Global Focus on Knowledge Lecture Series

Wed, 27 May 2009

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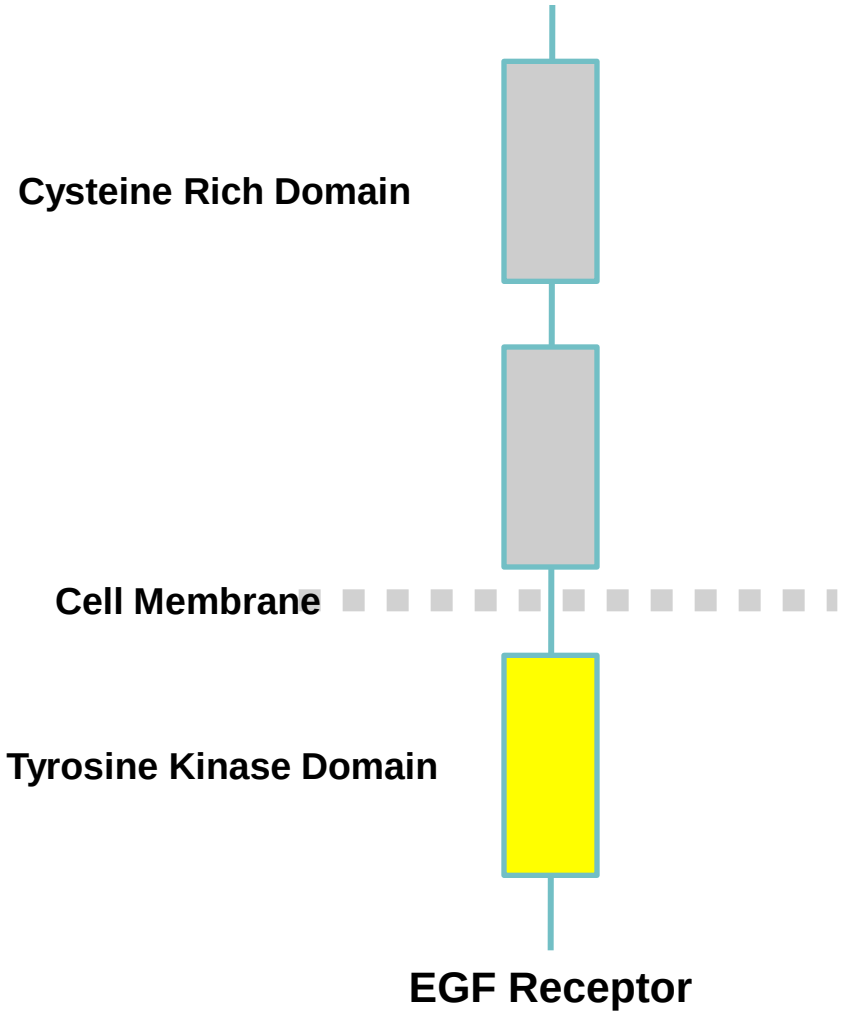
Cell Signaling Systems:

Cell Signaling — From Membrane Receptors to Drugs

Intracellular Signaling Mechanisms
(signal transduction)

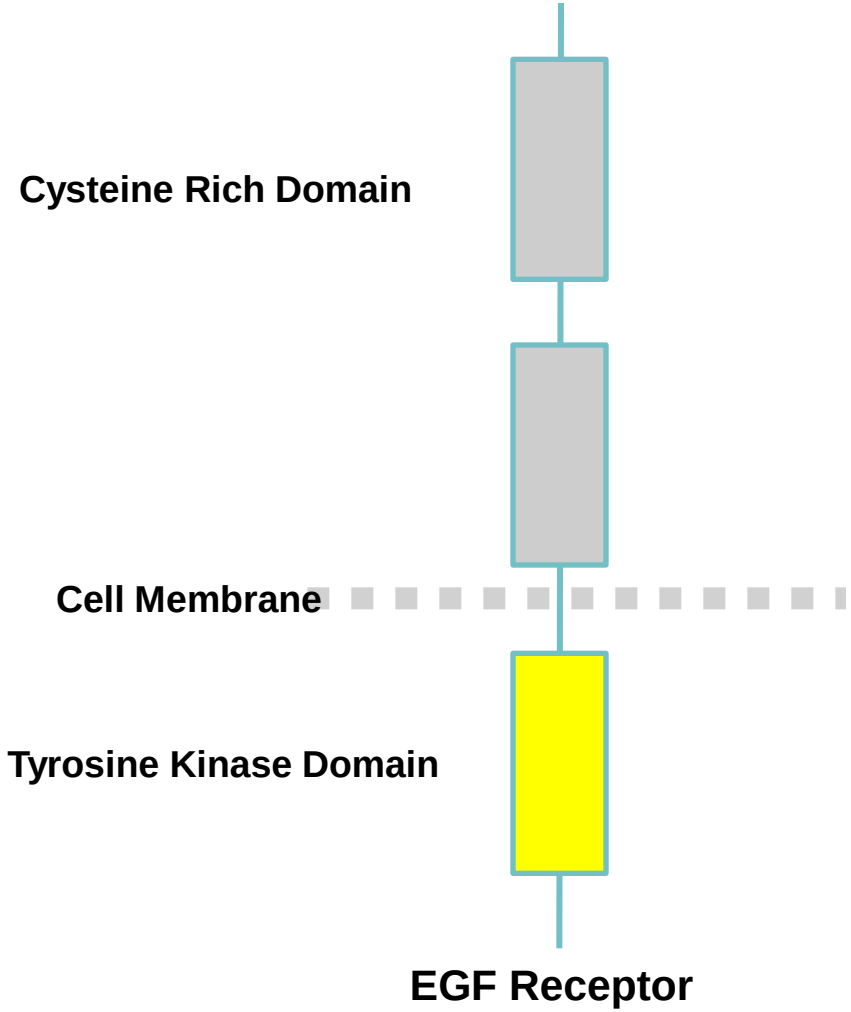
How do cells multiply after receiving
an external stimulus?

The Epidermal Growth Factor (EGF) Receptor

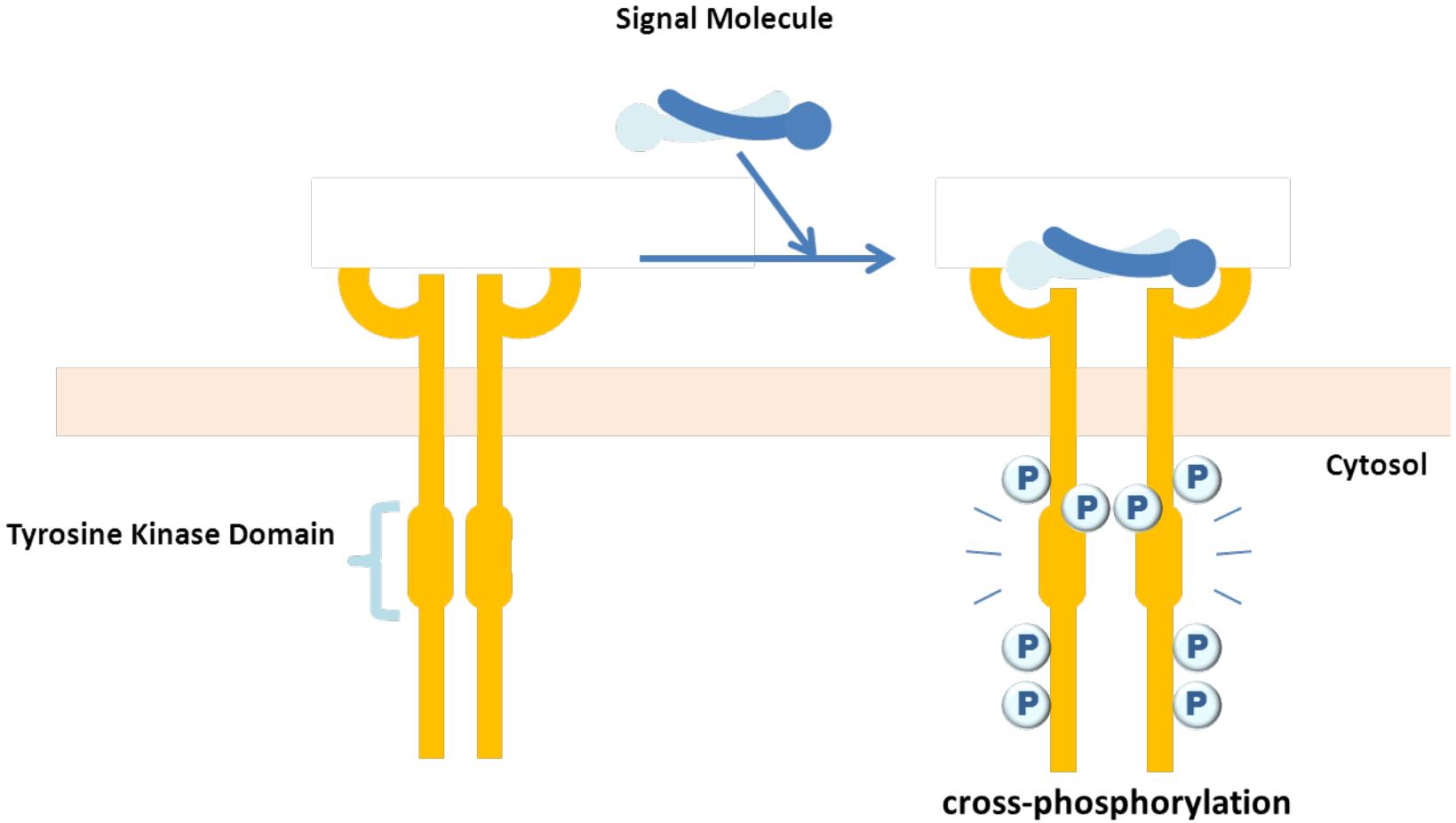


The Epidermal Growth Factor (EGF) Receptor

- Characterized by the presence of tyrosine kinase, which phosphorylates tyrosine residues in the cell.

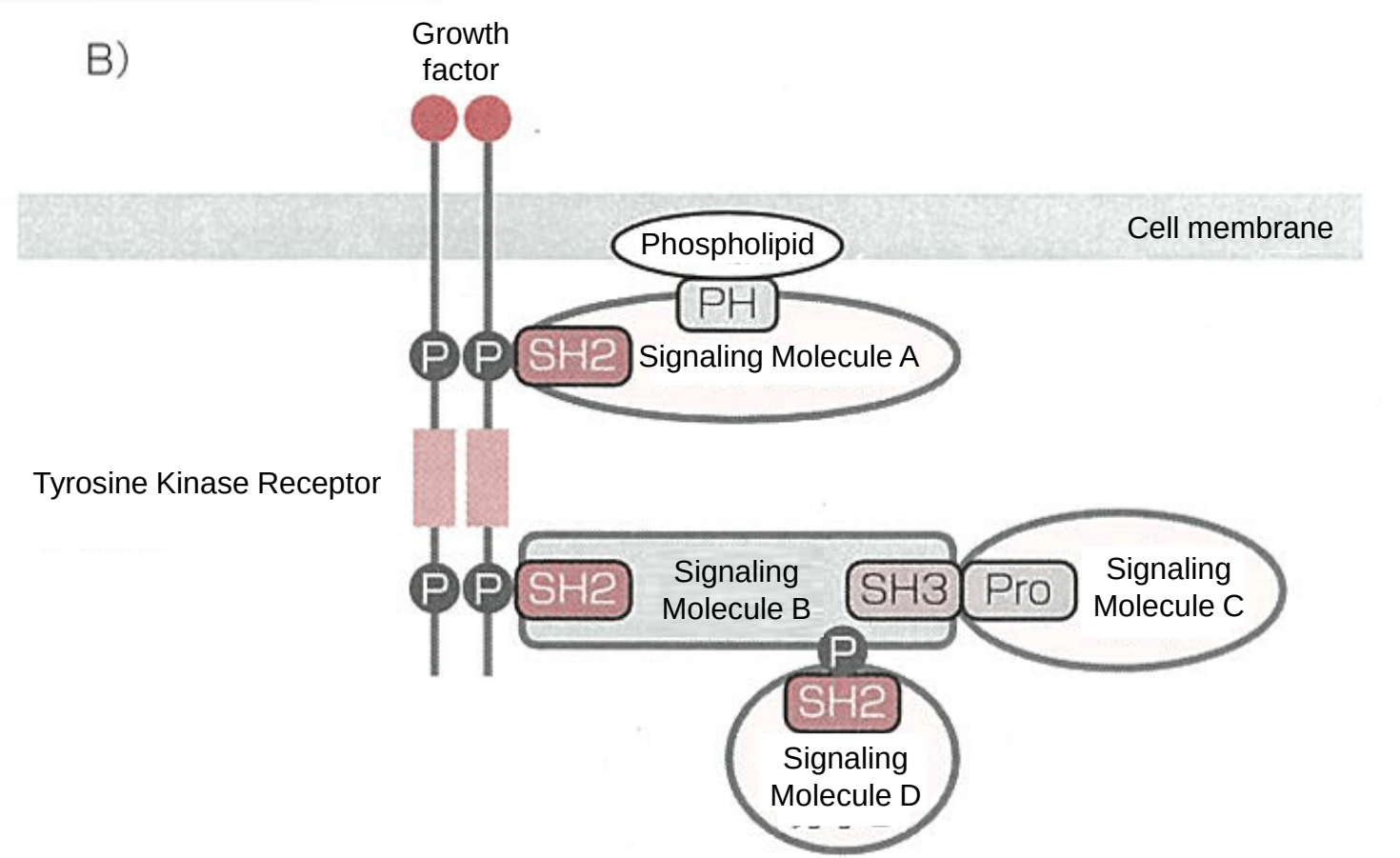


Growth Factor Promotes Receptor Dimerization



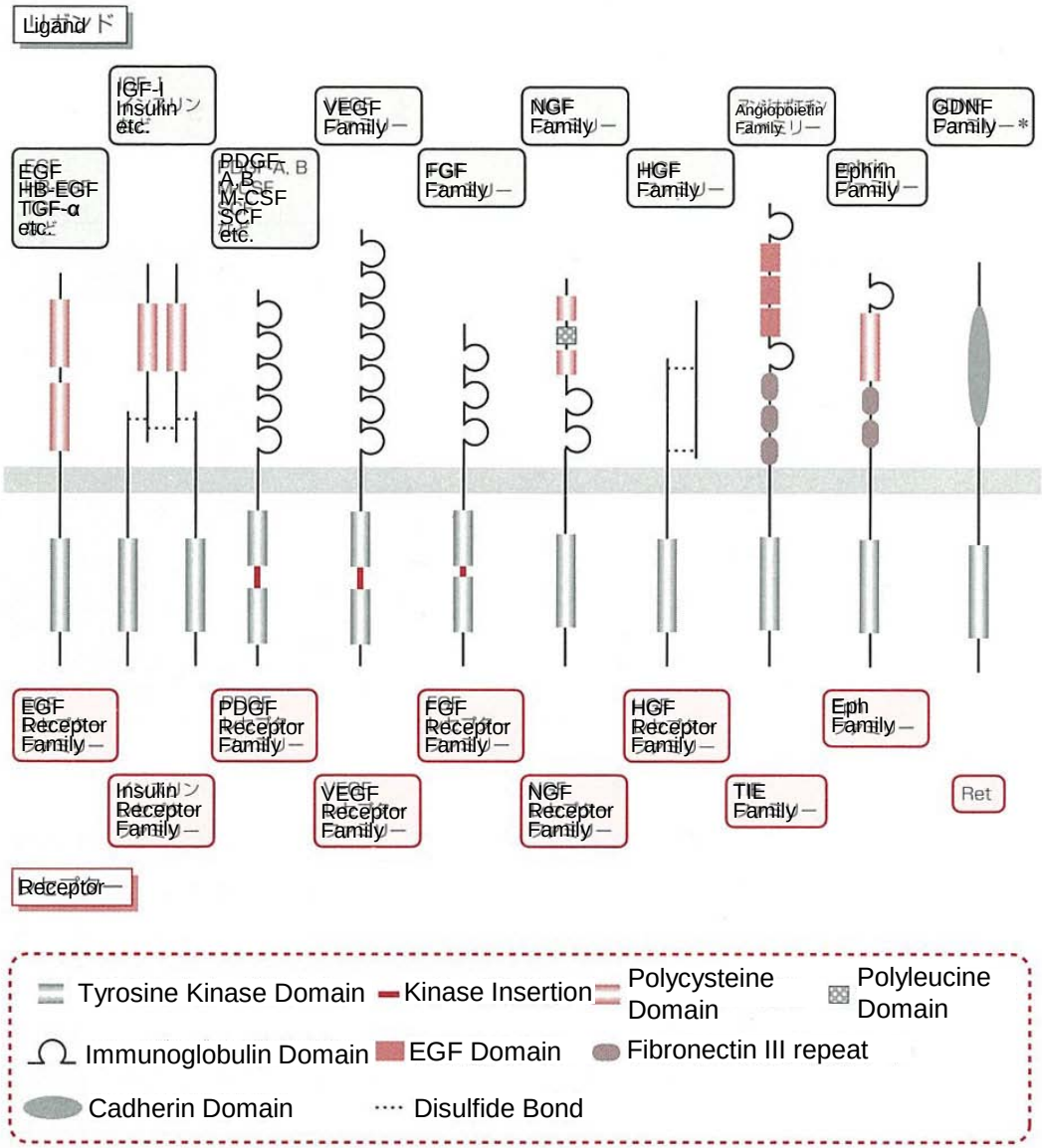
RTK: receptor tyrosine kinase

Different Intracellular Signal Molecules Bond to Phosphorylated Tyrosine



‡ K. Miyazawa, K. Yokote, K. Miyazono (2000)
"Biology of a Factor that Propagates New Cell (Shin saibou zoshoku inshi no biology)"
Yodosha

Primary Tyrosine Kinase Receptors and Their Ligands



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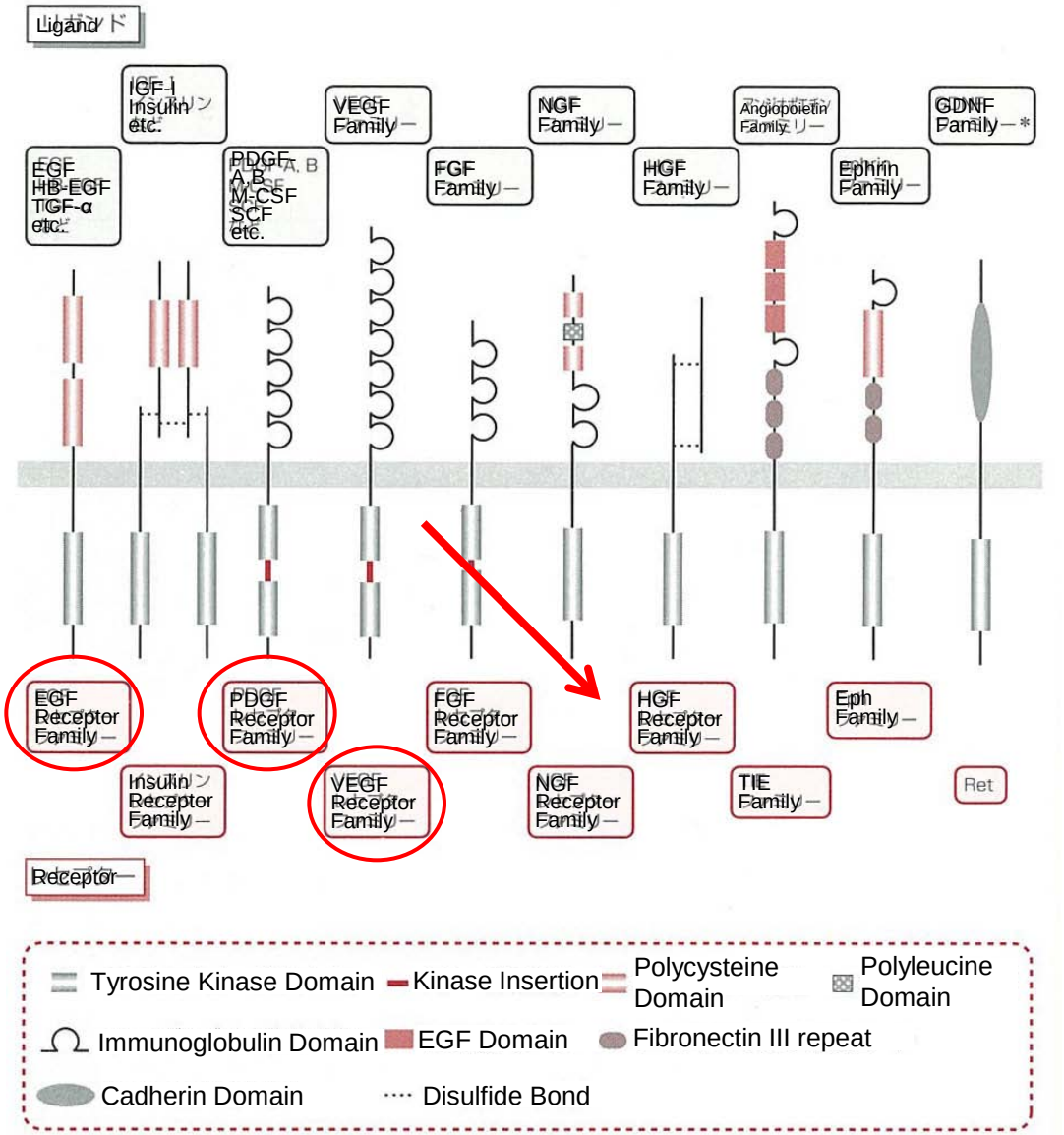

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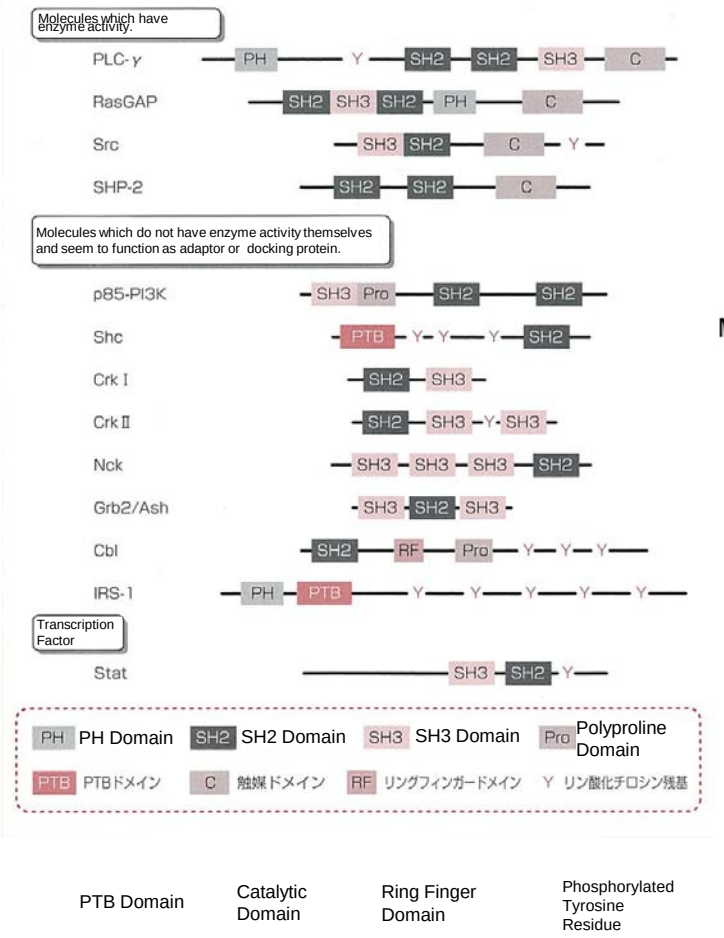
Different Intracellular Signal Molecules Bond to Phosphorylated Tyrosine

Fig. 2-7 Main Signaling Substances in Cell Which Are the Target of Tyrosine Kinase Receptor

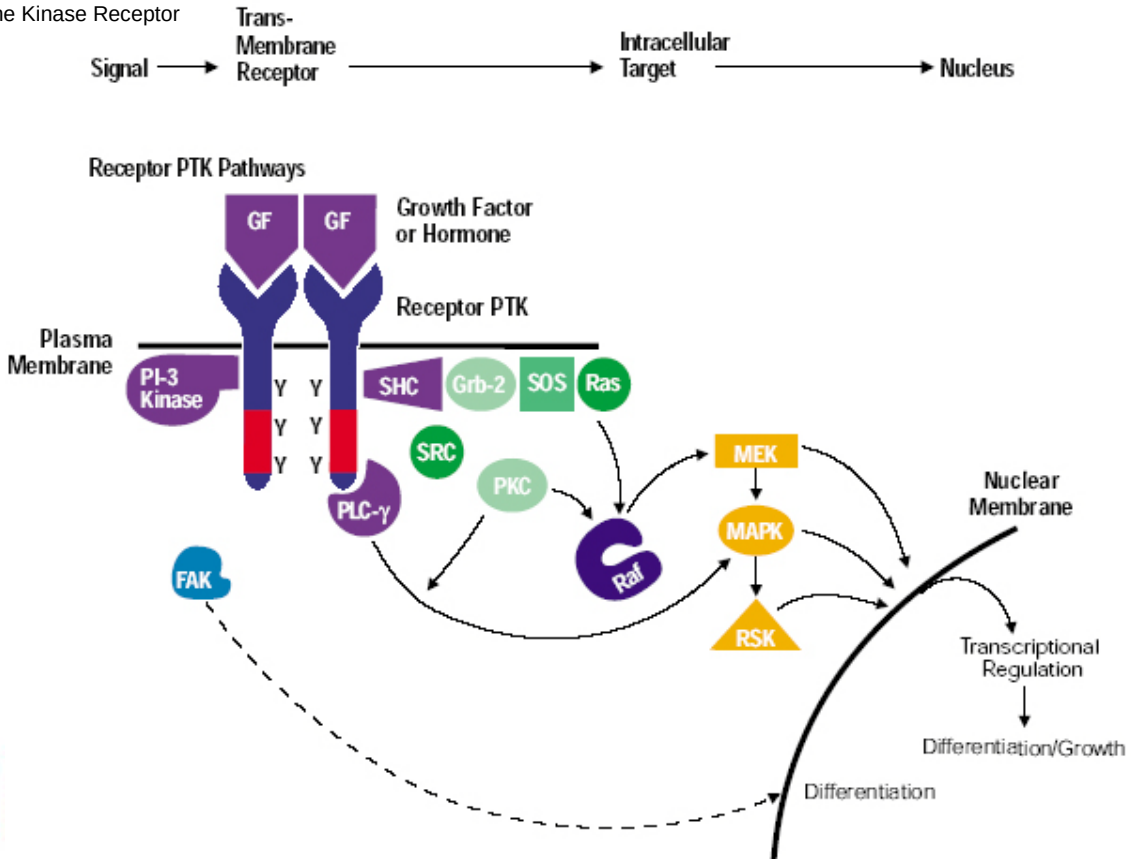


PTB Domain

Catalytic Domain

Ring Finger Domain

Phosphorylated Tyrosine Residue



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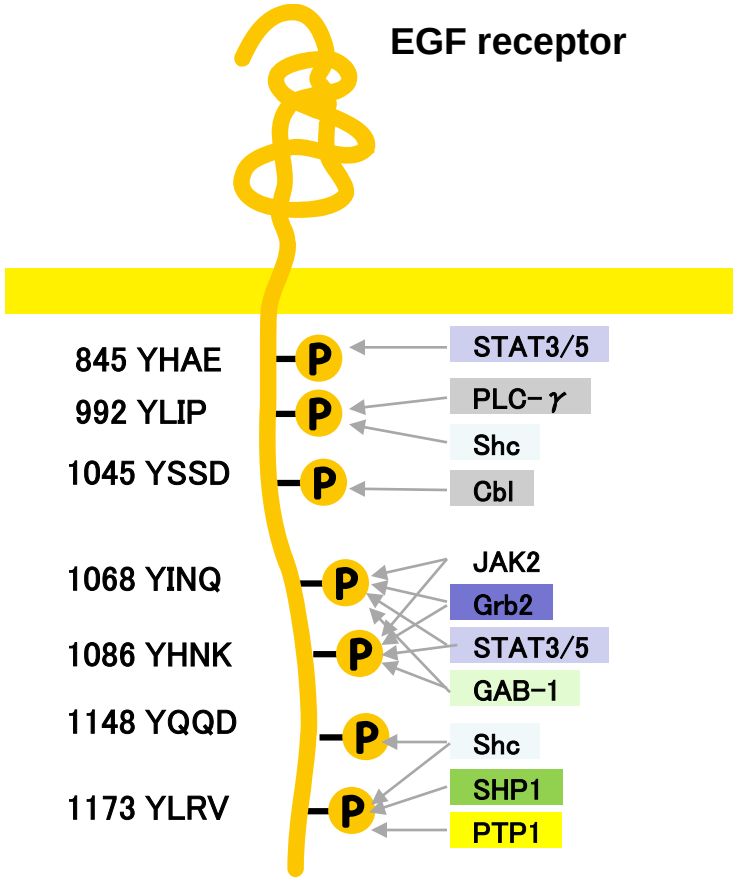

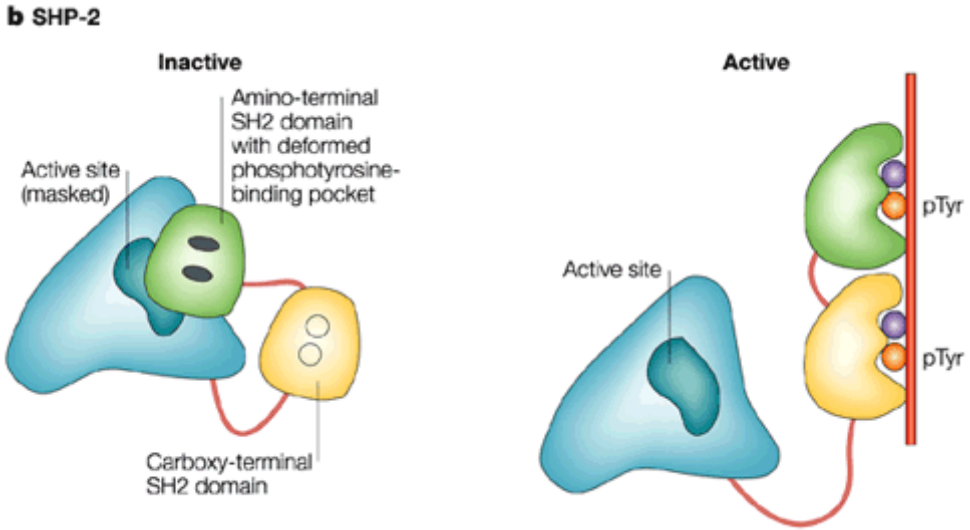

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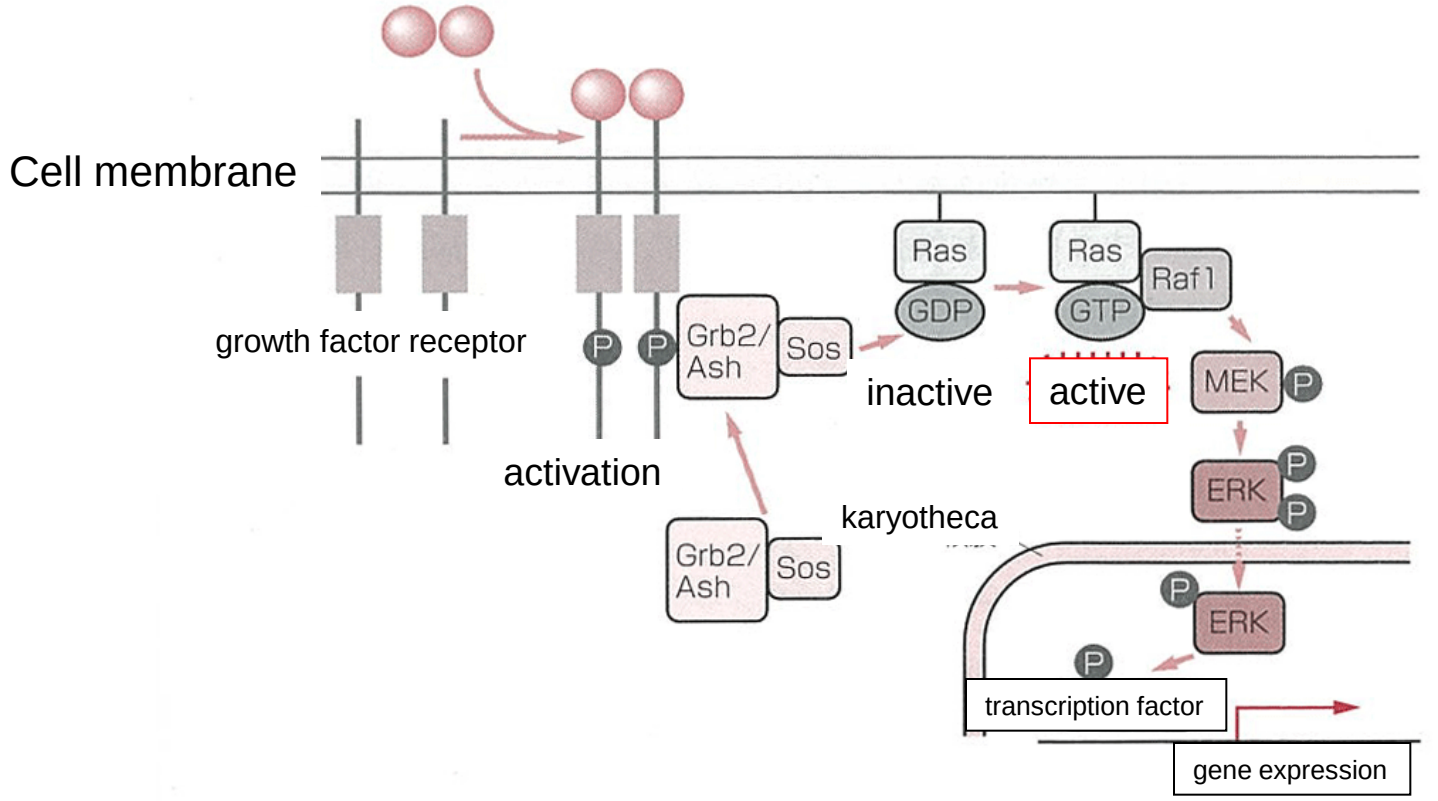
Bonded Intracellular Signal Molecules then Transmit the Signal to the Next Molecule

Mechanism of the activation of Ras/MAP kinase pathway by growth factor and its receptor



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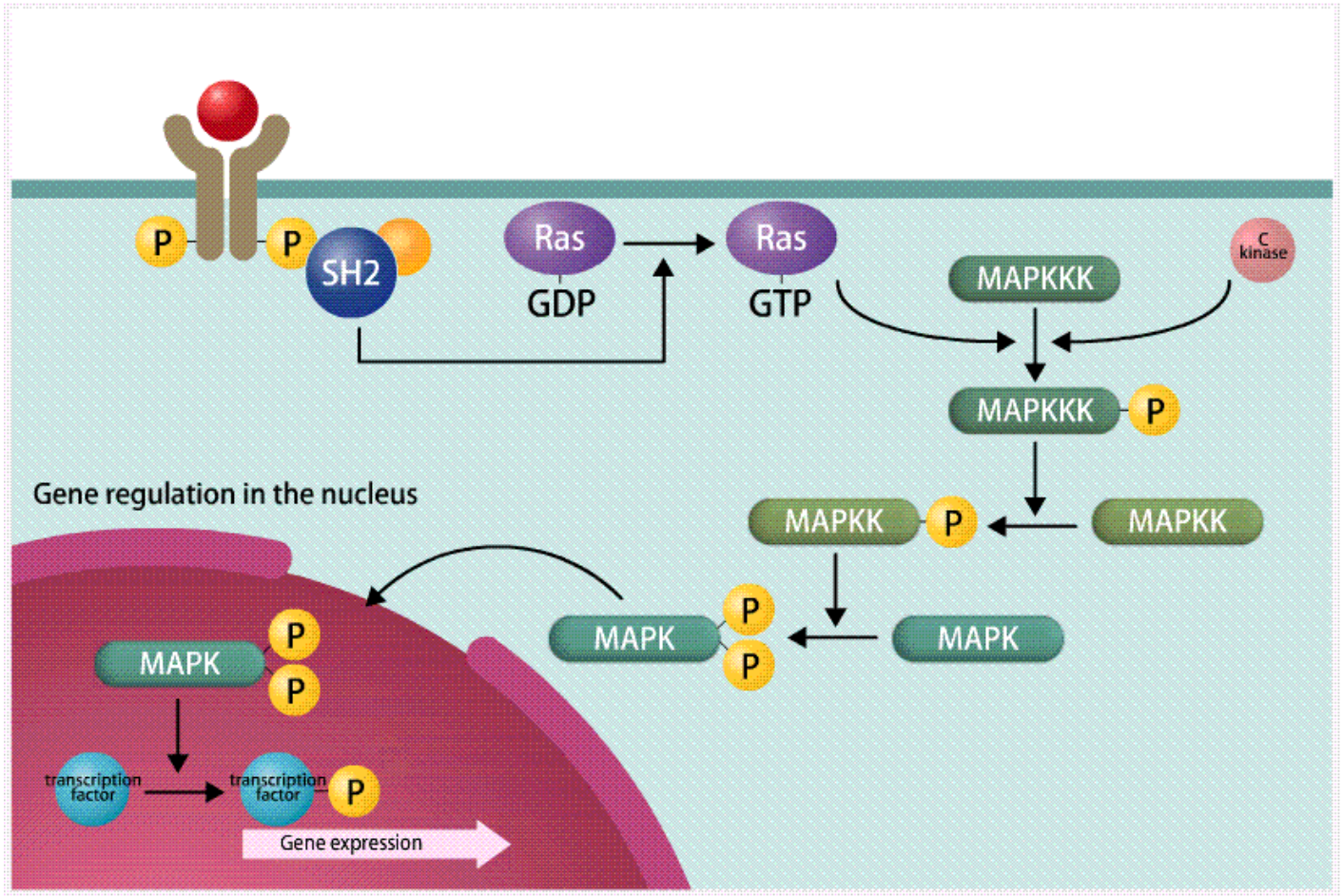
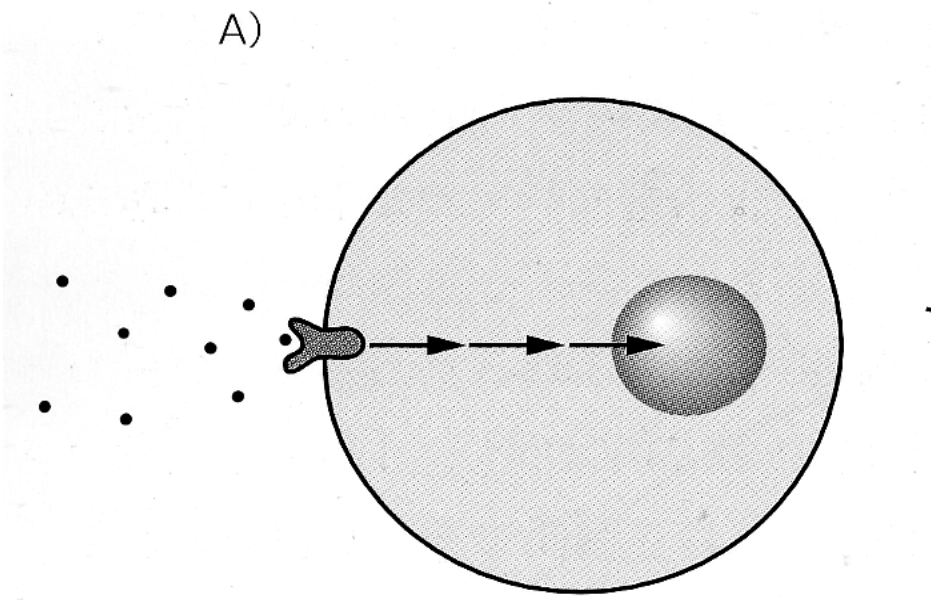
Example of a Growth Factor Signaling Cascade



‡ Life Science Educational Digital Image Repository, Center for Structuring Life Sciences, The University of Tokyo
http://csls-db.c.u-tokyo.ac.jp/

Growth Factor Signaling and Cancer

Normal cell



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Growth Factor Signaling and Cancer

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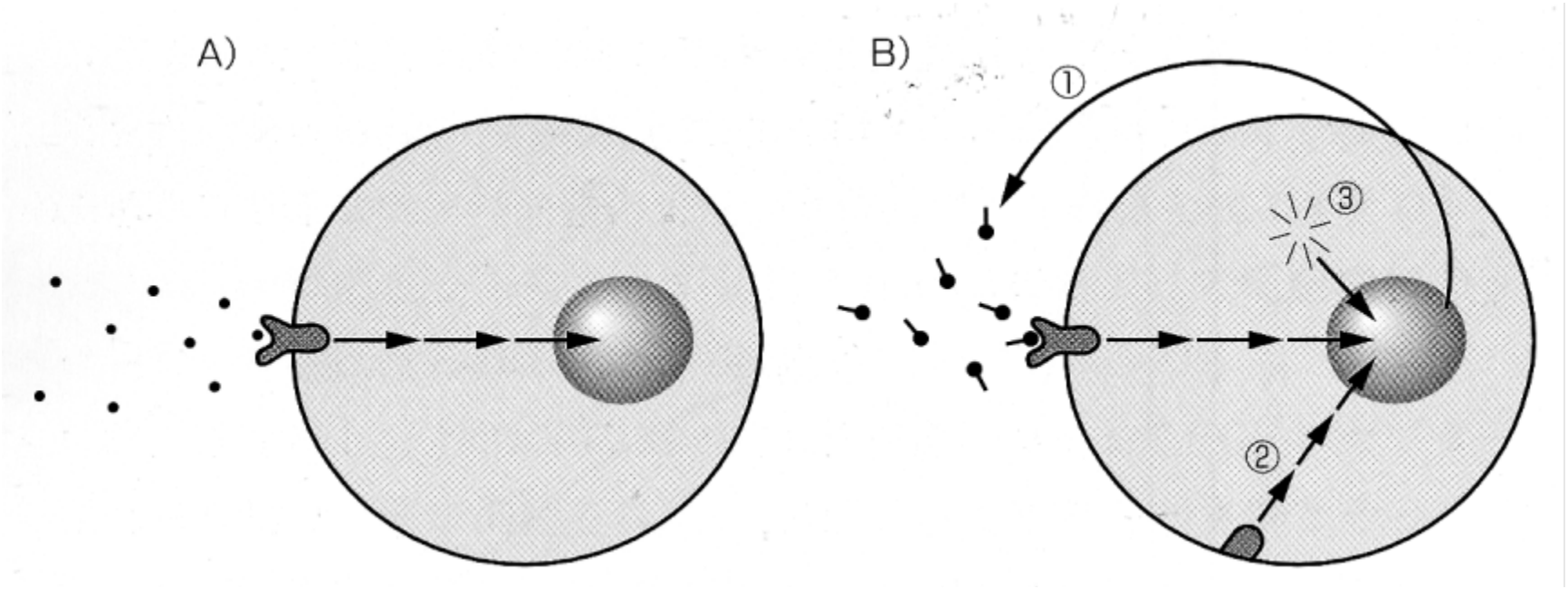
Cancer cell



Cancer cells exhibit excessive growth factor signaling.

→ Runaway signaling

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Growth Factors and Oncogenes

Oncogene	Growth factor	Human cancers
sis	PDGF-B chains	Brain, bone
erb-B1	EGF receptor	Lung
ras	Signaling molecules	Lung, pancreas, colon, other

sis (simian sarcoma virus)
erb-B1 (avian erythorblastosis virus)

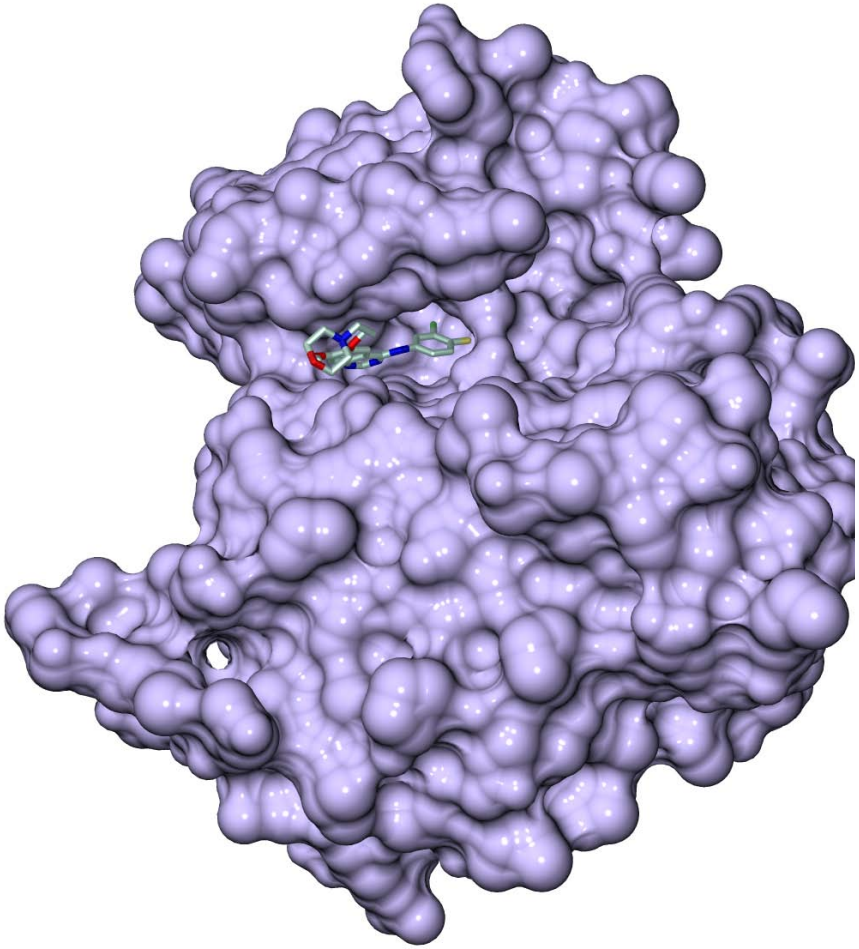
Iressa Interferes with the Functioning of EGF Receptors

Figure removed due to
copyright restrictions

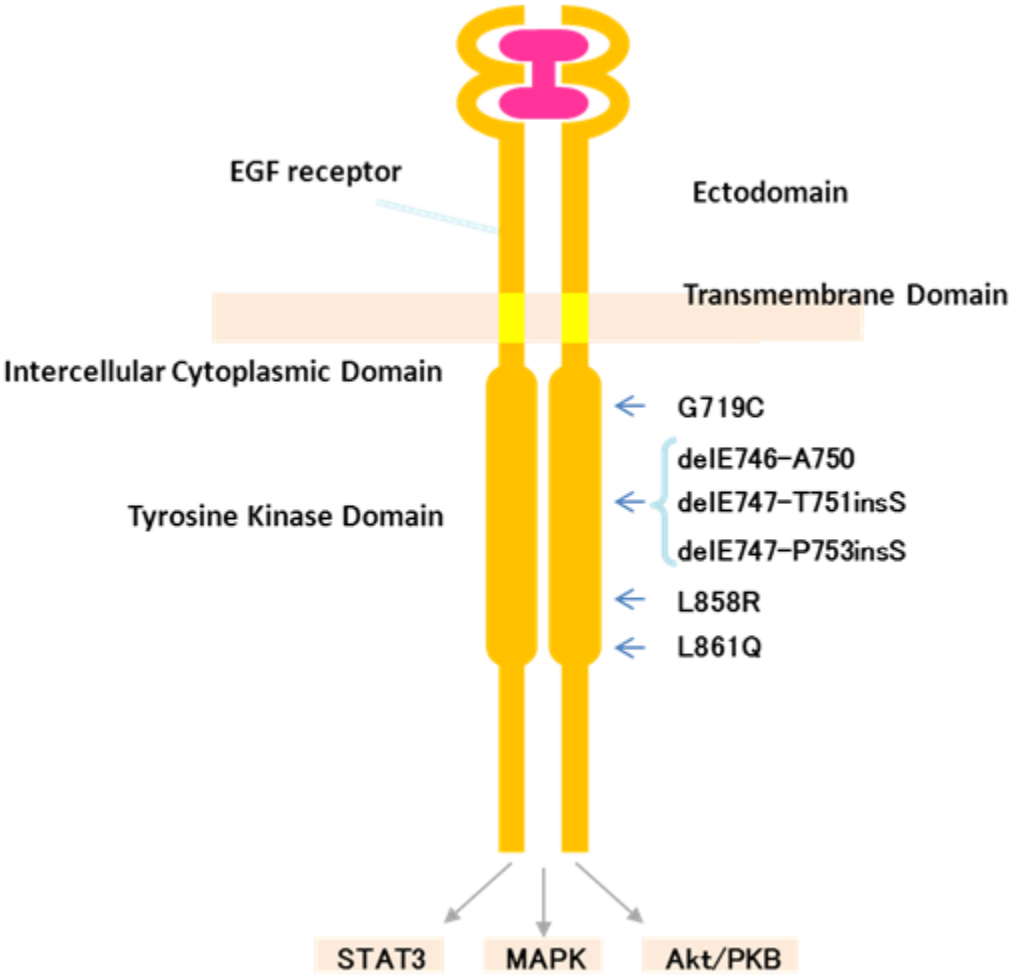
Robert A. Weinberg, 2007, *The Biology of Cancer*,
Garland Science, Figure 16.33(A)

Dramatically effective against some lung cancers

Mutations Seen in EGF Receptors



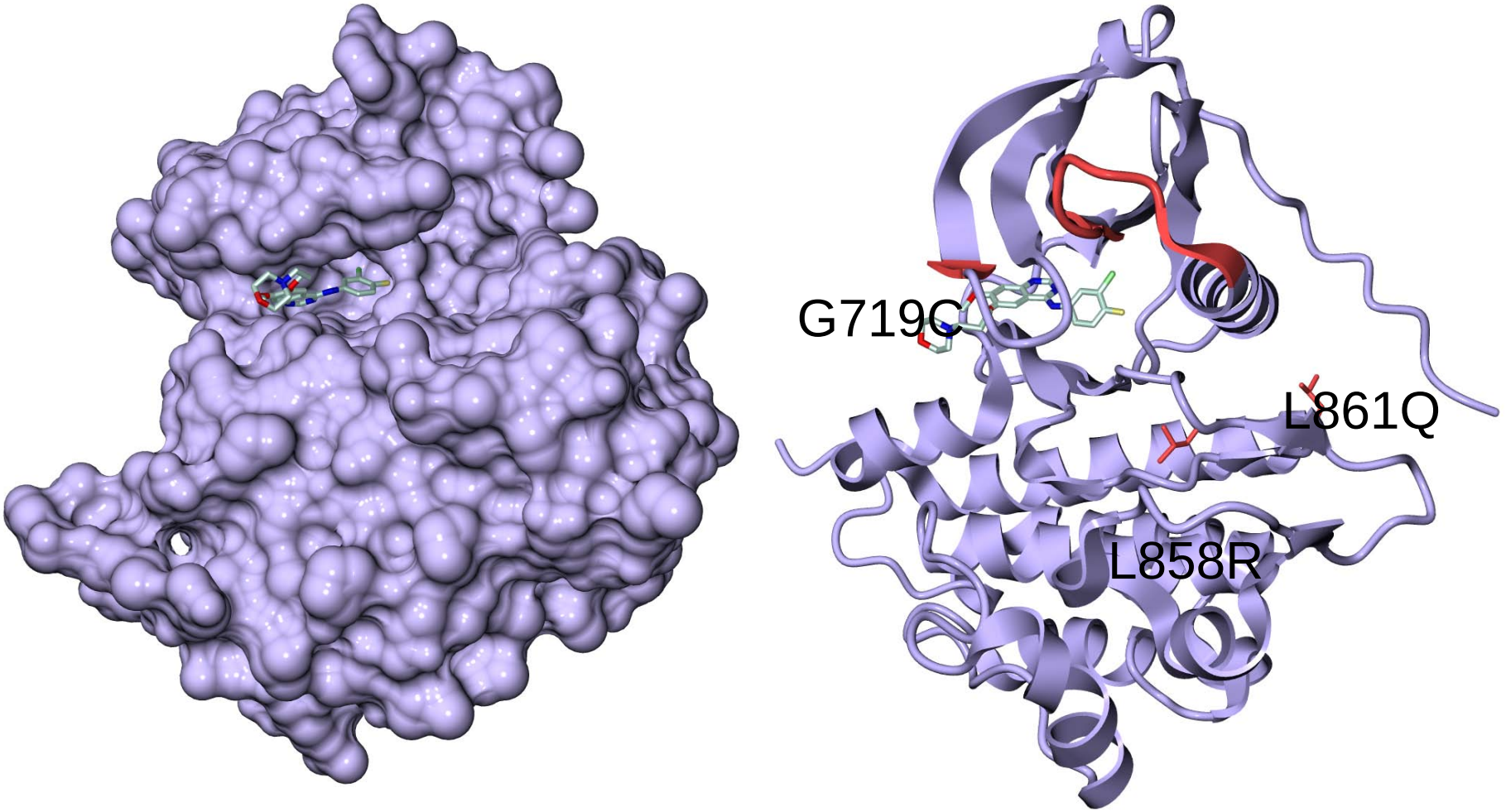
Courtesy of Prof. Osamu Nureki,
U. Tokyo Institute of Medical Science



Blocks the kinase ATP-binding pocket "at source"

→ Especially effective against lung cancers in Japanese women

Iressa Interference in EGFR Kinase Domain



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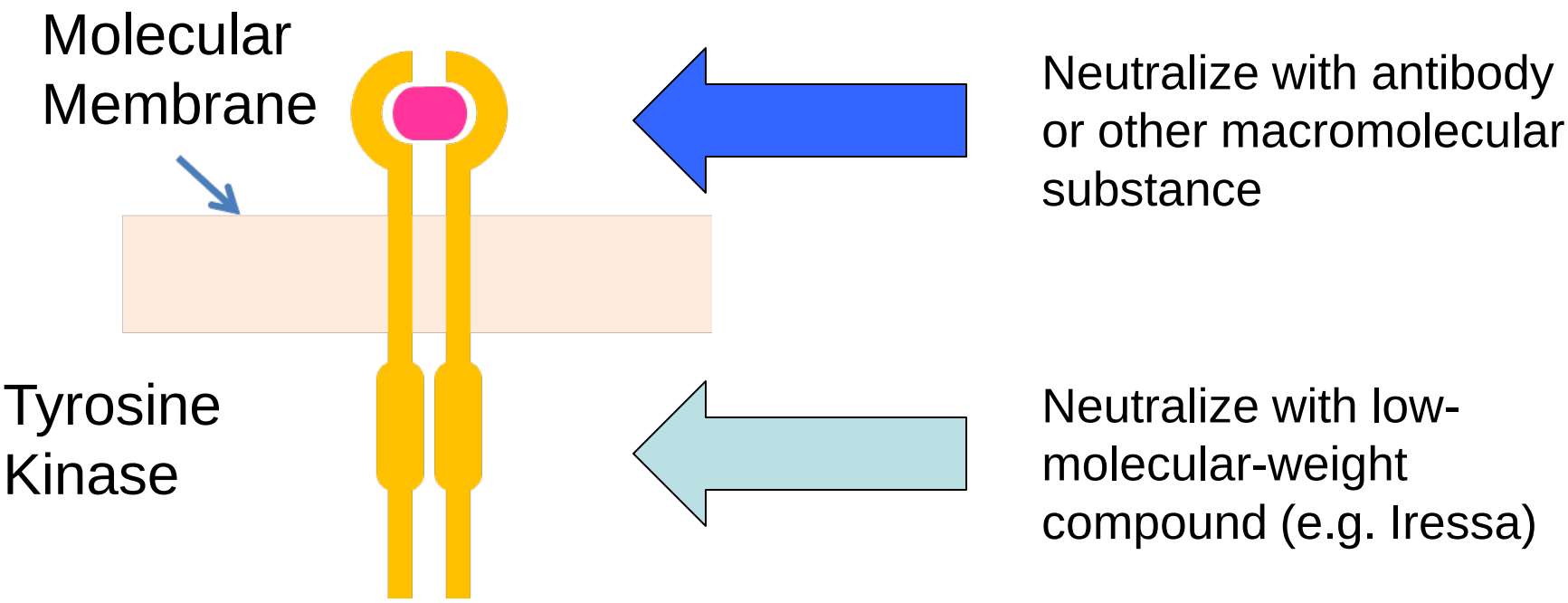
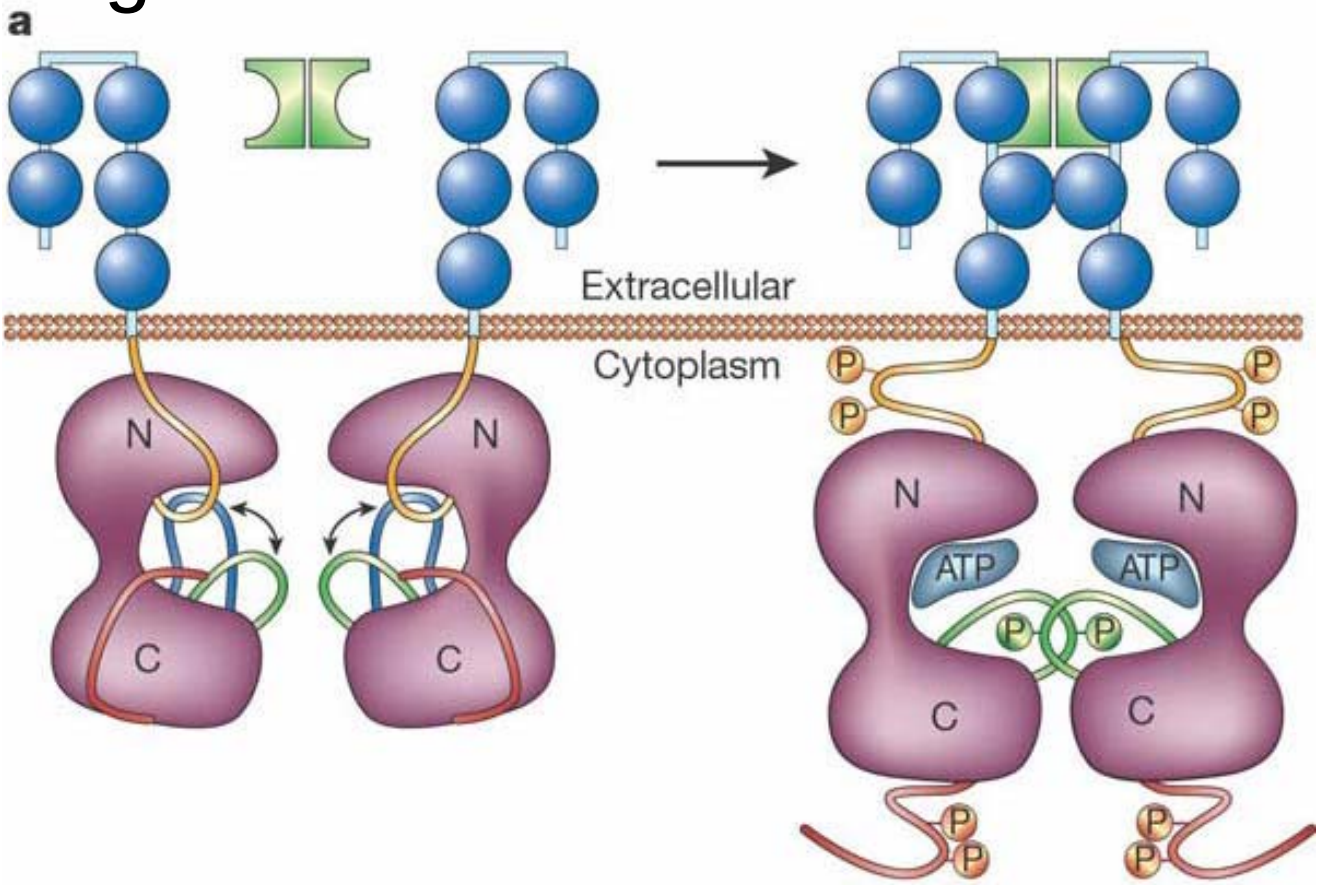
How to Cut Off Growth Factor Signals?



Trans-membrane Growth Signal Activation Mechanisms



PDGF results from two peptides forming a dimer

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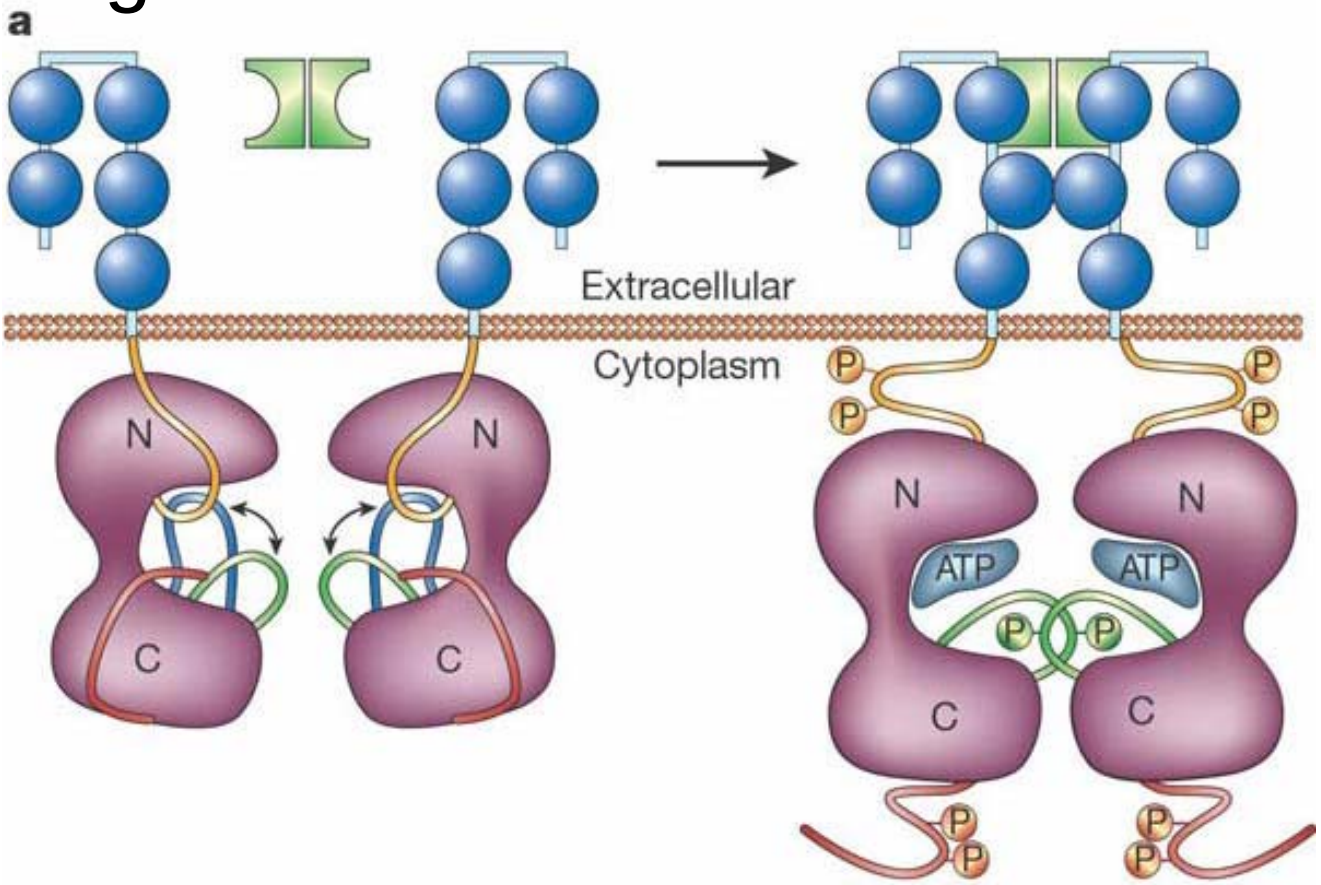
Blume-Jensen, P. and Hunter, T., Nature 411, 355-365, copyright (2001)

Trans-membrane Growth Signal Activation Mechanisms



PDGF results from two peptides forming a dimer

PDGF receptors are also activated by dimerization

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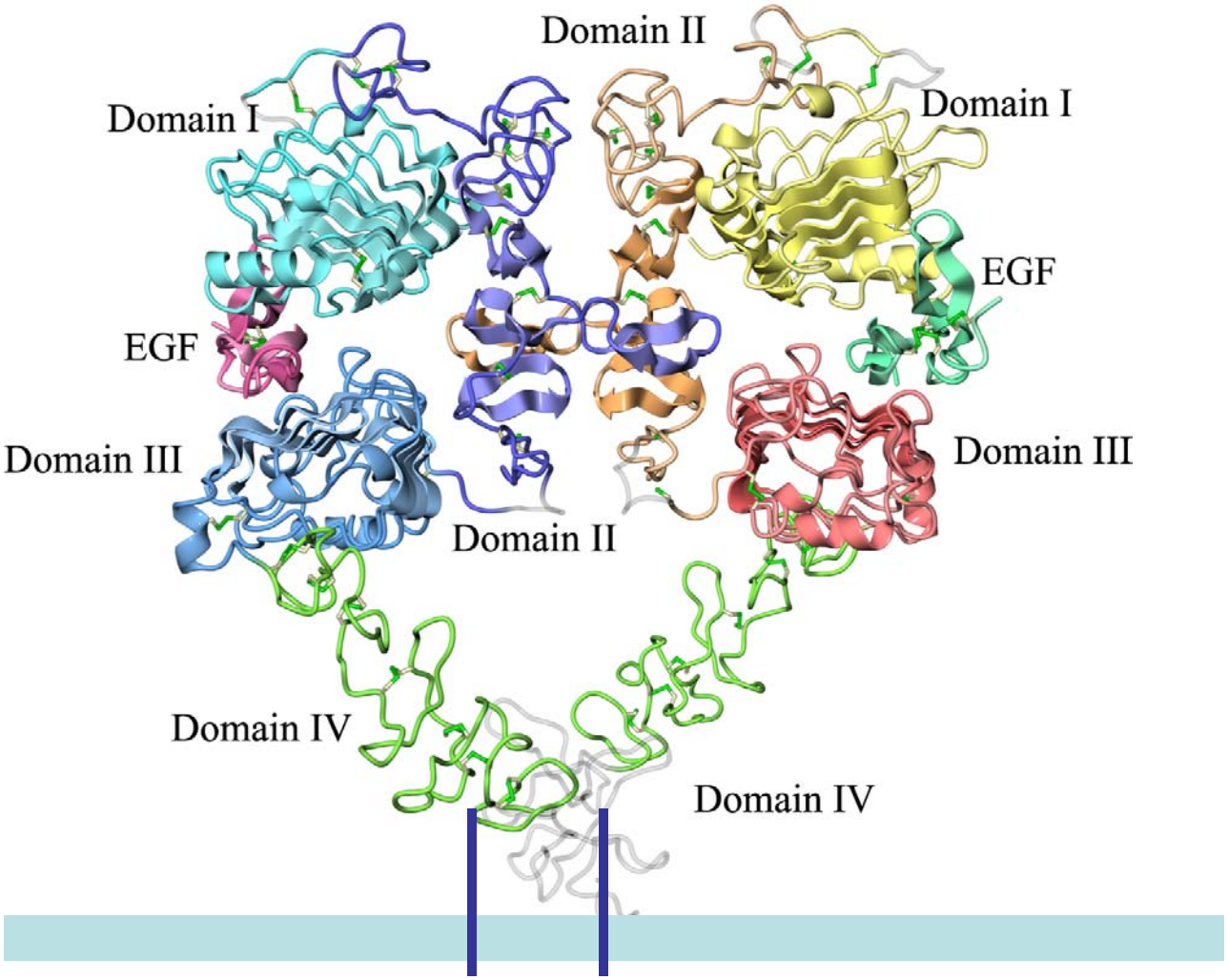
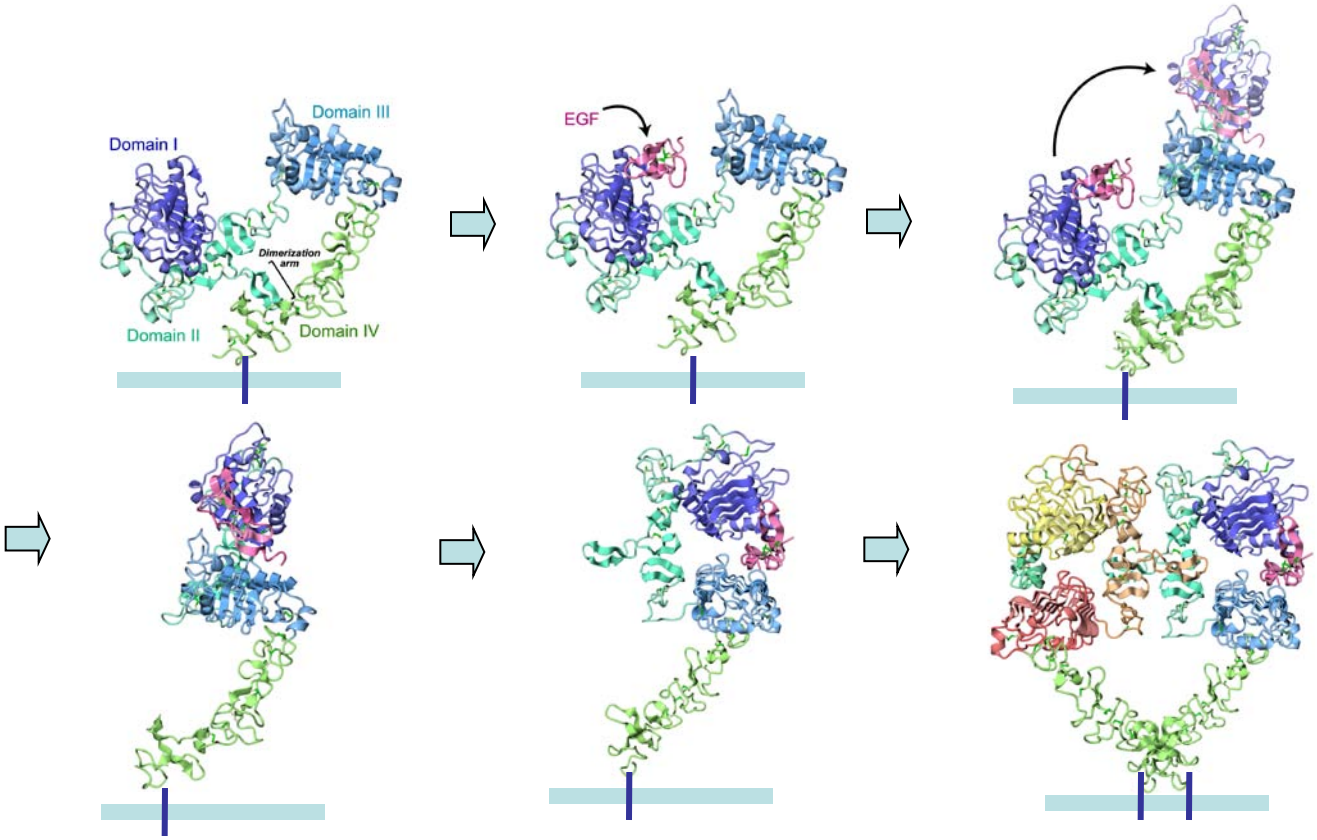
3D Structure of EGF and EGF Receptors



Ogiso *et al.* Cell (2002)

Courtesy of Prof. Osamu Nureki, U. Tokyo Institute of Medical Science

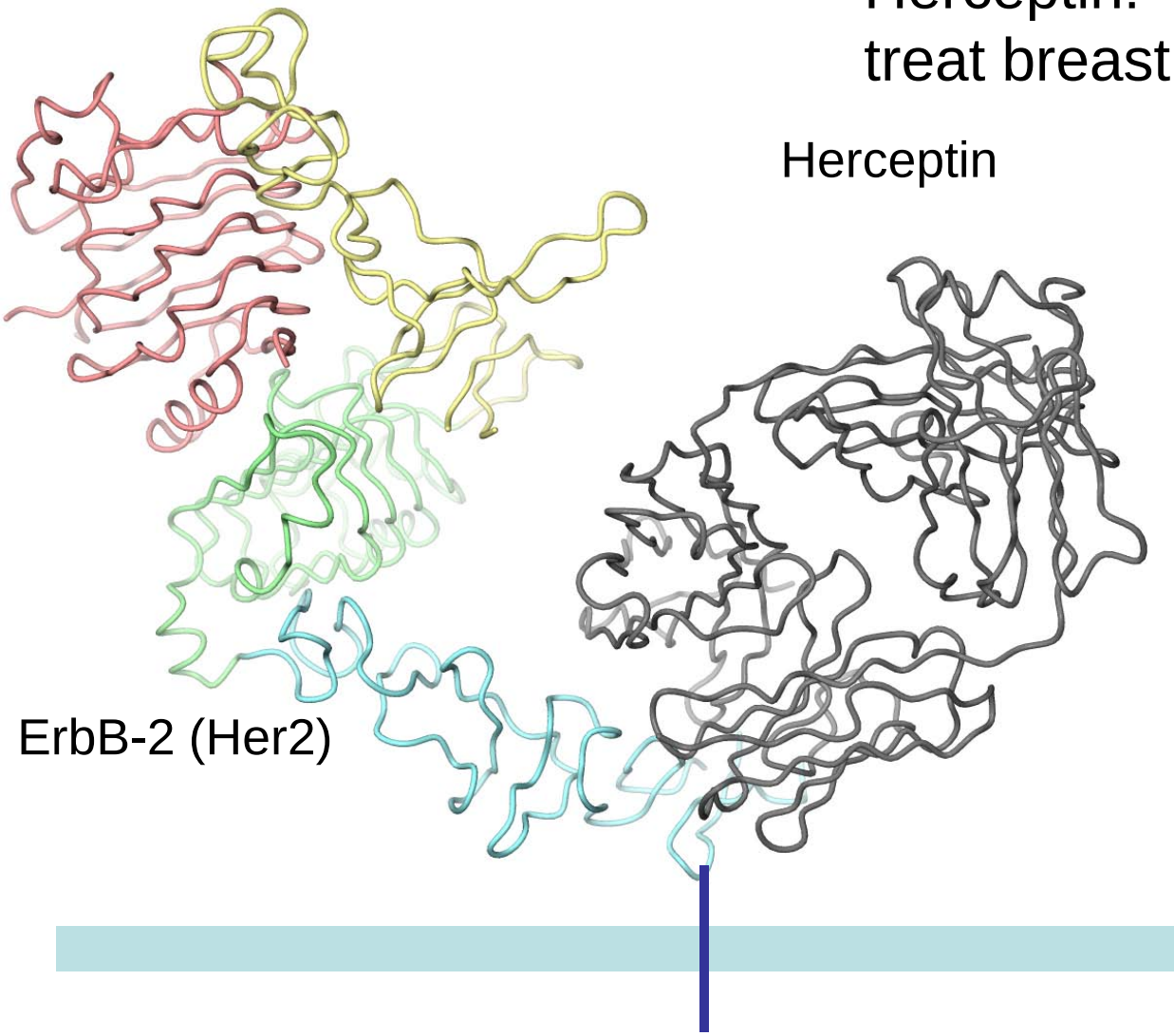
Mechanism of EGF Receptor Activation by EGF



Courtesy of Prof. Osamu Nureki, U. Tokyo Institute of Medical Science

Herceptin Interference with EGFR Activation

Herceptin: Used to treat breast cancer



Blocks the dimerization site in the EGF receptor

Courtesy of Prof. Osamu Nureki, U. Tokyo Institute of Medical Science

Mechanism of Antibody Binding to the EGF Receptor Family

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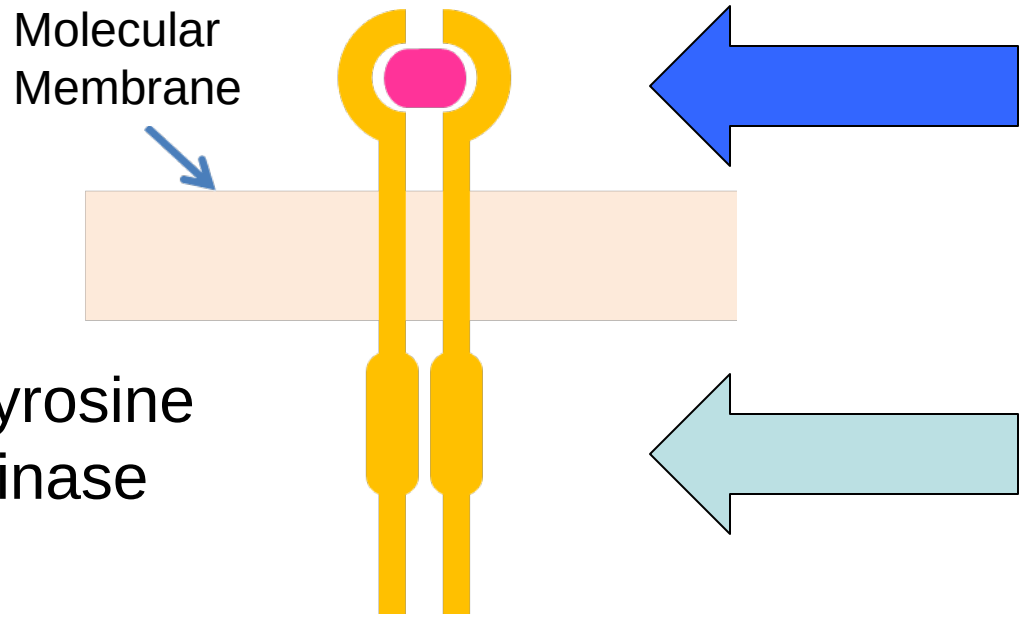
Robert A. Weinberg, 2007, *The Biology of Cancer*, Garland Science, Figure 15.38b

Blocks ligand binding site

Blocks HER2 dimerization

How to Cut Off Growth Factor Signals?

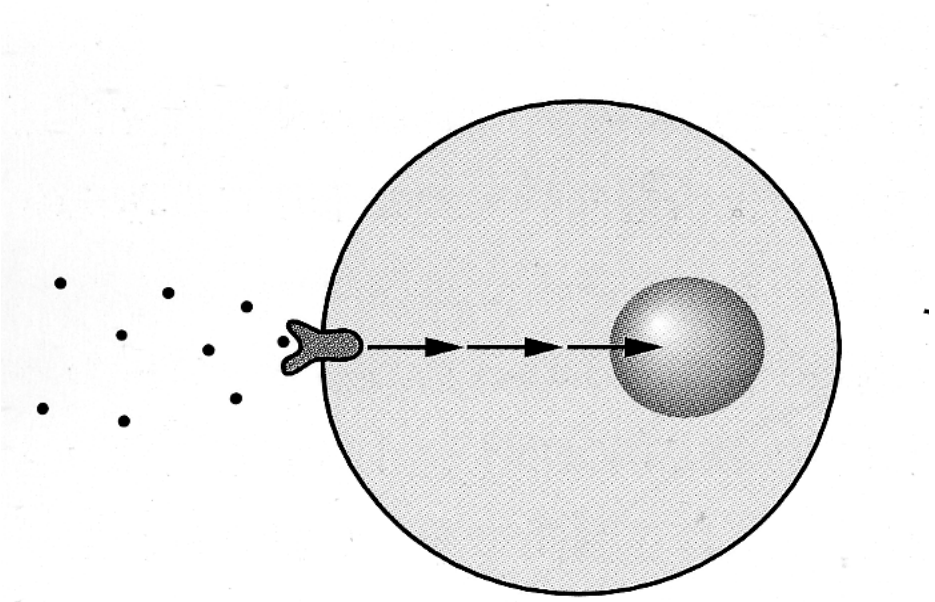


Neutralize with antibody or other macromolecular substance

Neutralize with low-molecular-weight compound (e.g. Iressa)

Growth Factor Signaling and Cancer

Normal cell



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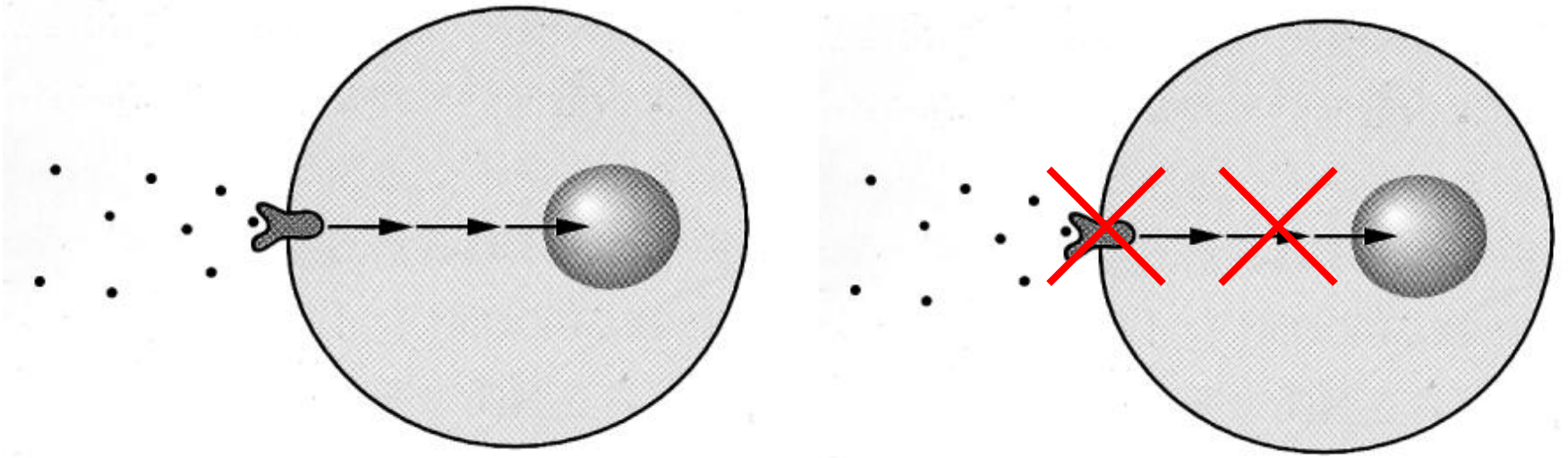
Growth Factor Signaling and Cancer

Normal cell

Cancer cell



Cancer cells exhibit excessive growth factor signaling.

→ Runaway signaling

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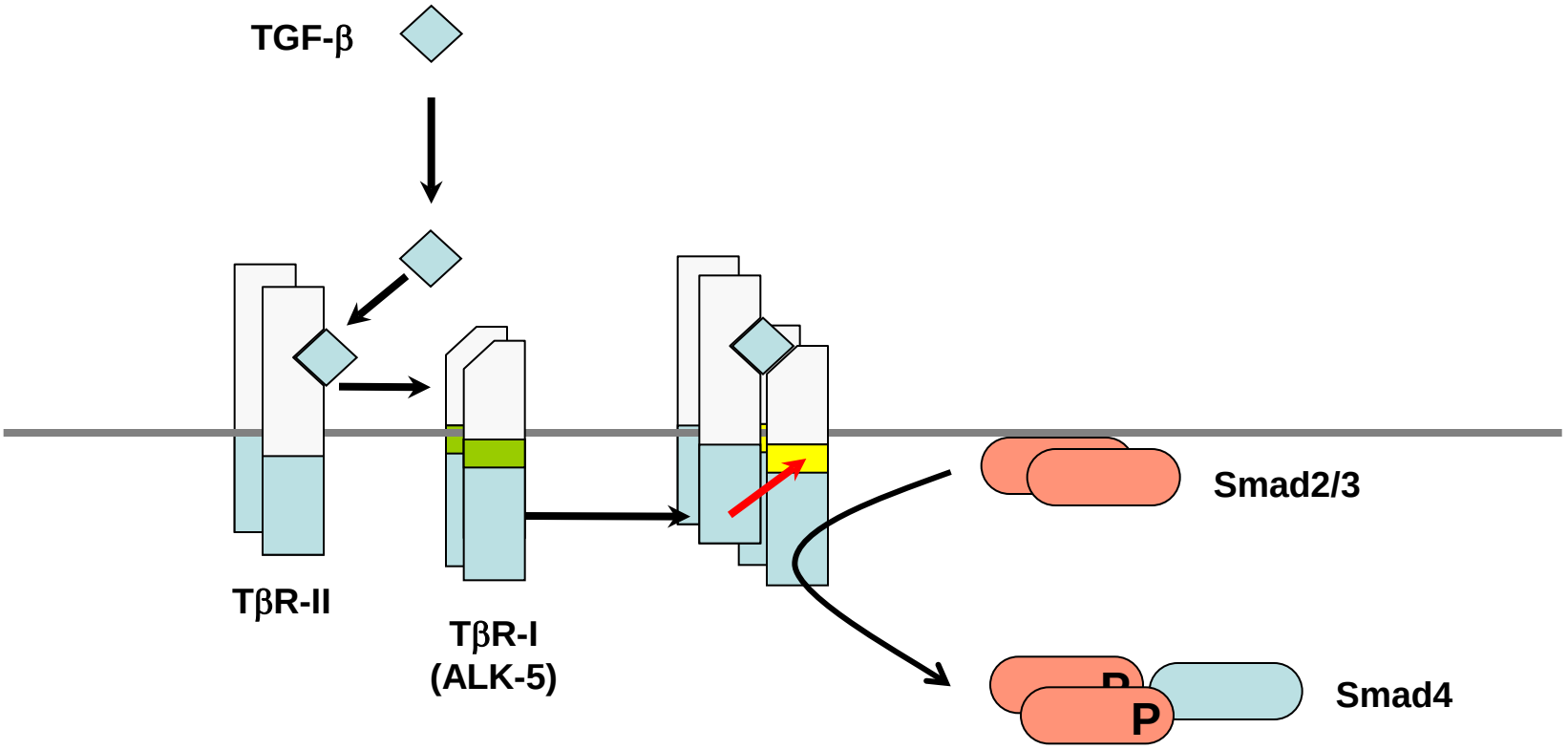
Yodosha

Transforming Growth Factor-β (TGF-β)

- Inhibits growth in many cells.
- Promotes production of extracellular matrix.
- Induces EMT
  (epithelial-mesenchymal transition).

TGF-β–Smad Signaling



TGF-β binds to type II and type I receptors.
Both type II and type I receptors have a serine-threonine kinase region.

R-Smad and Co-Smad

- R-Smad (receptor-regulated Smad) undergoes phosphorylation by type I receptors.

- Co-Smad (common partner Smad) forms a complex with phosphorylated R-Smad.

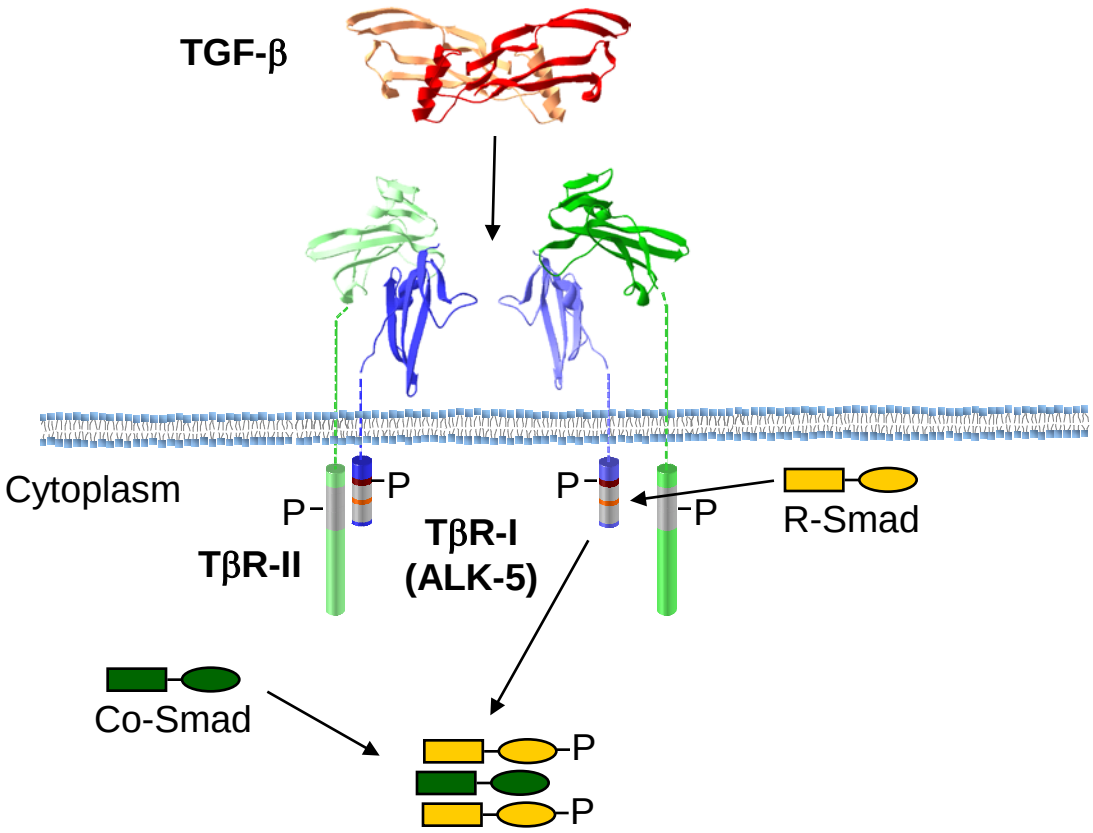
- R-Smad:

  The R-Smads activated by TGF-β are Smad2 and Smad3.
  The R-Smads activated by BMP are Smad1, Smad5 and Smad8.

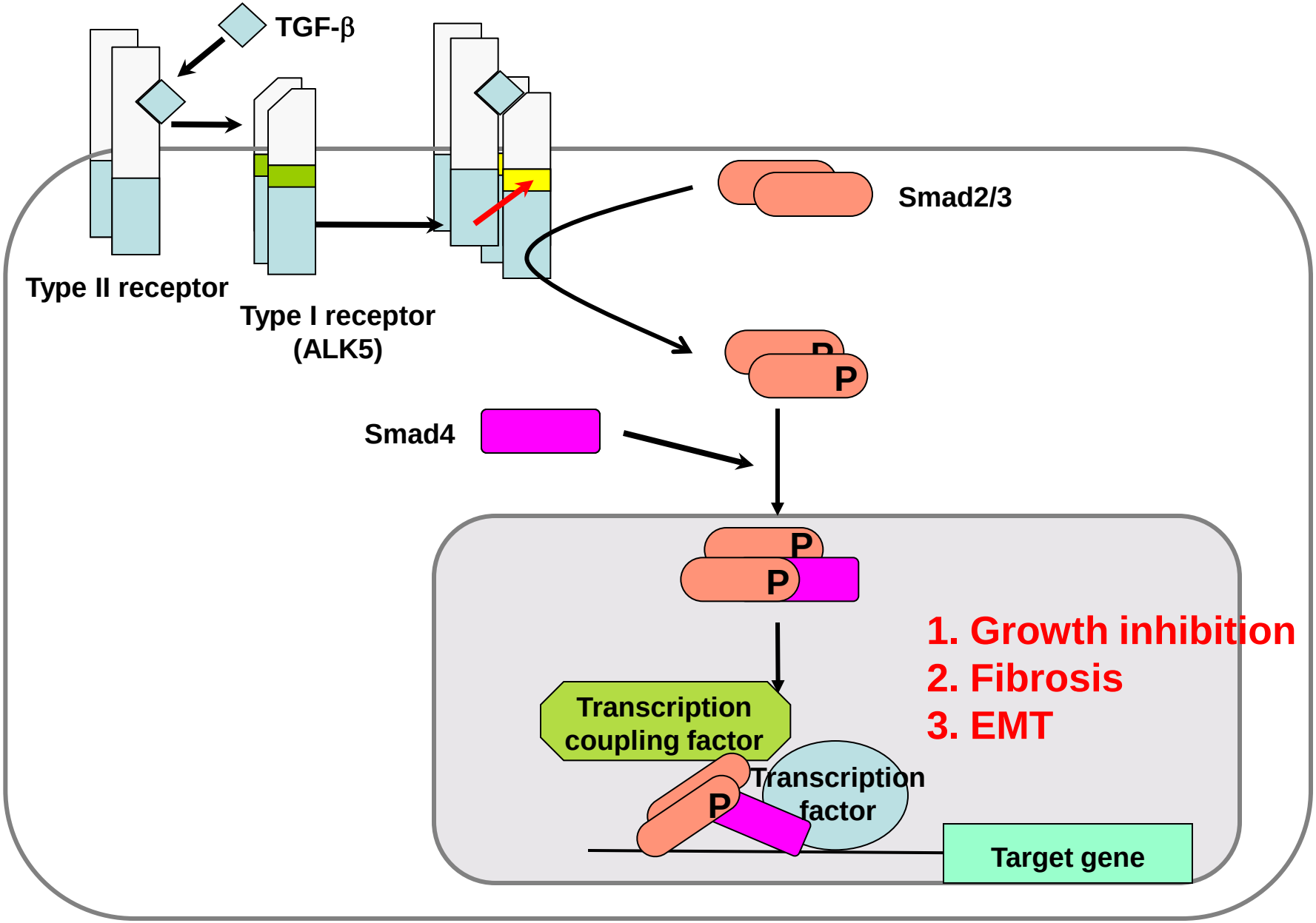
- Co-Smad:

  Only Smad4 is present in mammals.

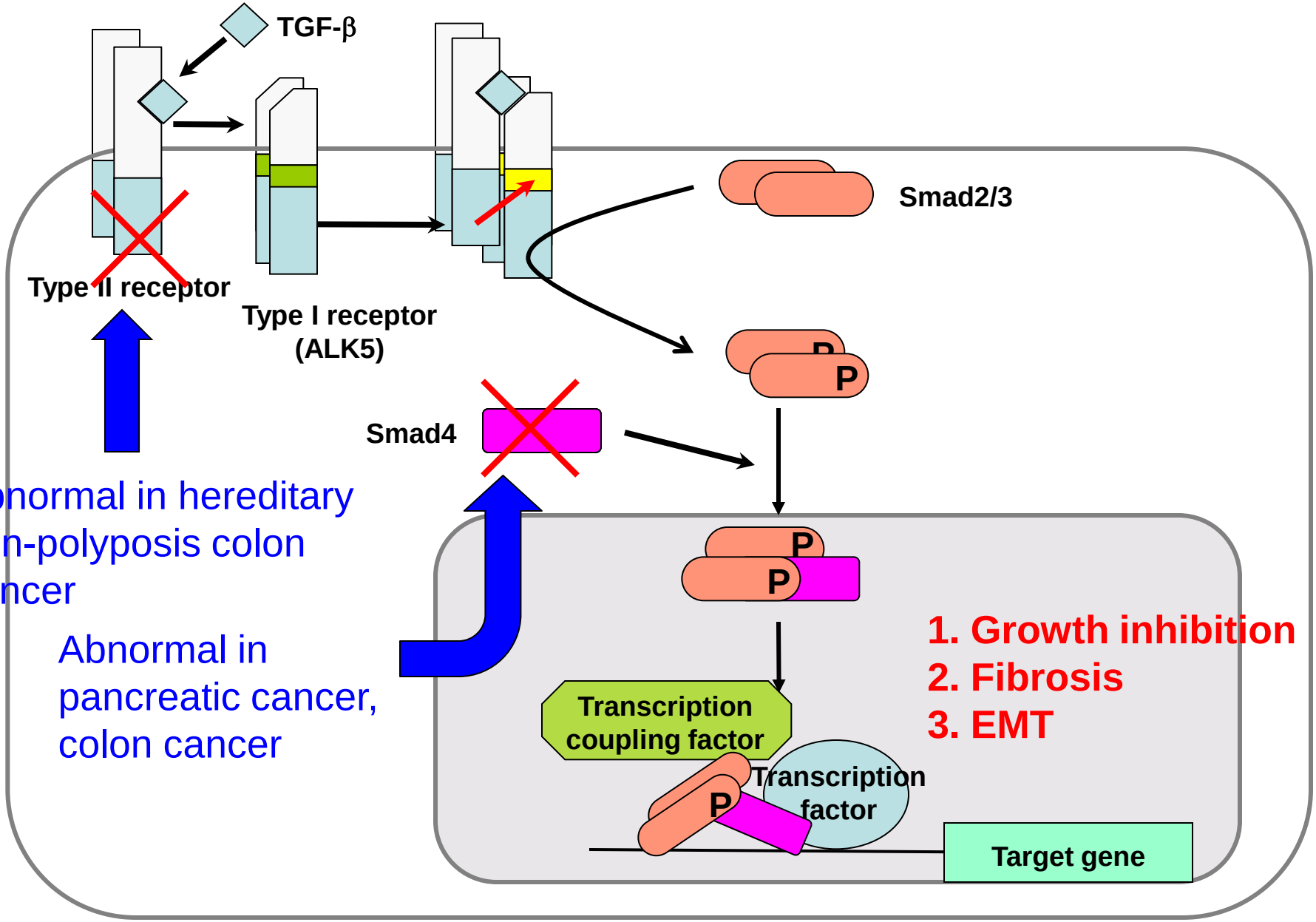
TGF-β–Smad Signaling



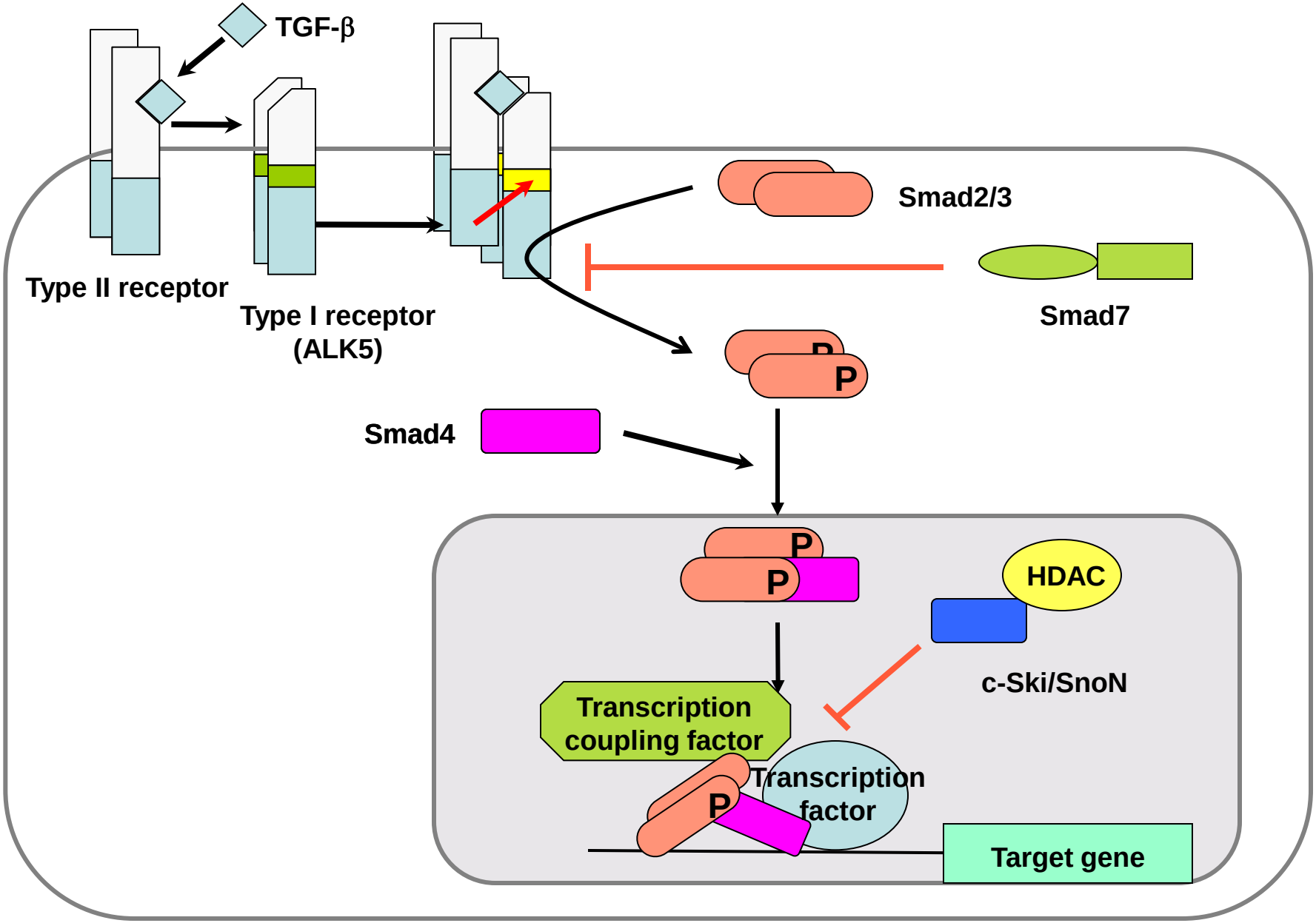
TGF-β Signaling



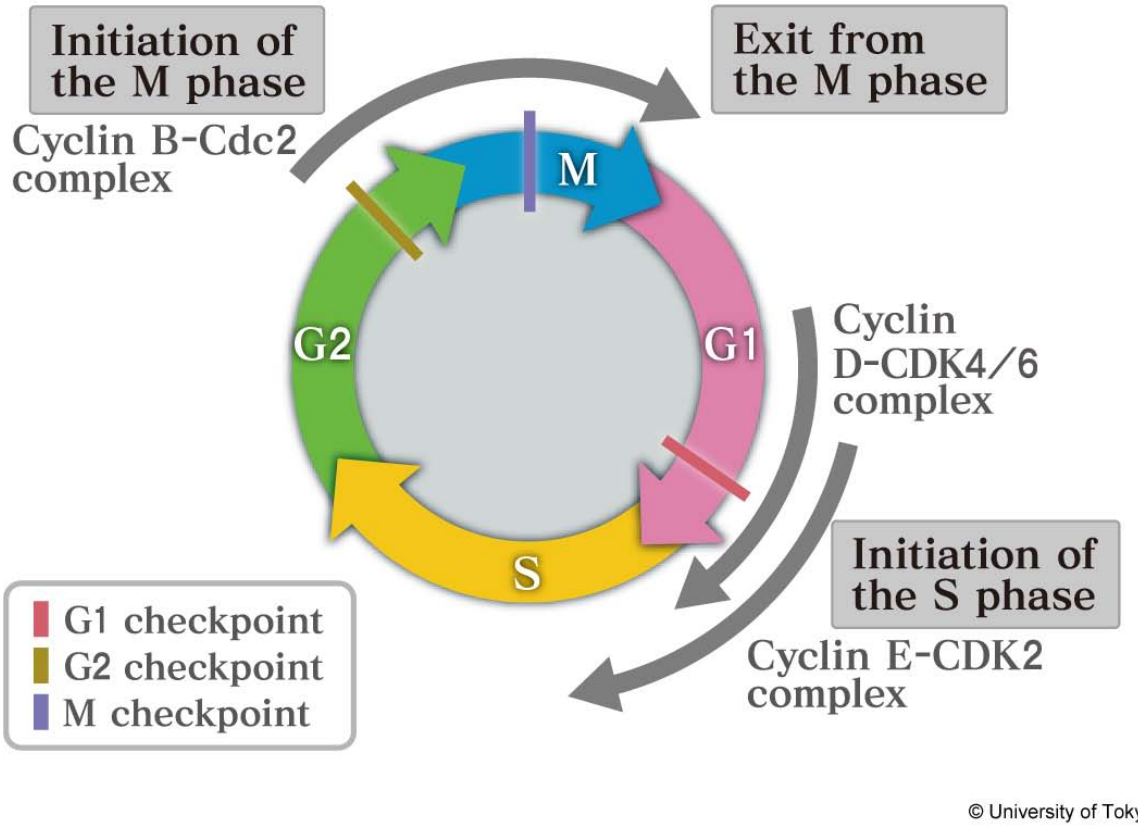
TGF-β Signaling



Negative Regulation of TGF-β Signaling

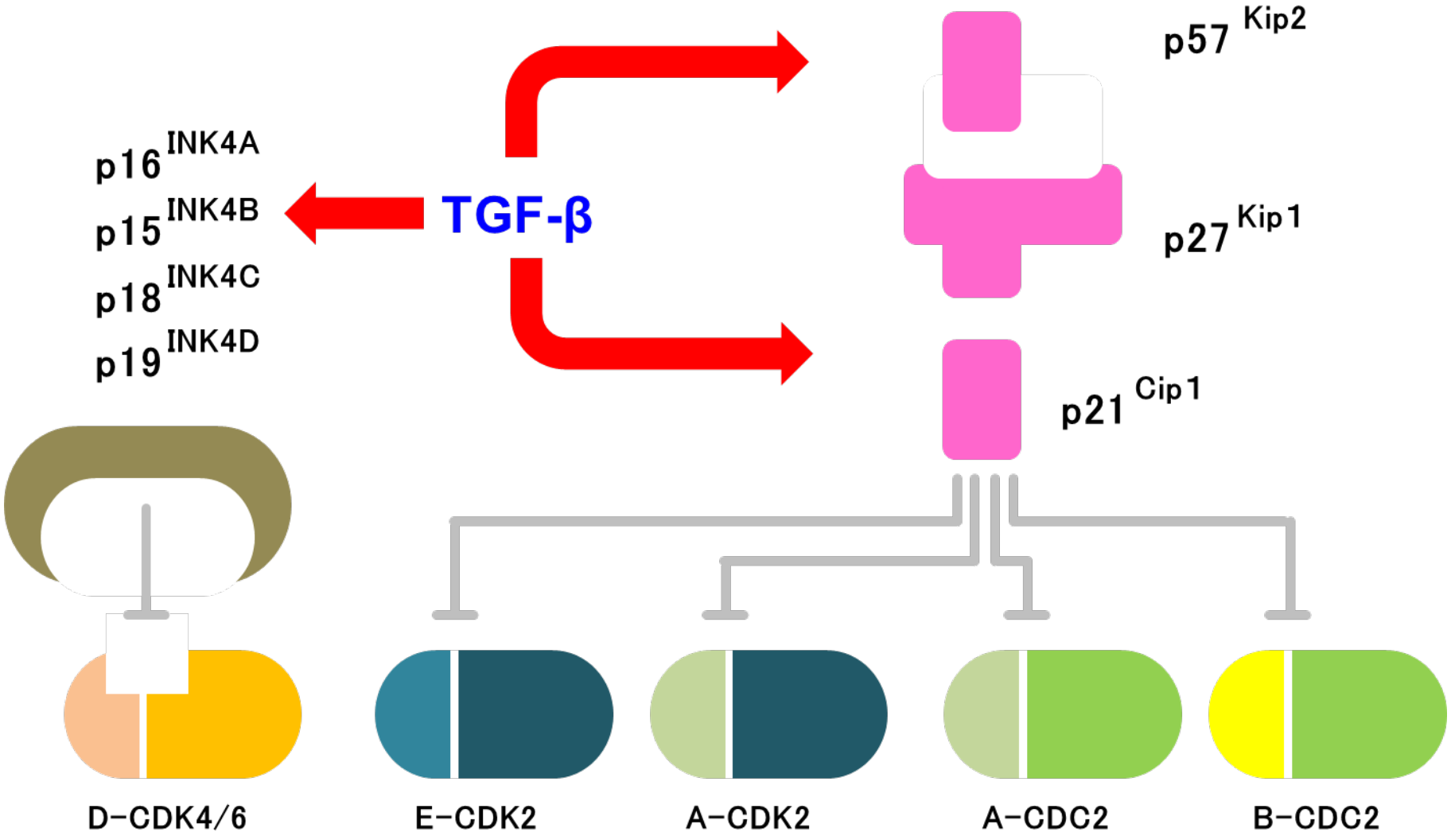


Cyclin and CDK in the Cell Cycle, and the Role of CDK-Inhibitors

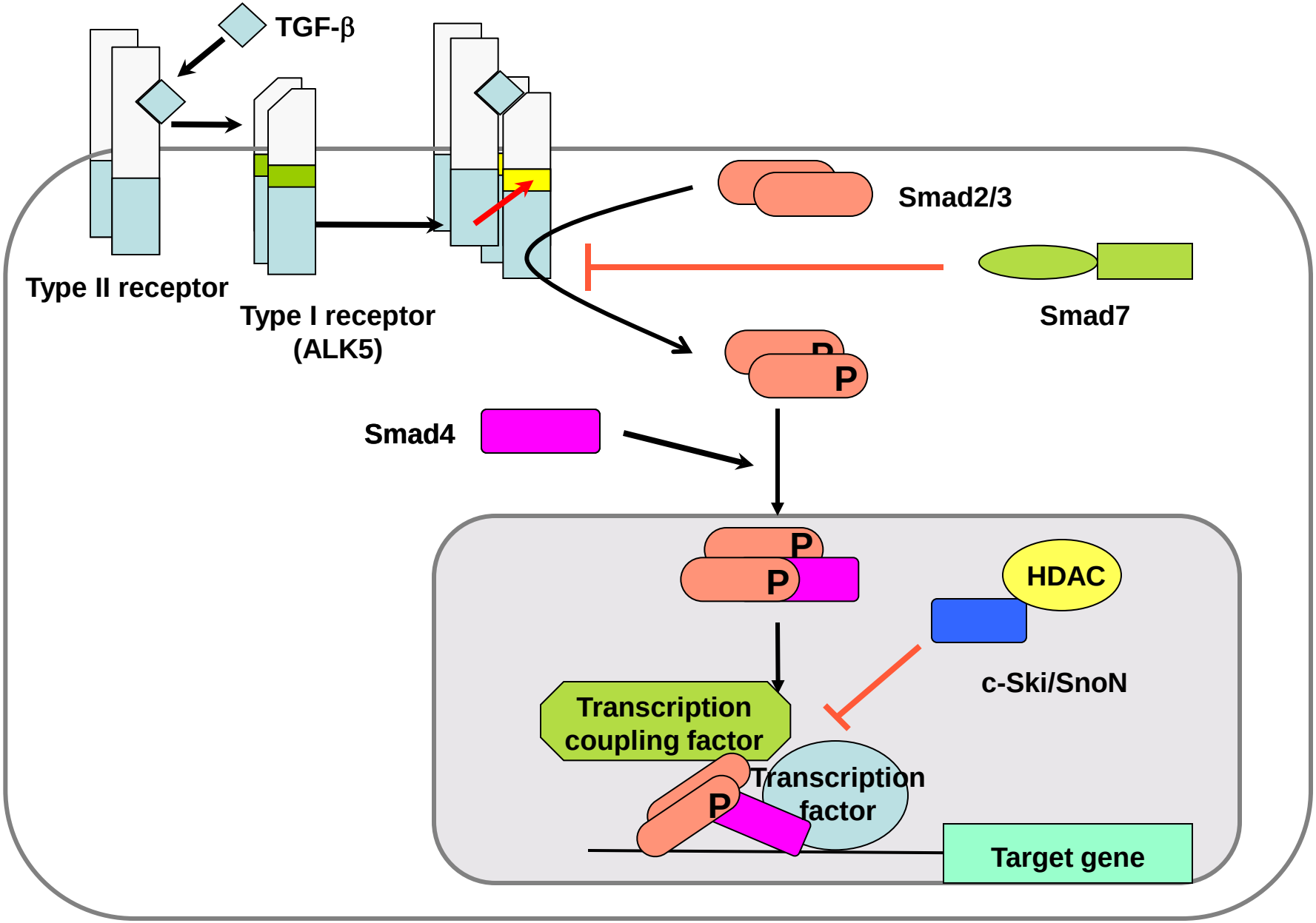


CDK: cyclin-dependent kinase

CDK-Inhibitor Functions



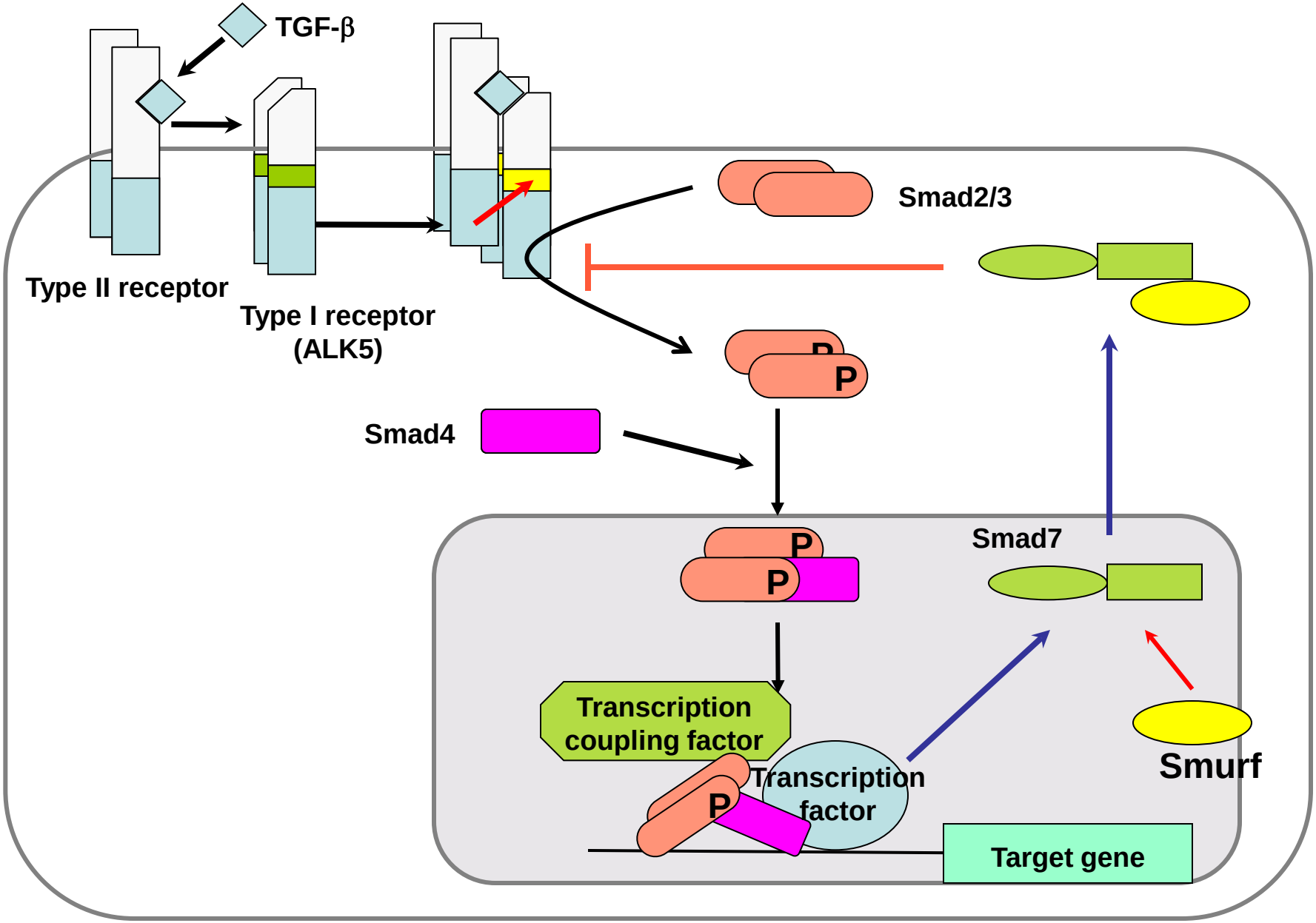
TGF-βシグナルの負の制御



Inhibitor Smads (I-Smads)

- In mammals, Smad6 and Smad7 function as I-Smads.
- C-terminal regions (MH2 domains) resemble R-Smads and Co-Smads.
- Smad7 inhibits both TGF-β and BMP signals, and Smad6 mainly BMP signals.
- I-Smad expression is induced by such signaling molecules as TGF-β and BMP, and by such agencies as shear stress, IFN-g, CD40 and UV irradiation.

Inhibitor Smads (I-Smads)



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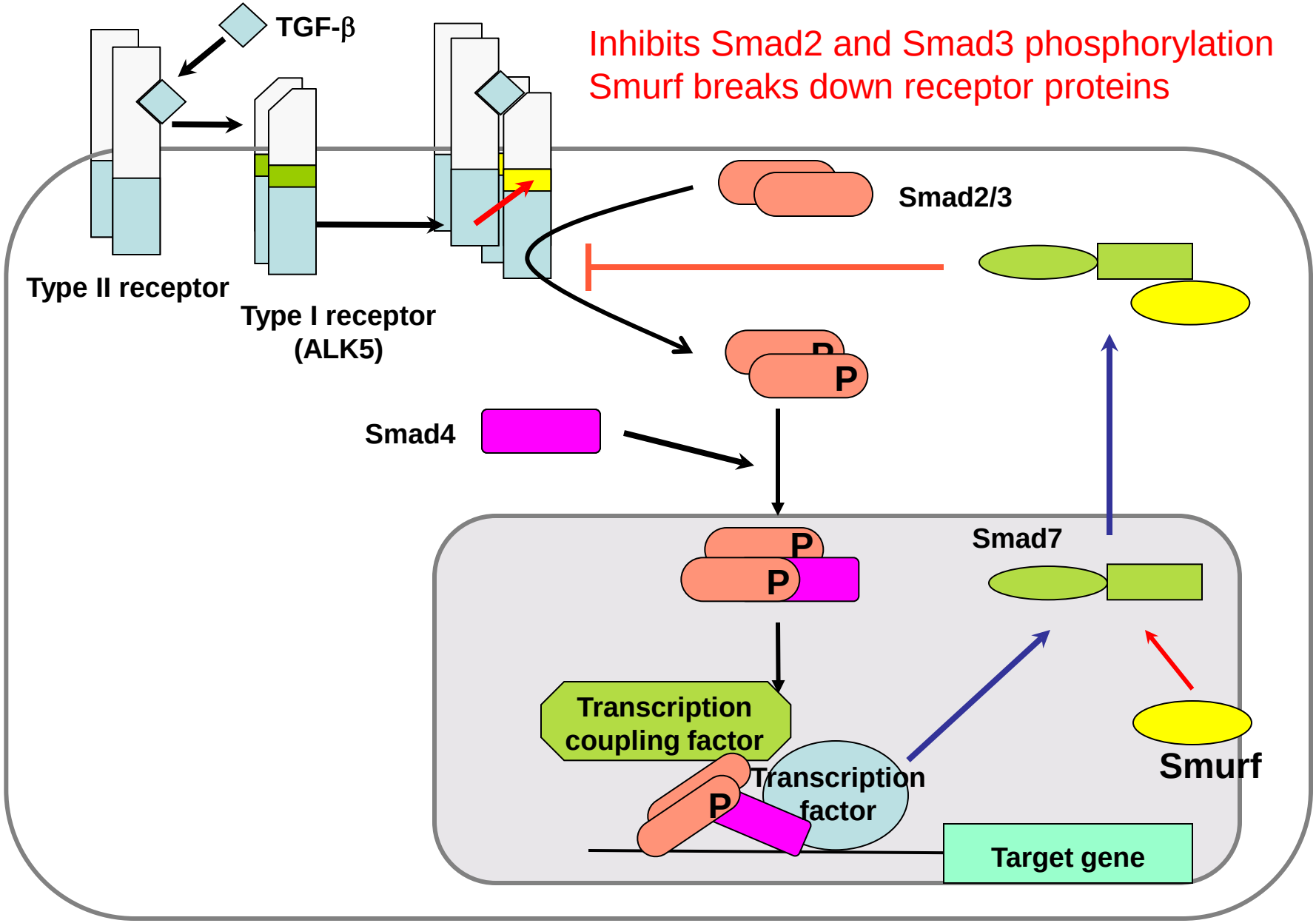
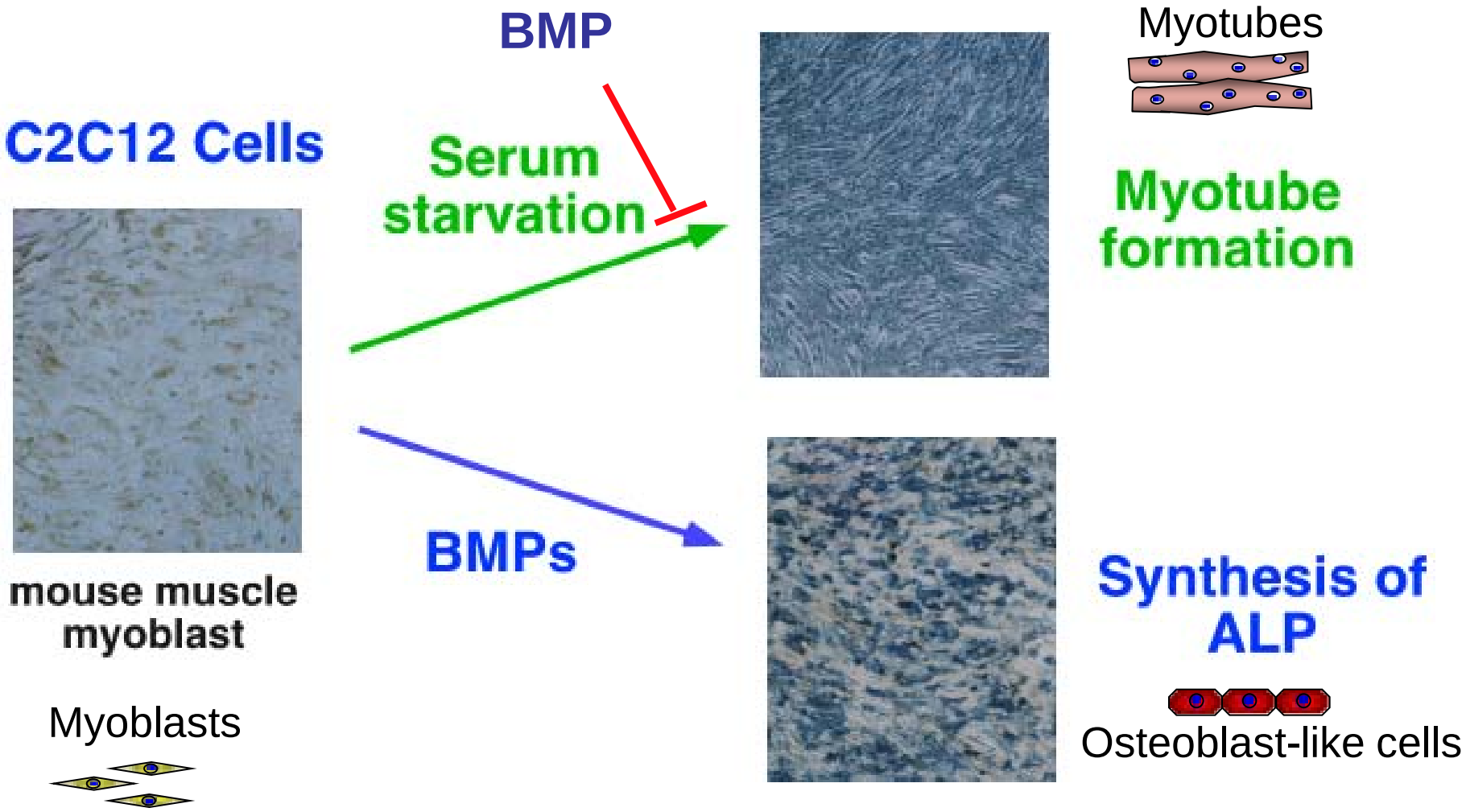


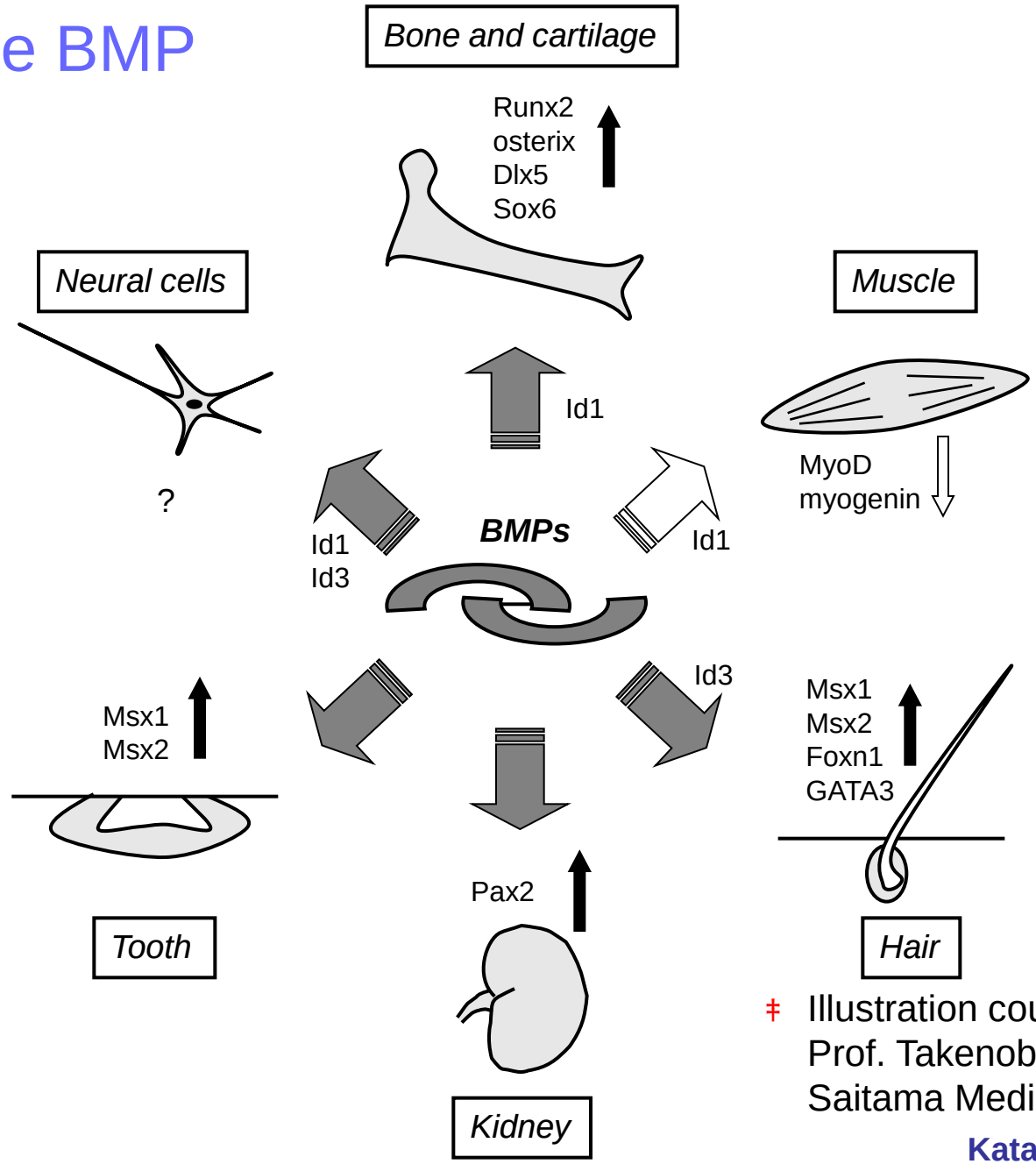
Bone Morphogenetic Proteins (BMPs)

- Belong to the TGF-β family.
- Discovered as factors promoting the formation of bone and cartilage.
- Also present in invertebrates, and play an important role in development.

Differentiation of Mesenchymal Progenitor Cells by BMP



Versatile BMP



‡ Illustration courtesy of Prof. Takenobu Katagiri, Saitama Medical University

Katagiri et al., 2007

Versatile BMP

More examples

BMP–type II receptor mutation:
Cause of idiopathic pulmonary arterial hypertension

BMP–ALK-1 (type I receptor) mutation:
Cause of hereditary hemorrhagic telangiectasia

BMP-6 abnormality:
Abnormal iron absorption

R-Smad and Co-Smad

- R-Smad (receptor-regulated Smad) undergoes phosphorylation by type I receptors.

- Co-Smad (common partner Smad) forms a complex with phosphorylated R-Smad.

- R-Smad:

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- Co-Smad:

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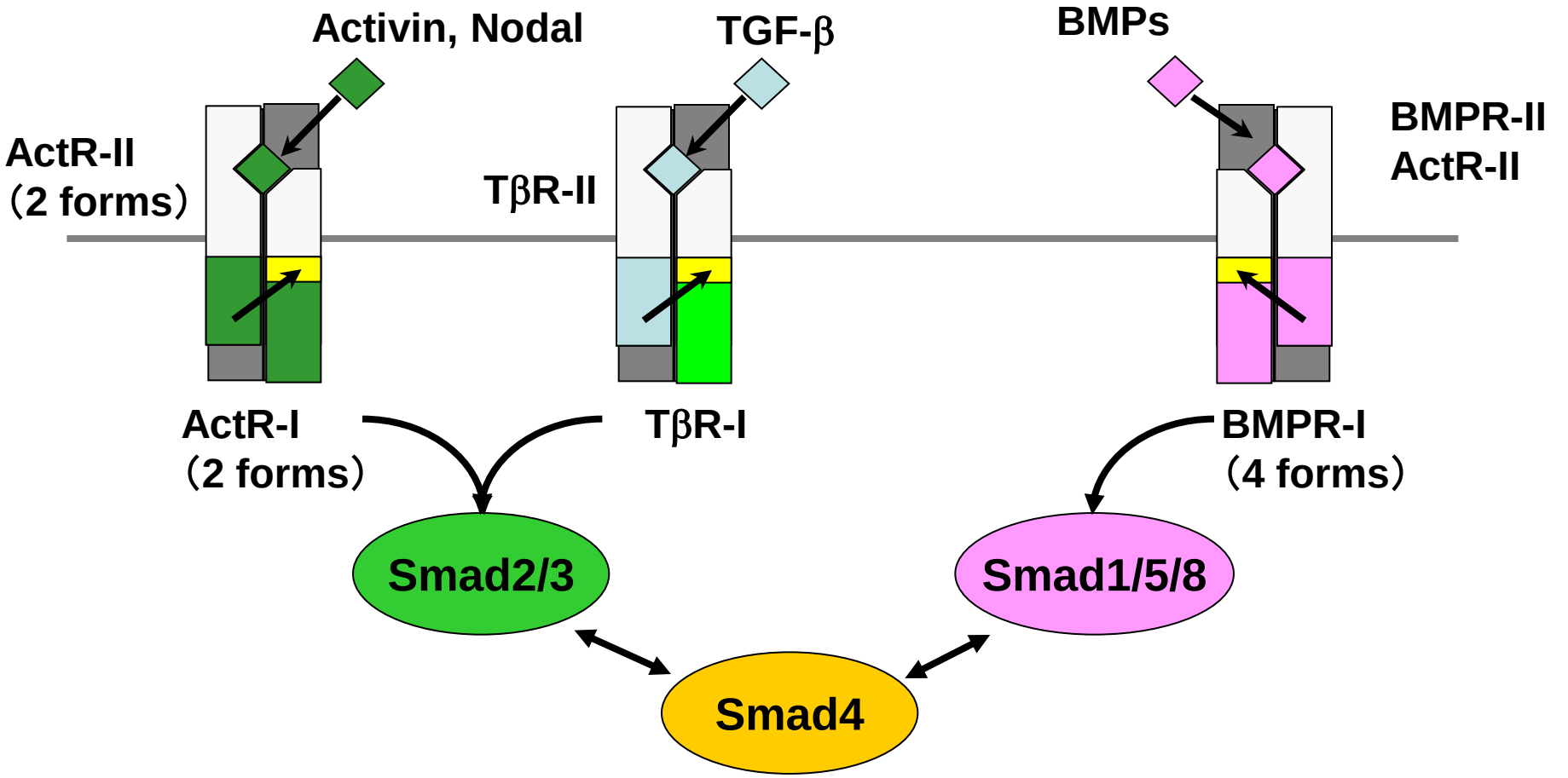
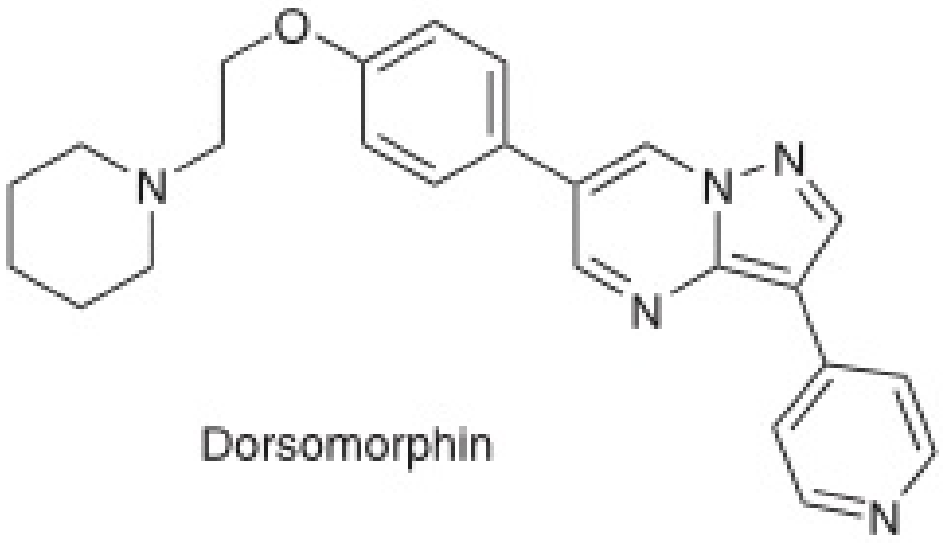
Activation of TGF-β Family Receptors



Development of Inhibitors for BMP Type I Receptors

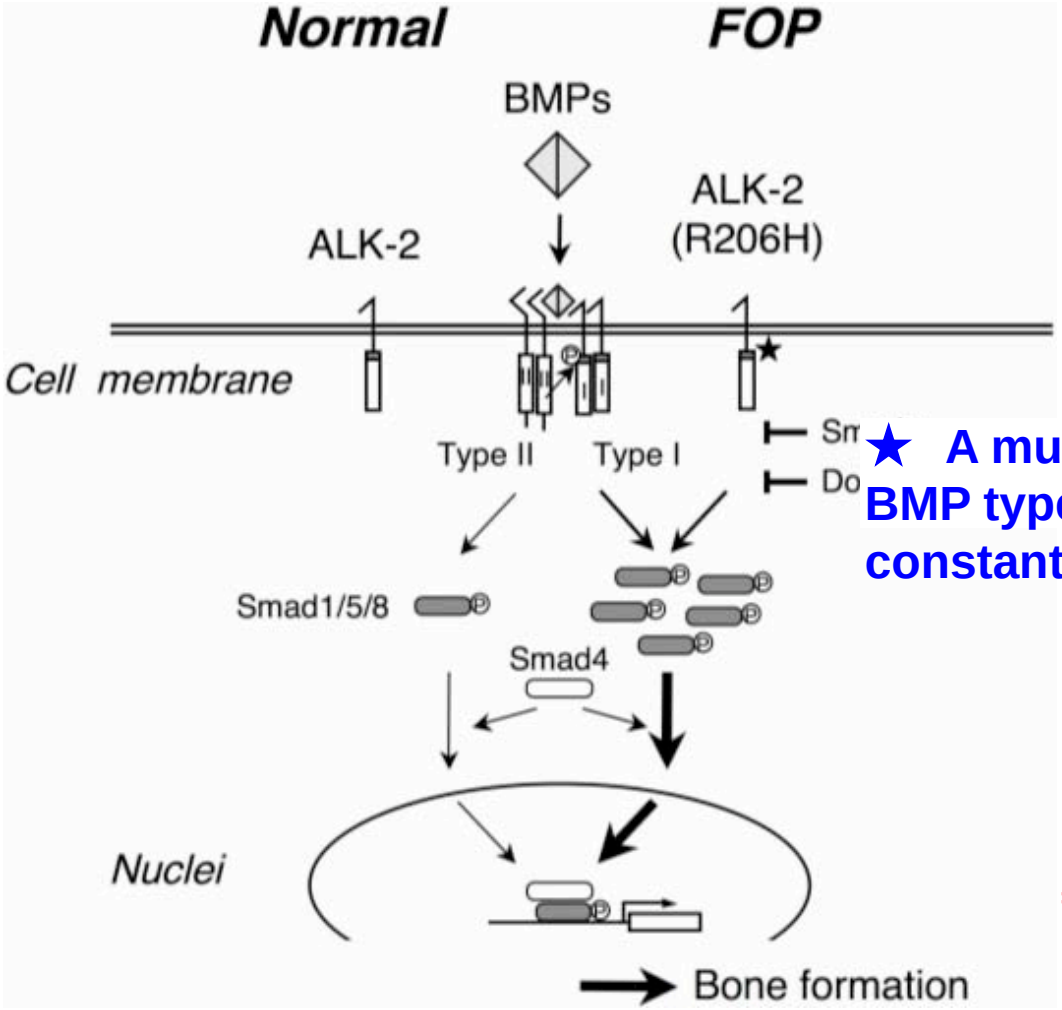
Dorsomorphin



Dorsomorphin

Specific inhibition of BMP type I receptors, originally found as an AMP kinase inhibitor

Progressive ossifying myositis (Fibrodysplasia Ossificans Progressiva (FOP))



★ **A mutation occurs in ALK-2, a BMP type I receptor, leaving it constantly activated.**

‡ Illustration courtesy of Prof. Takenobu Katagiri, Saitama Medical University

Kaplan, FS et al. 2006

Progressive ossifying myositis
(Fibrodysplasia Ossificans Progressiva (FOP))

Designated a "specified disease“
by the Health, Labor & Welfare Ministry, 2007

‡From *Black Jack vol.6*,
by Osamu Tezuka
published by Akitashoten

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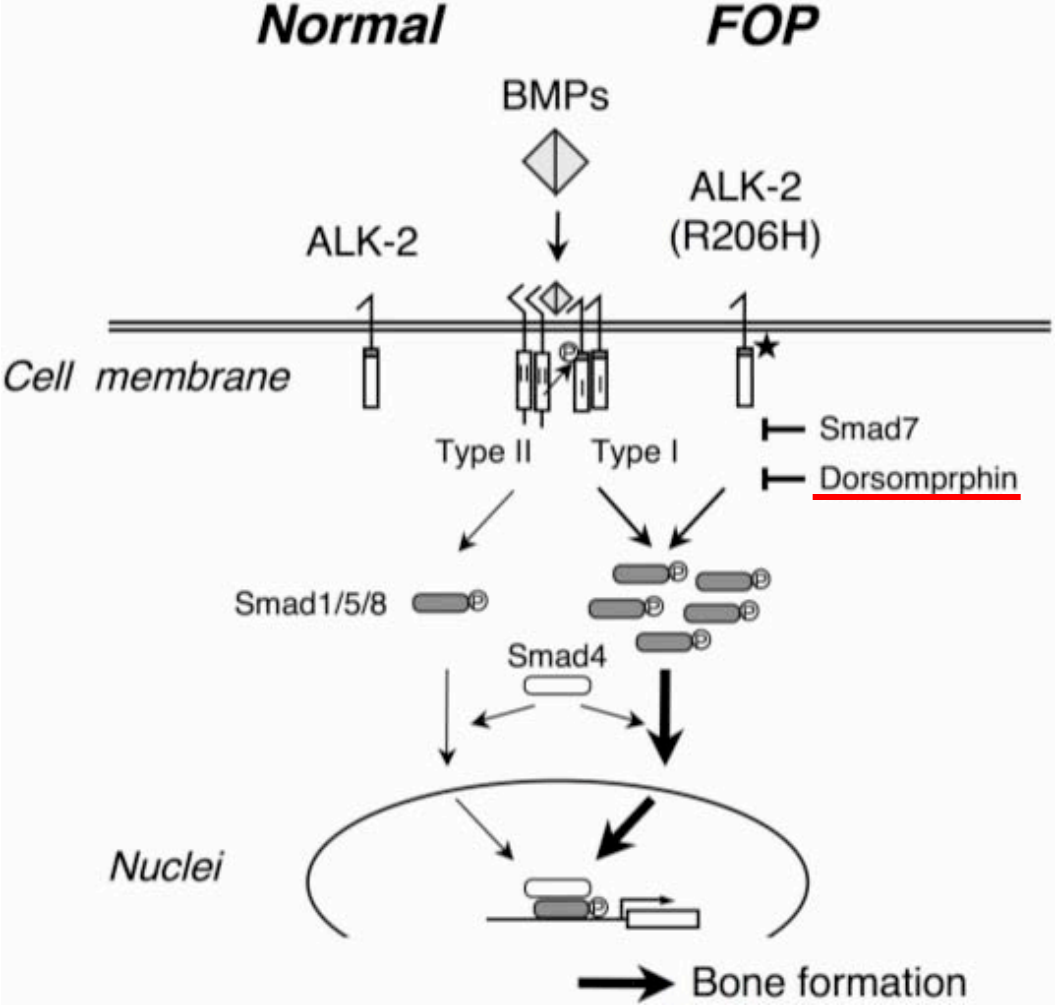
26/09/2007(Wed) Yomiuri-shimbun evening edition
Zoom Up Weekly

Progressive ossifying myositis (Fibrodysplasia Ossificans Progressiva (FOP))



‡ Illustration courtesy of Prof. Takenobu Katagiri, Saitama Medical University

Summary

- The signals of growth factors such as EGF and PDGF are transmitted by tyrosine kinase receptors.

- TGF-β family signals are transmitted by serine-threonine kinase receptors.

- Signaling studies lead to pharmaceutical development.

- Kinase activity inhibitors may serve as therapeutic agents for cancer and other diseases.

- Extracellular receptor antibodies may also serve as therapeutic agents.