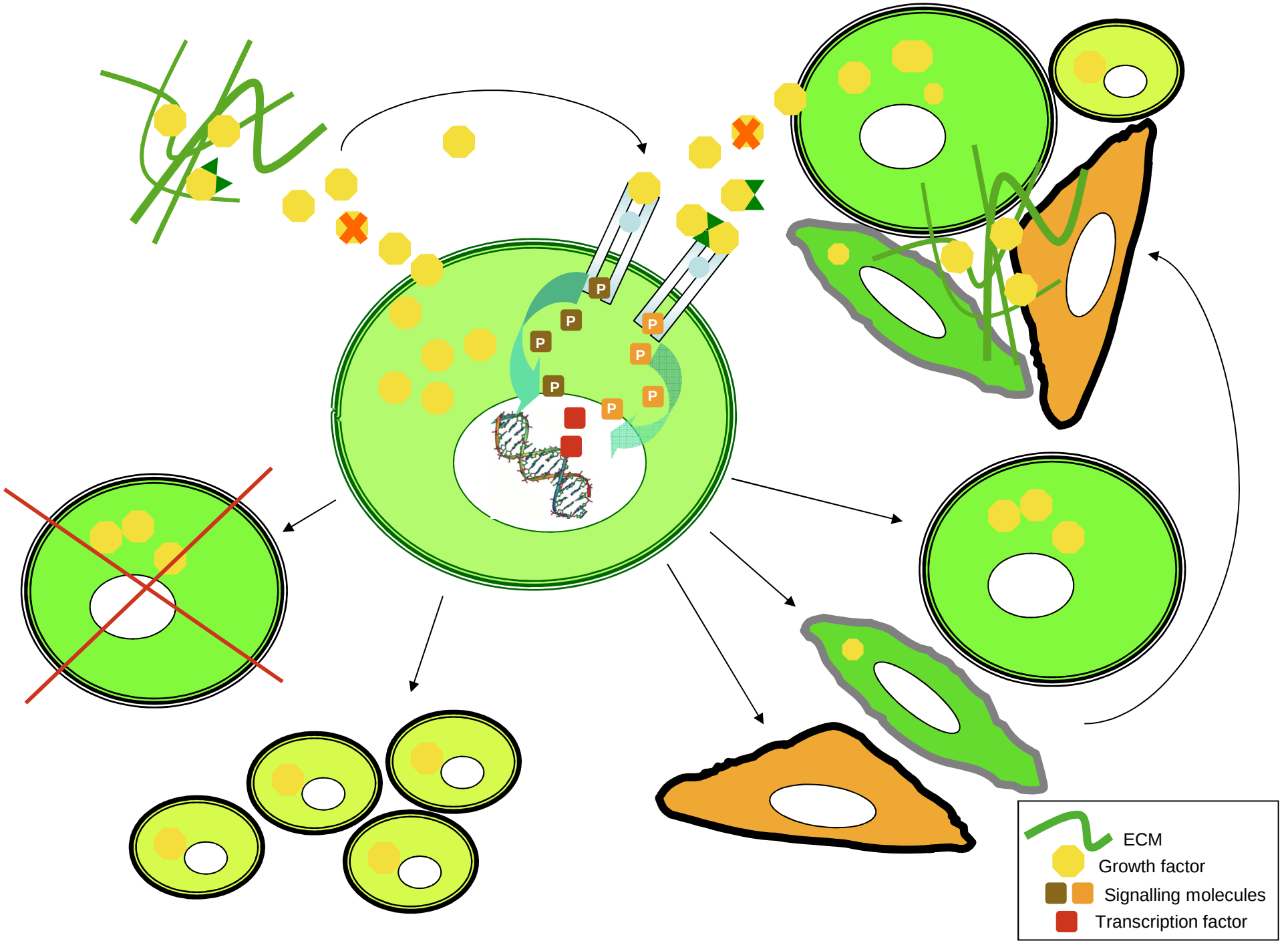
Buněčná signalizace a diferenciace buňky

Pavel Krejčí


P
P
P
P
P
P
P
ECM
Growth factor
Signalling molecules
Transcription factor

Definition I: growth factors are small proteins, present in animal tissues at very low concentrations, but having enormously high biological activity* that are responsible for controlling some of the most essential of biological functions of cells, such as growth, differentiation, migration, and survival

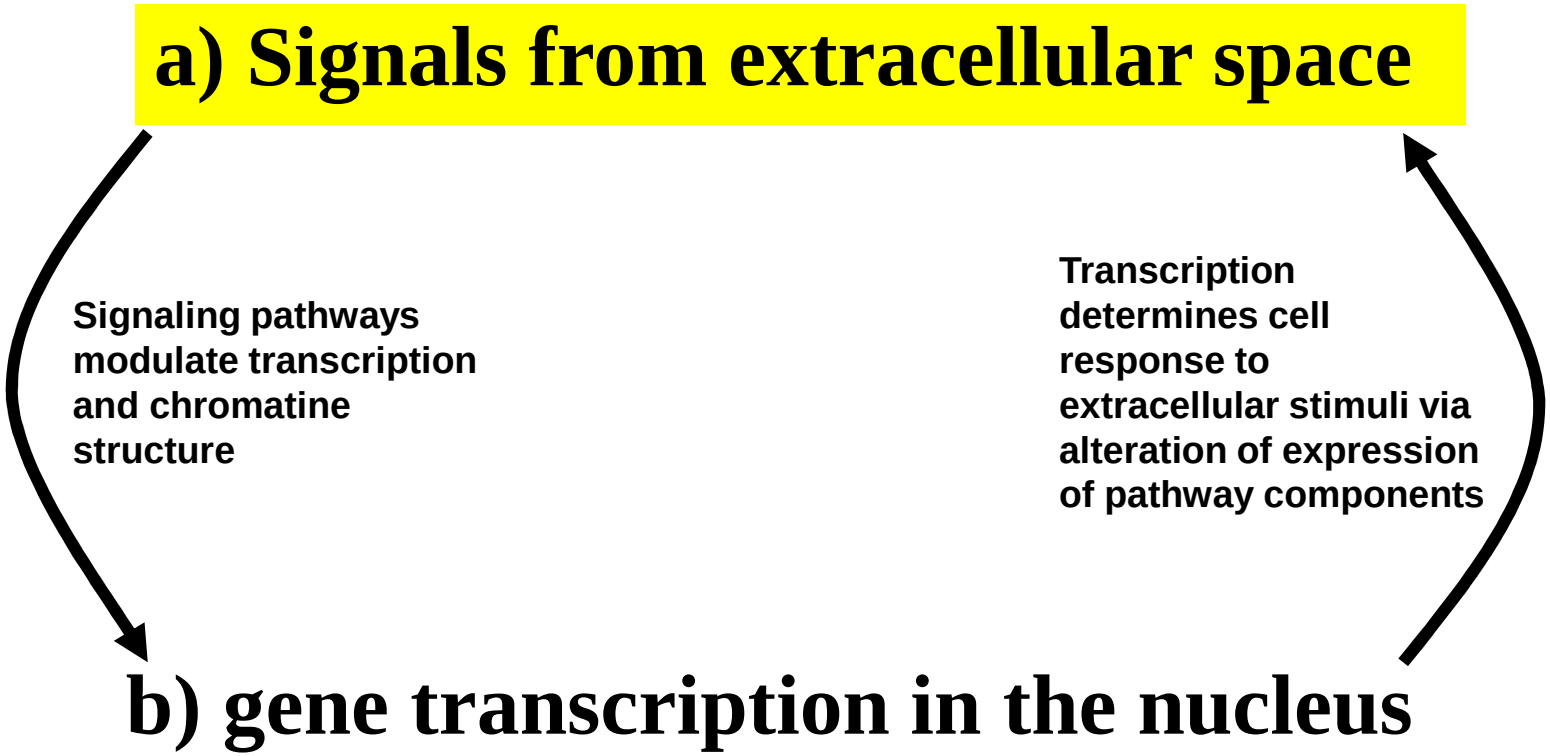
*** ~10^{-9} – 10^{-11} M**

Definition II: signalling pathways are activated by complex mechanisms where growth factors first exert their action by binding to specific receptors on the surface of the target cells. These receptors then produce metabolic changes within the target cell, which eventually activate or repress specific genes to bring about a change in cellular behaviour

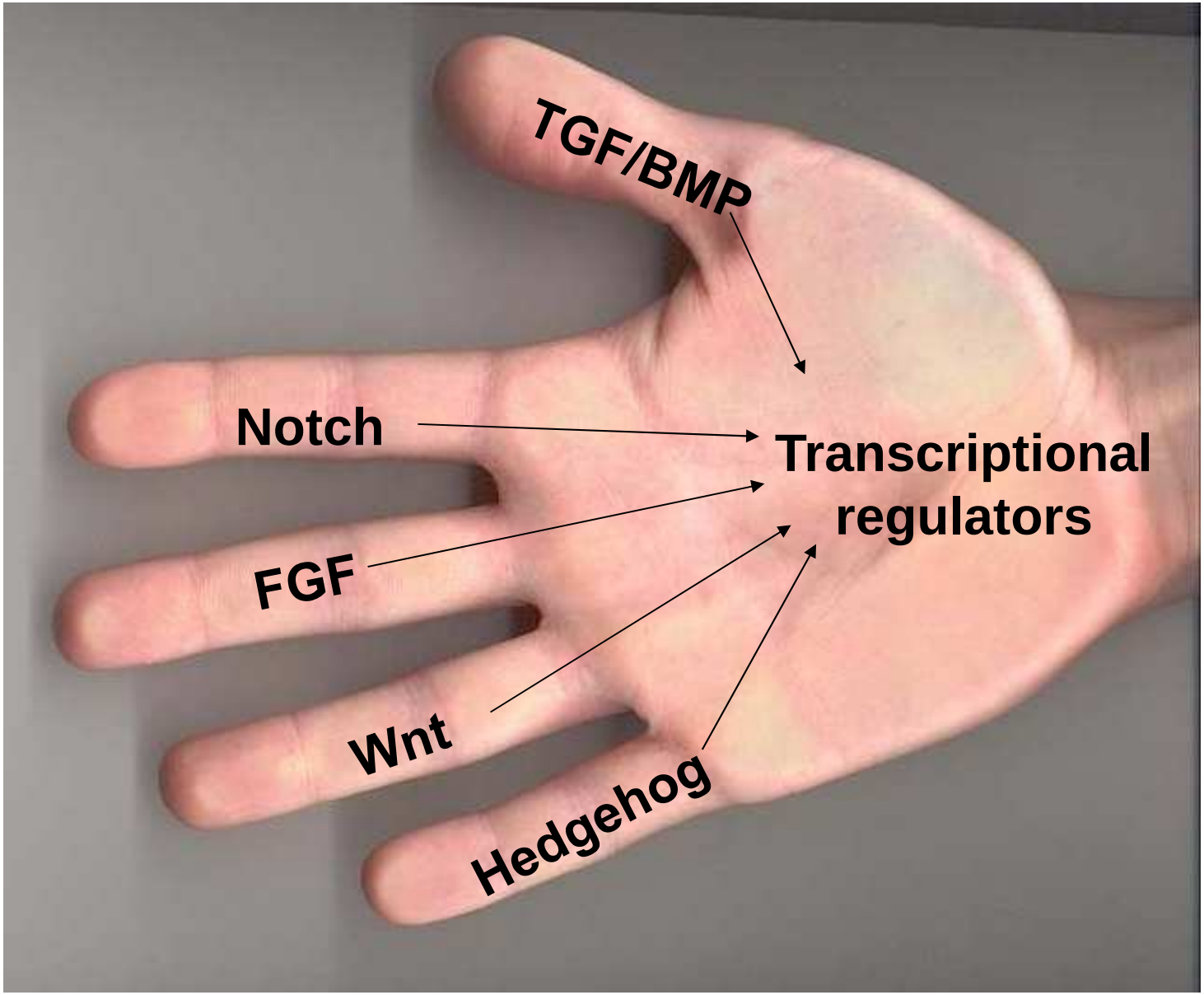
Major characteristics of signal transduction pathways:

- The ability of cells to accept signal and initiate the mechanism of signal transduction that eventually results in cell response is defined by the **presence or absence of specific receptors** on the surface of cells
- **The presence or absence of membrane receptors is controlled by genetic programme** that is specific for each cell type
- **The number of receptors present on the surface of the target cells is critical** for subsequent signal transduction
- **Cell response involves dramatic changes** in gene expression, changes in cytoskeleton and changes in metabolism of cells
- **Any deregulation of the activity of growth factors and their receptors at any level of signal transduction may cause serious defects !!!**

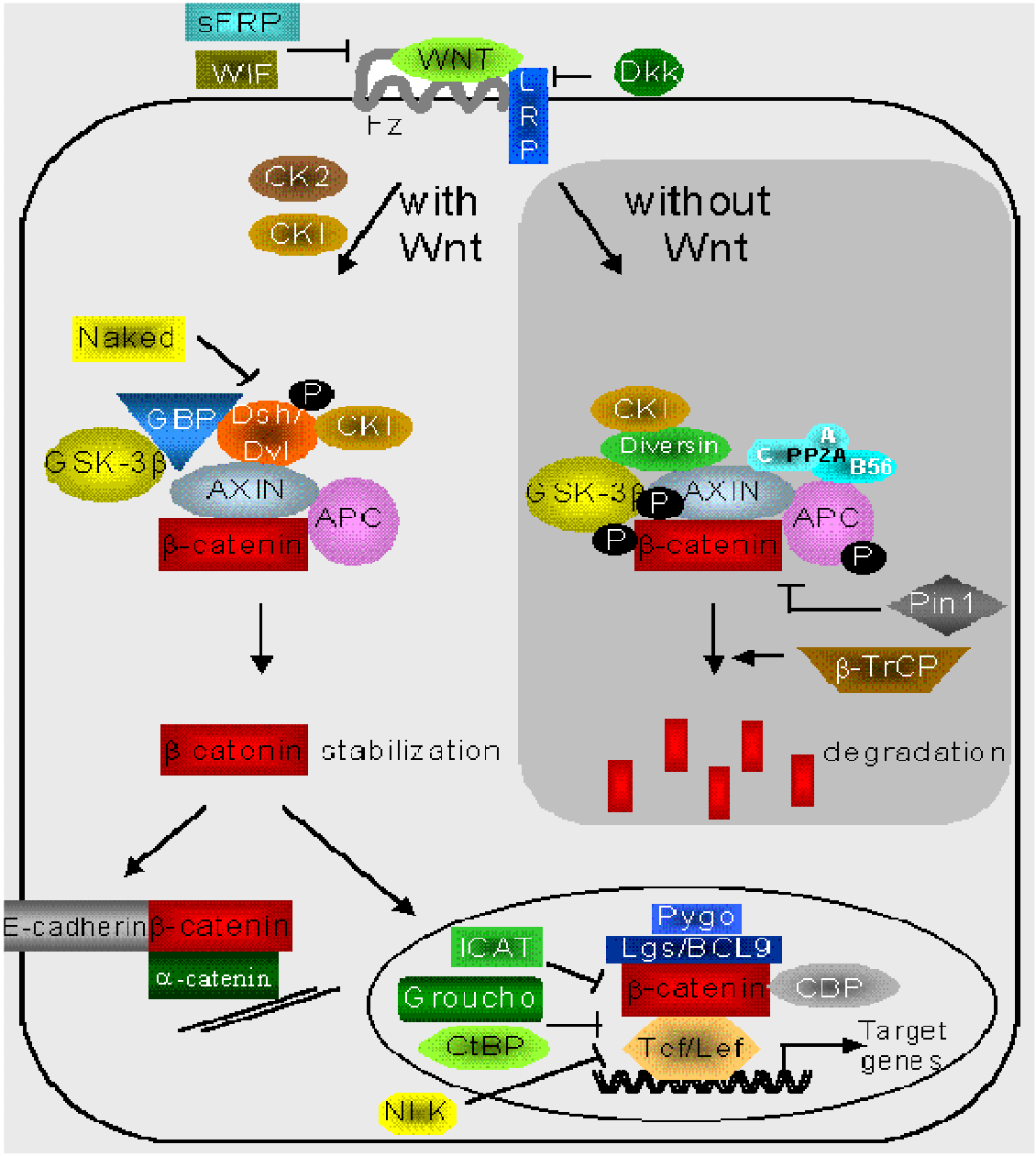
What gives information to cell?



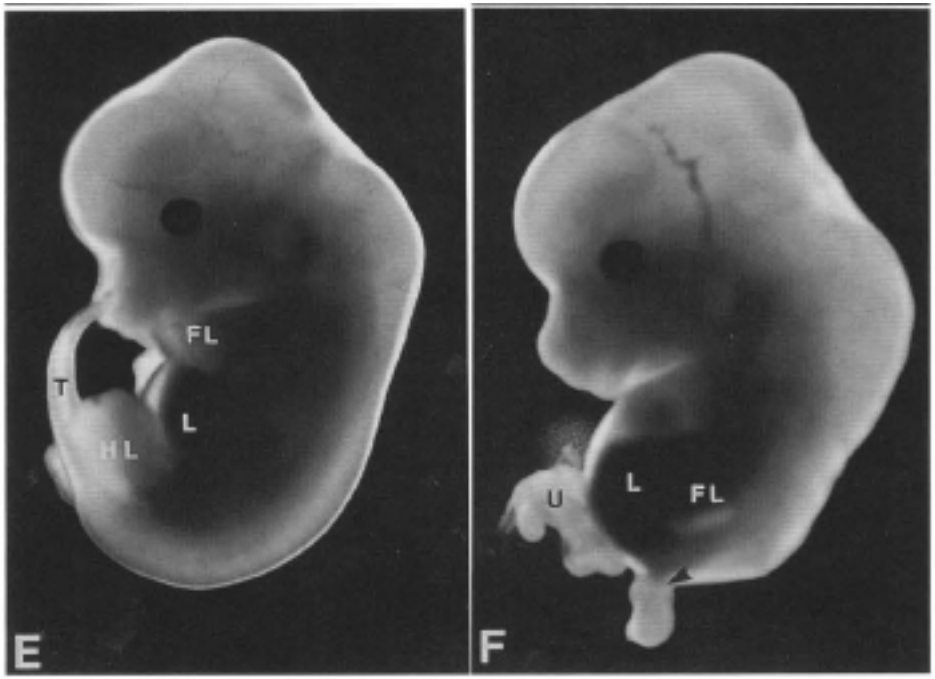
Extracellular signals



Wnt/β-kateninová dráha

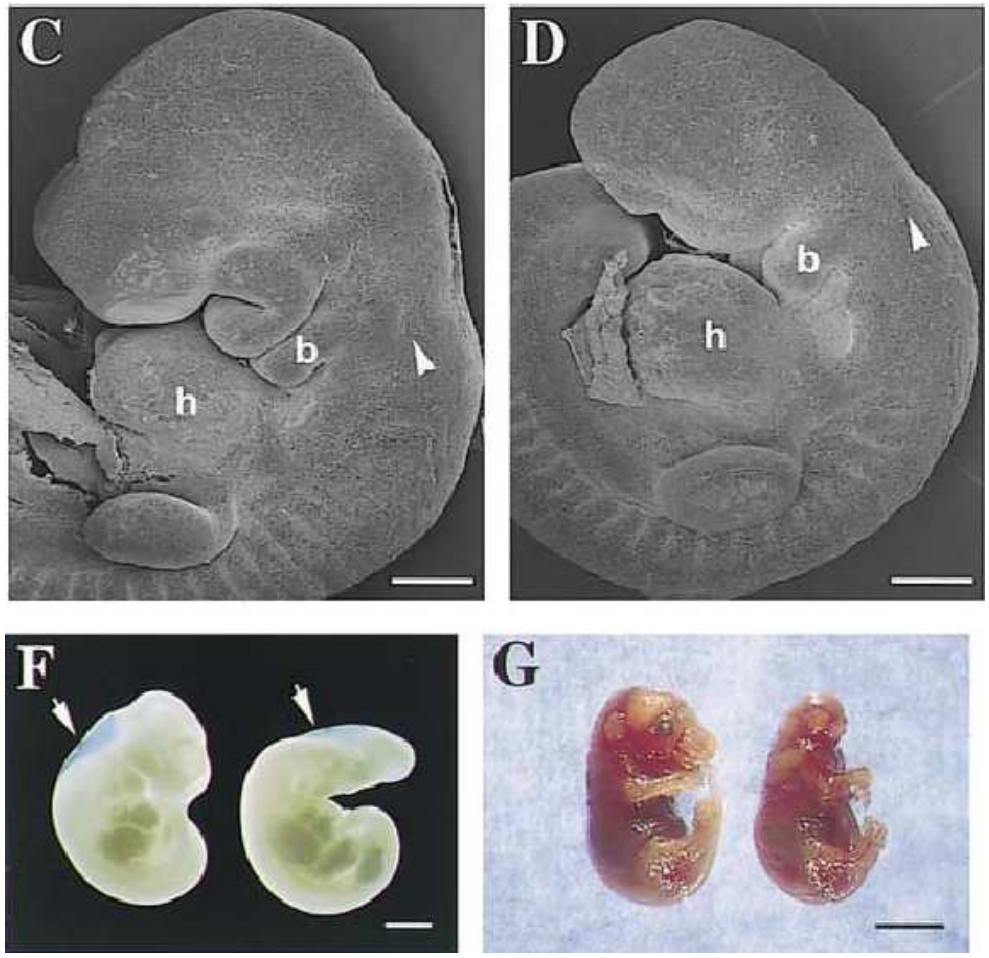


Deplece Wnt/β-kateninové dráhy při gastrulaci = ztráta zadních částí těla



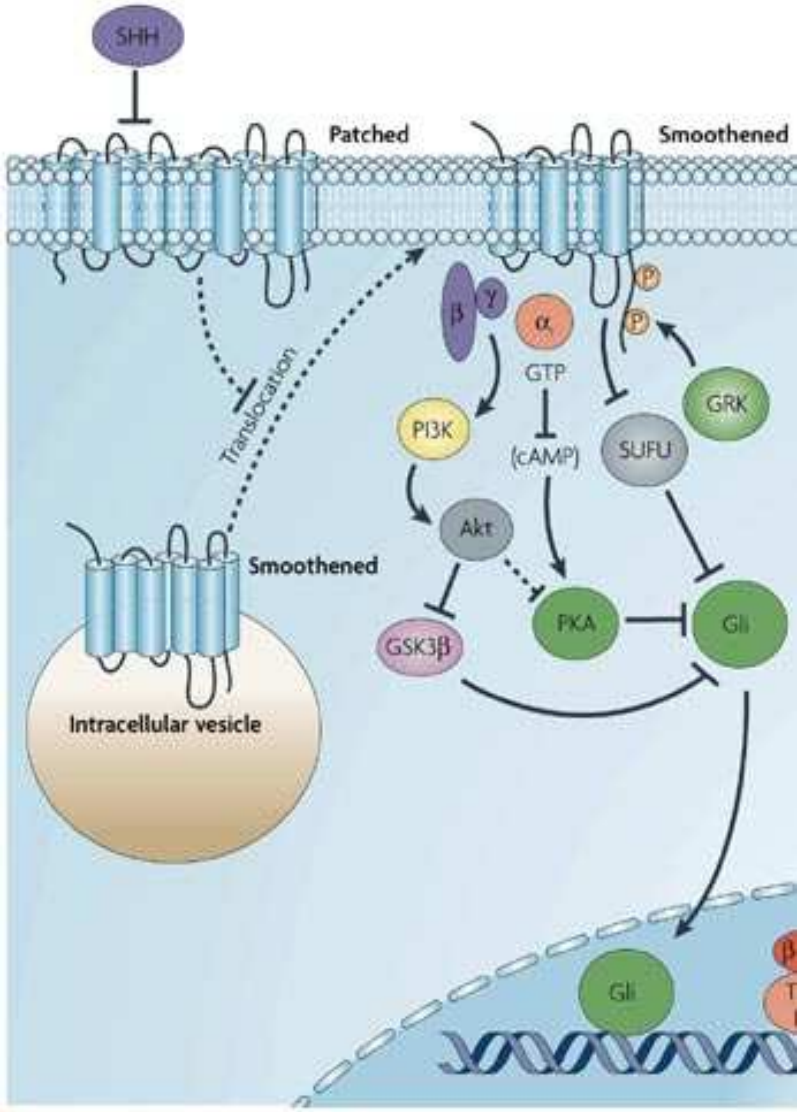
wild type **Wnt-3a knockout**

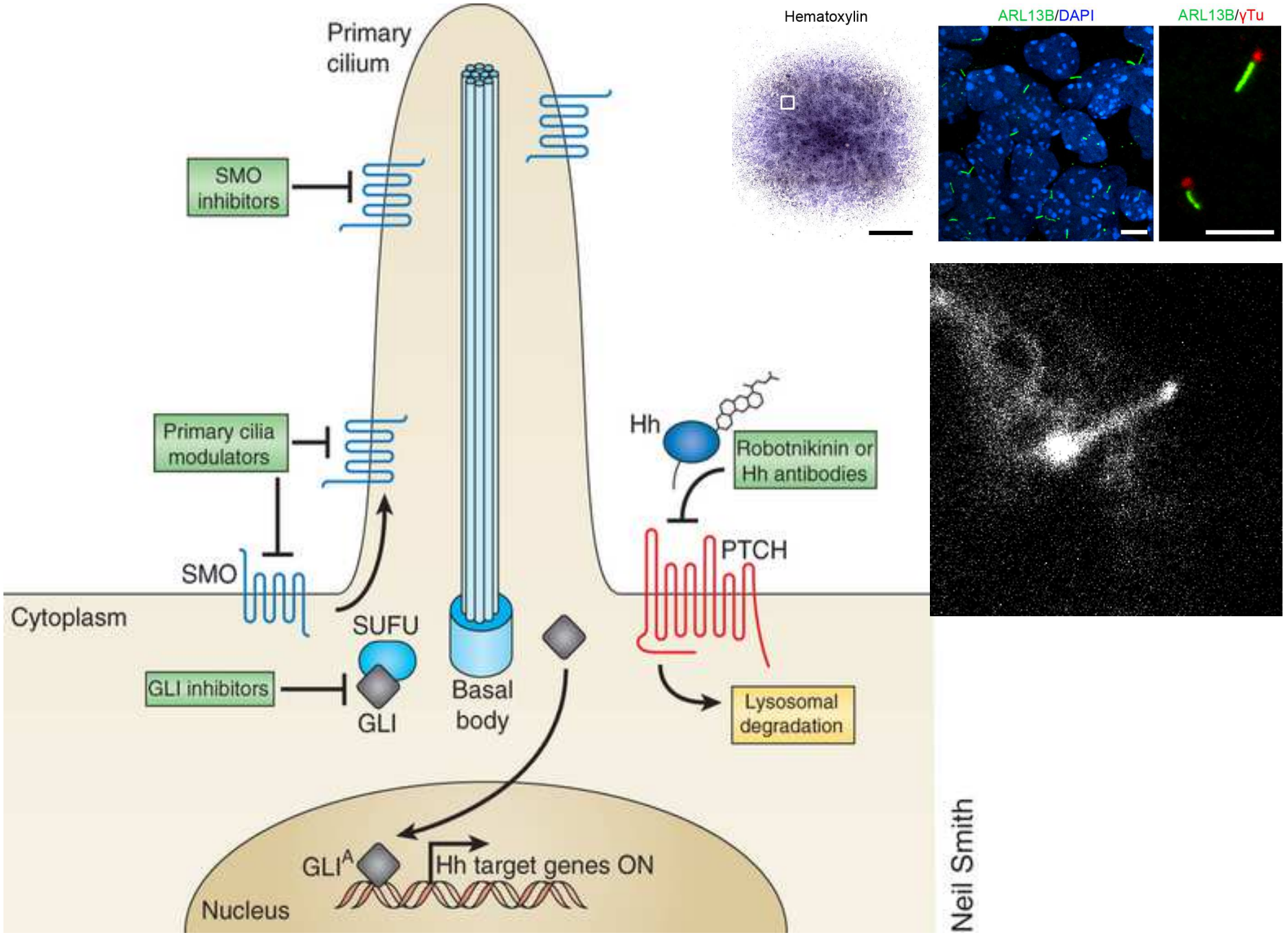
Deplece inhibitorů Wnt/β-kateninové dráhy při gastrulaci = ztráta předních částí těla



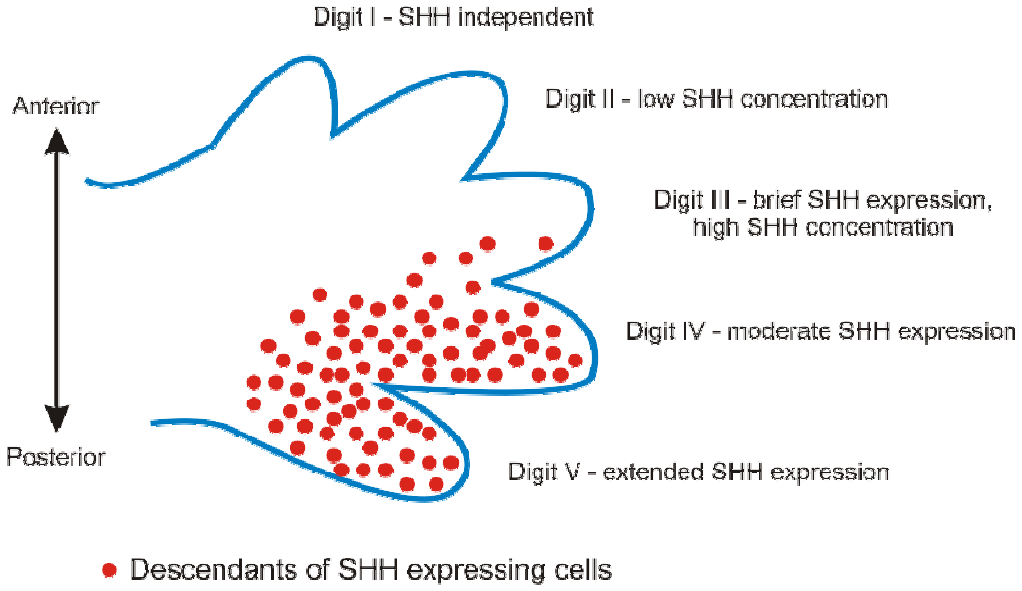
wild type vs. Dkk1 knockout

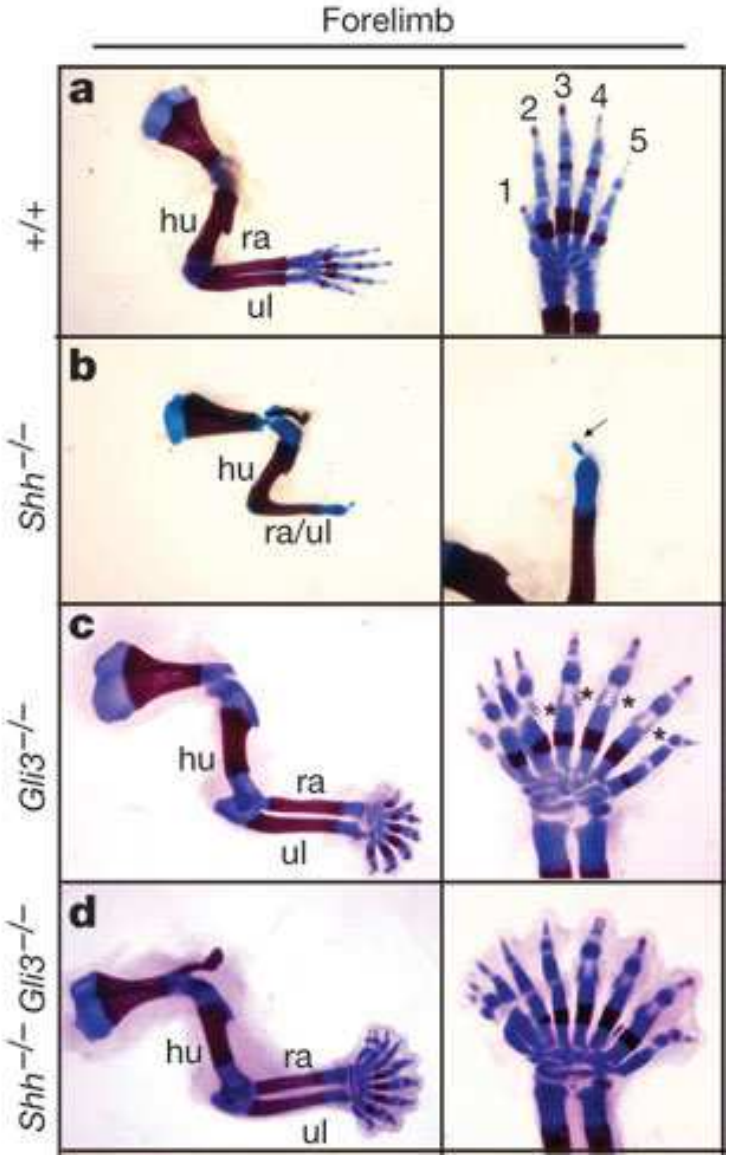
Shh – jeden z nejlépe popsaných klasických morfogenů (tzv. model francouzské vlajky) – v závislosti na koncentraci morfogenu se spouští odlišné transkripční programy



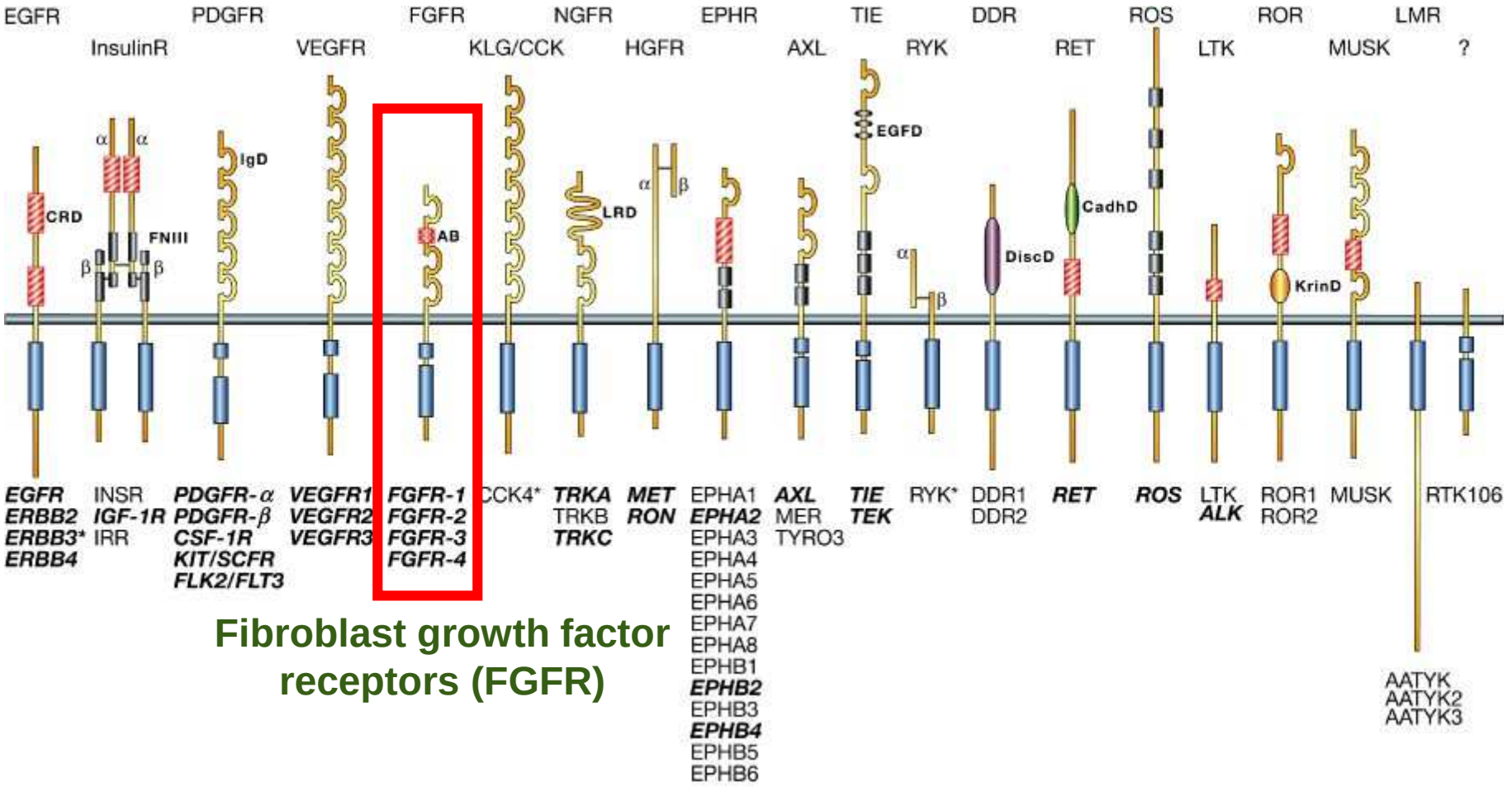

Primary cilium
SMO inhibitors
Primary cilia modulators
SMO
Cytoplasm
SUFU
GLI inhibitors
GLI
Basal body
Hh
Robotnikinin or Hh antibodies
PTCH
Lysosomal degradation
GLI^A
Hh target genes ON
Nucleus
Hematoxylin
ARL13B/DAPI
ARL13B/γTu
Neil Smith

Gradient Shh patternuje komponenty skeletu končetiny



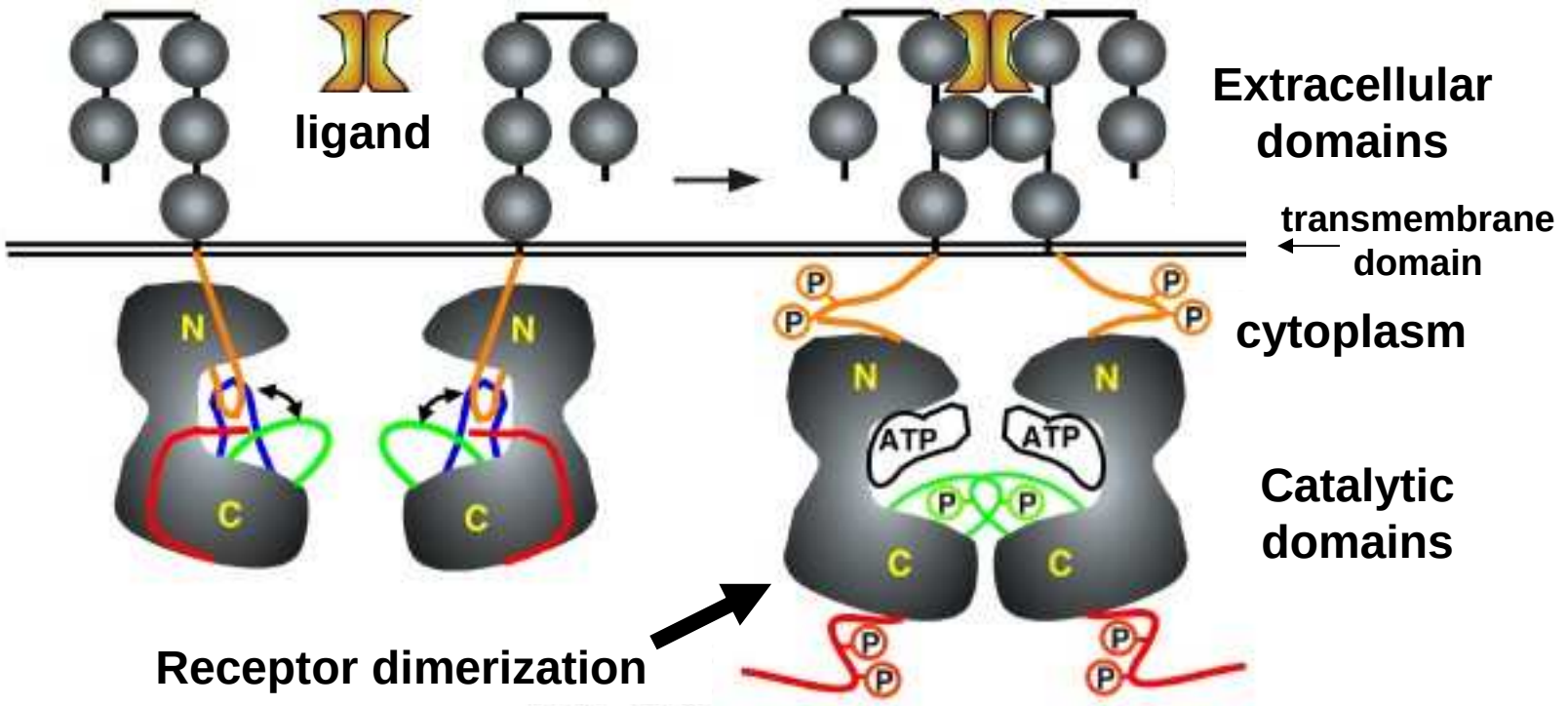


Protein tyrosine kinase (PTK) receptor family



- ✓In the human genome, 58 genes encode PTK receptors
- ✓Based on their overall structures, they can be placed into 20 subfamilies
- ✓Overactivity of PTK receptors has been implicated in number of diseases, particularly cancer. Several of PTK receptors were identified as **transforming oncogene products !!!**

Protein kinase receptor overview



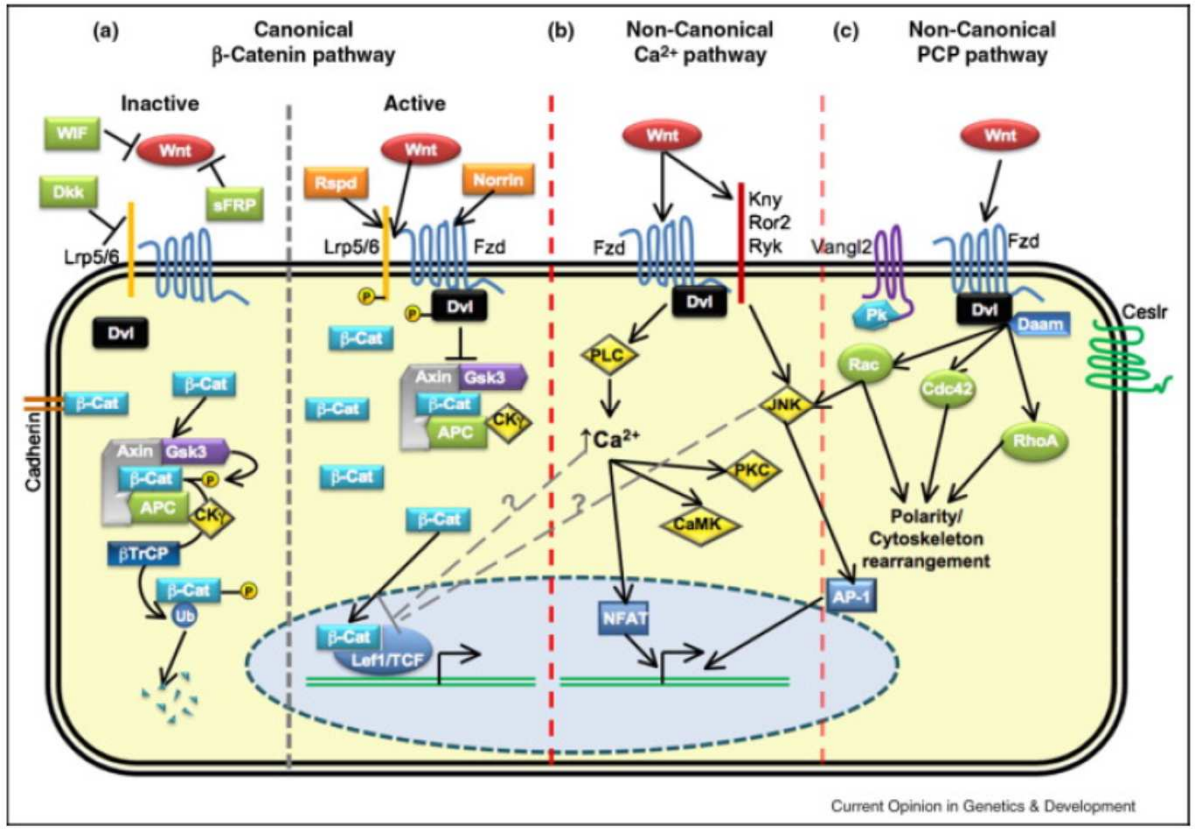
Structure of receptor kinases:

- Extracellular ligand binding domains
- Short transmembrane domain
- Intracellular kinase domains

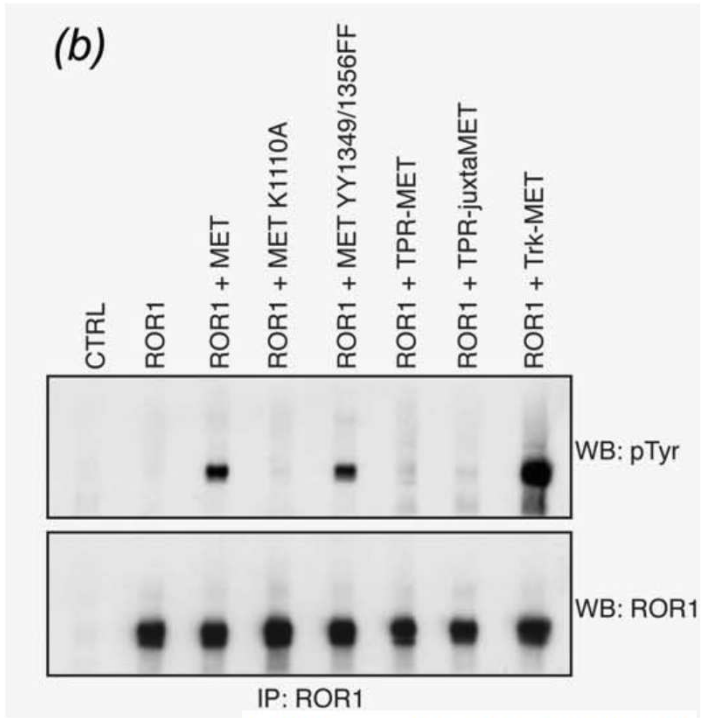
The most important family of protein kinase receptors are **protein tyrosine kinase receptors** that transduce signals regulating cell growth, differentiation, survival, and migration

Mode of action: **protein tyrosine kinase receptors are activated by ligand-induced dimerization. This brings the receptor kinase domains close to each other, which results in autophosphorylation within the intracellular kinase domains. The autophosphorylation occurs on tyrosine residues and triggers downstream signalling cascade that consists of recruiting and activation of multiple signal molecules**

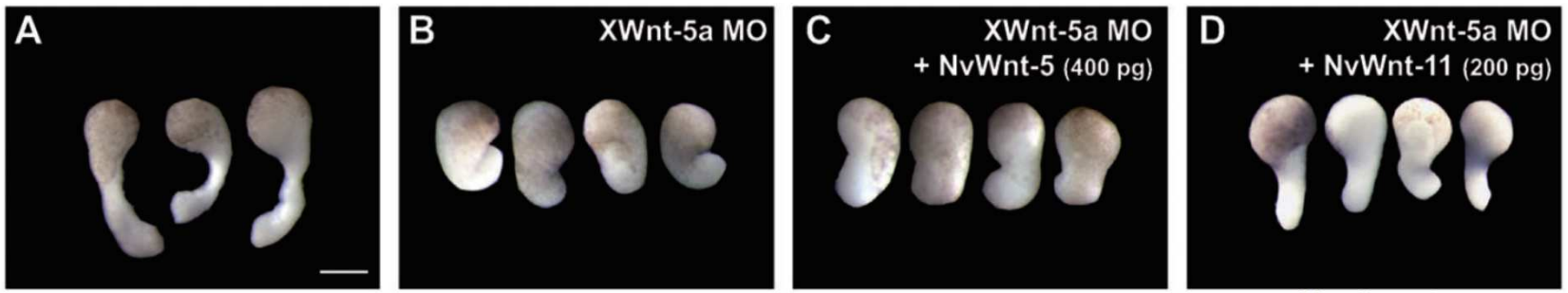
Pseudokinases in non-canonical WNT pathway and convergent extension



Current Opinion in Genetics & Development 2009, 19:476–483

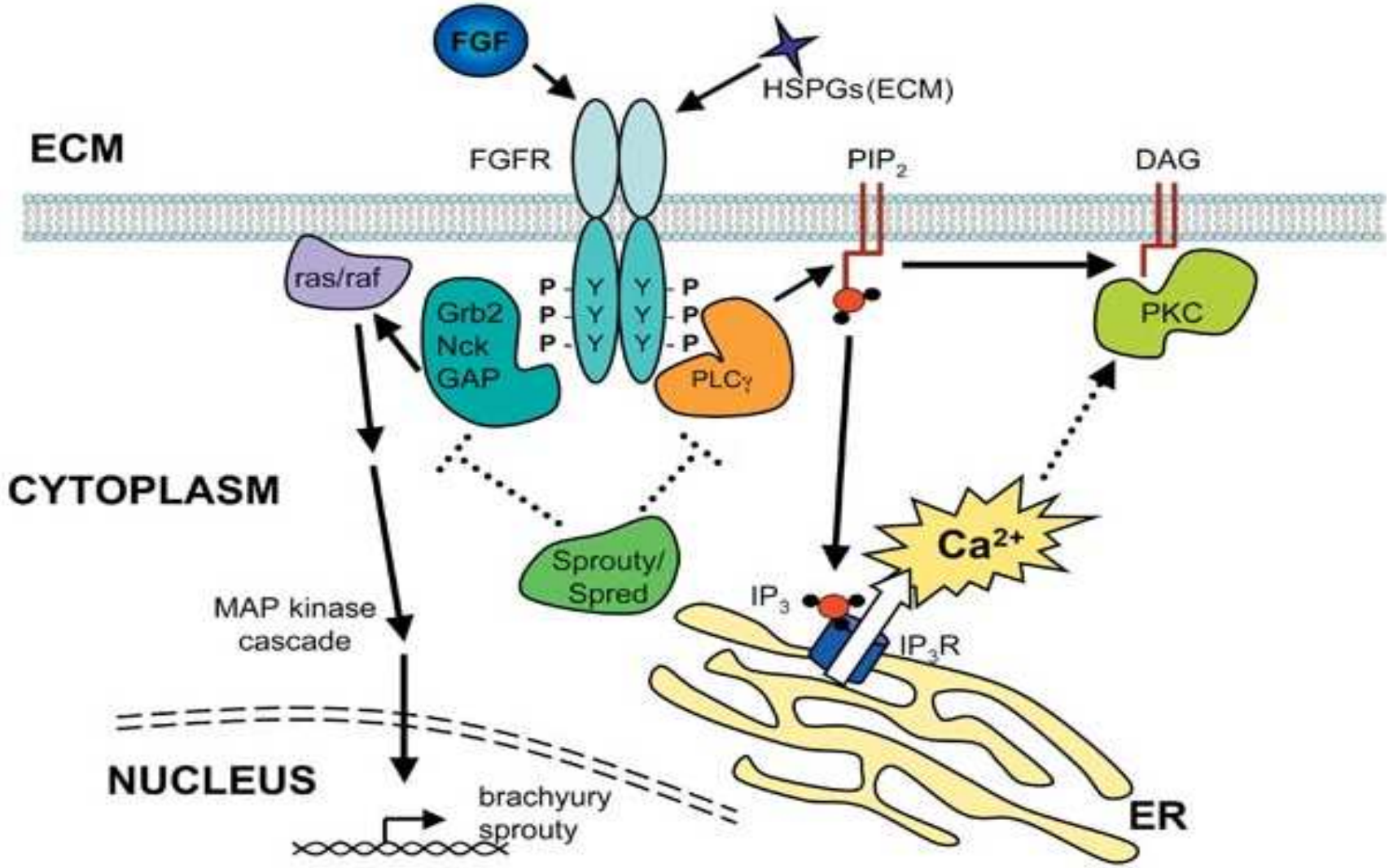


Int. J. Cancer: 135, 2305–2316 (2014)



doi: 10.1242/bio.2011021

4 receptors: FGFR1-4
18 ligands: FGF1-23



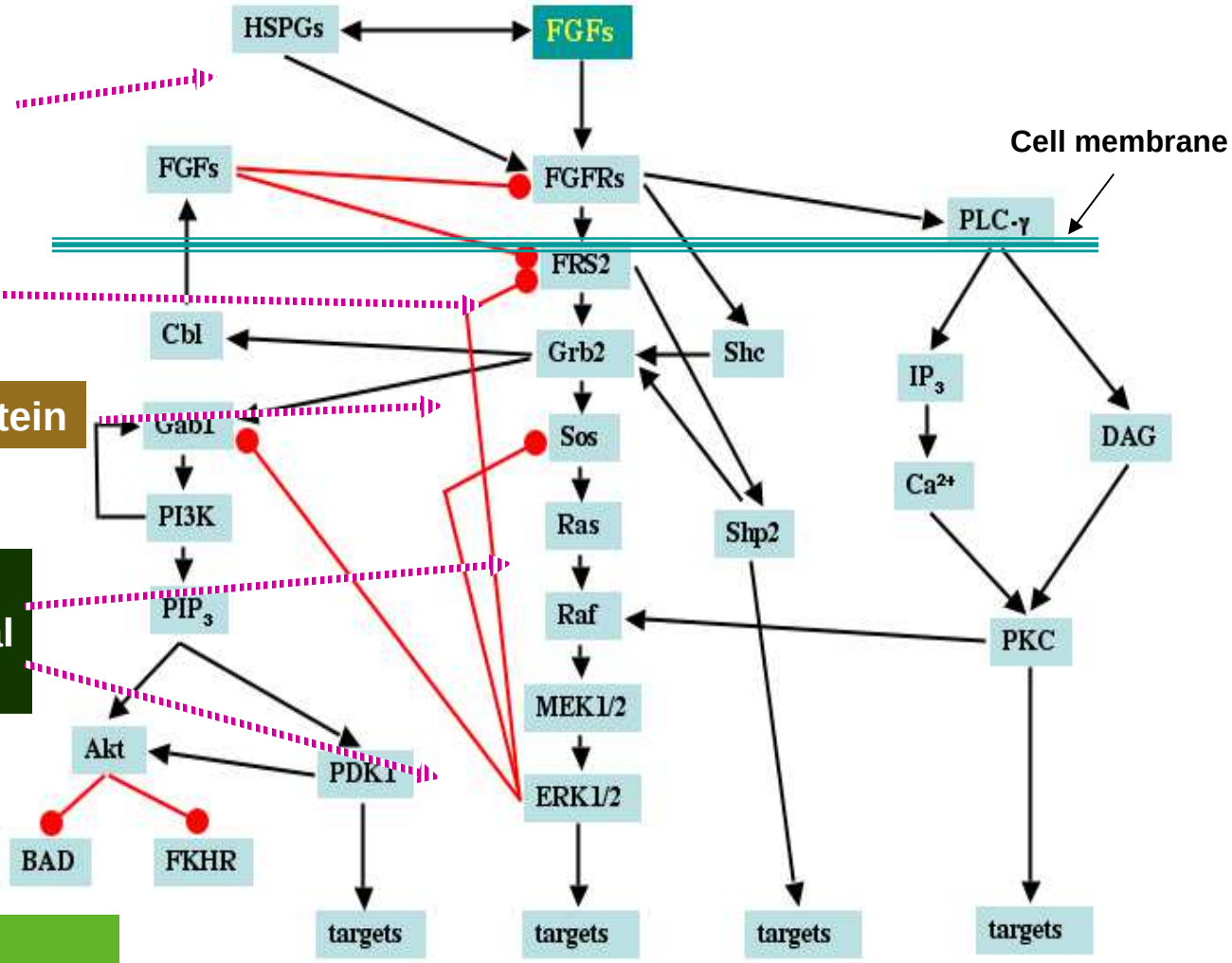
„Canonical“ signalling pathway of FGFs and FGFRs

Membrane proteoglycans

„docking site“

SH2 domain containing protein

Ras/Raf/MEK/ERK signalling pathway is crucial in cancer !!!



Changes in gene expression and cell response

Adapted from Schlessinger, 2004

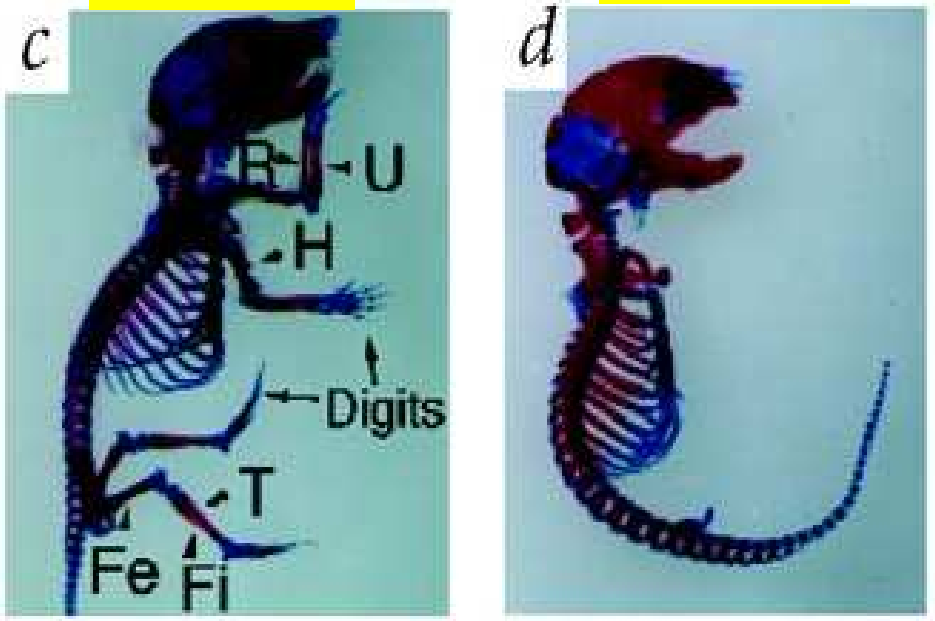
Genetic abnormalities found in FGFRs that participate in cancer:

- Chromosomal translocations
- Gene amplification and overexpression
- Activating mutations

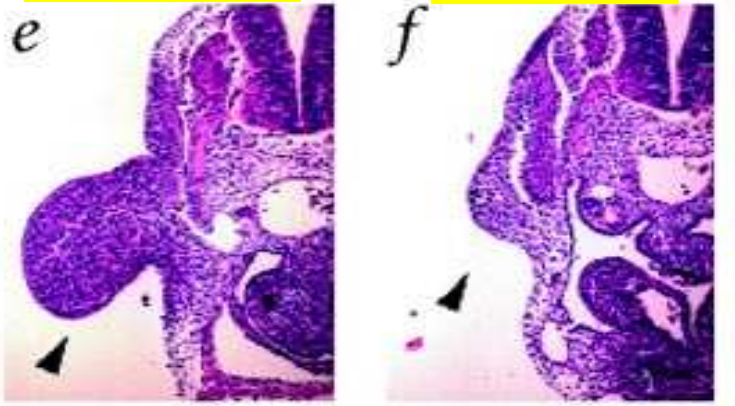
FGF10

FGF10 → mesenchymal proliferationu → limb bud growth

Wild-type *Fgf10$^{-/-}$*



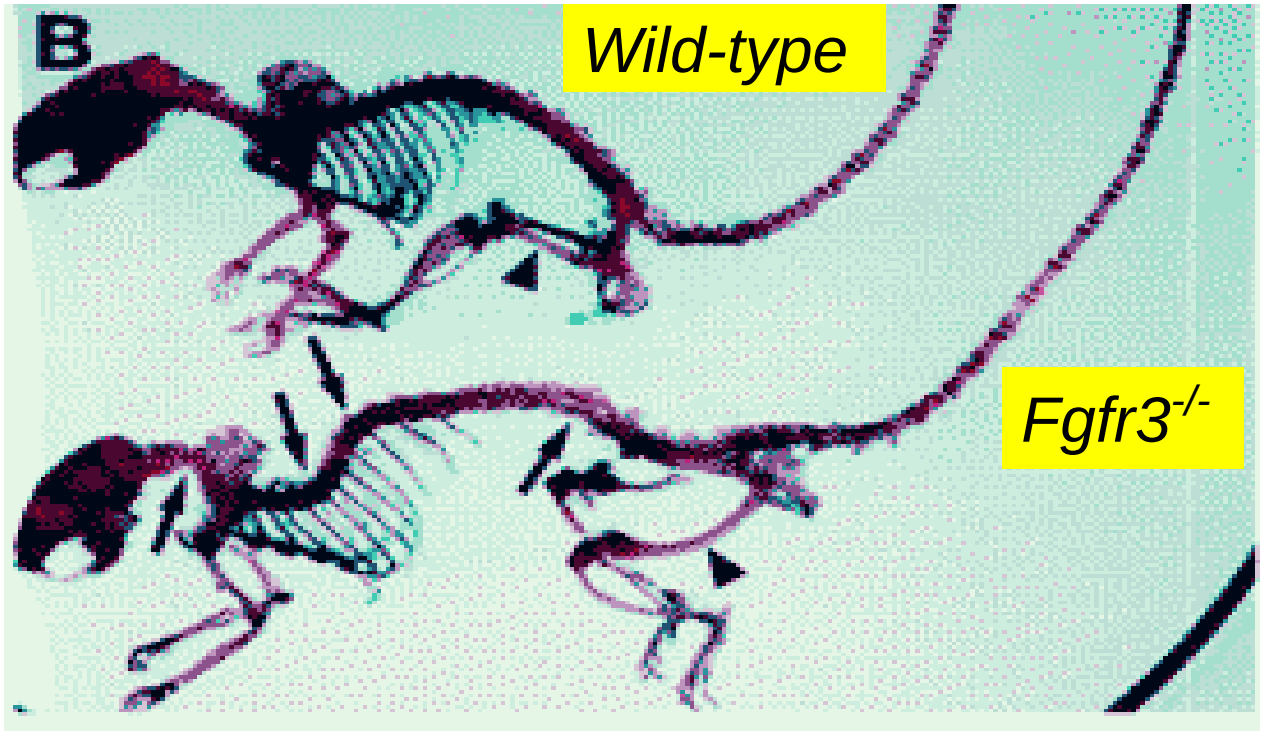
Wild-type *Fgf10$^{-/-}$*



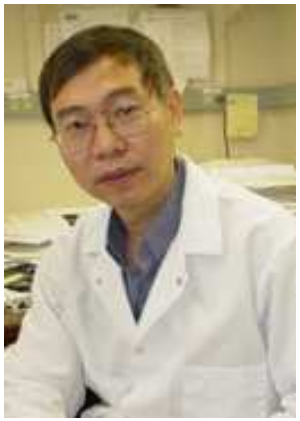
Fgf-10 is required for both limb and lung development and exhibits striking functional similarity to Drosophila branchless

Hosung Min, Dimitry M. Danilenko, Sheila A. Scully, et al.

Genes Dev. 1998 12: 3156-3161
Access the most recent version at doi:10.1101/gad.12.20.3156

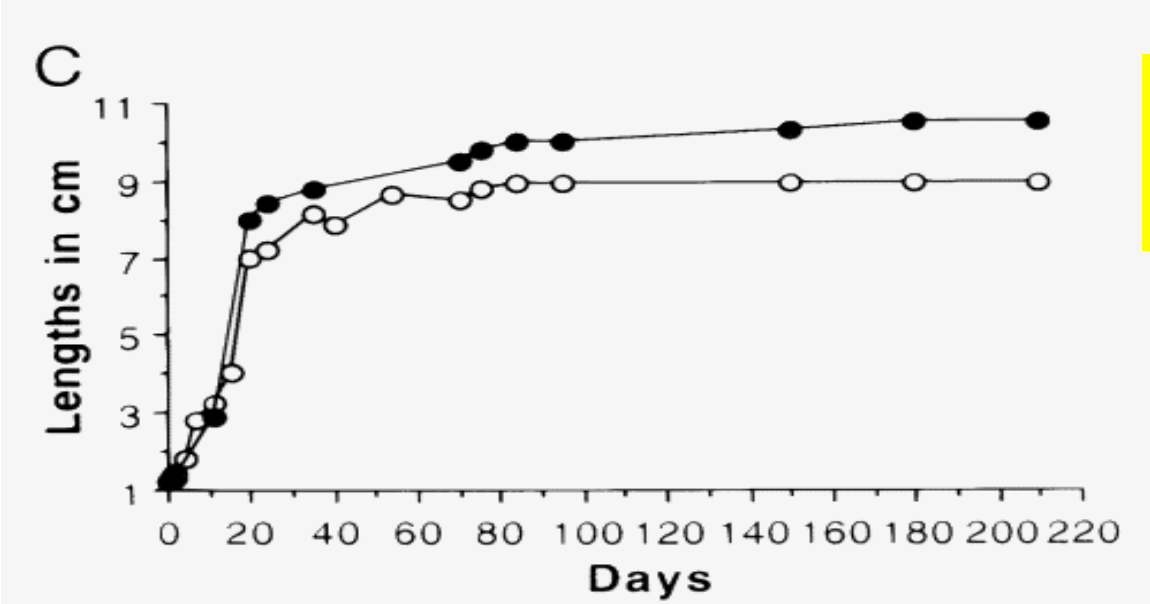


Chuxia Deng



Cell 1996, 84(6):911-21.

Tail



Fgfr3-/-
Wild-type

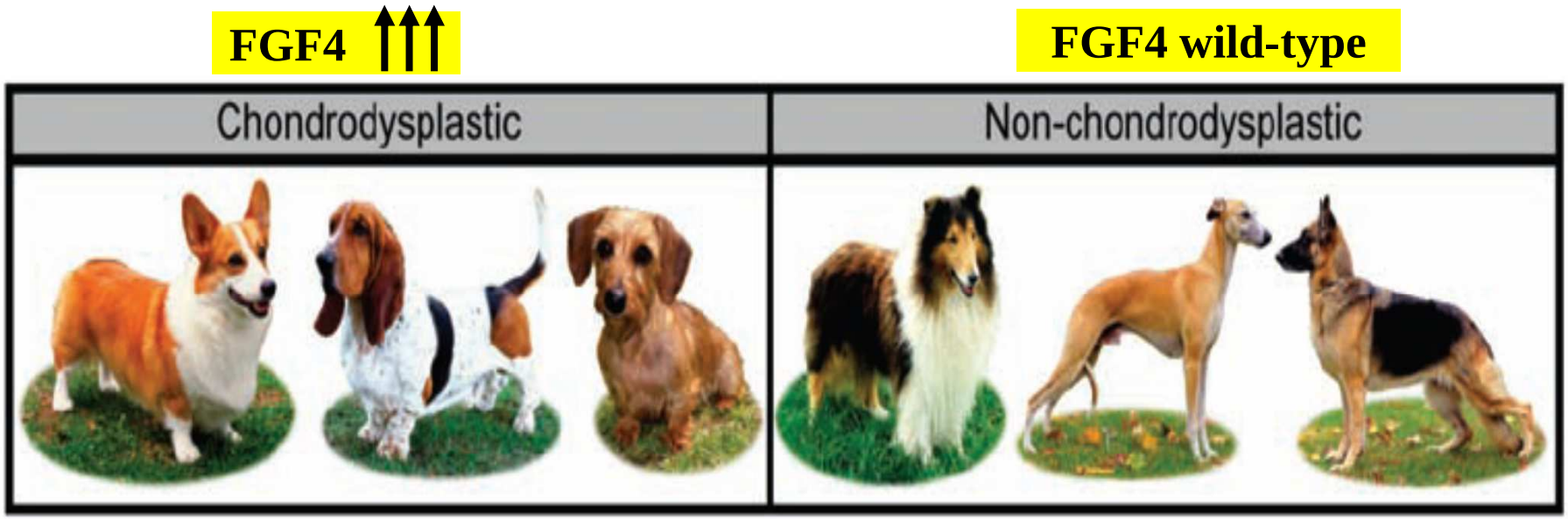
An Expressed *Fgf4* Retrogene Is Associated with Breed-Defining Chondrodysplasia in Domestic Dogs

Heidi G. Parker,[1] Bridgett M. VonHoldt,[2] Pascale Quignon,[1] Elliott H. Margulies,[3] Stephanie Shao,[1] Dana S. Mosher,[1] Tyrone C. Spady,[1] Abdel Elkahloun,[1] Michele Cargill,[4]* Paul G. Jones,[5] Cheryl L. Maslen,[6] Gregory M. Acland,[7,8] Nathan B. Sutter,[8] Keiichi Kuroki,[9] Carlos D. Bustamante,[10] Robert K. Wayne,[2] Elaine A. Ostrander[1]†

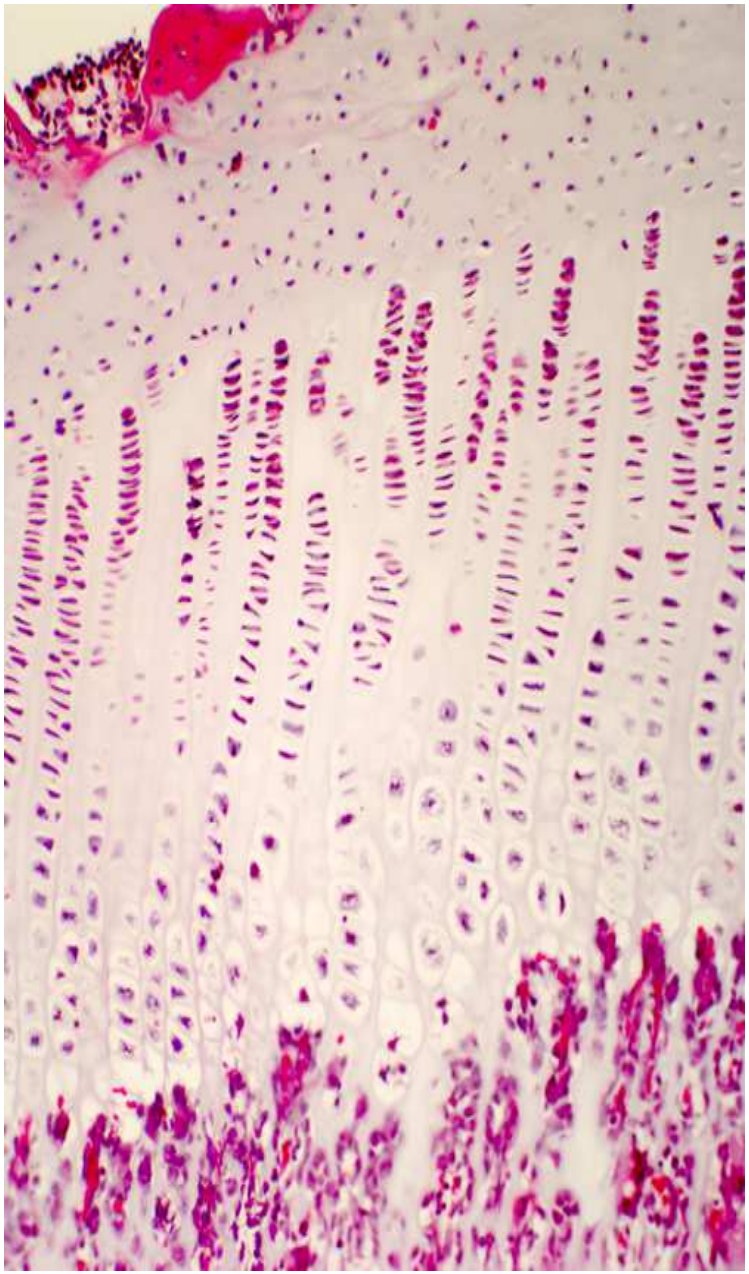
Retrotransposition of processed mRNAs is a common source of novel sequence acquired during the evolution of genomes. Although the vast majority of retroposed gene copies, or retrogenes, rapidly accumulate debilitating mutations that disrupt the reading frame, a small percentage become new genes that encode functional proteins. By using a multibreed association analysis in the domestic dog, we demonstrate that expression of a recently acquired retrogene encoding fibroblast

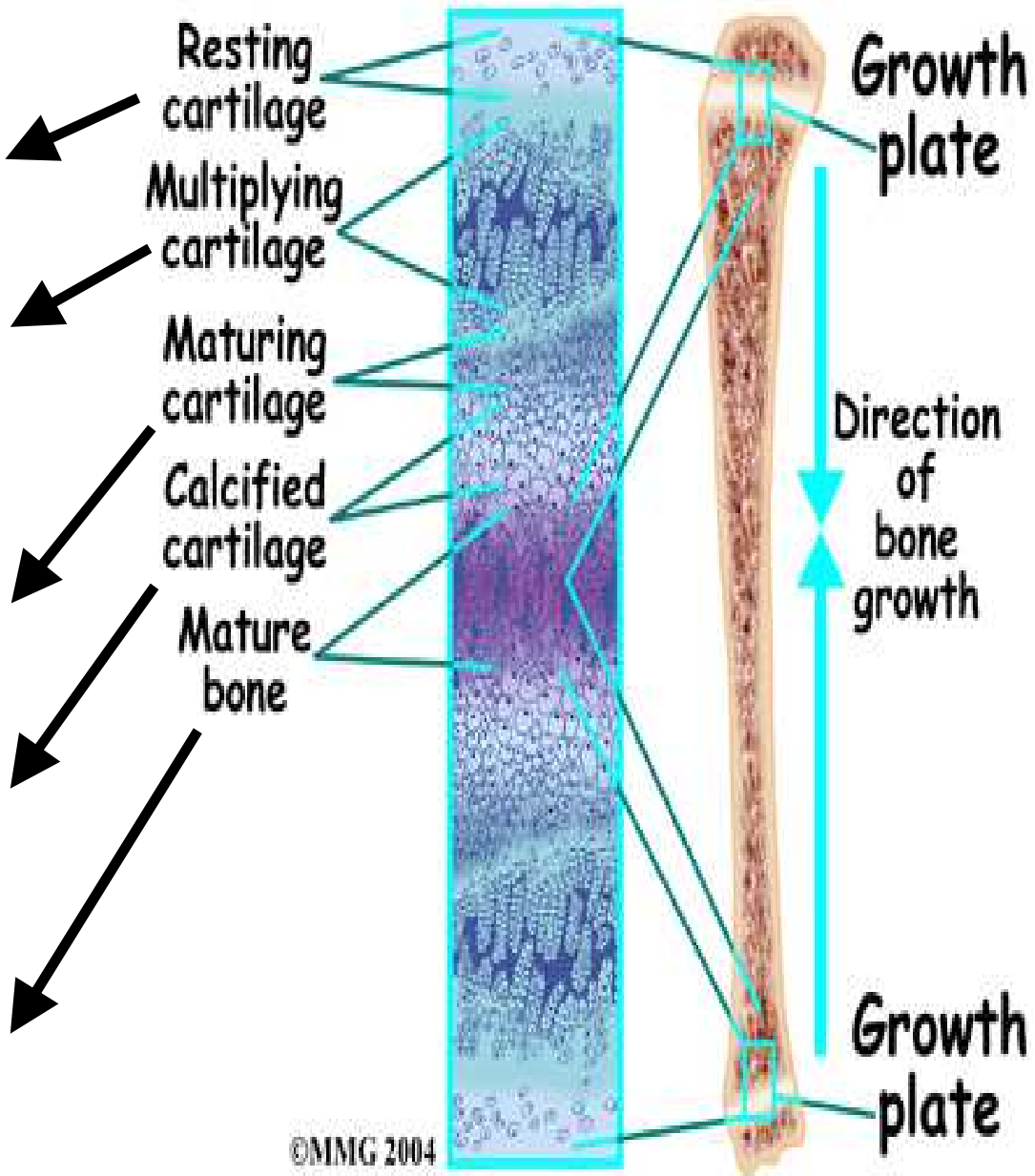
dachshund, Pekingese, and basset hound, where it was found to be dominant and allelic on the basis of arranged crosses (*5*). The phenotype primarily affects the length of the long bones, with growth plates calcifying early in development, thus producing shortened bones with a curved appearance (Fig. 1A) (*6*, *7*).

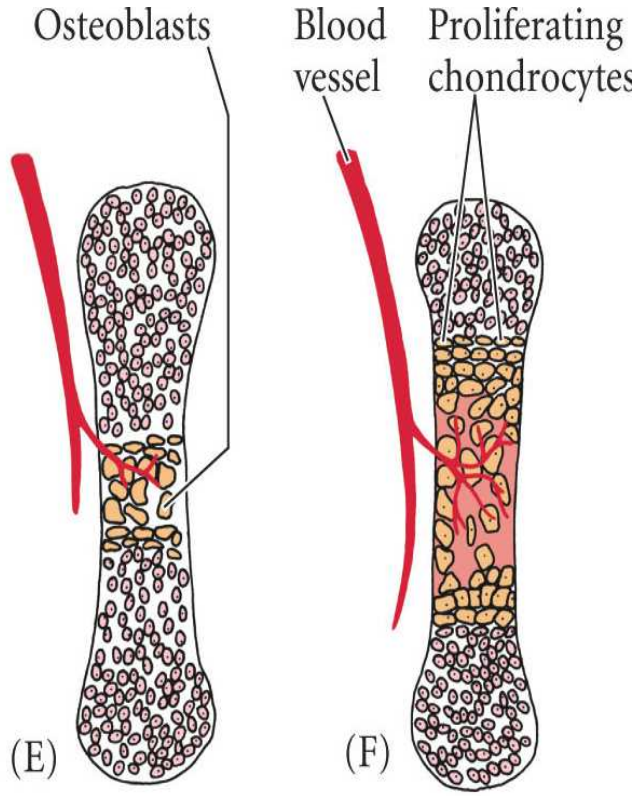
To identify the genetic foundations of breed-defining phenotypes such as canine chondrodysplasia, we developed a multibreed approach for mapping fixed canine traits. A total of 835 dogs from 76 distinct breeds that provided maximal coverage of phenotypic variation were genotyped by using the Affymetrix version 2.0 single-nucleotide polymorphism (SNP) chip (*8*, *9*). Chondrodysplastic breeds, or cases, were defined on the basis of specific morphologic criteria set forth in each

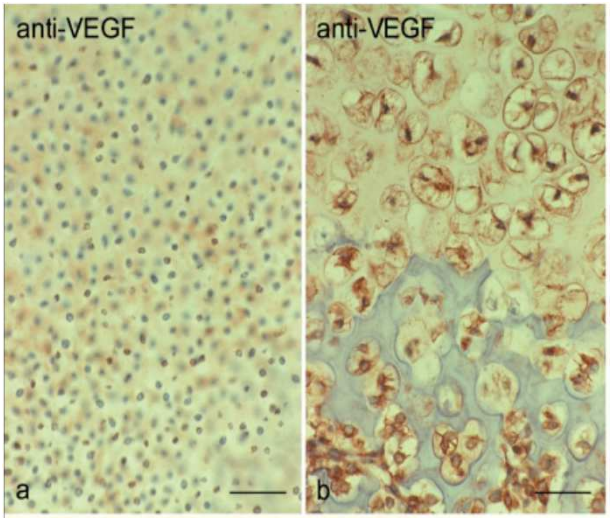


Science 2009;325:995-8.




Resting cartilage
Multiplying cartilage
Maturing cartilage
Calcified cartilage
Mature bone
Growth plate
Direction of bone growth
Growth plate
©MMG 2004





VEGFA is necessary for chondrocyte survival during bone development

Elazar Zelzer[1], Roni Mamluk[2], Napoleone Ferrara[3], Randall S. Johnson[4], Ernestina Schipani[5] and Bjorn R. Olsen[1,*]

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[2]Department of Surgical Research, Children's Hospital and Harvard Medical School, Boston, MA 02115, USA
[3]Department of Molecular Oncology, Genentech, South San Francisco, CA 94080, USA
[4]Molecular Biology Section, Division of Biology, University of California, San Diego, CA 92093, USA
[5]Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
*Author for correspondence (e-mail: bjorn_olsen@hms.harvard.edu)

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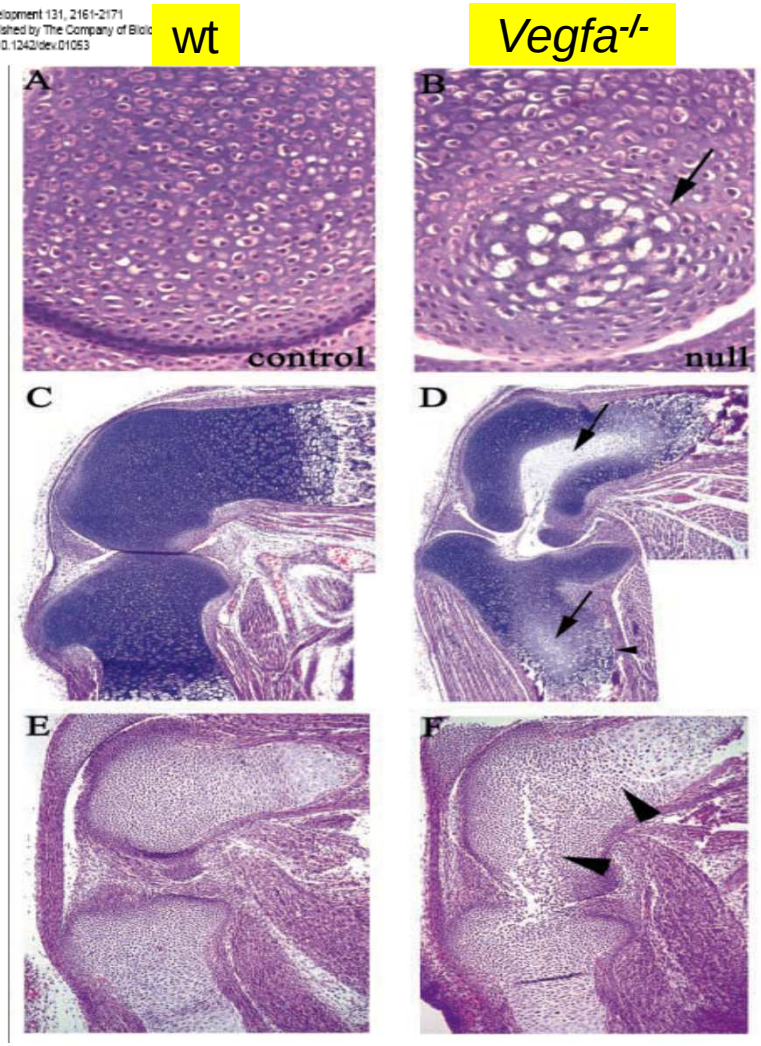
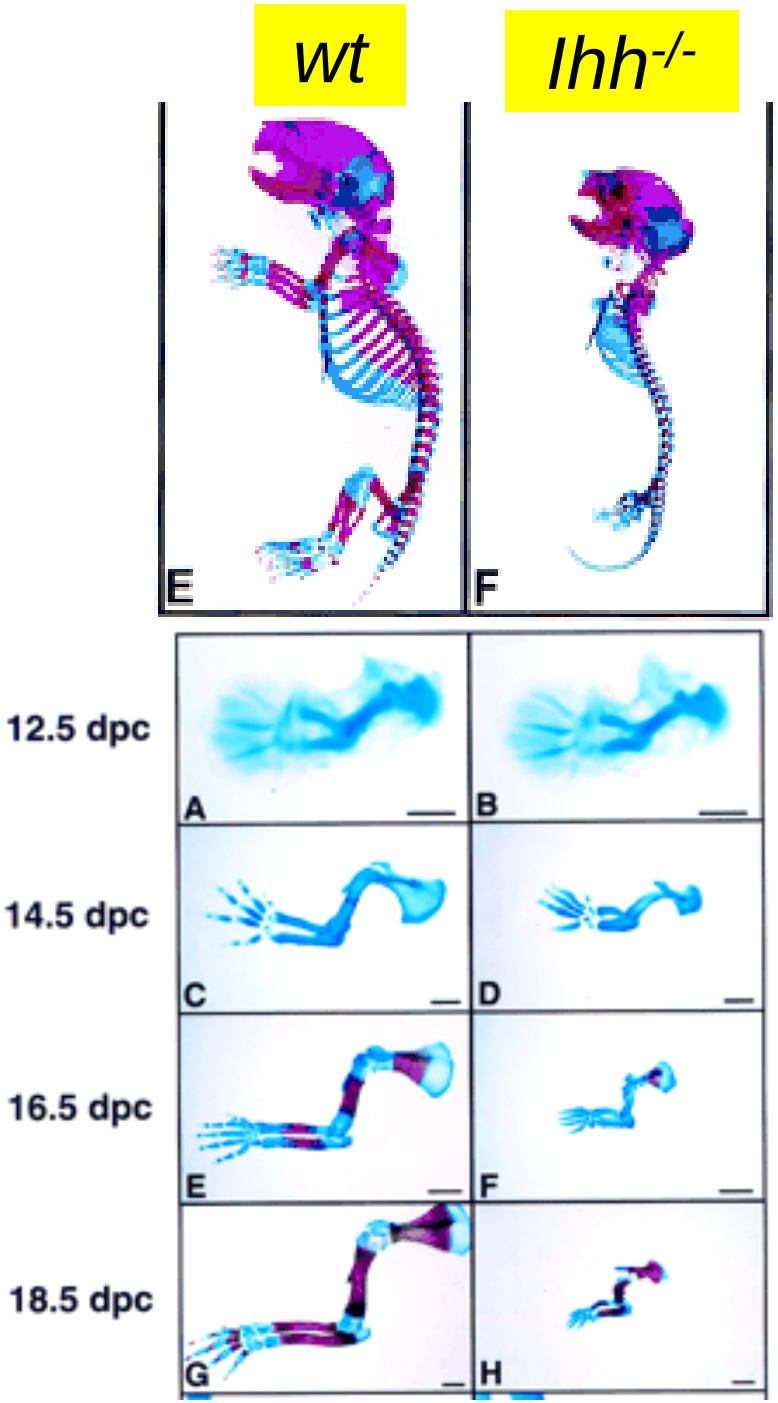
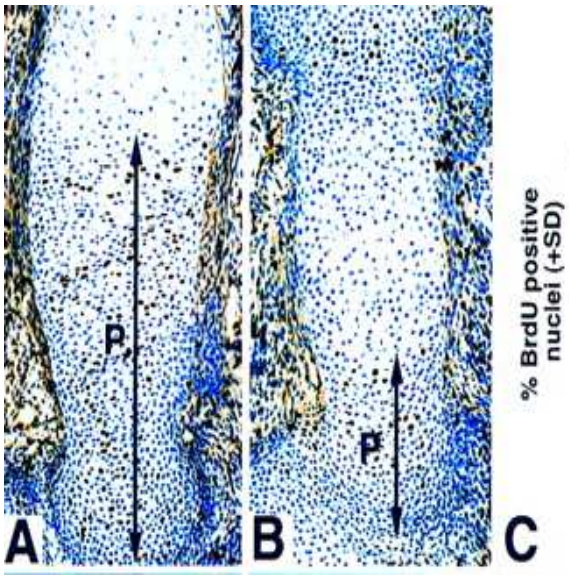
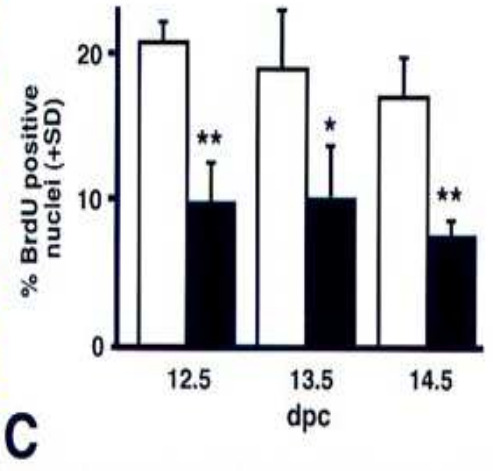
doi:10.1242/dev.01053



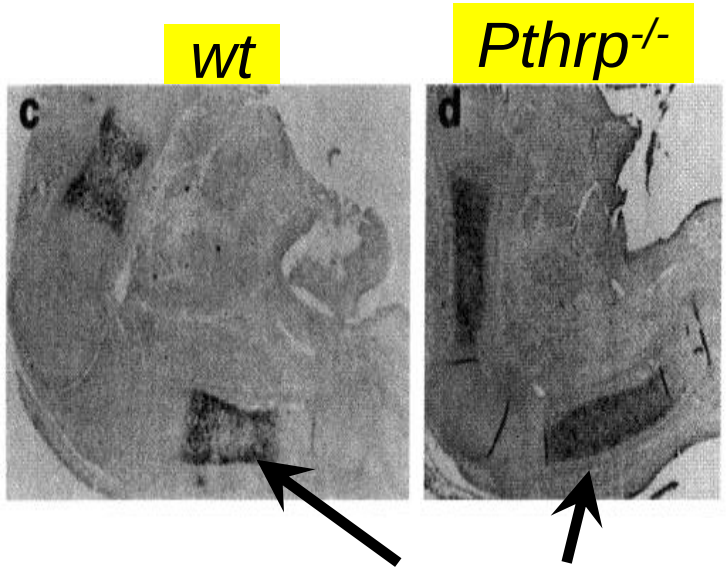
Indian hedgehog (Ihh)





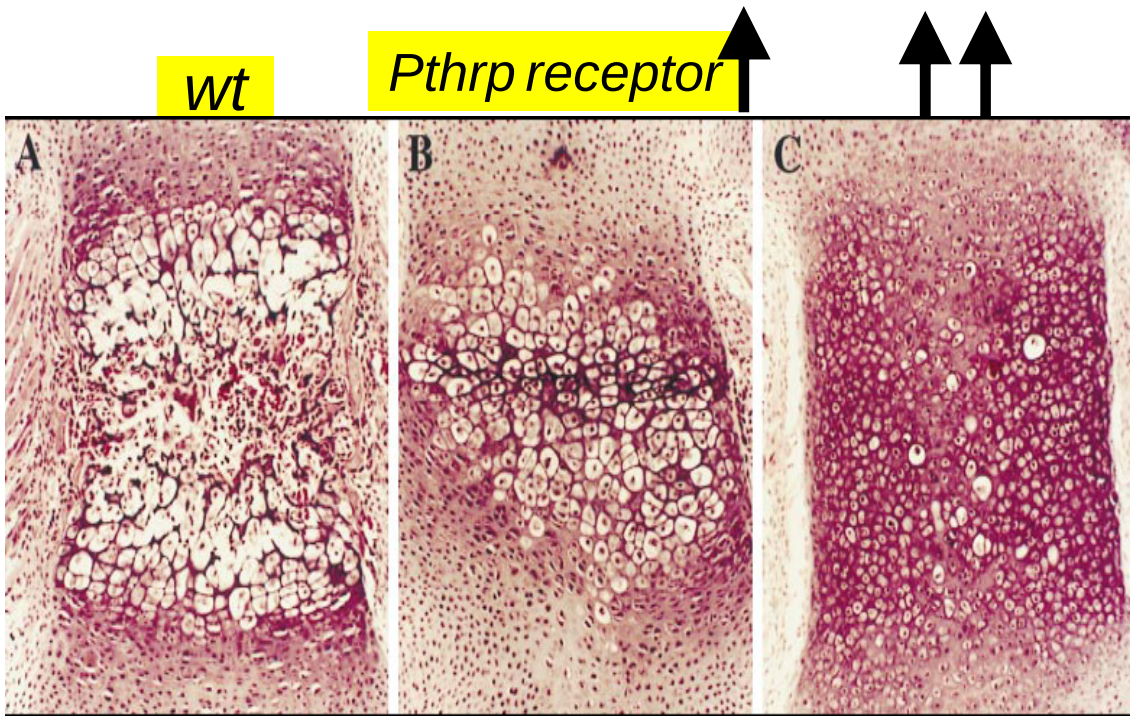


St-Jacques et al., Genes Dev 13 (1999)

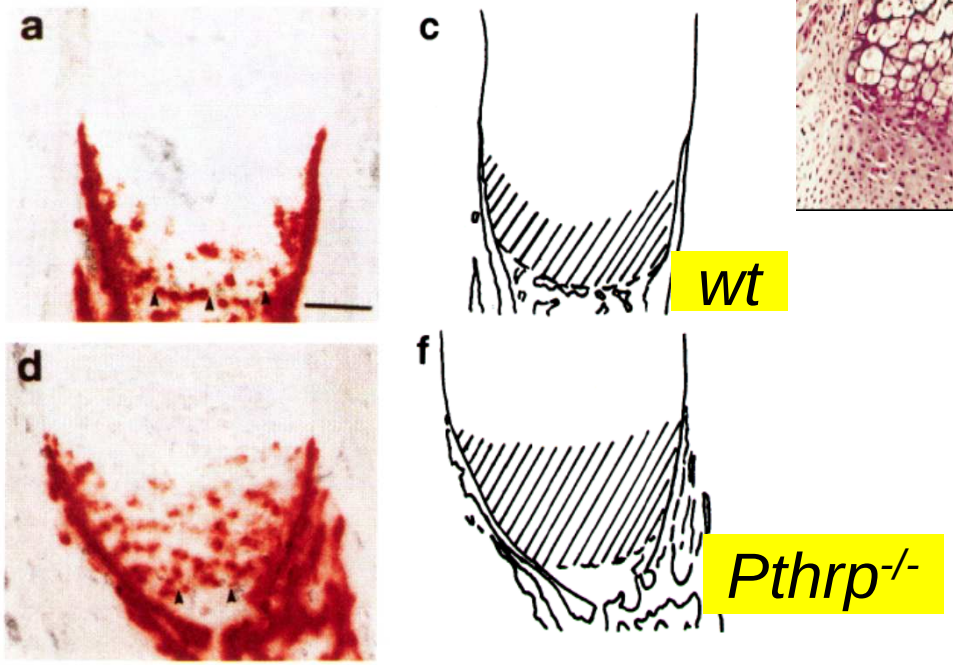


Coll type X in situ

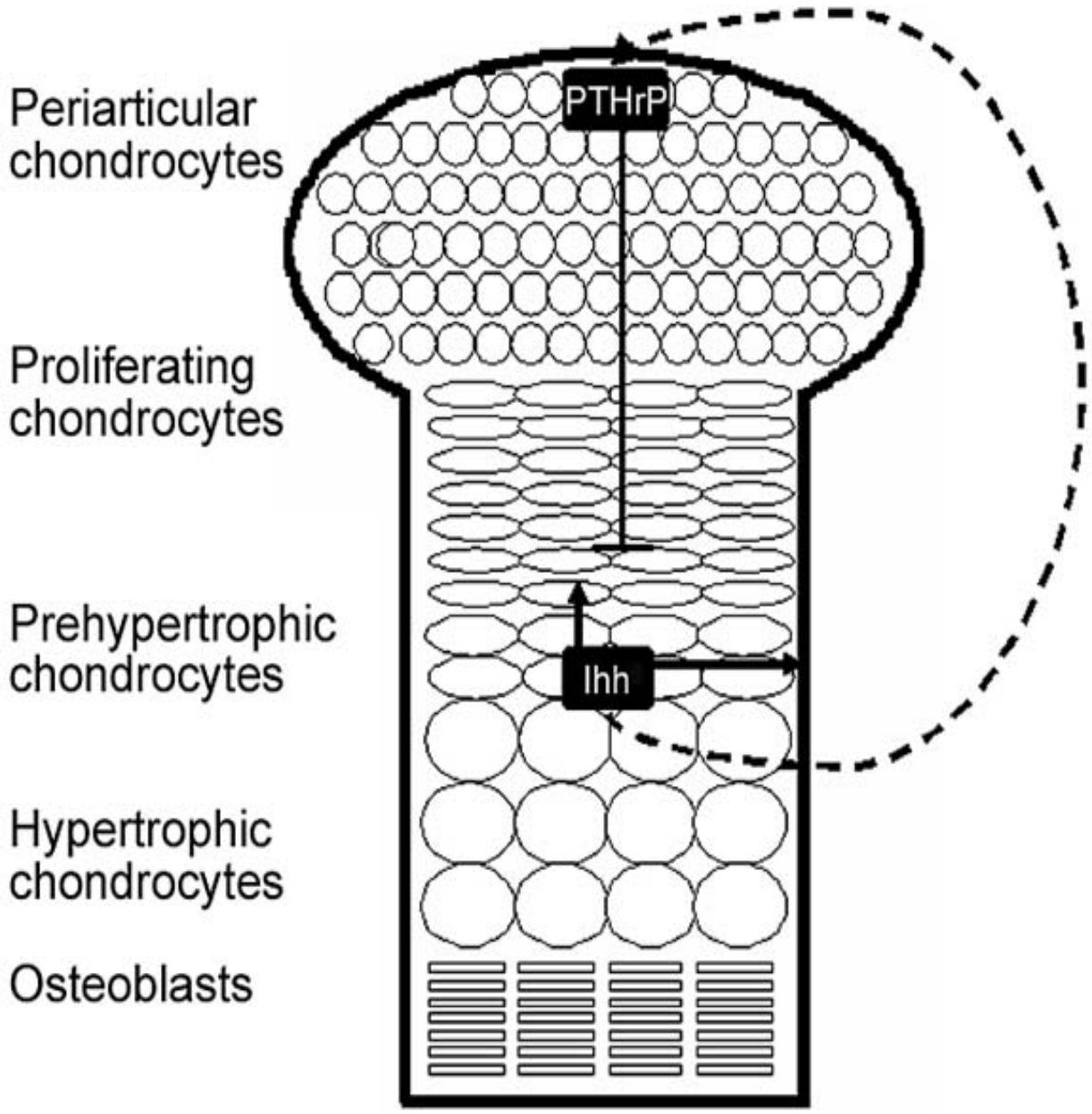
Parathyroid hormone-related peptide (PTHrP)



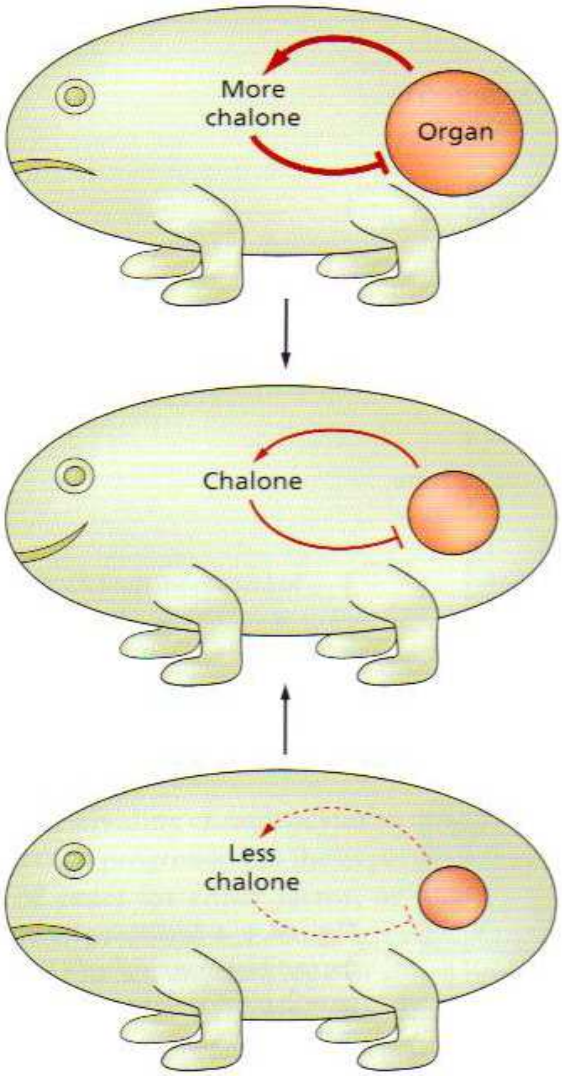
Sternal cartilage



Karp et al., Development 127 (2000)


Periarticular chondrocytes
Proliferating chondrocytes
Prehypertrophic chondrocytes
Hypertrophic chondrocytes
Osteoblasts
PTHrP
Ihh

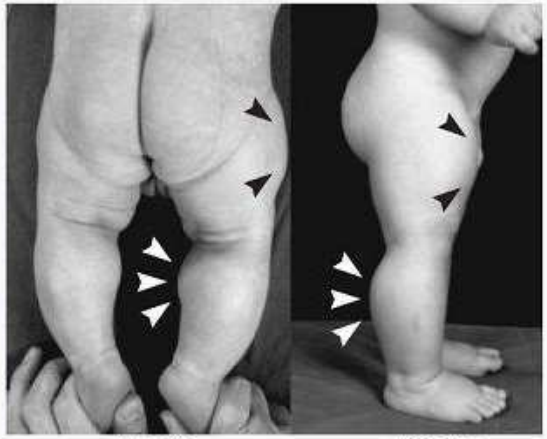
CONTROL OF RELATIVE PROPORTION: This is an important problem in growth control, even if the overall size of the organism is correct. How can it be guaranteed that different body parts expand in proportion to one another? The coordinated growth of body parts is explained by **feedback inhibition** of each body part on itself (chalone model).



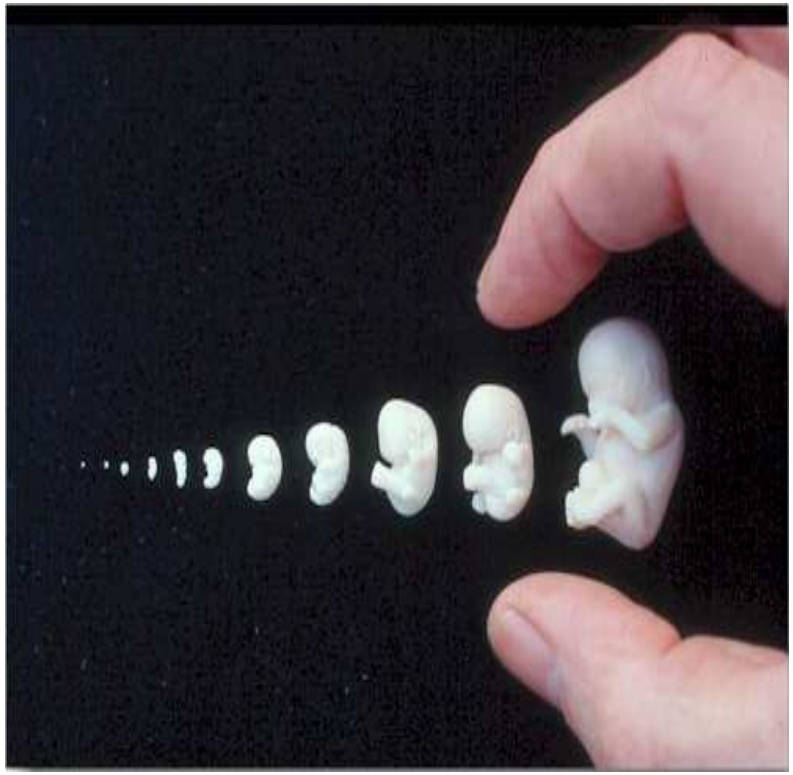
Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child

Markus Schuelke, M.D., Kathryn R. Wagner, M.D., Ph.D., Leslie E. Stolz, Ph.D., Christoph Hübner, M.D., Thomas Riebel, M.D., Wolfgang Kömen, M.D., Thomas Braun, M.D., Ph.D., James F. Tobin, Ph.D., and Se-Jin Lee, M.D., Ph.D.

N ENGL J MED 350;26 WWW.NEJM.ORG JUNE 24, 2004



Pattern and shape vs. Growth and proportions



$\times 10^9 =$