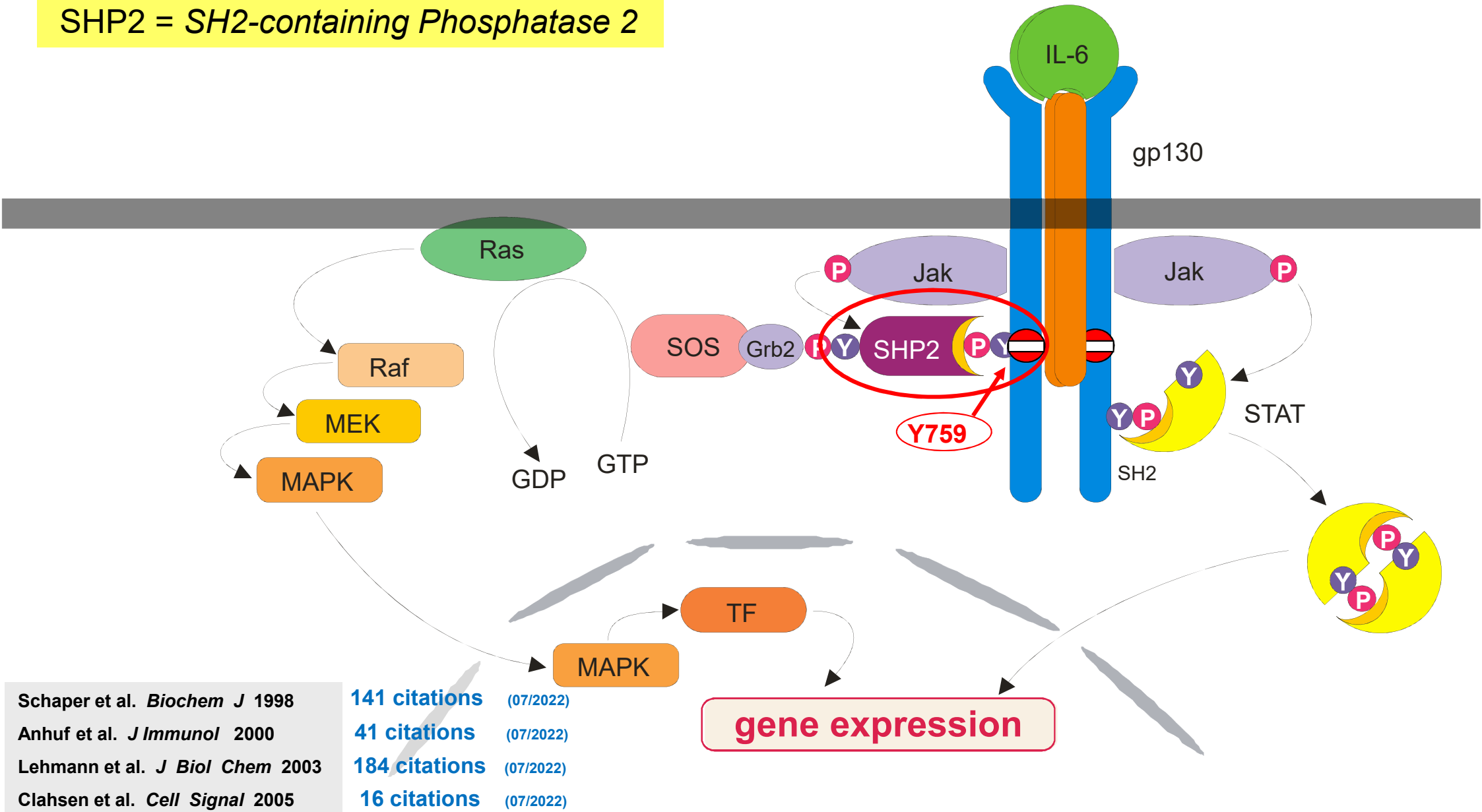


Inhibition of IL-6 signaling through SHP2

SHP2 = *SH2-containing Phosphatase 2*



Schaper et al. *Biochem J* 1998	141 citations	(07/2022)
Anhuf et al. *J Immunol* 2000	41 citations	(07/2022)
Lehmann et al. *J Biol Chem* 2003	184 citations	(07/2022)
Clahsen et al. *Cell Signal* 2005	16 citations	(07/2022)

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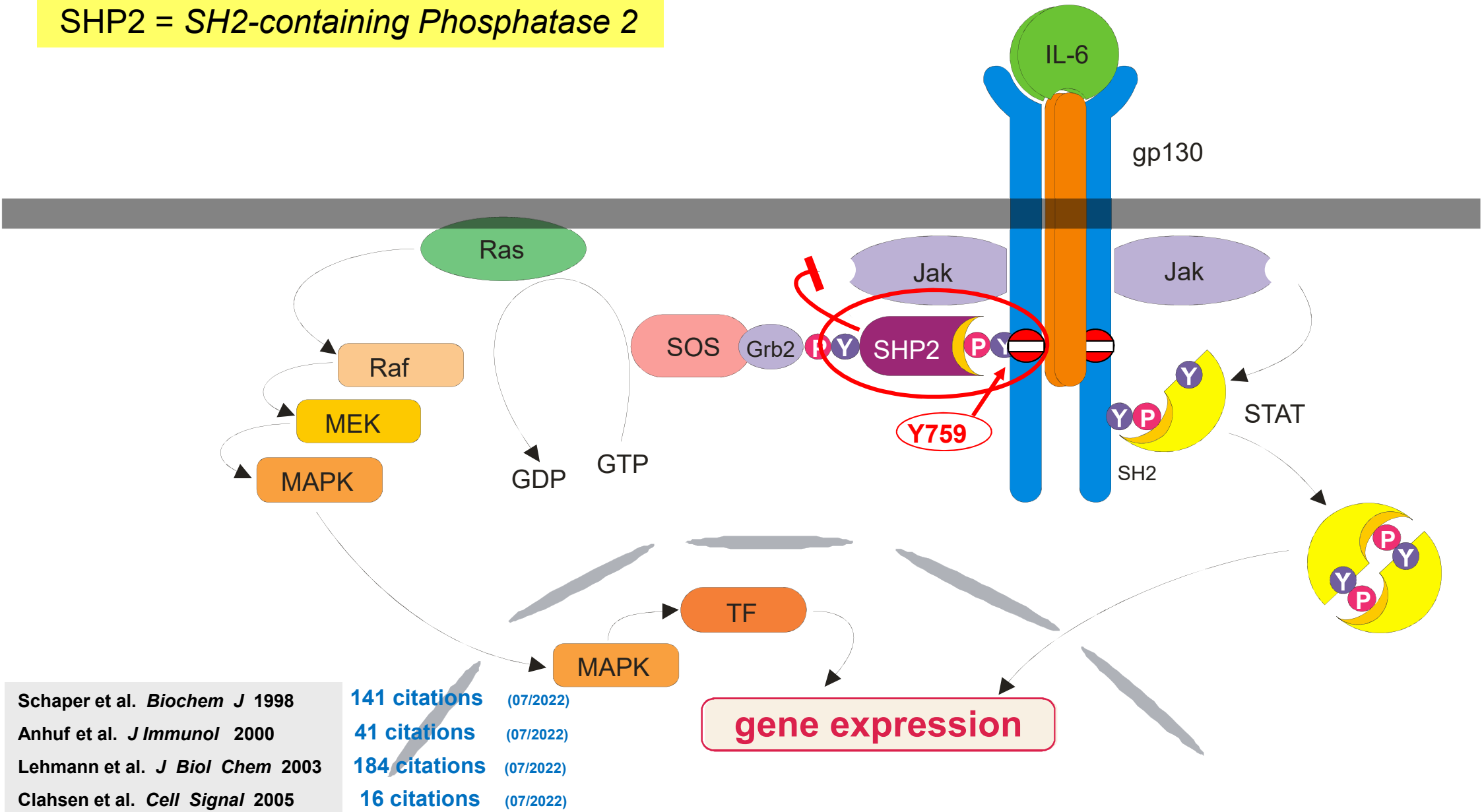

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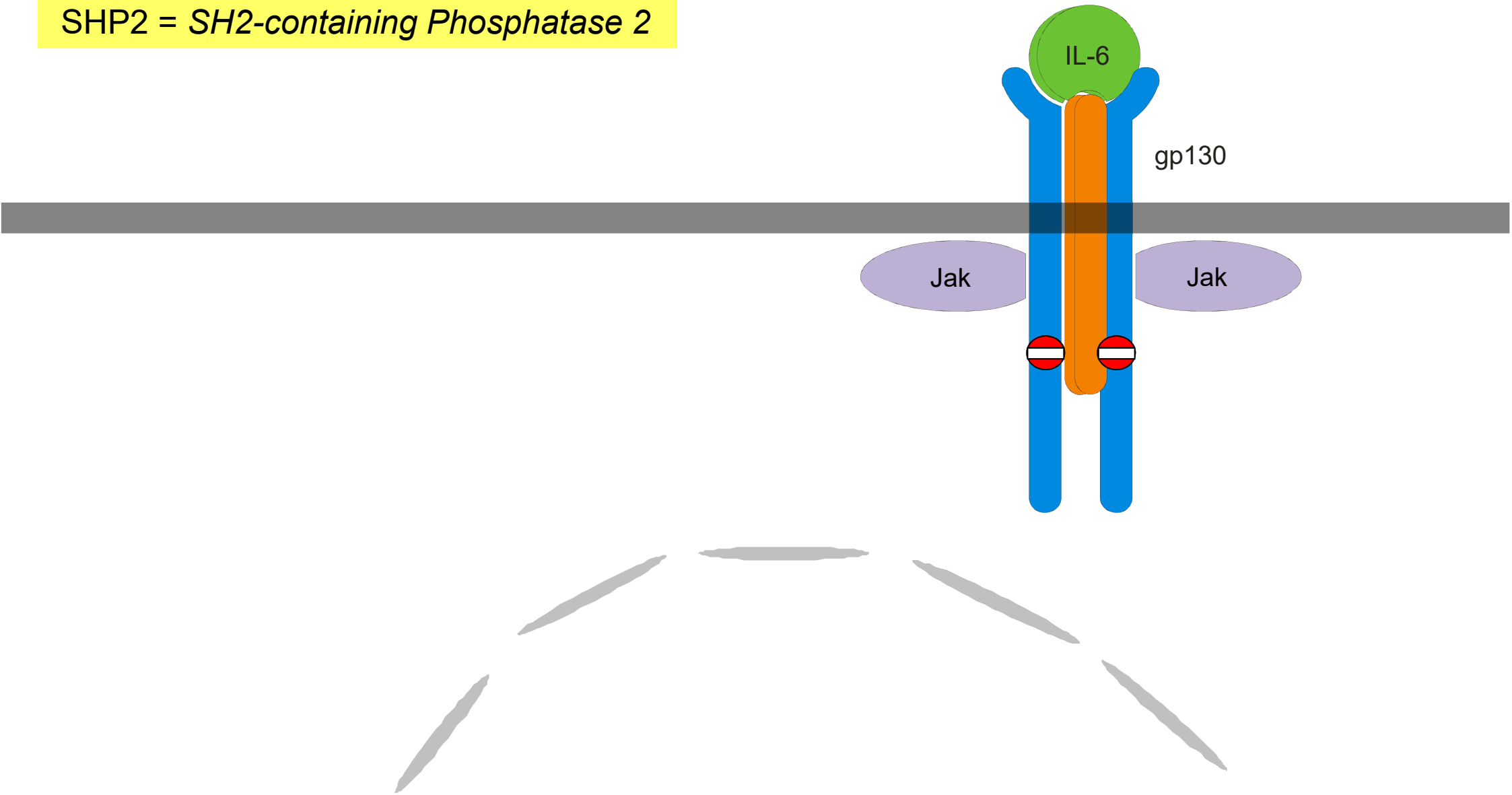
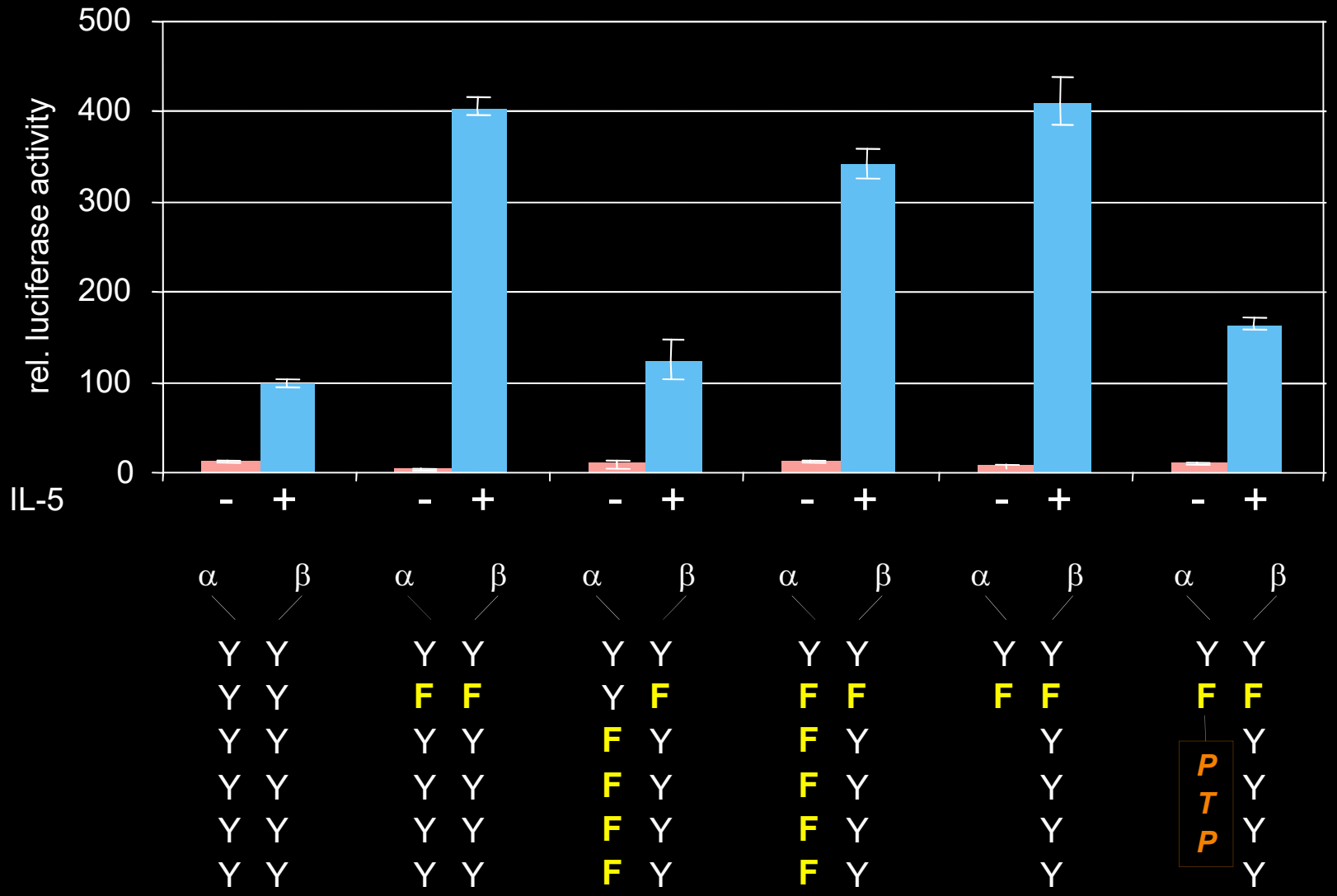


Receptor-targeted SHP2 counteracts gp130-dependent gene induction

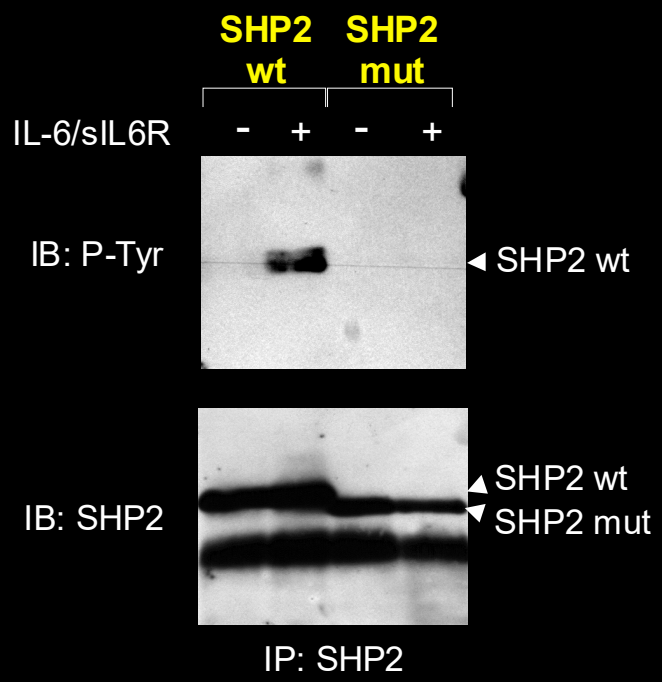


HepG2

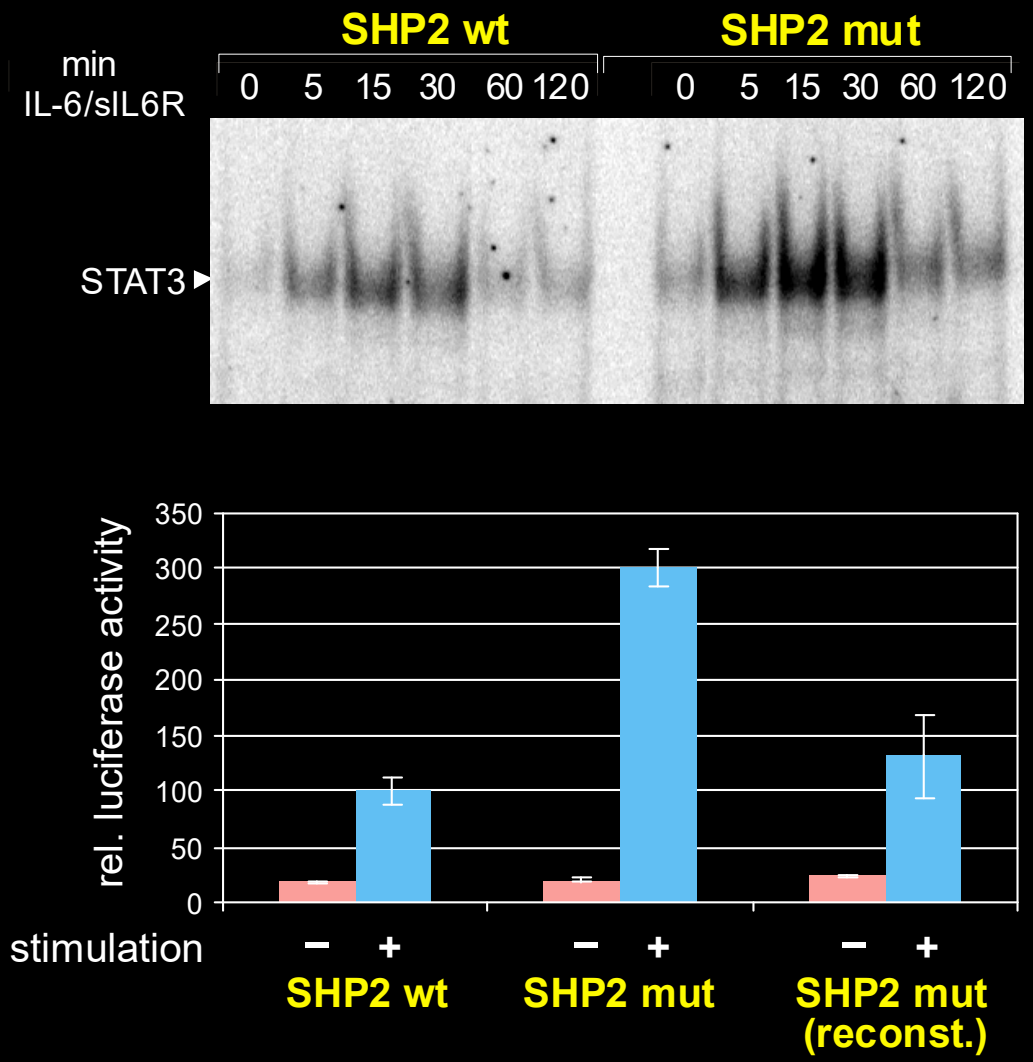
Lehmann et al. (2003) J Biol Chem 278, 661-671

155 citations (2018)

SHP2 counteracts gp130-mediated signal transduction



murine embryonal fibroblasts



Lehmann et al. (2003) J Biol Chem 278, 661-671

Affinities of SOCS3 and SHP2 to murine pY757-gp130 peptide

	K_D [nM]
SHP2-SH2 (N)	1200
SHP2-SH2 (C)	550
SHP2-SH2 (N) + SH2 (C)	170
SOCS3 full length	42
SOCS3-SH2-domain	140

KIR Kinase Inhibitory Region
SH2 Src Homology 2
ESS Extended SH2 Subdomain

De Souza et al. (2002) Biochemistry *41, 9229-9236*

Outline: Interleukin-6 signal transduction and its regulation

Part 1: **Molecular mechanisms of IL-6 signal transduction**

Part 2: **Regulation of IL-6 signal transduction**

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- Polar expression of IL-6 receptor-α (gp80)
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  - IL-1 stabilizes SOCS3-mRNA
  - IL-1 accelerates the internalization of the signal transducer gp130

1997

SOCS proteins (suppressors of cytokine signaling) were independently discovered in 3 different laboratories.

A family of cytokine-inducible inhibitors of signalling

Robyn Starr*, Tracy A. Willson*, Elizabeth M. Viney*, Leecia J. L. Murray*, John R. Rayner†, Brendan J. Jenkins†, Thomas J. Gonda†, Warren S. Alexander*, Donald Metcalf*, Nicos A. Nicola* & Douglas J. Hilton*

** The Walter and Eliza Hall Institute for Medical Research and The Cooperative Research Center for Cellular Growth Factors, Parkville, Victoria, Australia 3052*
† The Hanson Centre for Cancer Research, IMVS, Adelaide, Southern Australia, Australia 5000

Nature **volume 387**, pages 917–921
Citations 1727 (07/2022)

A new protein containing an SH2 domain that inhibits JAK kinases

Takaho A. Endo*†, Masaaki Masuhara*†, Masahiro Yokouchi*†‡, Ritsu Suzuki*‡, Hiroshi Sakamoto*, Kaoru Mitsui*, Akira Matsumoto*, Shyu Tanimura*, Motoaki Ohtsubo*, Hiroyuki Misawa*, Tadaaki Miyazaki§, Nogueira Leonor§, Tadatsugu Taniguchi§, Takashi Fujita‖, Yuzuru Kanakura¶, Seturo Komiya‡ & Akihiko Yoshimura*

** Institute of Life Science, and ‡ Department of Orthopedic Surgery, Kurume University, Aikawamachi 2432-3 Kurume 839, Japan*
§ Department of Immunology, Faculty of Medicine, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan

Nature **volume 387**, pages 921–924
Citations 1184 (07/2022)

Structure and function of a new STAT-induced STAT inhibitor

Tetsuji Naka*, Masashi Narazaki*, Moritoshi Hirata*, Tomoshige Matsumoto*, Seijiro Minamoto*, Atsufumi Aono*, Norihiro Nishimoto†, Tadahiro Kajita‡, Tetsuya Taga§, Kazuyuki Yoshizaki†, Shizuo Akira‖ & Tadamitsu Kishimoto*

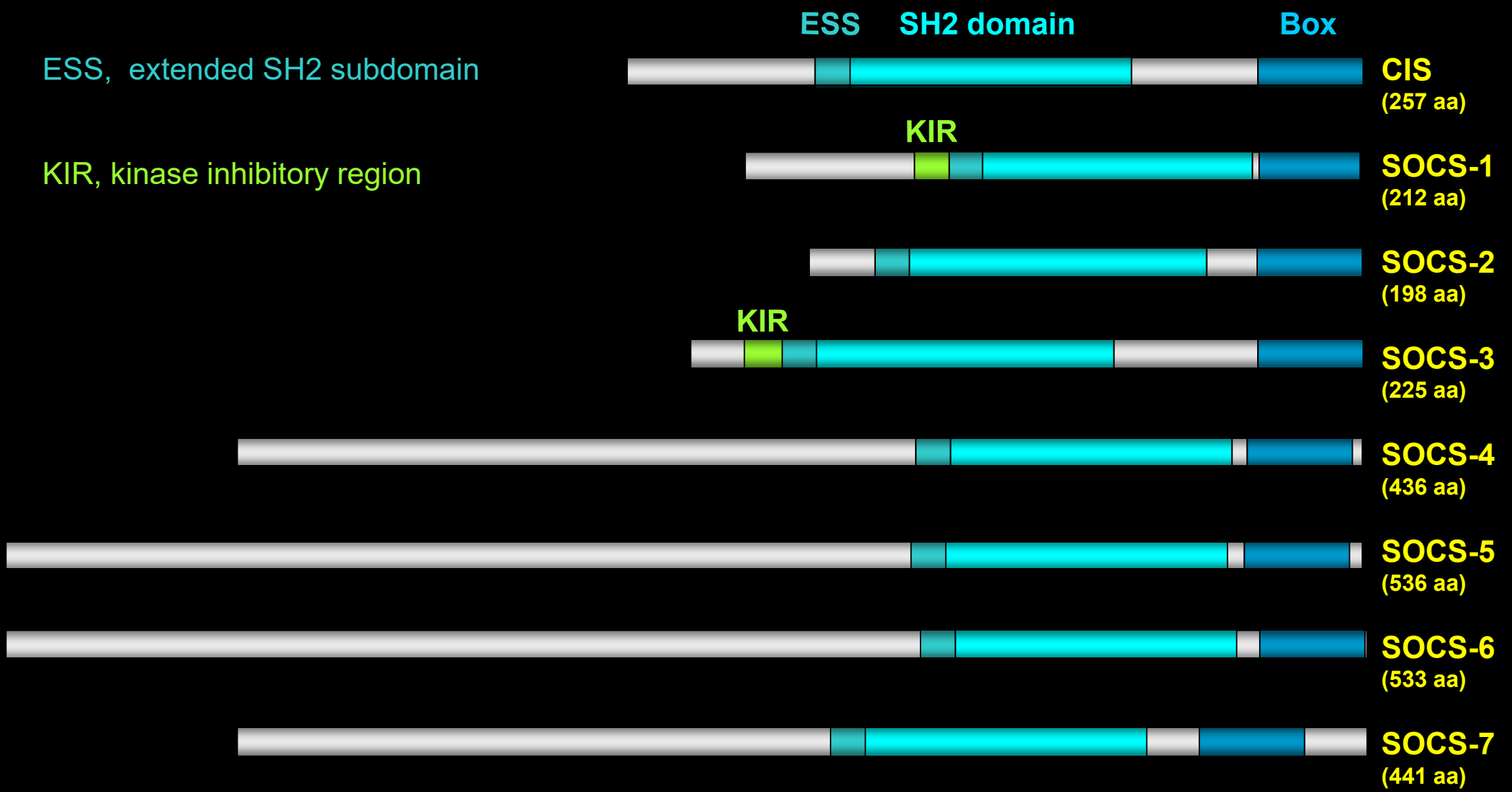
** Osaka University Medical School Department of Medicine III. 2-2, Yamada-Oka, Suita, Osaka 565, Japan*

Nature **volume 387**, pages 924–929
Citations 1096 (07/2022)

The SOCS (SUPPRESSORS OF CYTOKINE SIGNALING) family

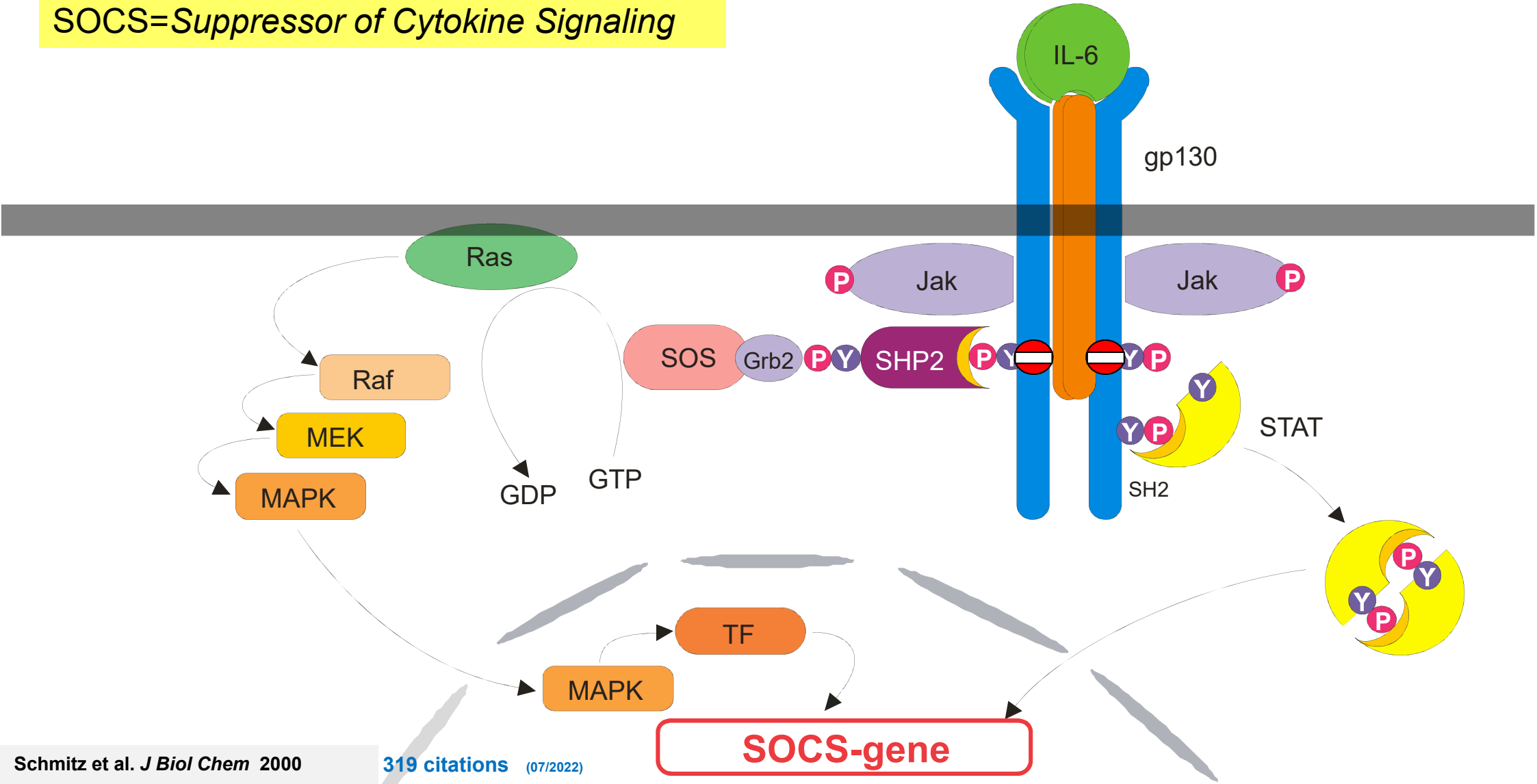
ESS, extended SH2 subdomain

KIR, kinase inhibitory region



Inhibition through SOCS-*feedback* inhibitors

SOCS=*Suppressor of Cytokine Signaling*



Schmitz et al. *J Biol Chem* 2000 — 319 citations (07/2022)

Friederichs et al. *Eur J Biochem* 2001 — 23 citations (07/2022)

Fischer et. al. *Biochem J* 2004 — 58 citations (07/2022)

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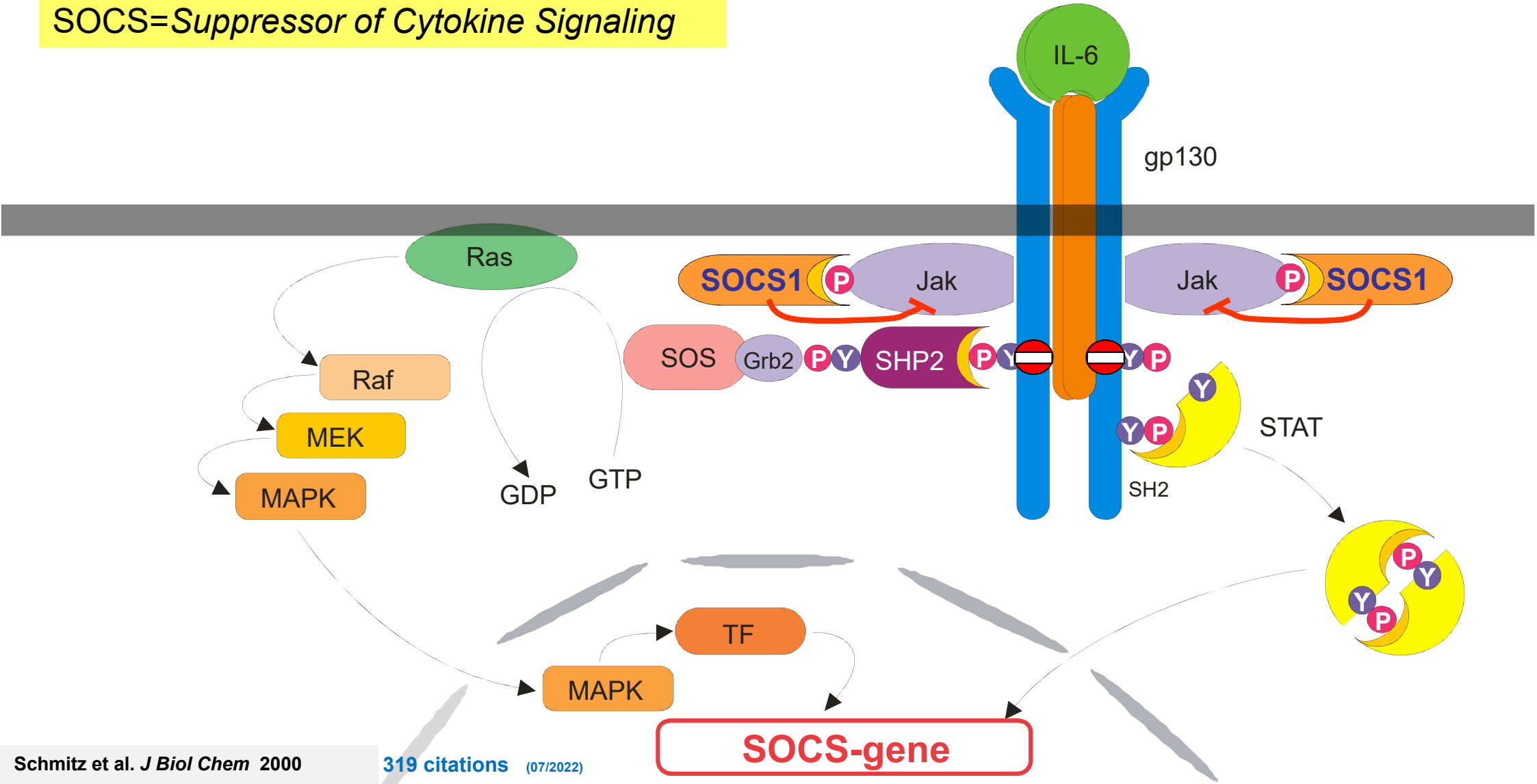

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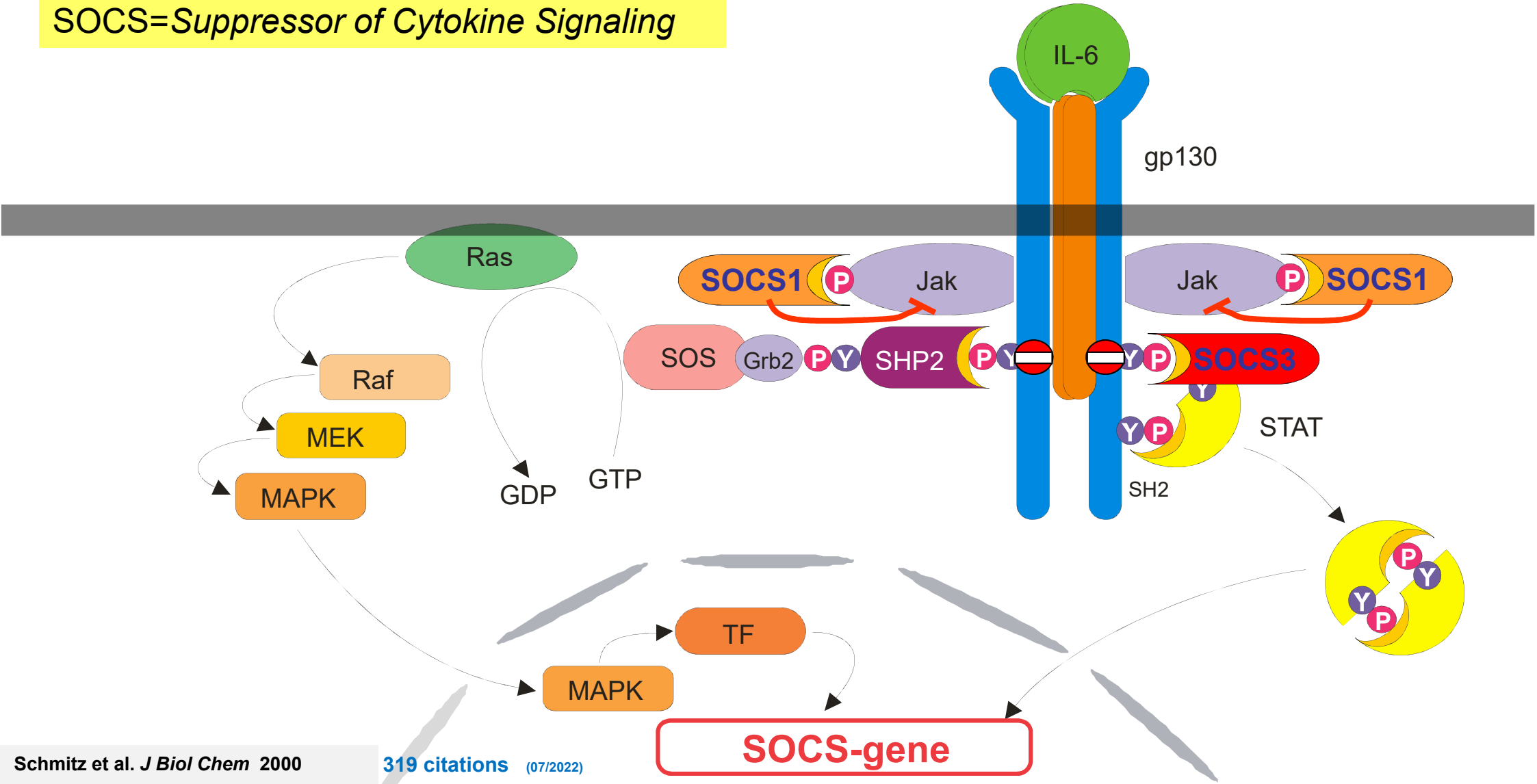

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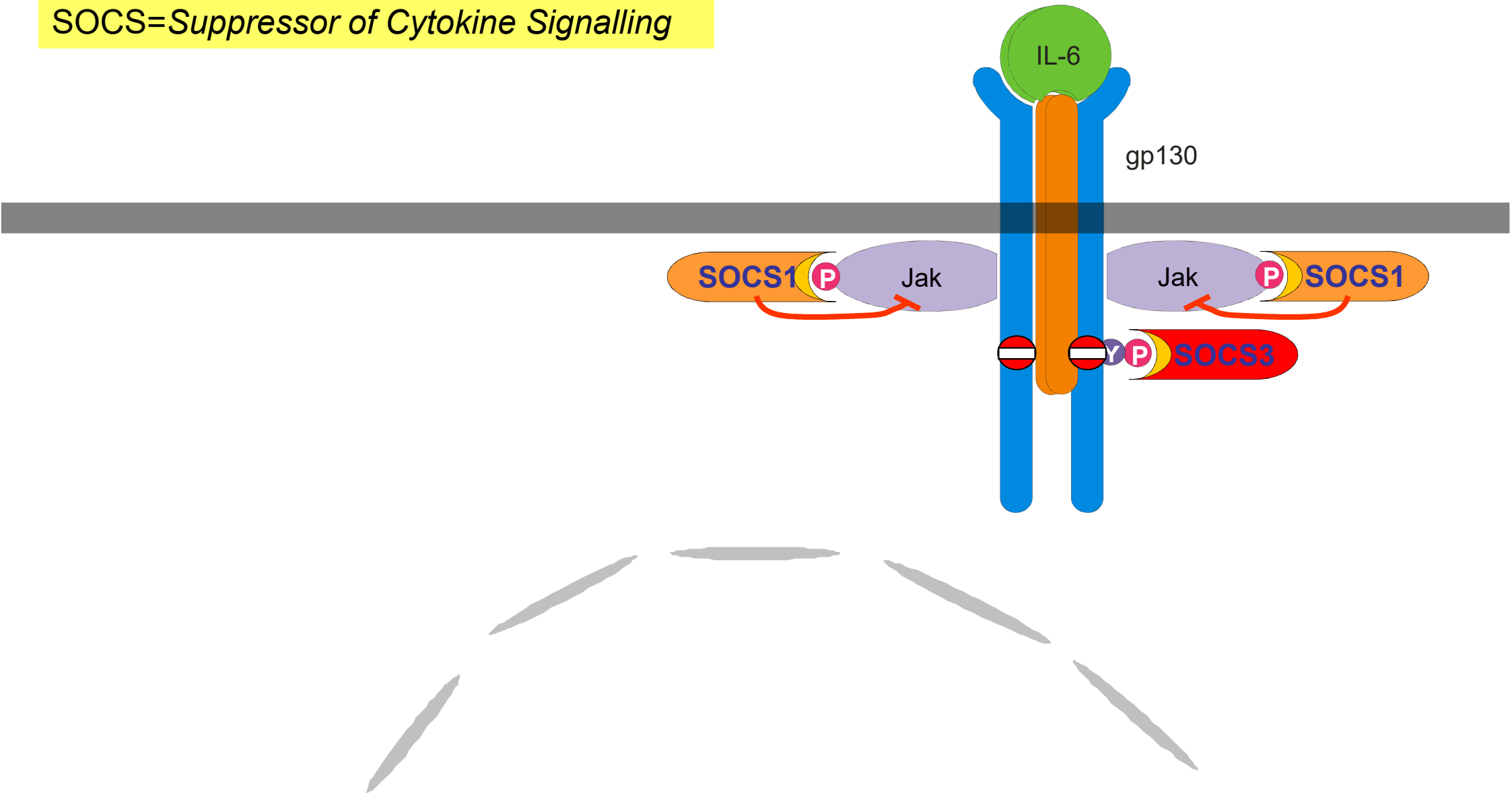
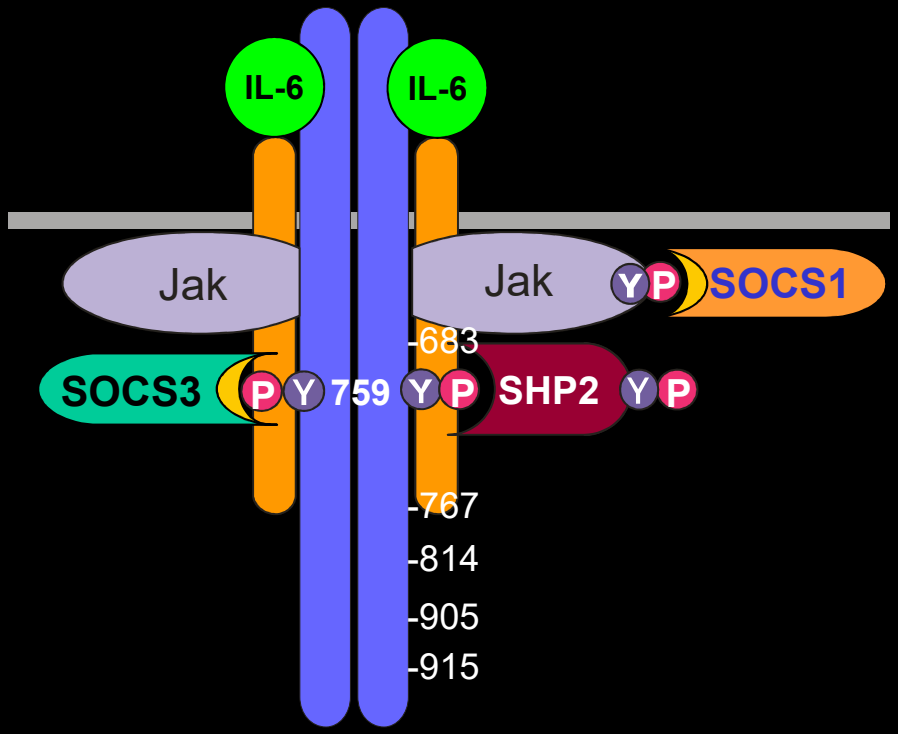
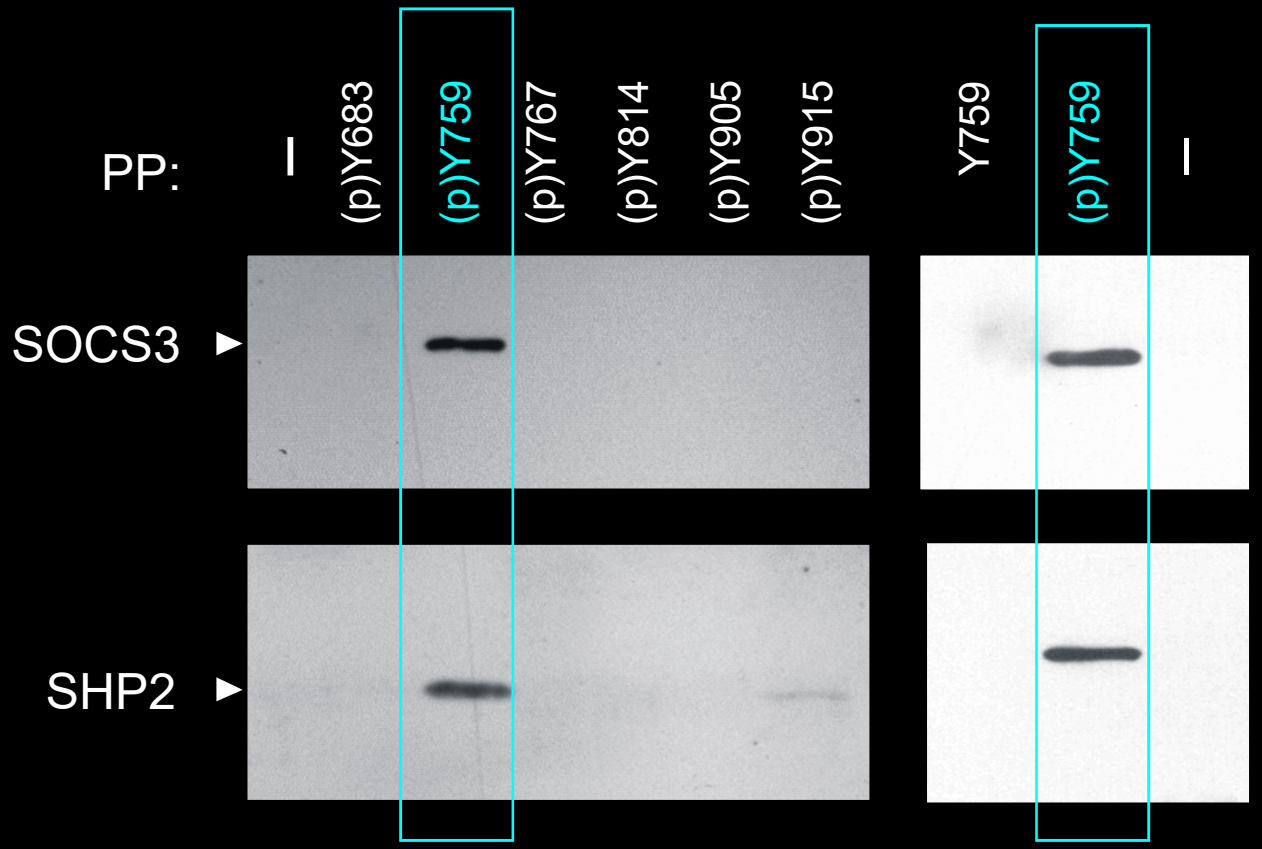


SOCS3 binds the phosphotyrosine motif 759 of gp130



binding to gp130 phospho-peptides (13-mers)

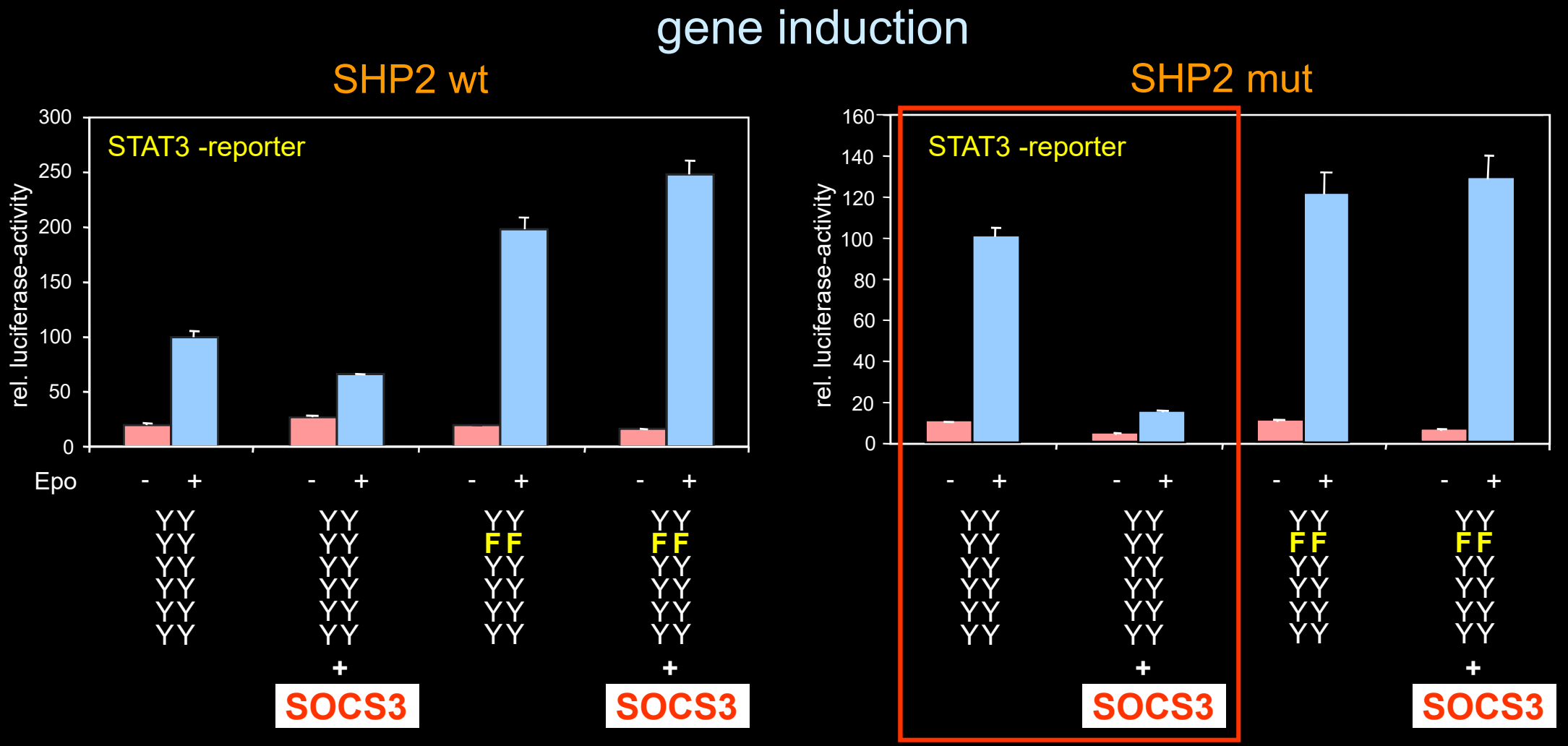


COS7 cells

- SOCS1 inhibits *via* direct binding to JAKs
- SOCS3 inhibits *via* receptor binding

Schmitz et al. (2000) J Biol Chem 275, 12848-12856 **319 citations** (07/2022)

SOCS3-mediated signal attenuation is SHP2-independent



Lehmann et al. (2003) J Biol Chem 278, 661-671

184 citations (07/2022)

SOCS3 Exerts Its Inhibitory Function on Interleukin-6 Signal Transduction through the SHP2 Recruitment Site of gp130*

(Received for publication, May 27, 1999, and in revised form, January 19, 2000)

Jochen Schmitz, Manuela Weissenbach, Serge Haan, Peter C. Heinrich‡, and Fred Schaper

From the Institut für Biochemie, Rheinisch-Westfälische Technische Hochschule Aachen, Pauwelsstraße 30, D-52074 Aachen, Germany

319 citations (07/2022)

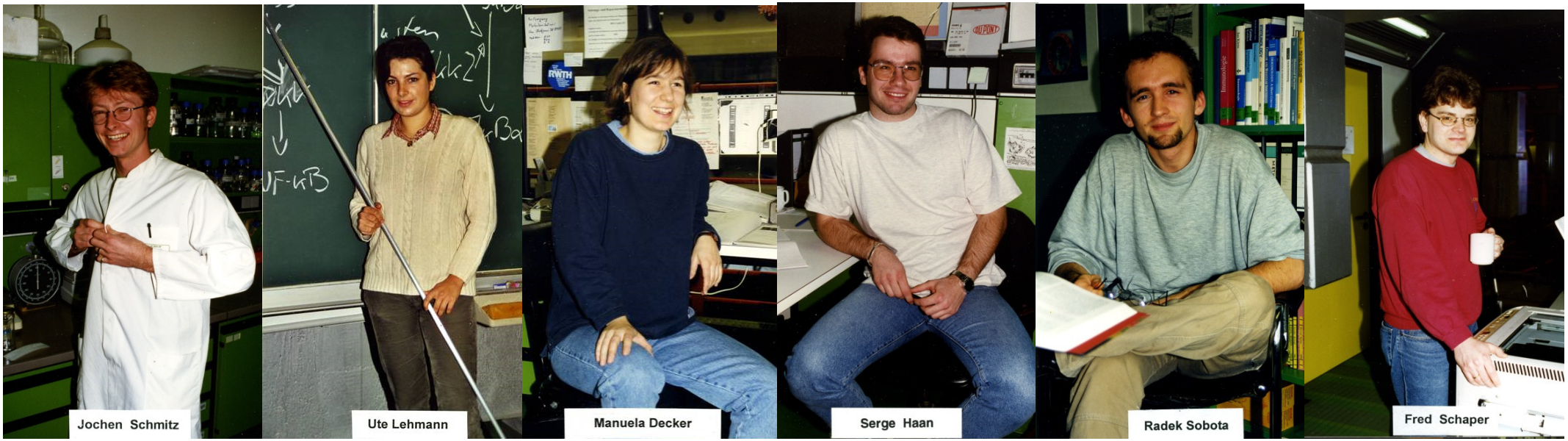
SHP2 and SOCS3 Contribute to Tyr-759-dependent Attenuation of Interleukin-6 Signaling through gp130*

Received for publication, October 15, 2002
Published, JBC Papers in Press, October 27, 2002, DOI 10.1074/jbc.M210552200

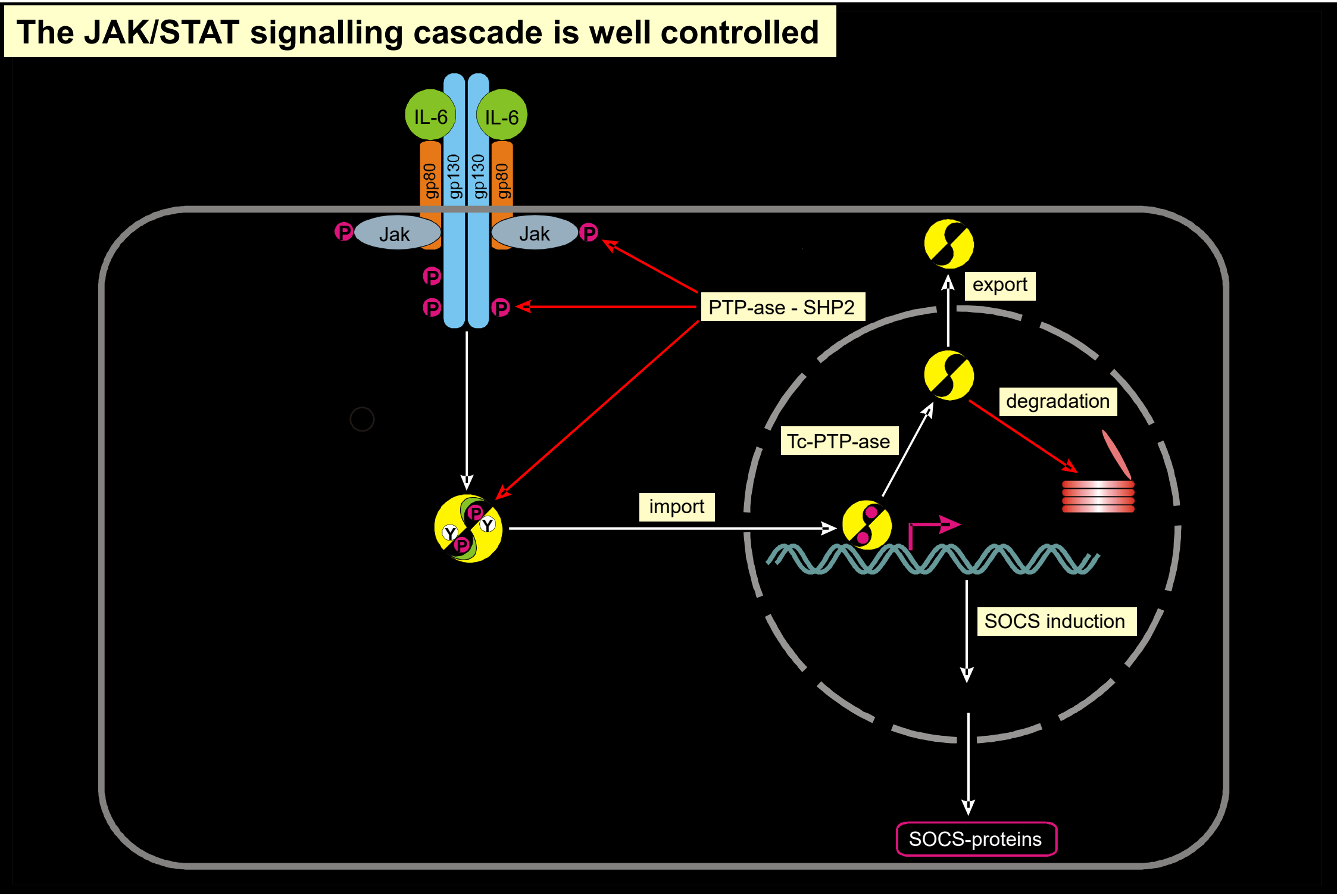
Ute Lehmann‡§, Jochen Schmitz‡§, Manuela Weissenbach‡, Radoslaw M. Sobota‡, Michael Hörtner¶, Kerstin Friederichs‡, Iris Behrmann‡, William Tsiaris‖, Atsuo Sasaki, Jens Schneider-Mergener‡‡, Akihiko Yoshimura**, Benjamin G. Neel‖, Peter C. Heinrich‡§§, and Fred Schaper‡§§§**

184 citations (07/2022)

Jochen Schmitz as a post-doc at DNAX cloned IL-33



The JAK/STAT signalling cascade is well controlled



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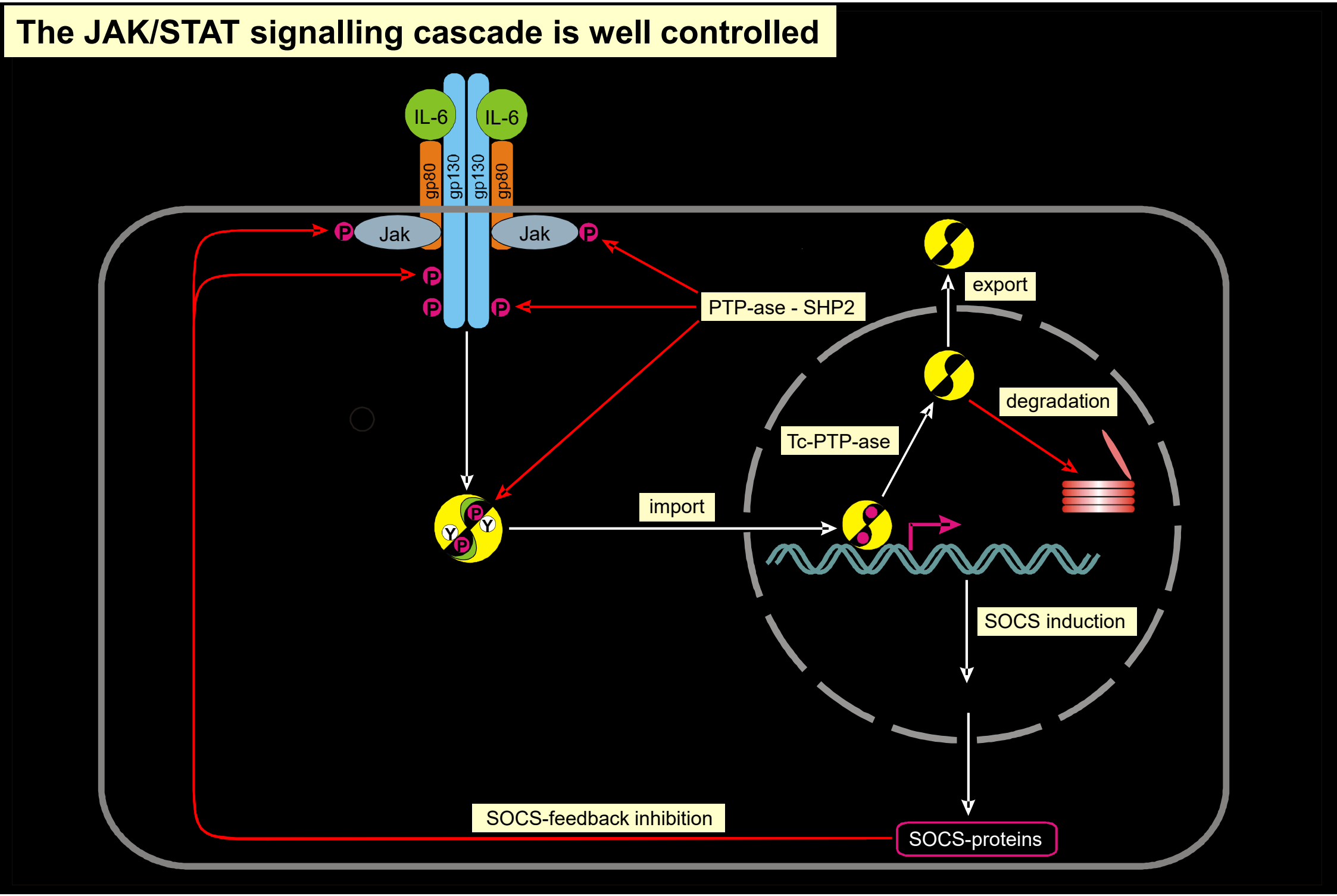

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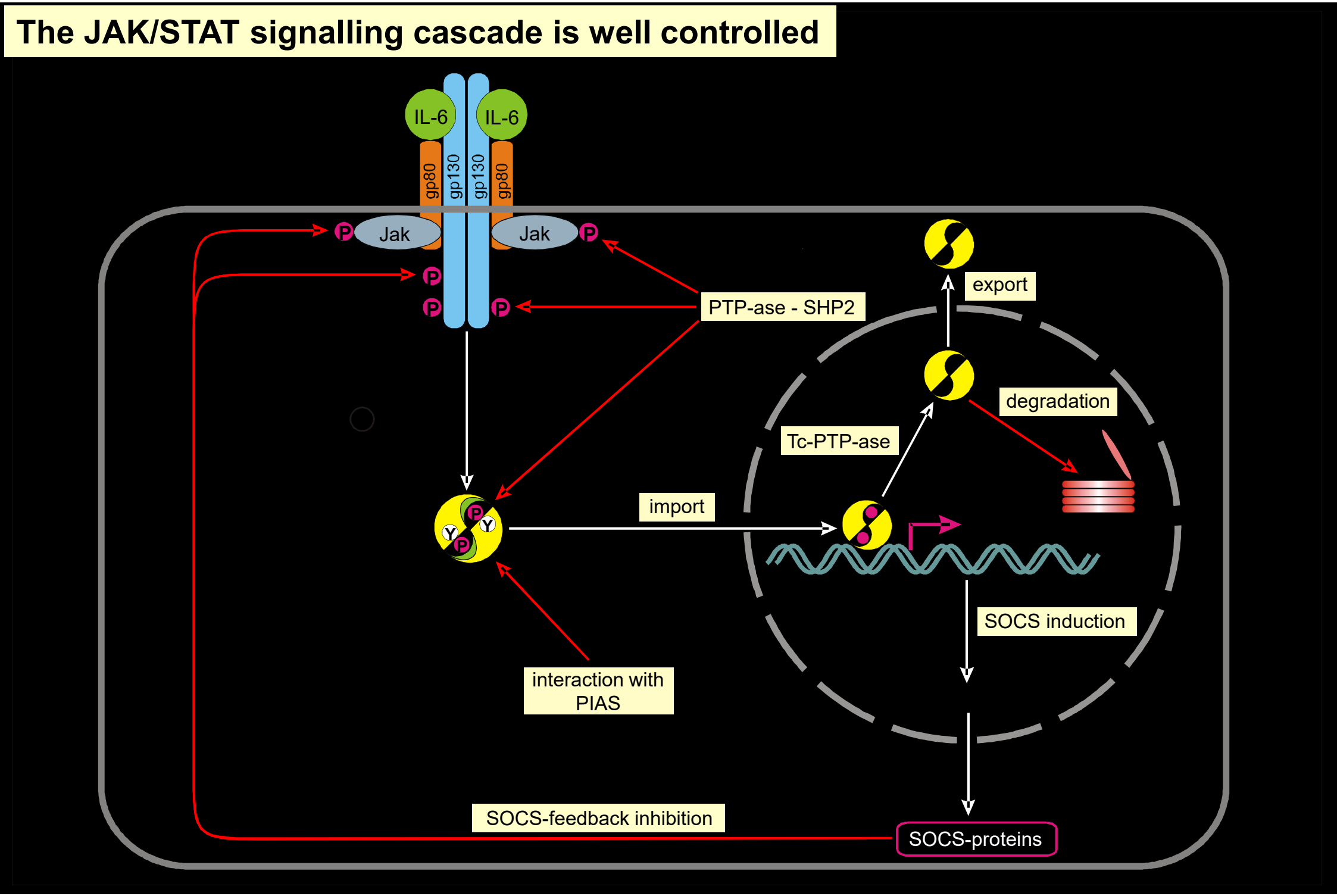

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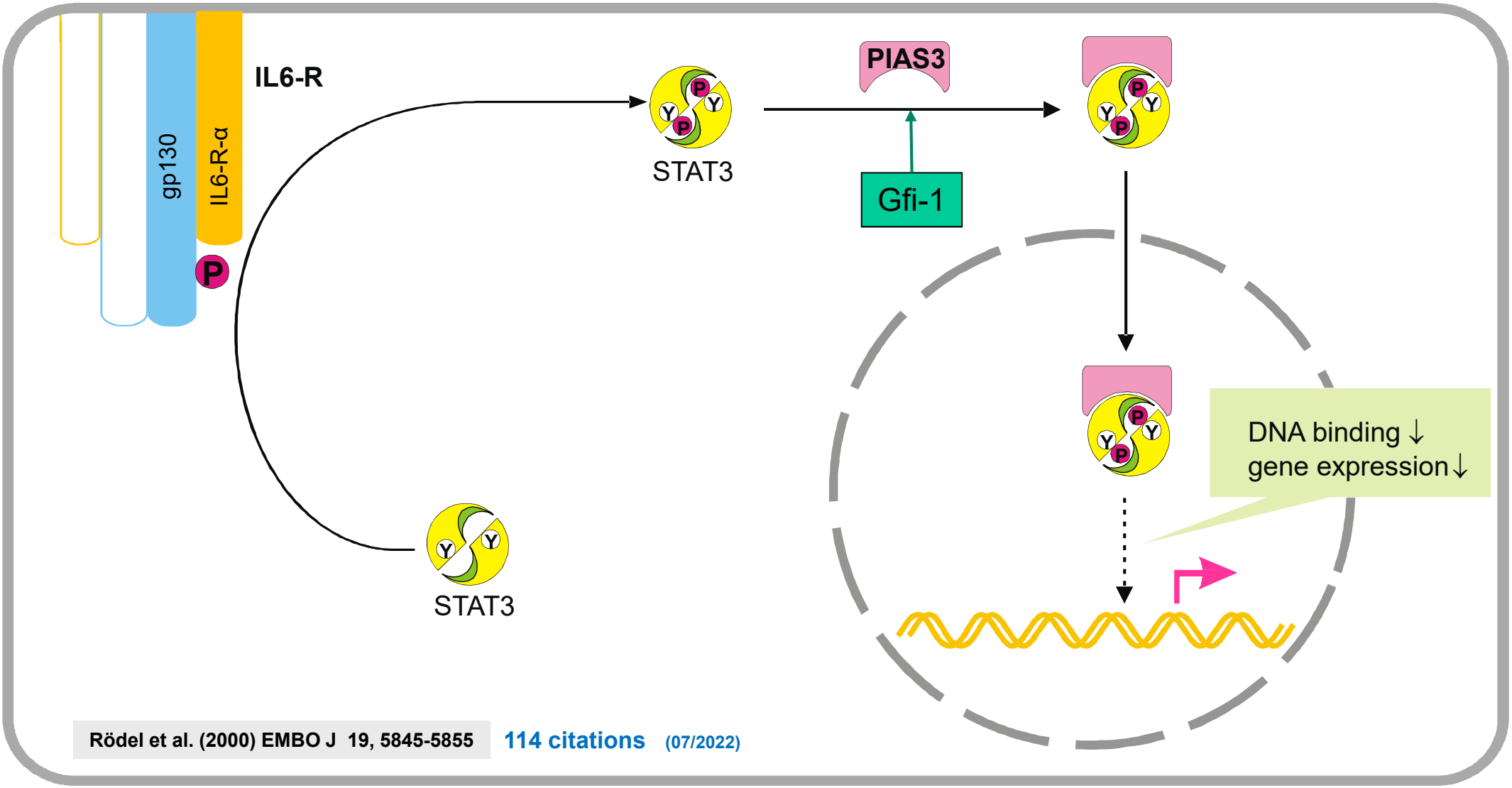
PIAS3 exerts a profound inhibitory effect on STAT3-mediated transcription of target promoters, the zinc finger protein Gfi-1 can overcome the PIAS3 block



Rödel et al. (2000) EMBO J 19, 5845-5855 114 citations (07/2022)

The EMBO Journal Vol. 19 No. 21 pp. 5845–5855, 2000

2000

The zinc finger protein Gfi-1 can enhance STAT3 signaling by interacting with the STAT3 inhibitor PIAS3

114 citations (07/2022)

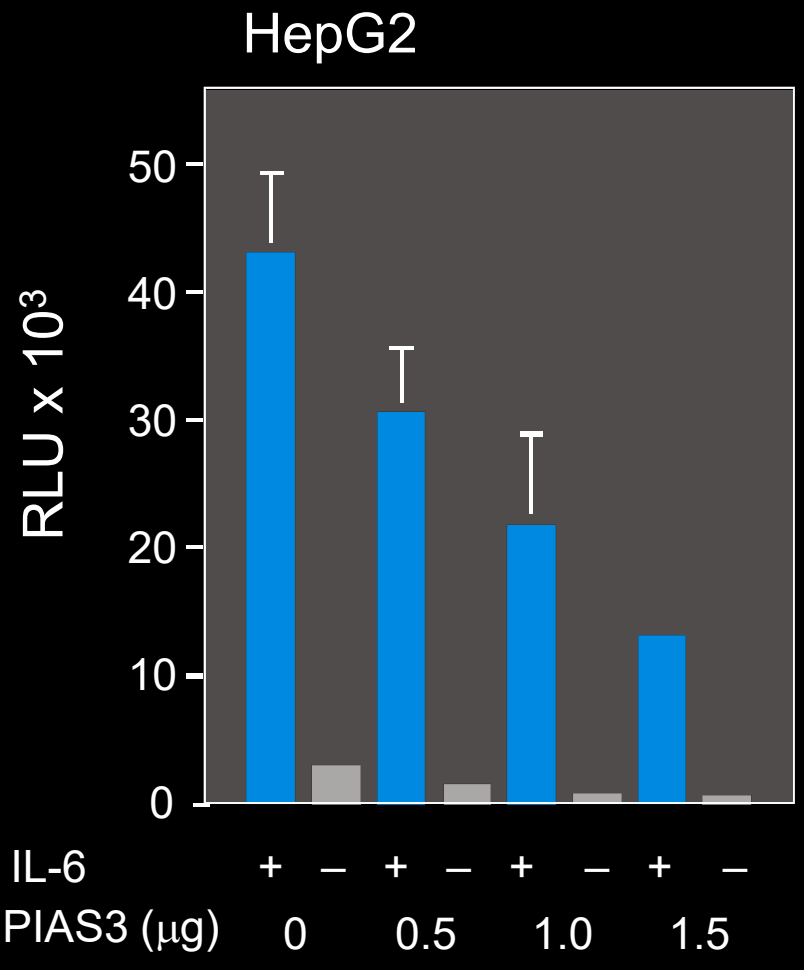
Bernd Rödel, Kamiab Tavassoli, Holger Karsunky, Thorsten Schmidt[1], Malte Bachmann, Fred Schaper[2], Peter Heinrich[2], Ke Shuai[3], Hans Peter Elsässer[4] and Tarik Möröy[5]

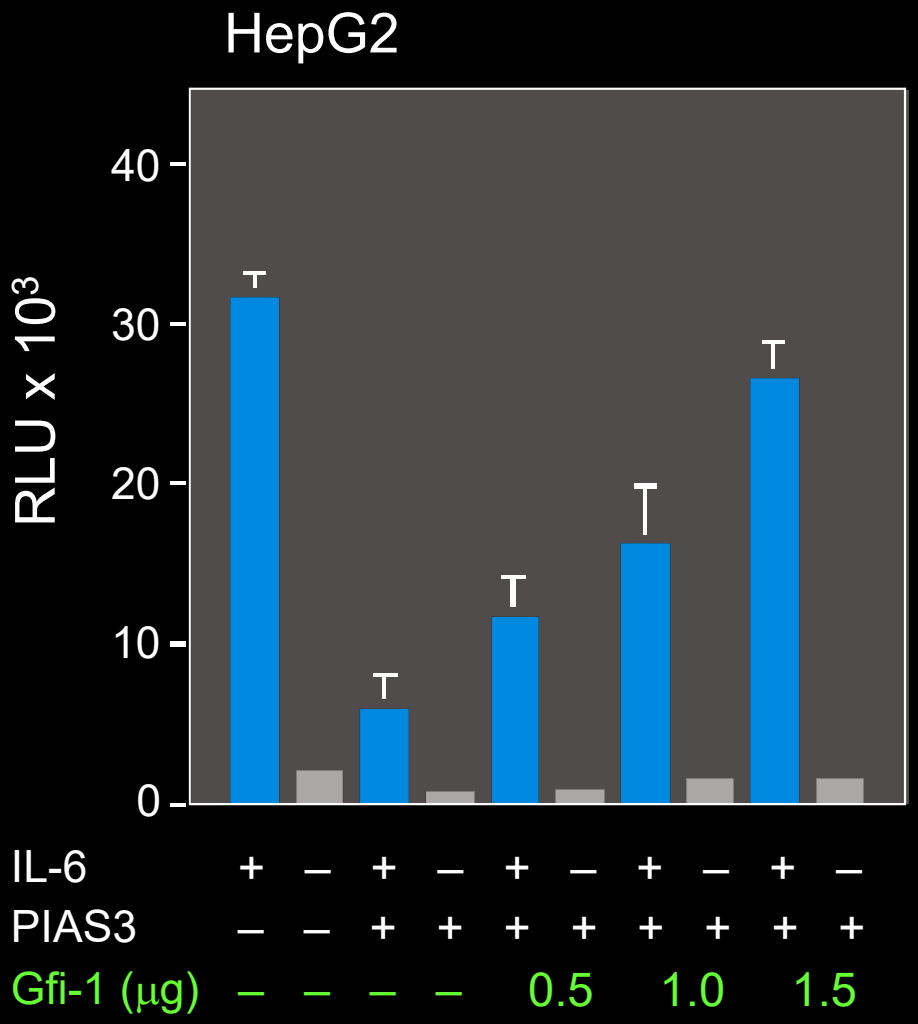
Institut für Zellbiologie (Tumorforschung), IFZ, Universitätsklinikum Essen, Virchowstrasse 173, D-45122 Essen, [1]Bayer AG, Apratherweg 18a, D-42096 Wuppertal, [2]Institut für Biochemie, Universitätsklinikum, RWTH Aachen, Pauwelsstrasse 30, D-52074 Aachen, [4]Institut für Zytobiologie und Zytopathologie, Philipps Universität Marburg, D-35033 Marburg, Germany and [3]Division of Hematology/Oncology, UCLA School of Medicine, Los Angeles, CA, USA

[5]Corresponding author
e-mail: moeroey@uni-essen.de

B.Rödel and K.Tavassoli contributed equally to this work

The Zn-finger protein Gfi relieves the PIAS3-mediated block of STAT3-induced α1-antichymotrypsin gene activation





Rödel et al. (2000) EMBO J 19, 5845-5855 **114 citations** (07/2022)

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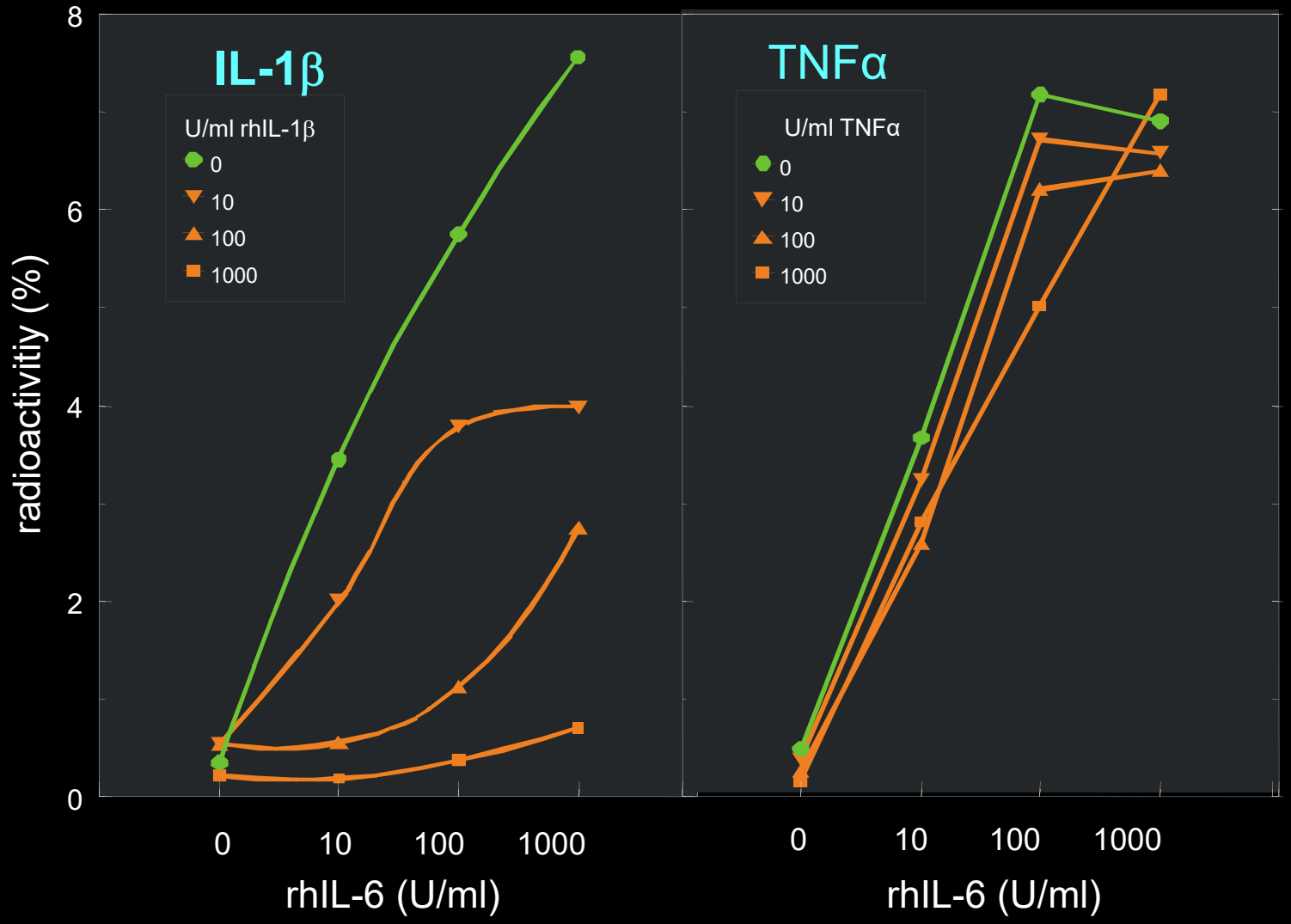
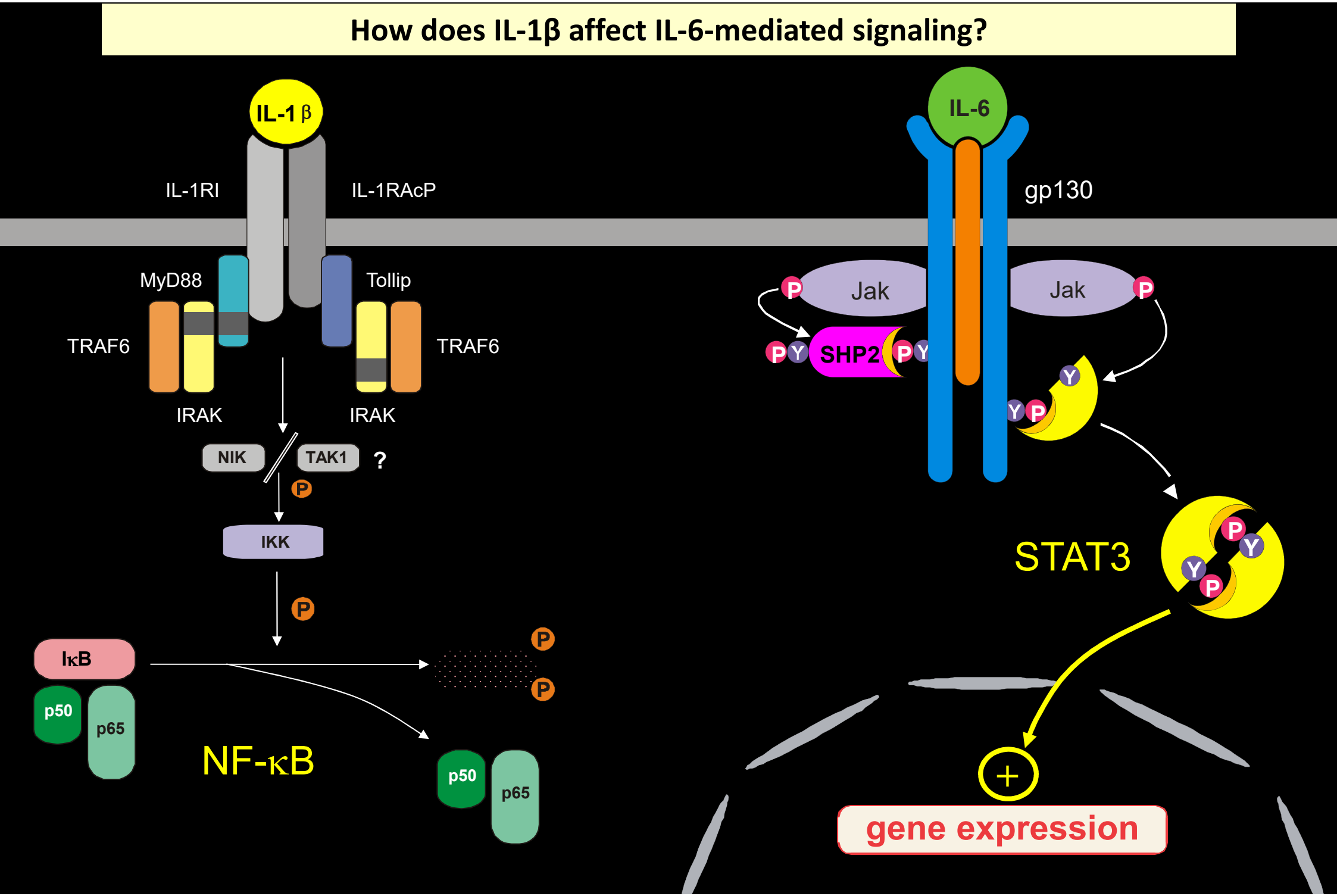
IL-1β inhibits IL-6-induced $\alpha_2$macrogloblin synthesis in rat hepatocytes

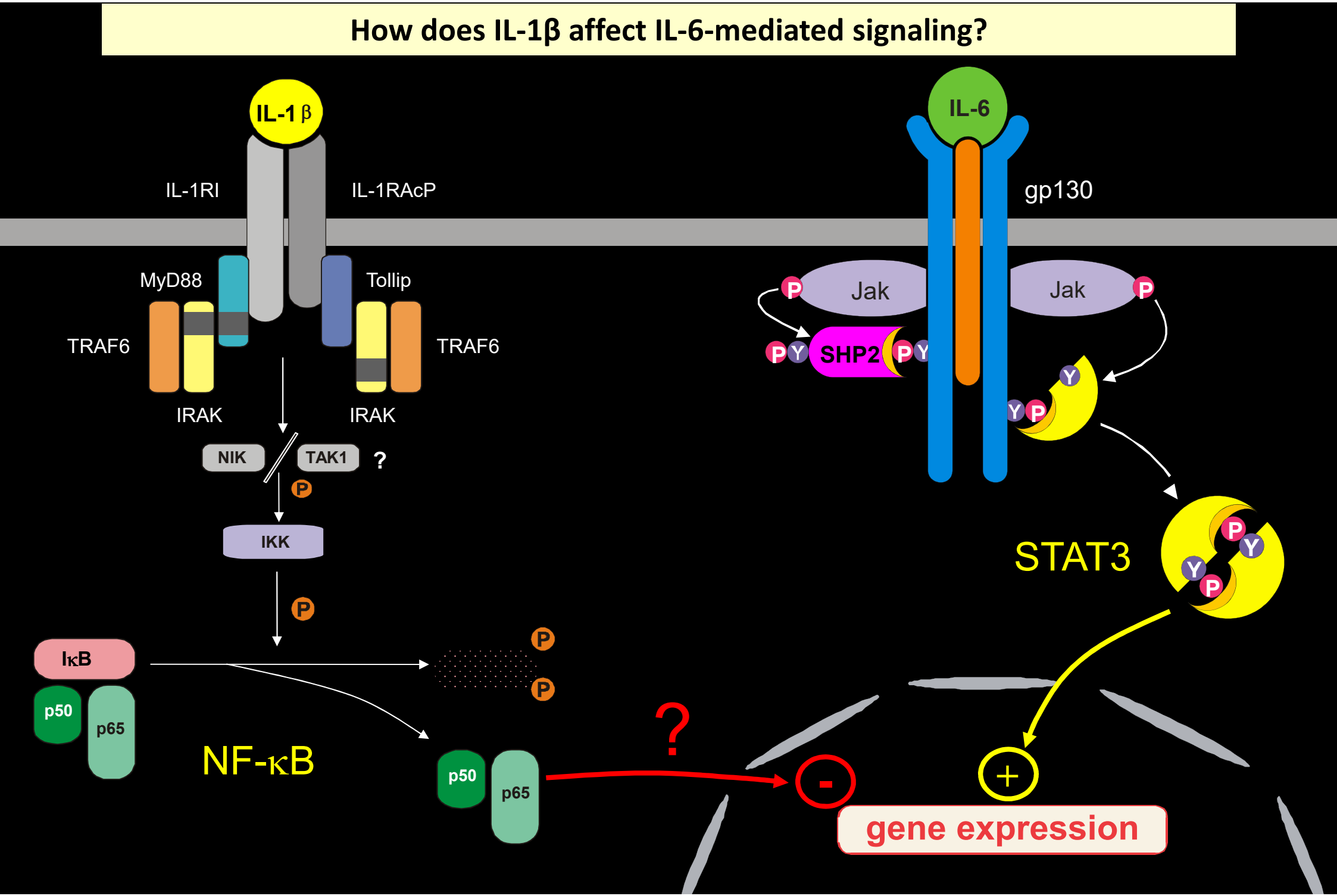


Andus et al. (1988) Eur J Biochem 173, 287 - 293

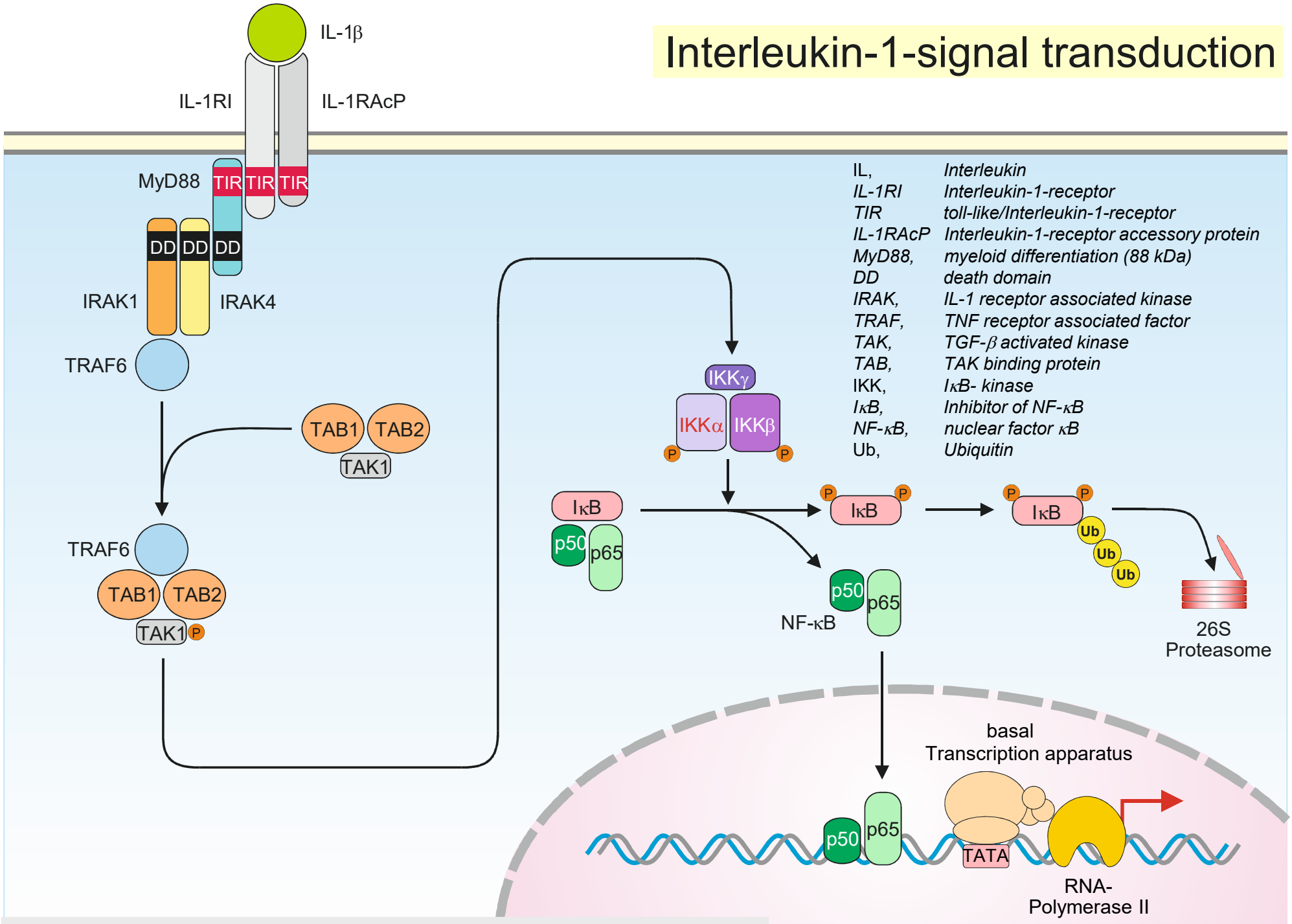
178 citations (07/2022)

How does IL-1β affect IL-6-mediated signaling?



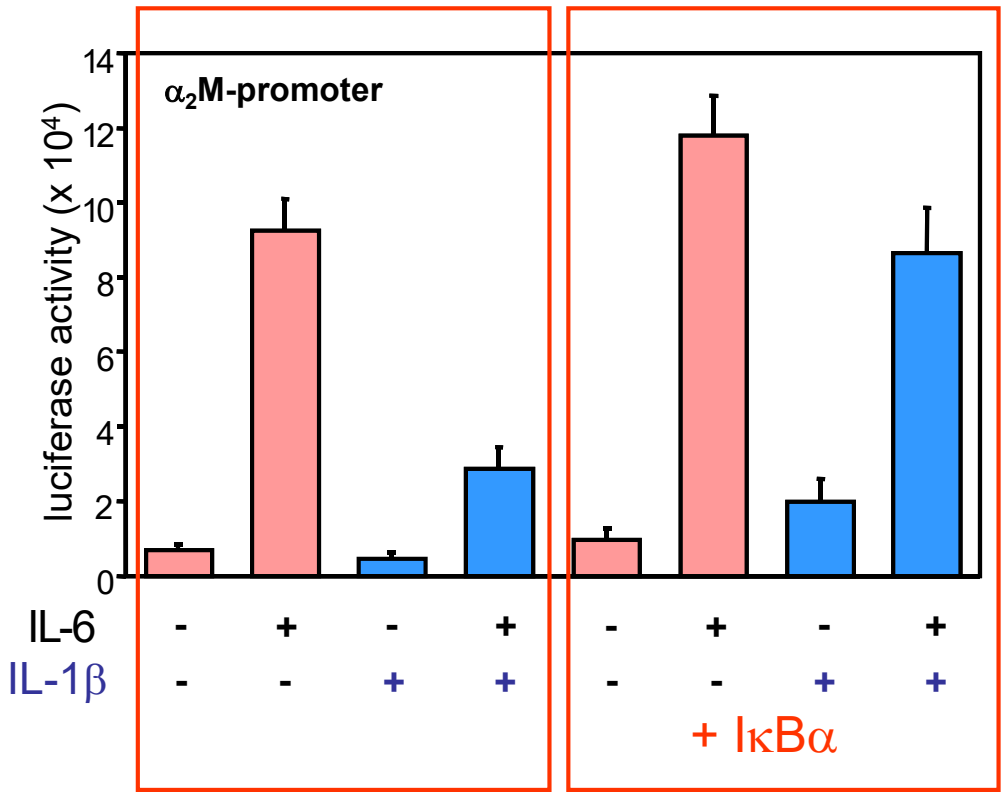

How does IL-1β affect IL-6-mediated signaling?
IL-1 β
IL-1RI
IL-1RAcP
MyD88
Tollip
TRAF6
TRAF6
IRAK
IRAK
NIK
TAK1
?
P
IKK
P
IκB
p50
p65
P
P
NF-κB
p50
p65
?
-
+
gene expression
IL-6
gp130
P
Jak
Jak
P
P
Y
SHP2
P
Y
Y
Y
P
STAT3
P
Y
Y
P

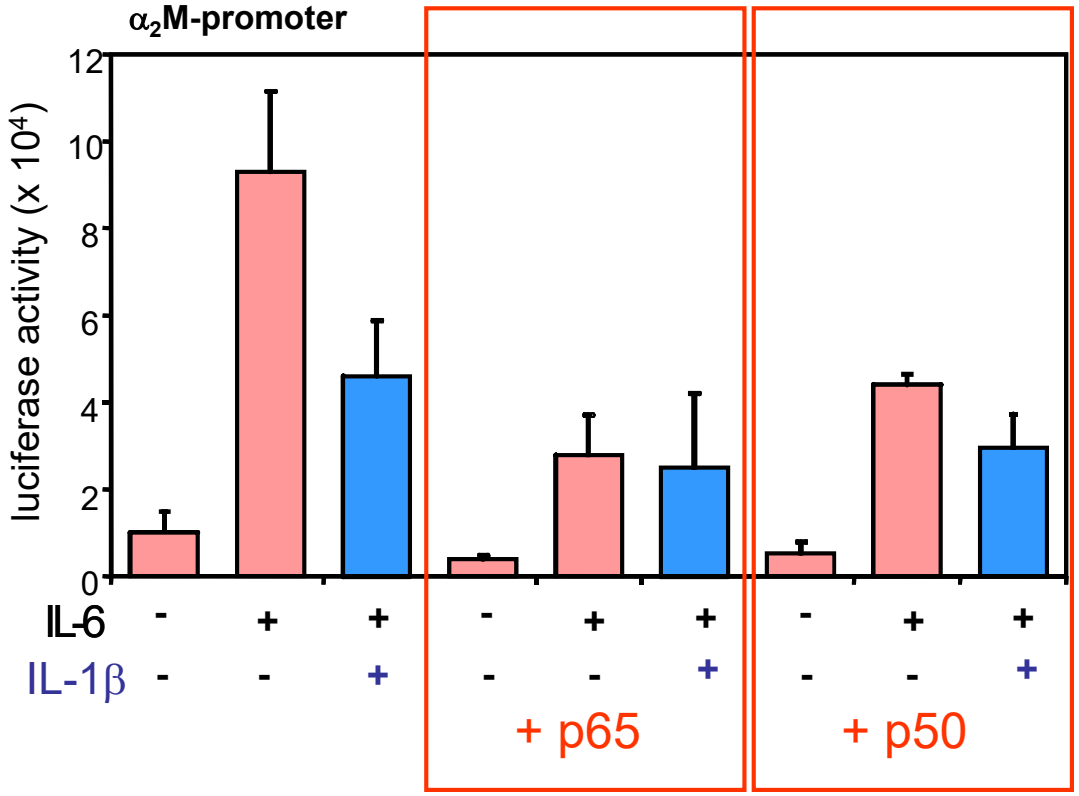
Interleukin-1-signal transduction

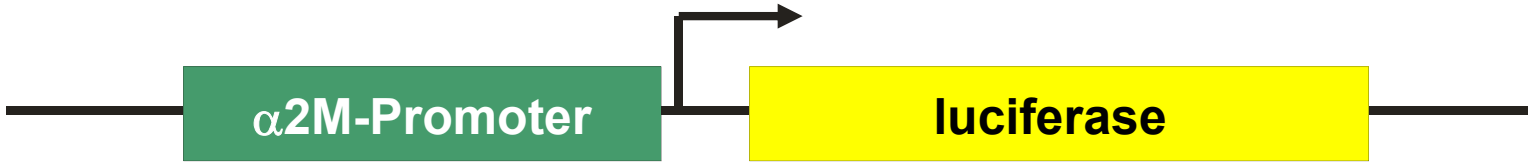


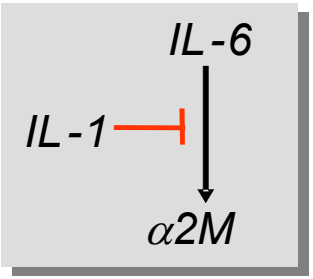
IL,	*Interleukin*
IL-1RI	*Interleukin-1-receptor*
TIR	*toll-like/Interleukin-1-receptor*
IL-1RAcP	*Interleukin-1-receptor accessory protein*
MyD88,	*myeloid differentiation (88 kDa)*
DD	*death domain*
IRAK,	*IL-1 receptor associated kinase*
TRAF,	*TNF receptor associated factor*
TAK,	*TGF-β activated kinase*
TAB,	*TAK binding protein*
IKK,	*IκB- kinase*
IκB,	*Inhibitor of NF-κB*
NF-κB,	*nuclear factor κB*
Ub,	*Ubiquitin*

IL-1β inhibits α_2M-promoter-activity via NF-κB activation





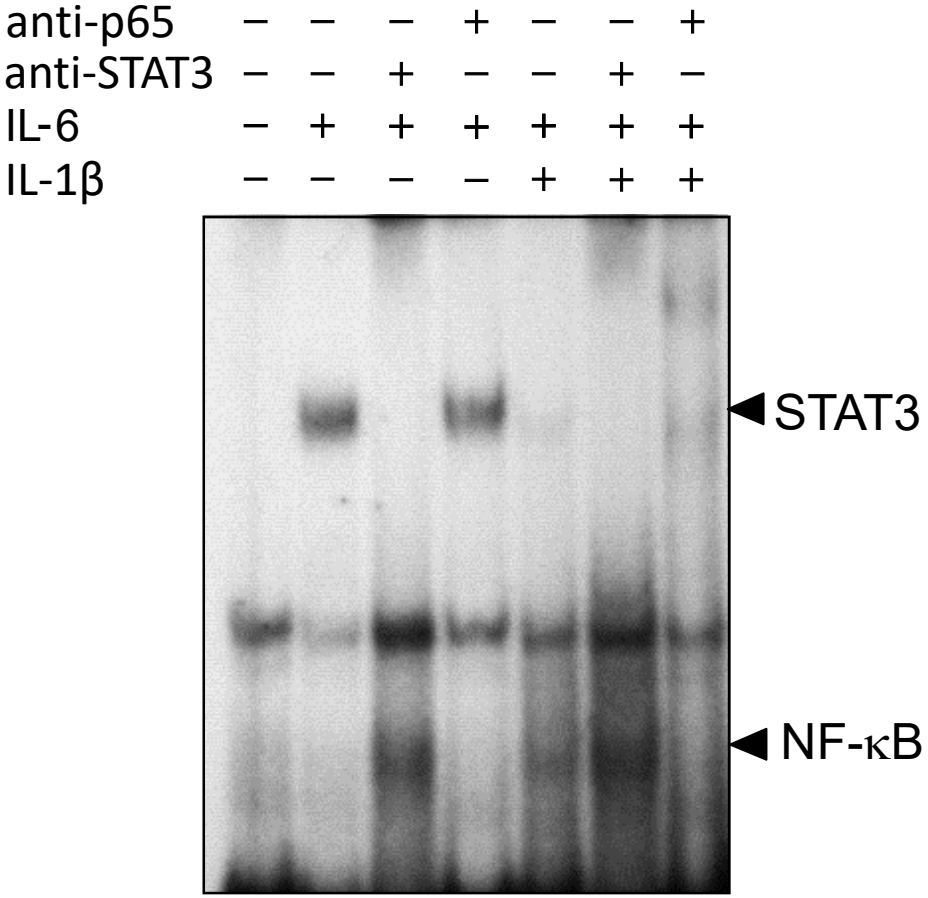


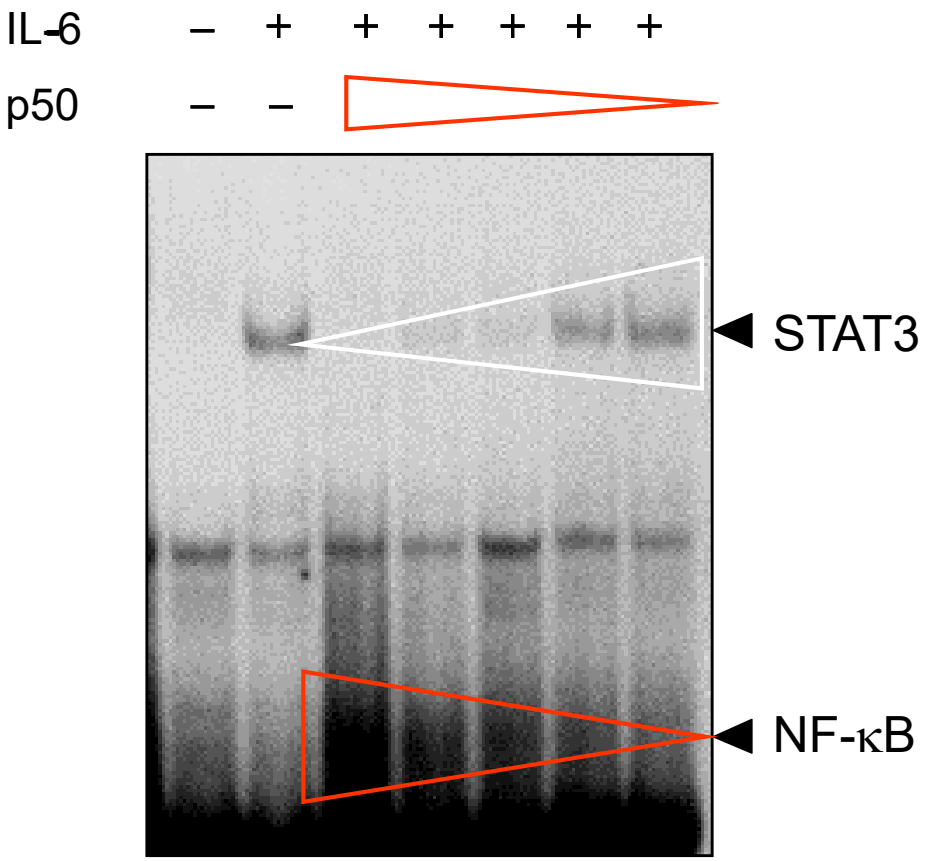


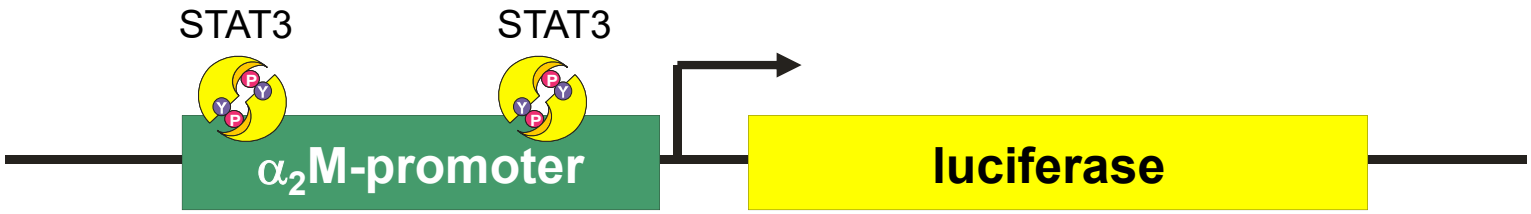
HepG2

Bode et al. (2001) J Immunol 167, 1469 - 1481 43 citations (07/2022)

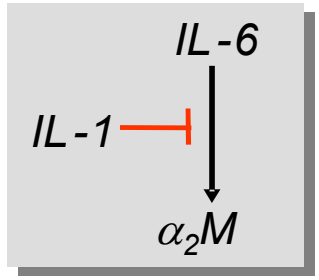
NF-κB and STAT3 bind to the α_2M-promoter







HepG2



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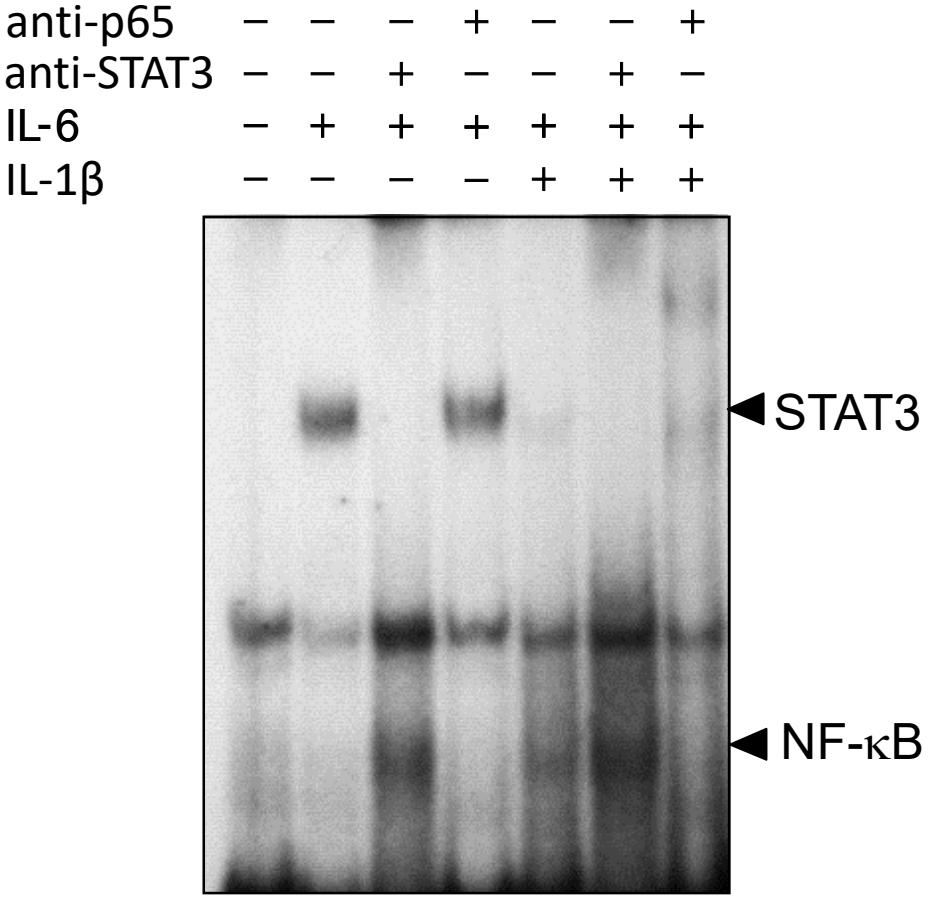

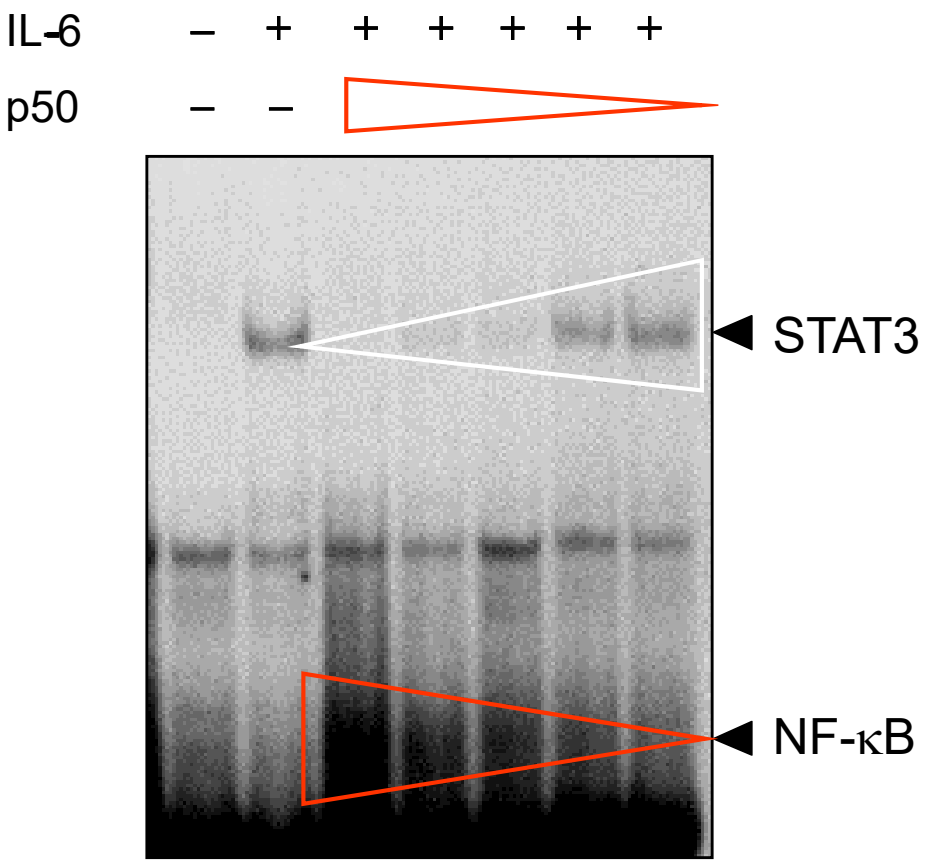

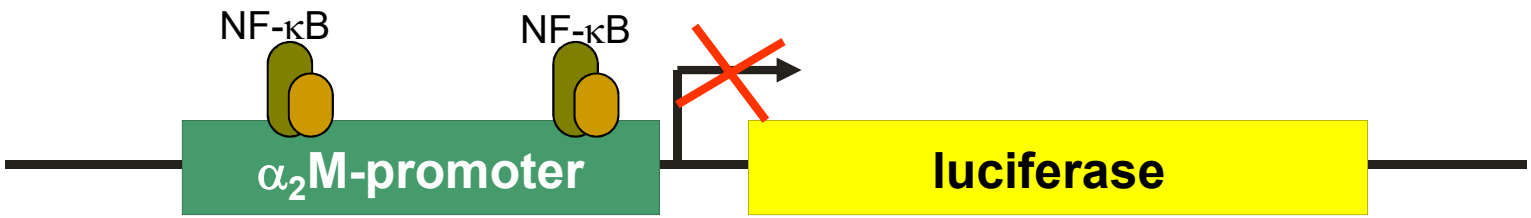

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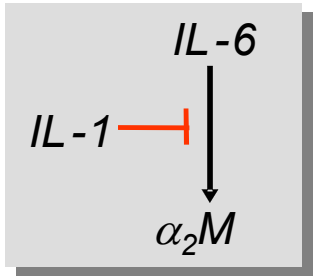

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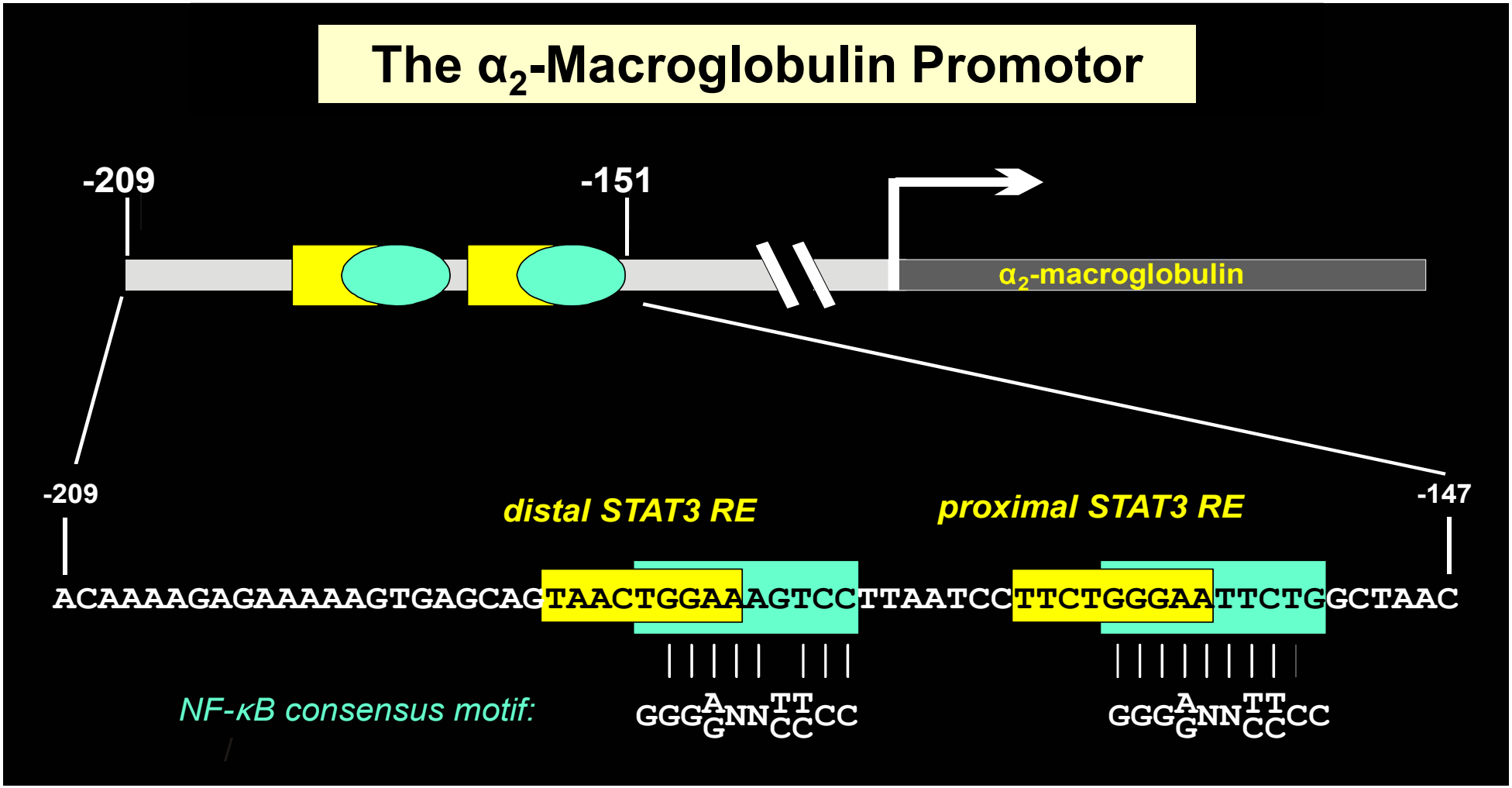

STAT3 and NF- κB compete for an overlapping response element

The Inhibitory Effect of IL-1β on IL-6-Induced α2-Macroglobulin Expression Is Due to Activation of NF-κB[1]

Journal of Immunology, 2001, 167:1469-1481

Johannes G. Bode,[2]* Richard Fischer,† Dieter Häussinger,† Lutz Graeve,* Peter C. Heinrich,[3]* and Fred Schaper* 43 citations (07/2022)