Regulation of Cell Function by FGFR3

Pavel Krejci

Limb development: At the beginning there was retinoic acid…

LETTERS TO NATURE

Limbs generated at site of tail amputation in marbled balloon frog after vitamin A treatment

P. Mohanty-Hejmadi, S. K. Dutta & P. Mahapatra

Department of Zoology, Utkal University, Bhubaneswar 751004, Orissa, India

NIAZI and Saxena[1] first observed that vitamin A has an inhibitory and modifying influence on tail regeneration in *Bufo andersonii* tadpoles. A positive relationship was later found between the inhibiting influence of vitamin A and the developmental stage of the regenerating tail in the same species[2]. There have been several subsequent reports[3–7] on the effects of vitamin A and its derivatives on limb development and regeneration. Thus in regenerating amphibian limbs, application of retinoids produces pattern duplication in the proximodistal and anteroposterior axes of the limb[3,8,9], and local application of retinoic acid to the anterior side of developing chick limbs causes duplications in the anteroposterior axis of limb[10,11]. Here we show that vitamin A can cause limb development when applied to amputated tail stumps of the tadpoles of the marbled balloon frog *Uperodon systoma* (Anura Microhylidae). This is the first report of homeotic transformation mediated through vitamin A in vertebrates.

Following amputation through the middle of the tail at the hind-limb bud stage, tadpoles were exposed to a solution of 10 IU per ml vitamin A palmitate (Arovit, Roche; see Table 1 for details) for 24 h (set I), 48 h (set II), 72 h (set III), 96 h (set

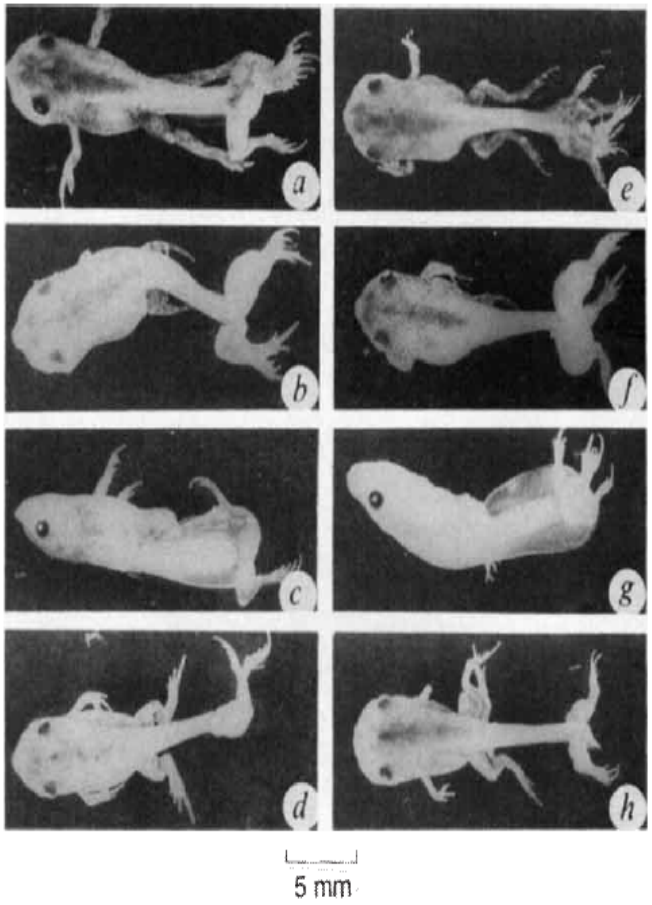
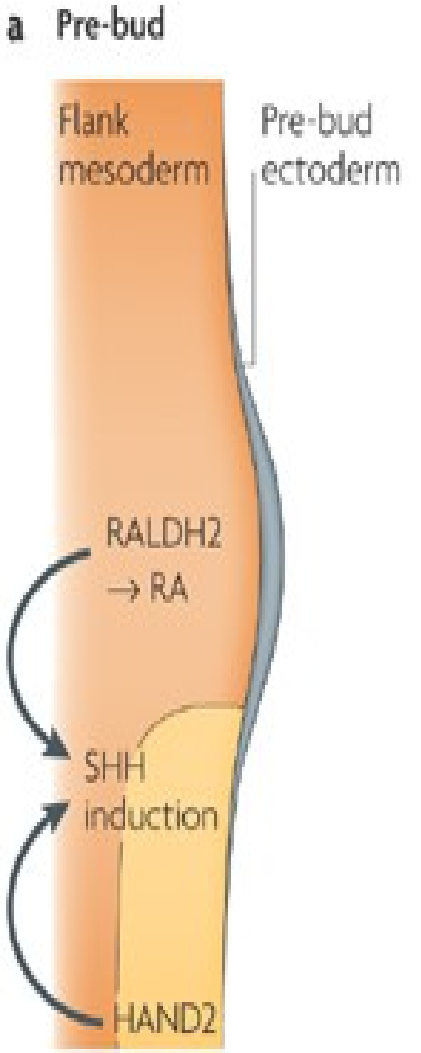
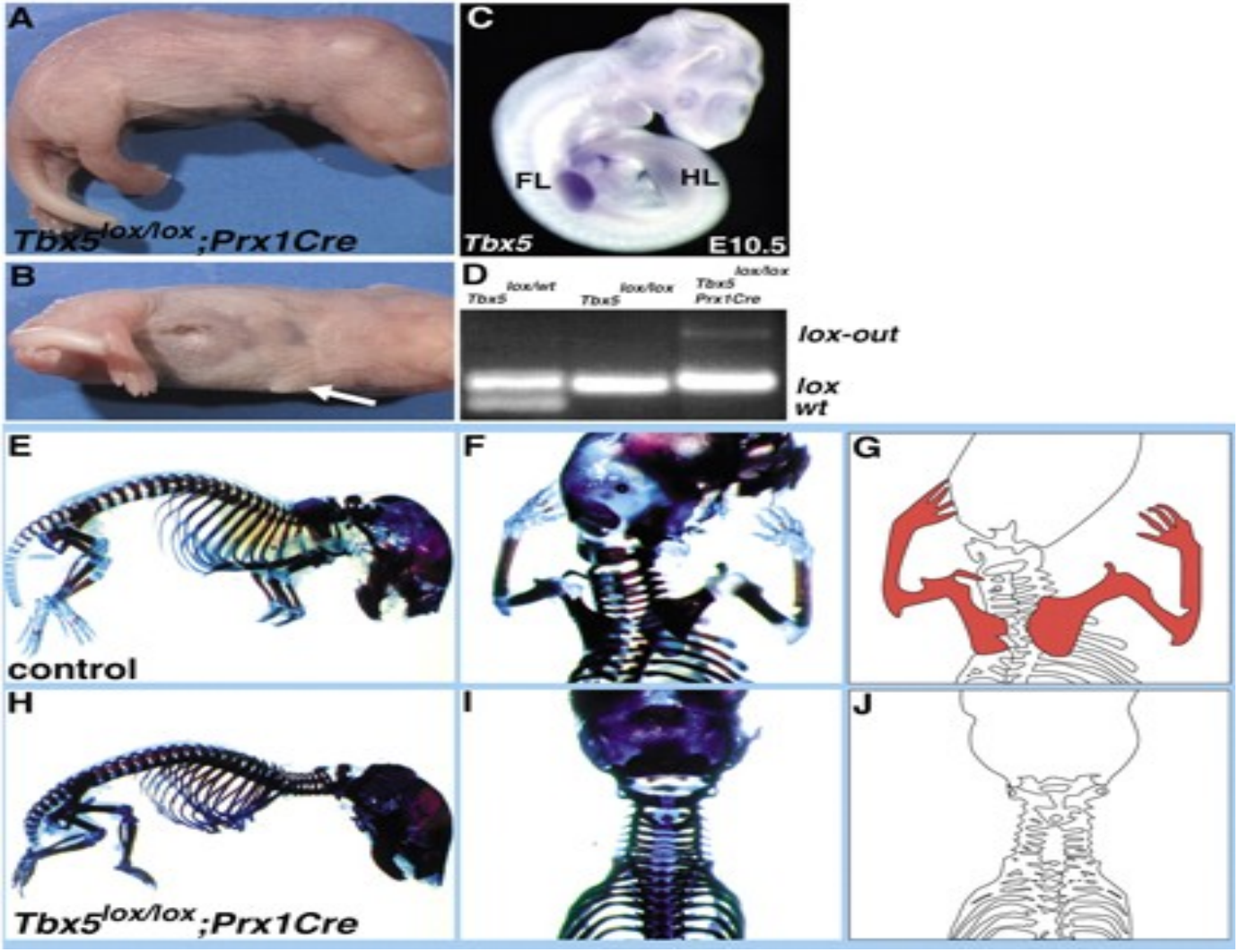


FIG. 1 Effects of vitamin A (10 IU) treatment for various times on limb generation from amputated tail stump. *a*, Treatment for 24 h, 3 limbs are generated; *b*, 72 h, 4 limbs; *c* and *d*, 96 h, 2 limbs; *e*, 120 h, 7 limbs; *f*, 120 h, 3 limbs; *g*, 144 h, 3 limbs; *h*, 144 h, 2 limbs, plus an extra pair of limbs below the original hindlimb.



Later came TBX

DNA binding domain derived from the prototype gene called transcription factor T. Limb identity factors Tbx4 (hindlimb) and Tbx5 (forelimb)

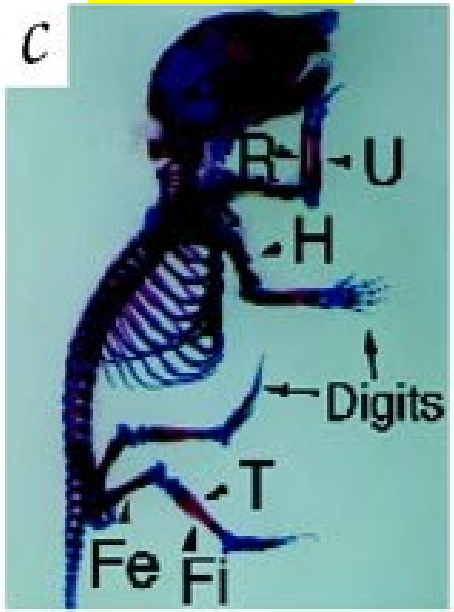


Development 2003;130:2741-51

……followed by FGF10

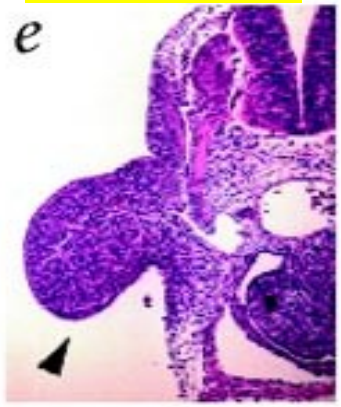
FGF10 → proliferace mesodermu → růst končetinového pupene

Wild-type

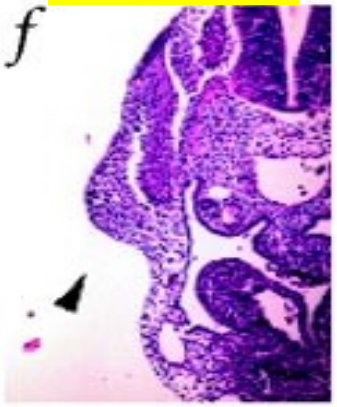


Fgf10$^{-/-}$

Wild-type



Fgf10$^{-/-}$

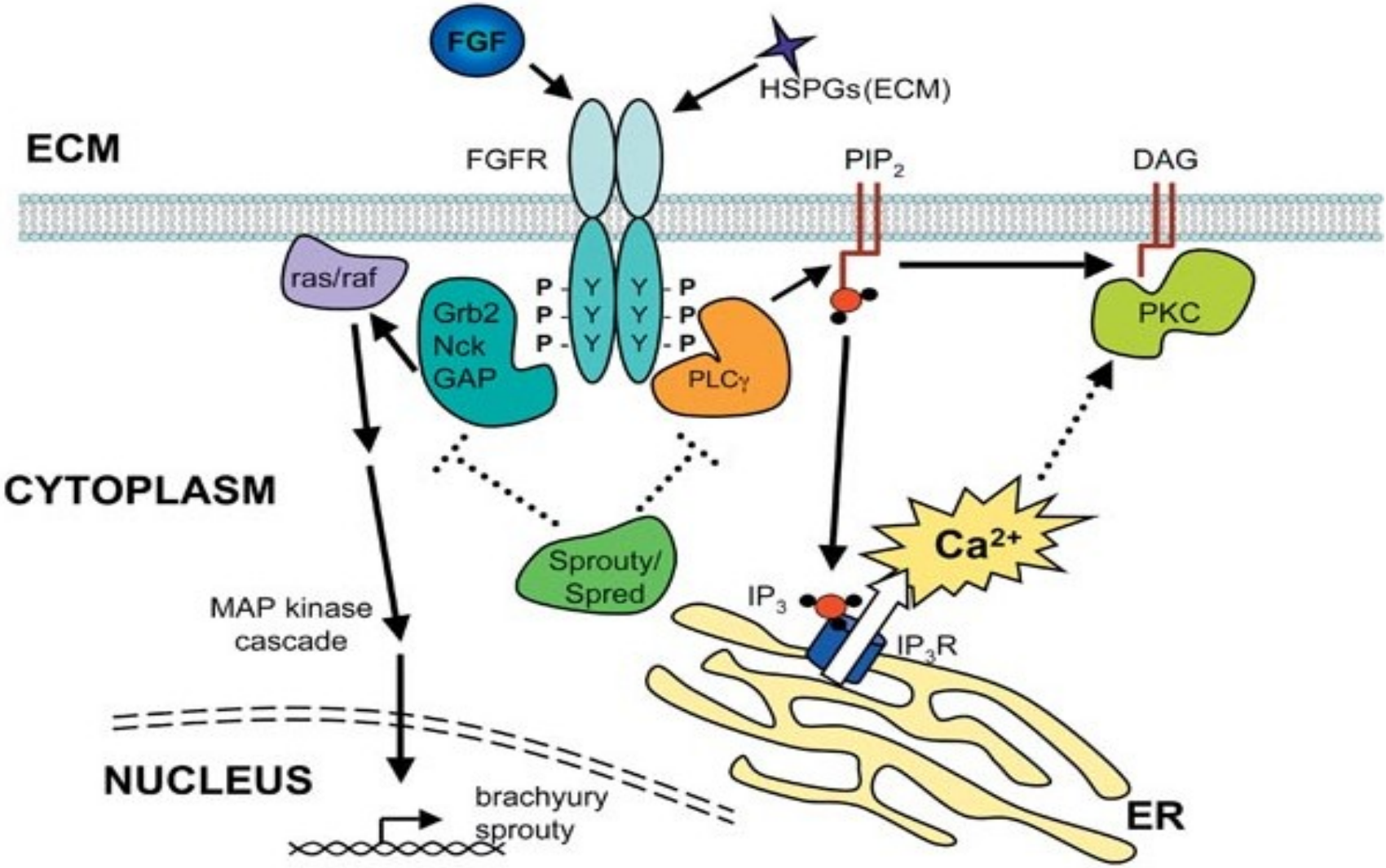


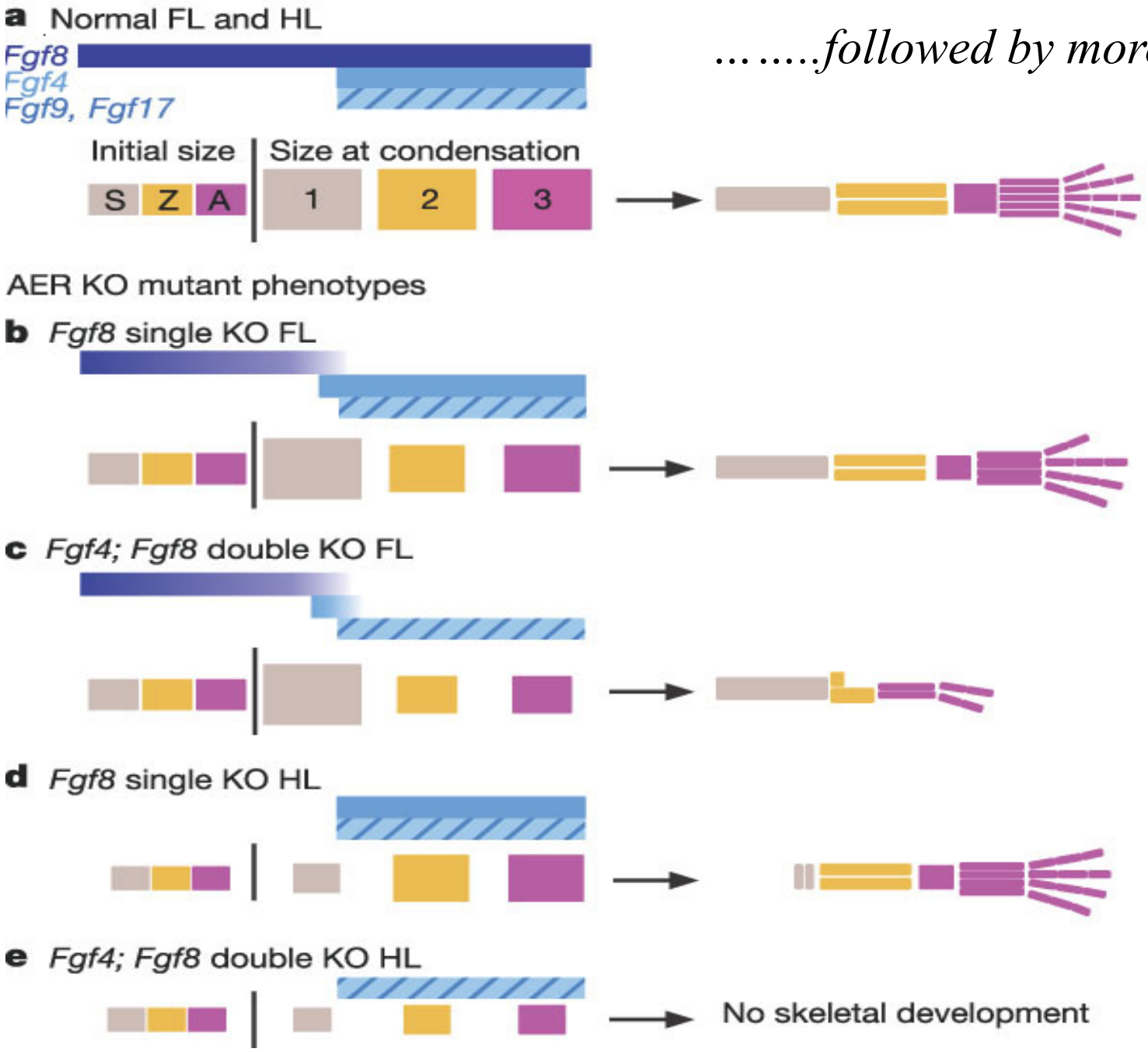
Fgf-10 is required for both limb and lung development and exhibits striking functional similarity to Drosophila branchless

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

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

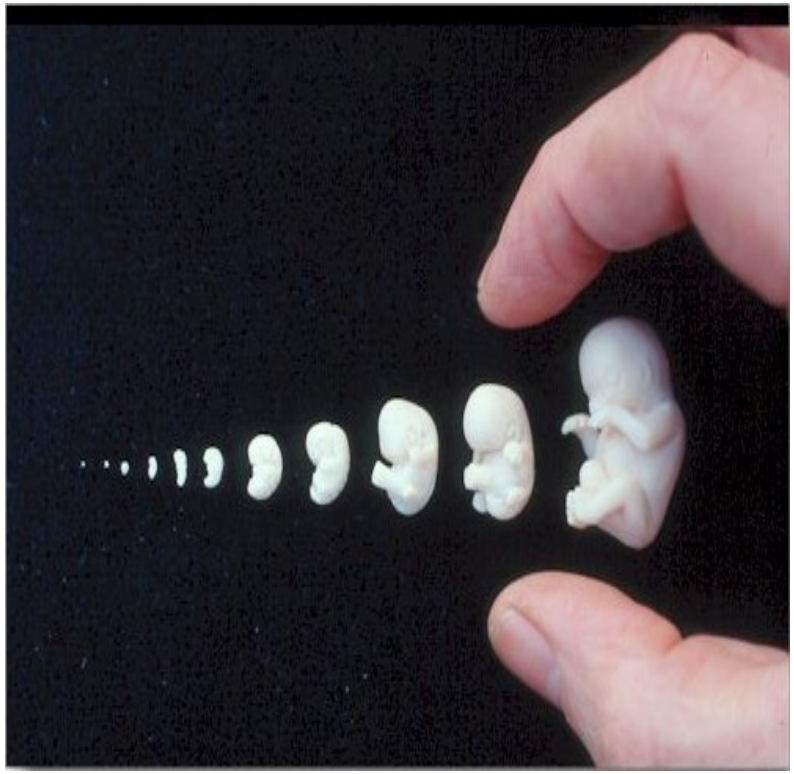




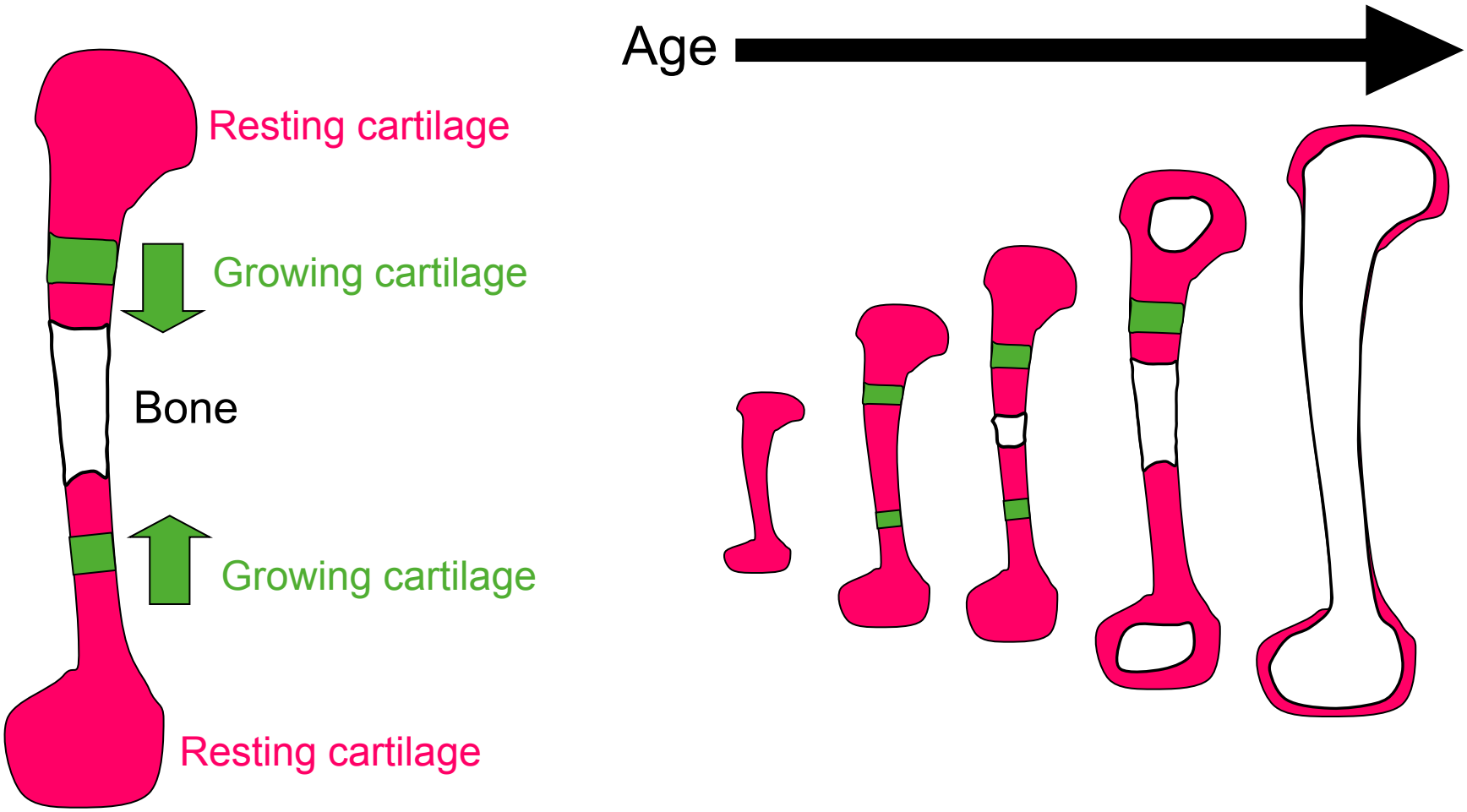
…….followed by more FGF

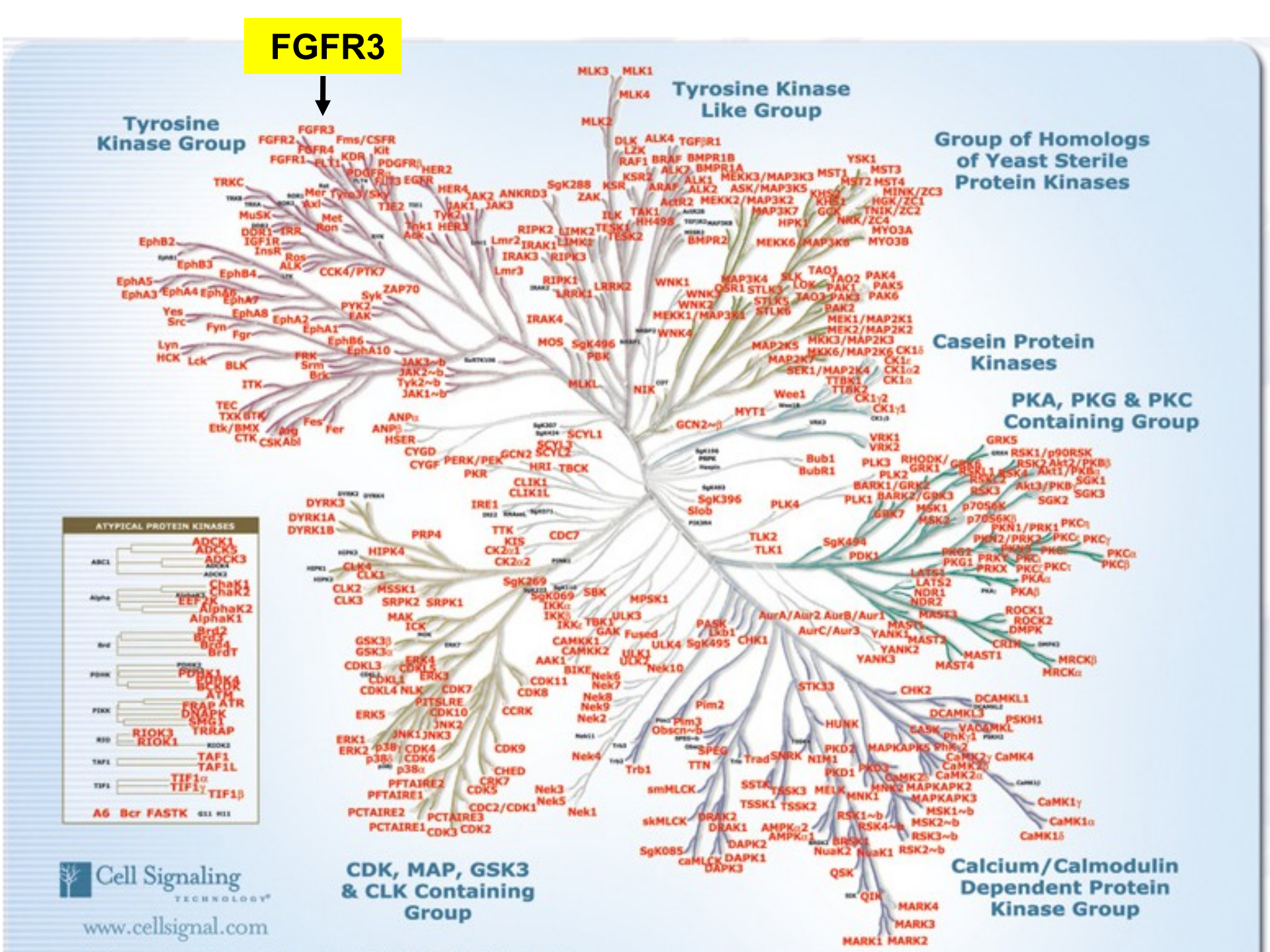
G. Martin

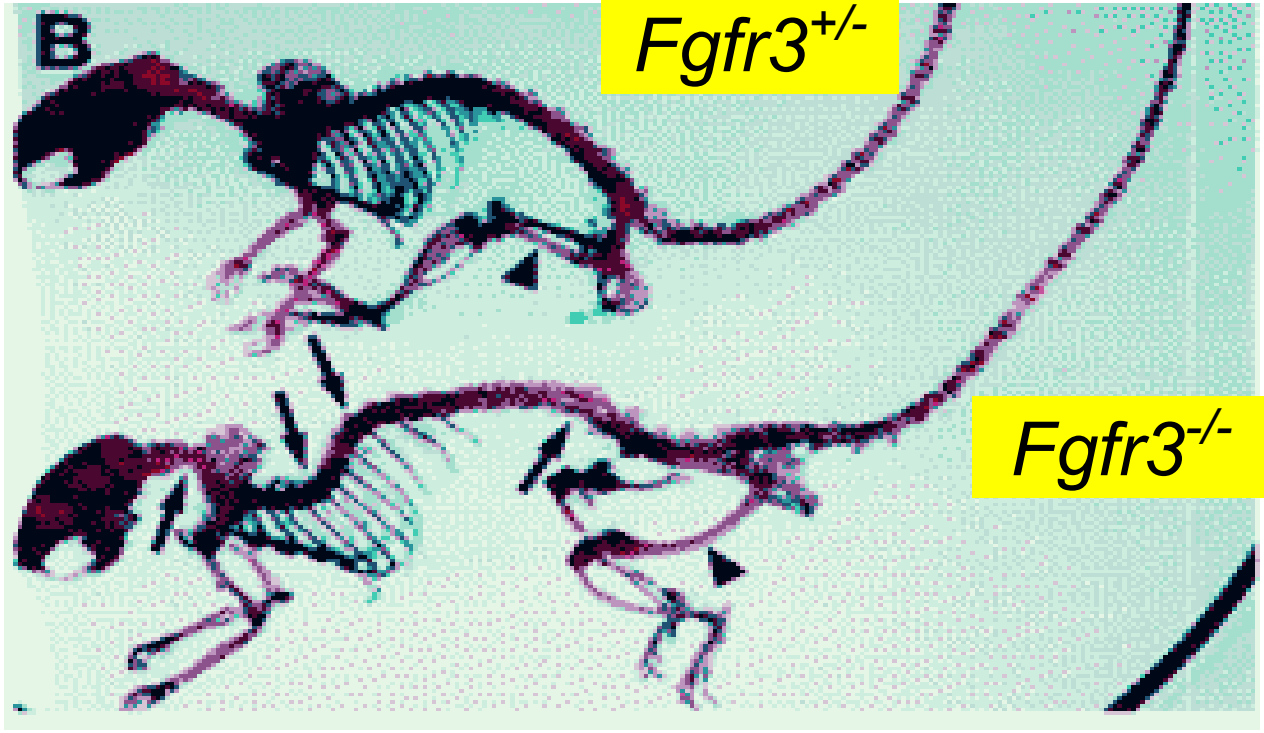
Pattern and Shape vs. Growth and Proportions

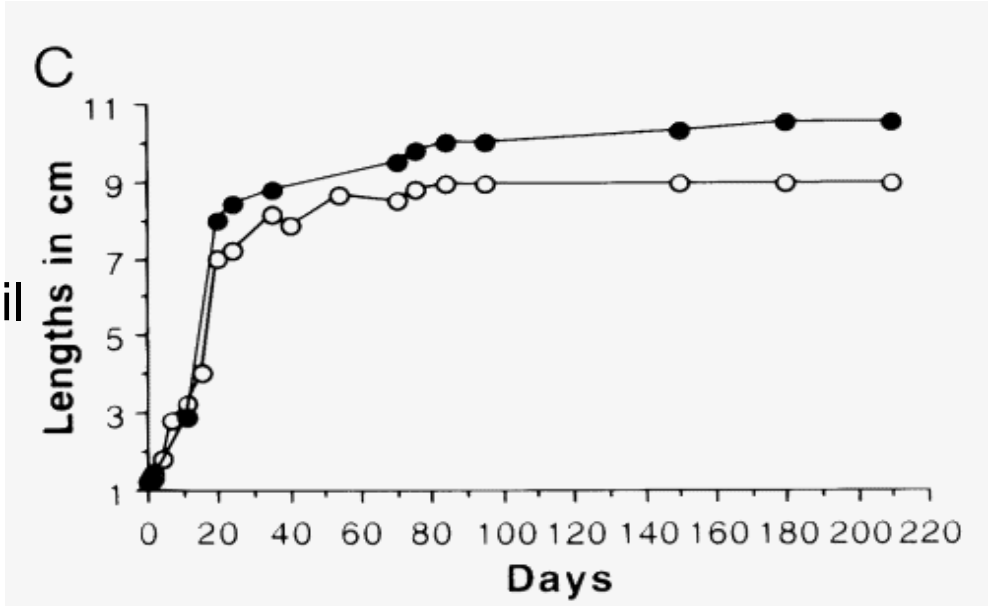


x 10^9 =


Resting cartilage
Growing cartilage
Bone
Growing cartilage
Resting cartilage
Age


FGFR3
Tyrosine Kinase Group
Tyrosine Kinase Like Group
Group of Homologs of Yeast Sterile Protein Kinases
Casein Protein Kinases
PKA, PKG & PKC Containing Group
CDK, MAP, GSK3 & CLK Containing Group
Calcium/Calmodulin Dependent Protein Kinase Group
ATYPICAL PROTEIN KINASES
Cell Signaling TECHNOLOGY
www.cellsignal.com





Tail

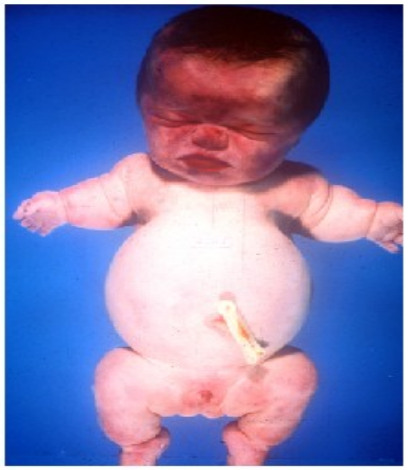
Fgfr3+/-
Fgfr3-/-

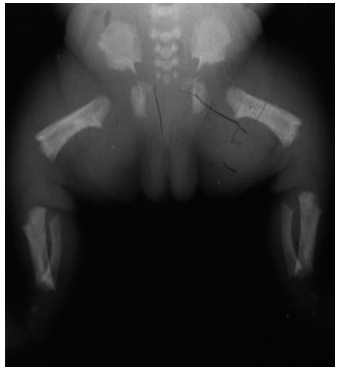
Cell 1996, 84(6):911-21.

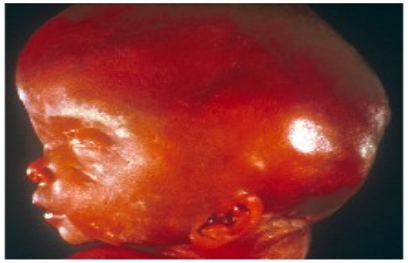
FGFR3-related skeletal dysplasias

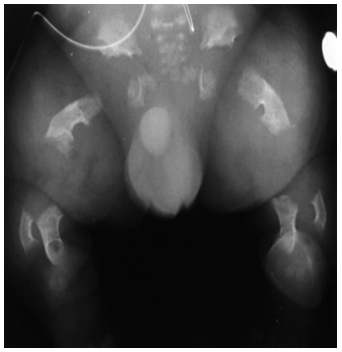
Achondroplasia

Thanatophoric Dysplasia









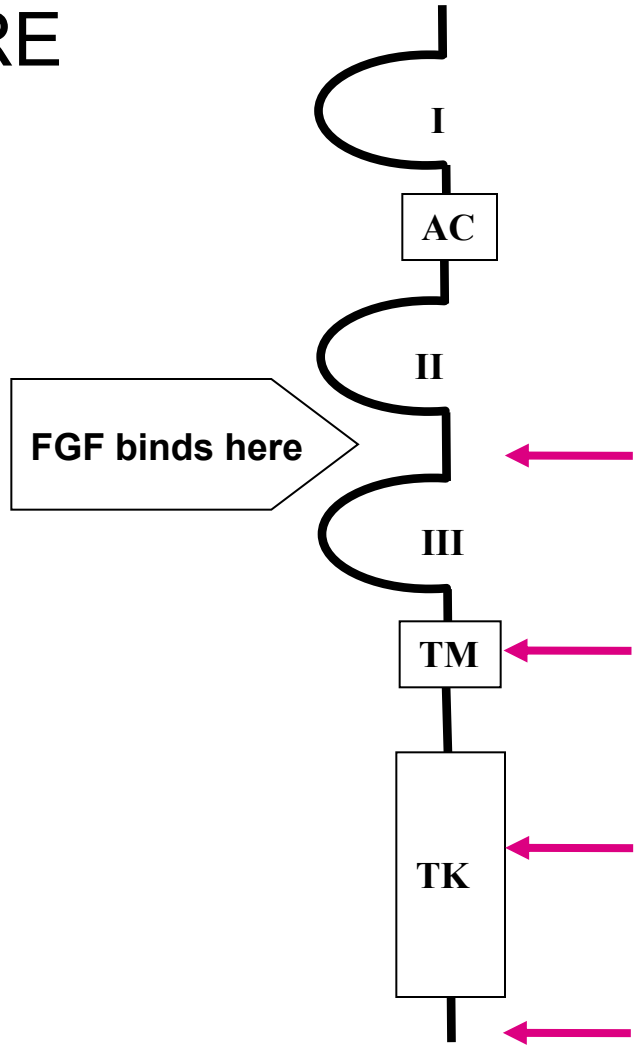
- short long bones
- brachydactyly
- macrocephaly
- low nasal bridge
- spinal stenosis
- temporal lobe malformations

Nat Genet 1995, 9:321-8.

FGFR3-related skeletal dysplasia

STATURE

Hypochondroplasia
Achondroplasia
SADDAN
Thanatophoric Dysplasia



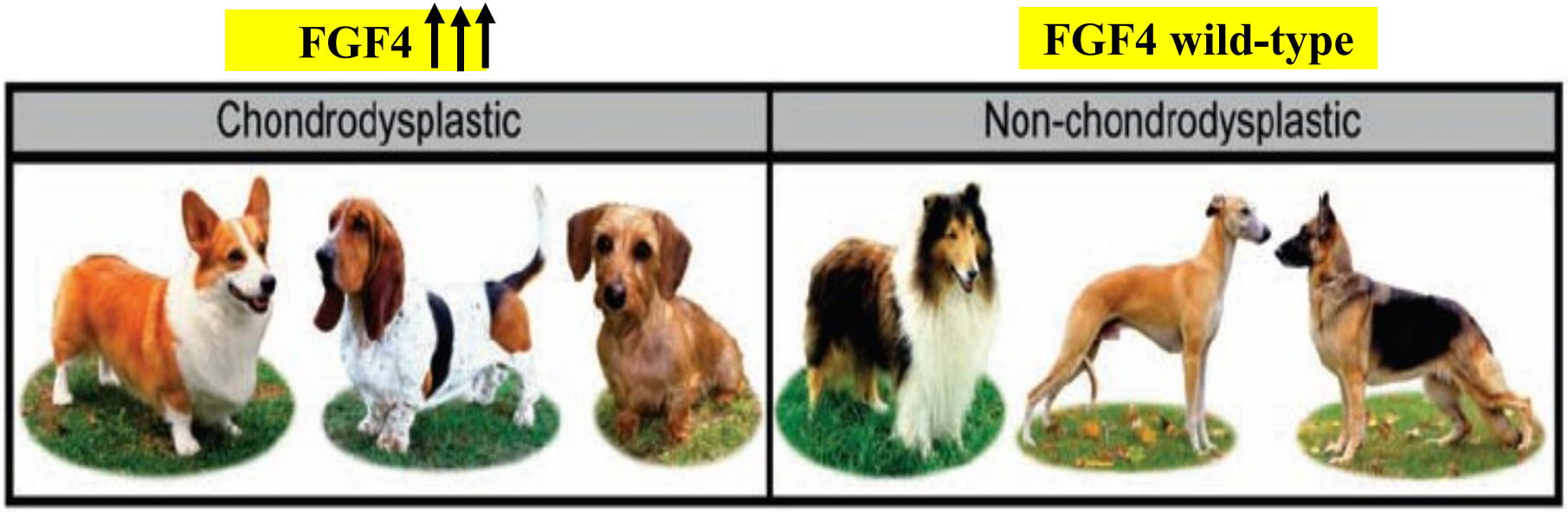
An Expressed *Fgf4* Retrogene Is Associated with Breed-Defining Chondrodysplasia in Domestic Dogs

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



Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas

epithelia (data not shown), we examined the expression and mutational status of *FGFR3* in a series of bladder and cervix carcinomas to determine whether FGFR3 is involved in epithelial tumorigenesis.

We assessed transcript levels of the two *FGFR3* variants[14], *FGFR3b* and *FGFR3c*,

Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3

Marta Chesi[1], Elena Nardini[2], Leslie A. Brents[1], Evelin Schröck[3], Thomas Ried[3], W. Michael Kuehl[1] & P. Leif Bergsagel[2]

Activating mutations in *FGFR3* and *HRAS* reveal a shared genetic origin for congenital disorders and testicular tumors

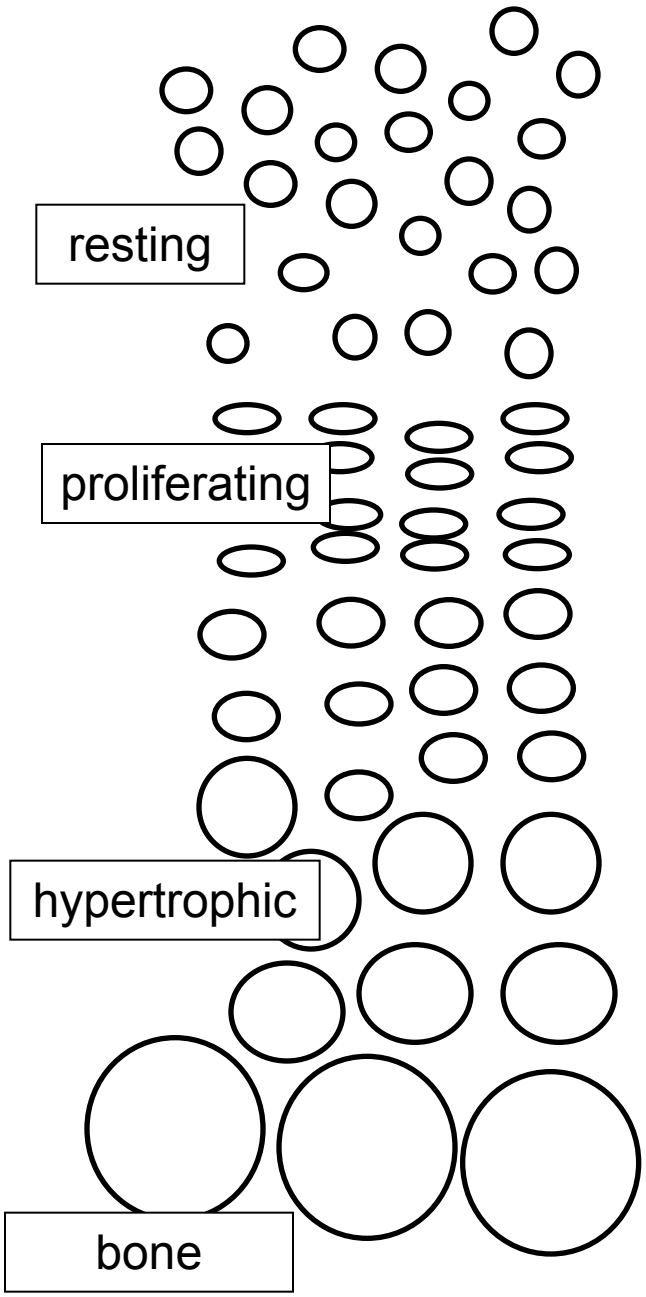
Anne Goriely[1], Ruth M S Hansen[1], Indira B Taylor[1], Inge A Olesen[2], Grete Krag Jacobsen[3], Simon J McGowan[4], Susanne P Pfeifer[5], Gilean A T McVean[5], Ewa Rajpert-De Meyts[2] & Andrew O M Wilkie[1]

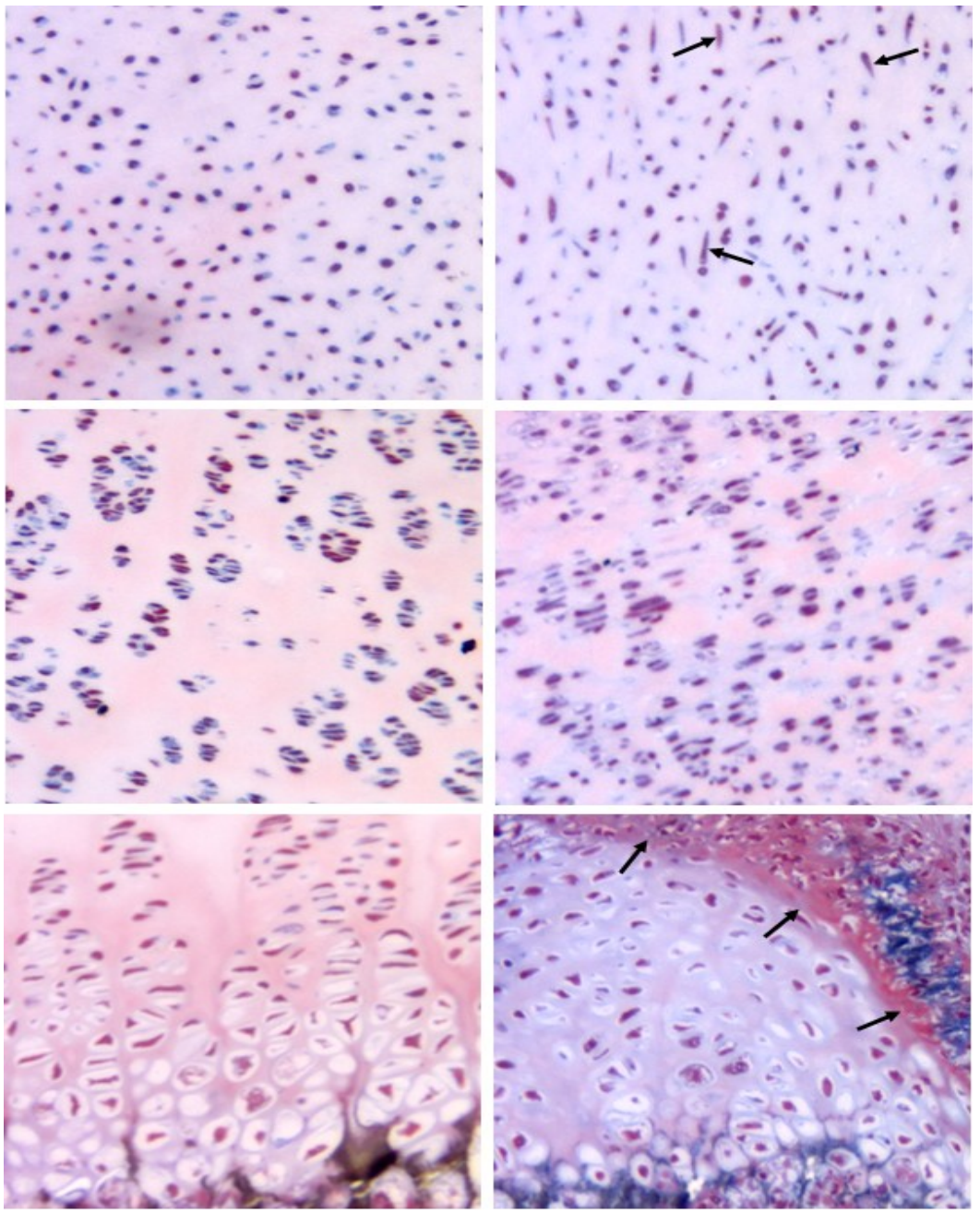
Skeleton: hypochondroplasia, achondroplasia, thanatophoric dysplasia, SADDAN, Muenke syndrome

Skin: epidermal nevi, seborrhaeic keratosis, acanthosis nigricans

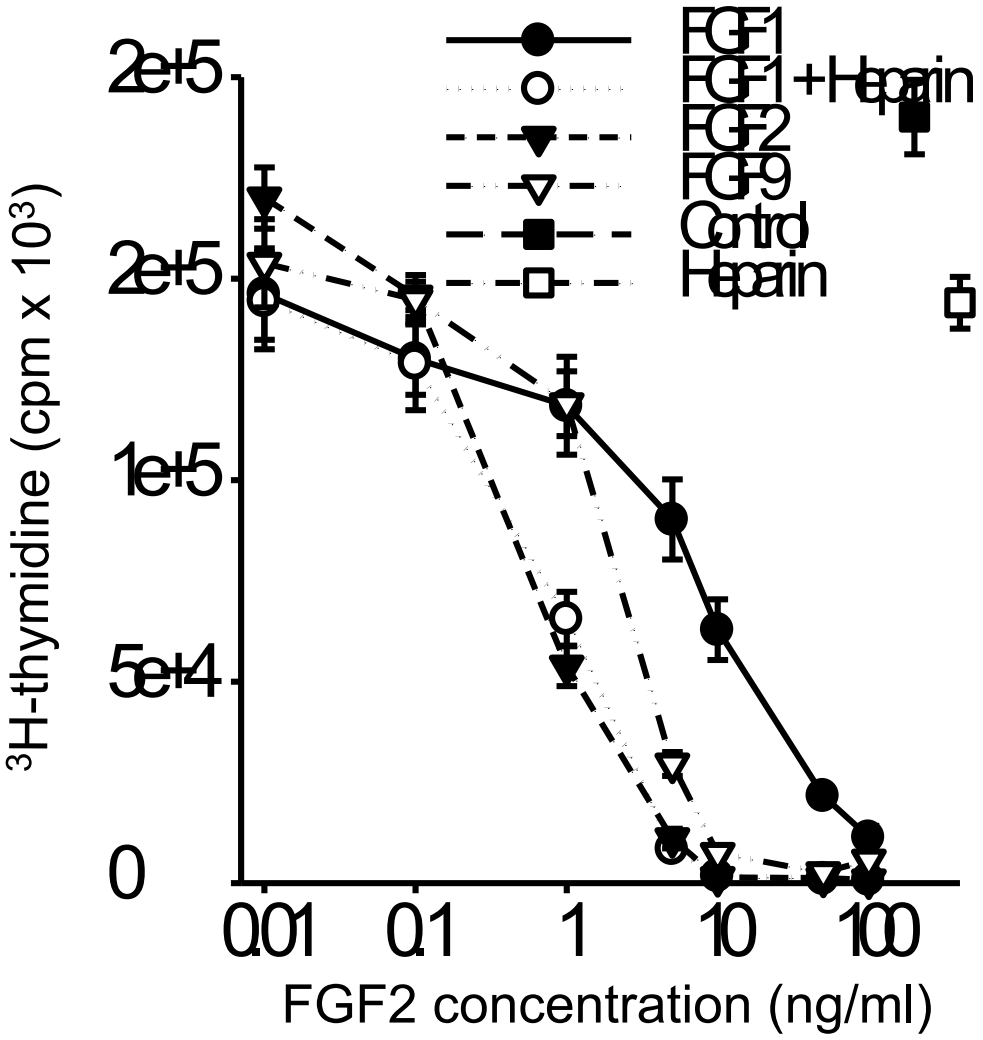
Cancer: multiple myeloma, bladder cancer, seminoma, other.

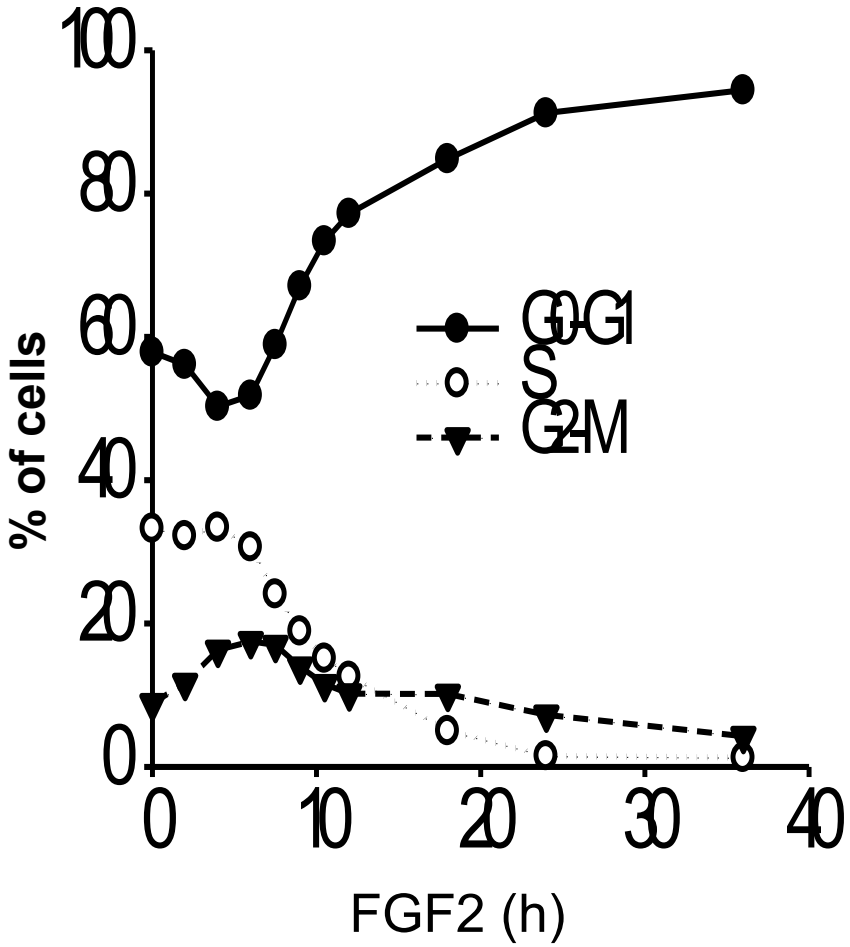
Exp Cell Res. 2004;297:152-64.
J Cell Sci. 2005; 118: 5089-100.
J Biol Chem. 2007 ;282:2929-36.
Pediatr Res. 2007; 61(3):267-72.
Invest New Drugs 2007; 25:391-95.
PLoS One 2008; 3:e3961.
J Cell Sci 2008; 121:272-81.
Cell Signal 2009; 21:151-60.
Hum Mol Genet. 2009; 18:227-40.
J Biol Chem 2010; 285:20644-53.
Bone 2010; 47:102-10.
Leukemia 2011; 25:538-50.
Human Mutation 2012; 33:29-41.
Am J Hum Genet. 2012;90(3):550-7.
PLoS One. 2012;7(4):e35826.
J Clin Invest. 2012;122(6):2153-64.
PLoS One. 2014;9(1):e86470.
Mutat Res Rev. 2014 Jan-Mar;759:40-8.


resting
proliferating
hypertrophic
bone


healthy
TD

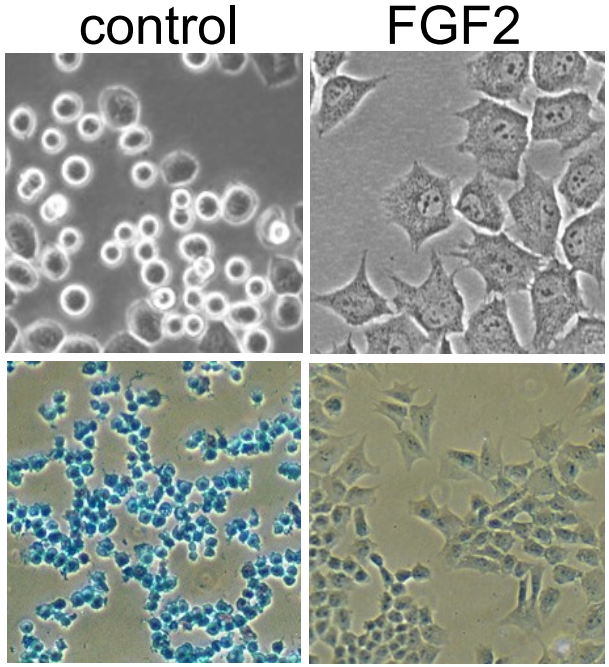
FGFR3 inhibits chondrocyte proliferation by arresting their cell cycle in G1 phase

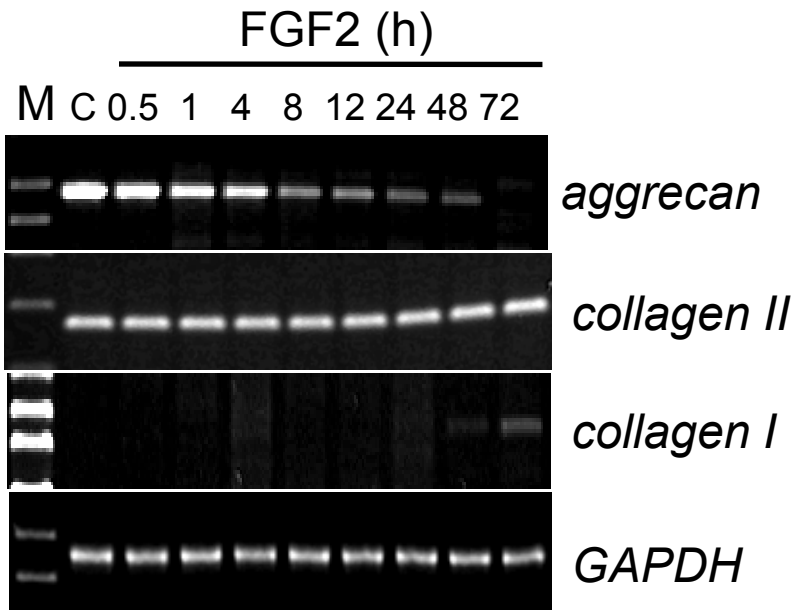


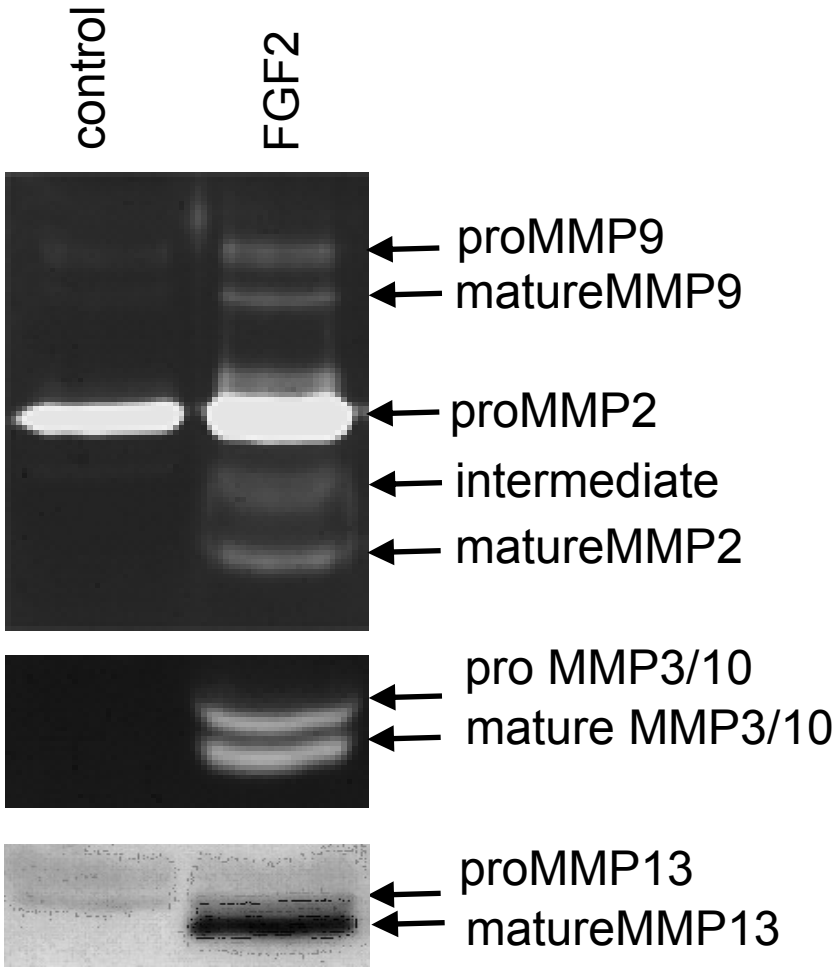


Exp Cell Res 2004, 297:152-64.

FGFR3 alters the cartilage-like phenotype of chondrocytes

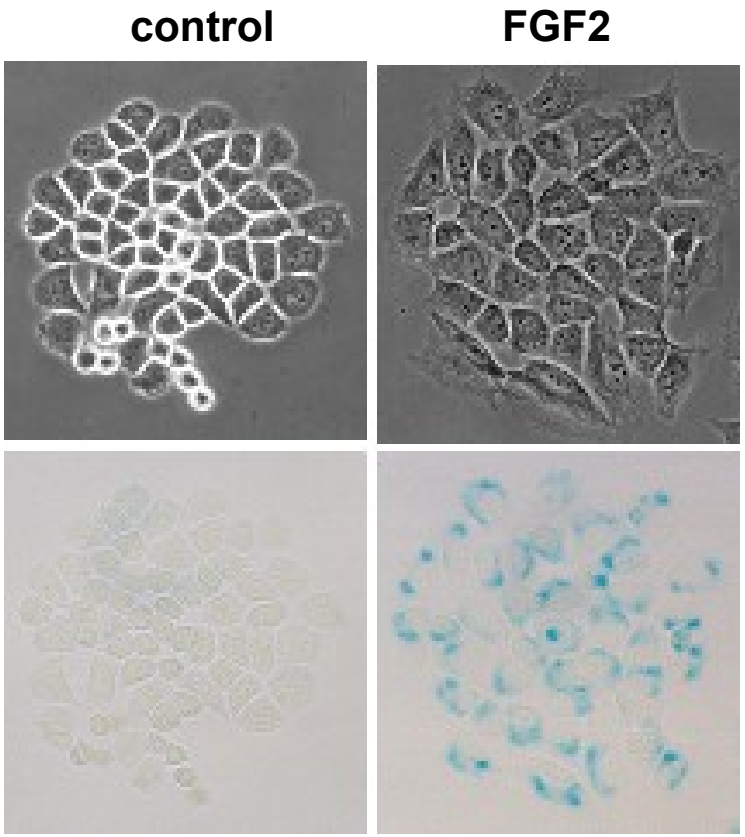


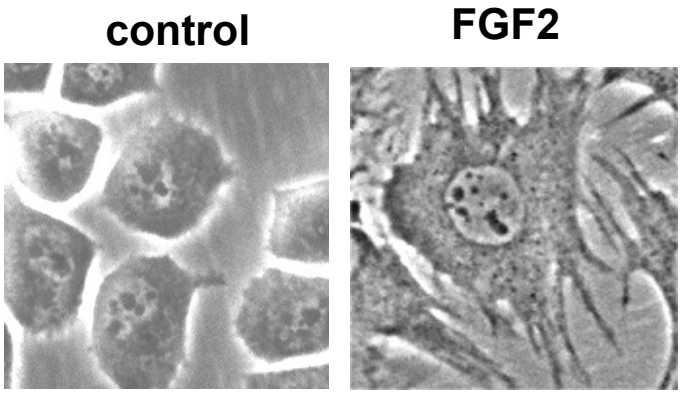


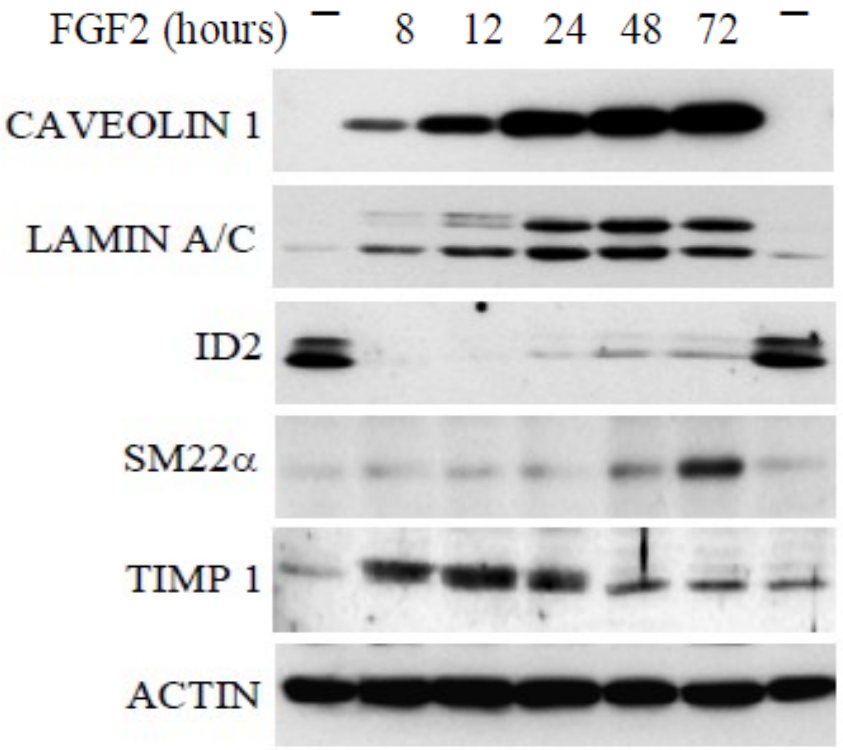


J Cell Sci. 2005; 118: 5089-100.

FGFR3 causes premature senescence in chondrocytes

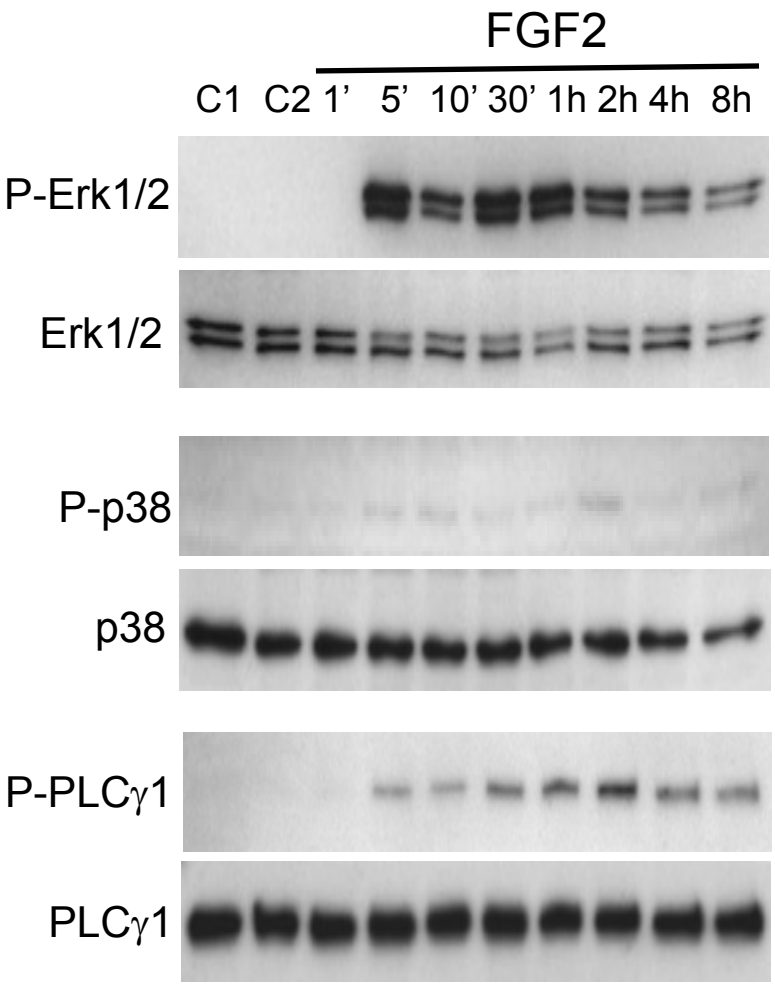


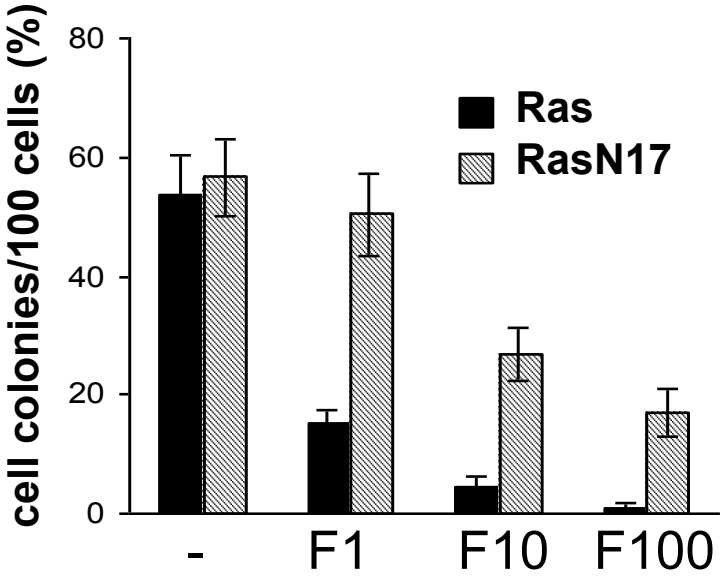


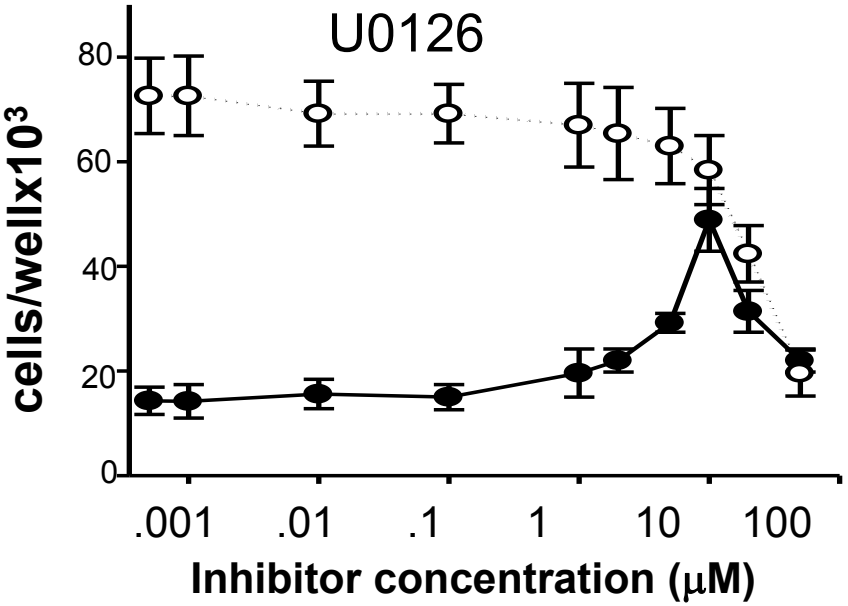


Bone 2010; 47:102-10.

FGFR3 arrests chondrocyte growth via RAS-ERK MAP kinase pathway

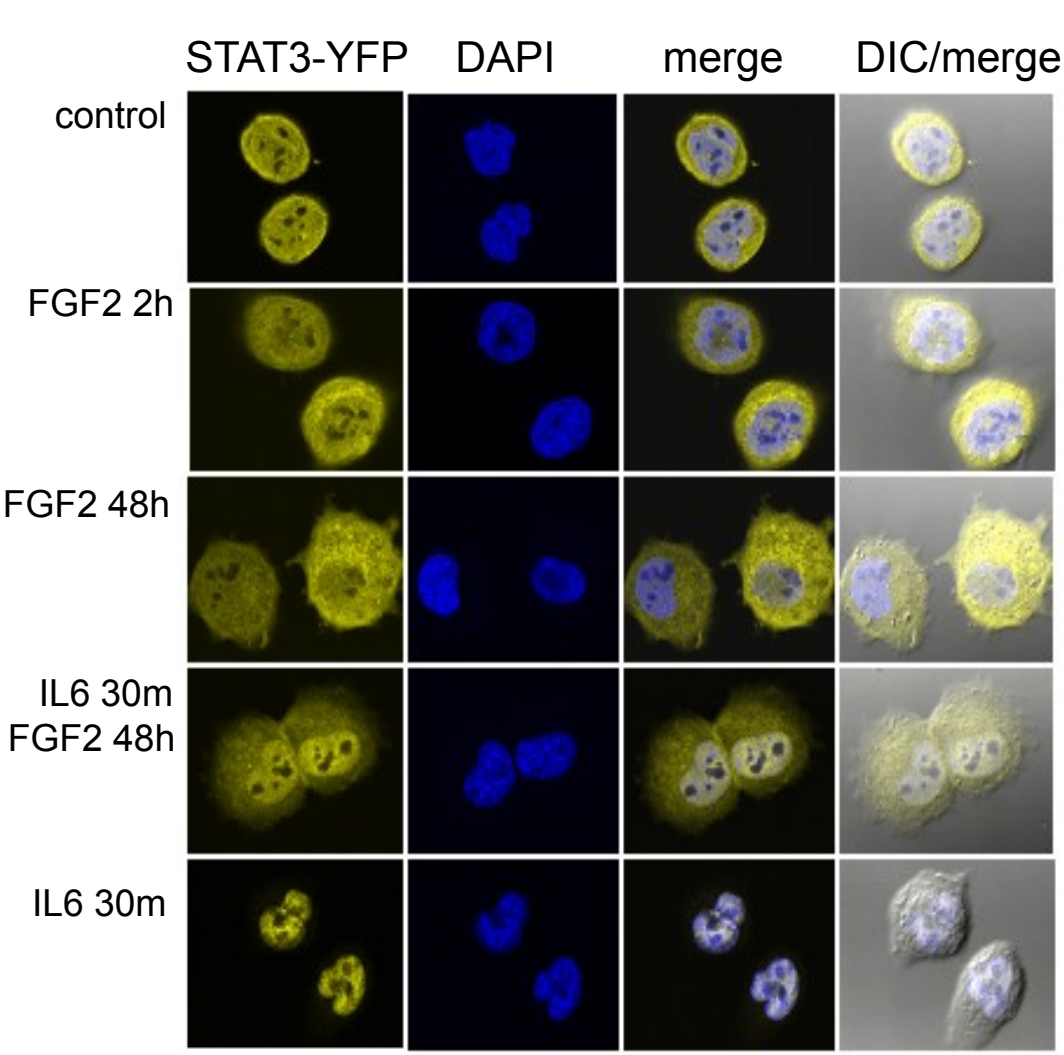


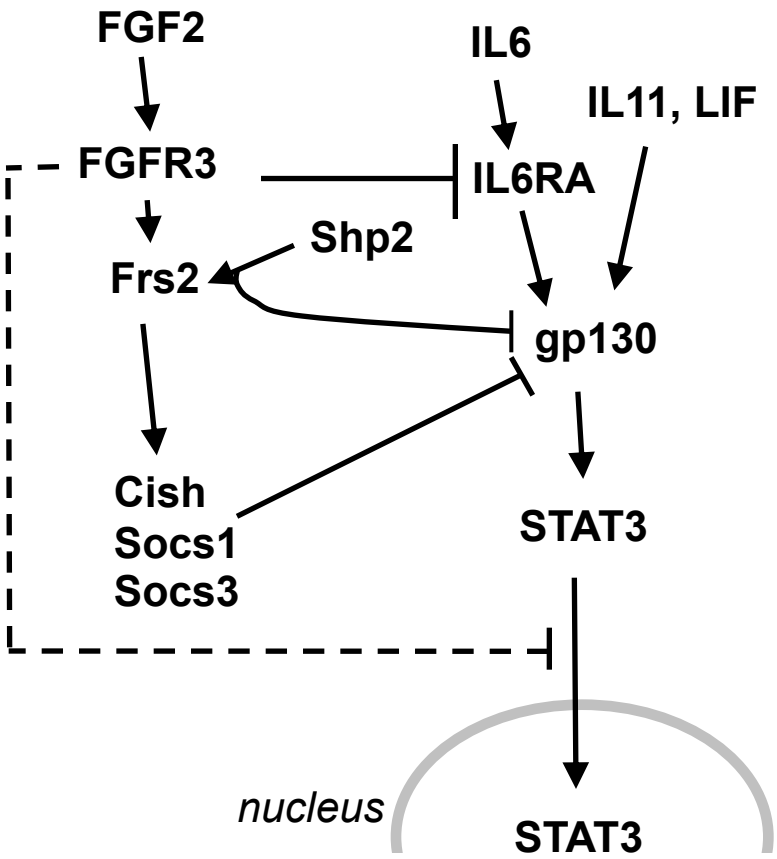




Exp Cell Res 2004, 297:152-64.

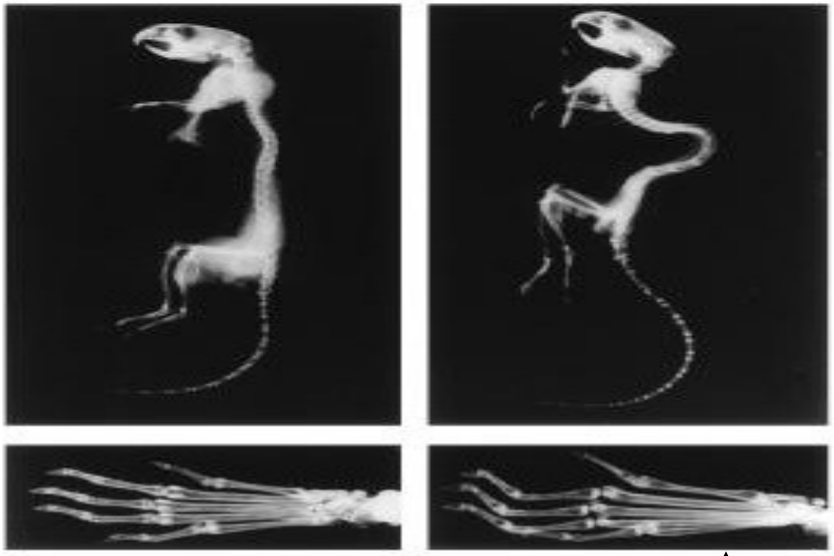
Chronic FGFR3 activation inhibits cytokine/STAT signaling in chondrocytes

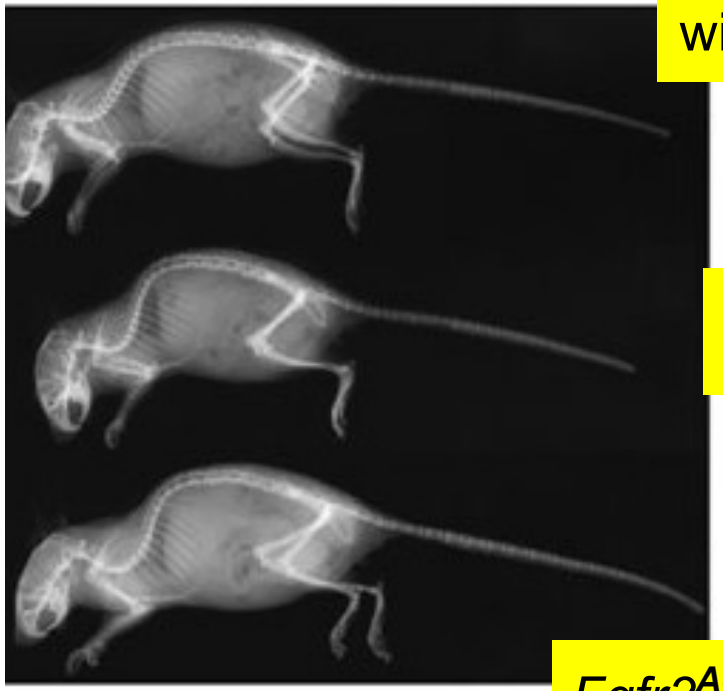




Cell Signal 2009;21:151-60.

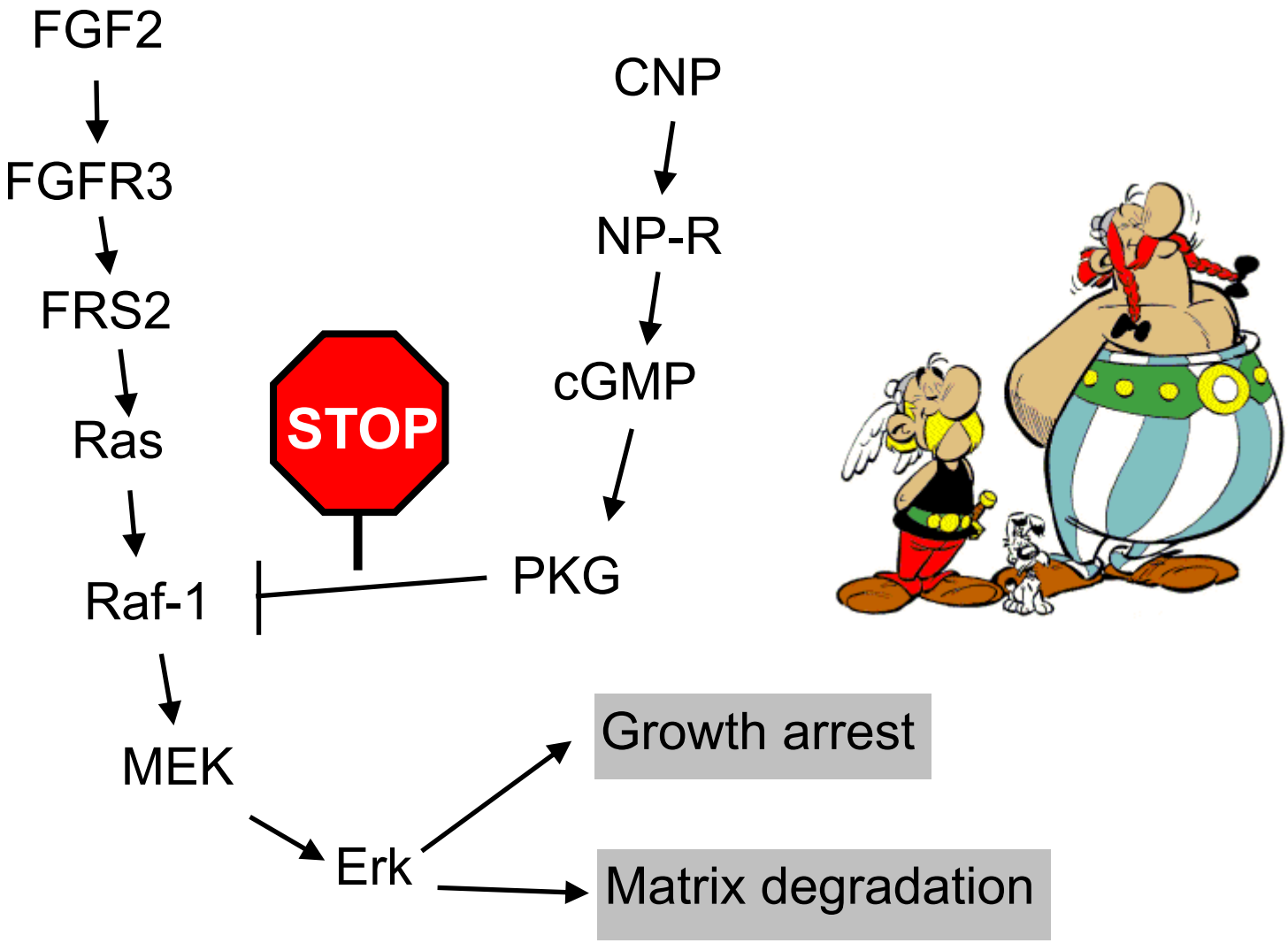
C-natriuretic peptide (CNP)





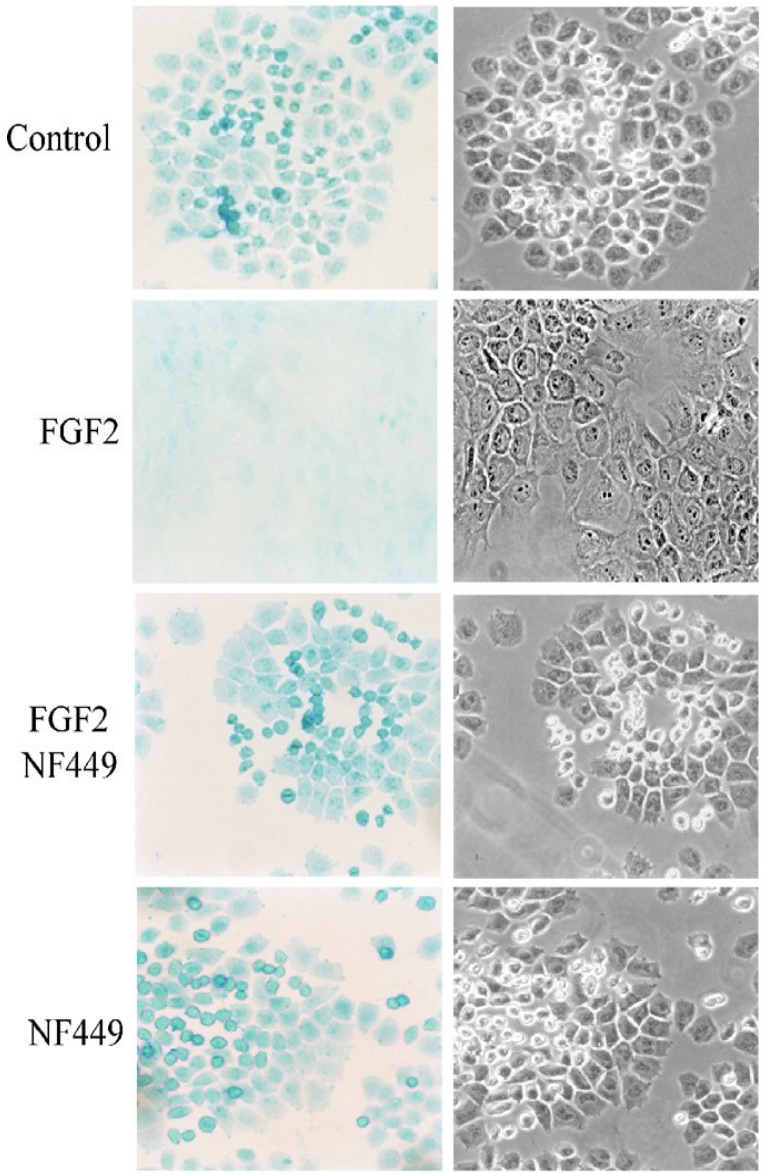
Kazuwa Nakao

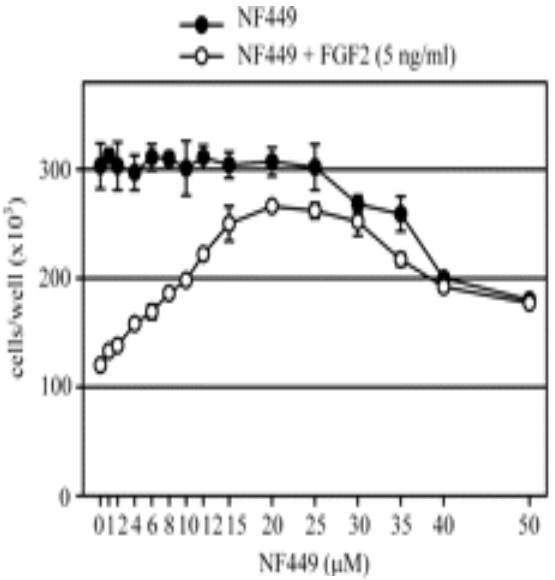
Nature Medicine 10, 80-86 (2004).

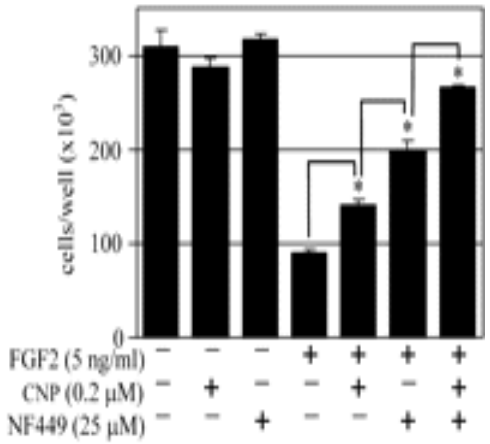


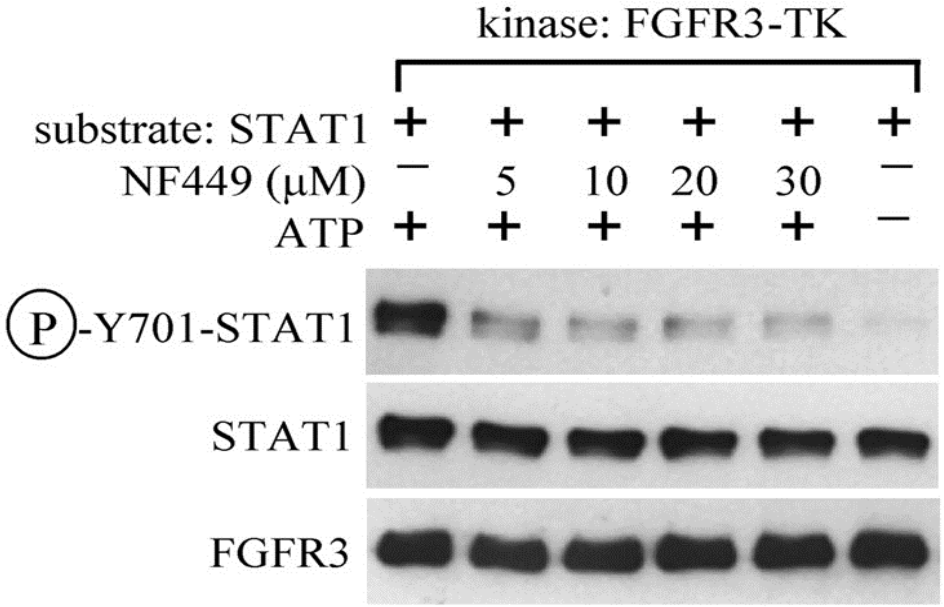
J Cell Sci. 2005; 118: 5089-100.

NF449

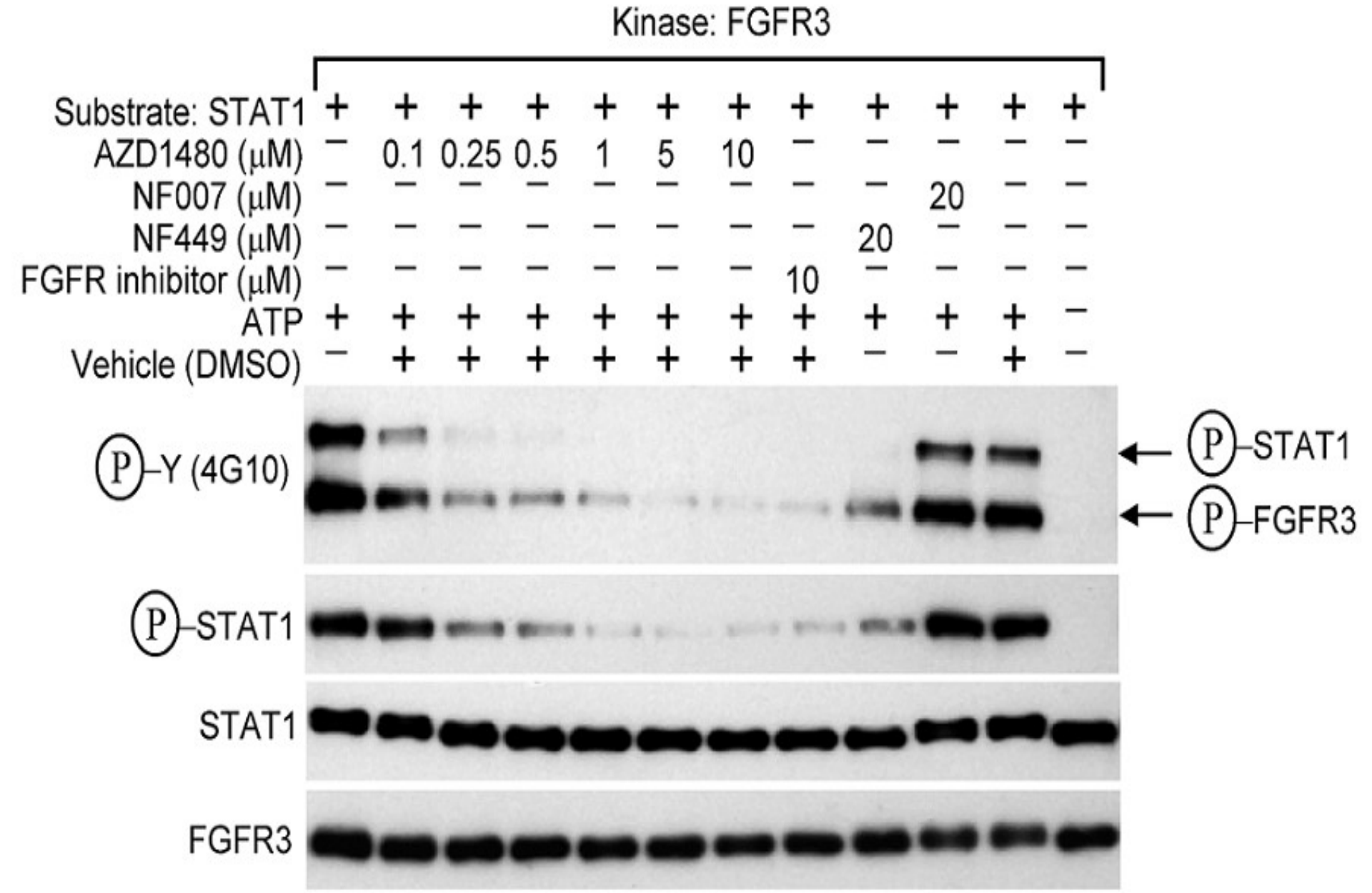








J Biol Chem 2010; 285:20644-53.



Leukemia 2011. *25:538-50.*

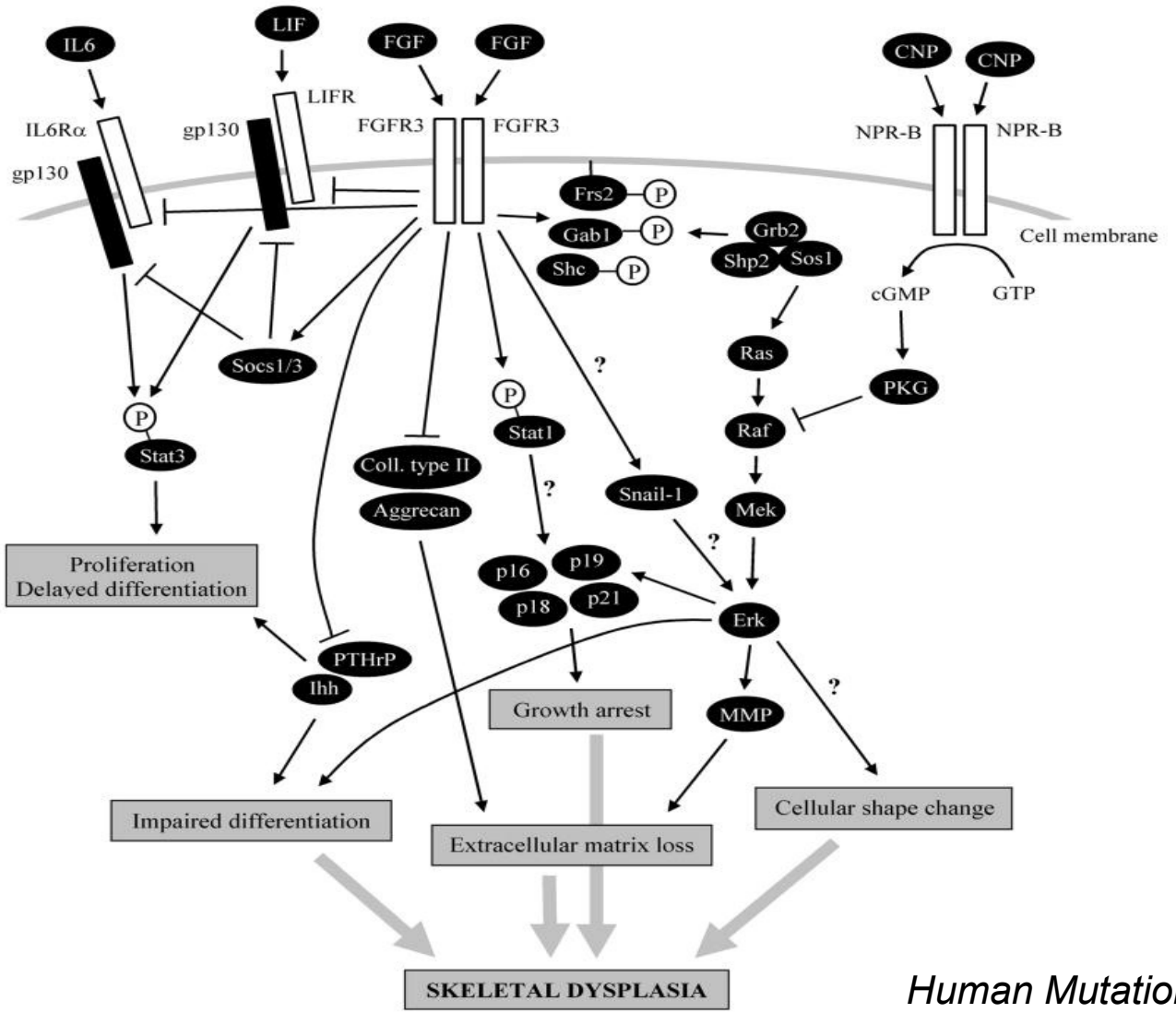
REVIEW

Human Mutation

OFFICIAL JOURNAL
HGVS
HUMAN GENOME VARIATION SOCIETY
www.hgvs.org

Sixteen Years and Counting: The Current Understanding of Fibroblast Growth Factor Receptor 3 (FGFR3) Signaling in Skeletal Dysplasias

Silvie Foldynova-Trantirkova,[1] William R. Wilcox,[2,3] and Pavel Krejci[2,3,4,5]*



Human Mutation 2012; 33:29-41.

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Press Release

BioMarin Initiates Phase 1 Trial for BMN-111 for the Treatment of Achondroplasia

NOVATO, Calif., Feb. 16, 2012 (GLOBE NEWSWIRE) -- BioMarin Pharmaceutical Inc. (Nasdaq:BMRN) announced today the initiation of a Phase 1 study in healthy volunteers for BMN-111, an analog of C-type Natriuretic Peptide (CNP), for the treatment of achondroplasia. The company expects to report results from this trial in the third quarter of 2012.