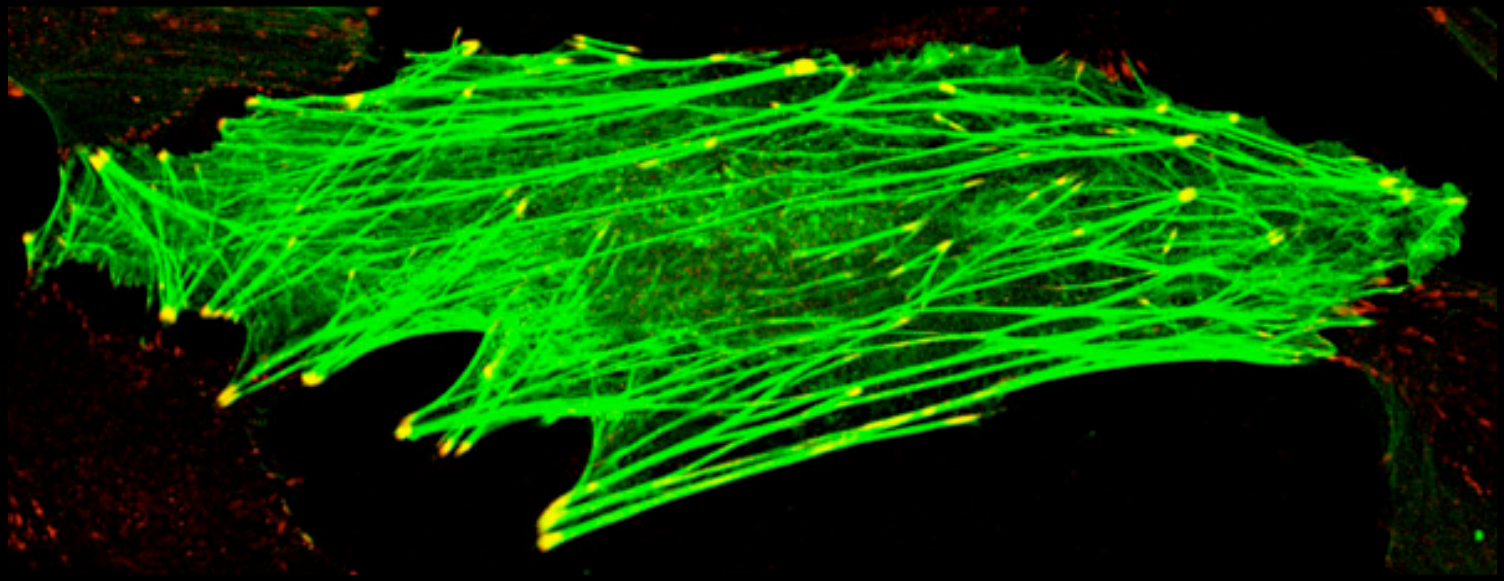
FAK KINASE



- PTK2 protein tyrosine kinase 2 (PTK2)/Focal Adhesion Kinase (FAK) is a focal adhesion-associated protein kinase involved in cellular adhesion and spreading processes.
- With the exception of certain types of blood cells, most cells express FAK.
- FAK activity elicits intracellular signal transduction pathways that promote the turn-over of cell contacts with the extracellular matrix, promoting cell migration.
- FAK is required during development: its KO is lethal

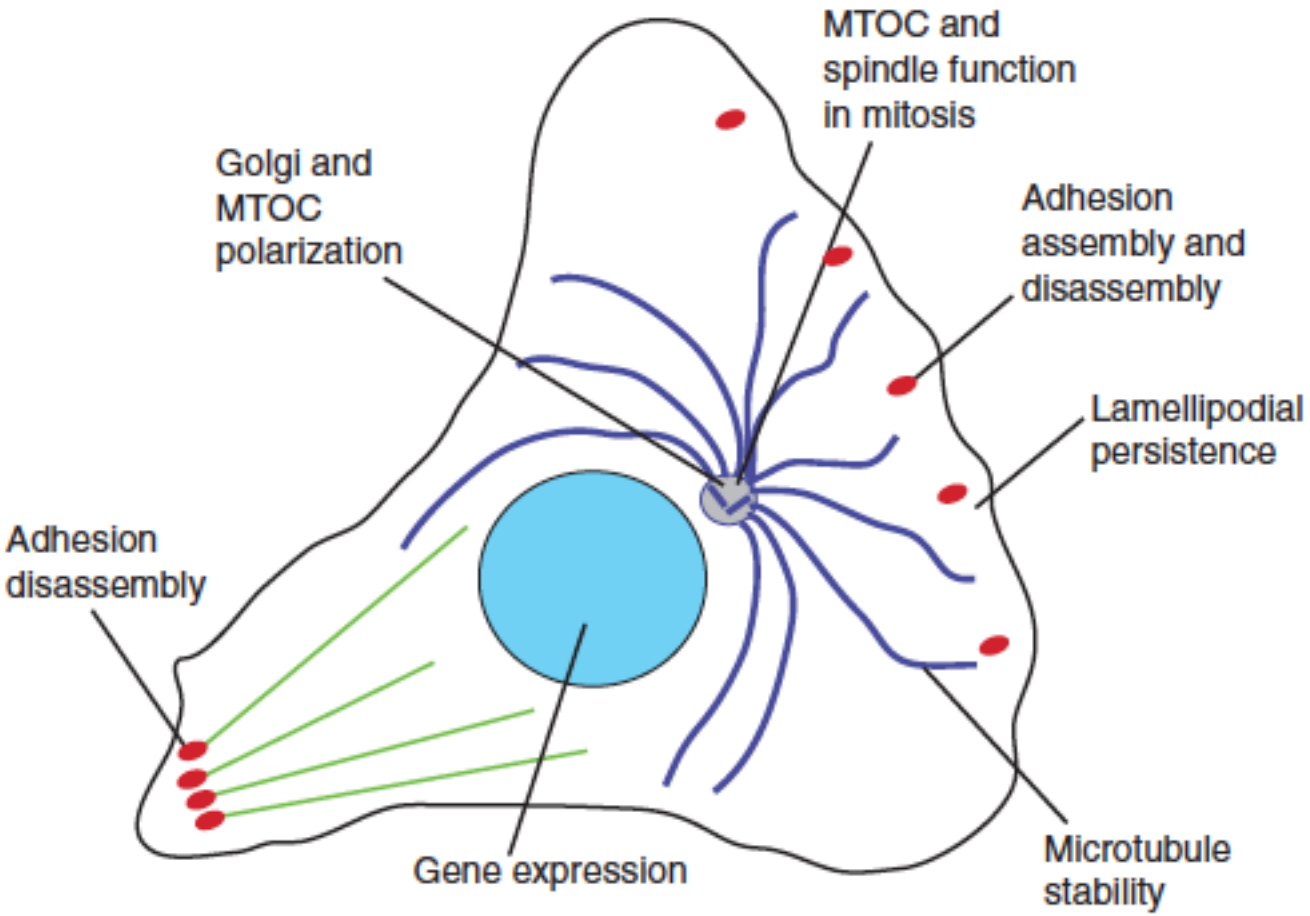


Fig. 2. Major cellular functions of FAK. A migrating cell with the leading edge (right) and trailing edge (left) is shown. Cell-ECM adhesions (red), stress fibers (green), microtubules (dark blue), the MTOC (grey) and nucleus (blue) are illustrated. Black lines denote cellular targets of FAK signaling.

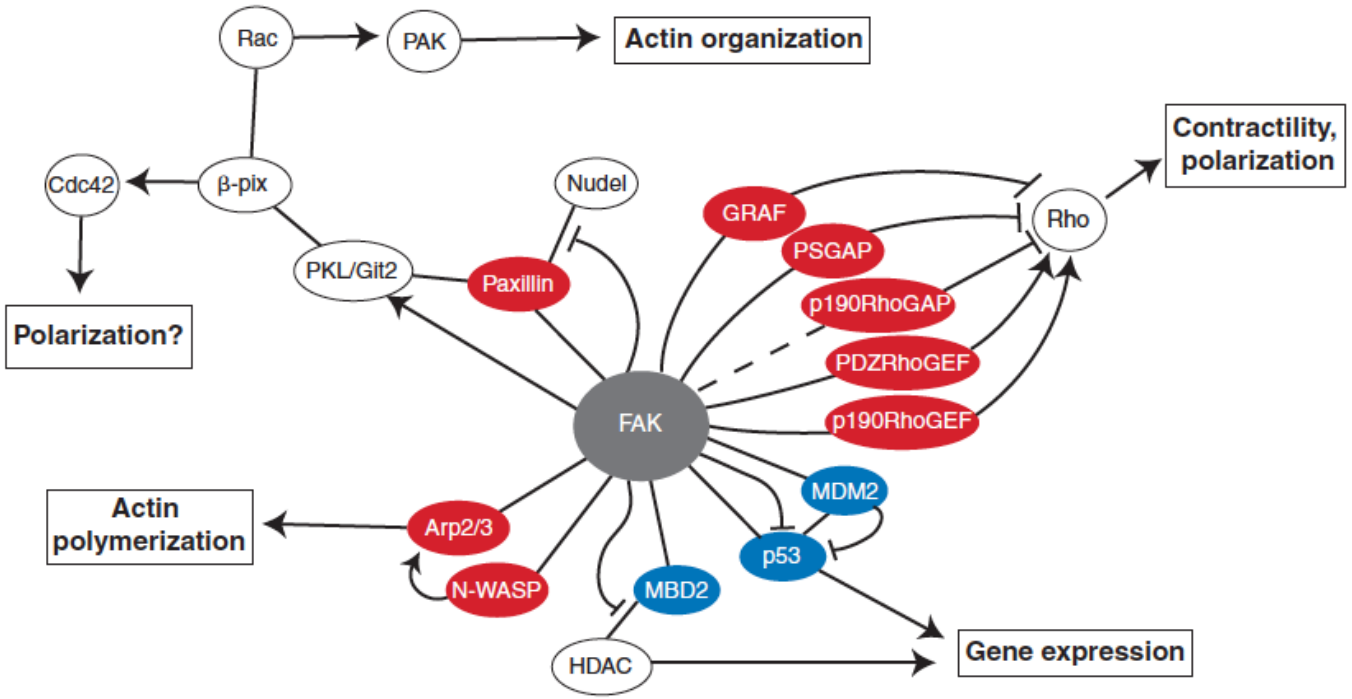


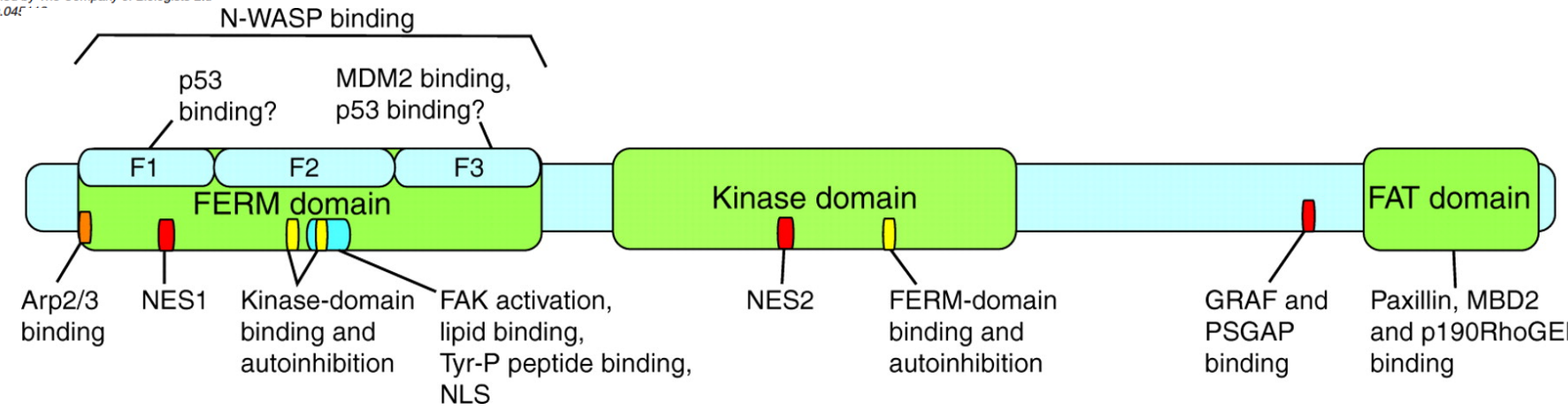
Fig. 3. Networks of FAK signaling that control the actin cytoskeleton and gene expression. Solid lines link proteins that physically interact and dashed lines denote indirect protein-protein interactions. Red proteins are FAK binding partners that are implicated in the regulation of the actin cytoskeleton and blue proteins are FAK binding partners that are implicated in regulating gene expression. Positive (arrows) and negative (bars) regulation of downstream proteins and/or events is indicated.

Cellular functions of FAK kinases: insight into molecular mechanisms and novel functions

Michael D. Schaller
1 Medical Center Drive, Department of Biochemistry, Mary Babb Randolph Cancer Center and Center for Cardiovascular and Respiratory Sciences, West Virginia University School of Medicine, PO Box 9142, Morgantown, WV 26506, USA
mschaller@hsc.wvu.edu

Journal of Cell Science 123, 1007-1013

doi:10.1242/jcs.045



Sequence and structural analysis reveals 4 distinct domains:
① an N-terminal FERM domain;
② a centrally located catalytic tyrosine kinase domain;
③ a C-terminal focal-adhesion targeting (FAT) domain (a four-helix bundle);
④ and an unstructured proline-rich region between the catalytic and FAT domains

The FERM domain docks with the catalytic domain to autoinhibit kinase activity, but also interacts with other molecules to control FAK signaling. The FAT domain and proline-rich region are also docking sites for binding partners that function in localization and downstream signaling.

MOLECULAR AND CELLULAR BIOLOGY, Feb. 2002, p. 1203–1217 Vol. 22, No. 4
0270-7306/02/$04.00+0 DOI: 10.1128/MCB.22.4.1203–1217.2002

Focal Adhesions Require Catalytic Activity of Src Family Kinases To Mediate Integrin-Matrix Adhesion

Leiming Li,[1,2] Masaya Okura,[1]† and Akira Imamoto[1,2,3]*

The Ben May Institute for Cancer Research and Center for Molecular Oncology,[1] Committee on Cell Physiology,[2] and Committee on Cancer Biology,[3] The University of Chicago, Chicago, Illinois 60637

Received 9 July 2001/Returned for modification 17 August 2001/Accepted 20 November 2001

Cytokine Receptors Activate Multiple Cytoplasmic PTK Families

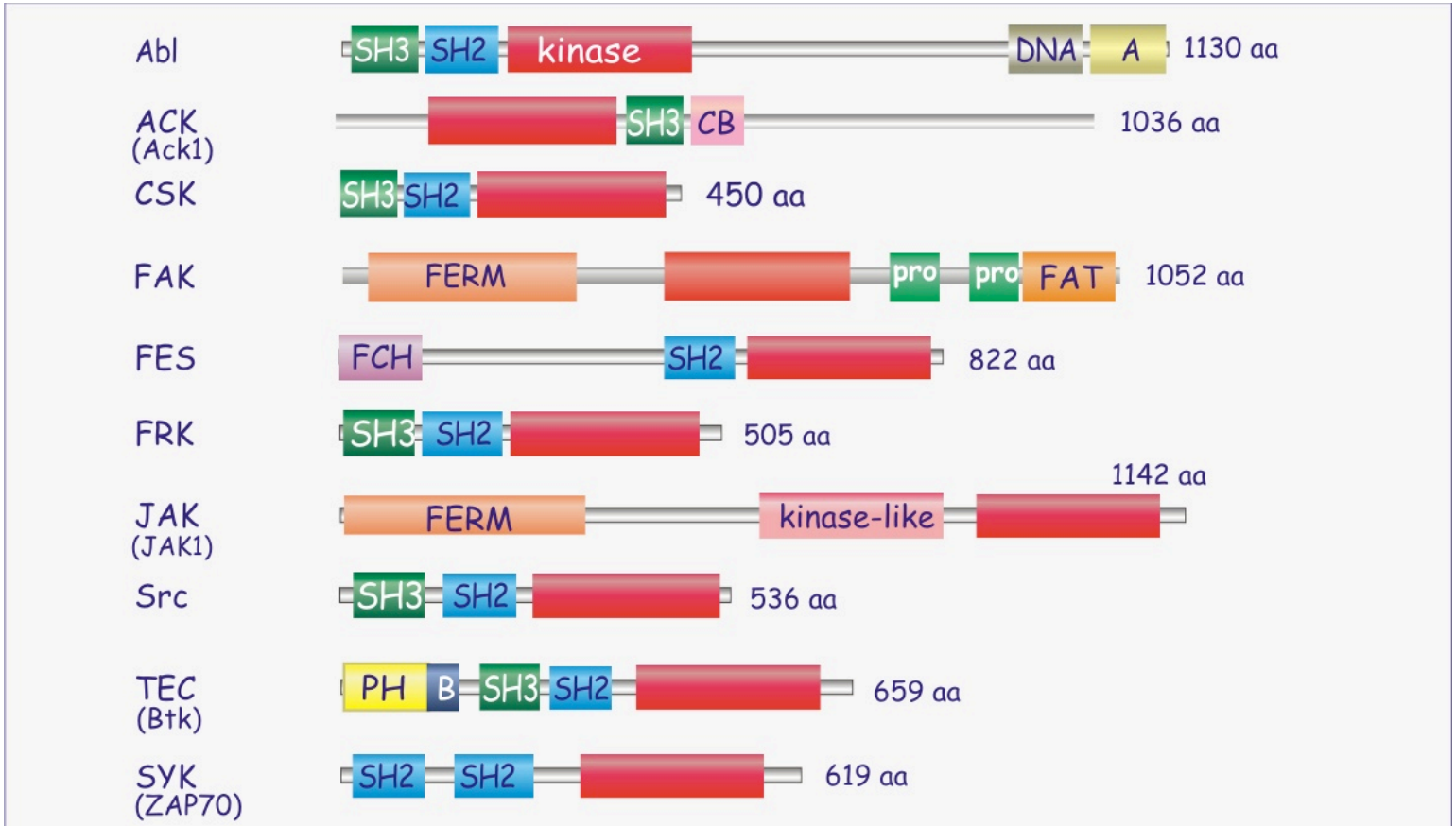


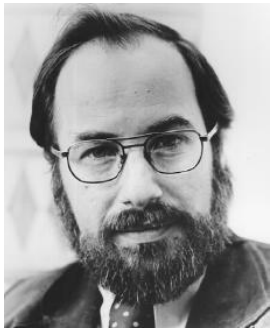
Table 1 Characteristics of Src family kinases

Src family member[a]	*Pattern of expression*	*Isoforms*	*Oncogenic forms*[b]
Blk	B cells		
Fgr	Myeloid cells, B cells		Oncogenic fusion with gag sequences in feline sarcoma virus; overexpressed in some leukemias and lymphomas
Fyn	Ubiquitous	T-cell-specific isoform (Fyn T)	
Hck	Myeloid cells	Two different translational starts	
Lck	T cells, NK cells, brain		Overexpressed in T-cell acute lymphocytic leukemias
Lyn	Brain, B cells, myeloid cells	Two alternatively spliced forms	
Src	Ubiquitous	Neuron-specific isoforms	Mutated and truncated in retroviruses; truncated in colon cancer; overexpressed in mammary, pancreatic and other cancers
Yes	Ubiquitous		Oncogenic fusion with gag sequences in avian sarcoma viruses; highly expressed in colon, malignant melanoma and other cancers
Yrk	Ubiquitous		

[a]Thomas and Brugge (1997). [b]Blume-Jensen and Hunter (2001)

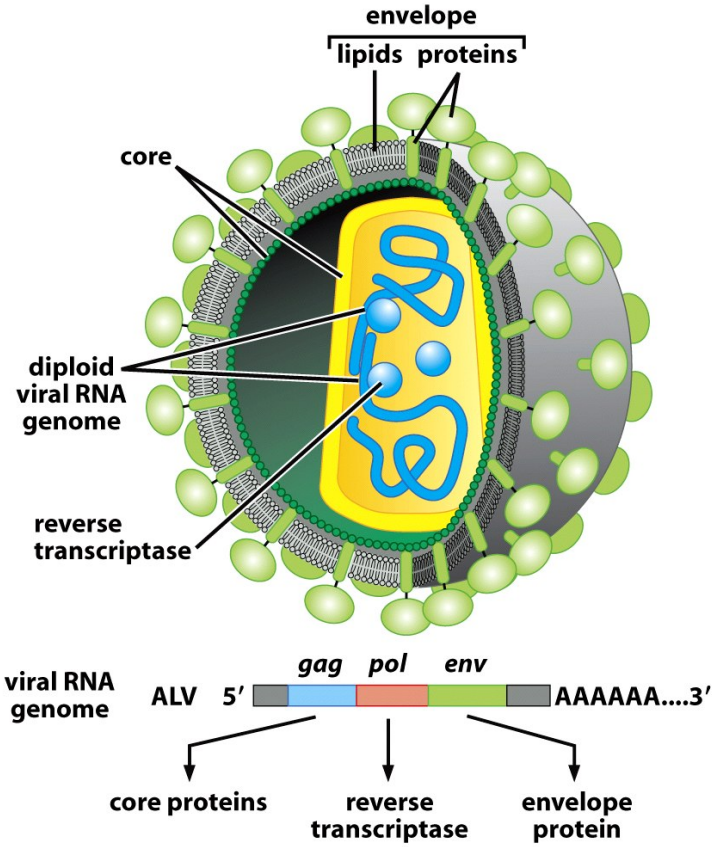
The story of Src

What Viruses and Nobel Laureates Taught Us About Cancer



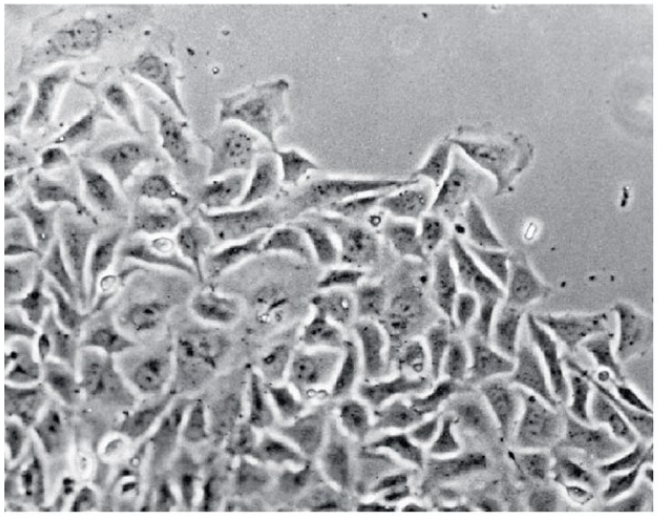
Howard Temin and David Baltimore

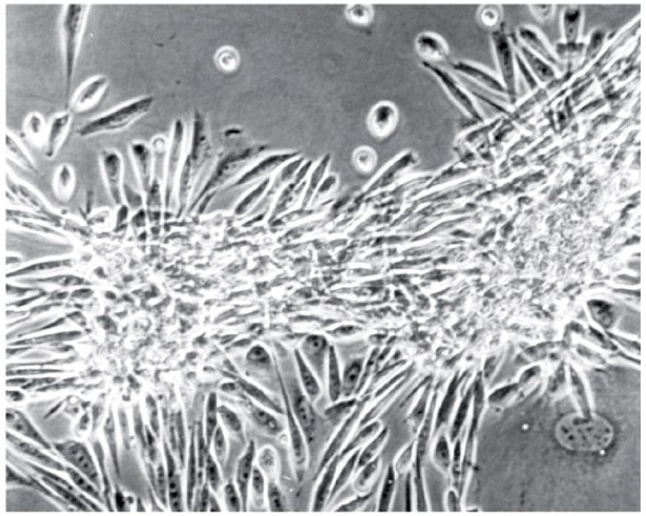
Nobel Prize in Physiology and Medicine 1975



No contact inhibition of cell division

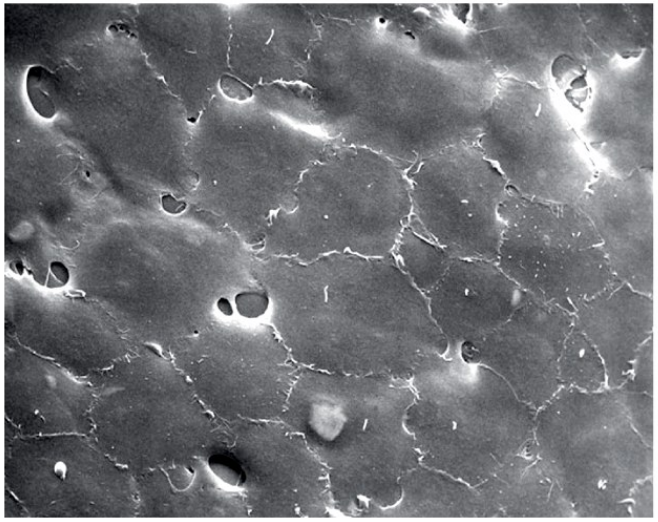
Normal

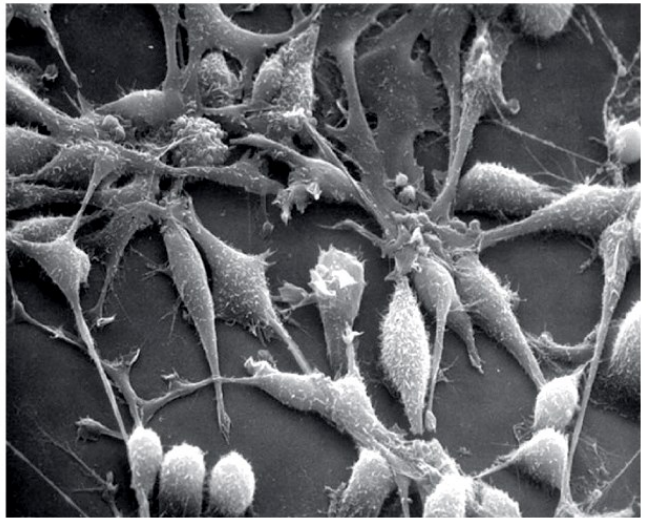




Cancer

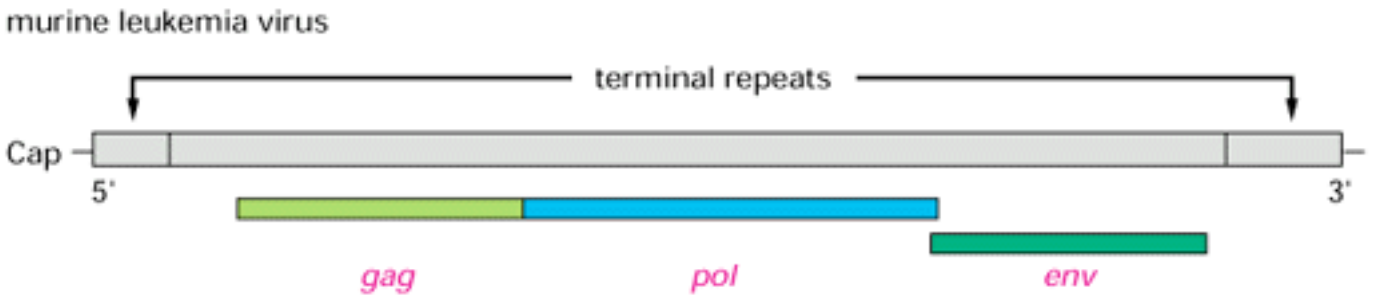
Normal





Cancer

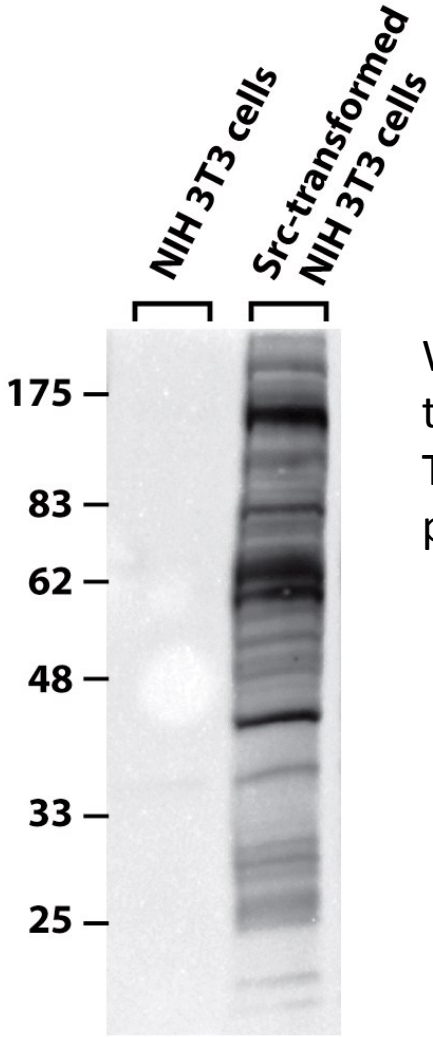
RSV is a retrovirus
These viruses make a DNA copy of their RNA genome
and insert it into your DNA



Alberts et al. Fig. 24-23

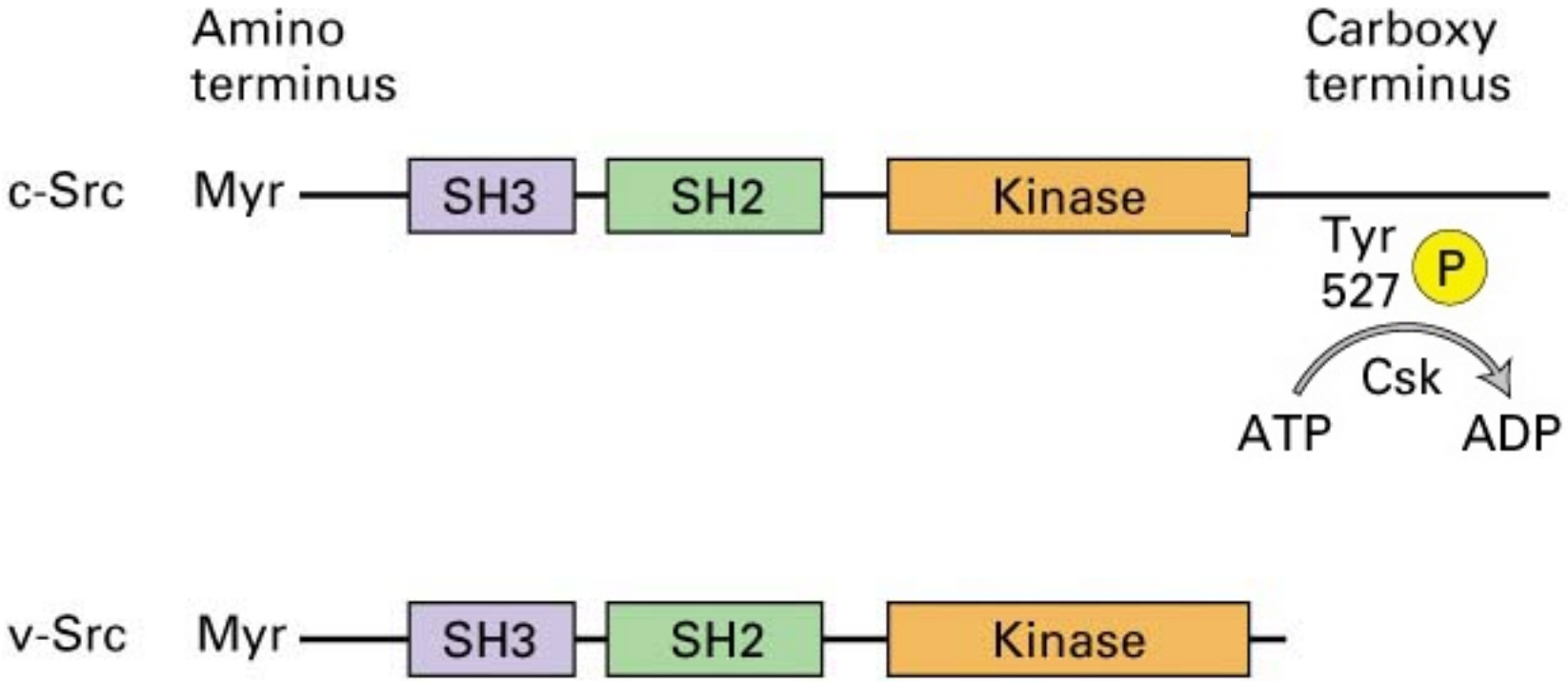
Normally, Src kinase intrinsic activity is low

What makes Src so active in transformed cells?



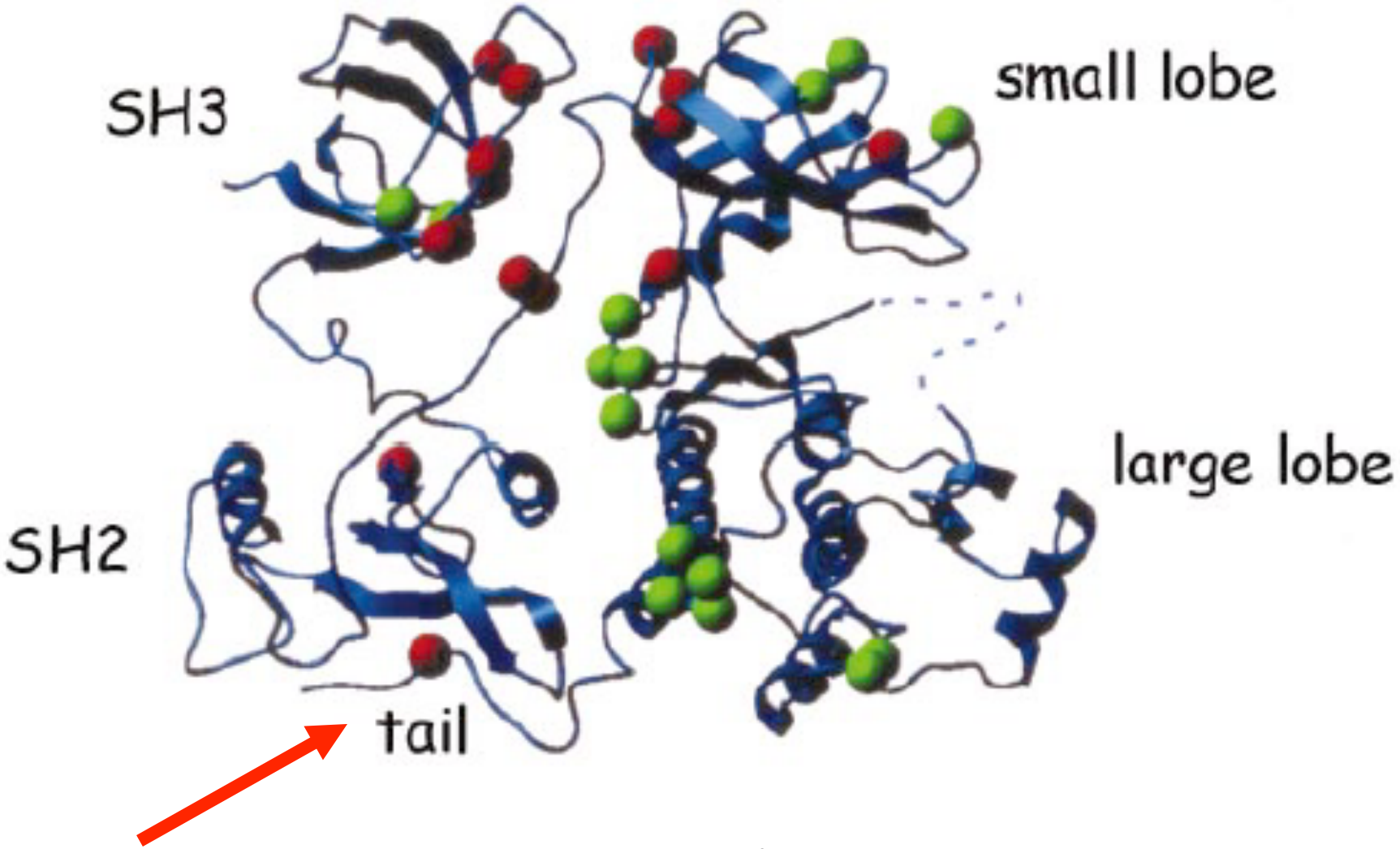
Western Blot with antibody that recognizes Tyr phosphorylated proteins

The structures of c-src and v-src provided an important clue!



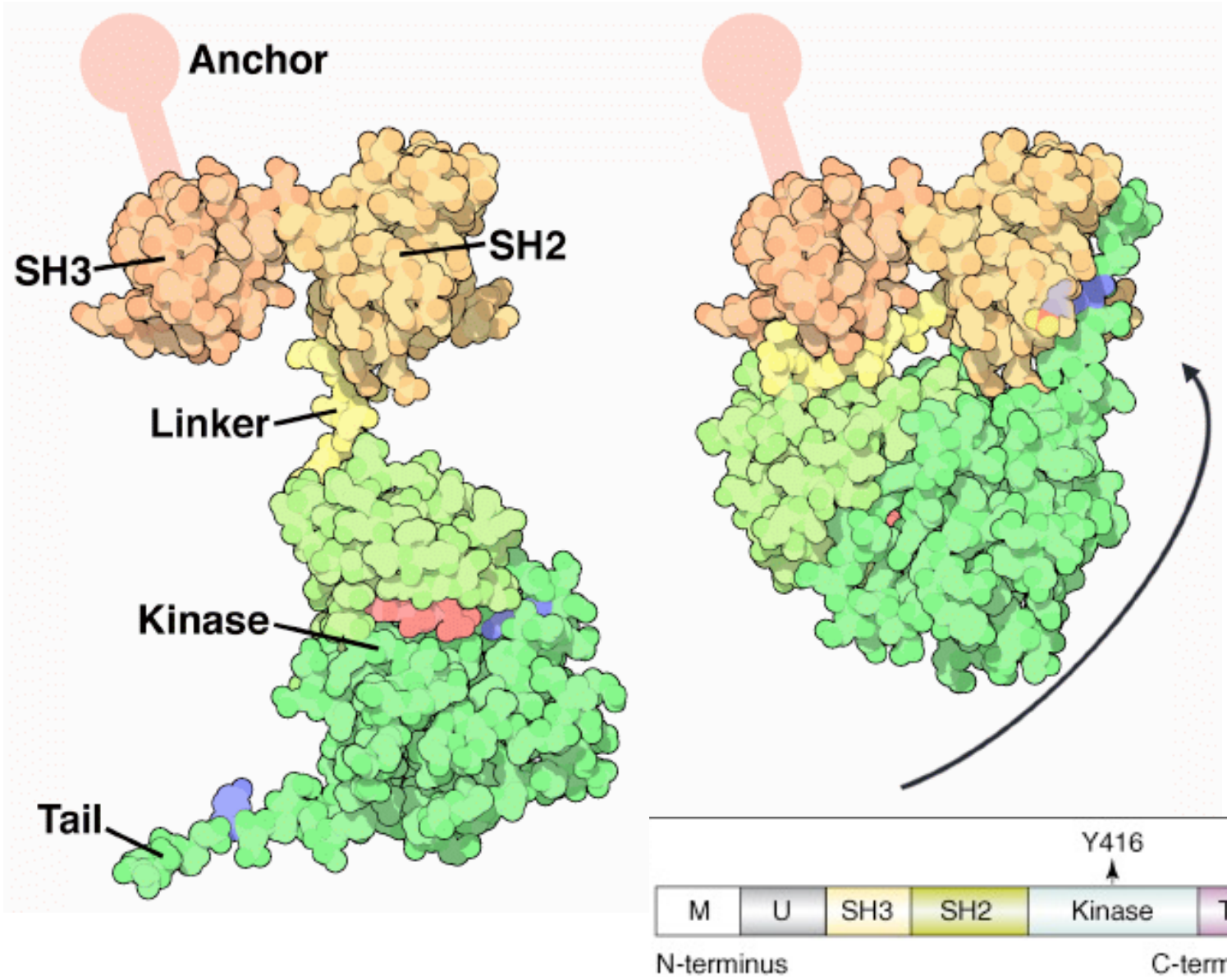
Lodish et al. Fig. 24-17

Scientists have determined the precise 3-dimensional structure of Src

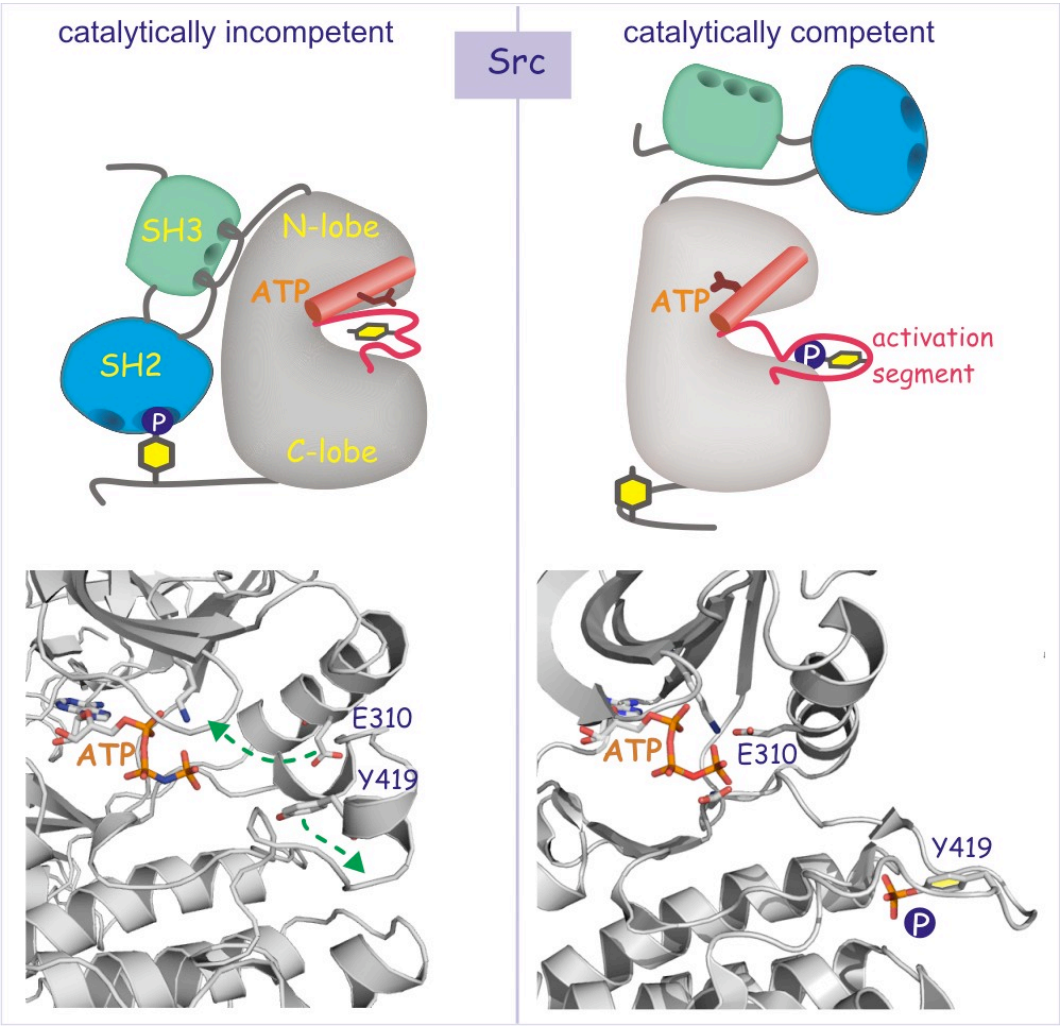


Xu et al. Nature. 1997 385:595-602

Tyrosine phosphorylation of the C-terminus creates an intramolecular and inhibitory interaction



Regulation of Src kinase activity

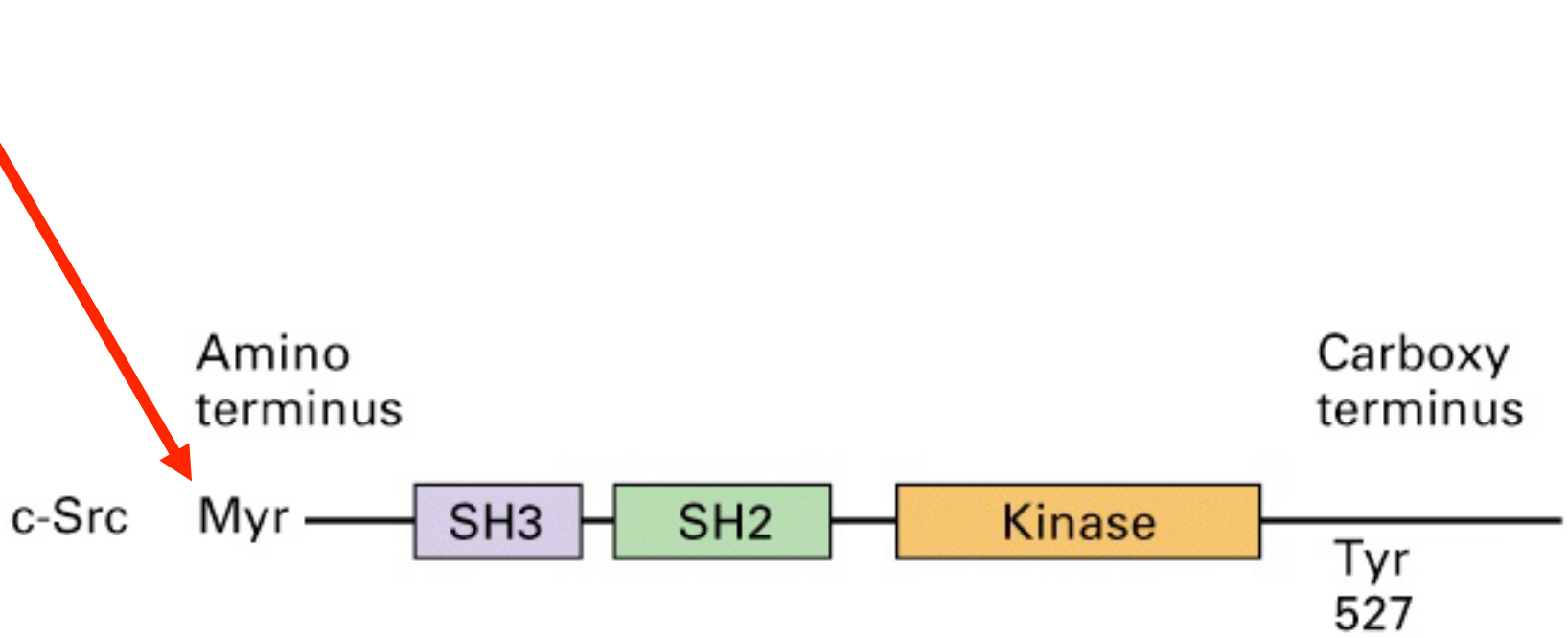


Phosphorylation of the C-terminal tyrosine of Src causes binding of its own SH2 domain. This event places the SH3 domain adjacent to the N-terminal lobe of the kinase domain which affects the coordination of ATP (orange). Detachment of the SH2 domain, through dephosphorhylation of the carboxy-terminal tyrosine (or through binding of the SH2 domain to tyrosine phosphates of other proteins) removes this restraint.

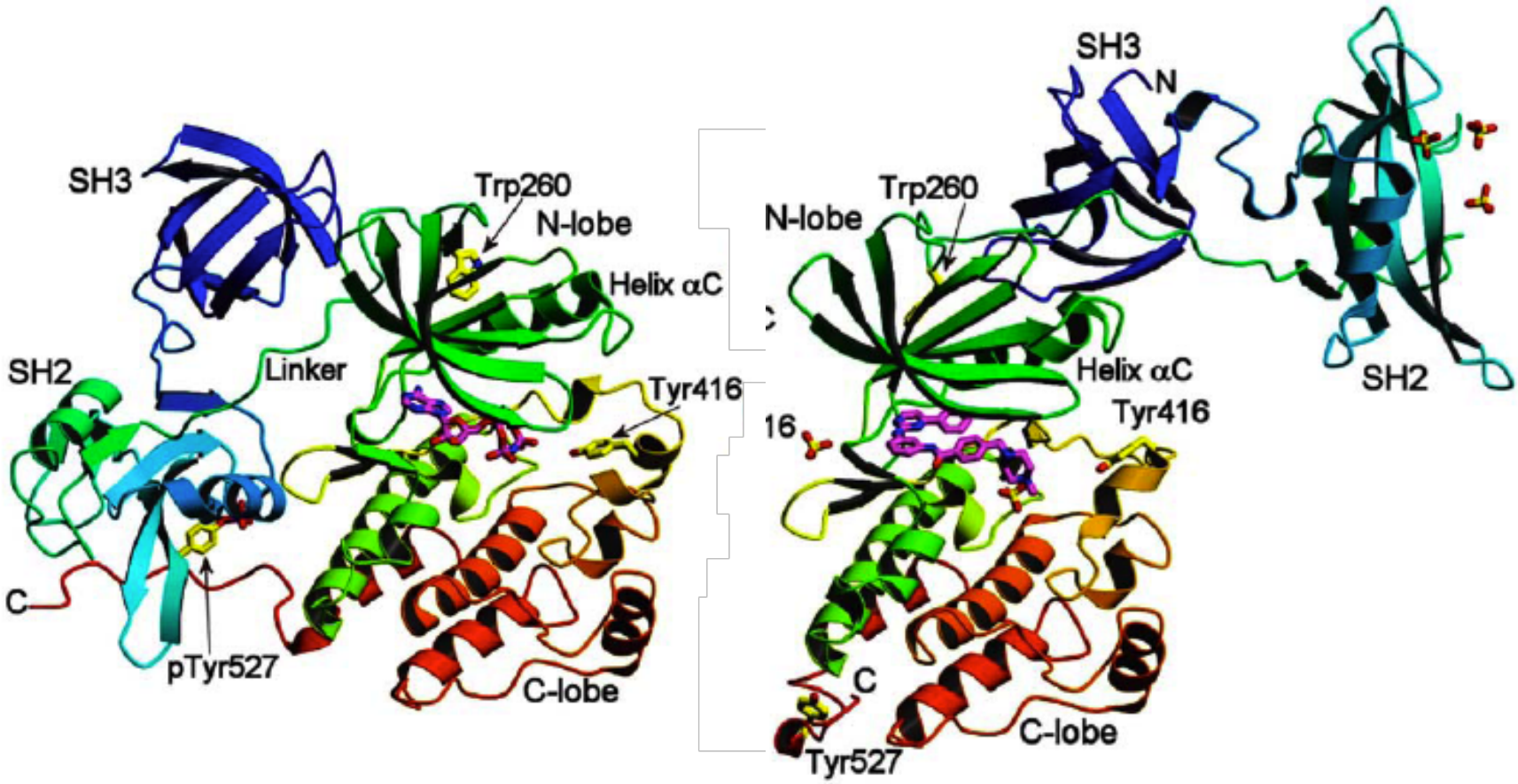
Subsequent phosphorylation of tyrosine-419 in the activation segment liberates the entry path for substrate; the protein kinase is now catalytically competent.

Where is Src within cells?

This is a covalently attached lipid: what might that mean?



A more detailed model of Src activation

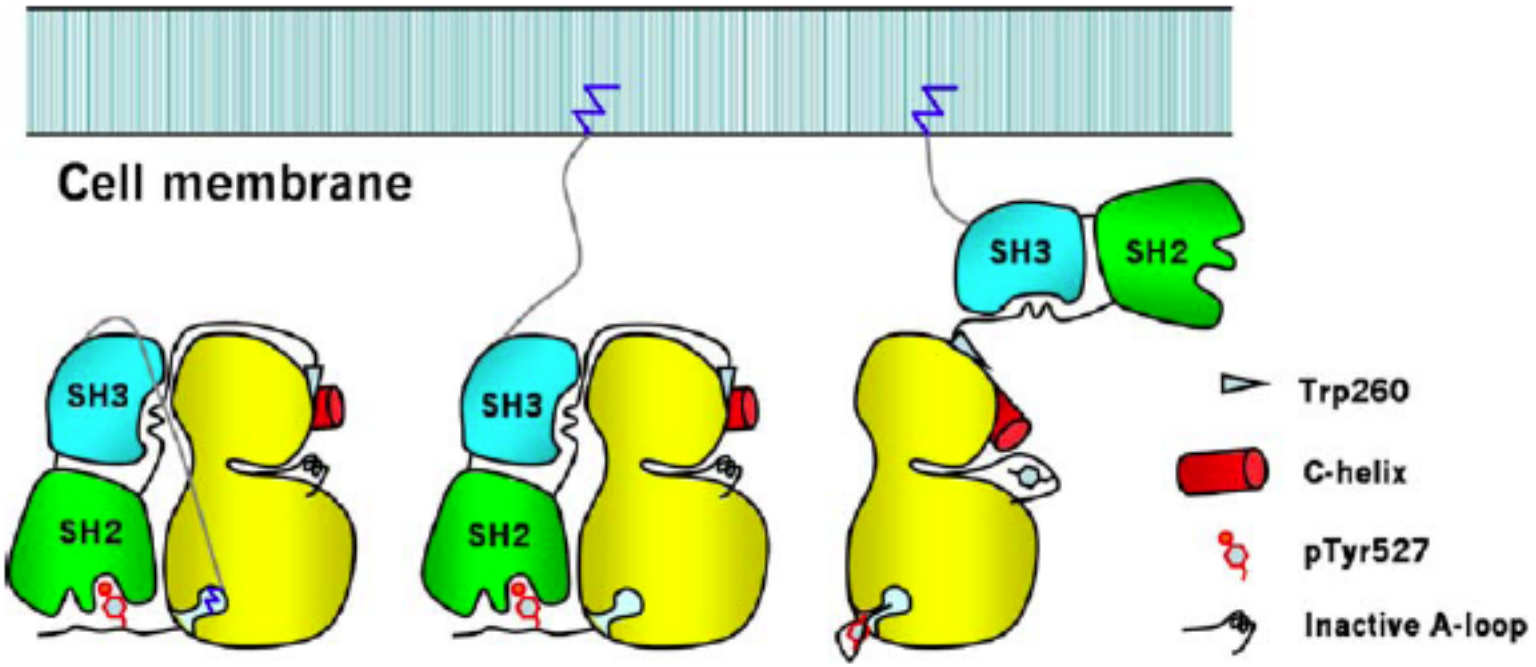


Closed = OFF

Open = ON

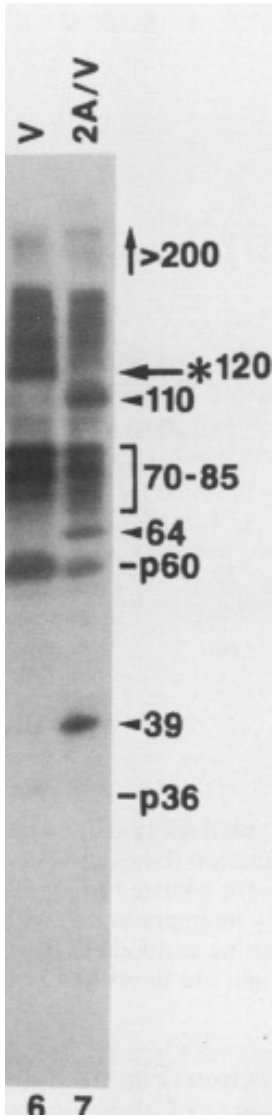
Cowen-Jacob et al. Structure 13, 861-871 (2005)

A more detailed model of Src activation



Cowen-Jacob et al. Structure 13, 861-871 (2005)

Identifying The Targets of Src: 1989…



Western blotting with anti-phosphotyrosine antibodies

V = v-Src transfected cells

2A/V = non-myristylated v-Src transfected cells

p120 catenin: modulates cell-cell adhesion

Reynolds et al. MCB (1989)

Identifying the targets of Src

Few Examples

- STAT3: modulates cell-cell adhesion
- p120 catenin: modulates cell-cell adhesion
- Cortactin A: regulates actin polymerization
- Focal Adhesion Kinase: involved in cell-matrix interactions

Mike Schaller, ex-UNC

MOLECULAR AND CELLULAR BIOLOGY, Feb. 2002, p. 1203–1217 Vol. 22, No. 4
0270-7306/02/$04.00+0 DOI: 10.1128/MCB.22.4.1203–1217.2002

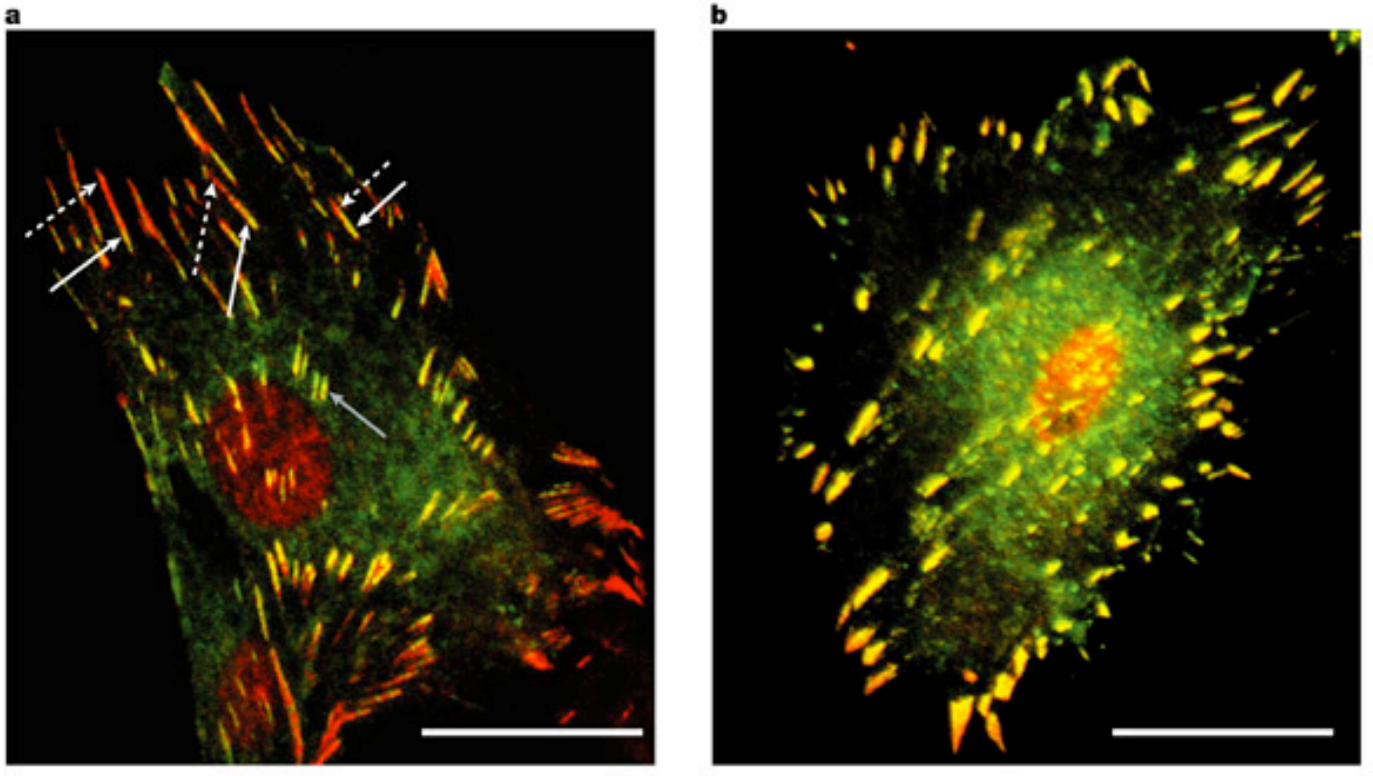
Focal Adhesions Require Catalytic Activity of Src Family Kinases To Mediate Integrin-Matrix Adhesion

Leiming Li,[1,2] Masaya Okura,[1]† and Akira Imamoto[1,2,3]*

The Ben May Institute for Cancer Research and Center for Molecular Oncology,[1] Committee on Cell Physiology,[2] and Committee on Cancer Biology,[3] The University of Chicago, Chicago, Illinois 60637

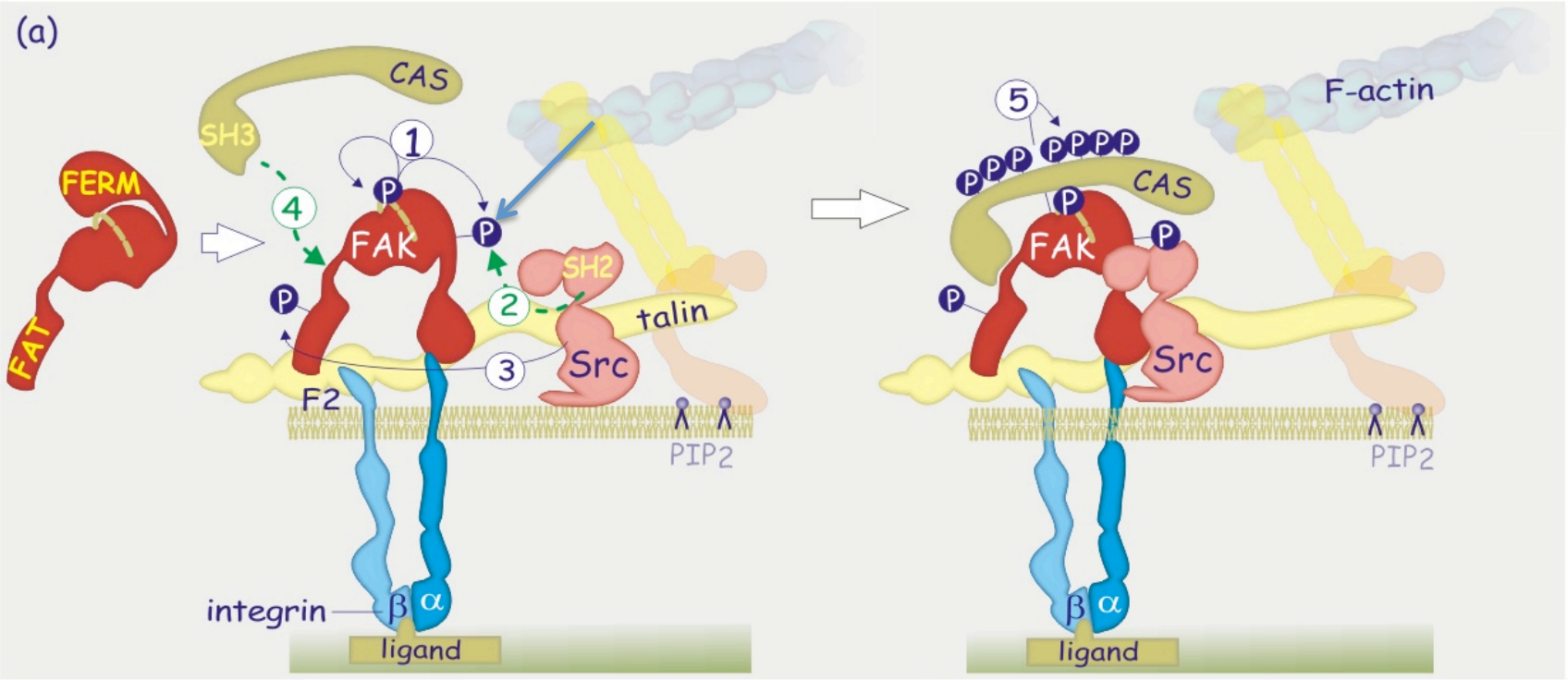
Received 9 July 2001/Returned for modification 17 August 2001/Accepted 20 November 2001

(A) In the case od inactive src, the focal adhesions are enlarged (at the termini of stabilized actin cables).
FAK is already at the membrane proximal region (broken arrow) and FAK–v-Src-KD is localized at the membrane-distal region.



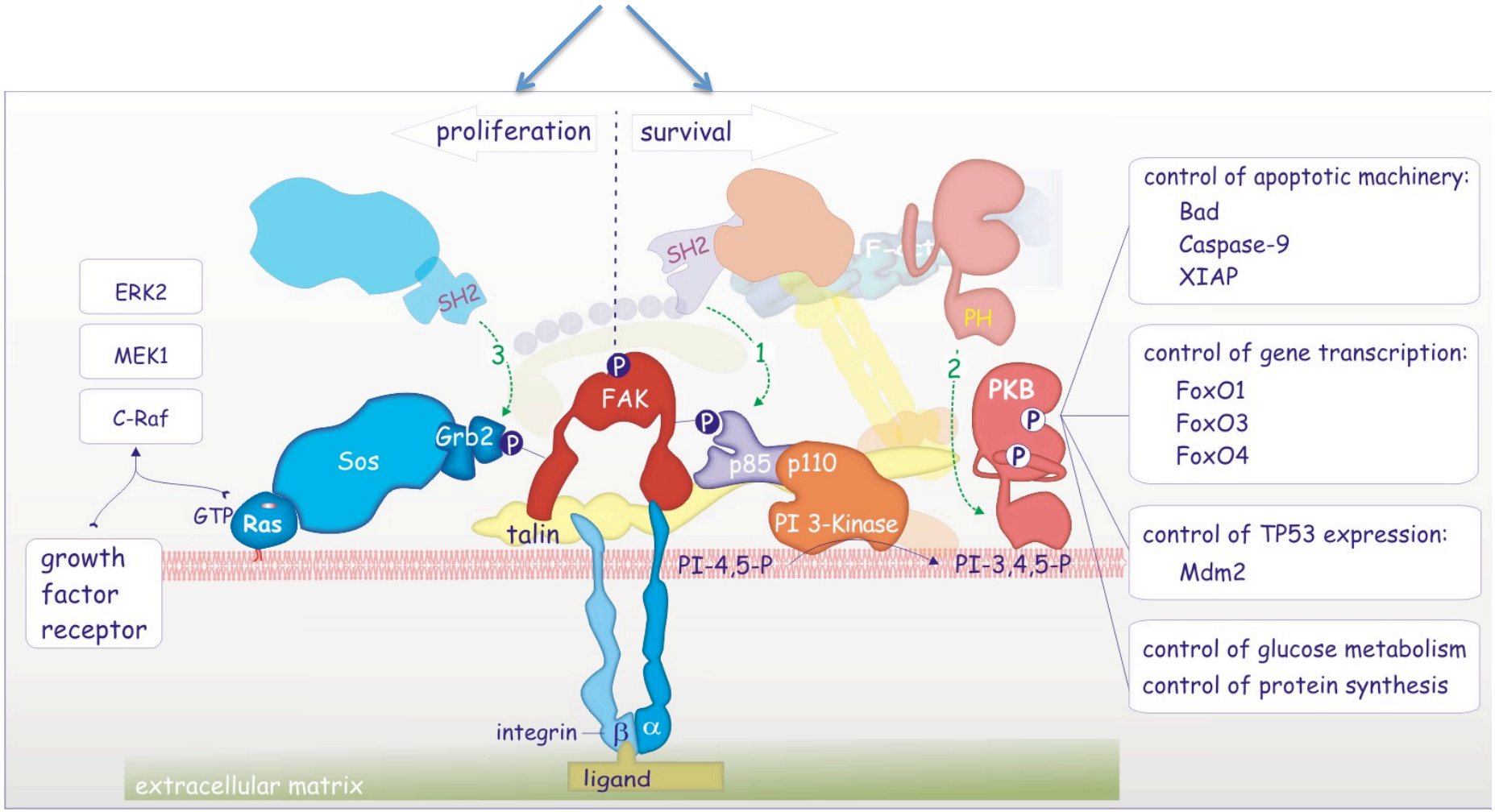
(B) FAK (red) and v-Src (green) co-localize in smaller adhesion structures at the cell periphery when v-Src is active, and focal adhesions (and the associated actin filaments) are dynamically regulated. These adhesion characteristics indicate that v-Src-KD impairs adhesion turnover and that focal-adhesion size is linked to Src-dependent dynamic regulation

Integrin signaling complex

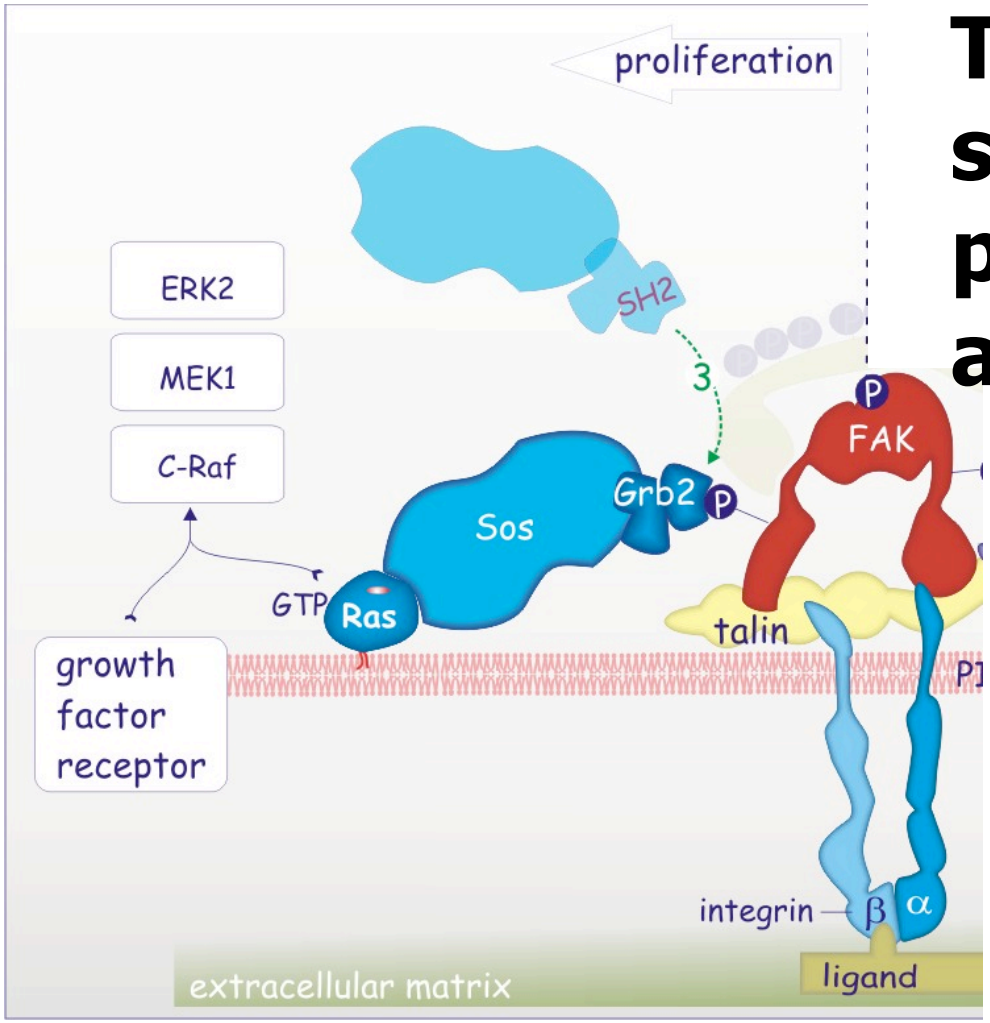


The focal adhesion kinase FAK associates with talin. Autophosphorylation of FAK then generates a docking site for the SH2 domain of Src which phosphorylates FAK at Y925. Src and FAK next phosphorylate the FAK-associated docking protein CAS at multiple sites.
An integrin-signalling complex is formed that acts in a manner similar to growth factor-receptor signaling complexes, i.e. attachment of adaptors and effectors and tyrosine phosphorylation substrates.

Integrin signaling



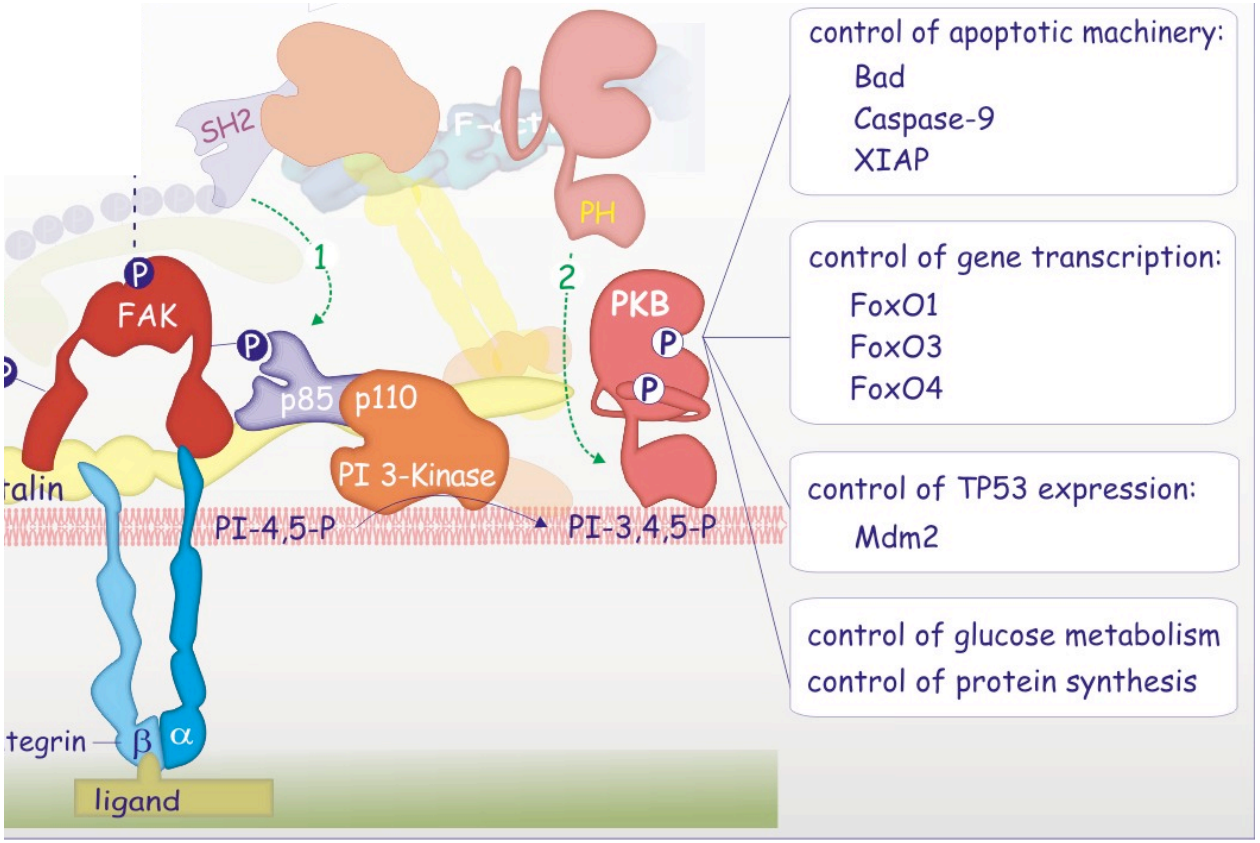
The focal adhesion site promotes cell proliferation through activation of Ras



Phosphorylated focal adhesion kinase (FAK) is a binding site for Grb2. This interaction recruits the Ras guanine exchange factor Sos, leading to activation of Ras.

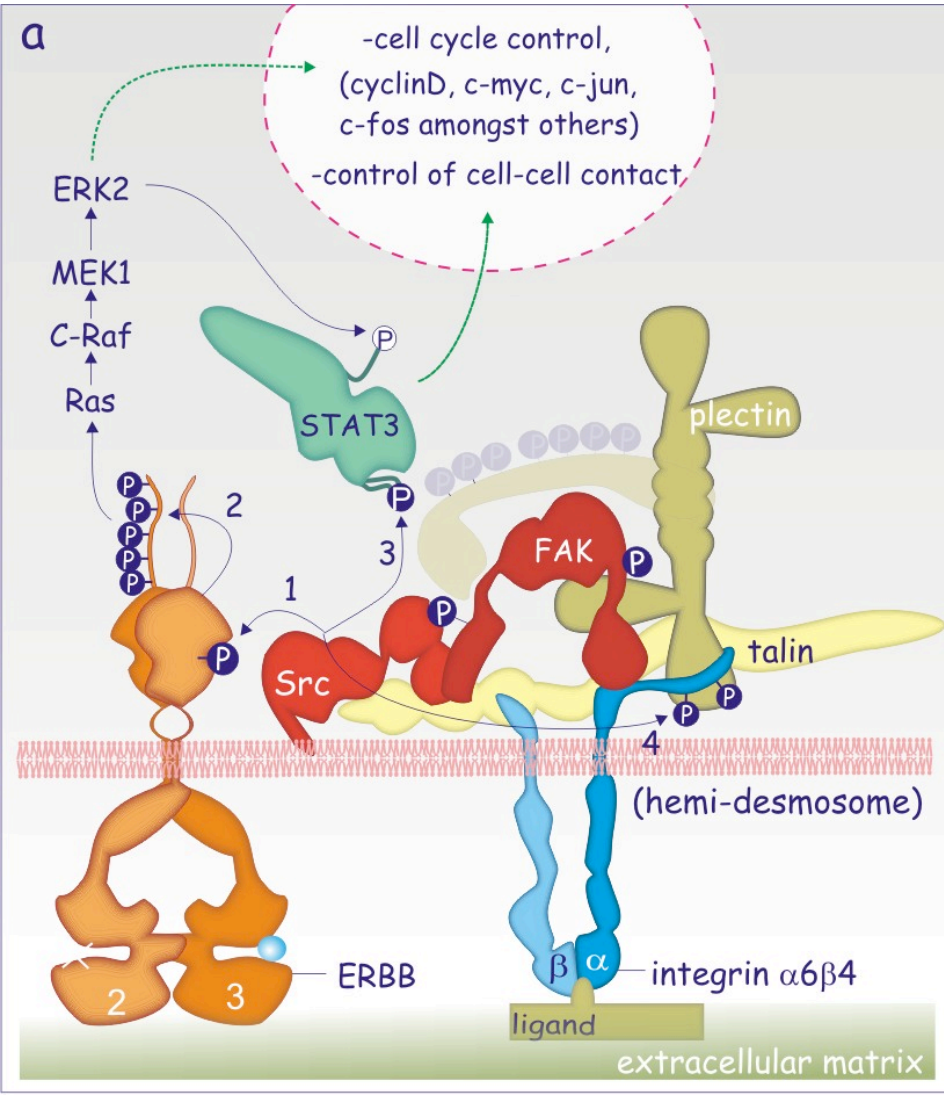
Ras-GTP initiates the activation of the Raf-ERK pathway, necessary for initiation of the cell cycle.

The focal adhesion site promotes cell survival through activation of PKB



Phosphorylated focal adhesion kinase (FAK) binds the SH2 domain of the regulatory subunit (p85) of PI 3-kinase. Subsequent production of PIP3 provides a binding site for PKB (and PDK1). After its activation PKB phosphorylates a large number of proteins that directly or indirectly deal with cell death.

Adhesion-mediated cell cycle control



In epithelial cells, integrin α6β4, forms a special adhesion complex named *hemi-desmosome*. These complexes are linked to intermediate filaments via **plectin**.

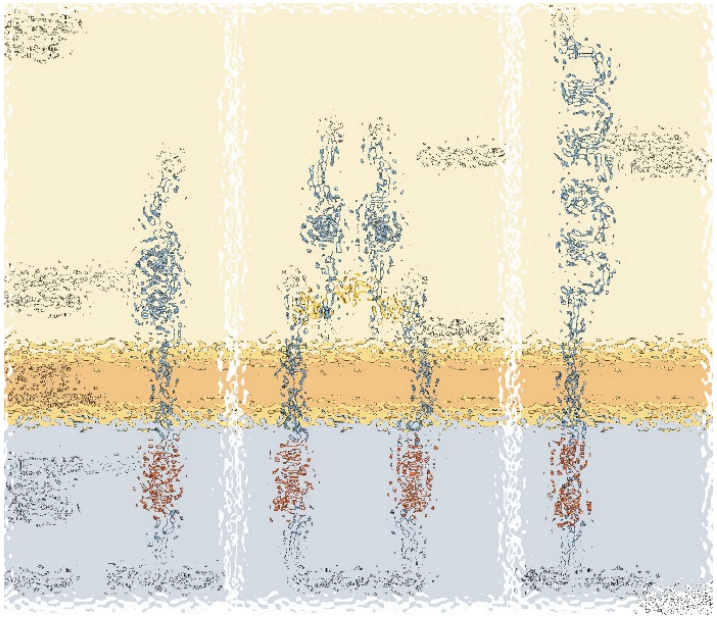
ERBB2/3 receptors are recruited into these complexes leading to phosphorylation of ERBB2 by Src bound to FAK.

Src also phosphorylates STAT3 and this signal is enforced by a second phosphorylation on serine through ERK2. Both phosphorylations enhance its transcriptional activity.

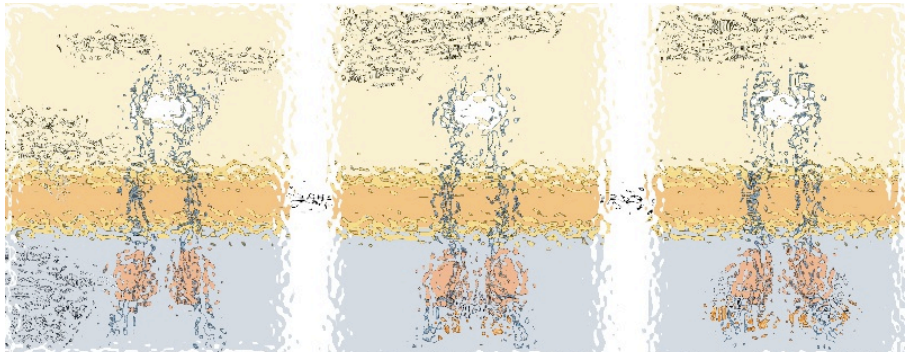
In the case of breast tumor cells, this pathway promotes cellular invasion.

Enzyme-linked receptors fall into 3 categories:

- **Tyrosine Kinase Receptors**
  - Not only a receptor
  - Also an enzyme: Tyrosine kinase



- **Cytokine superfamily receptors**
  - No catalytic domain
  - Interact with non receptor protein-tyrosine kinases
    - Src family
    - JAK family



- **TGF-β receptors**

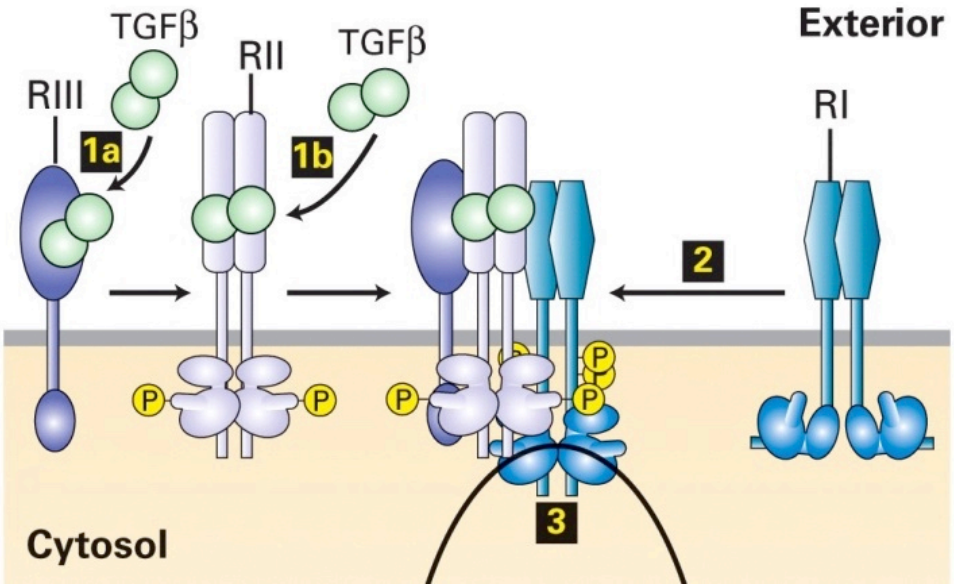
TGFβ

- TGFβ (Transforming Growth Factor β) superfamily proteins play important roles in regulating development of vertebrates and invertebrates
  - Bone Morphogenic Protein (BMP) is one of the TGFβ superfamily important in regulating formation of mesoderm and the earliest blood forming cells
  - GDF11
  - TGFβ-1 is another member of the TGFβ superfamily proteins which can induce a transformed phenotype of certain cells in culture
- There are three human TGFβ isoforms known to have potent anti-proliferative effects on many types of mammalian cells. Mutation of TGFβ will result in releasing cells from growth inhibition (frequently occurs in human tumors)
- TGFβ also promotes expression of cell-adhesion molecules and extracellular matrix molecules

TGFβ Signaling Receptors Have Serine/Threonine Kinase Activity

- Three different polypeptides with apparent molecular weights of 55, 85 and 280 kDa were purified, referred to as types RI, RII and RIII TGFβ receptors
- Type RIII TGFβ receptor is a **cell-surface proteoglycan**, also called **β-glycan** which bind and concentrate TGFβ near the cell surface
- Type RI and type RII receptors are dimeric transmembrane proteins with serine/threonine kinases as part of their cytosolic domains

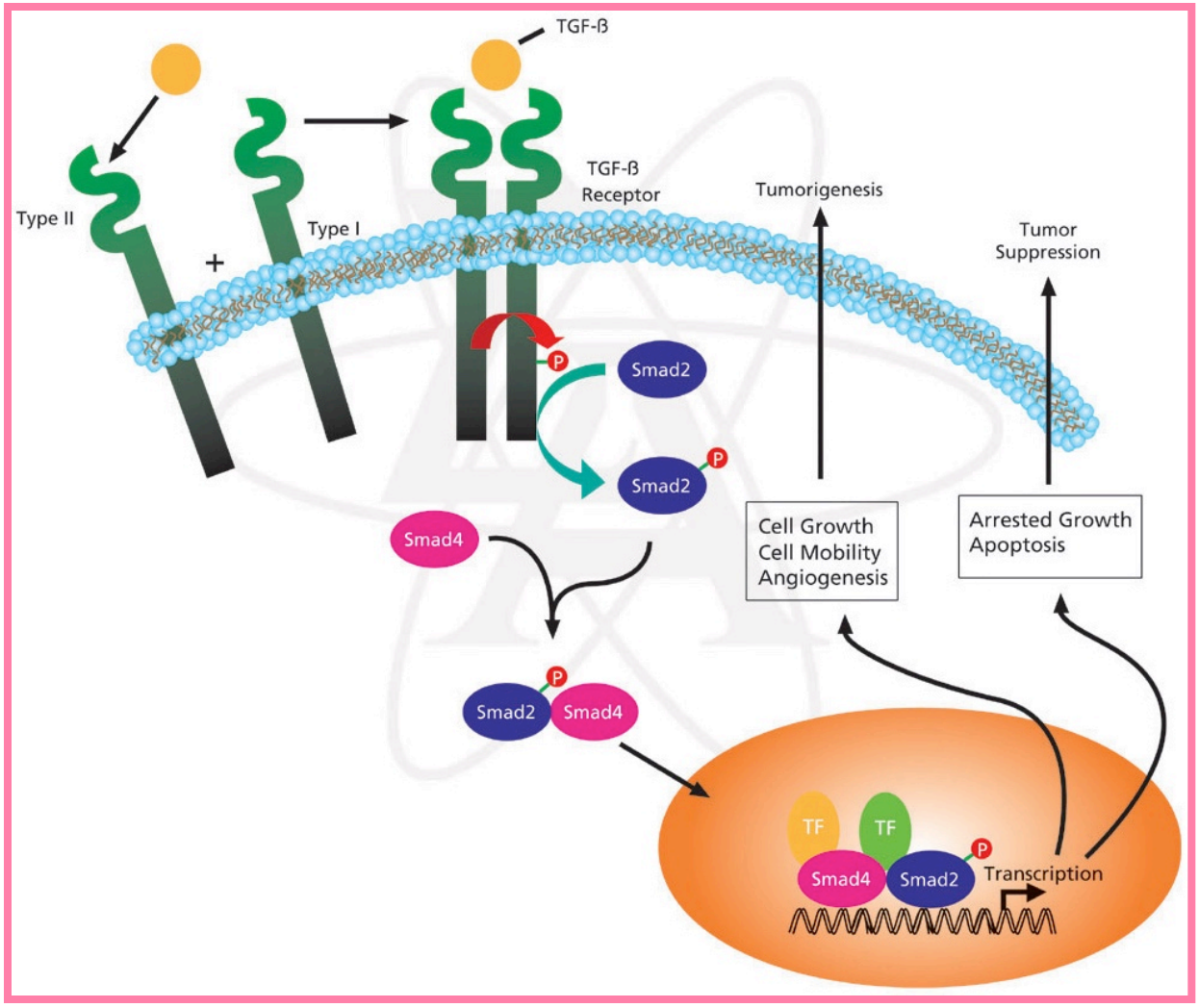
- RII is a constitutively active kinase that phosphrylates itself in the absence of TGFb
- Binding of TGFβ induces the formation of two copies each of RI and RII. A RII then phophorylates serine/threonine of RI adjacent to the cytoplasm and thus activate the RI kinase activity



TGFβ Receptor Signaling:
a logic resembling the STAT-family

STAT-related logic

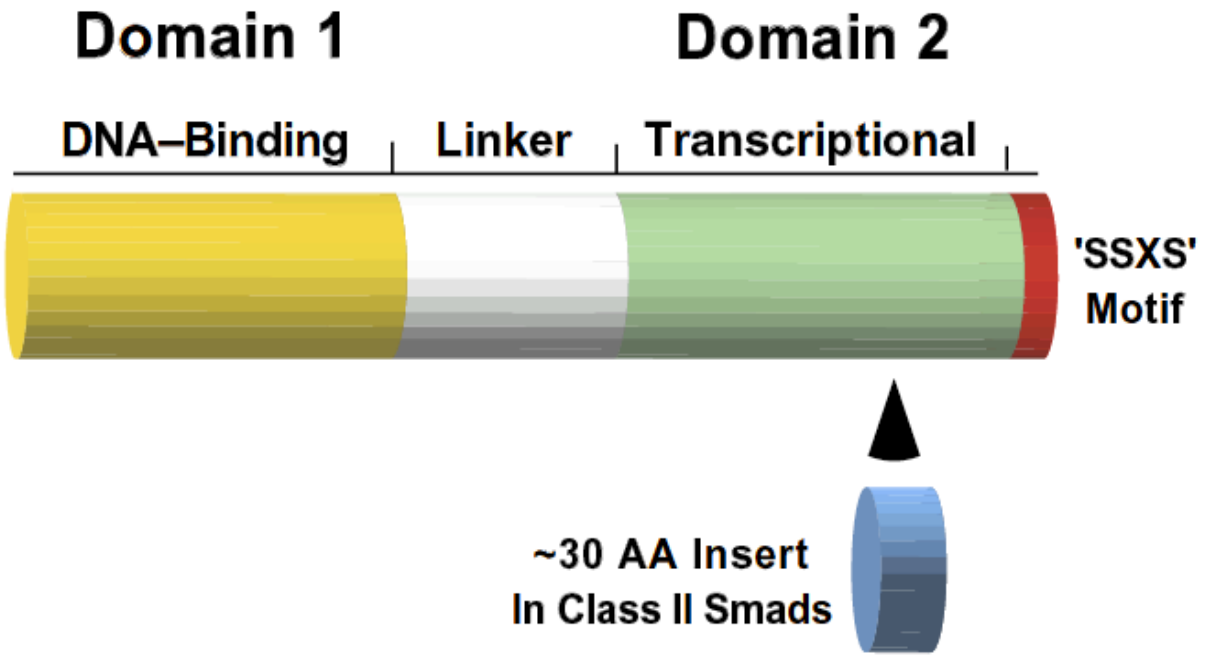
- TGFß-receptors are activated by binding of ligand (TGFb).
- Activated receptor kinases phosphorylate specific Smad-factors
- Phosphorylated Smad-factors associate with a common Smad-factor (Smad4)
- The generated heteromeric complexes migrate to the nucleus as transcription factors



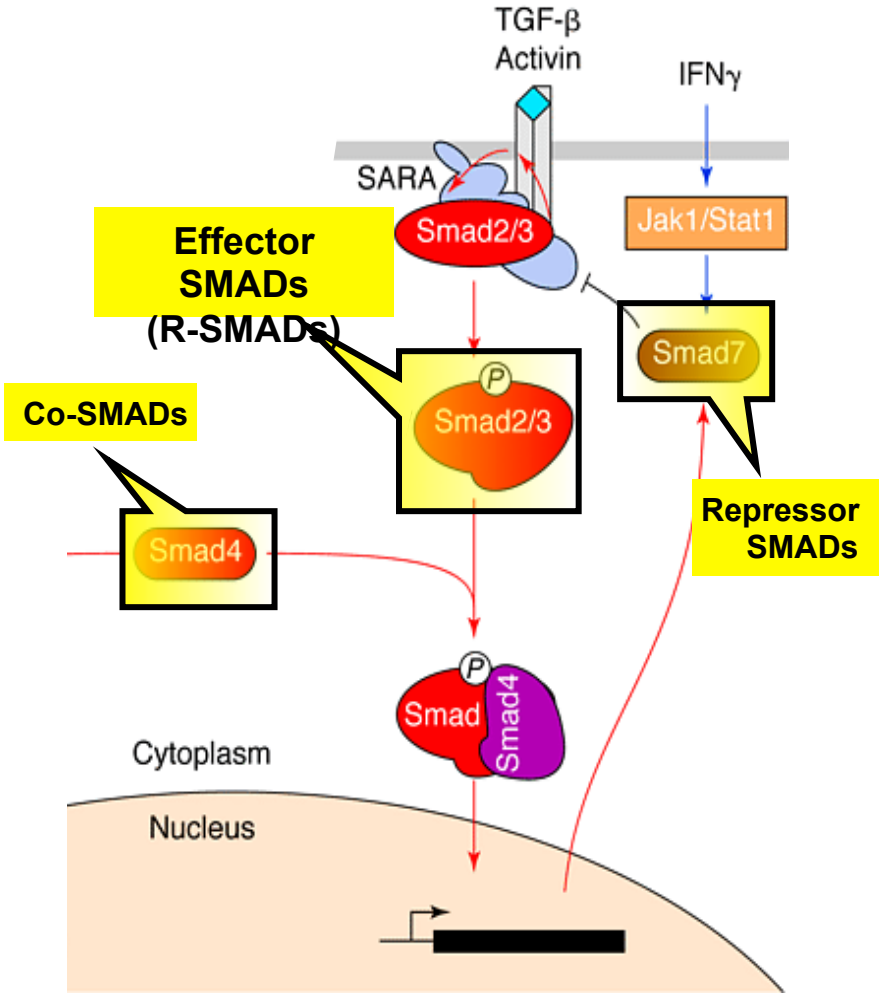
Classification

- Smad-factors: design and classification

  - Nine different Smad-factors identified in vertebrates
  - common conserved domains: N-terminal MH1-domain (DBD) + C-terminal MH2-domain



Three groups of SMADs

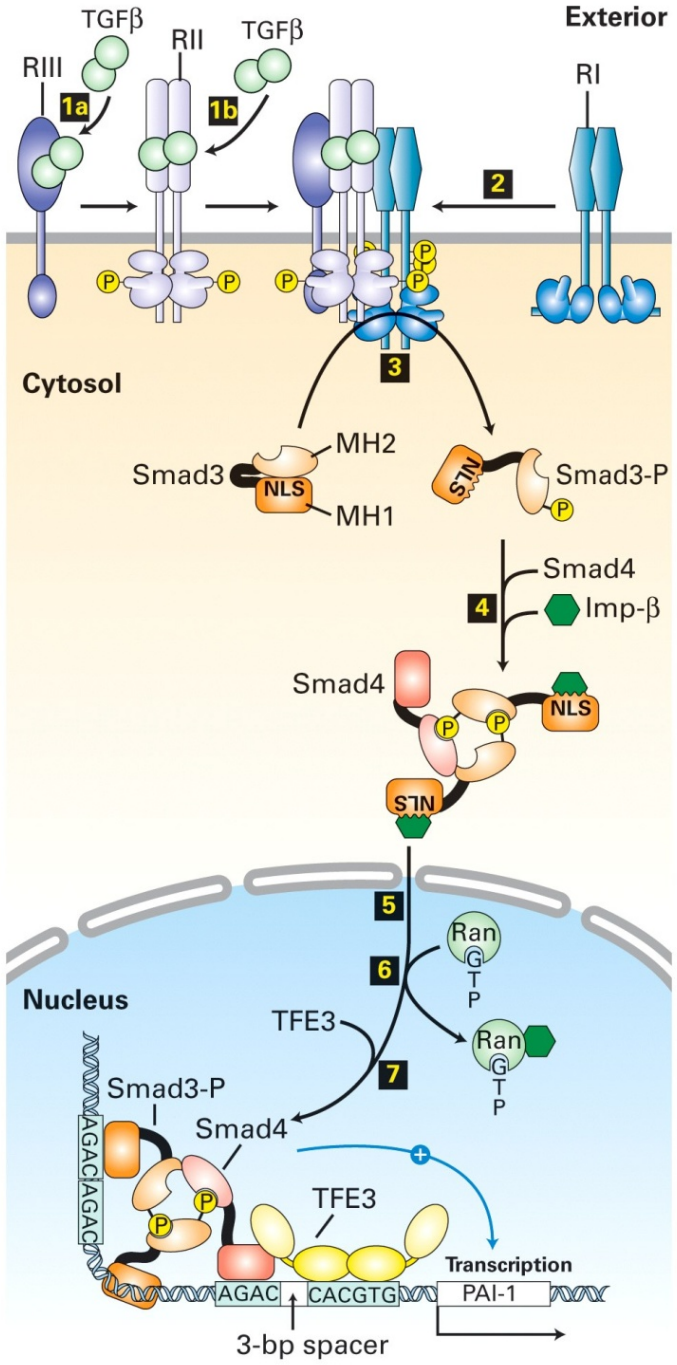


1: **Effector SMADs** (also called the Receptor-SMADs) are ser-phosphorylated by the activated receptor. Smad1, 5, 8, 9 are phosphorylated in response to bone morphogenetic morphogenetic protein (BMP) and growth and differentiation factor (GDF); Smad2 and 3 are phosphorylated in response to the activin/nodal branch of the TGF-β pathway.

2: **Regulatory or co-SMADs** (common SMADs). They are Smad4 and Smad4β.

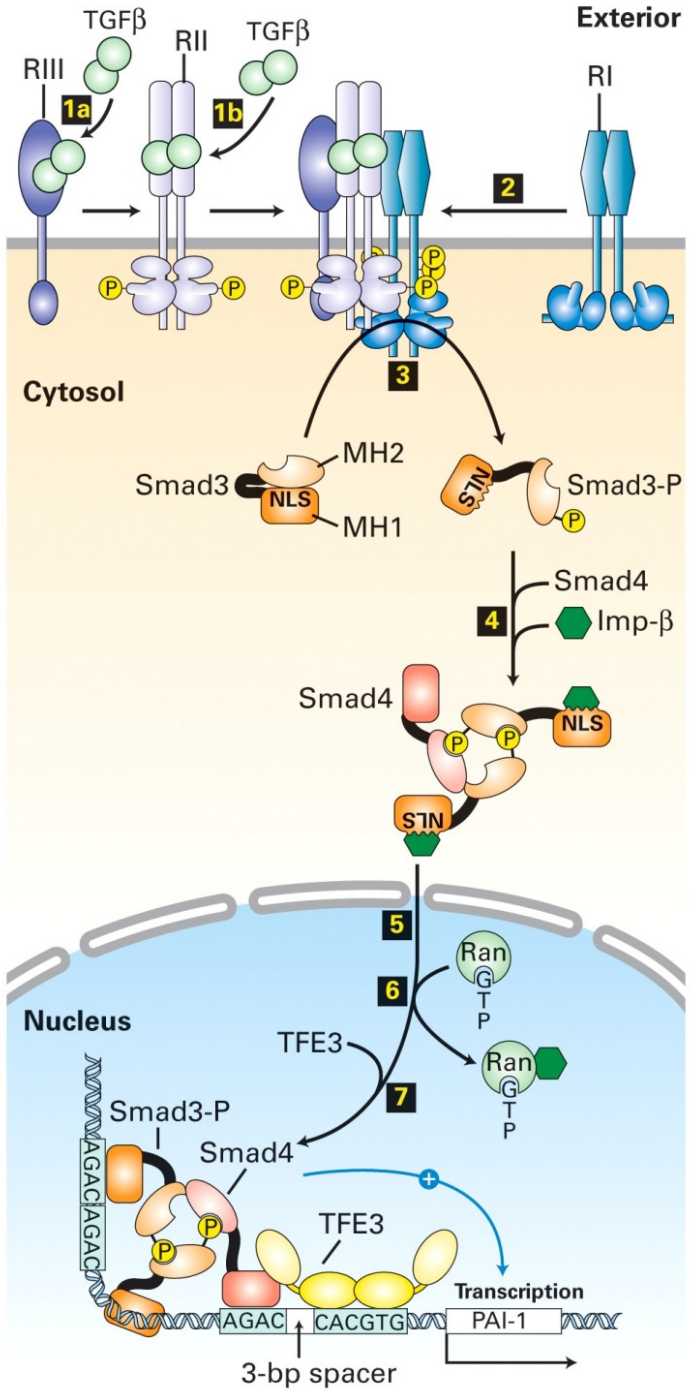
The regulatory Smad4 binds to all effector SMADs in the formation of transcriptional complexes, but it does not appear to be required for nuclear translocation of the effector molecules.

3: Two **inhibitory SMADs**, Smad6 and Smad7, provide negative regulation of the pathway by blocking Smad4 binding.



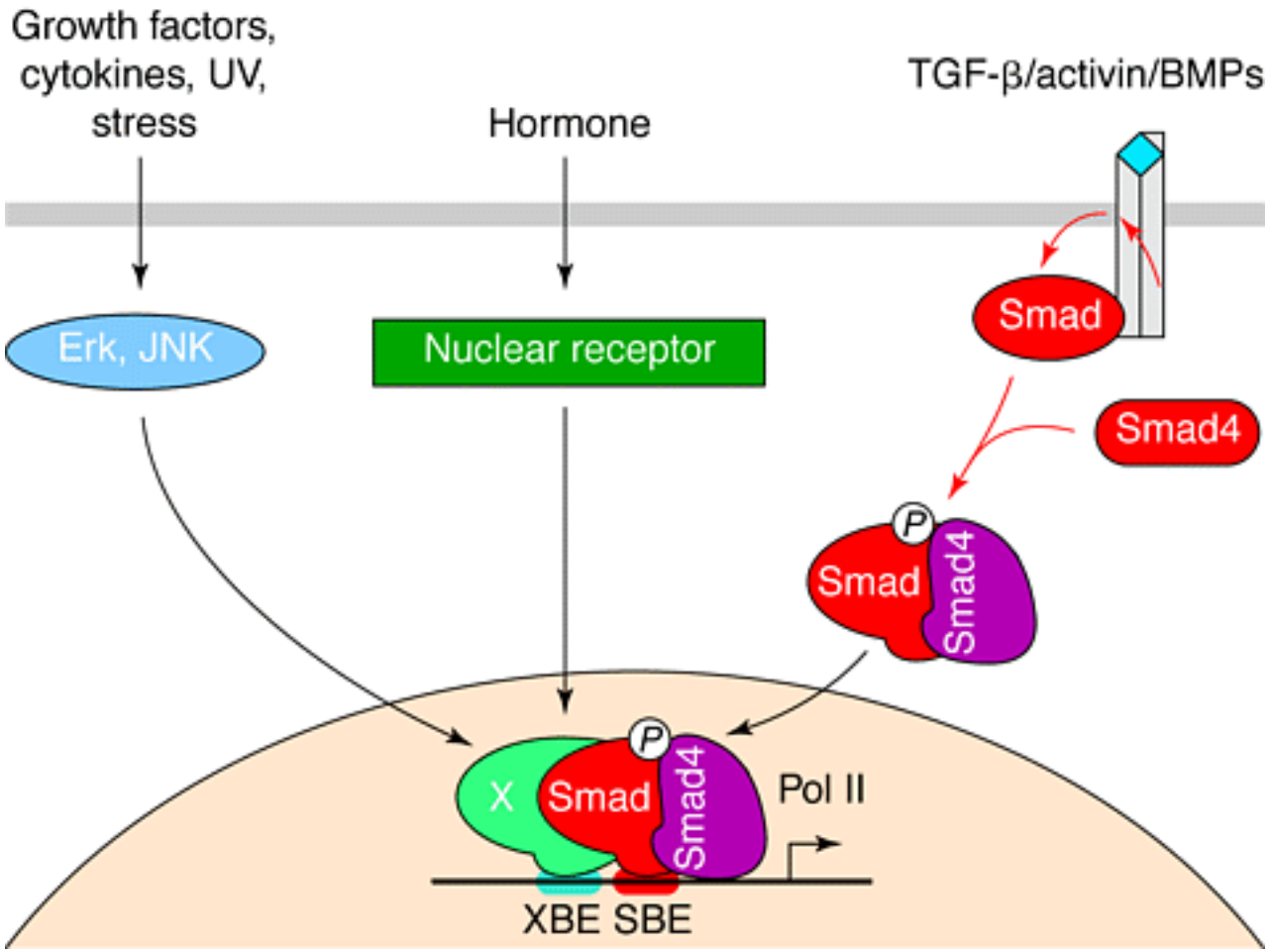
Activated Type I TGFβ Receptors Phosphorylate Smad Transcription Factors

- R-Smads contain two domains, MH1 and MH2, separated by a flexible linker region. The N-terminus of the MH1 contains a specific DNA binding segment and a NLS sequence
- When R-Smads are in inactive state, the NLS is masked and the MH1 and MH2 domains associate in a way that they can not bind to DNA or to a co-Smad
- Phosphorylation of three serine residues near the C-terminus of a R-Smad (Smad2 or Smad3) by activated type I TGFβ receptors separates the domains, allowing binding of importin β to the NLS

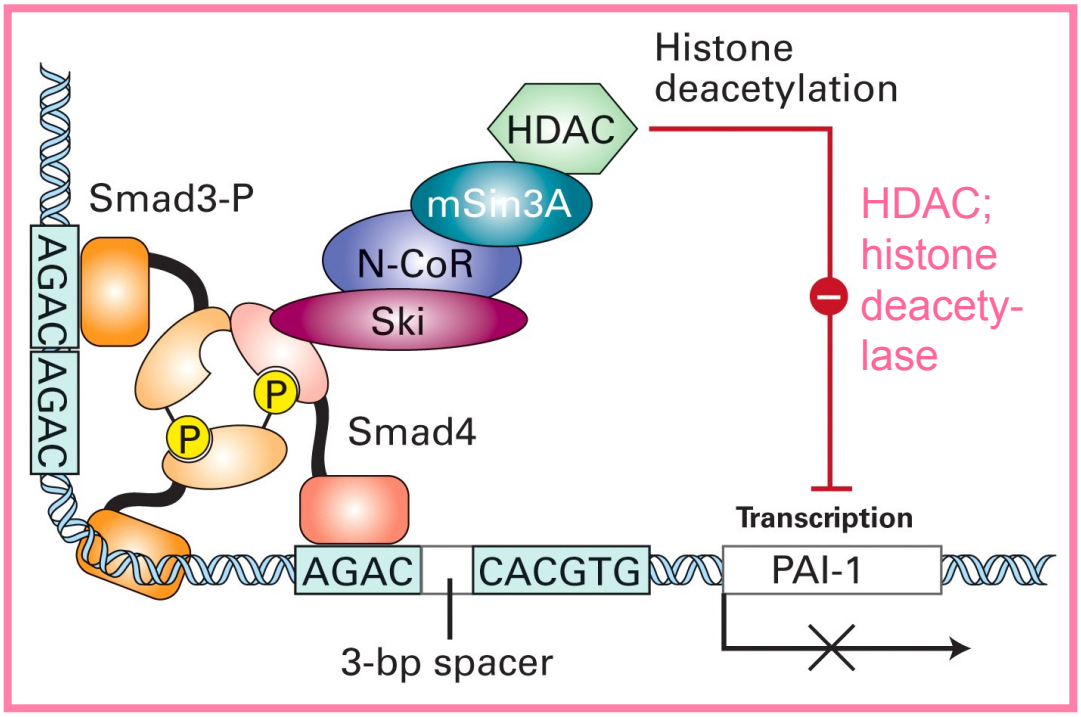


- A complex containing two molecules of Smad3 (or Smad2) and one molecule of a co-Smad (Smad4) forms in the cytosol
- The complex is stabilized by binding two phosphorylated serines in both the Smad3 and the Smad4 MH2 domains
- The importin β–bound heteromeric R-Smad3/ Smad4 complex translocates into nucleus
- After importin β dissociates from the complex in the nucleus, the Smad2 (or 3)/Smad4 will cooperate with other transcription factors to turn on specific target genes
- In the nucleus, R-Smads are continuously dephosphorylated, resulting in the dissociation of the R-Smad /co-Smad complex and export of these Smads from the nucleus. Therefore, the concentration of the active Smads in the nucleus closely reflects the levels of the activated TGFβ receptors on the cell surface

The Smad-factors activate their target genes in combination with other TFs



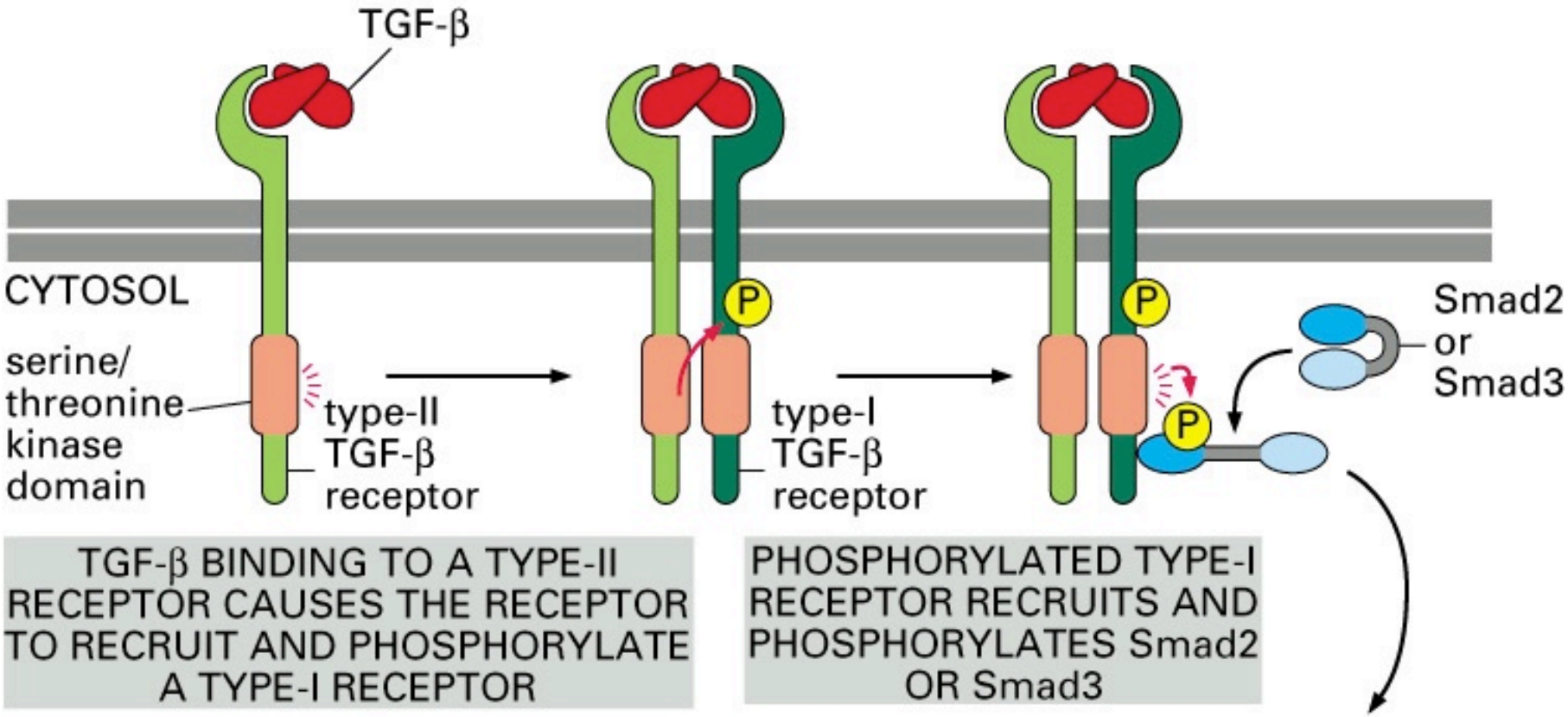
Oncoproteins and I-Smads Regulate Smad Signaling via Negative Feedback Loop



- Smad signaling is regulated by additional intracellular proteins including *SnoN and Ski (Ski stands for "Sloan-Kettering Cancer Institute")*
- These proteins are oncoproteins since they cause abnormal cell proliferation when over expressed in cultured fibroblasts

- SnoN and Ski can bind to Smad2/Smad4 or Smad3/Smad4 complex after TGFβ stimulation
- Binding of SnoN and Ski to Smad2/Smad4 or Smad3/Smad4 will block transcriptional activation of target genes, making cells resistant to growth inhibition induced by TGFβ
- PAI-1 gene: encodes plasminogen activator inhibitor-1

Summary


TGF-β
CYTOSOL
serine/
threonine
kinase
domain
type-II
TGF-β
receptor
P
type-I
TGF-β
receptor
P
P
Smad2
or
Smad3
TGF-β BINDING TO A TYPE-II RECEPTOR CAUSES THE RECEPTOR TO RECRUIT AND PHOSPHORYLATE A TYPE-I RECEPTOR
PHOSPHORYLATED TYPE-I RECEPTOR RECRUITS AND PHOSPHORYLATES Smad2 OR Smad3

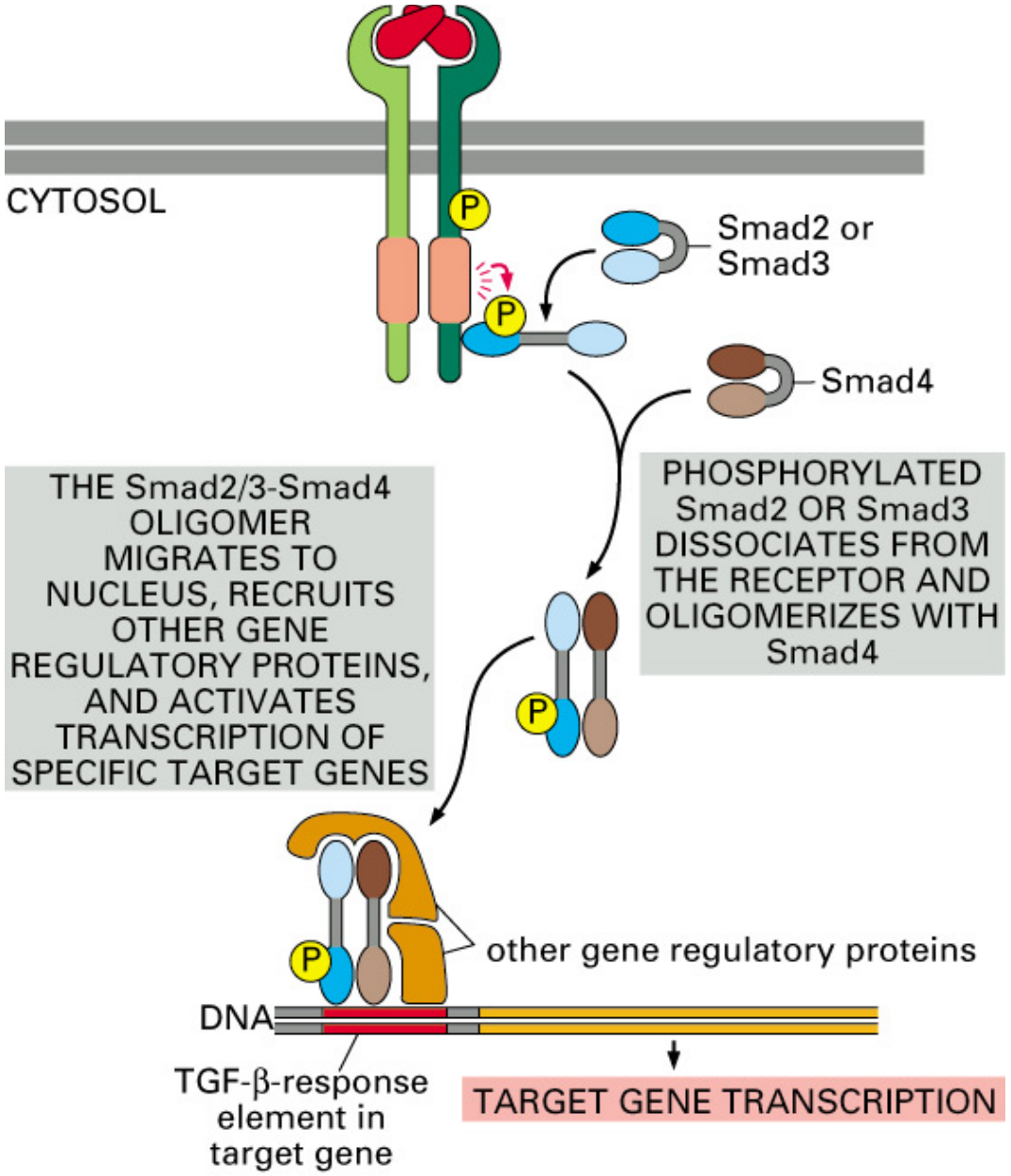
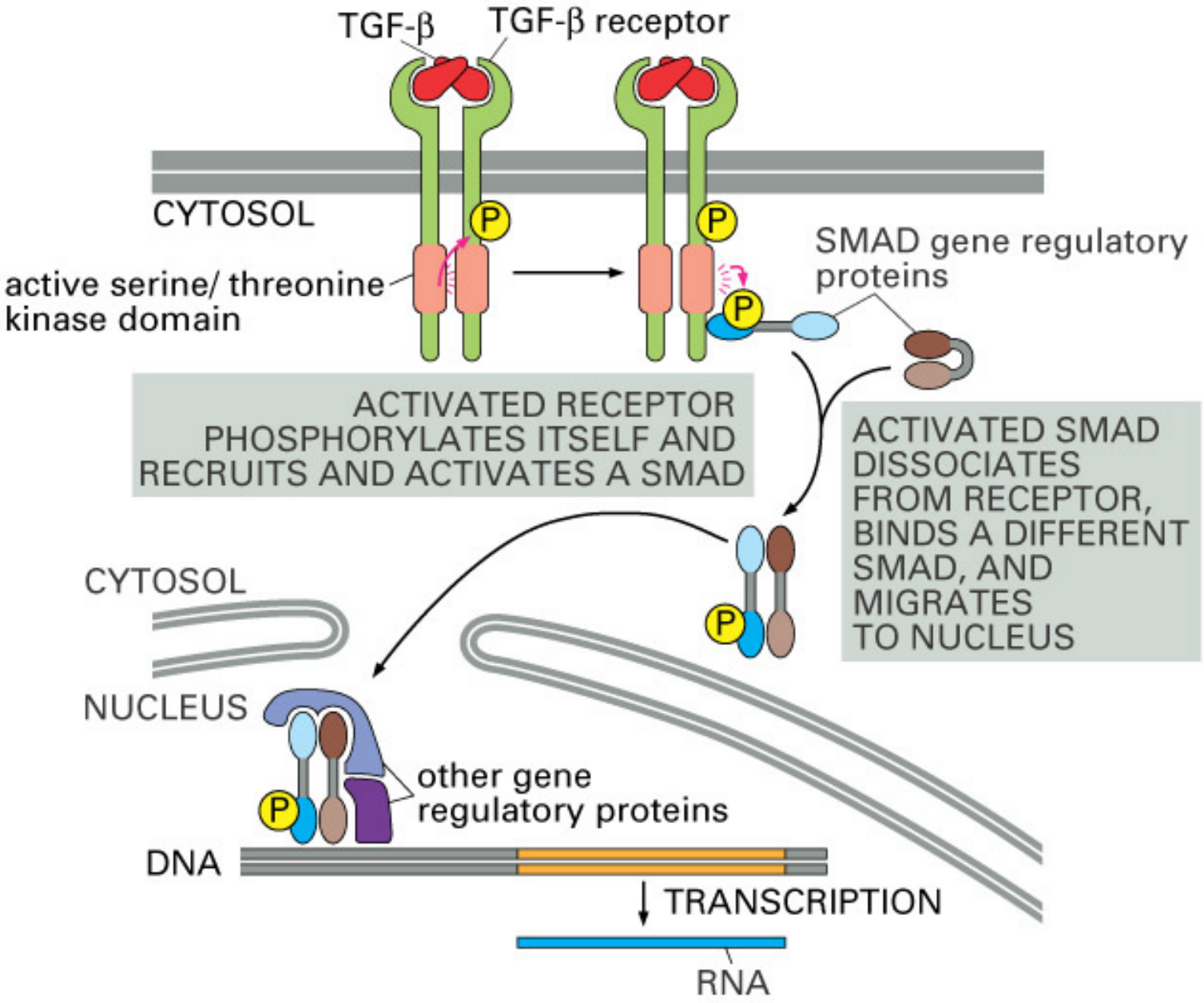
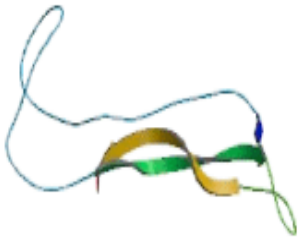


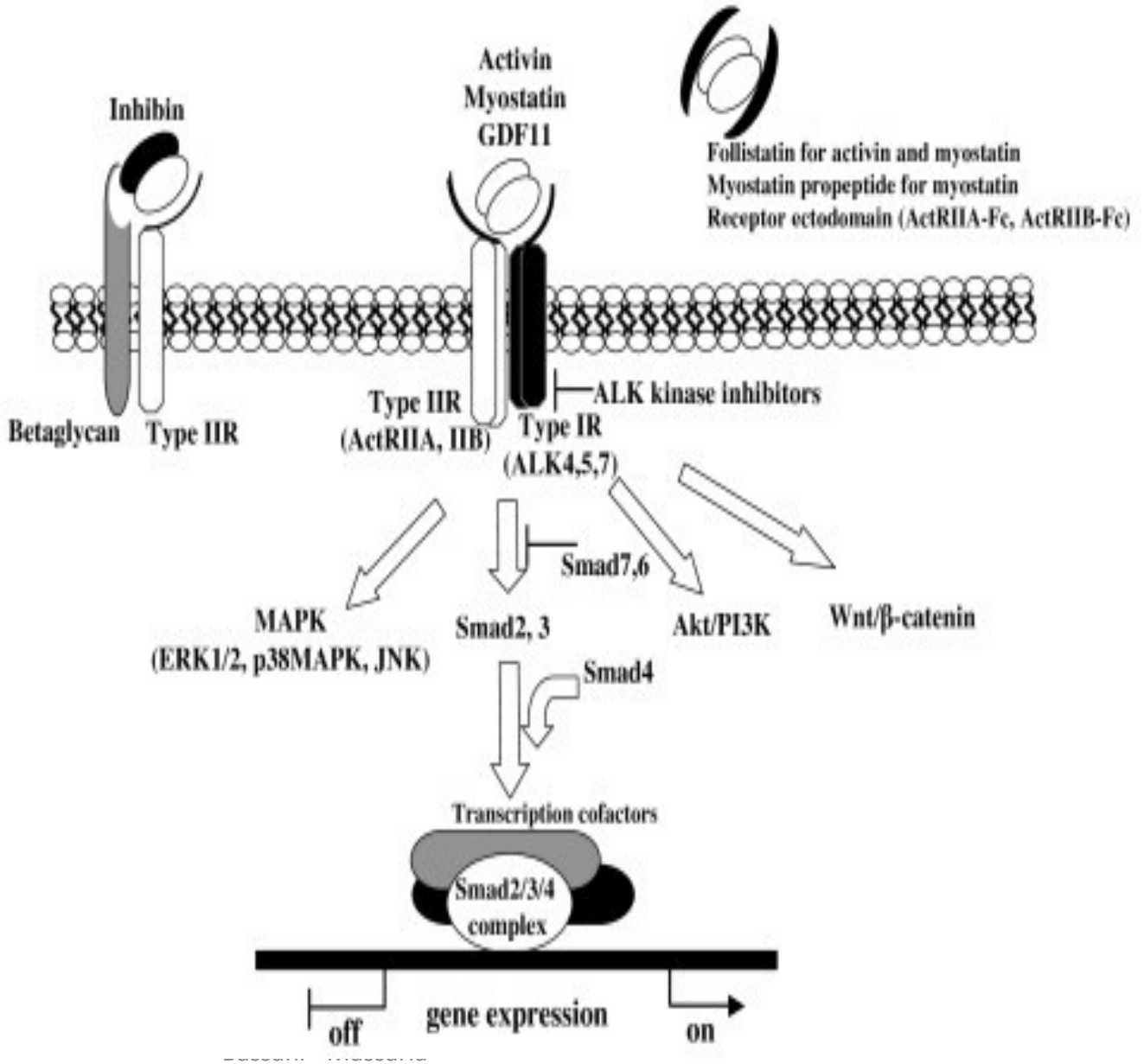
Figure 15–65 part 2 of 2. Molecular Biology of the Cell, 4th Edition.


TGF-β
TGF-β receptor
CYTOSOL
active serine/ threonine kinase domain
P
SMAD gene regulatory proteins
ACTIVATED RECEPTOR PHOSPHORYLATES ITSELF AND RECRUITS AND ACTIVATES A SMAD
ACTIVATED SMAD DISSOCIATES FROM RECEPTOR, BINDS A DIFFERENT SMAD, AND MIGRATES TO NUCLEUS
CYTOSOL
NUCLEUS
other gene regulatory proteins
DNA
TRANSCRIPTION
RNA

GFD11



- Membro della superfamiglia di TGF β
- Regolatore della crescita cellulare e differenziamento dei tessuti
- Omologia di sequenza del 90% con la miostatina



828 Cell *153*, 828–839, May 9, 2013 ©2013 Elsevier Inc.

Growth Differentiation Factor 11 Is a Circulating Factor that Reverses Age-Related Cardiac Hypertrophy

Francesco S. Loffredo,[1,2] Matthew L. Steinhauser,[2] Steven M. Jay,[1,2] Joseph Gannon,[2] James R. Pancoast,[2] Pratyusha Yalamanchi,[2] Manisha Sinha,[1,3] Claudia Dall'Osso,[1,3] Danika Khong,[1,3] Jennifer L. Shadrach,[1,3] Christine M. Miller,[1,4] Britta S. Singer,[5] Alex Stewart,[5] Nikolaos Psychogios,[6] Robert E. Gerszten,[6] Adam J. Hartigan,[1,4] Mi-Jeong Kim,[1,4] Thomas Serwold,[1,4] Amy J. Wagers,[1,3,4,7,*] and Richard T. Lee[1,2,7,*]

[1]Harvard Stem Cell Institute

[2]Cardiovascular Division, Department of Medicine
Brigham and Women's Hospital, Boston, MA 02115, USA

[3]Howard Hughes Medical Institute and Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA 02138, USA

[4]Joslin Diabetes Center, Boston, MA 02215, USA

[5]SomaLogic, Inc., Boulder, CO 80301, USA

[6]Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Charlestown, MA 02129, USA

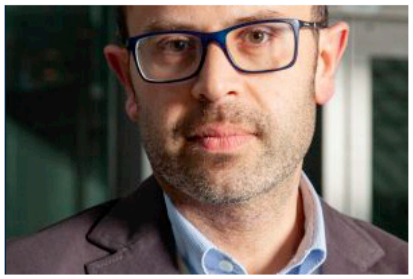
[7]These authors contributed equally to this work

*Correspondence: amy_wagers@harvard.edu (A.J.W.), rlee@partners.org (R.T.L.)

http://dx.doi.org/10.1016/j.cell.2013.04.015

April 14, 2020

Dr. Francesco Loffredo, Molecular Cardiology Unit, on Covid-19 from the front line



Dr. Francesco Loffredo, Medical doctor and scientist - for ICGEB from the front line during Covid19

"*This situation makes me appreciate both my role as a medical doctor, and as a scientist, but above all the mission and dedication to cure people.*"

Francesco Loffredo joined the ICGEB to head the Molecular Cardiology Group in 2015. He is currently both Visiting Scientist, Molecular Cardiology Unit, ICGEB, Trieste, and Professor of Applied Medical Sciences, Università della Campania "L. Vanvitelli", Naples, Italy.

Working on the front line at the "Azienda Ospedaliera Universitaria", of the University during the pandemic, and the "Ospedali dei Colli", which includes the Monaldi and Cotugno Hospitals where the cardiology division and most of the COVID patients are hosted, respectively, he is attending the ICGEB Group Leaders' meetings and providing clinical insights and therapeutic protocols where necessary.

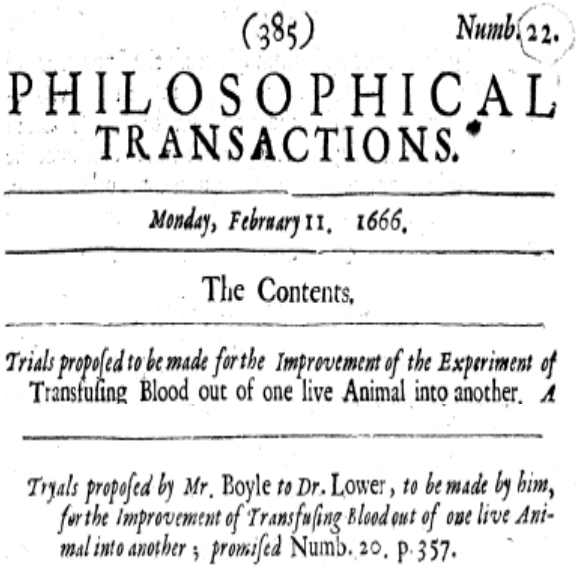
Writing from Naples, he states, "It is a daily battle to cure and maintain contact with patients and transmit humanity and reassurance through the protective clothing, that both shields us from the virus, but that inexorably increases distance and amplifies fear."

"I don't deny also experiencing fear in certain moments, I have seen colleagues and nurses to whom I was close through our shared profession, but also through friendship, leave us. Being part of a united team gives you strength and in the end we shall win this battle."

"I must say I am glad to have been directly involved, and feeling the warmth and support of the people in Trieste is a great help."

On our side, we are extraordinarily proud to have Dr. Loffredo as our colleague.

Young Blood has Good Stuff: this concept is also not really that new…



(385) Numb. 22.

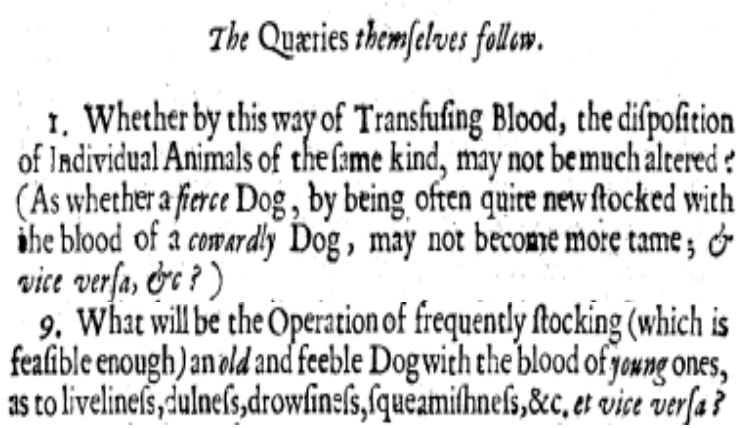
PHILOSOPHICAL TRANSACTIONS.

Monday, February 11. 1666.

The Contents.

Trials propoſed to be made for the Improvement of the Experiment of Transfuſing Blood out of one live Animal into another. *A*

Tryals propoſed by Mr. Boyle *to Dr.* Lower, *to be made by him, for the improvement of Transfuſing Blood out of one live Animal into another; promiſed* Numb. 20. p. 357.



The Quæries *themſelves follow.*

1. Whether by this way of Transfuſing Blood, the diſpoſition of Individual Animals of the ſame kind, may not be much altered? (As whether a *fierce* Dog, by being often quite new ſtocked with the blood of a *cowardly* Dog, may not become more tame; *& vice verſa, &c?*)

9. What will be the Operation of frequently ſtocking (which is feaſible enough) an *old* and feeble Dog with the blood of *young* ones, as to livelineſs, dulneſs, drowſineſs, ſqueamiſhneſs, &c. *et vice verſa?*

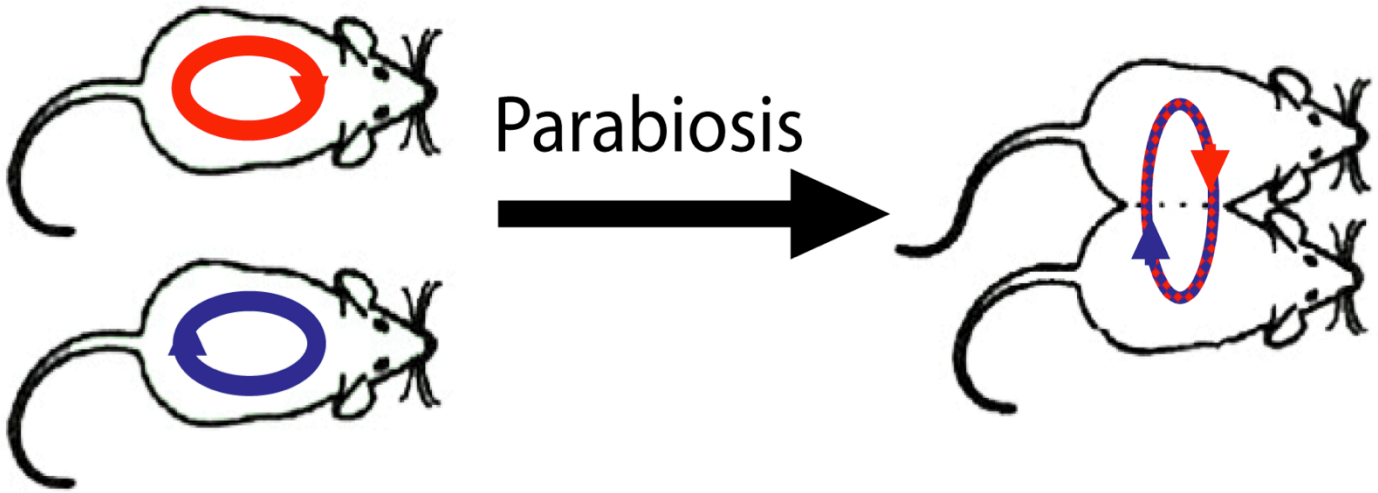
Philosophical Transactions started in 1665 and may be the first and longest running science journal.

Blood and Rejuvenation

In 1492, Pope Innocent VIII was possibly asked to drink the blood of three young boys to restore his youthful vigor.

"The Story of a Blood Transfusion of a Pope"
Lindeboom GA, Journal of the History of Medicine, 1954

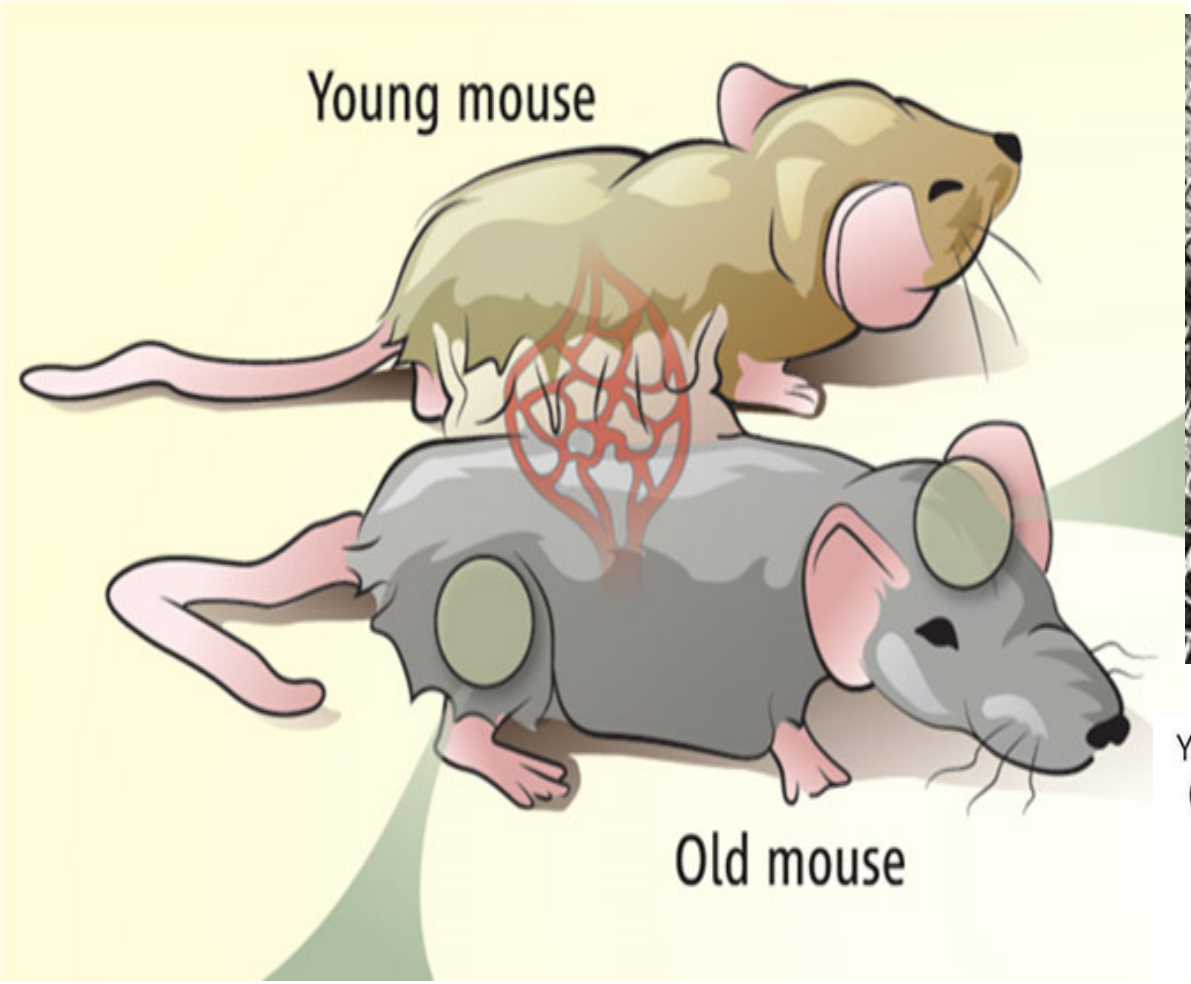
Approach: Parabiosis is the surgical act of artificially creating conjoined twins of two organisms.

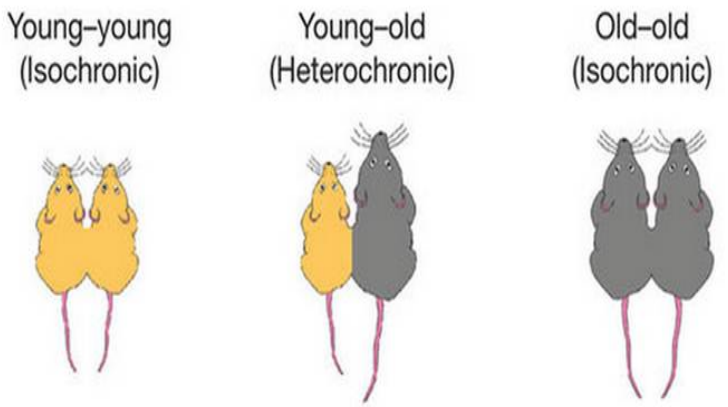


- Cross-circulation is established 2-3 days after joining.
- Blood chimerism reaches ~50% by 7-10 days.
- Rapid exchange (~1%/min.) of cells and factors across the vascular junction.

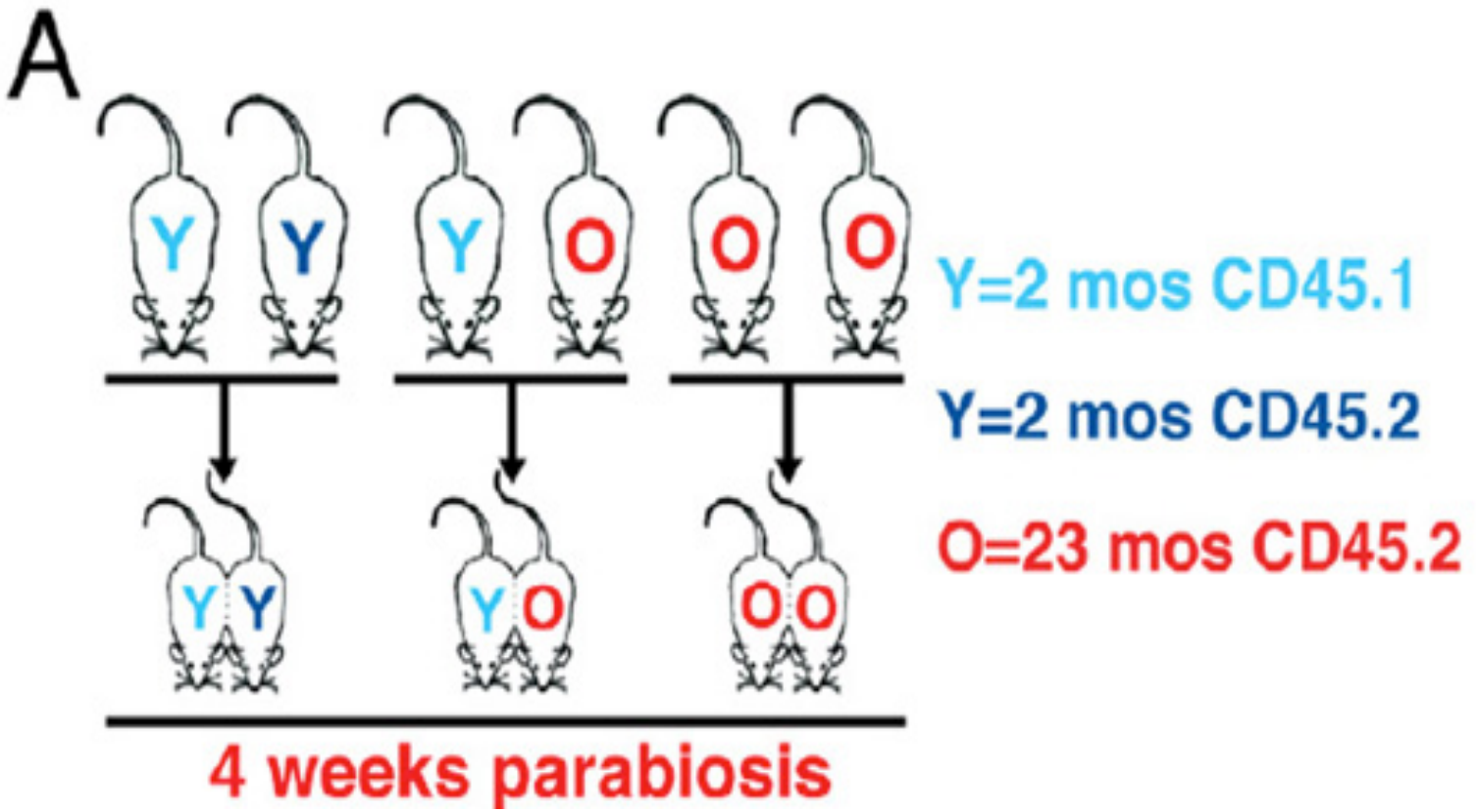
Wright, Wagers et al. Science 2001

PARABIOSI


Young mouse
Old mouse

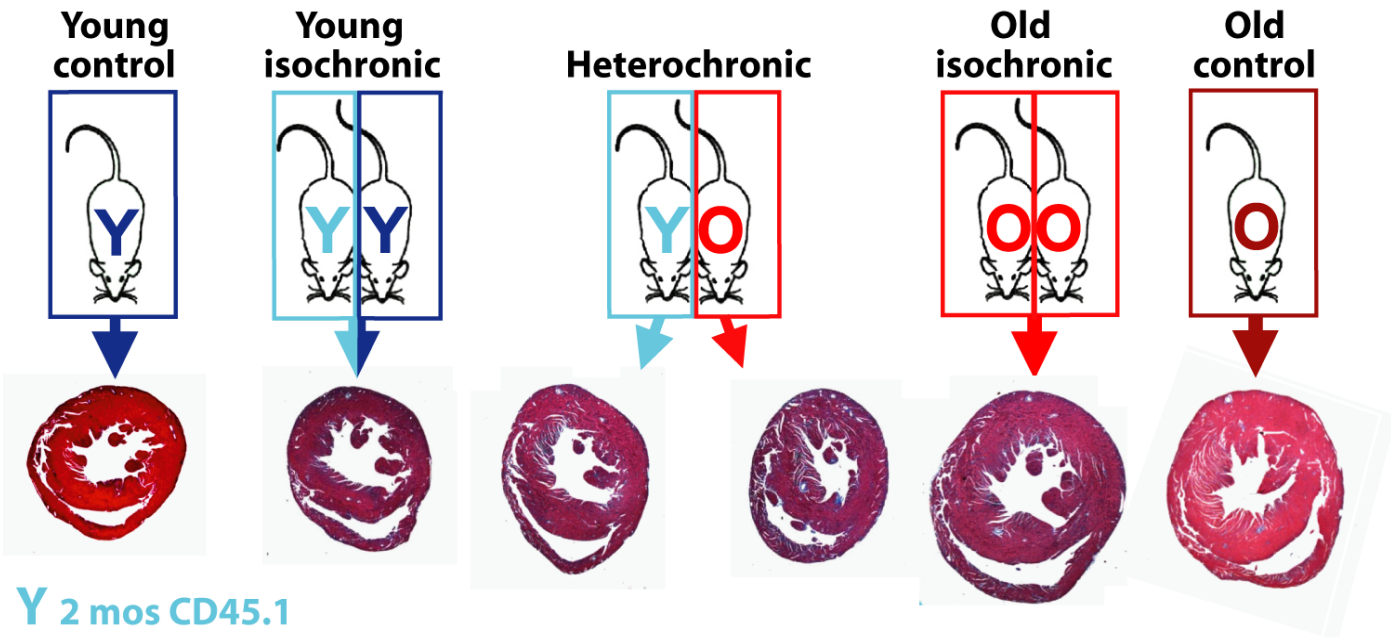

Young–young
(Isochronic)
Young–old
(Heterochronic)
Old–old
(Isochronic)

PARABIOSI



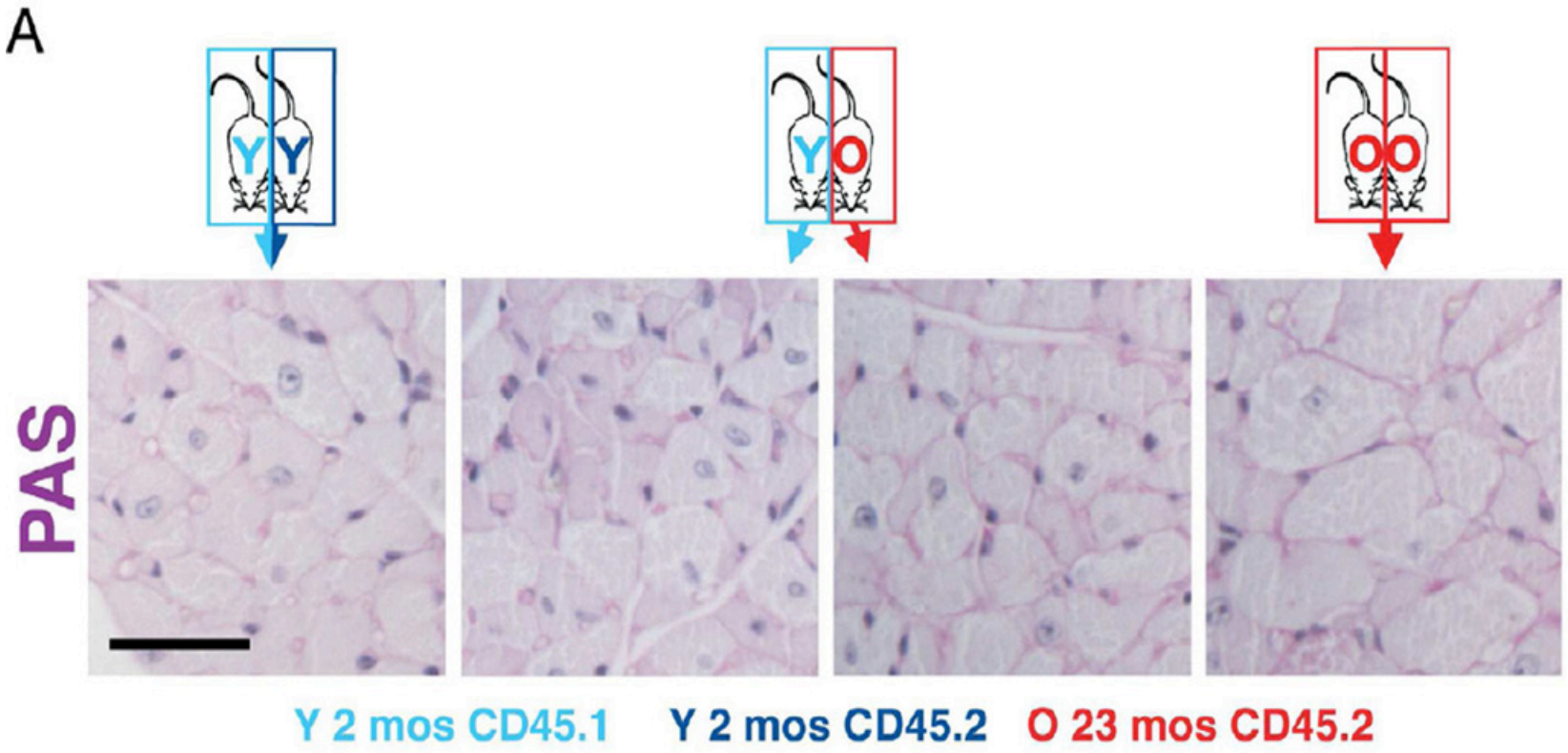
Vengono generate coppie isocroniche di topi giovani, anziani e coppie eterocroniche.
Dopo quattro settimane, i topi vengono sacrificati e i tessuti utilizzati per le analisi.

Exposure to a young circulatory system reduces gross cardiac size in aged mice



Hearts from old mice exposed to a young circulation for 4 wks were noticeably smaller than hearts from isochronic old mice

The study was conducted in a randomized and blinded fashion.

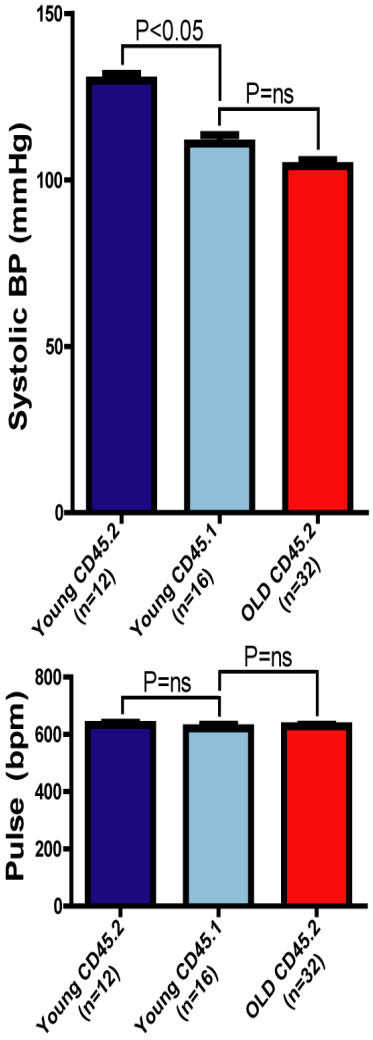


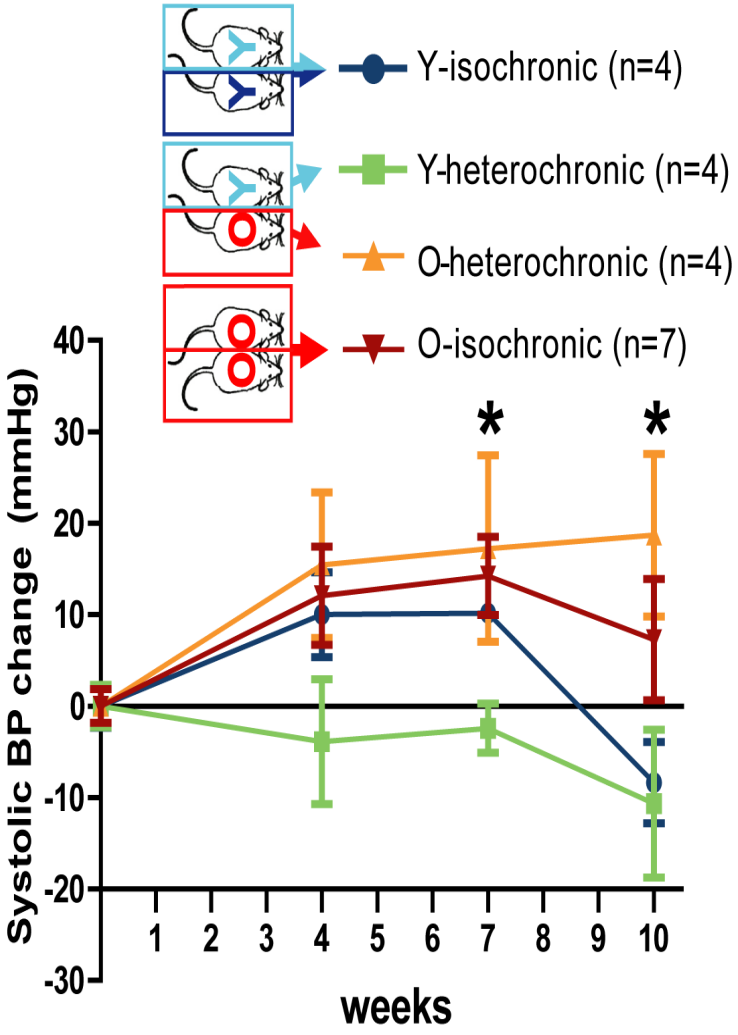
TOPO ANZIANO ESPOSTO A GIOVANE → CAMBIA LA MORFOLOGIA DELLE CELLULE: DA IPERTROFICHE REGREDISCONO A CELLULE TIPICHE DI TOPI GIOVANI

Changes in blood pressure do not explain the reversal of age-related cardiac hypertrophy.

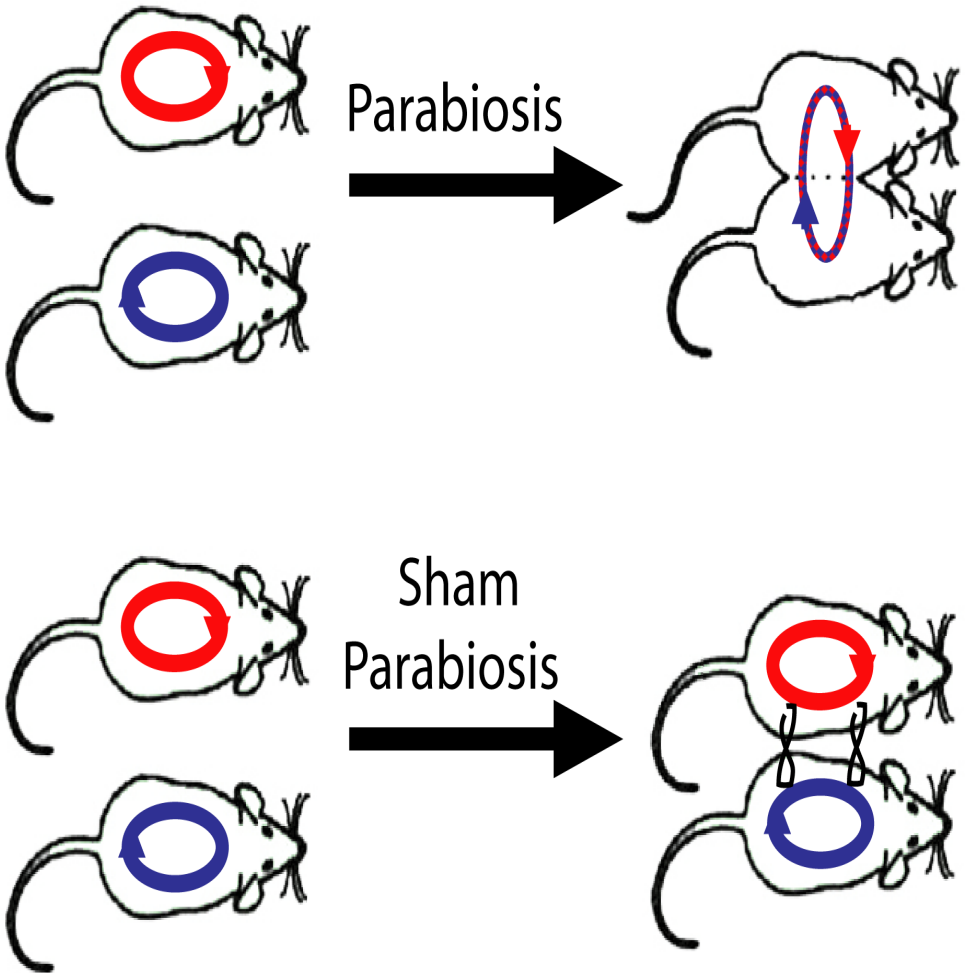
Custom built blood pressure measuring device

Y 2 mos CD45.1
Y 2 mos CD45.2
O 23 mos CD45.2

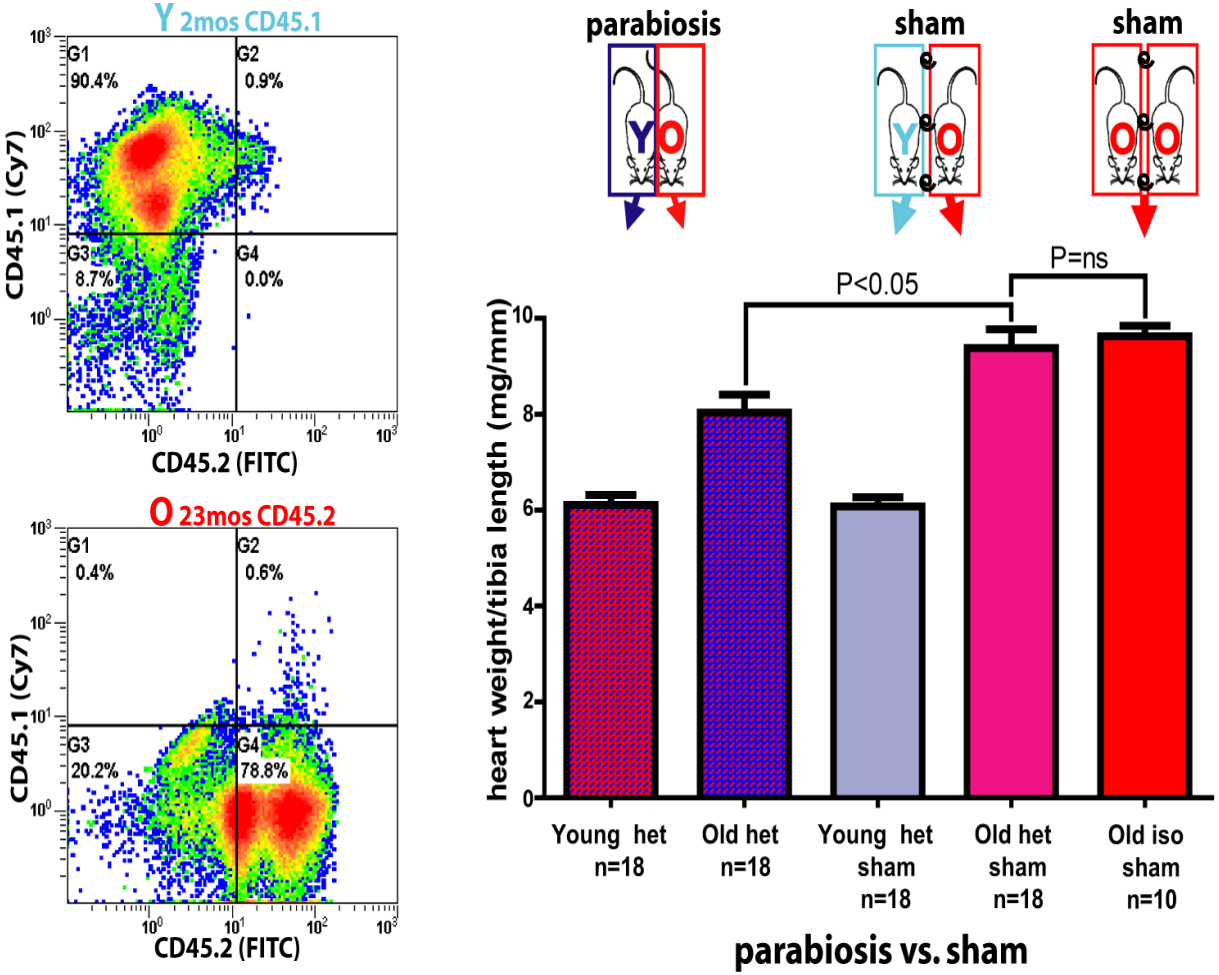




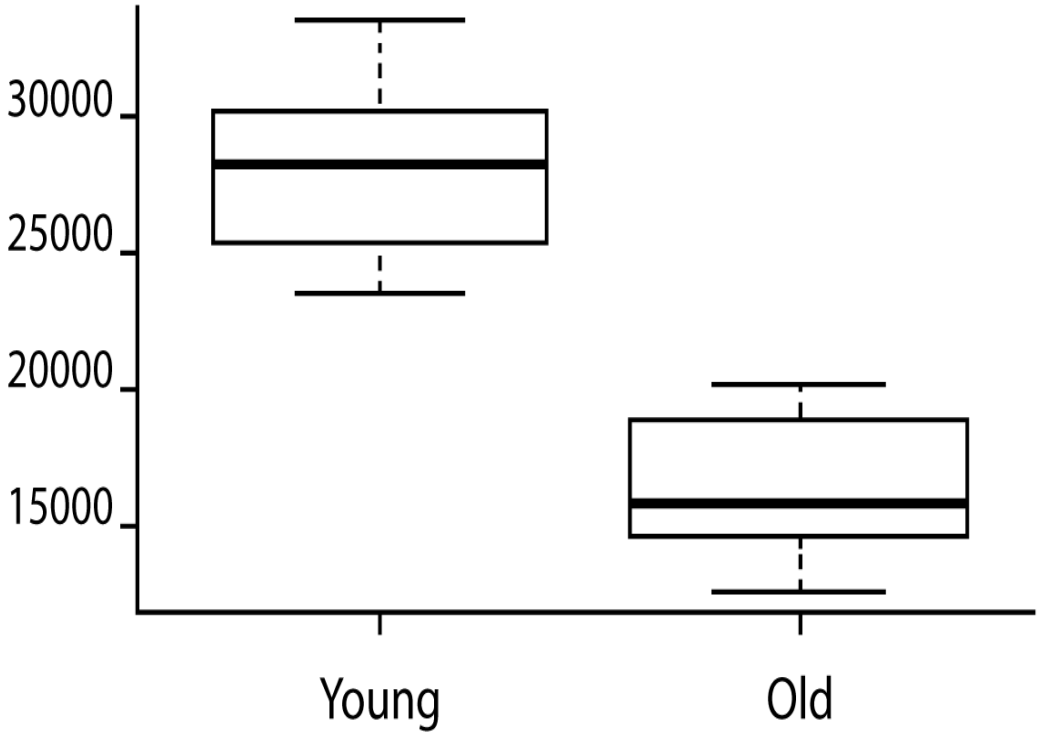
In sham parabiosis, mice are joined by suturing olecranon and knees; there is no contact between internal flaps of the incised skin.



Sham parabiosis does not reverse cardiac hypertrophy in aging mice.



Aptamer based proteomic analysis shows reduced plasmatic levels of Growth differentiation factor 11 (GDF11) in aging mice



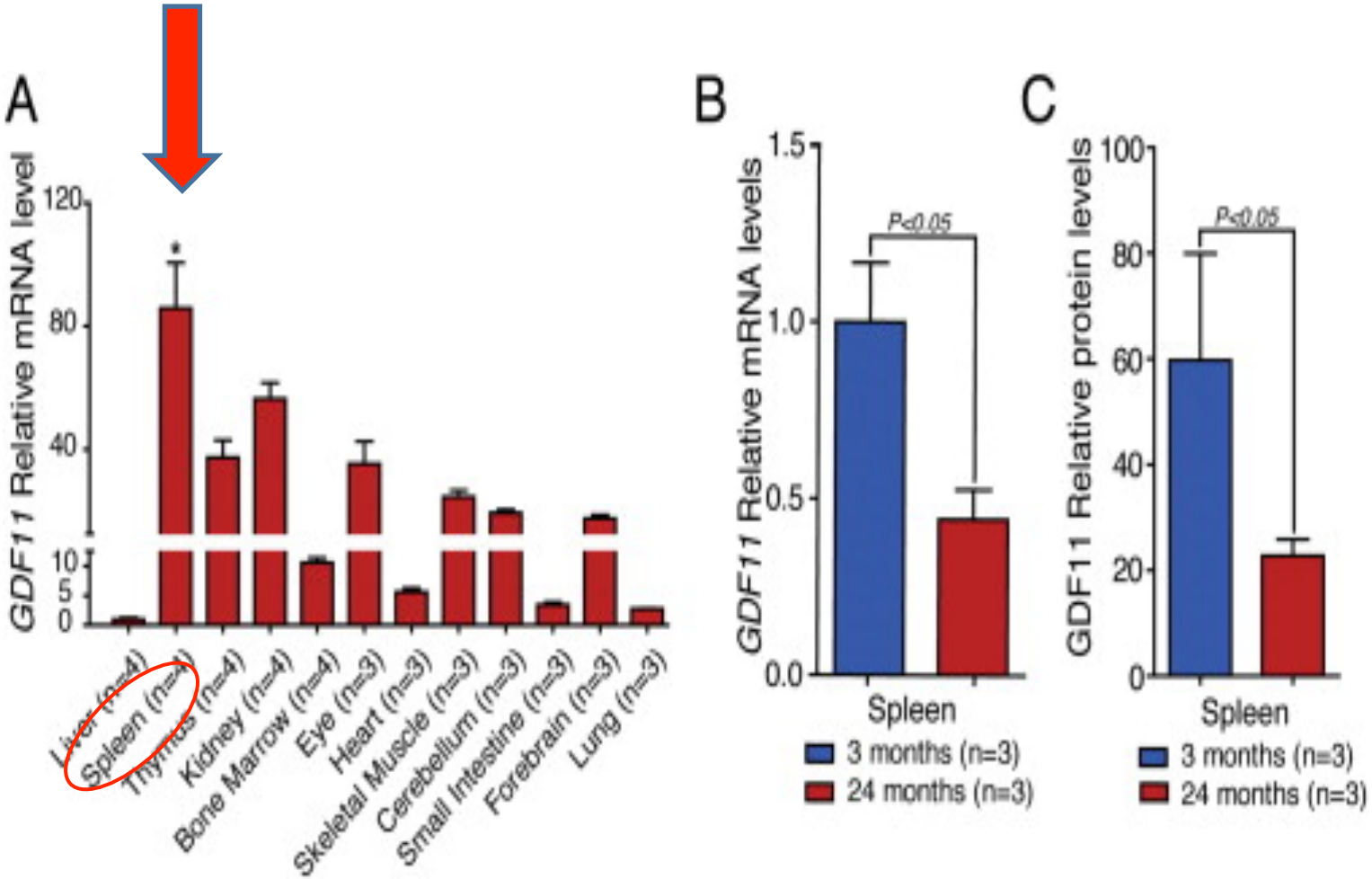
GDF11 controls anterior-posterior patterning during mouse development

- GDF11 also known as bone morphogenetic protein 11 (BMP-11) is a protein that belongs to the transforming growth factor beta superfamily and controls anterior-posterior patterning.

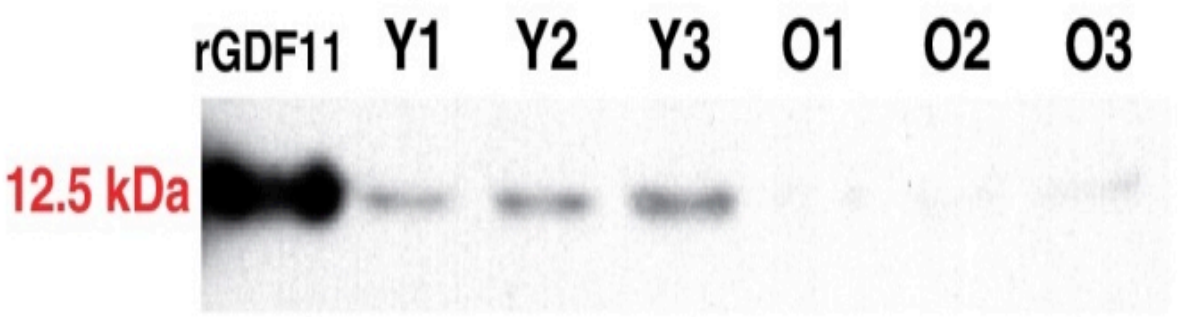
- It is involved in neurogenesis in the spinal cord and olfactory bulb. GDF11 also regulates kidney development and endocrine pancreas development.

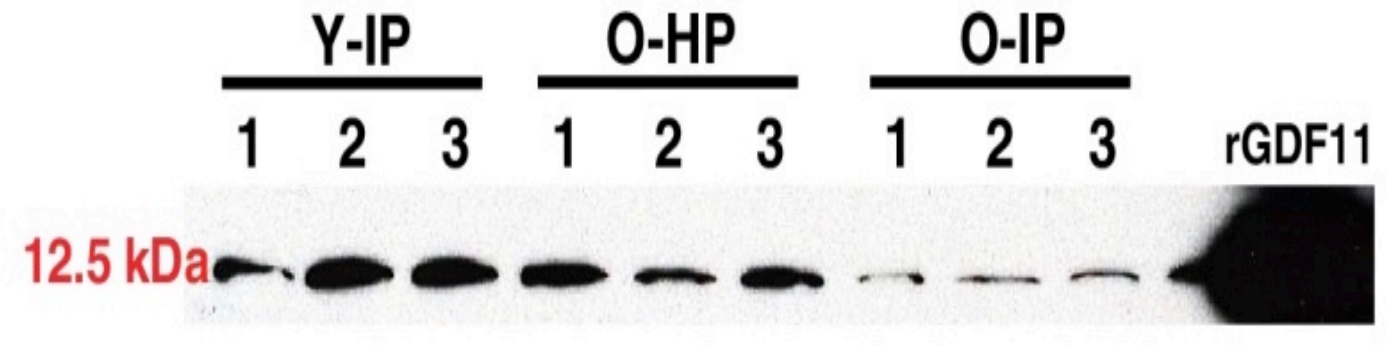
- The mature form of GDF11 (12.5 kDa) can bind type I TGF-beta superfamily receptors ACVR1B (ALK4), TGFBR1 (ALK5) and ACVR1C (ALK7), but predominantly uses ALK4 and ALK5 for signal transduction

LIVELLI
GDF11

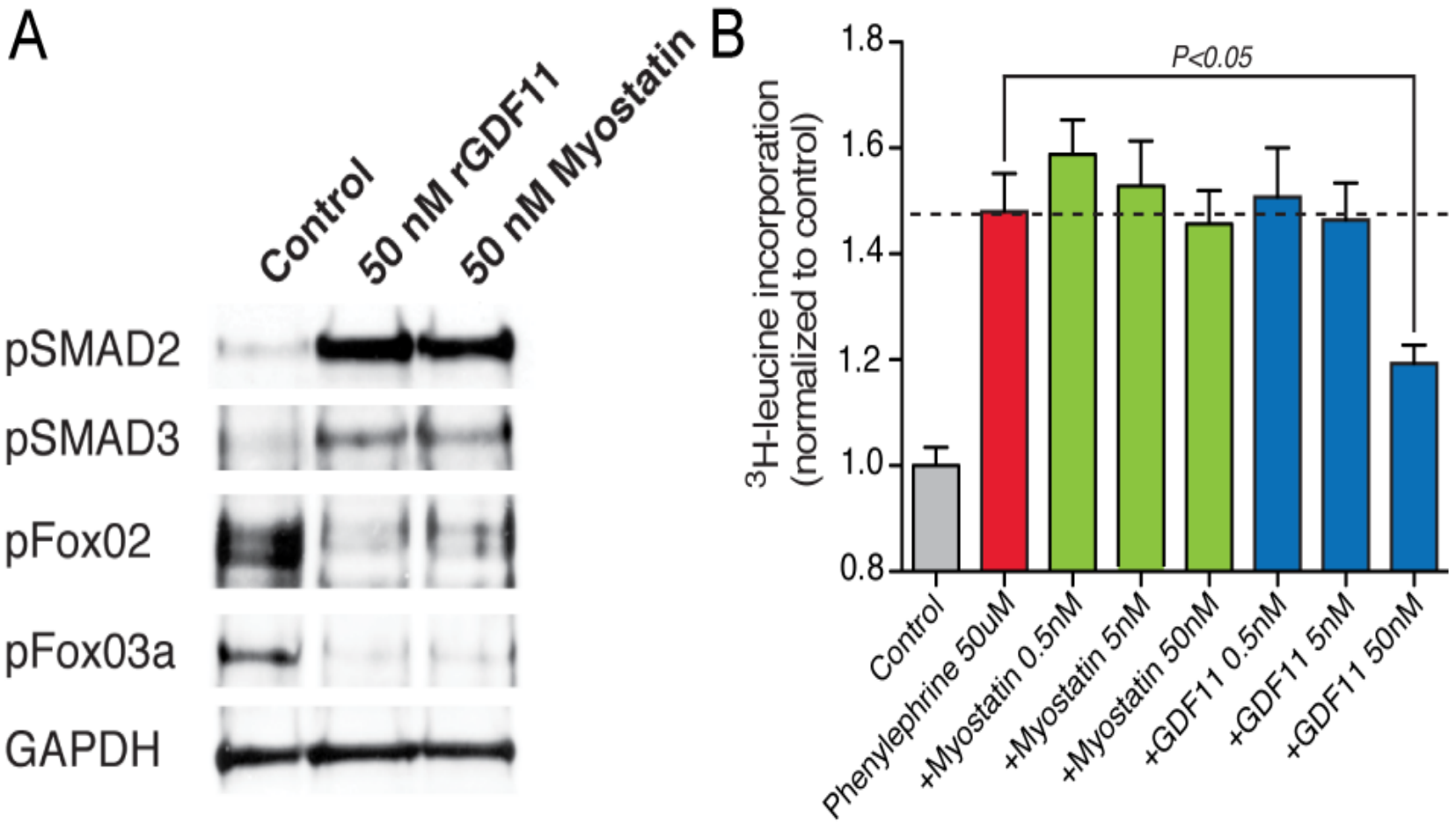


GDF11 is reduced in the circulation of aged mice and “youthful” levels are restored by heterochronic parabiosis.

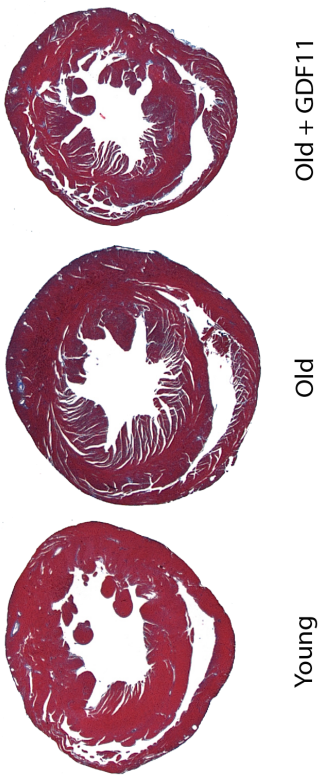


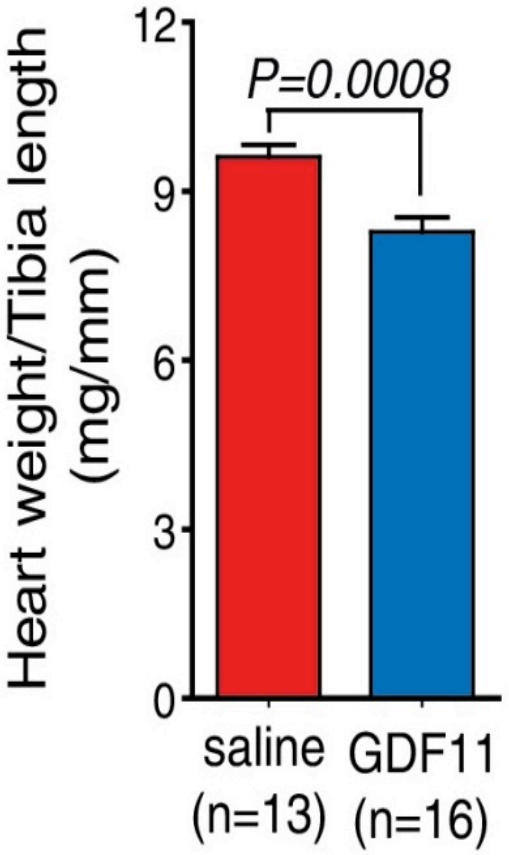


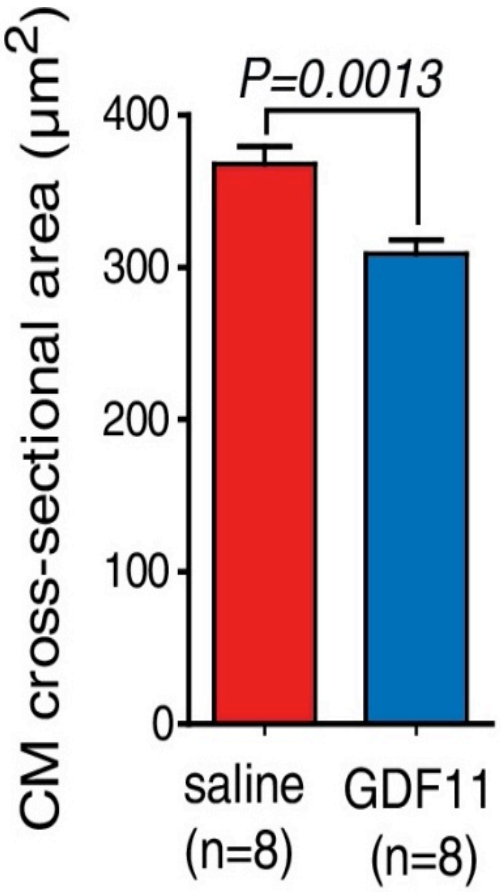
GDF11 stimulate TGFβ signaling pathways including anti-hypertrophic FoxO factors

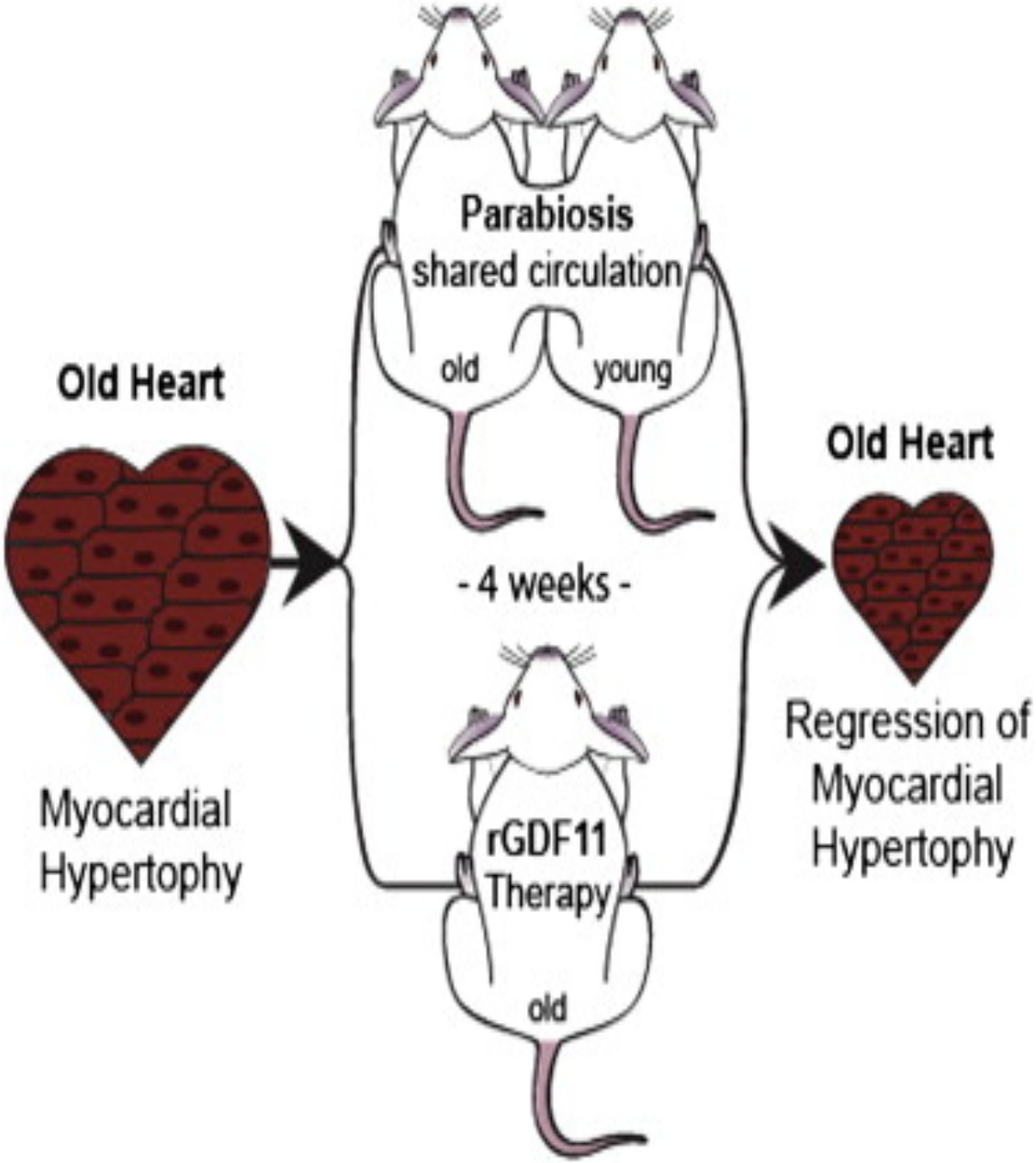


When GDF11 levels of aged mice
are restored to “youthful” levels, the hypertrophy
of cardiac aging is reversed in 4 weeks.







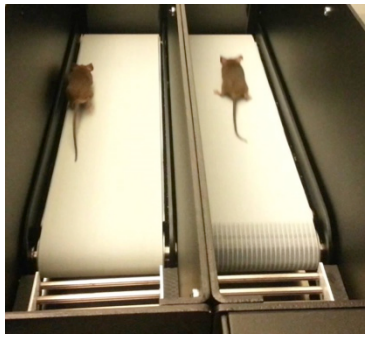

Old Heart
Myocardial Hypertophy
Parabiosis
shared circulation
old
young
- 4 weeks -
rGDF11 Therapy
old
Old Heart
Regression of Myocardial Hypertophy

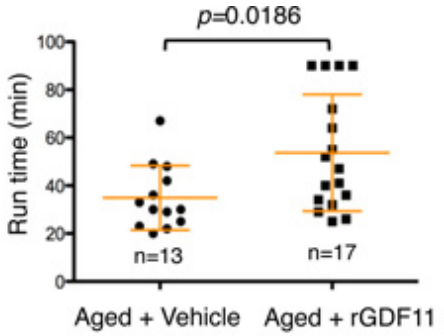
Does Restoration of Youthful GDF11 Levels in Old Mice Reverse Non-Cardiac Aging Phenotypes?

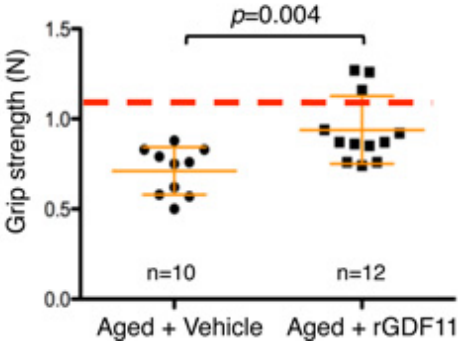
SCIENCE VOL 344 9 MAY 2014

Restoring Systemic GDF11 Levels Reverses Age-Related Dysfunction in Mouse Skeletal Muscle

Manisha Sinha,[1,2,3,4]* Young C. Jang,[1,2,4]* Juhyun Oh,[1,2,4] Danika Khong,[1,2,4] Elizabeth Y. Wu,[1,2,4] Rohan Manohar,[1,2,4] Christine Miller,[1,2,4] Samuel G. Regalado,[1,5] Francesco S. Loffredo,[1,6] James R. Pancoast,[1,6] Michael F. Hirshman,[2] Jessica Lebowitz,[1,2,4] Jennifer L. Shadrach,[1,2,3] Massimiliano Cerletti,[1,2]† Mi-Jeong Kim,[2] Thomas Serwold,[2] Laurie J. Goodyear,[2,7] Bernard Rosner,[8] Richard T. Lee,[1,6] Amy J. Wagers[1,2,3,4]‡



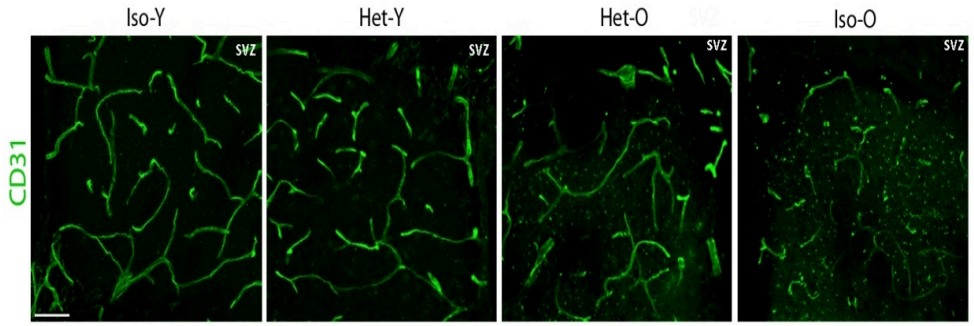


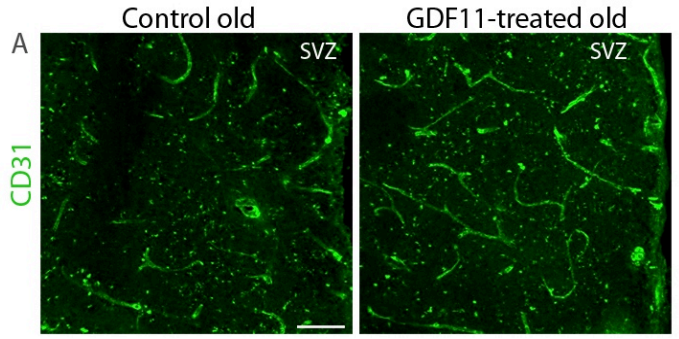


9 MAY 2014 VOL 344 SCIENCE

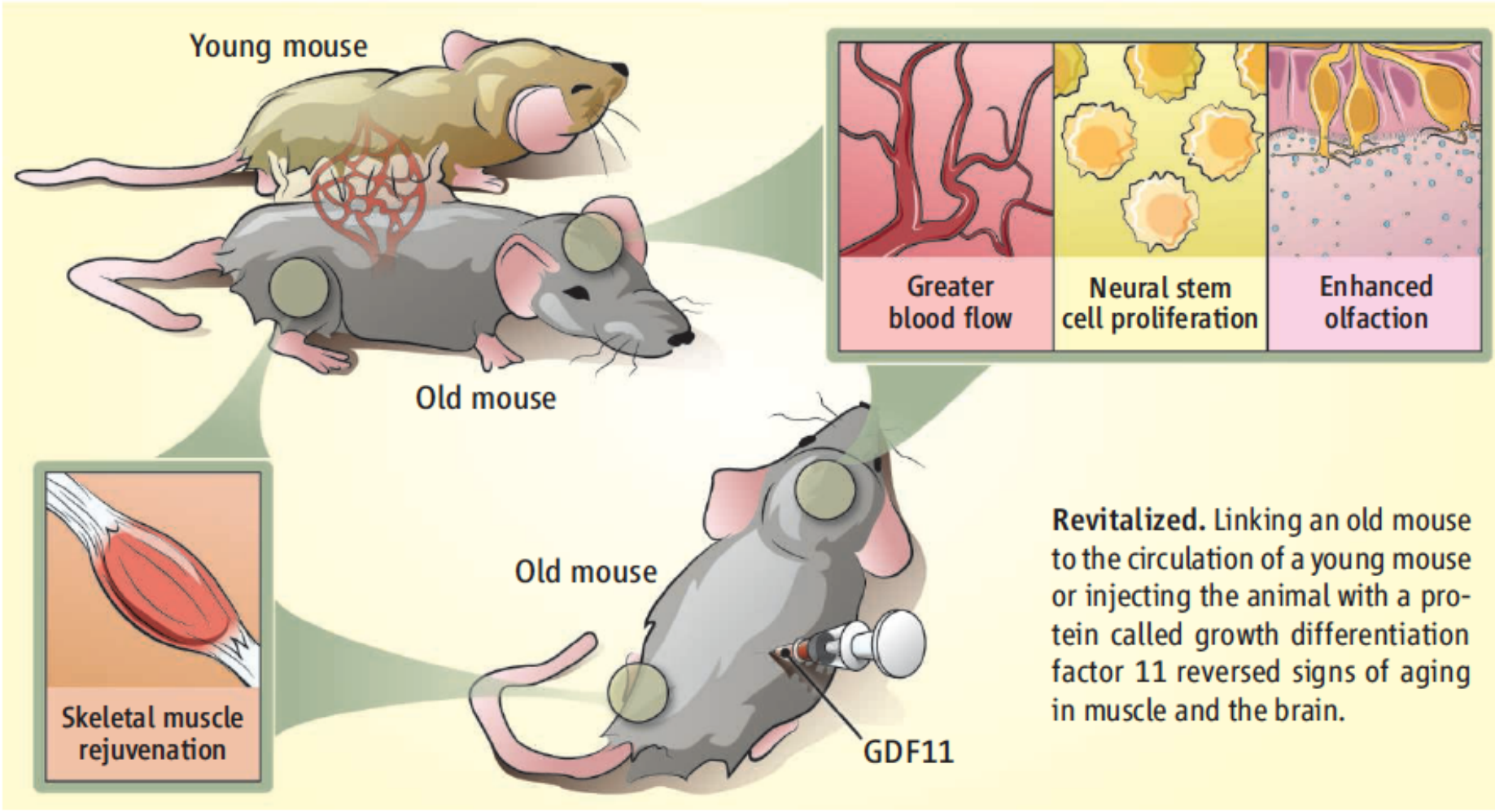
Vascular and Neurogenic Rejuvenation of the Aging Mouse Brain by Young Systemic Factors

Lida Katsimpardi,[1,2]* Nadia K. Litterman,[1,2] Pamela A. Schein,[1,2] Christine M. Miller,[1,2,3] Francesco S. Loffredo,[1,2,4] Gregory R. Wojtkiewicz,[5] John W. Chen,[5] Richard T. Lee,[1,2,4] Amy J. Wagers,[1,2,3] Lee L. Rubin[1,2]*





Blood vessels in the brain subventricular zone



Revitalized. Linking an old mouse to the circulation of a young mouse or injecting the animal with a protein called growth differentiation factor 11 reversed signs of aging in muscle and the brain.

The PLasma for Alzheimer's SymptoM Amelioration (PLASMA) Study

A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial of Intravenously Administered Plasma from Young Donors for Treatment of Mild-to-Moderate Alzheimer's Disease

Details: The PLASMA study is a clinical trial for patients with mild, moderate, or severe Alzheimer's disease and involves weekly infusions of "young blood".

Ambrosia “Clinical Trial”