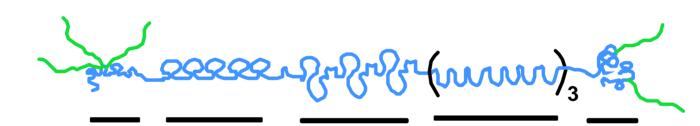
# Fibroblast Growth Factor Binding to Perlecan Isolated from the Growth Plate

#### Perlecan

- Originally identified as a HS containing proteoglycan in basement membranes
- Also present in cartilage as a HS and CS containing proteoglycan (25%HS)
- Has a large, alternately spliced (400-450 kD) multi-domain core protein with GAG chains at both ends

#### Perlecan Structural Model



Domain > **I**Homology > Unique

LDLr

II

Lam A/B

short arm

Ш

NCAM

IV

Lam A/B globular arm

 $\mathbf{V}$ 

GAG chains at Domains I and V

#### Perlecan Knockouts

- Nematode: defective muscle formation resulting in paralysis (unc-52)
- Fruit fly: impaired proliferation of neuroblasts resulting in terribly reduced optic lobes (trol)
- Mouse: defective long bone growth resulting in fetal dwarfism

### Mouse Perlecan KO



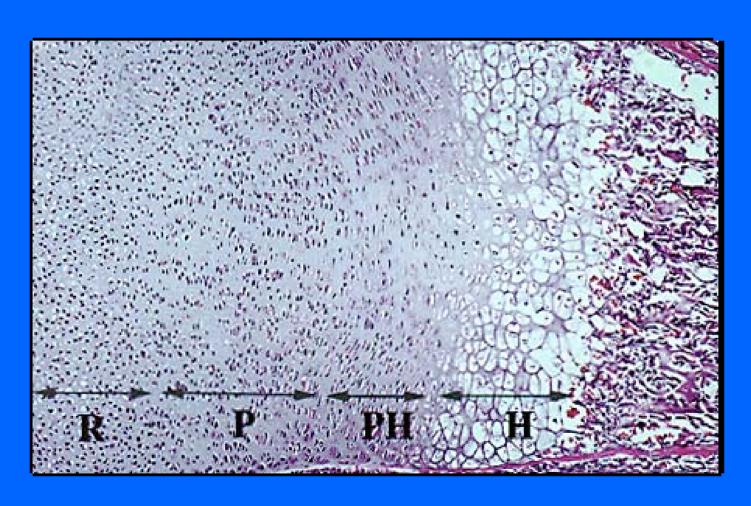
## Forlimbs



+/+

-/-

## Developing Growth Plate



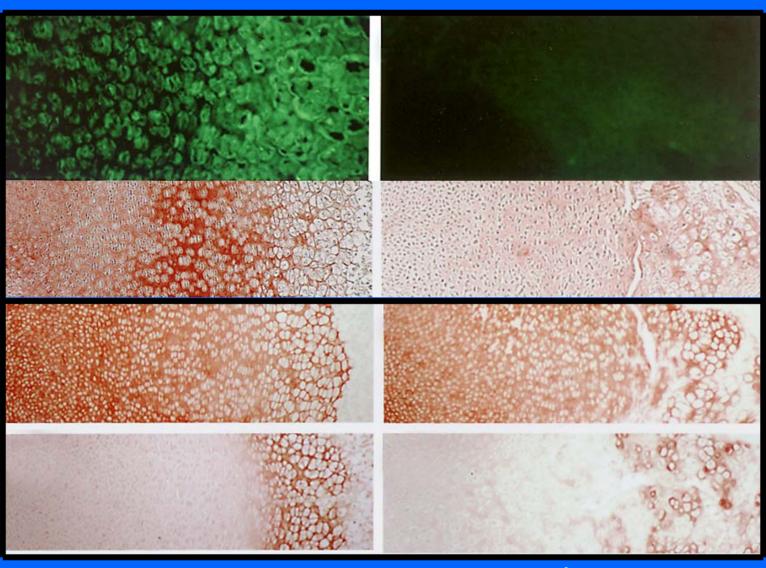
### **Developing Growth Plate**

Perl

Agg

Col II

Col X

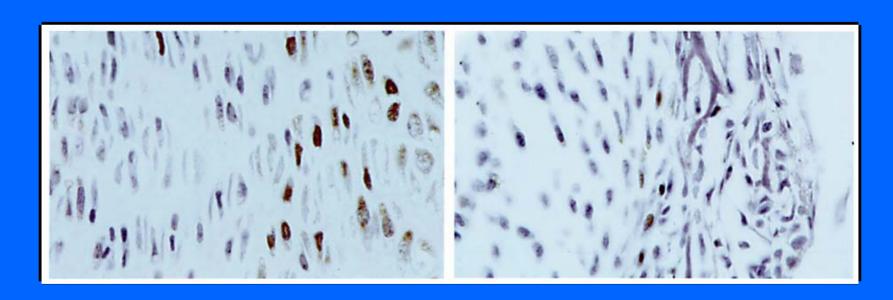


+/+

-/-

### **Developing Growth Plate**

#### **PCNA Staining**



# Mutations in the Human Perlecan Gene (HSPG2)

- Dyssegmental dysplasia, Silverman-Handmaker type
- Schwartz-Jampel syndrome

#### Formation of Cartilage and Bone

**Mesenchymal Cells** Chondrogenesis Cell Aggregation **Chondrocytes** — Cartilage **Quiescence** (resting) Endochondral **Proliferation Ossification** Hypertrophy (Growth Plate) **Apoptosis** 

Bone

Osteoblasts — Matrix Scaffold

# In Vivo Regulation of Chondrocyte Proliferation

**Condition** 

**Phenotype** 

**FGF-2** Transgene

**Short Limbs** 

FGF R3 Null

**Long Limbs** 

**Perlecan Null** 

**Short limbs** 

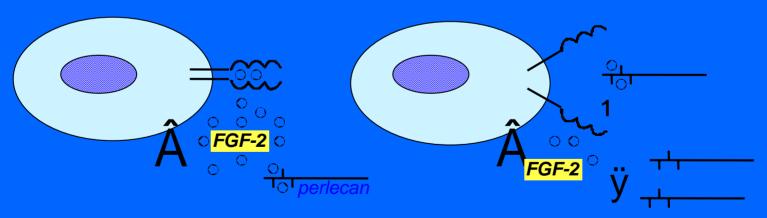
# In order for Perlecan to Stimulate Chondrocyte Proliferation

- Binding of FGF-2 to FGFR-3 would inhibit chondrocyte proliferation
- Perlecan would have to bind to FGF-2
- Perlecan would have to sequester FGF-2 away from FGFR-3

# Growth Plate Chondrocyte Activation by FGF-2 and FGFR-3

resting chondrocyte

proliferating chondrocyte



FGF-2 on receptor cells quiescent

FGF-2 off receptor cells proliferate