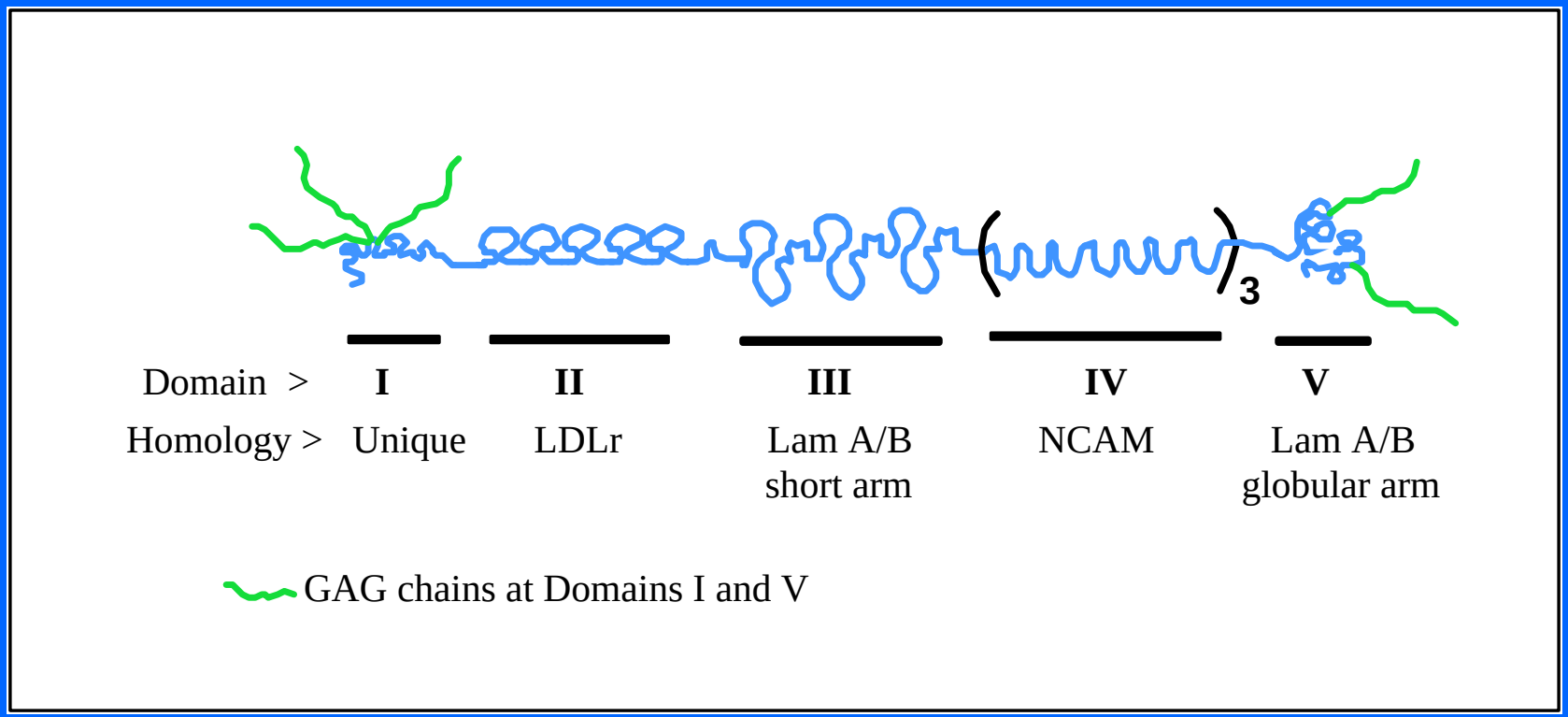
Fibroblast Growth Factor Binding to Perlecan Isolated from the Growth Plate

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

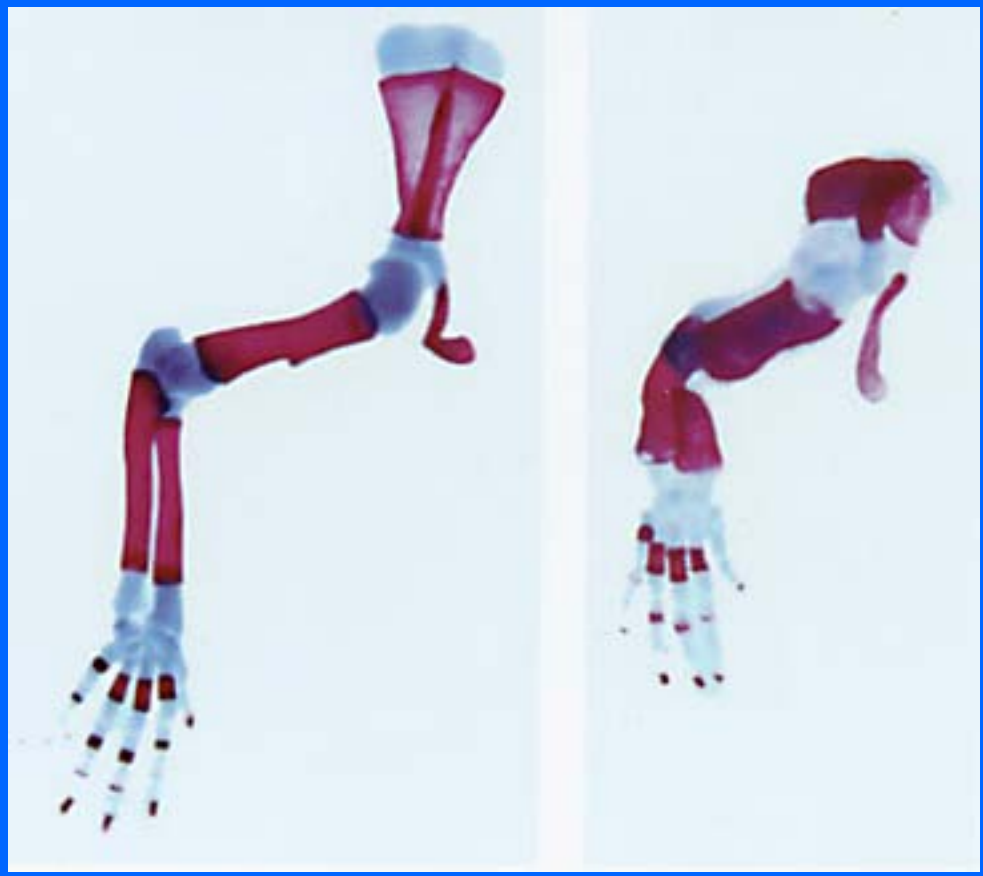


Perlecan Knockouts

- 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

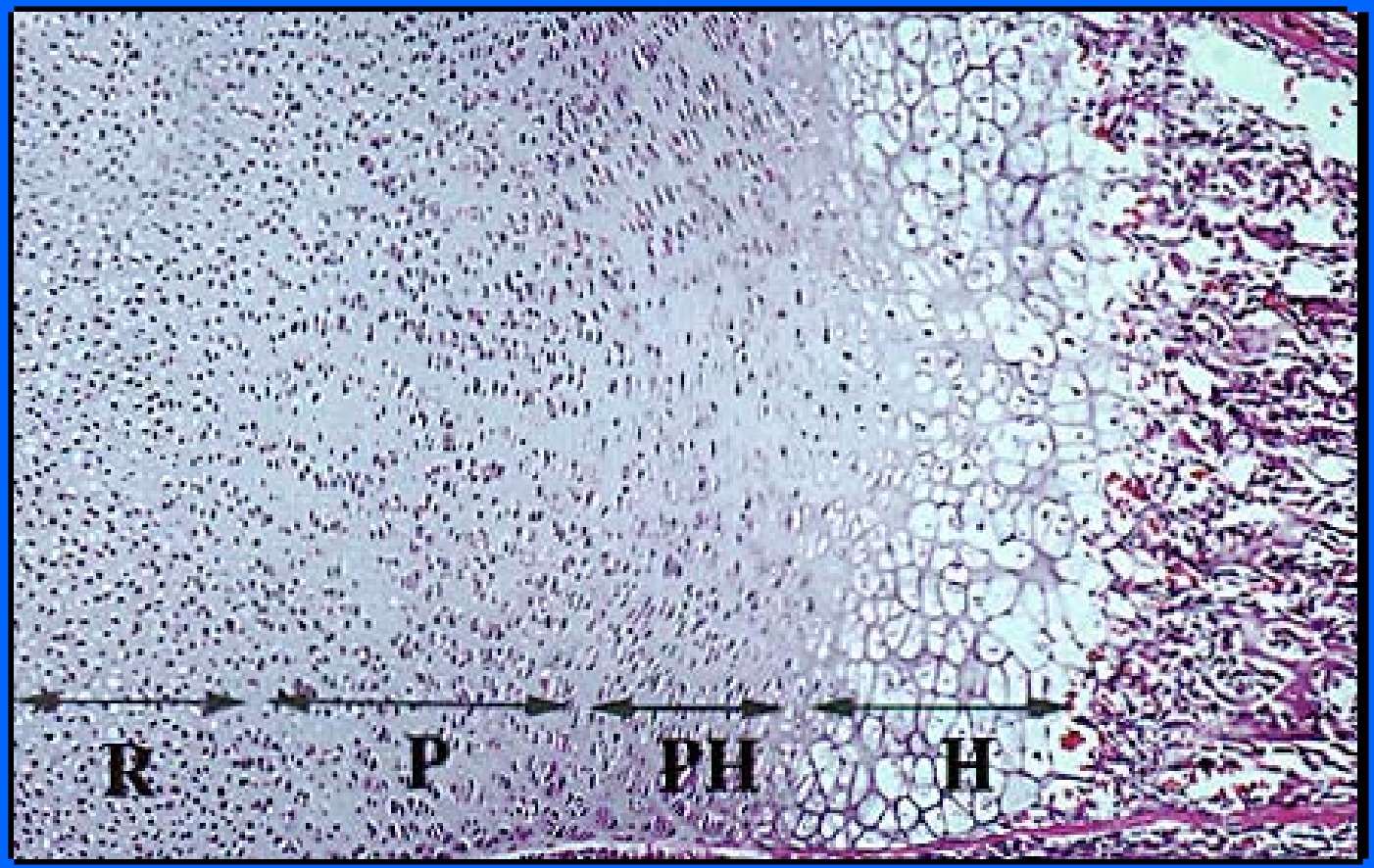
Mouse Perlecan KO

Forlimbs



+/+ -/-

Developing Growth Plate



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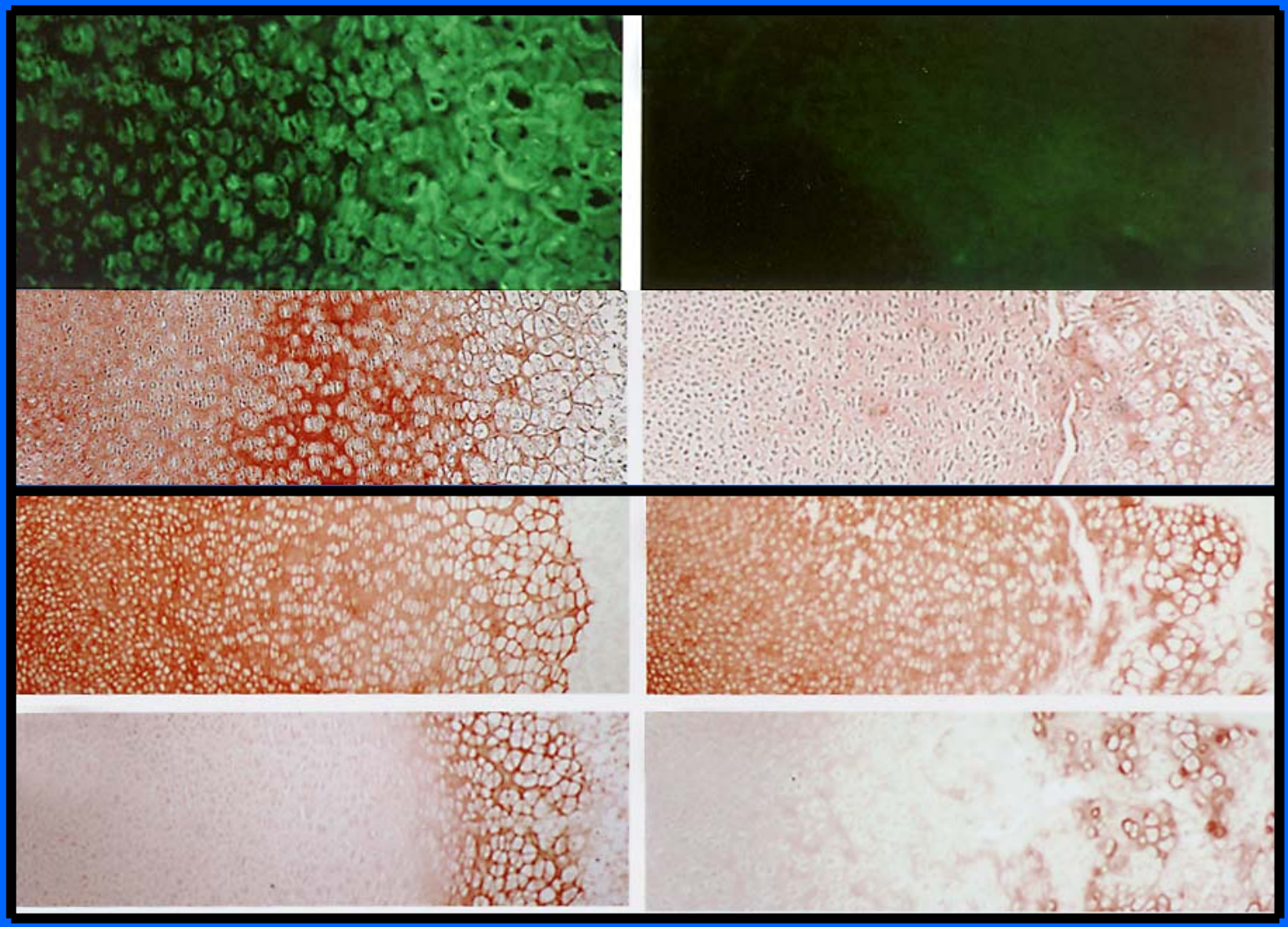
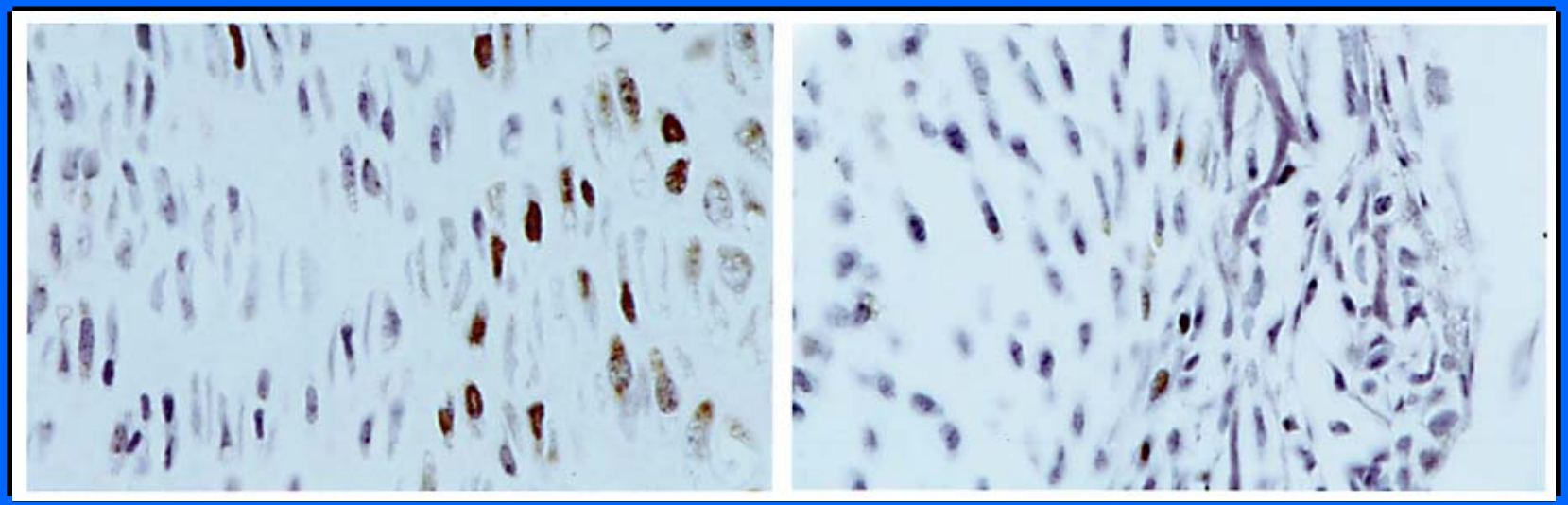
Developing Growth Plate



Developing Growth Plate

PCNA Staining



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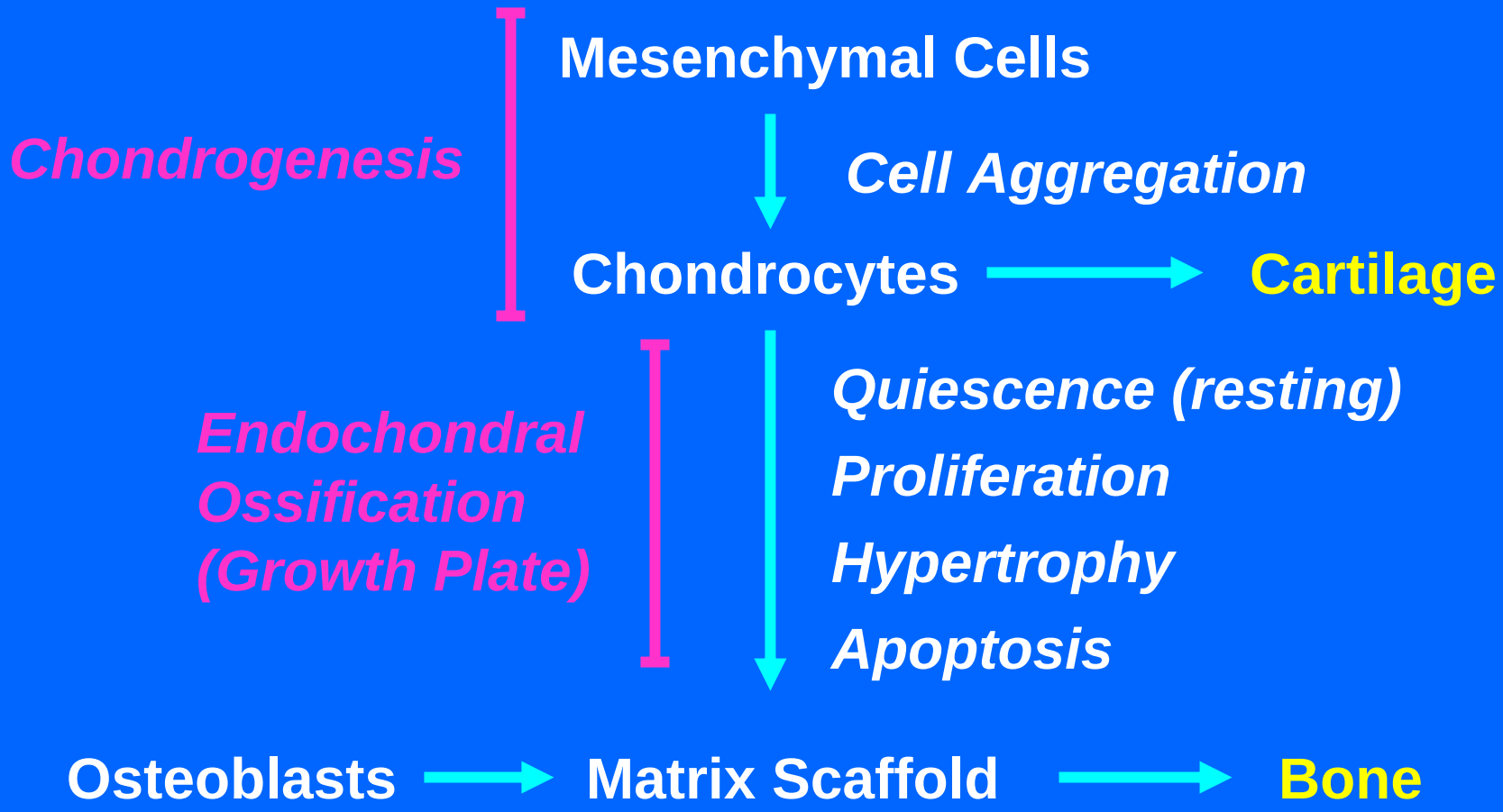
Mutations in the Human Perlecan Gene (HSPG2)

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

Formation of Cartilage and Bone



In Vivo Regulation of Chondrocyte Proliferation

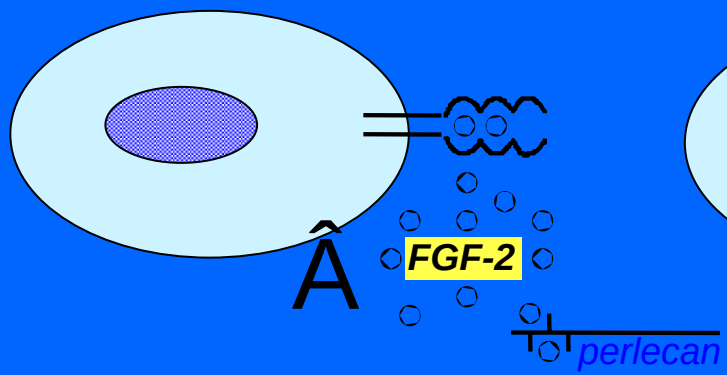
Condition	Phenotype
FGF-2 Transgene	Short Limbs
FGF R3 Null	Long Limbs
Perlecan Null	Short limbs

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

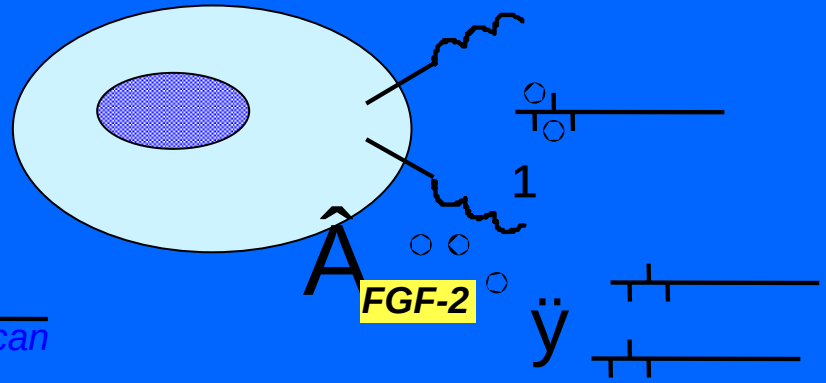
Growth Plate Chondrocyte Activation by FGF-2 and FGFR-3

resting chondrocyte



FGF-2 on receptor
cells quiescent

proliferating chondrocyte



FGF-2 off receptor
cells proliferate