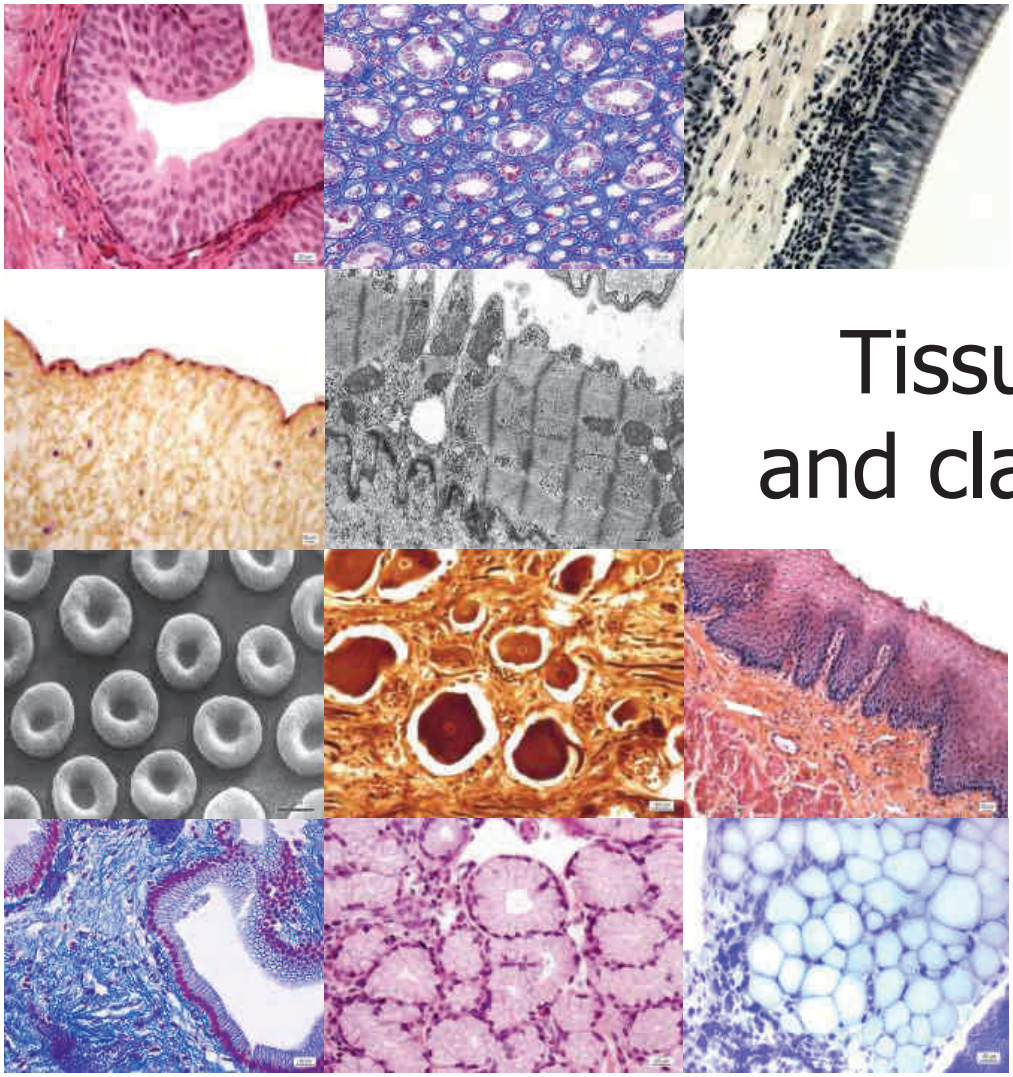

Tissue concept and classification

Petr Vaňhara, PhD

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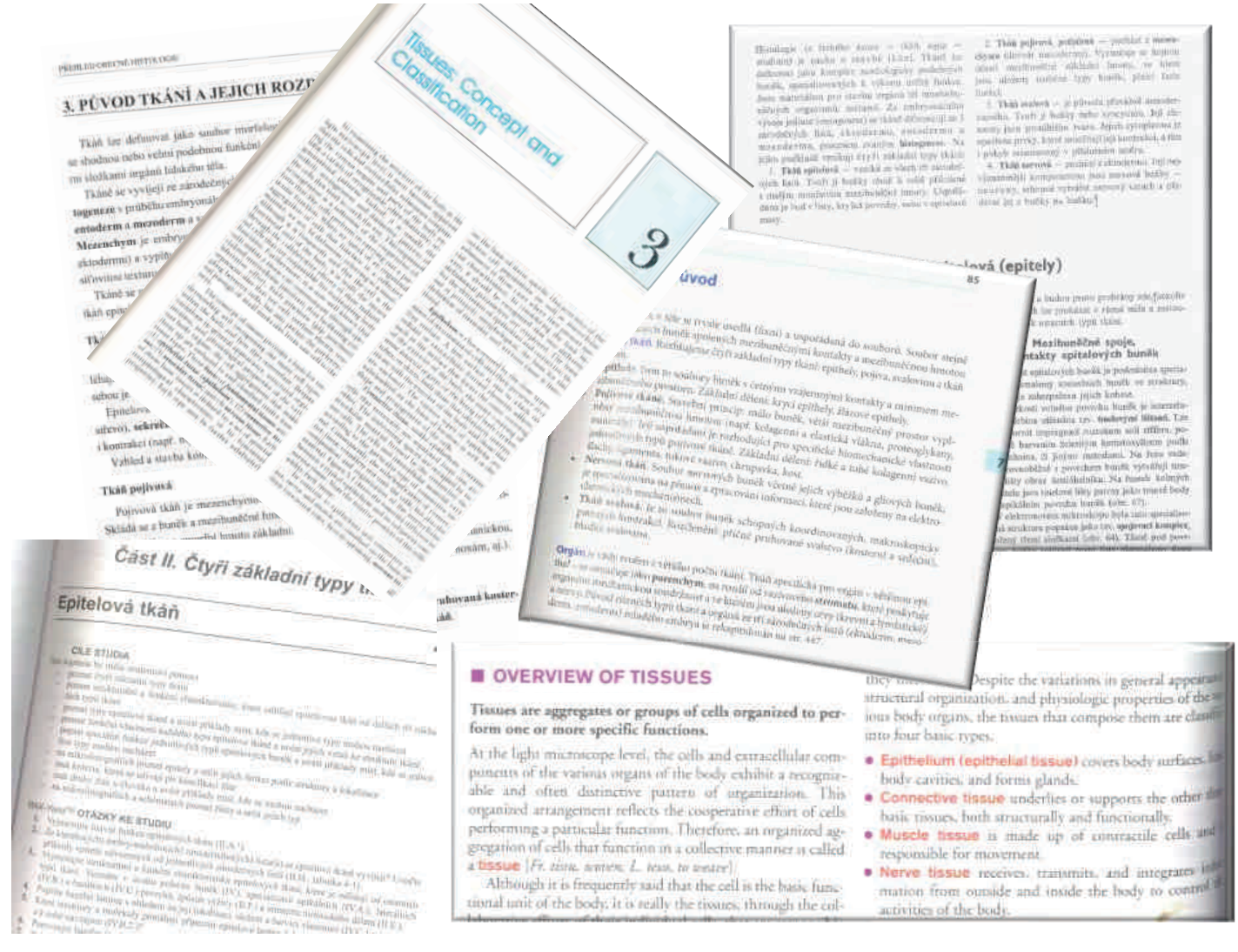
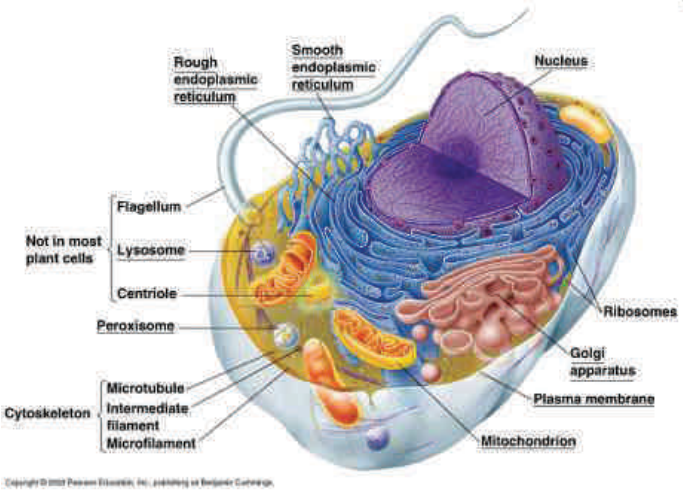
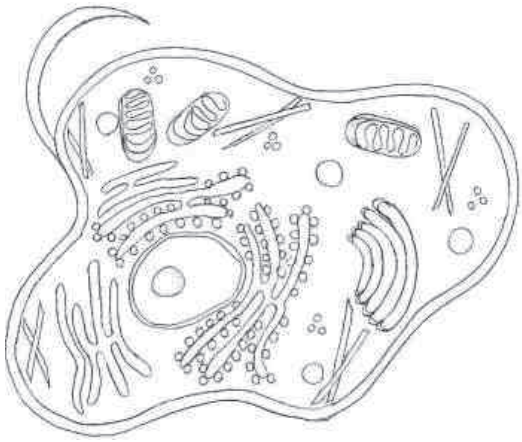


- Modern cell theory

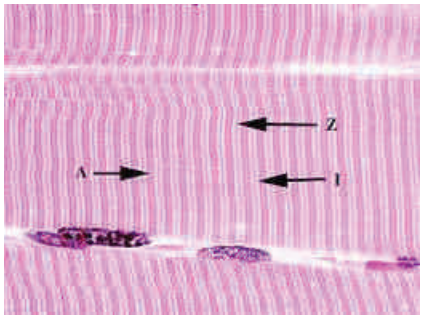
  - Cells are the **basic units** of any organism
  - New cells **origin** only **from other** cells
  - Cells **exchange energy** (open thermodynamic system)
  - Genetic **information** is **inherited** in new generations
  - Chemical and structural composition of cells is generally **identical**

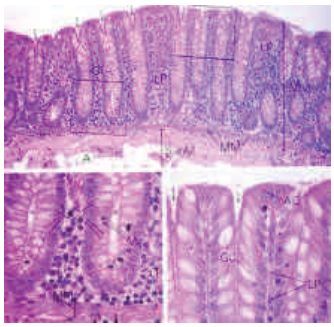




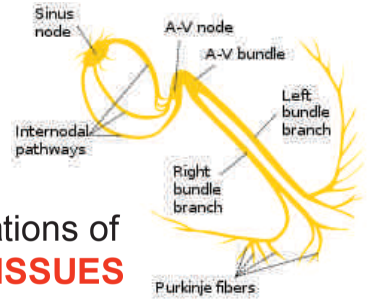
How do these cells differ?

How the variability of a multicellular body develops?



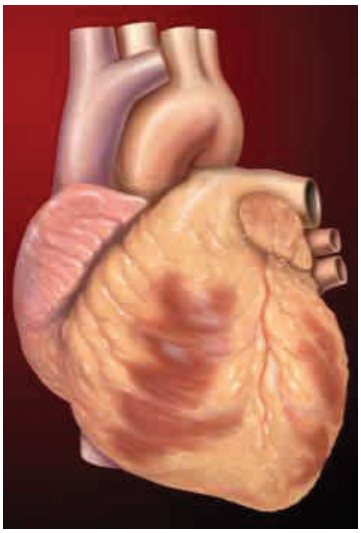


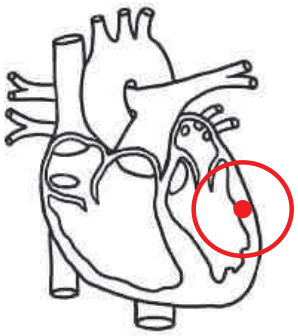
Tissues and organs

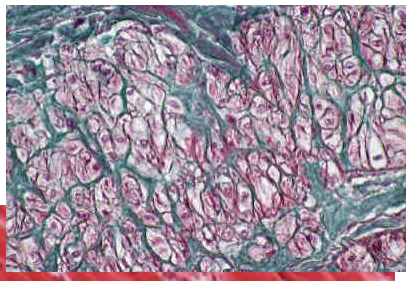


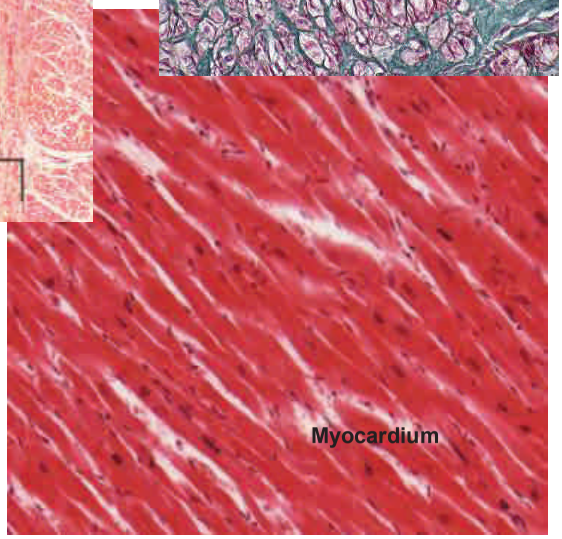
- **6** × **10^{13}** **CELLS** of **200** different types

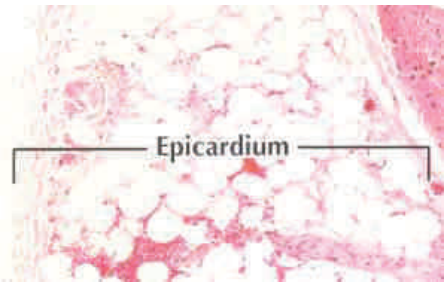
- cells form **functional**, **three-dimensional**, **organized** aggregations of morphologically similar cells and their products or derivatives - **TISSUES**
- tissues constitutes **ORGANS** and organ systems







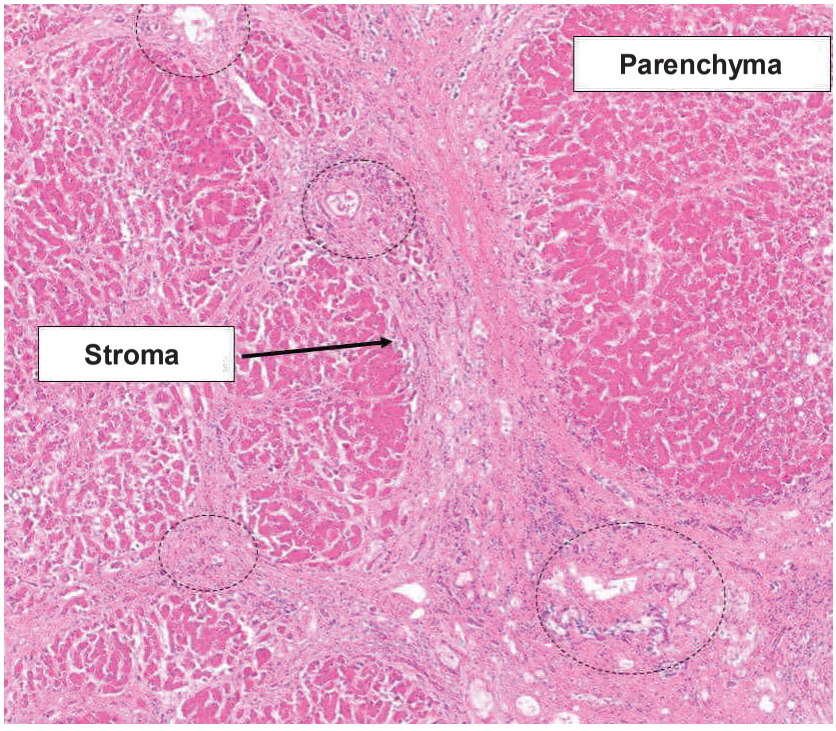




Tissues and organs

Parenchyma: functional component of a tissue (liver, lung, pancreatic, kidney parenchyma)

Stroma: surrounding, supportive tissue



LIVER

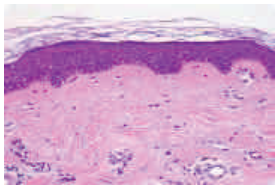
Parenchyma:
- Hepatocytes
- Sinusoids and adjacent structures

Stroma:
- Connective tissue and adjacent structures
- Vessels
- Nerves
- Bile ducts

Contemporary tissue classification

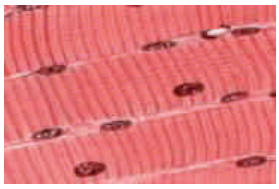
Based on **morphology** and **function**:

Epithelium



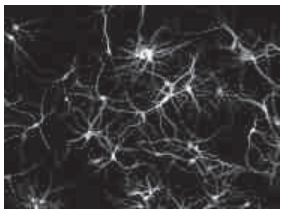
Continual, avascular layers of cells with different function, oriented to open space, with specific junctions and minimum of ECM and intercellular space.
Derivates of all three germ layers

Muscle



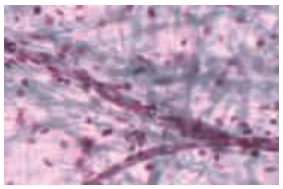
Myofibrils → contraction
Mesoderm – skeletal muscle, myocard, mesenchyme – smooth muscles
Rarely ectoderm (eg. m. sphincter a m. dilatator pupillae)

Nerve



Neurons and neuroglia
Reception and transmission of electric signals
Ectoderm, rarely mesoderm (microglia)

Connective

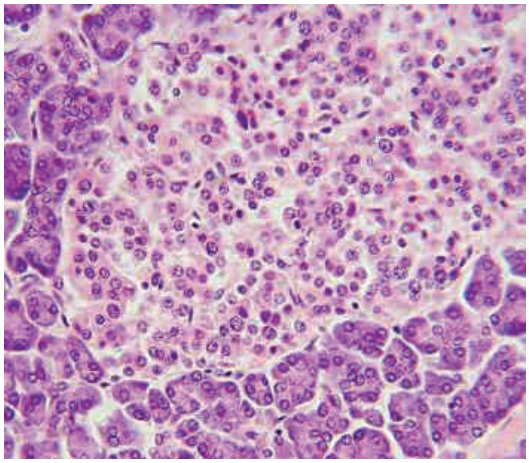


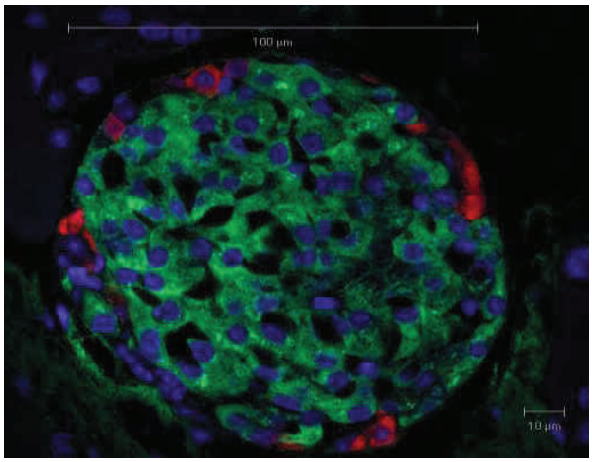
Dominant extracellular matrix
Connective tissue, cartilage, bone…
Mesenchyme

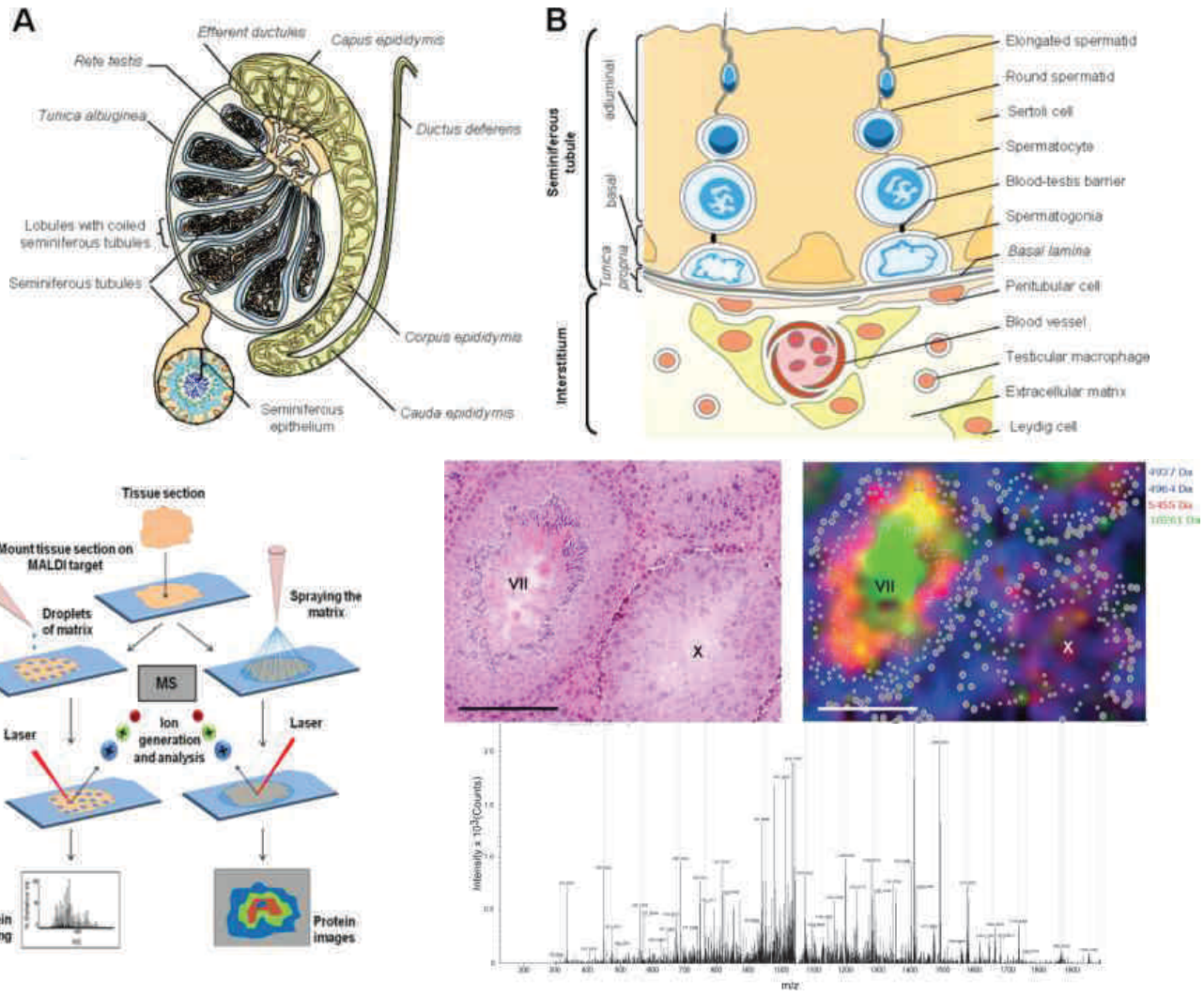
Definition of a tissue

Functional, three-dimensional, organized aggregation of morphologically similar cells, their products and derivatives

- classical histological definition is based on microscopic visualization

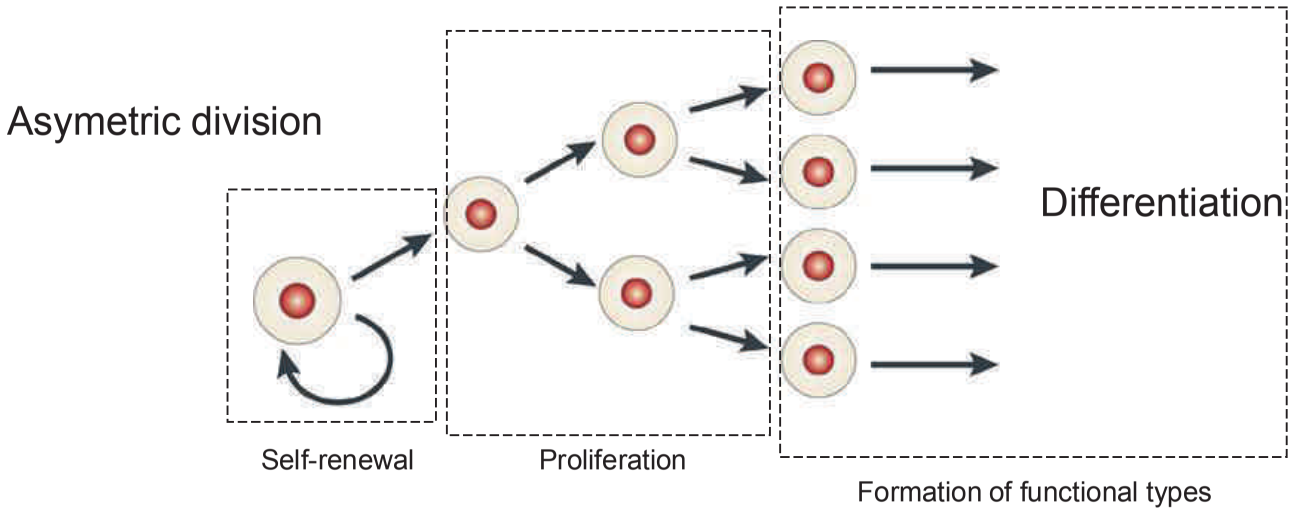






- Functional cells of tissues differentiate from stem cells

Stem cells are capable of differentiation and self-renewal



Knoblich JA. Asymmetric cell division during animal development. 2001. Nat Rev Mol Cell Biol

Stem cells

Totipotent

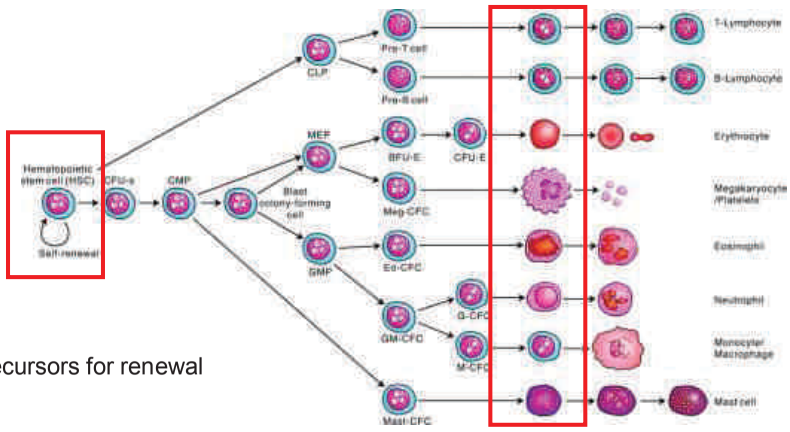
- Constitute all cells of the body incl. extraembryonic tissues
- Zygote and early stages

Pluripotent

- All cells in the body except for trophoblast
- Blastocyst – Inner cell mass - ICM (embryoblast)
- Embryonic stem cells

Multipotent

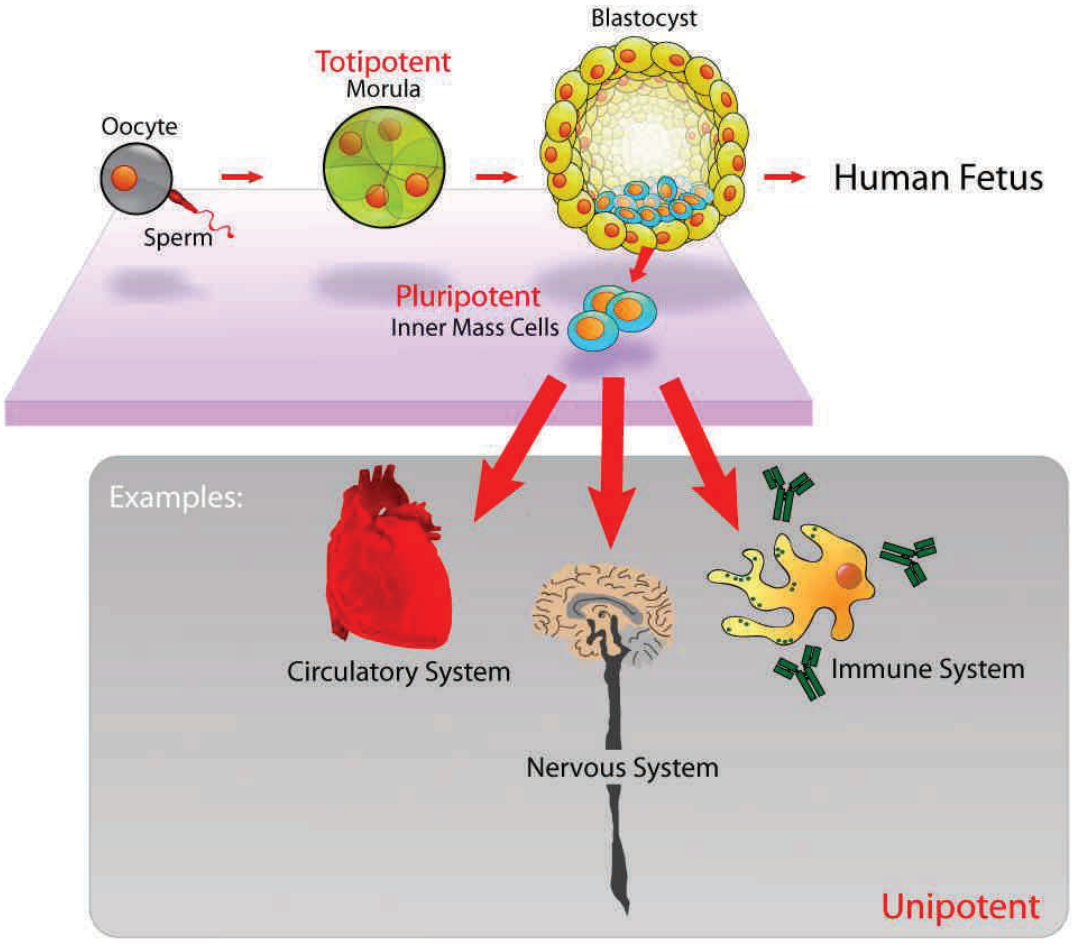
- Give rise to various cell types of a particular tissue
- Mesenchymal SC, hematopoietic SC



Oligo- a unipotent

- One or several cell types – hematopoietic, tissue precursors for renewal of intestinal epithelia, etc.

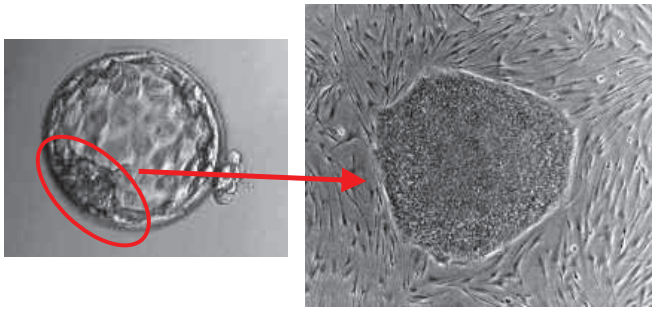
http://www.embryology.ch/anglais/evorimplantation/furchung01.html



Stem cells in human body

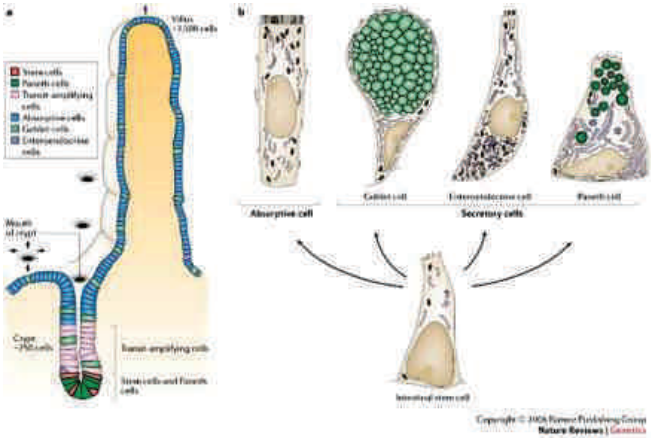
Embryonic stem cells (ESCs)

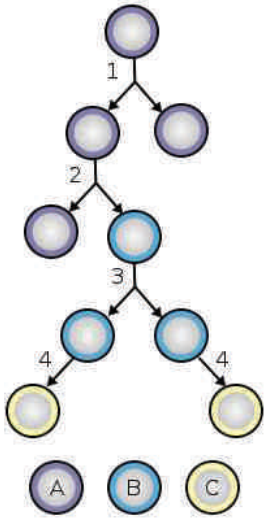
- embryoblast of blastocyst
- pluripotent
- modelling of early embryogenesis, regenerative medicine



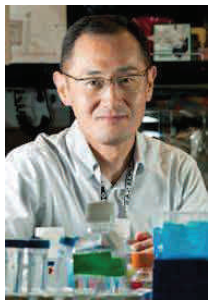
Tissue (adult) stem cells

- regeneration and renewal of tissues
- GIT, CNS, mesenchyme
- regenerative medicine, cancer biology





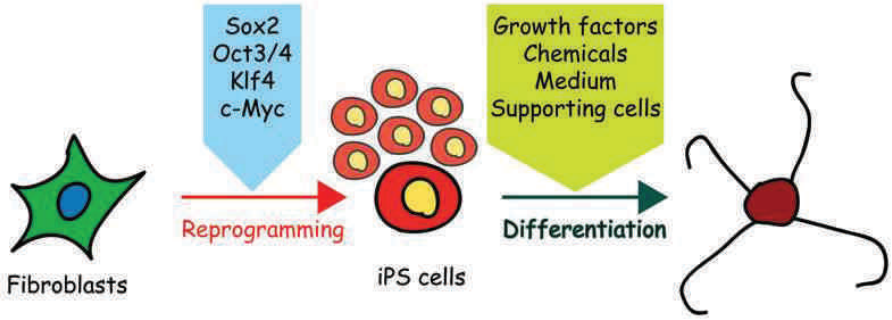
Stem cells as a research tool



Nobel prize 2012

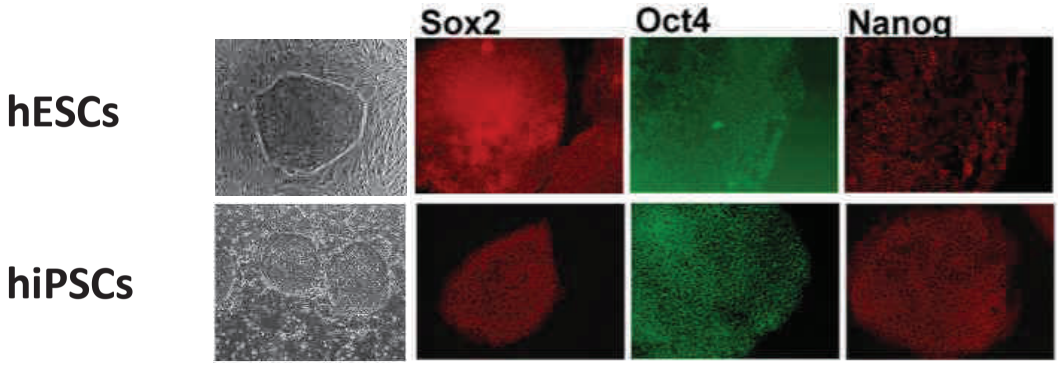
Induced pluripotent stem cells (iPSc)

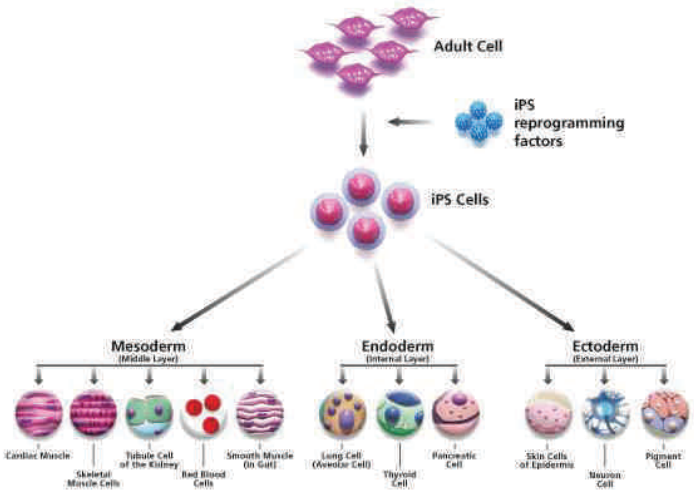
- adult differentiated cell (fibroblast) is reprogrammed into pluripotent state
- differentiation into desired cell type
- regenerative medicine, cell and gene therapy



Disease modelling
Drug testing
Tissue replacement
…

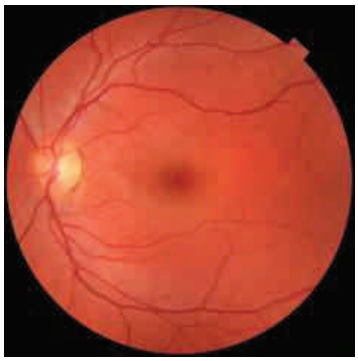
- Induced pluripotent stem cells share biological properties with embryonic stem cells



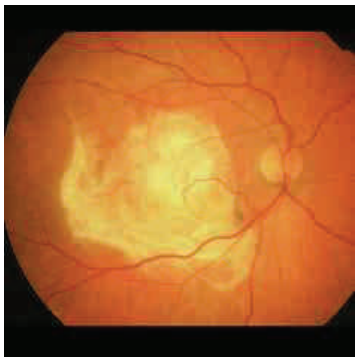


- Stem cells as a therapy

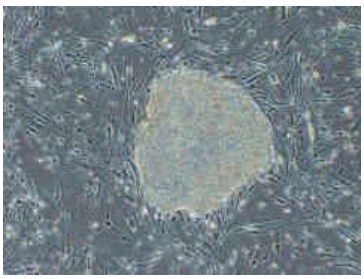
Age-related macular degeneration



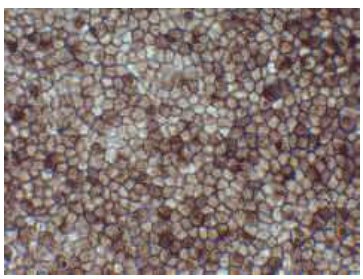
neovascularisation



hiPSCs

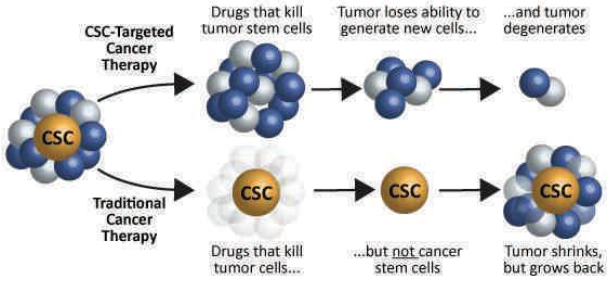


Retinal pigment epithelium



Clinical trial

Stem cells as a foe



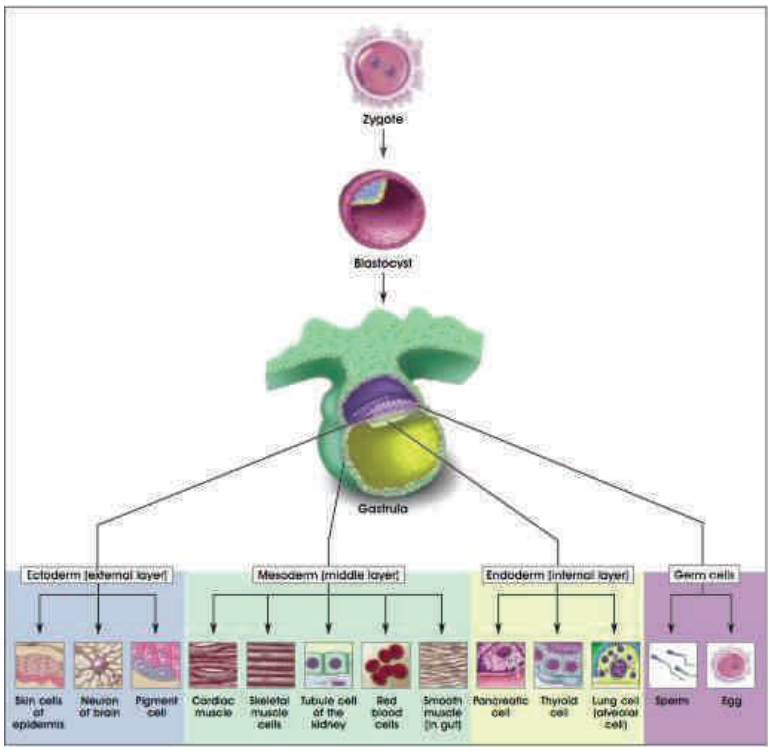
Cancer stem cells

- solid tumor is always heterogeneous

- small population of cells with stem cell character can repopulate tumor tissue after cytotoxic therapy

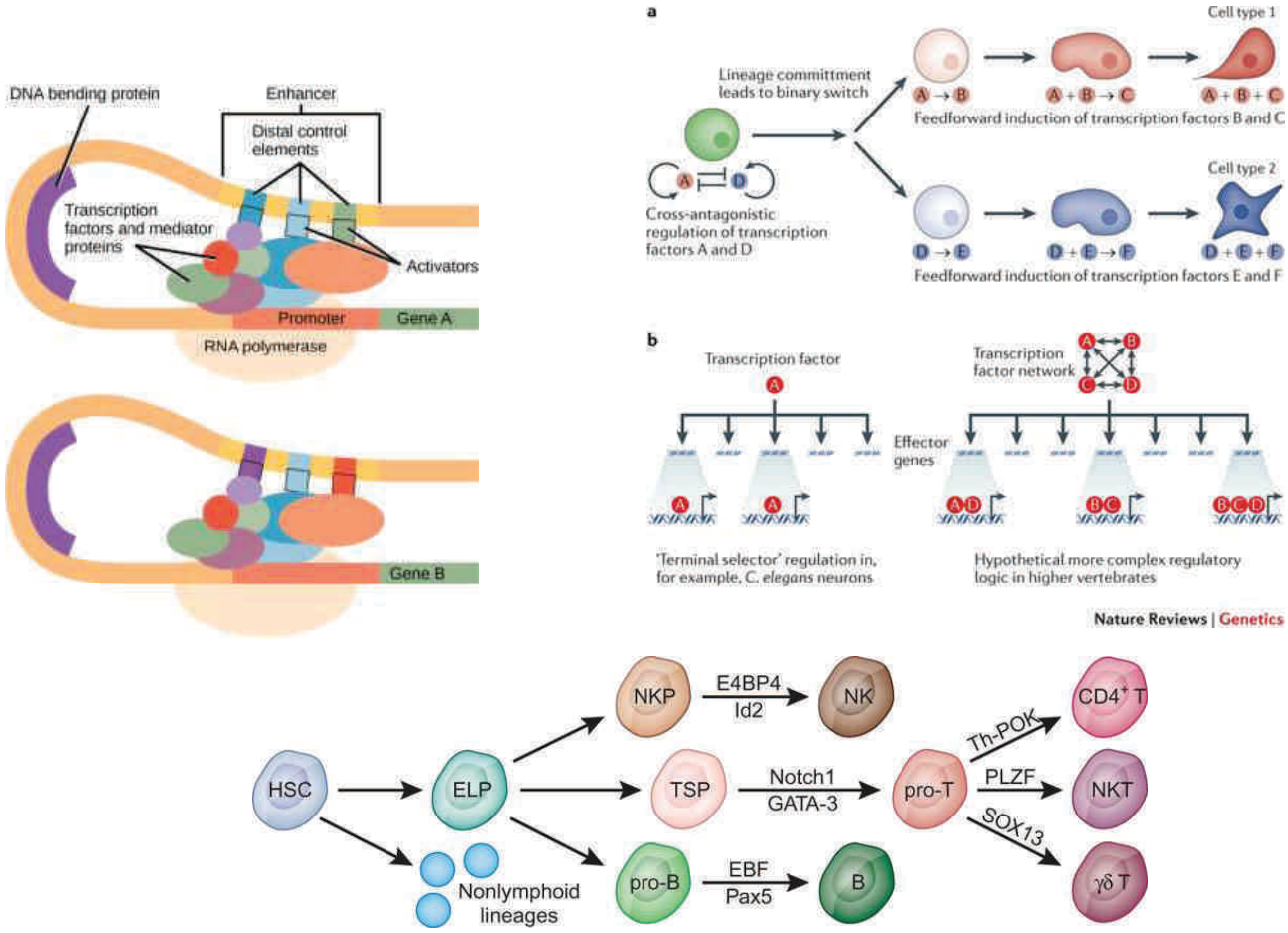
Tissue stem cells		Cancer stem cells
	Renewal	
	Quiescence	
	Multipotency	
	Low frequency (<1%)	
	Long life	
	Resistence	
	Tumorigenicity	
	Proliferation capacity	

Why are tissues different?

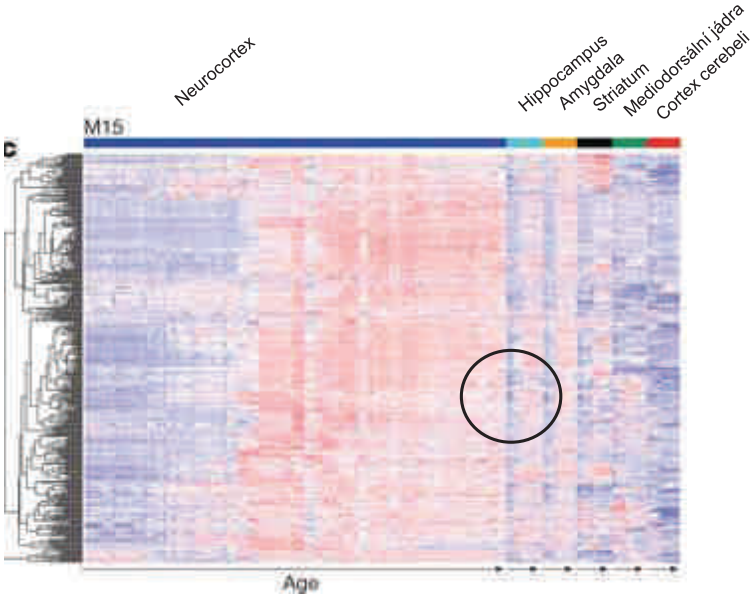


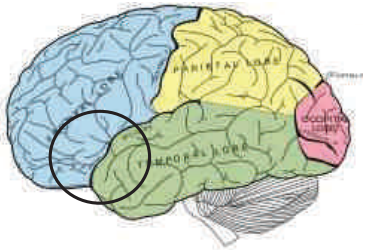
doi:10.1038/nrg3209

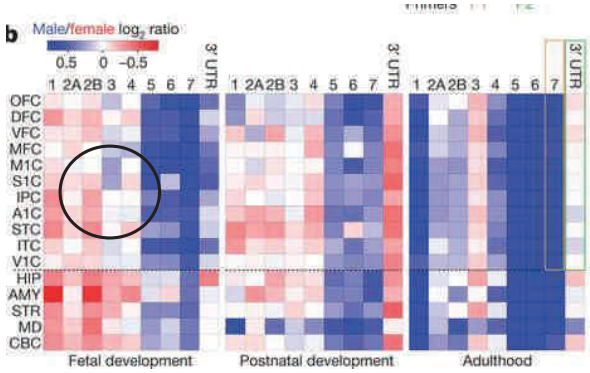
- Differentiation is driven by gene transcription



Tissue differ in their genetic and epigenetic profile

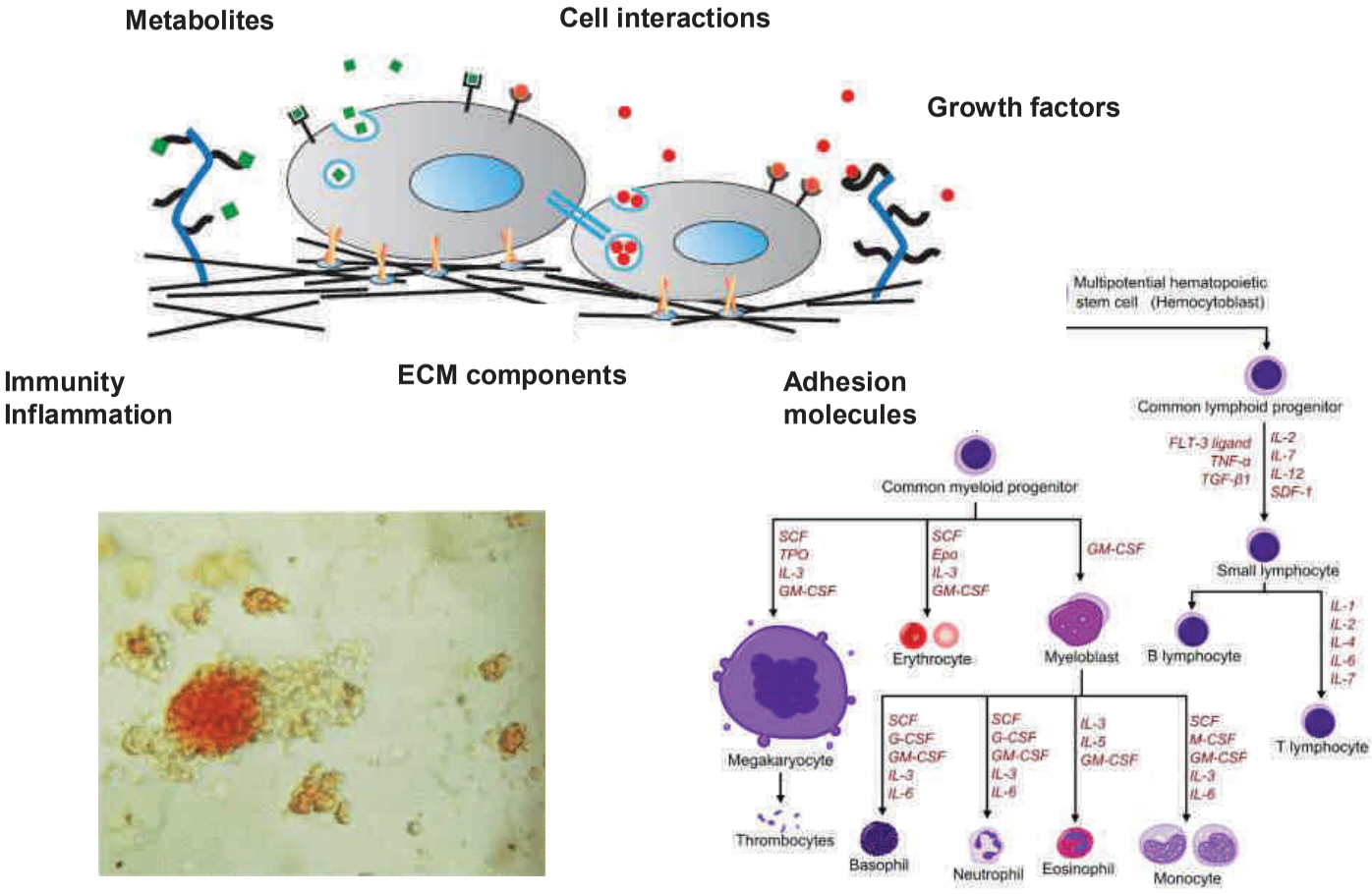






doi:10.1038/nature10523

Cells create unique microenvironment

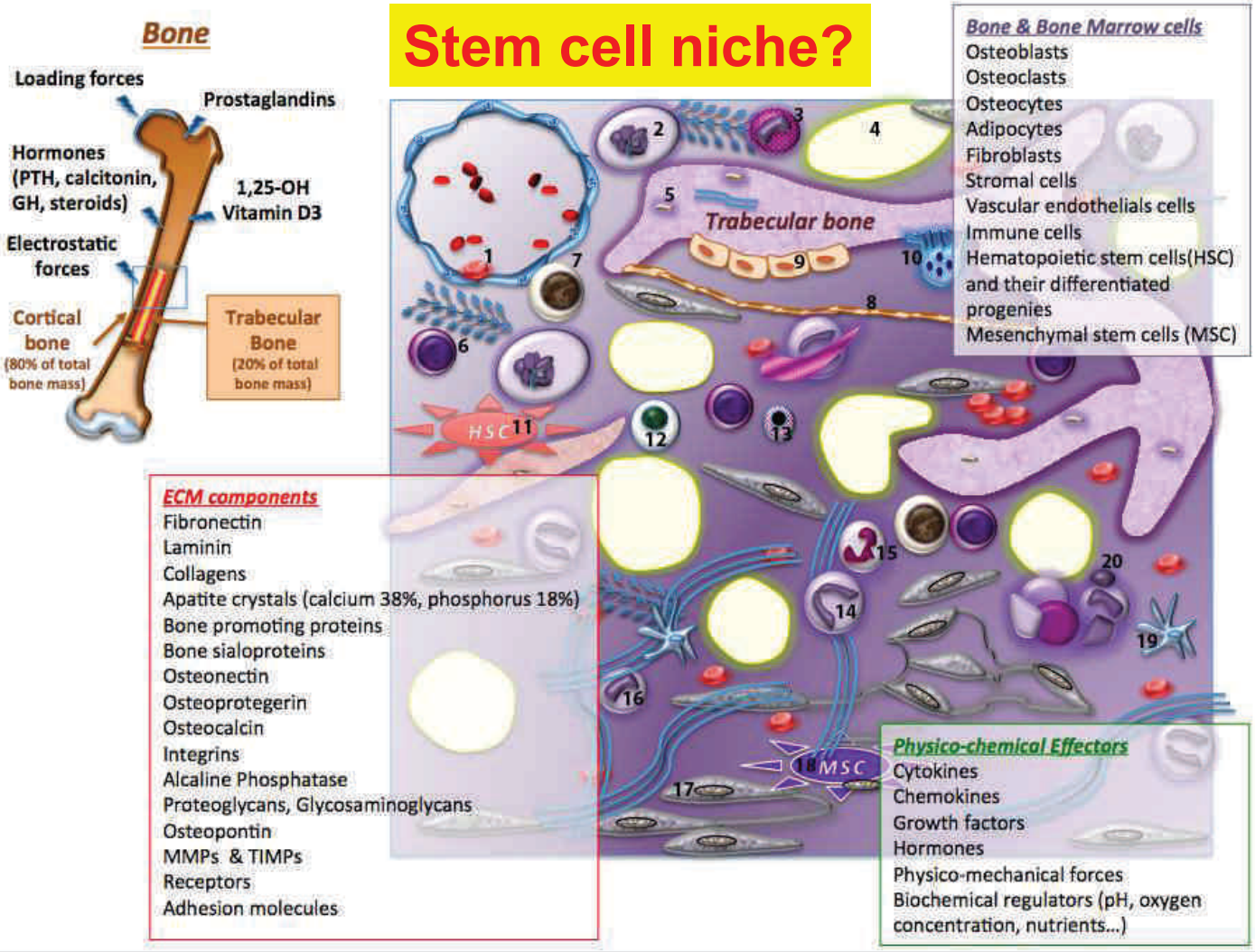


- Microenvironment regulates tissue function and reflects its tissue composition

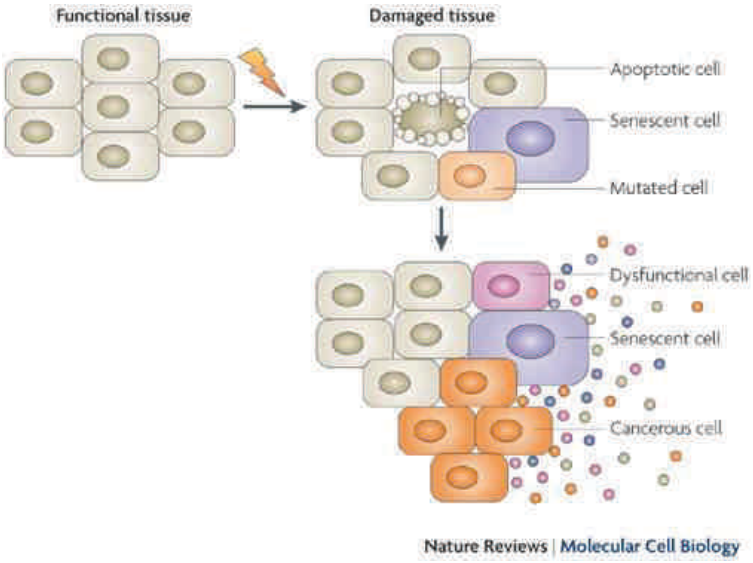
Huge number of **biological** and **physically-chemical** parameters

Stem cell niche

- Embryonic development
- Intercellular interaction
- Space organization (dimensionality)
- Gradient of morphogenes
- Epigenetic profile
- Gene expression dynamics
- Partial pressure of gases
- ECM composition
- Mechanical stimulation
- Perfusion and interstitial flows
- Local immunity response
- Metabolites



Microenvironment is necessary for tissue homeostasis



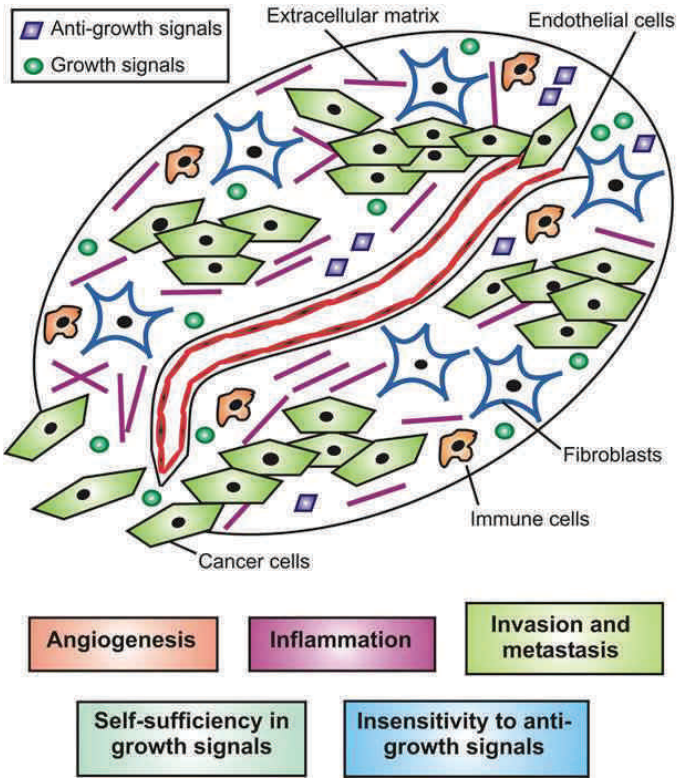
Apoptosis

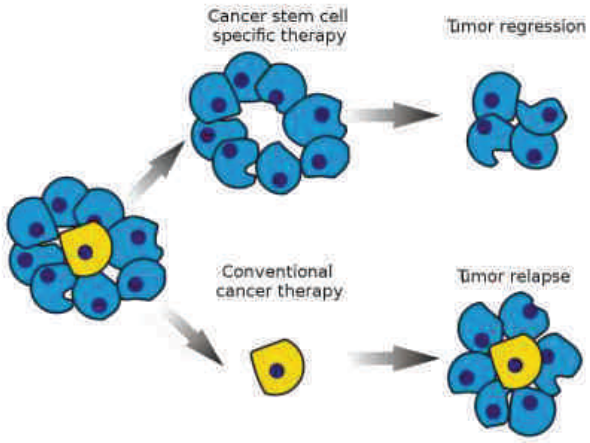
Regeneration

Senescence

Transformation

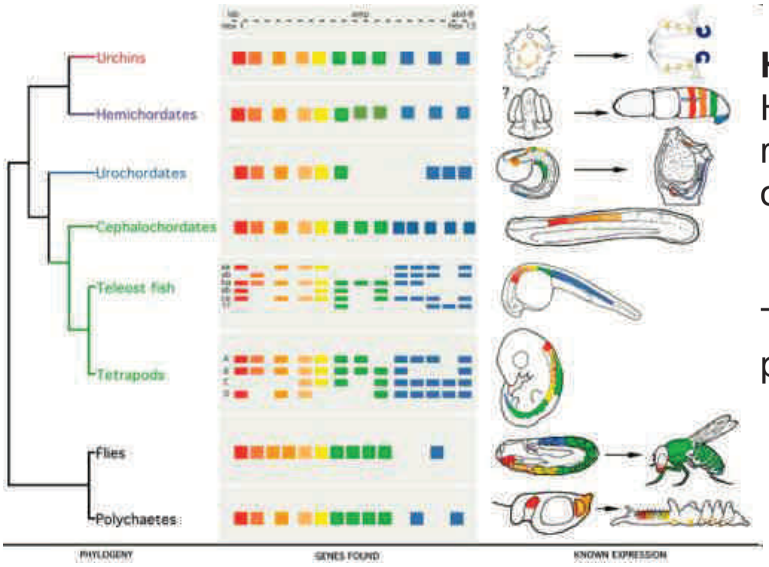
Microenvironment is of clinical importance





Molecular principles of histogenesis

Hox complex



doi:10.1038/sj.hdy.6800872

Hox genes
Highly conserved family of transcription regulators that determine body polarity, orientation and axis

Tissue differentiation along anterio-posterior axis

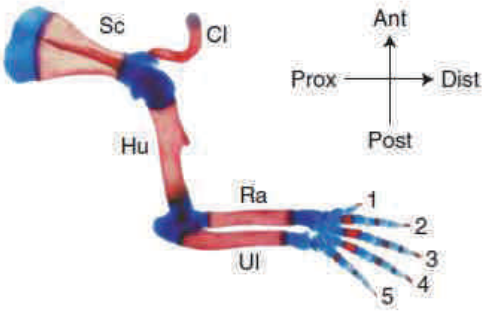
Human (39 genes)

Cluster	Chromosome	# Hox genes
HoxA	7	11
HoxB	17	10
HoxC	12	9
HoxD	2	9

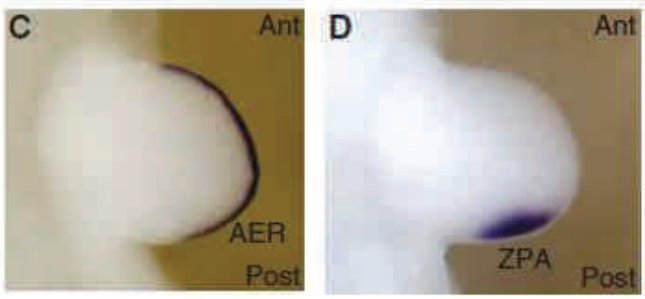
Congenital disorders and HOX genes

hand-foot-genital syndrome – mutation HOXA13
synpolydaktylia – mutation HOXD13

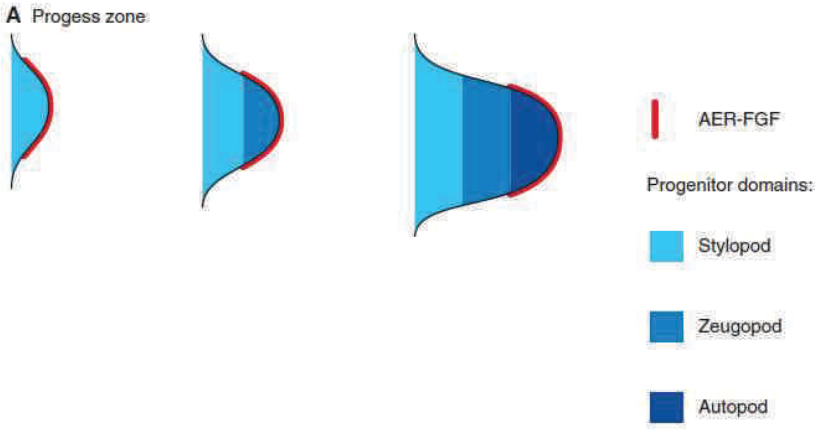
Microenvironment controls embryonic organogenesis



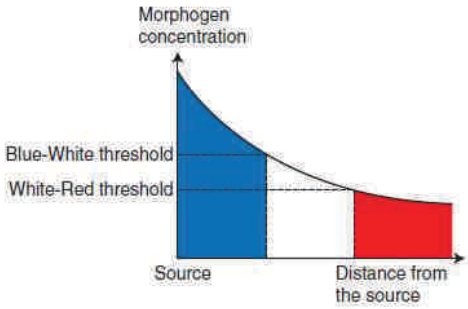
Apical ectodermal ridge (AER)



Zone of polarizing activity (ZPA)



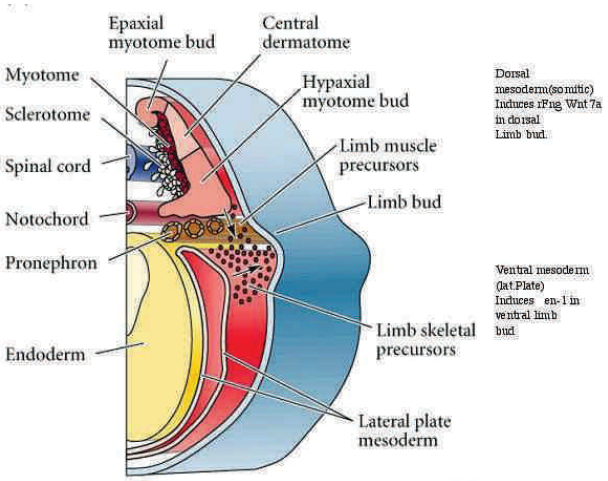
Lewis Wolpert

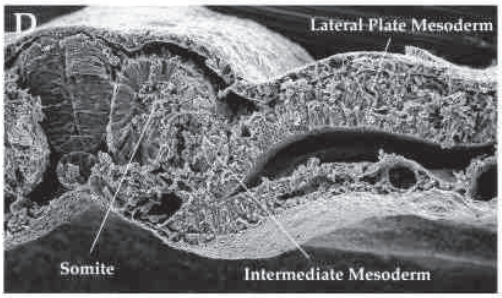


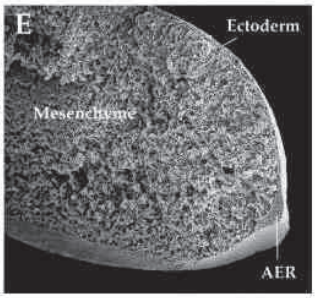
Temporo-spatial **expression** of different regulators determines final **localization**, **orientation** and **morphology** of a tissue.

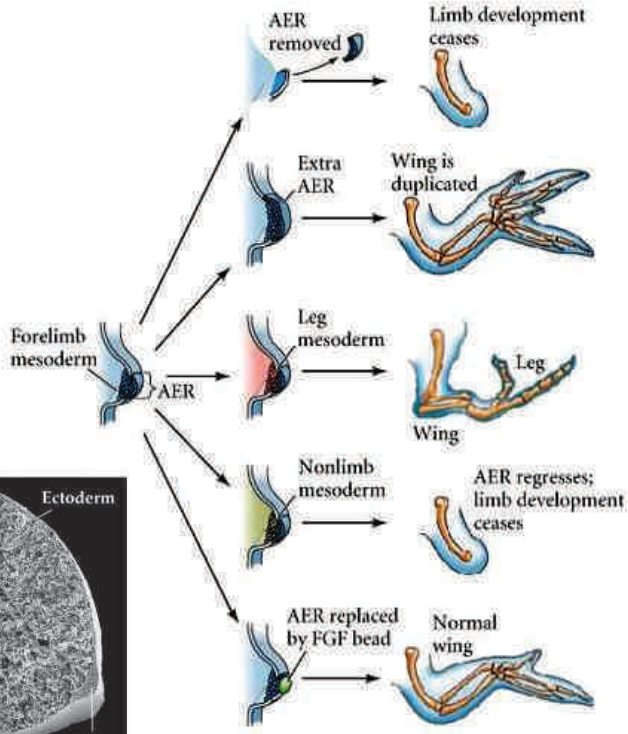
French flag model

Manipulation with AER changes the instructions for limb development

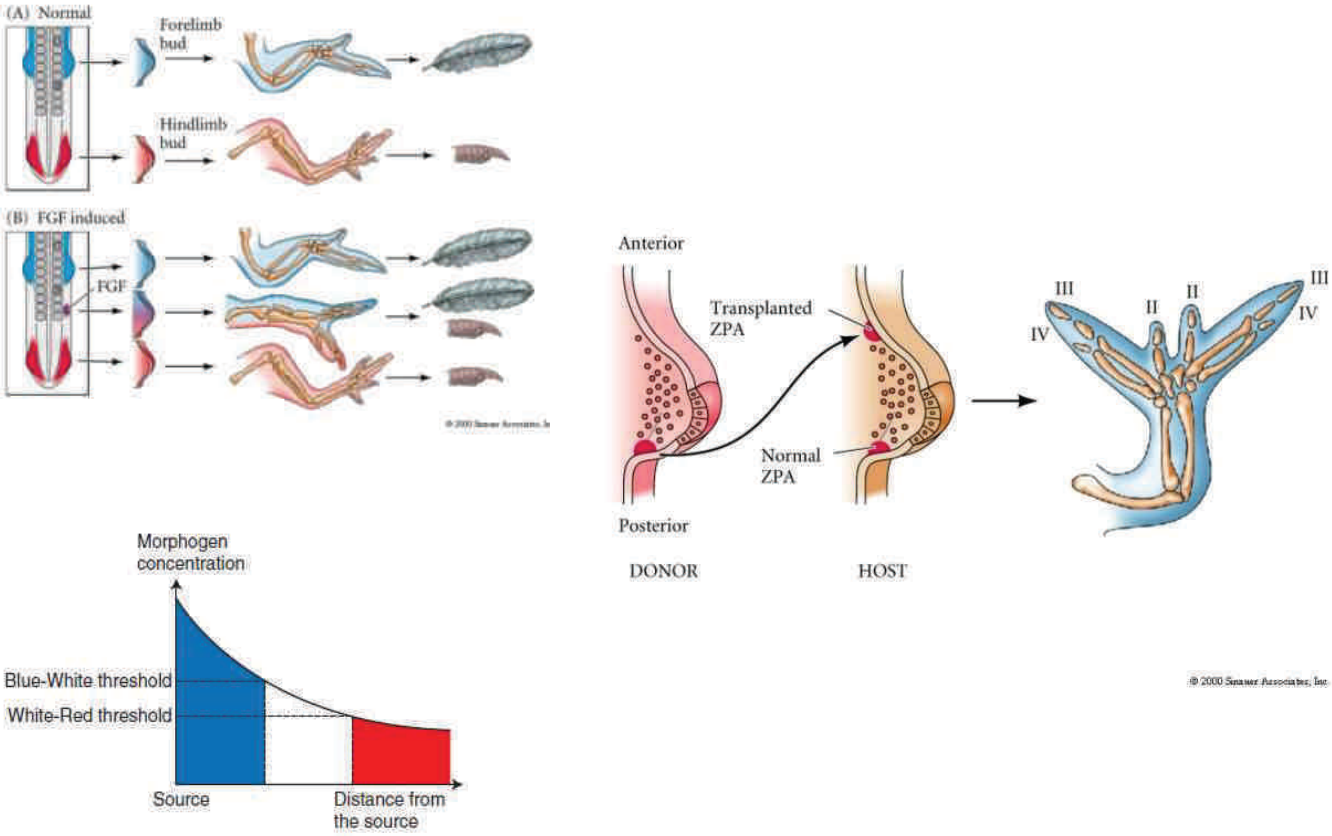






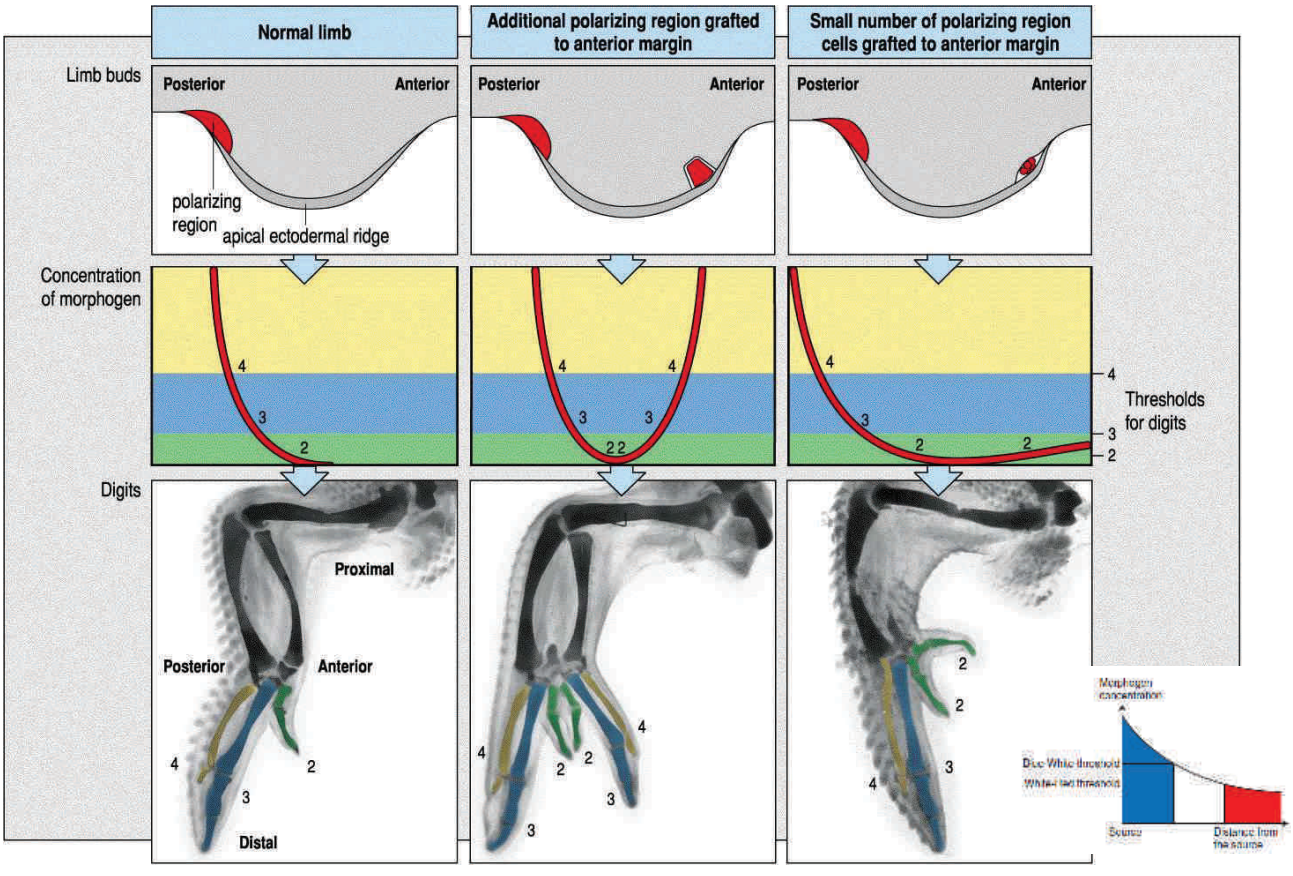


ZPA specifies positional infromation in limb bud

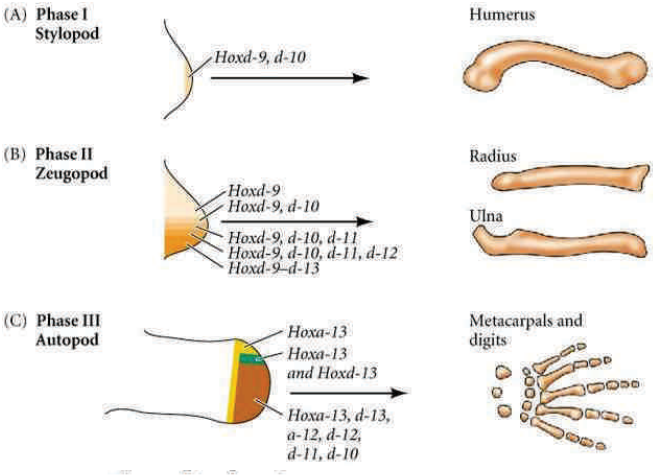


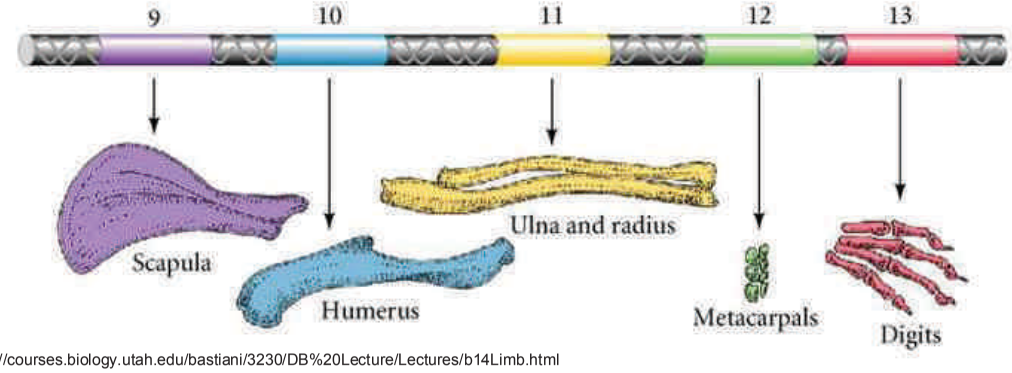
http://courses.biology.utah.edu/bastiani/3230/DB%20Lecture/Lectures/b14Limb.html

Gradients of morphogenes from AER and ZPA defines limb formation



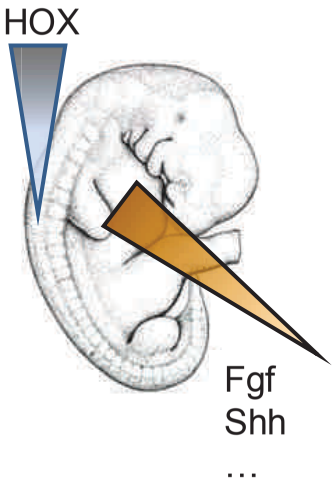
Hox pattern represent the transcription response and induces differentiation to cartilage and muscles

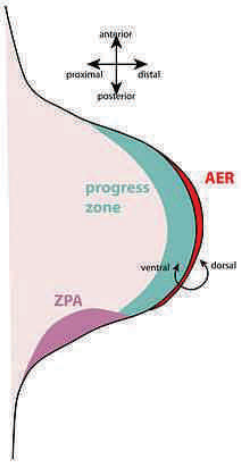




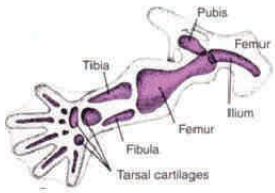
http://courses.biology.utah.edu/bastiani/3230/DB%20Lecture/Lectures/b14Limb.html

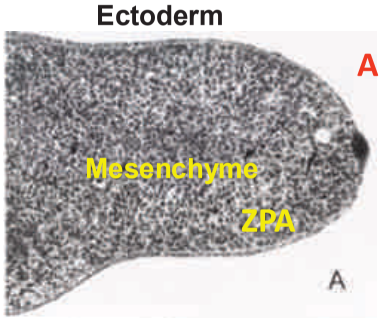
Thalidomid





Proliferation → Vascularisation ⊣ **Thalidomid**



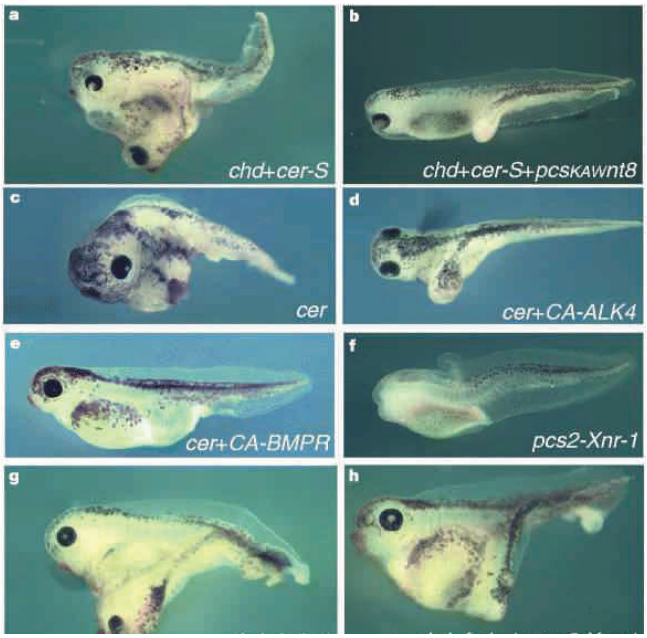


Morphogenes in notochord-neural tube formation

- Noggin Xenopus laevis notochord

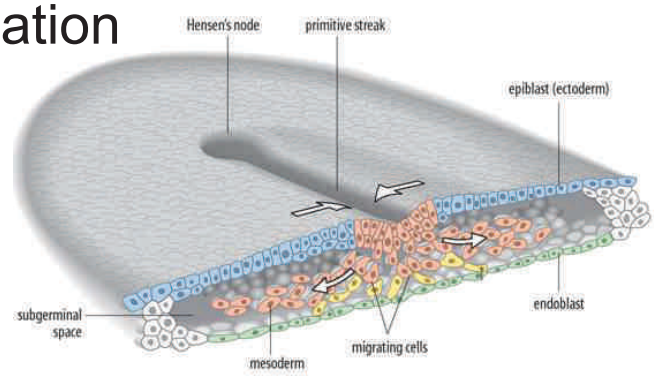
- Body axes
- Segmentation
- Limb buds

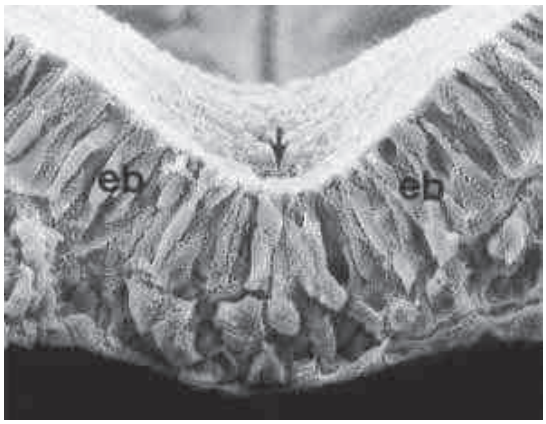
- Protein *Cerberos* induces head formation (Danio reiro)

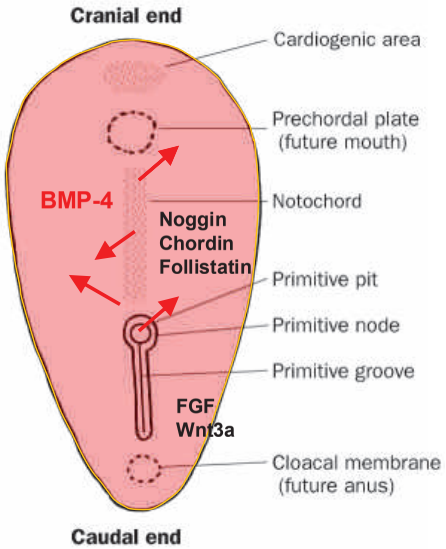


The head inducer Cerberus is a multifunctional antagonist of Nodal, BMP and Wnt signals
Stefano Piccolo, Eric Agius, Luc Leyns, Subha Bhattacharyya, Horst Grunz, Tewis Bouwmeester and E. M. De Robertis
Nature **397**, 707-710(25 February 1999)
doi:10.1038/17820

Neurulation







BMP-4
In whole embryo, ventralisation of endo- a mesoderm

Noggin
Chordin
Follistatin

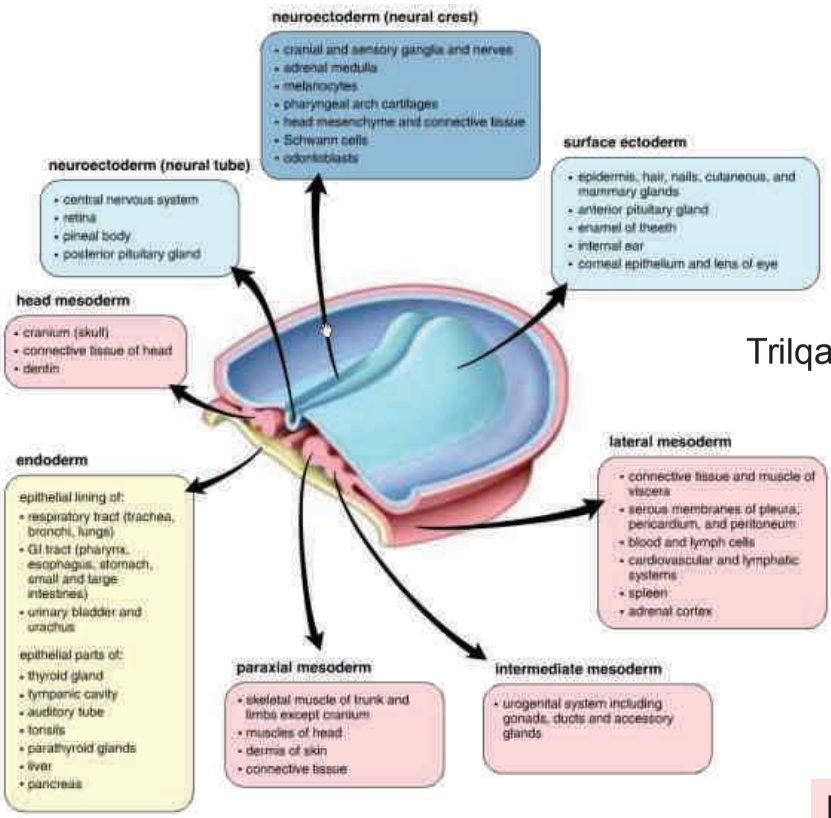
- In developing notochord, primitive pit, prechordal mesoderm
- Inhibit BMP-4
- Neurulation of ectoderm, development of fore- and midbrain

FGF
Wnt3a

- Caudal neural structures – hindbrain and spinal cord

Histogenesis and organogenesis

Ectoderm



Trilqaminar germ disc

(3rd week)

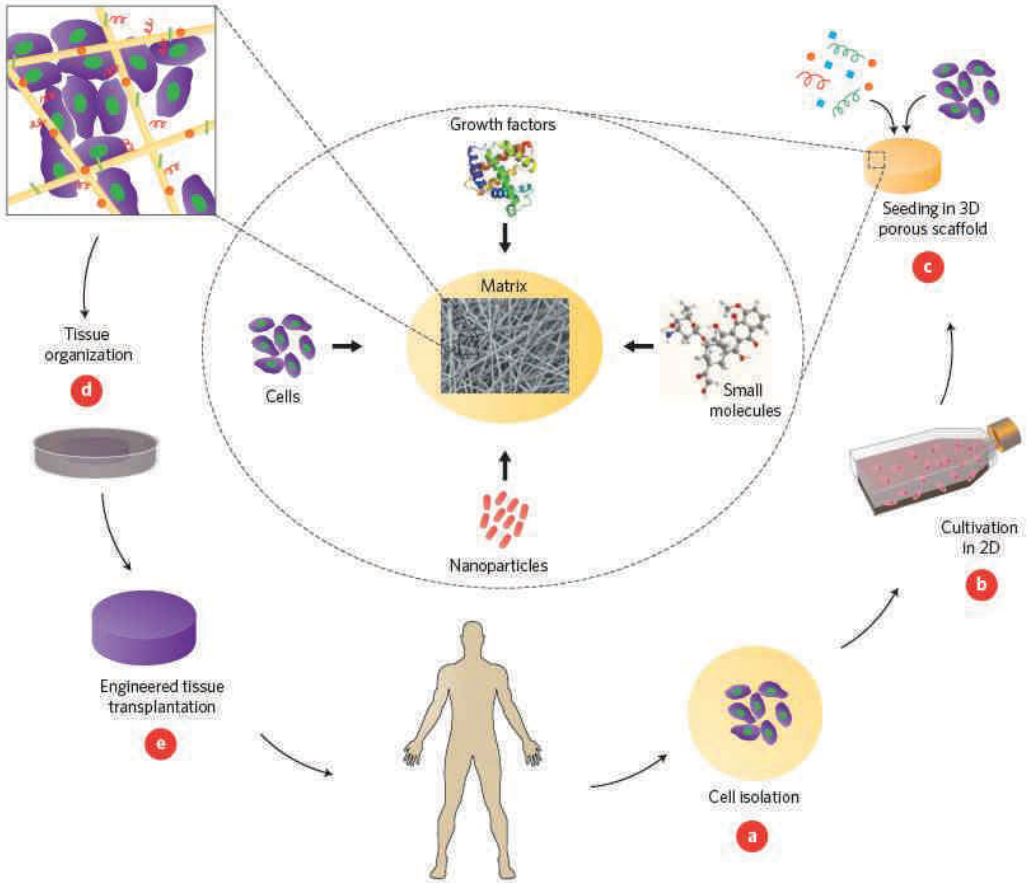
Entoderm

Mesoderm

Embryonic development

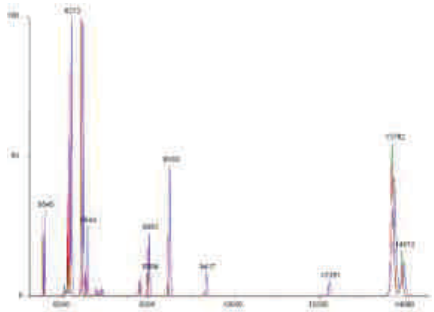
	Ectoderm	**Mesoderm**	**Endoderm**
Surface ectoderm	▪ Epidermis, hair nails, cutaneous and mammary glands ▪ Corneal epithelium and lens of eye ▪ Enamel of teeth ▪ Internal ear ▪ Anterior pituitary gland ▪ Epithelium of oral cavity and part of anal canal		
Neuroectoderm	▪ **Neural tube** and derivatives - CNS - Retina - Posterior pituitary gland - Pineal body ▪ **Neural crest** and derivatives: - Cranial and sensory ganglia and nerves - Schwann cells - adrenal medulla - Enteroendocrinne cells - Melanocytes - Head mesenchyme and connective tissue - Odontoblasts		
head		▪ Connective tissue of head ▪ Cranium, dentin	
Paraxial		▪ Skeletal muscle of trunk and limbs except cranium ▪ Dermis of skin ▪ Muscles of head	
Intermediate		▪ Urogenital system + ducts, glands and gonads	
Lateral		▪ Visceral muscle and connective tissue ▪ Serous membranes of pleura, peritoneum and pericardium ▪ Blood cells, leukocytes ▪ Cardiovascular and lymphatic system ▪ Spleen ▪ Adrenal cortex	
			▪ GIT epithelium except oral cavity and part of anal canal ▪ Extramural glands of GIT ▪ Epithelium of bladder ▪ Epithelium of respiratory system ▪ Thyroid gland, parathyroid glands, thymus ▪ Tonsils ▪ Epithelium of cavum tympani and Eustachian tube

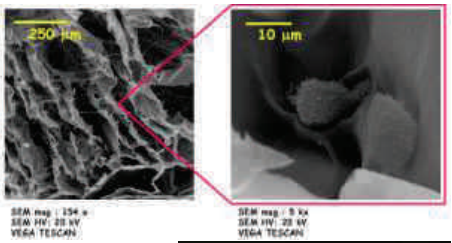
Tissue engineering

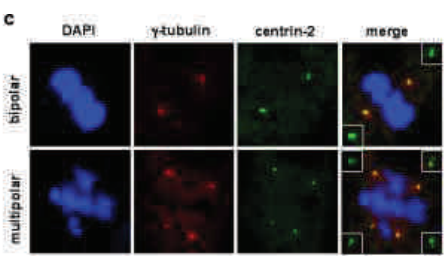


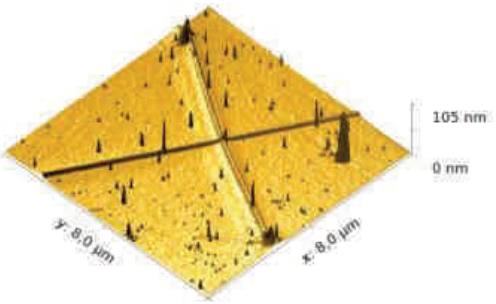
▪ Current histology and tissue engineering at Dpt. of histology and embryology LF MU

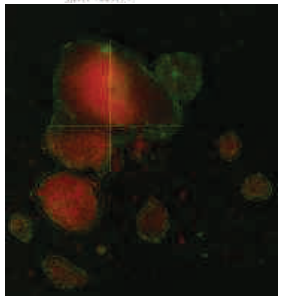
- Biology of embryonic stem cells
  - Cel cycle, mechanisms of differentiation and adaptation of SCs
  - Genome stability and phenotype plasticity
- New differentiation protocols of hESCs/iPSCs/MSCs
  - Neural crest, odontogenesis
  - Lung epithelia
  - Modeling of pathologies (e.g. cancer)
- Unique technologies and tissue engineering
  - Modeling of microenvironment and development of nanosurfaces
  - Bioanalytic profiling of cells and tissues (MALDI TOF MS)
  - 3D nanocarriers for modeling of interactions between cells and tissues
  - State-of-the-art microscopy

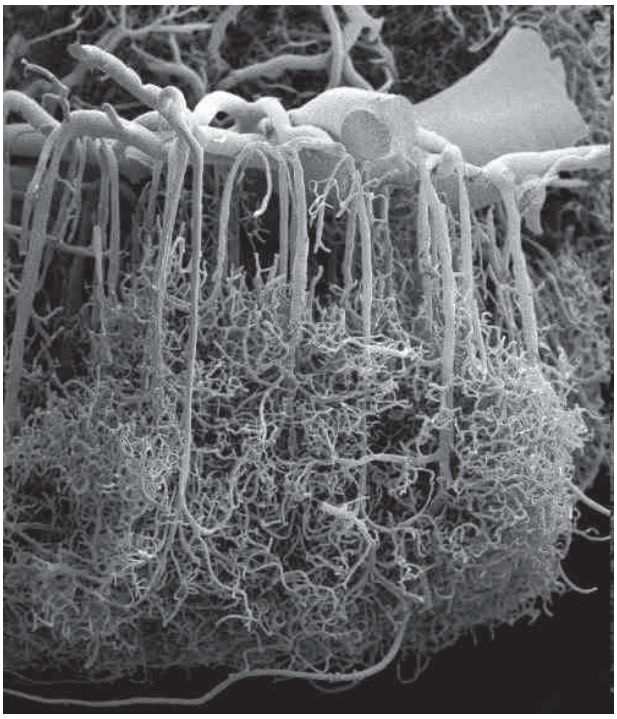






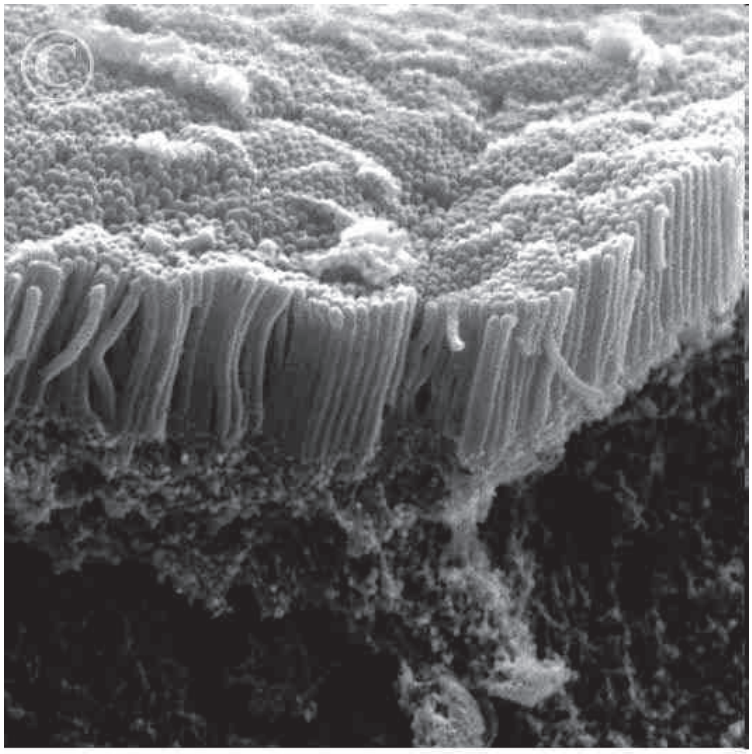






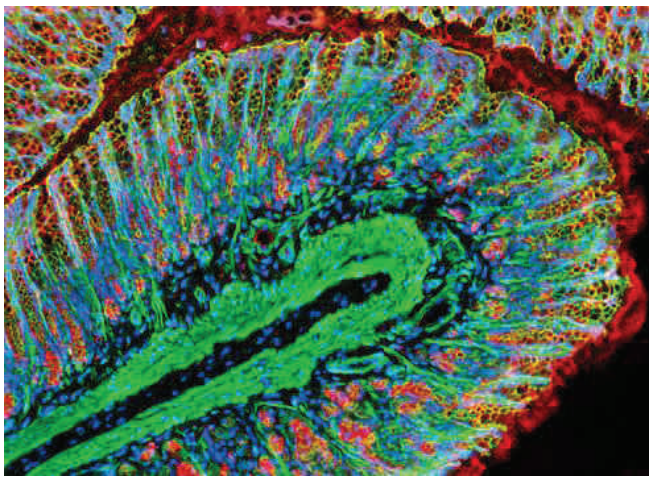
Isocortex vascularisation

Break



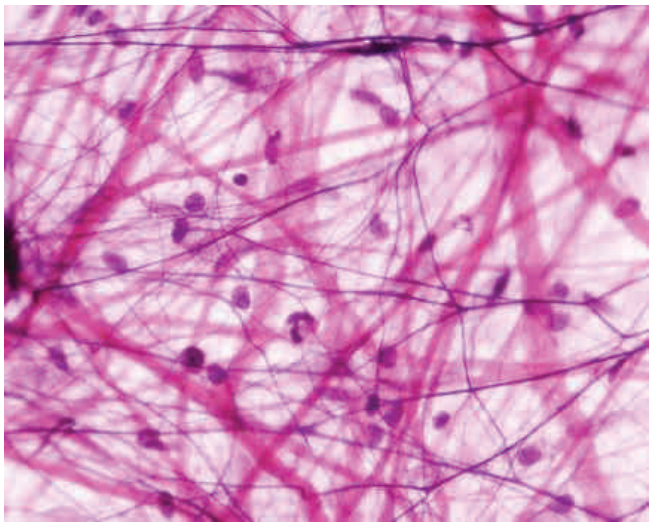
Microvilli on surface of small intestine

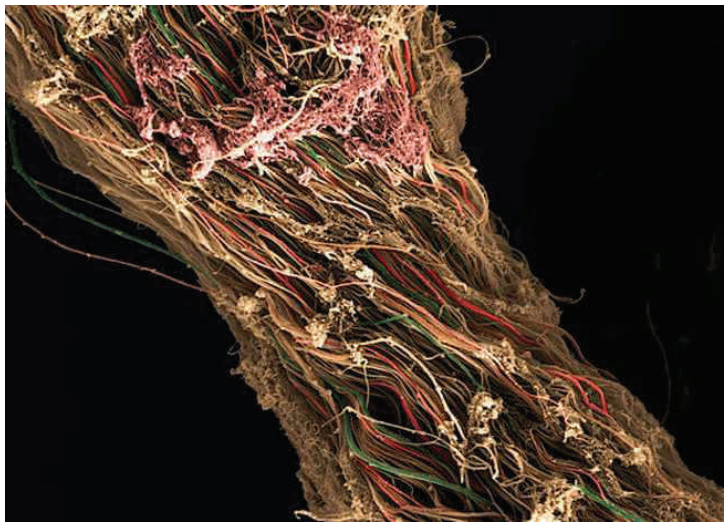
http://www.livescience.com/14413-brain-images-portraits-mind.html



6. Connective tissue

Not only a tissue glue…

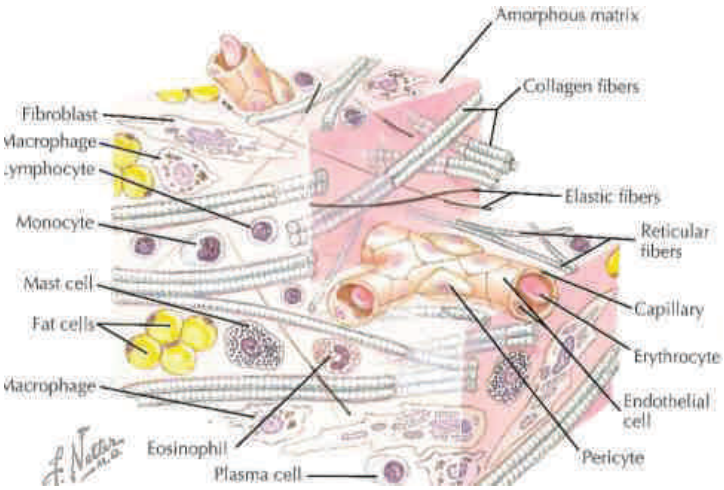




Connective tissue

Mechanical and biological properties

⟶ surrounds other tissues, compartmentalization, support, physico-chemical environment, immunological support, storage

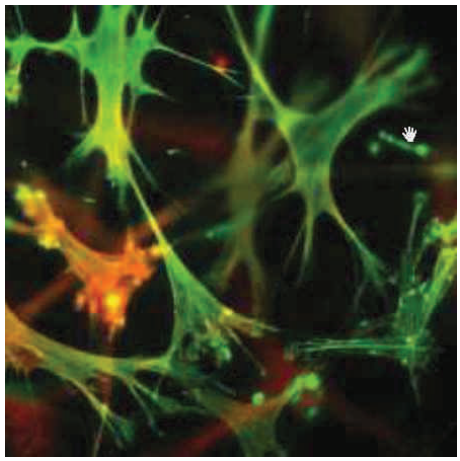


General composition of connective tissue (CT)

Cells and extracellular matrix

- **Cells**

Connective tissue – permanent and transient cell populations (fibroblasts/myofibroblasts, immune cells, adipocytes, adult stem cells)
Cartilage – chondroblasts/chondrocytes
Bone – osteoblasts/osteocytes/osteoclasts



- **Matrix** – fibrous and amorphous

Fibrous component
- collagen
- reticular
- elastic

Amorphous component (amorphous ground substance)
- Complex matrix consisting of glycosaminoglycans, glycoproteins and proteoglycans,

depending on tissue type (connective × ligament × cartilage × bone)

Classification of CT

Embryonic CT
- Mesenchyme
- Jelly-like CT (Wharton jelly, dental pulp, stroma of iris)

Adult CT
- Areolar (loose, interstitial) CT
- Dense collagen irregular CT

CT

- Dense collagen regular CT
- Fat (adipose tissue)
- Cartilage
- Bone

Specialized CT

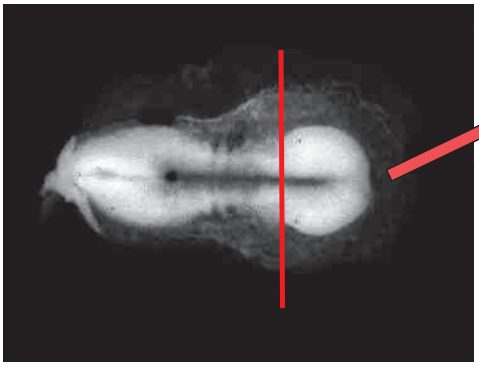
- Blood and hematopoietic tissue
- Lymphatic tissue

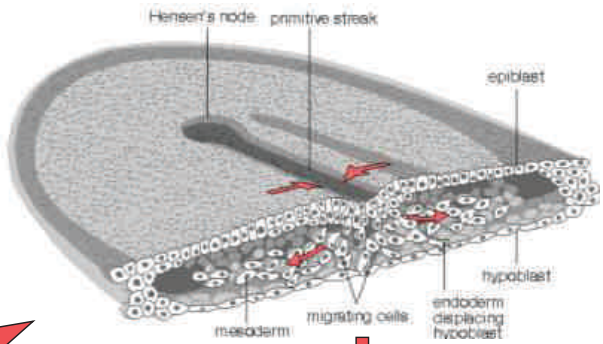
Trophic CT (body liquids)

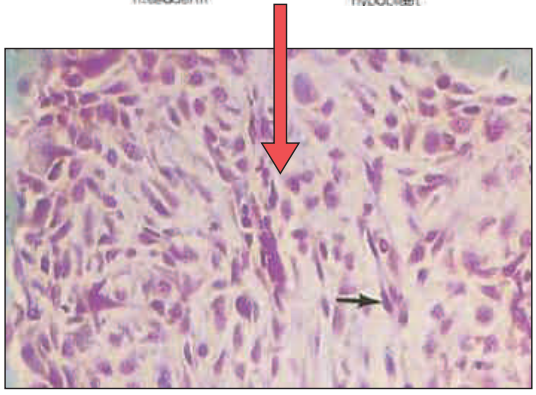
Embryonic origin of CT

- Mesenchyme = loose tissue between germ layers
- Complex network of star- or spindle-shaped cells
- Jelly-like amorphous ground substance

DAY 12 of embryonic development

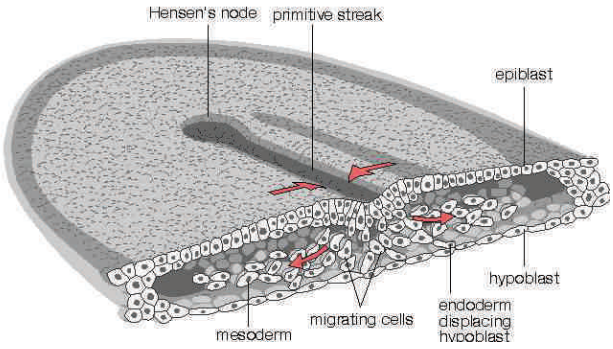


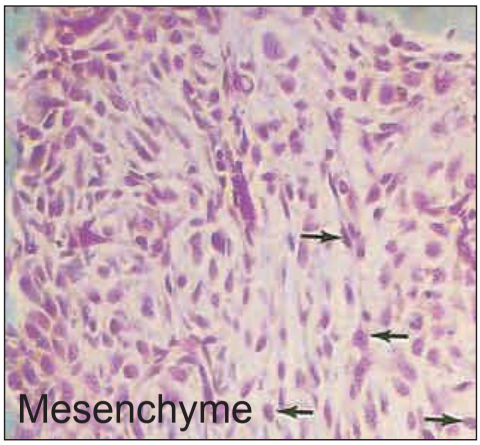


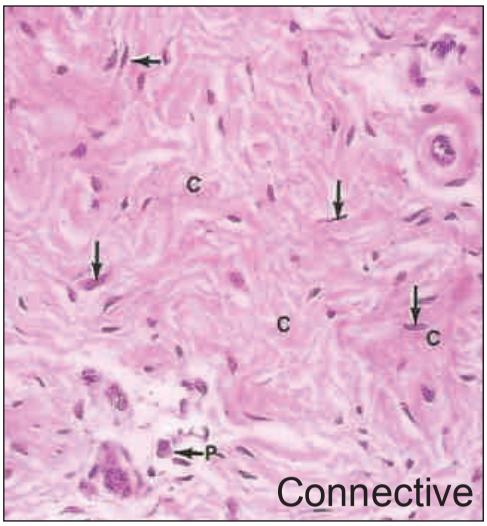


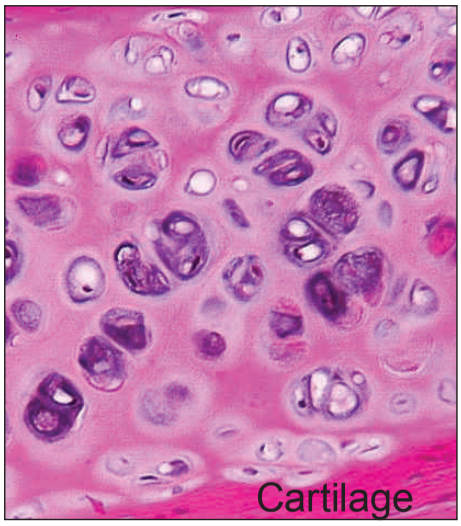
http://www.mun.ca/biology/desmid/brian/BIOL3530/DB_Ch02/DBNModel.html

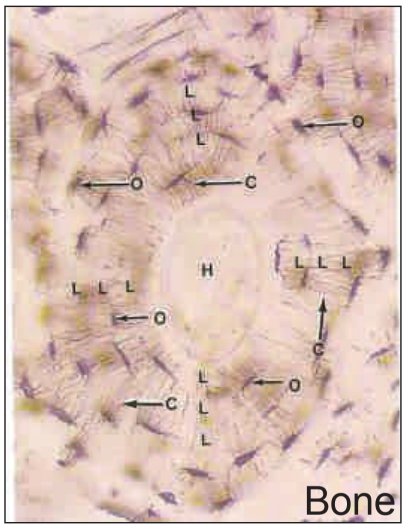
Basic derivatives of CT







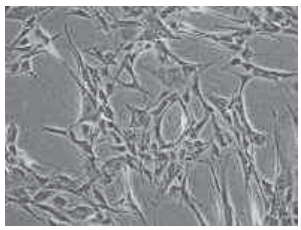


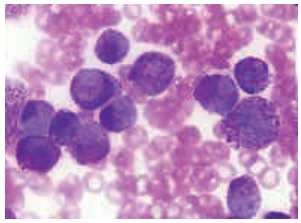


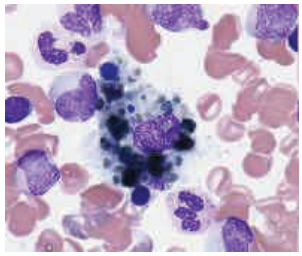
Cells of connective tissue

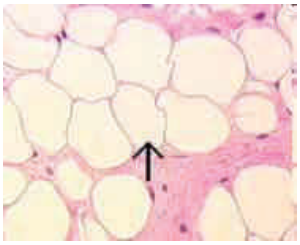
Cells

- Fibroblasts/fibrocytes/myofibroblasts
- Heparinocytes
- Macrophages of CT = histiocytes
- Plasma cells
- Lymphocytes
- Adipocytes
- Adult stem cells



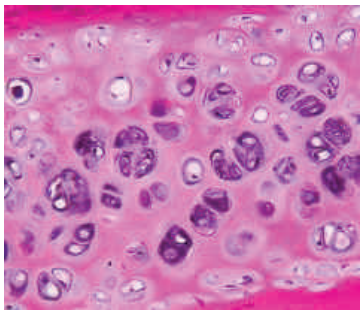


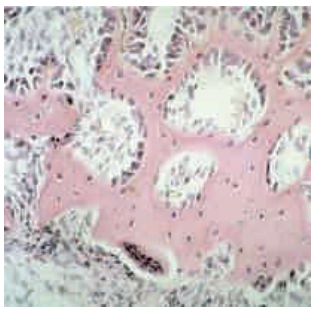


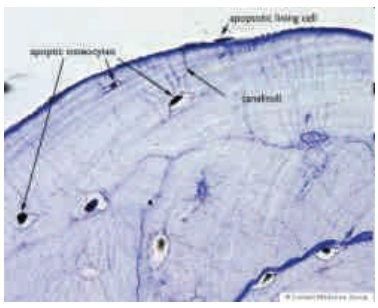


Extracellular matrix

- Fibrous compound
- Amorphous ground substance

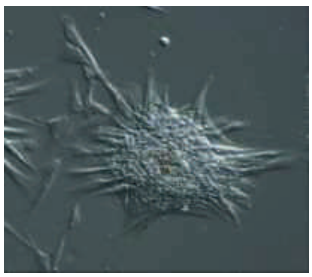


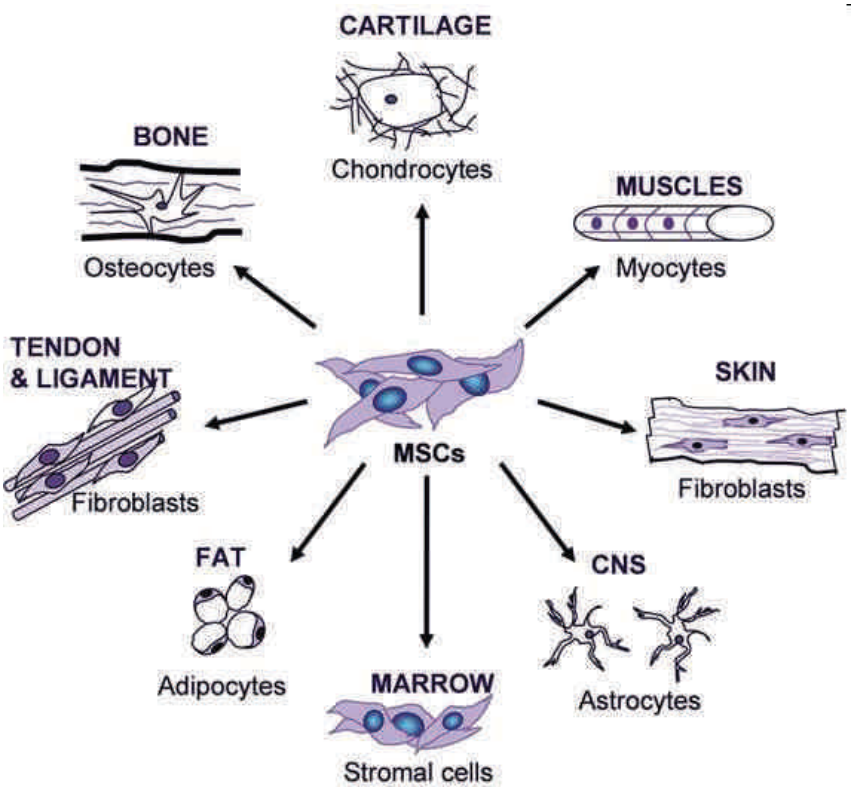




Cells of connective tissue

Mesenchymal (adult) stem cells



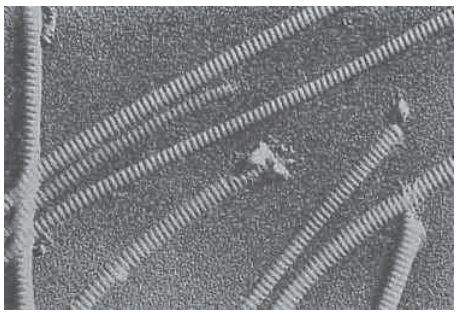


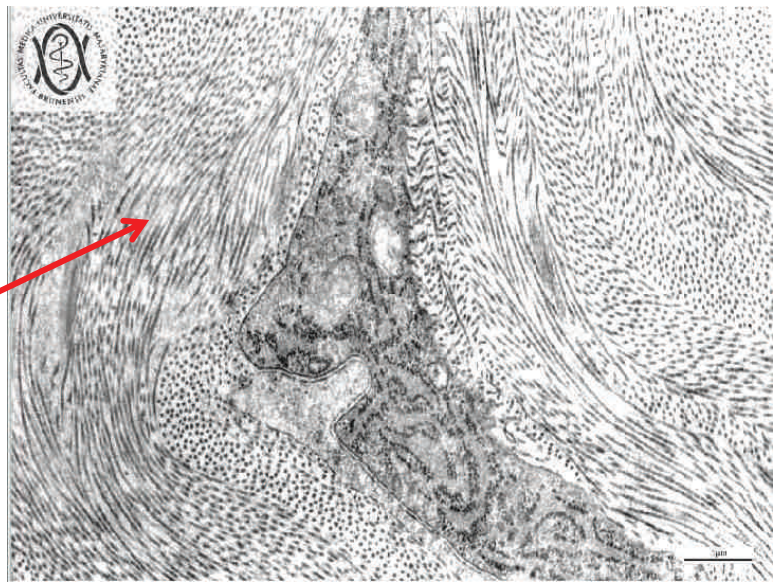
Koch *et al. BMC Biotechnology* 2007 7:26 doi:10.1186/1472-6750-7-26

Extracellular matrix – fibrous component

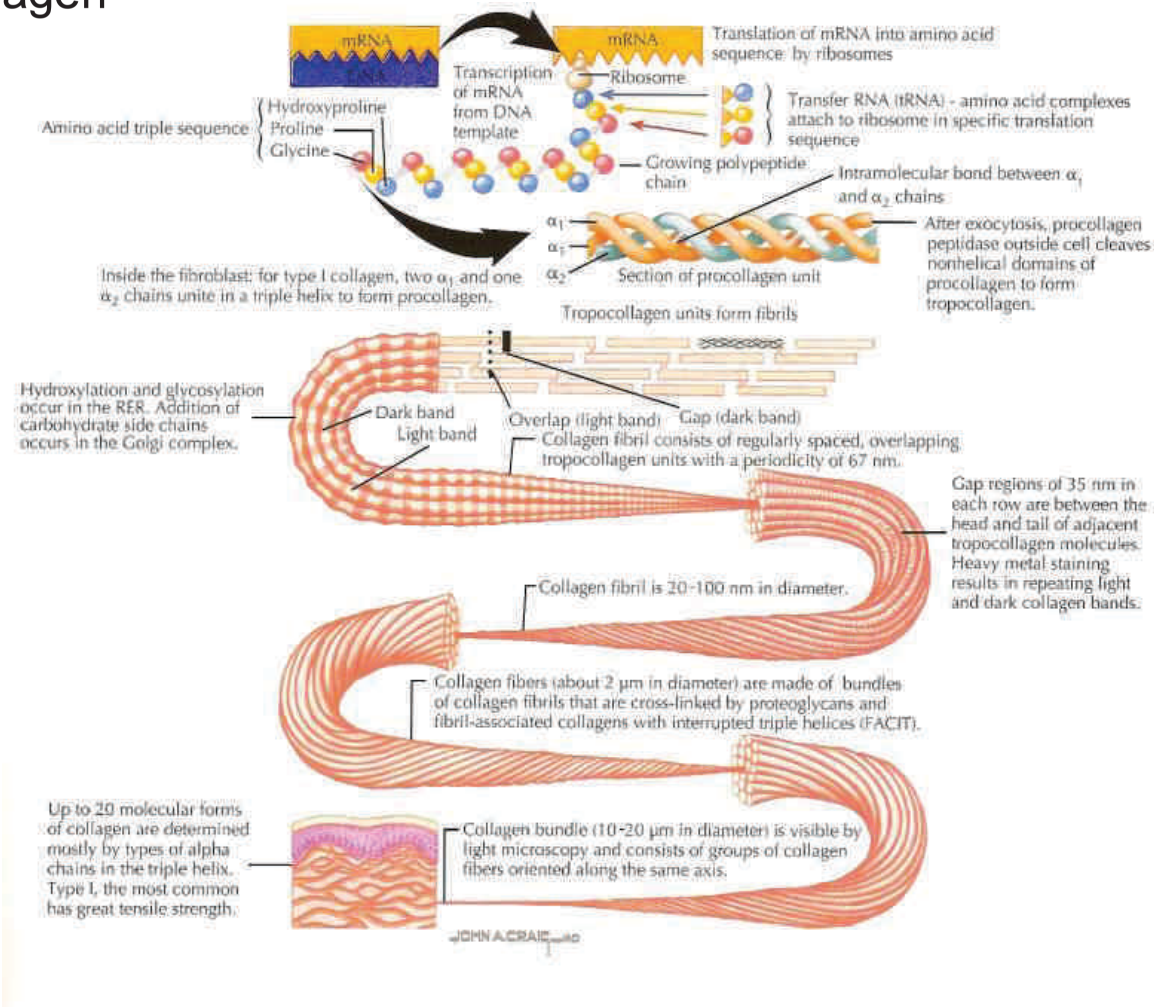
Collagen fibers

- family of fibrous proteins encoded by >35 genes (2013)
- polymer – subunit = tropocollagen; triple helix
- different structural and mechanical properties (strength, elasticity, pliability…)
- most abundant protein in human body (30% dry weight)





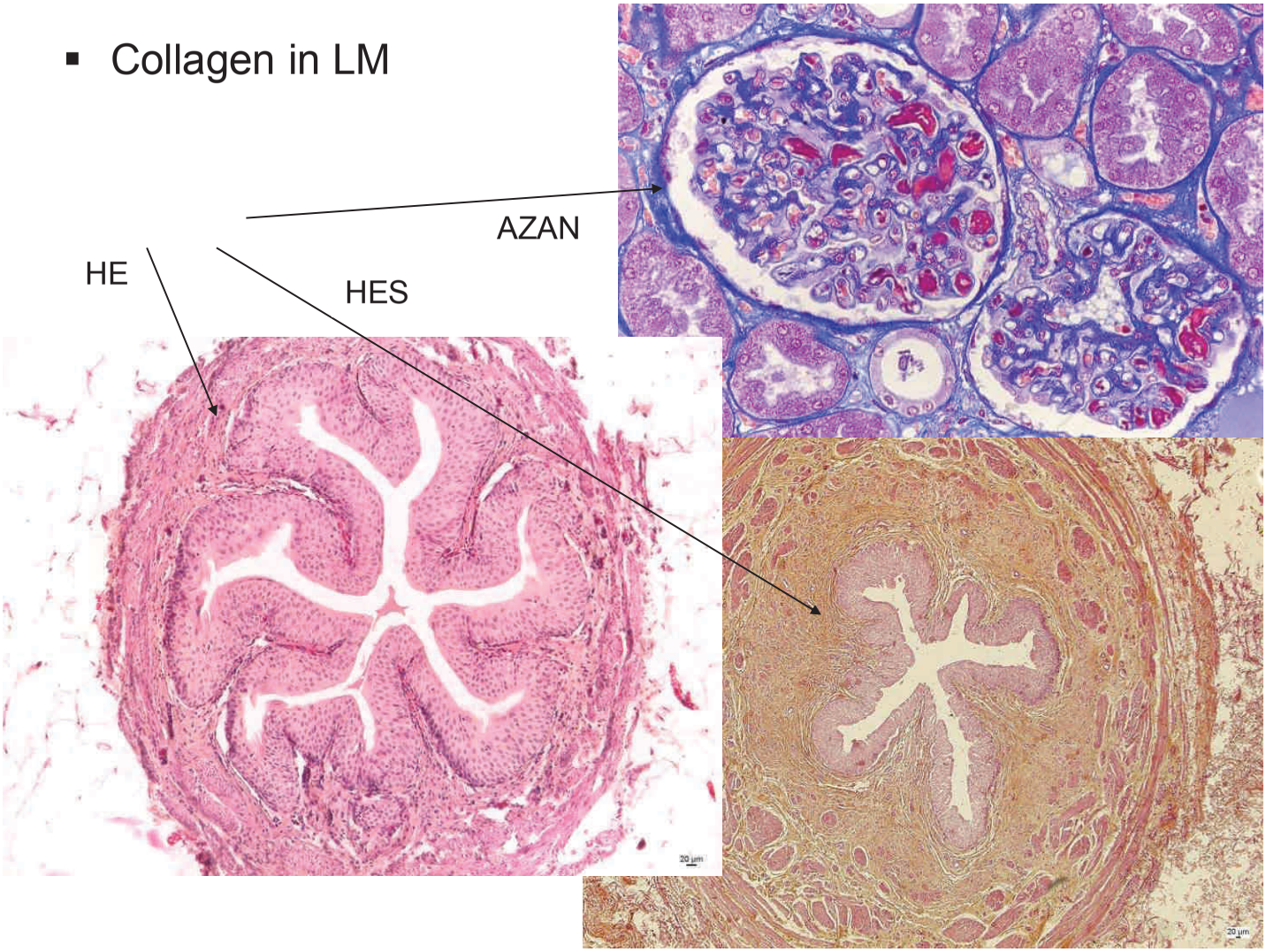
- Collagen



- Collagen

Type	Localization	Structure	Main function
I	Bone, tendons, meniscus, dentin, dermis, capsules of organs, loose CT 90% of type I	Fibrils (75nm) – fibers (1-20μm)	Resilience in pull
II	Hyaline and elastic cartilage	Fibrils (20nm)	Resilience in pressure
III	Skin, veins, smooth muscles, uterus, liver, spleen, kidney, lung	Like I, high content of proteoglycans and glycoprotiens, reticular network	Shape formation
IV	Basal lamina of epithelium and endtohelium, basal membranes	No fibrils or fibers	Mechanical support
V	Lamina of muscle cells and adipocytes, fetal membranes	Like IV	
VI	Interstitial tissue, chondrocytes – adhesion		Connecting dermis and epidermis
VII	Basal membrane of epithelium		
VIII	Some endothelia (Cornea)		
X	Growth plate, mineralized cartilage		Growth of bones, mineralization

- Collagen in LM



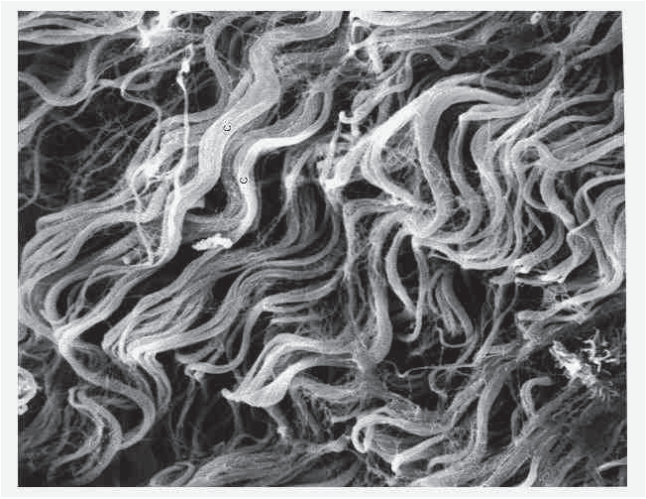
Julian Voss-Andreae "Unraveling Collagen",

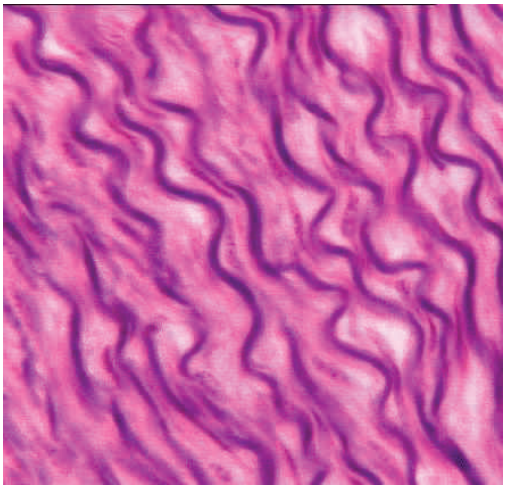
2005

Orange Memorial Park Sculpture Garden, City of South San Francisco, CA

Elastic fibers

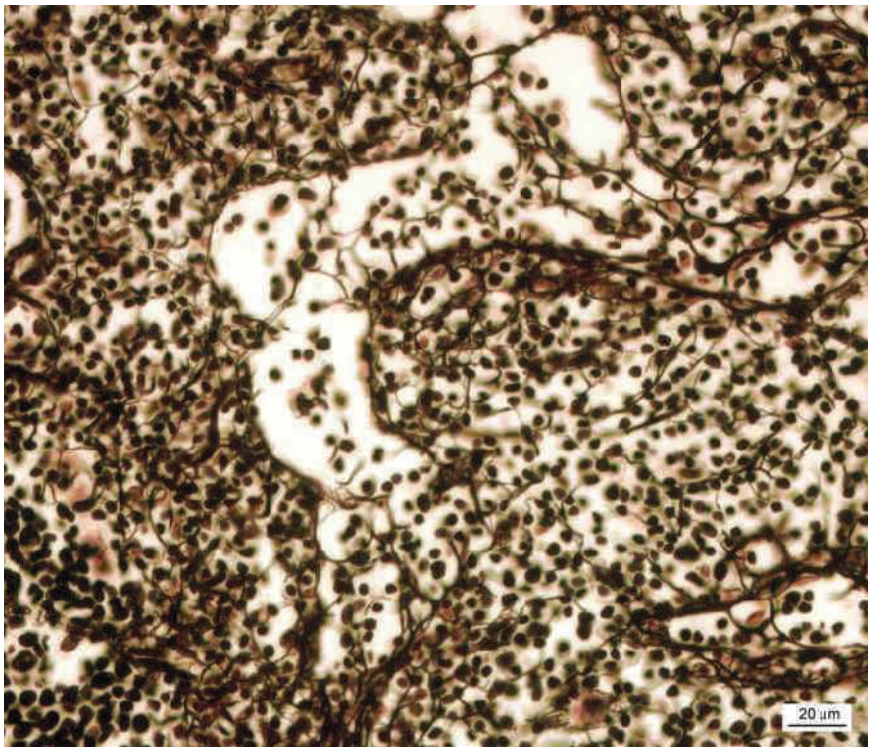
- less abundant than collagen
- polymer – tropoelastin
- minimal tensile resistance, loss of elasticity if overstretched
- reduction of hysteresis = allow return back to original state after mechanic change





Reticular fibers

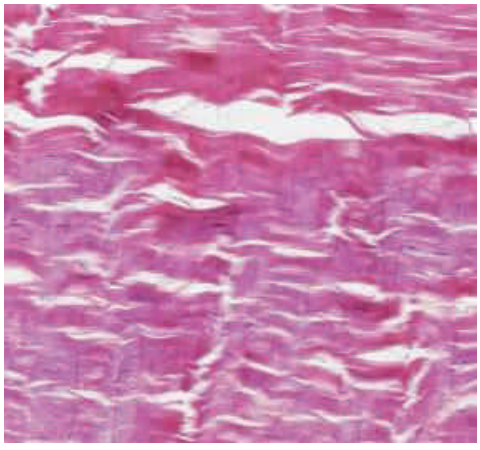
- collagen 3D meshwork
- bone marrow, spleen, lymphatic nodules
- microenvironment for e.g. hematopoietic stem cells and progenitors

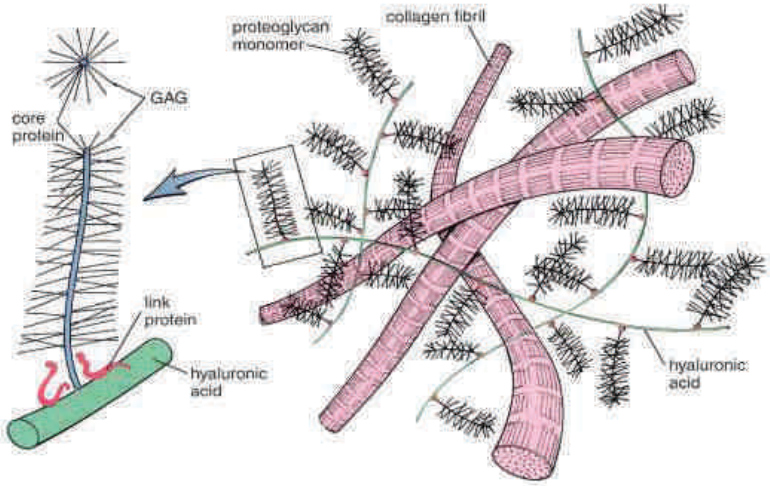


- Extracellular matrix – ground matrix

Amorphous extracellular matrix

Colorless, transparent, homogenous substance consisting of glycosaminglycans, proteoglycans and structural glycoproteins



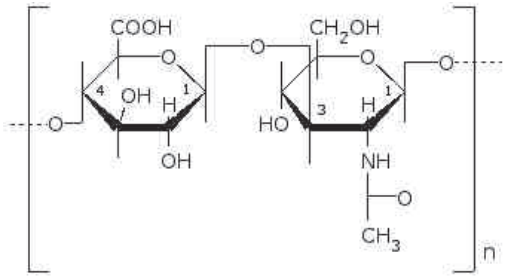


- Glycosaminoglycans

linear polysaccharides composed of two disaccharide subunits – uronic acid and hexosamine

polysaccharides rich in hexosamines = acid mukopolysaccharides

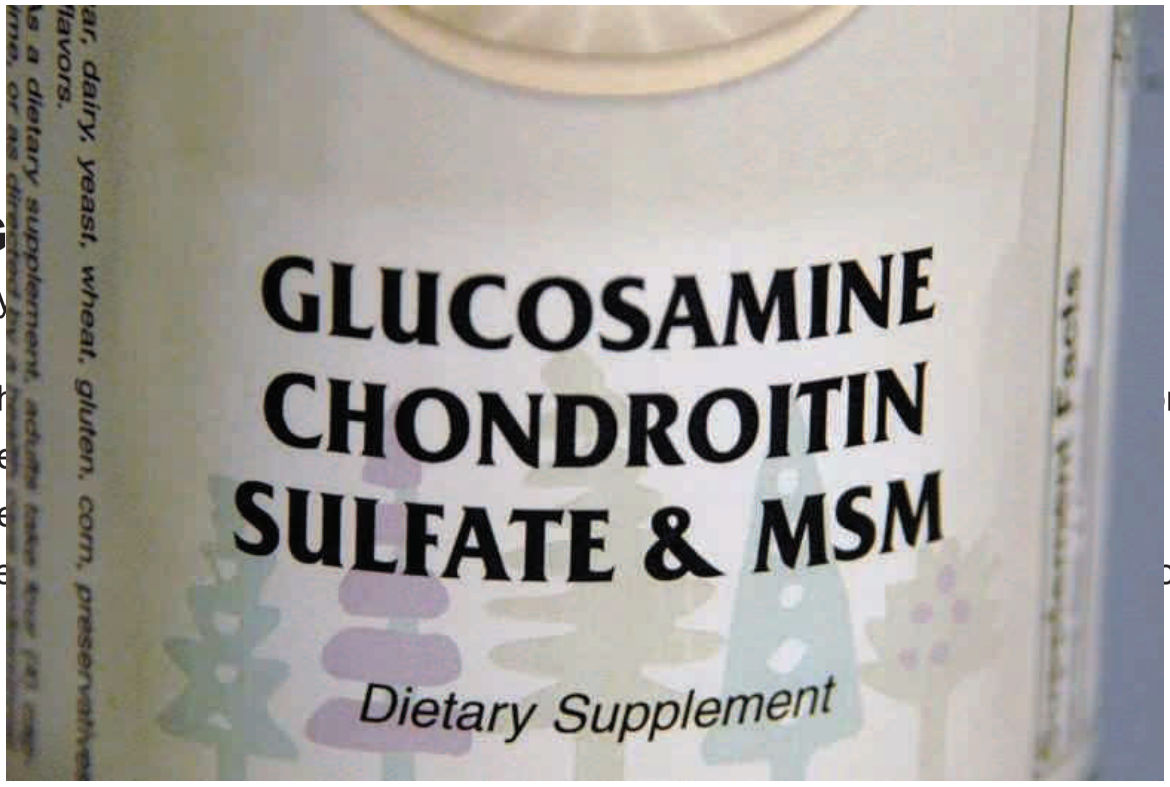
glucuronic or iduronic acid



glucosamin or galactosamin

- Glycosaminoglycans

They bind to protein structures (except for hyaluronic acid)



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Proteoglycans

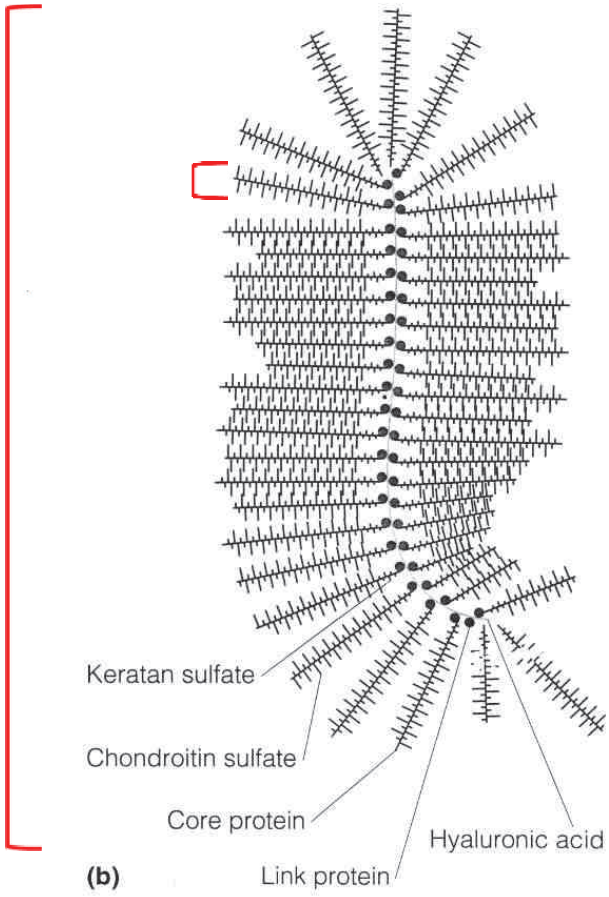
— protein + dominant linear saccharide component

— proteoglycan aggregates

— water-binding, volume dependent of hydratation

— aggrecan (cartilage)
— syndecan
— fibroglycan

Figure 9.25b Proteoglycan structure in bovine cartilage



From Mathews and van Holde: *Biochemistry 2/e.* © The Benjamin/Cummings Publishing Co., Inc.

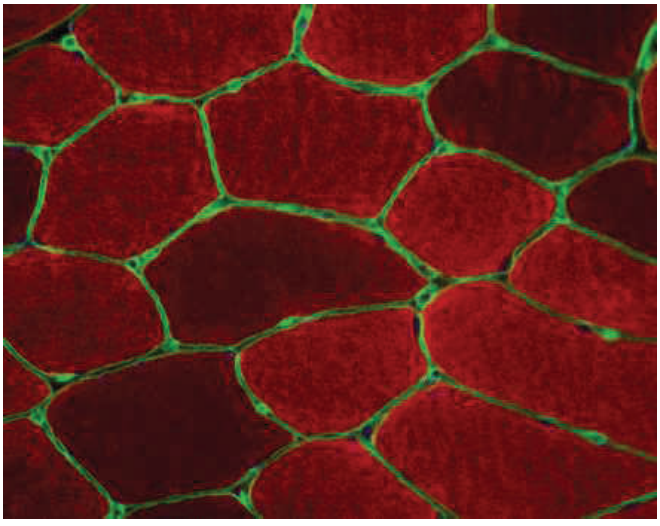
Structural glycoproteins

• dominant protein + branched saccharide component
• interaction between cells and ECM

— **fibronectin** – connects collagen fibers and glykosaminoglycans, cell adhesion and migration

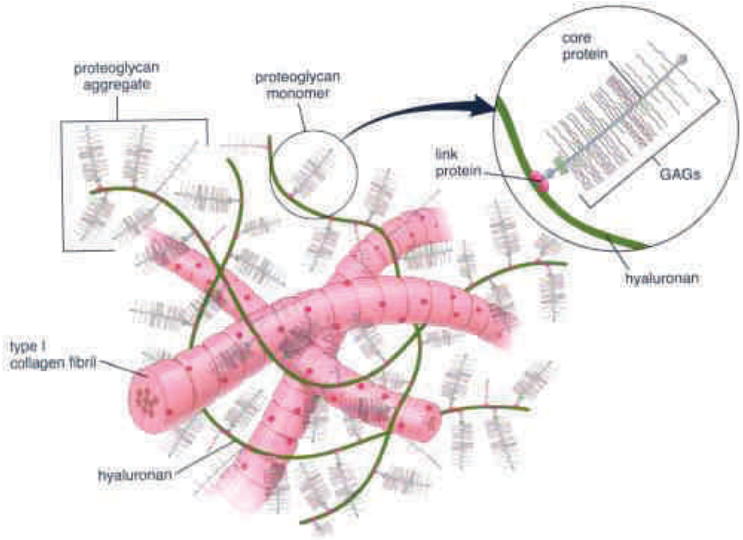
— **laminin** – basal lamina – epithelial integrity

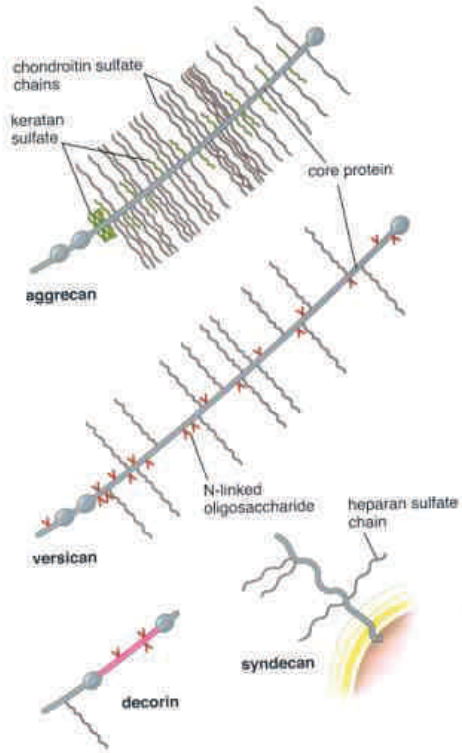
— **chondronectin** – cartilage – adhesion of chondrocytes to collagen



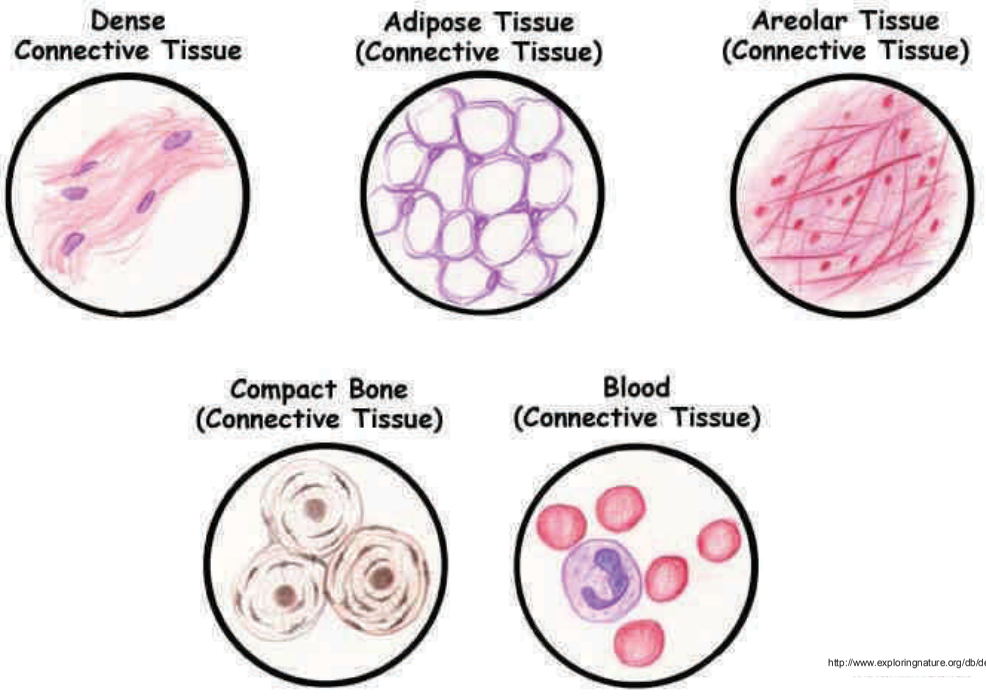
(J. Nutr. 136:2123-2126, 2006)

- Composition of amorphous ground matrix





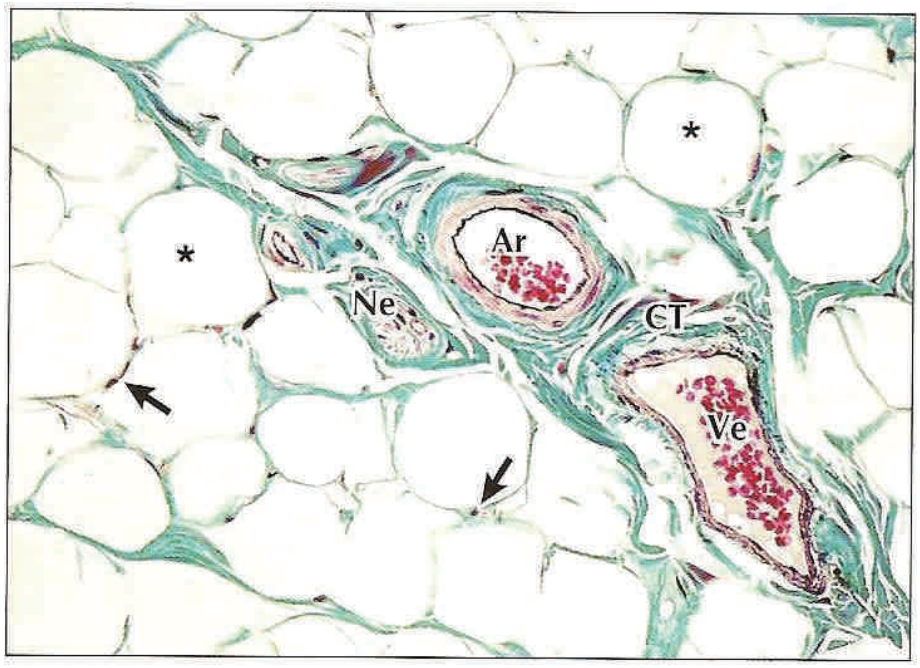
- **Classification of specialized connective tissue**



http://www.exploringnature.org/db/detail.php?dbID=21&detID=691

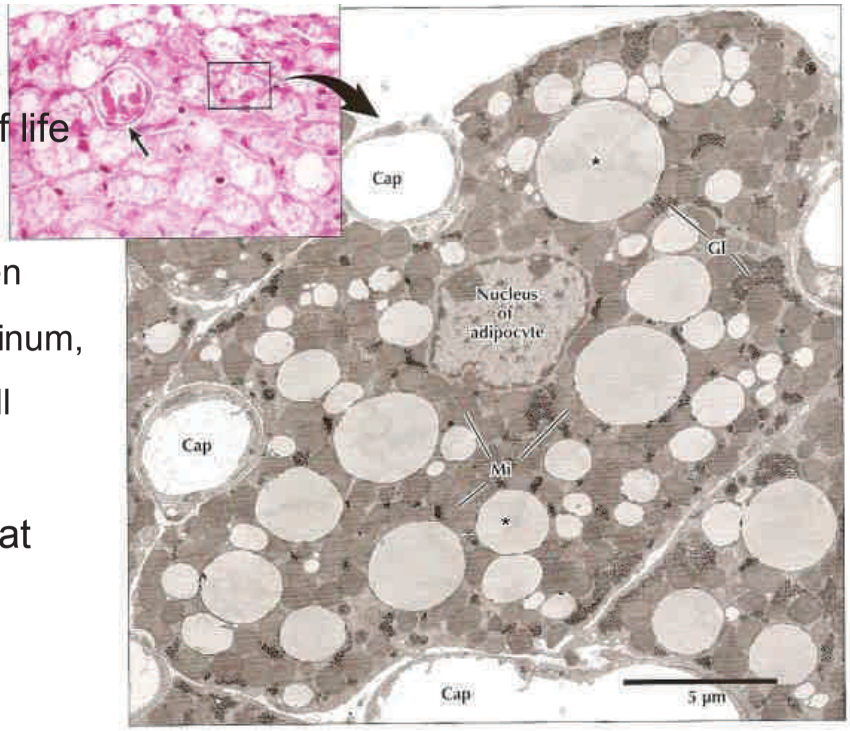
Adipose tissue

- Adipocytes, fibroblasts, reticular, collagen and elastic fibers, capillarie
- White and brown adipose tissue



Brown adipose tissue

- fetus and child to 1st year of life
- fast source of energy
- typical localization – between shoulder blades, axilla, mediastinum, around kidneys, pancreas, small intestine
- small cells with numerous fat droplets



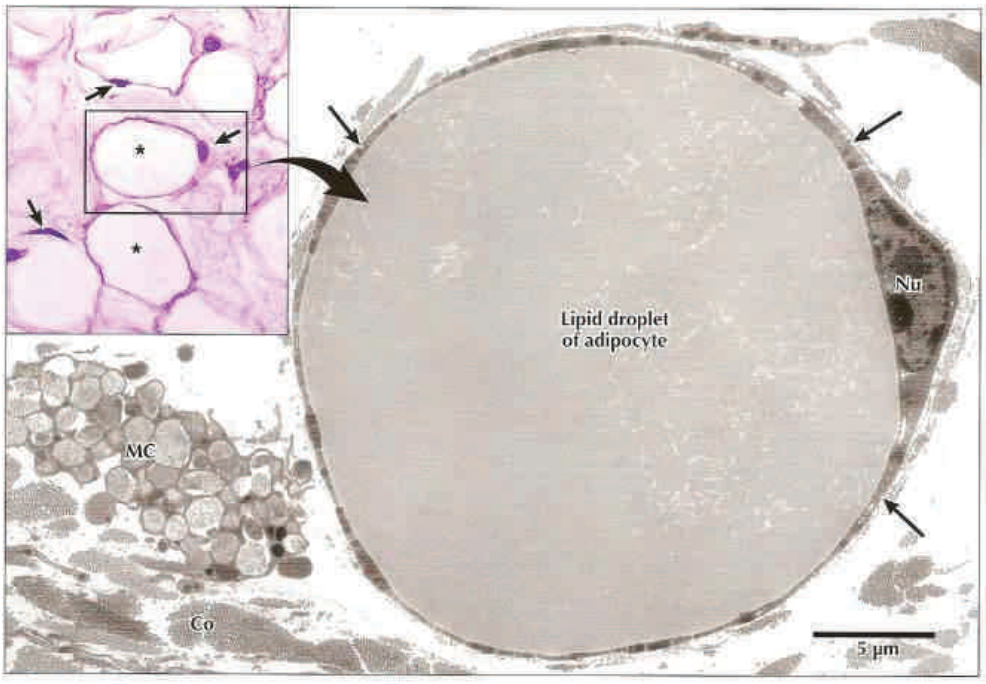
White adipose tissue

• adipocytes are actively form until 2nd year of life

• no innervations, but rich vascularisation

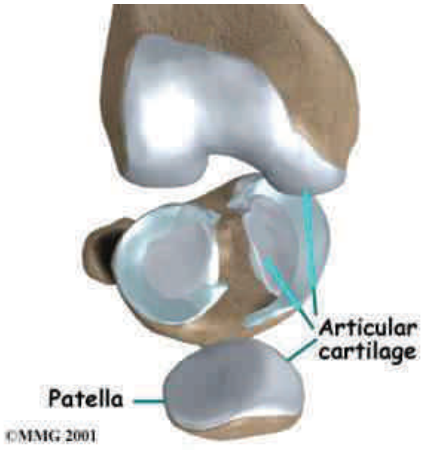
• adipocytes with only one lipid droplet

• leptin (adipokinins)



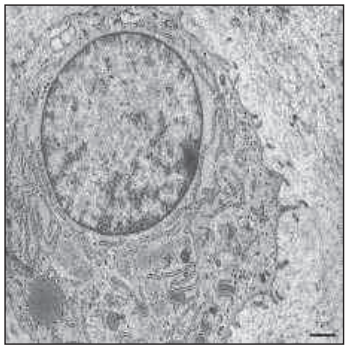
Cartilage

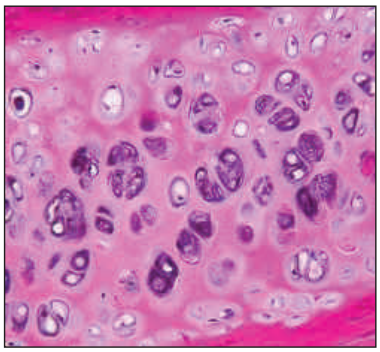
— specialized connective tissue with continuous ECM
— flexible, mechanically resistant
— avascular, no innervation
— support of soft tissues
— diarthrosis
— growth



Composition and structure

- perichondrium – connective tissue around cartilage (not present in joints)
- chondroblasts, chondrocytes
- extracellular matrix (collagen and elastic fibers, amorphous ground matrix)





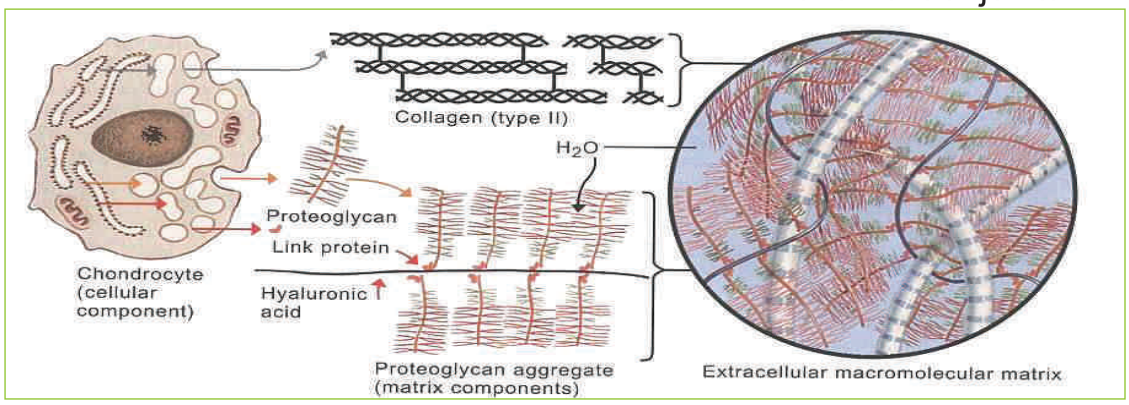
Collagen type II

Glykosaminoglycans

(Hyaluronic acid, chondroitinsulphate, keratansulphate)

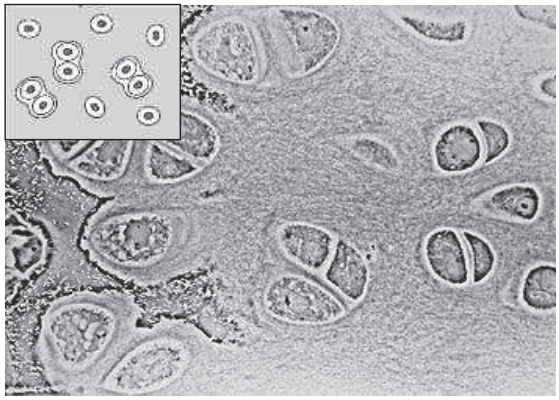
Proteoglycane aggregates

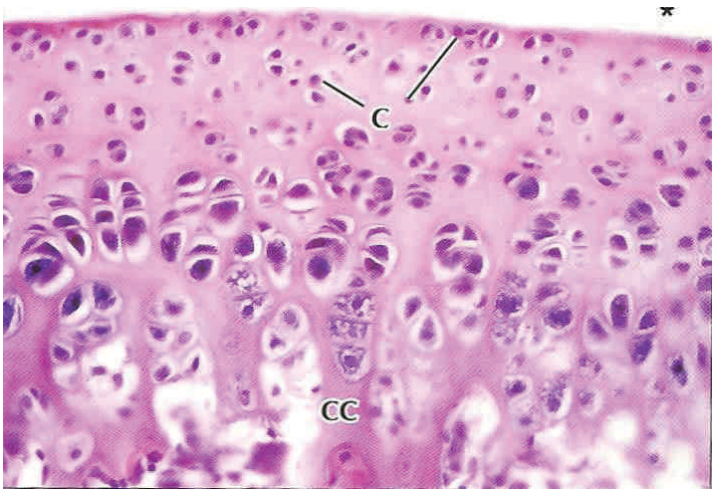
Hydrophilic character – holds water → low friction → smooth movement of joints

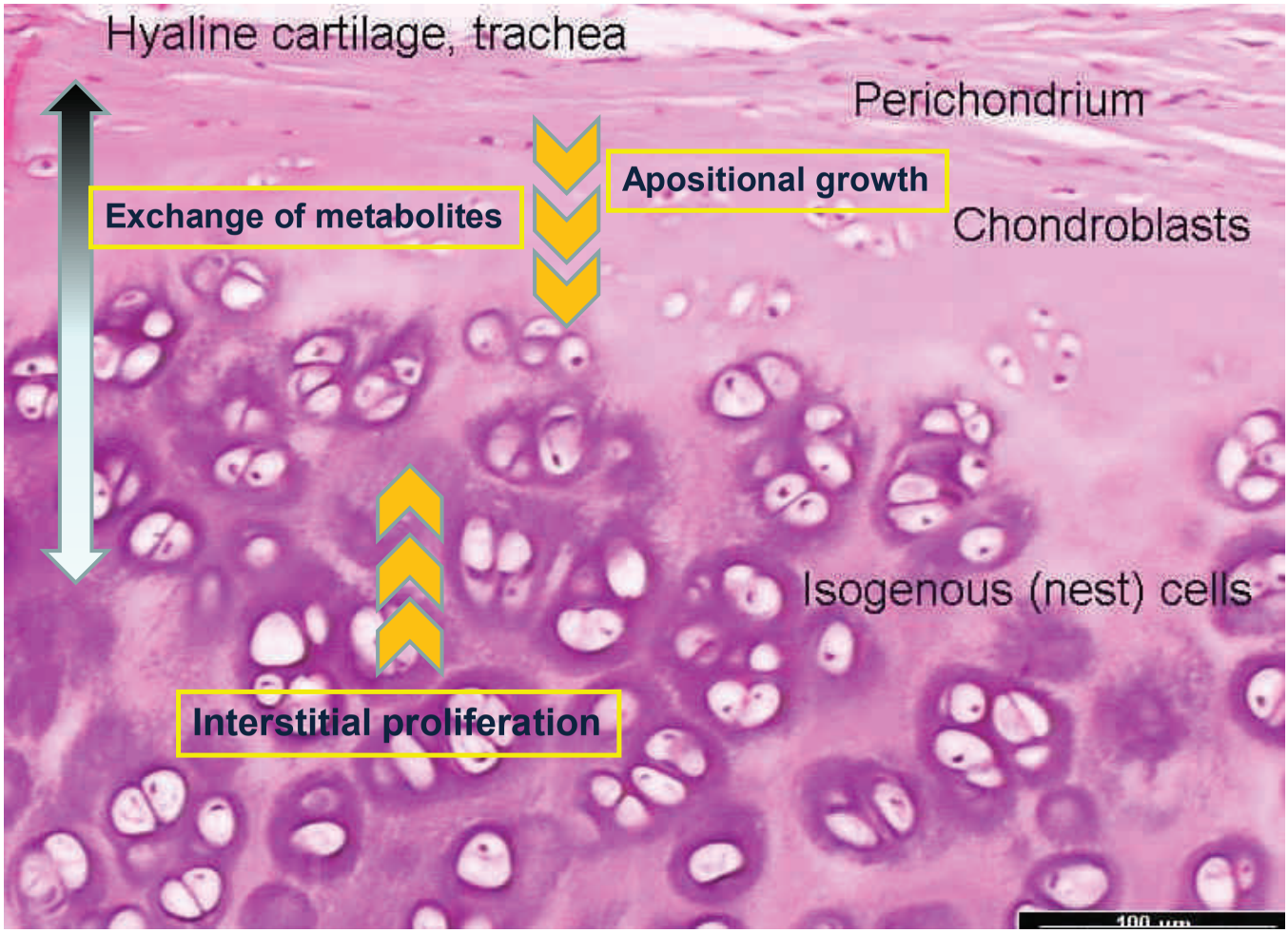


Hyaline cartilage

- most abundant
- temporary embryonal/fetal skeleton
- epiphyseal growth plate
- articulation (joints) respiratory passages
- isogenic groups





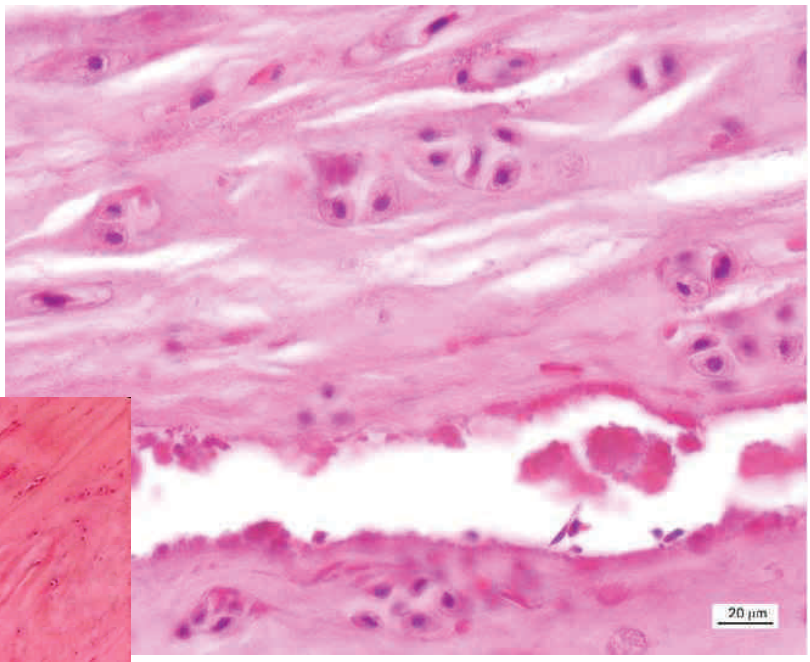


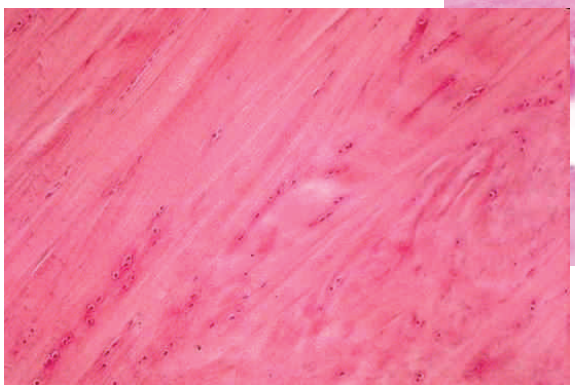
- Elastic cartilage

- Elastic fibers in matrix
- No isogenetic groups
- Auricula, meatus, larynx, epiglottis

Fibrocartilage

- Fibrous compound dominant – collagen I and II – mechanical durability
- Minimum of amoprhous matrix-fibers visible
- Intervertebral discs, symphysis pubis, articular discs, meniscus



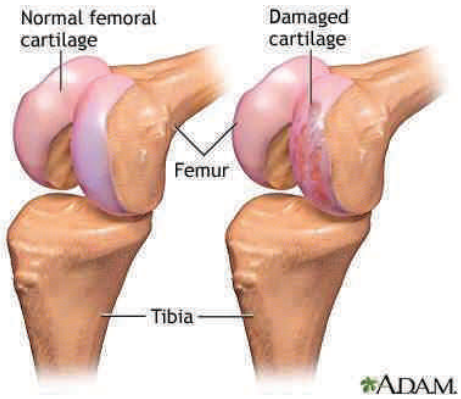


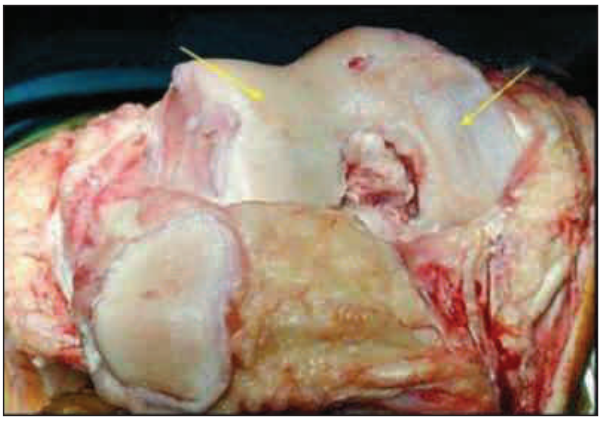
Clinical correlations

Cartilage – no innervation, no vascularization – no spontaneous regeneration

No migration of chondrocytes to site of damage

Initiation of other degenerative events leading to cartilage erosion (arthritis)





Therapy:

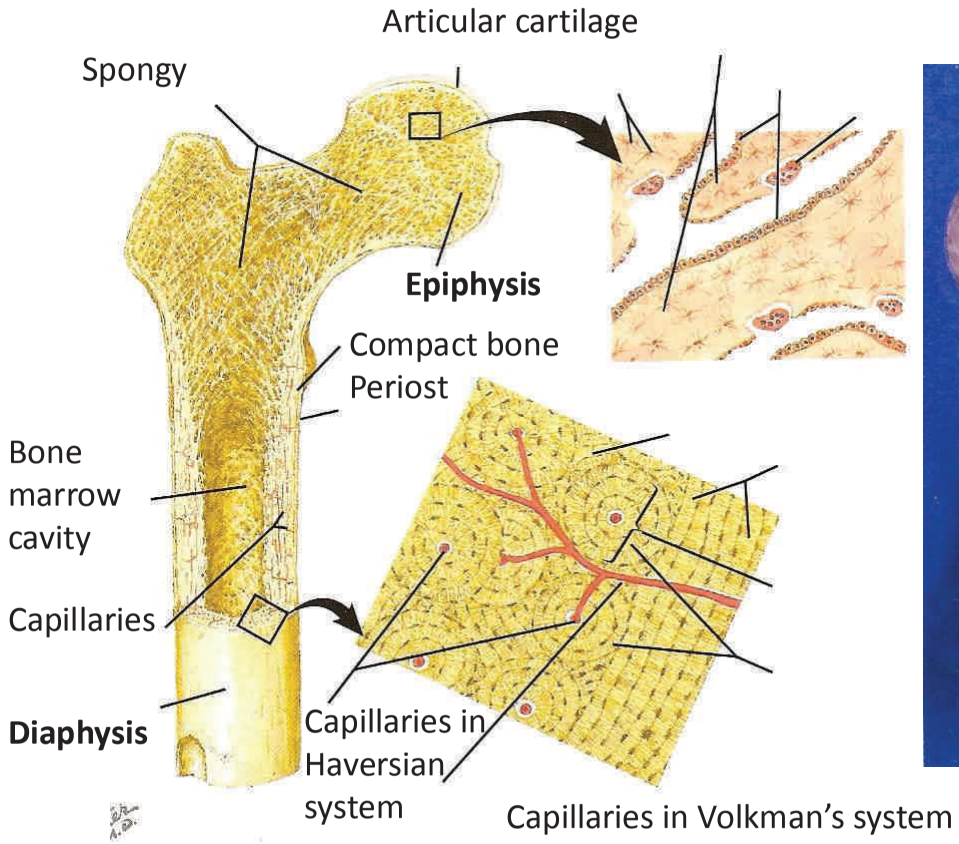
- joint mobility

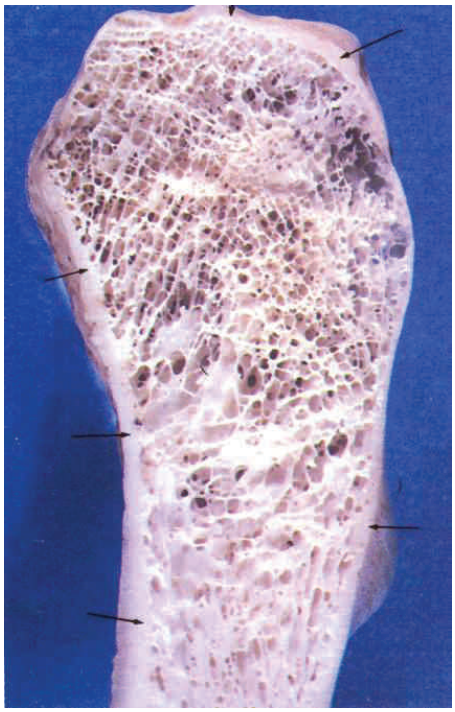
- restoration of biochemical and biophysical parameters of cartilage

- prevention of further damage

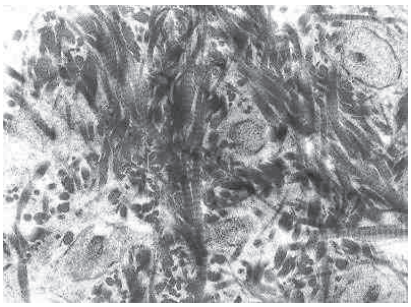
- removal of damaged tissue, autologous transplantation, MSCs on biocompatible scaffolds

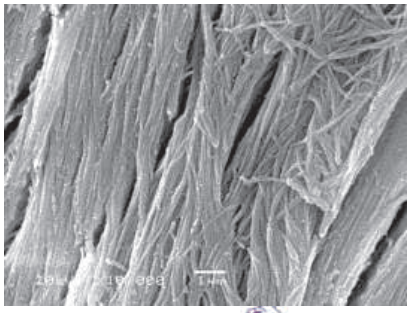
Bone

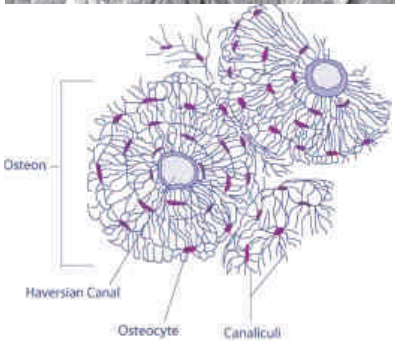




Histological classification of bone tissue







- **Primary (woven, fibrous)**

- Temporary, growth and regeneration of bones, collagen fibrils woven
- Replaced by secondary bone
- Remains only in some parts of body - sutures of skull, *tuberositas ossium*, tooth cement

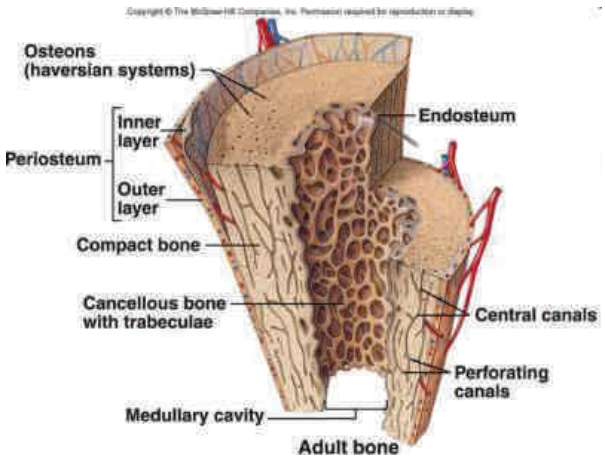
- **Secondary (lamellar)**

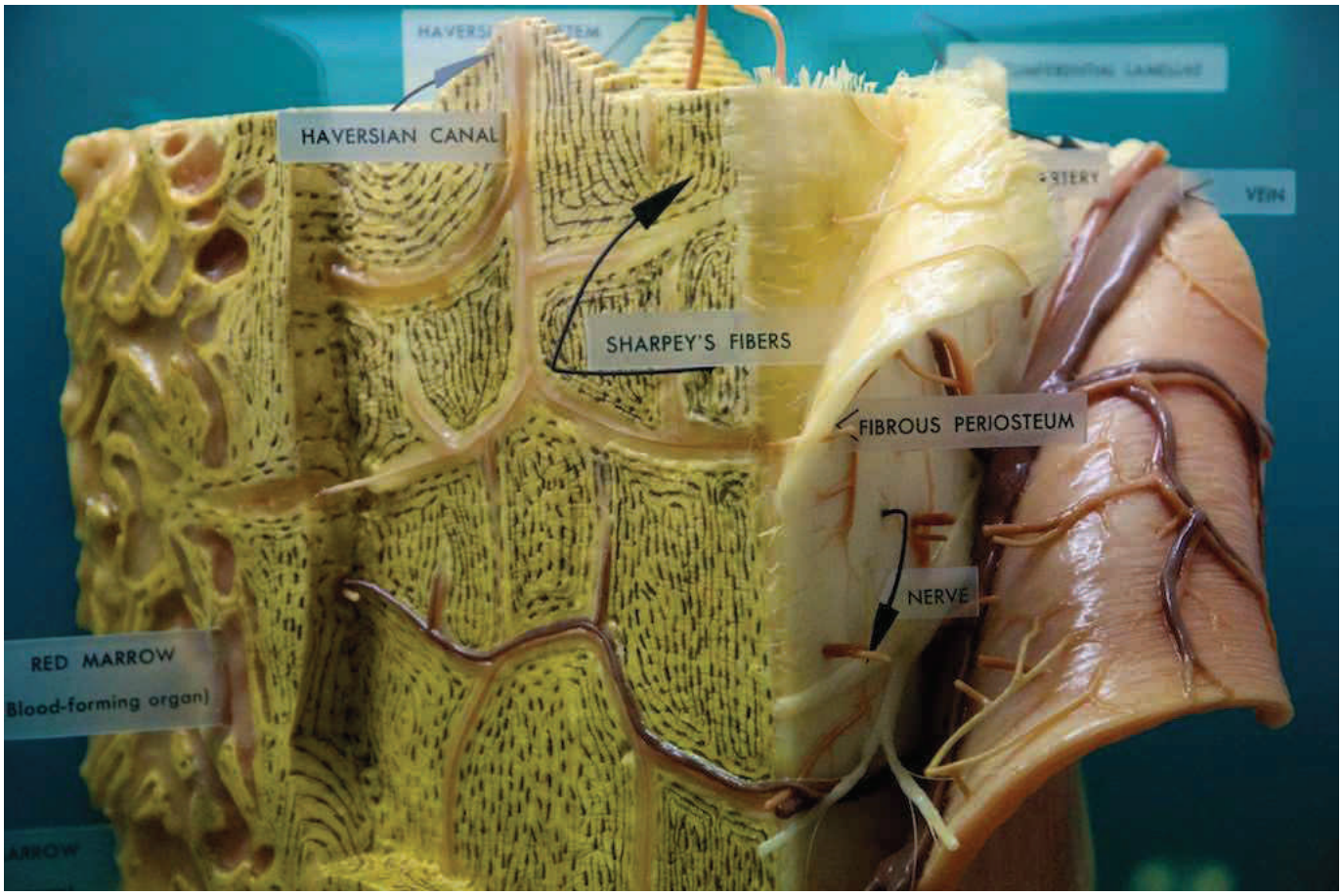
- Lamellae – collagen fibers in concentric layers (3-7μm) around a canal with capillaries = Haversian system (osteon)
- Spongy (trabecular)
  - Trabeculae, similar to compact
  - Epiphyses of long bones, short bones, middle layer of flat bones of the skull (*diploe*)
- Compact
  - Outer and inner coat lamellae typical Haversian systems
  - Volkmann's canals
  - Interstitial canals

Surface of compact bone

- **Outer surface**

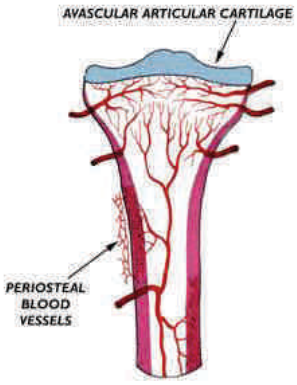
- Synovial joint – hyaline cartilage
- periosteum (periost) – membrane – dense CT, inner layer (osteoblasts) and outer layer (fibrous CT)
- Inactive bone - fibrous CT in periost dominant
- Collagen fibers – parallel to the bone surface
- Sharpey's fibers fix periost to the bone

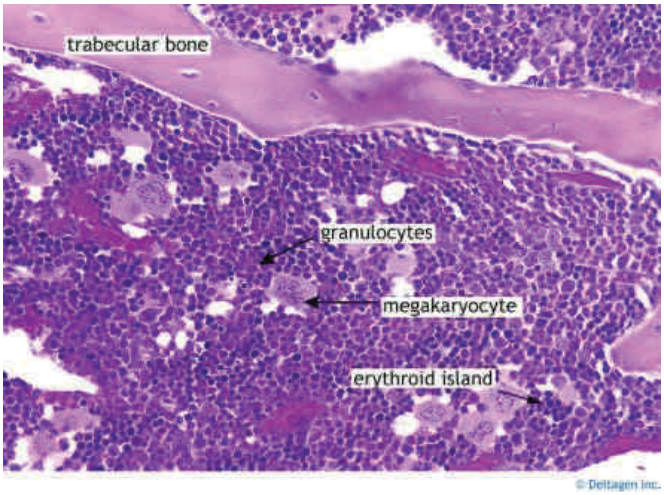


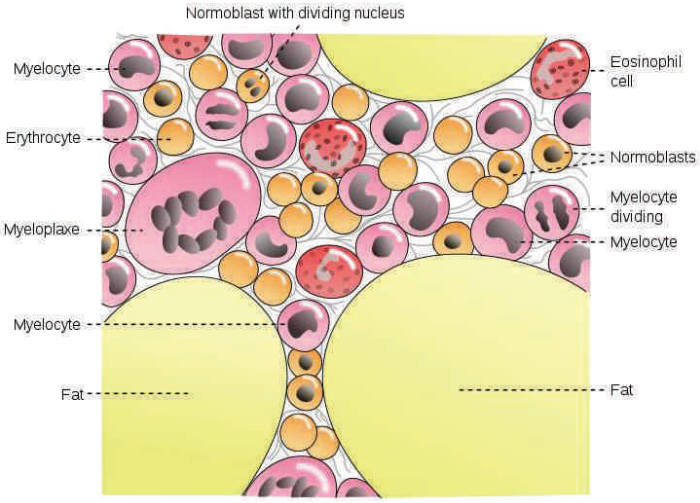


National Museum of Natural History NY, USA

- **Inner surface – cavities lining**
- Medullar cavity
- Endosteum (endost) – single cell lining – bone remodeling
- Red bone marrow – hematopoiesis
- Yellow and gray bone marrow – adipocytes or CT
- Rich vascularisation

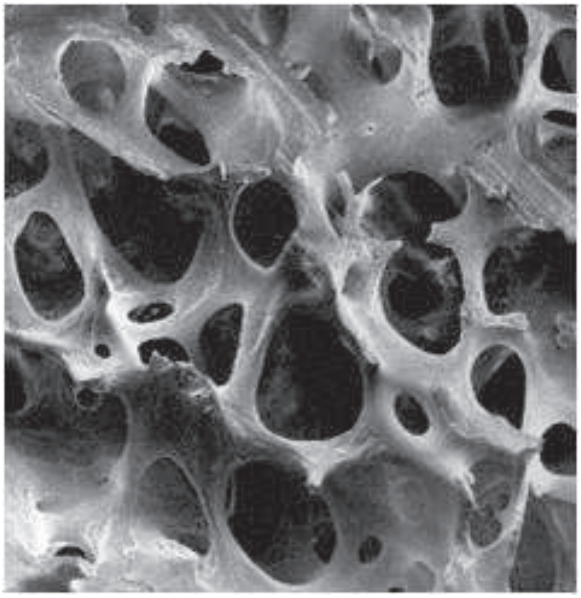


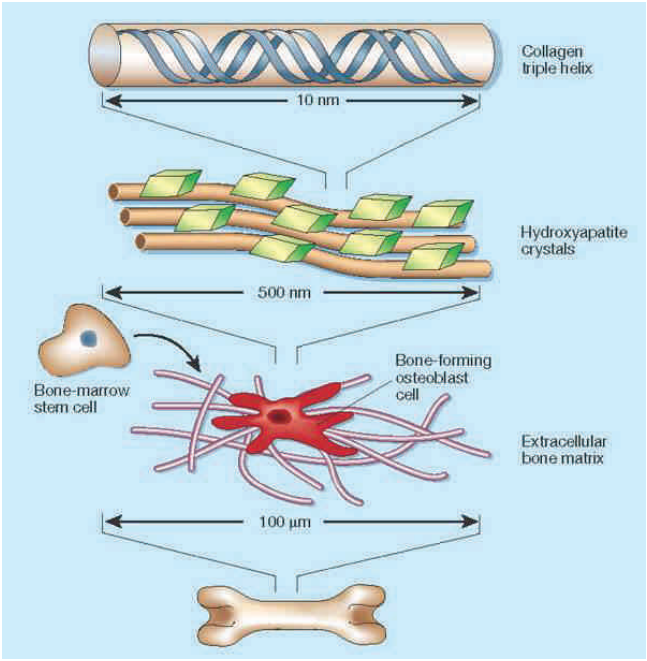




Bone matrix

- 60% mineral compound, 24% organic compound 12% H_20, 4% fat
- Crystals – calcium phosphate, hydroxyapatite

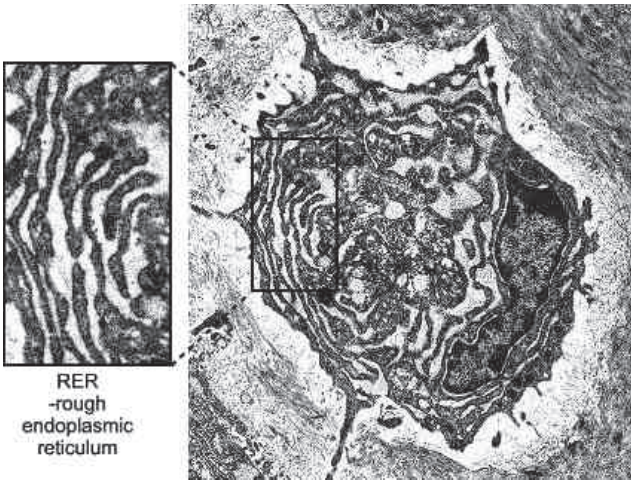


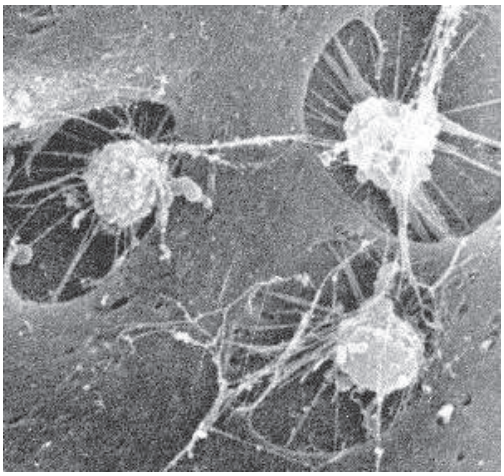


▪ Cells

- **Osteoblasts**

- specialized bone cells
- produce ECM – collagen (I) and noncollagenous proteoglycans, glycoproteins
- osteocytes

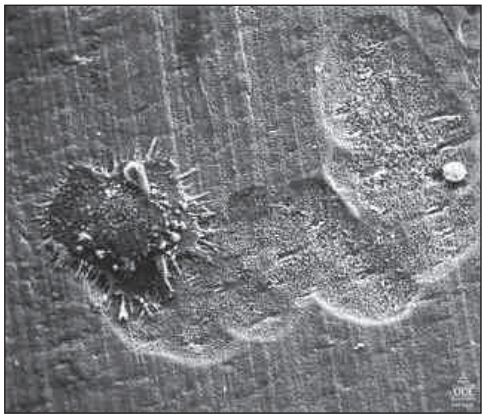


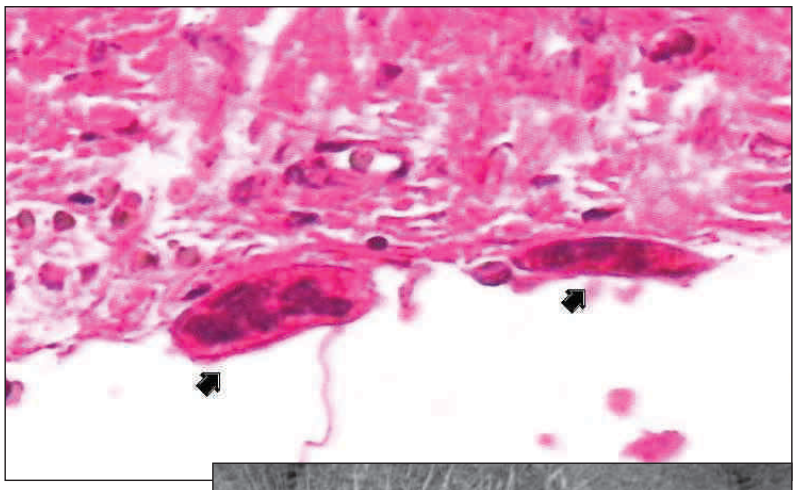


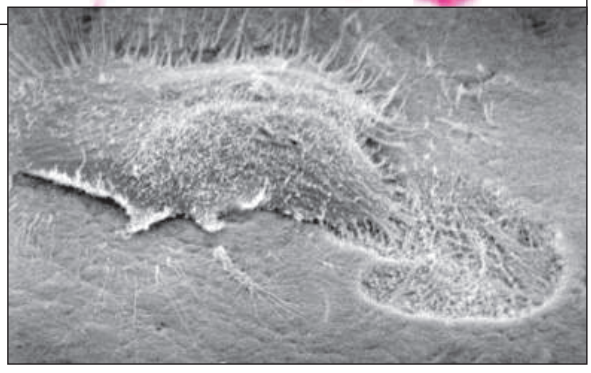
▪ Cells

- **Osteoclasts**

- multinuclear, form by fusion of macrophages
- bone matrix resorption

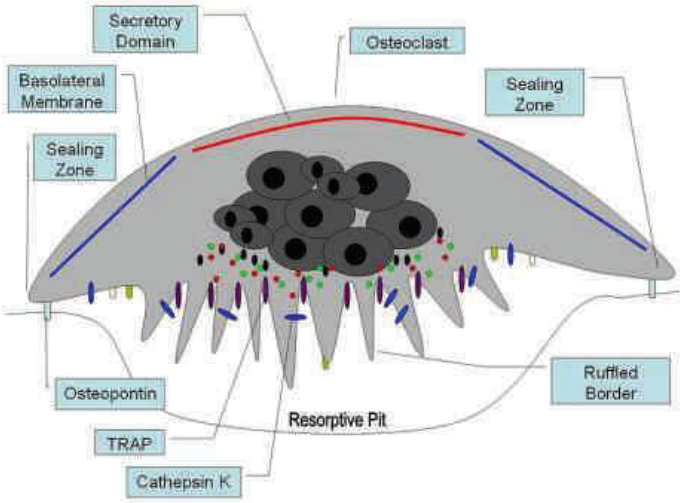


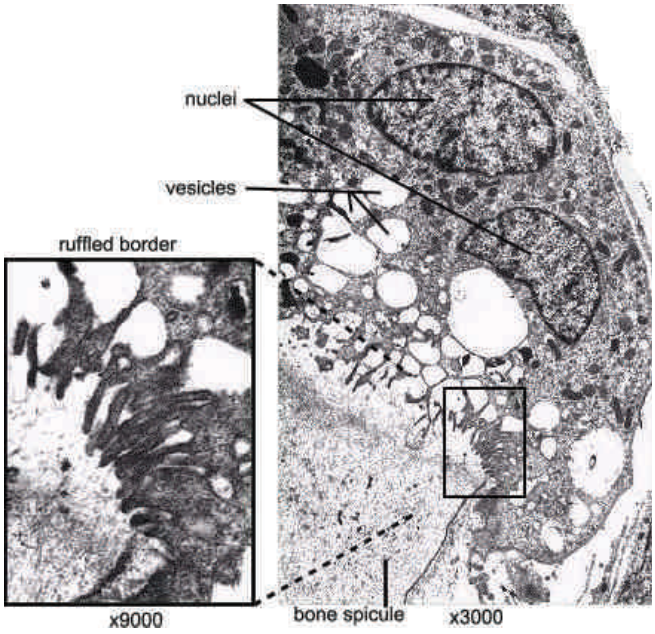




▪ Cells

- **Osteoclasts**
- Complex architecture
- Enzymes degrading organic matrix
- HCl





▪ Ossification

Intramembranoeous

- Mesenychymal cells → osteoblasts

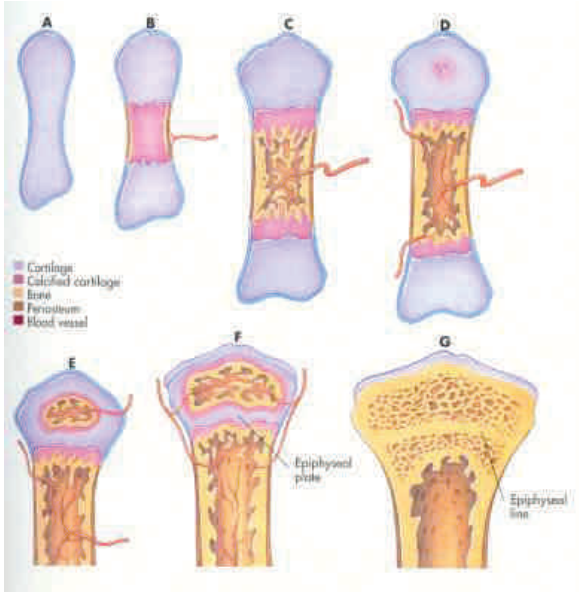
- Ossification center – rich vascularisation, differentiation of osteoblasts, synthesis of primary bone

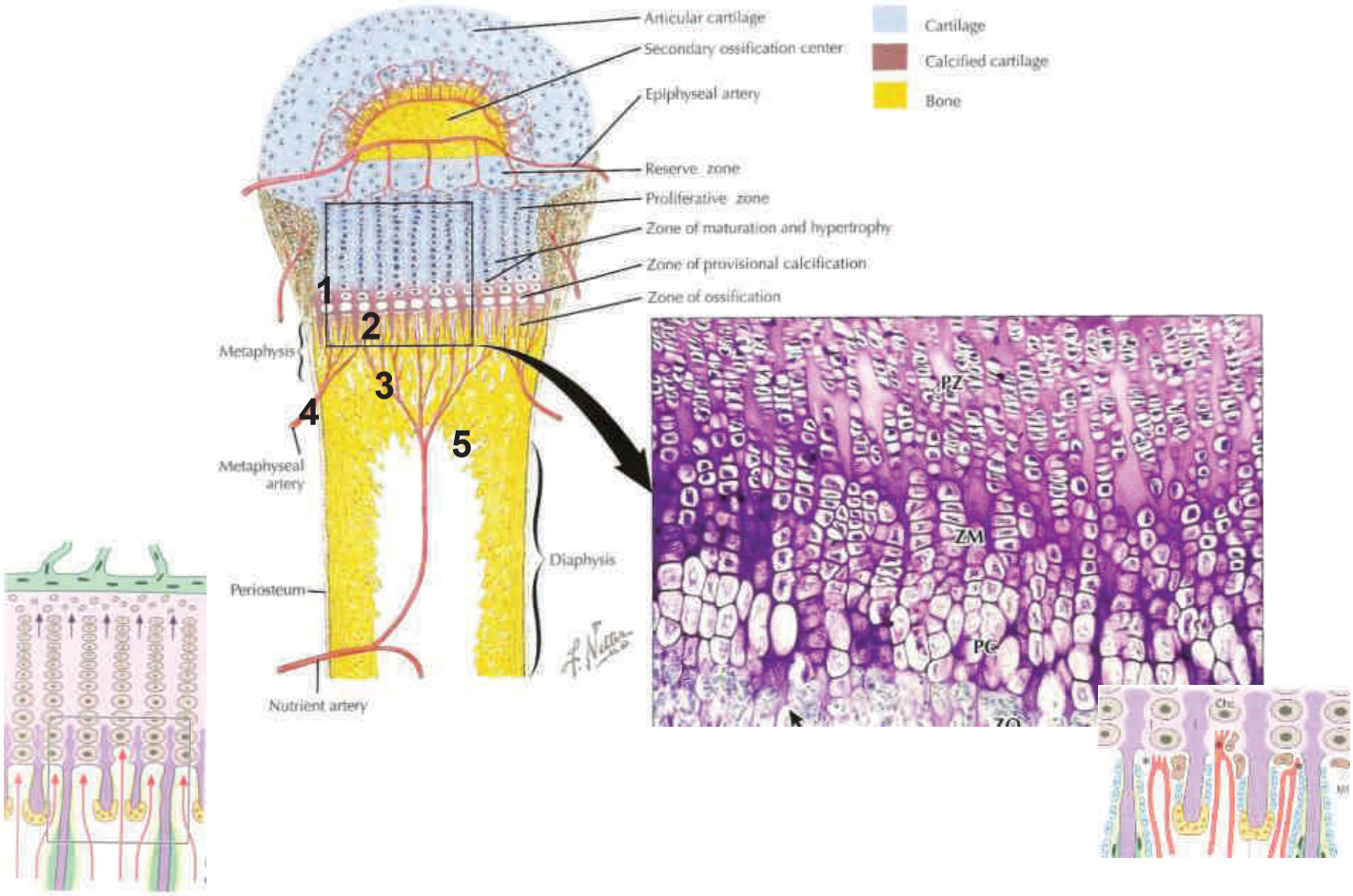
Endochondral

- Cartilage model

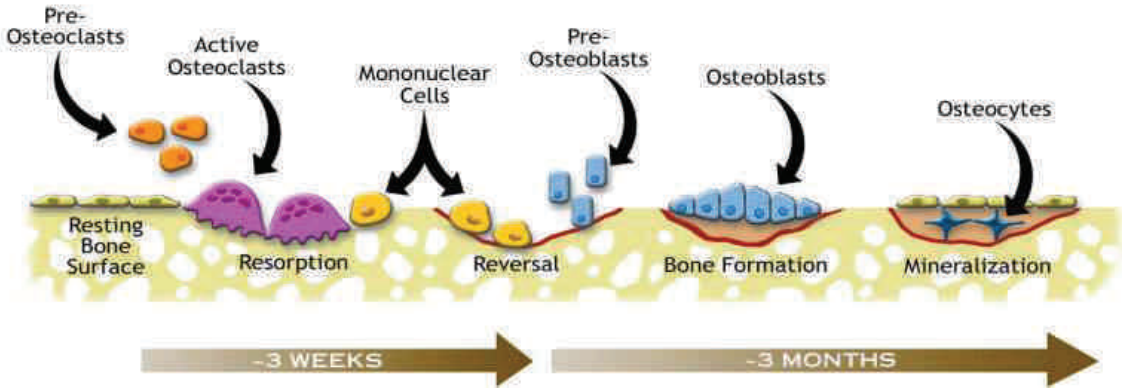
- Growth plate

- Primary and secondary ossification centers (diaphyse, epiphyses)





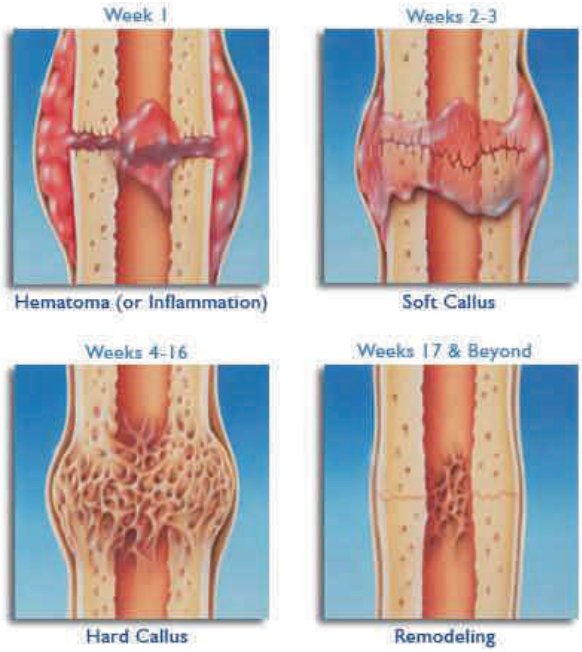
Bone Remodeling Cycle



http://ns.umich.edu/Releases/2005/Feb05/img/bone.jpg

- Clinical correlations

- **Fracture healing**



Reactive Phase
- Fracture and inflammatory phase
- Granulation tissue formation

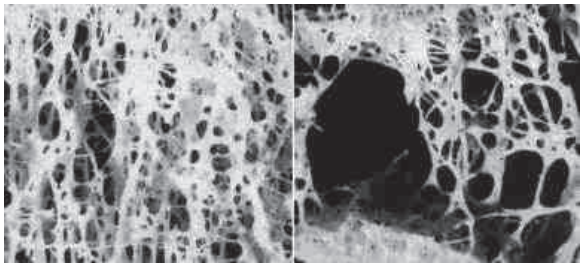
Reparative Phase
- Cartilage *callus* formation
- Lamellar bone deposition

Remodeling Phase
- Remodeling to original bone shape

- Clinical correlations

– disbalance in osteosynthesis and osteoresorption

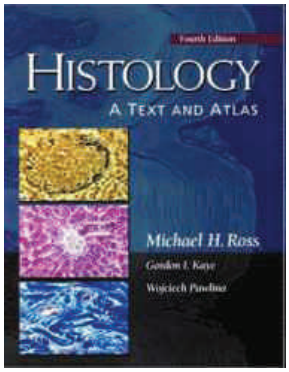
- OSTEOPOROSIS

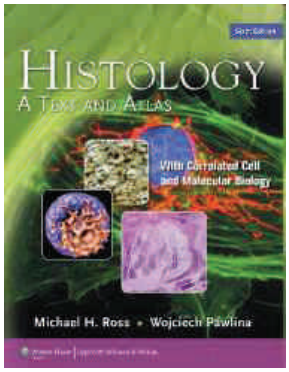


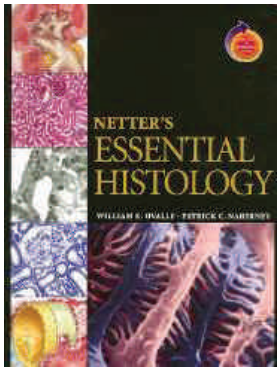
- OSTEOPETROSIS

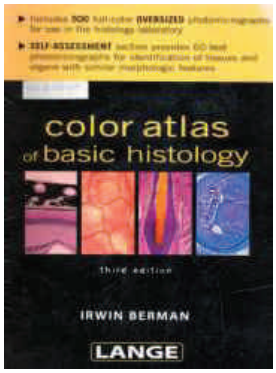
- REVMATOID ARTHRITIS

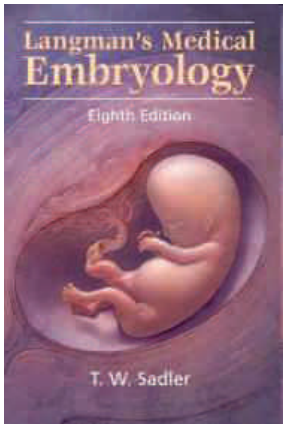
- Further study

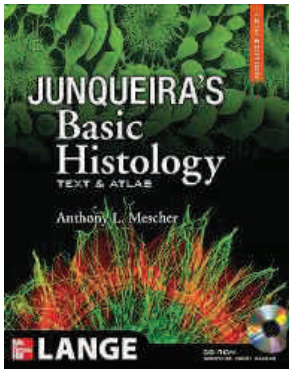












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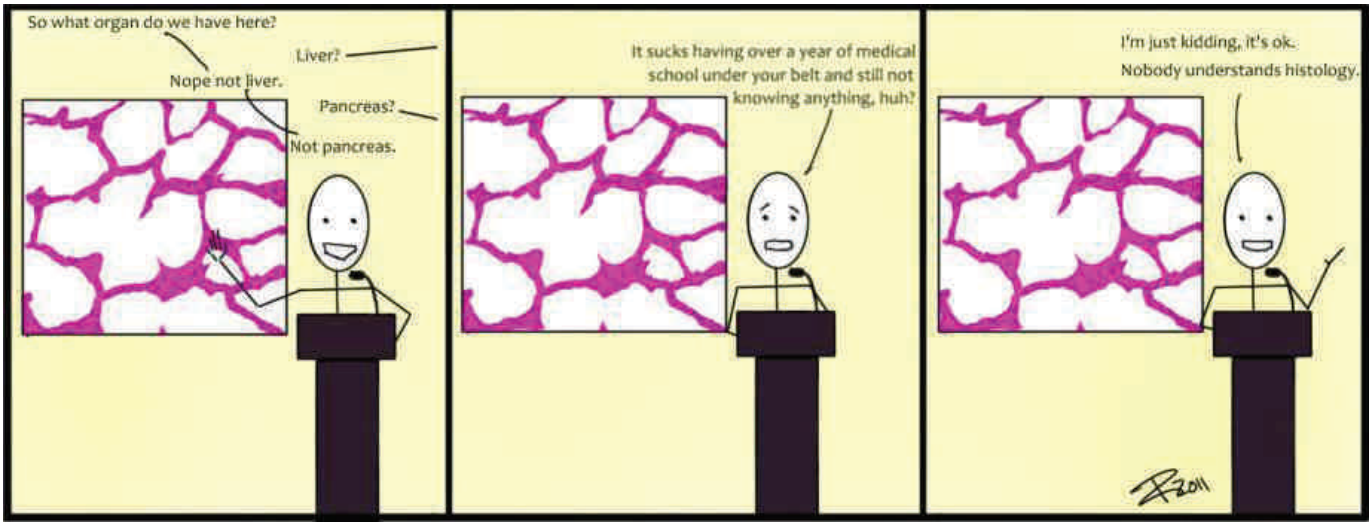
Med Atlas

or visit

http://www.med.muni.cz/histology

Thank you for your attention



However, you still need to learn it ;-)

Thank you for attention

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