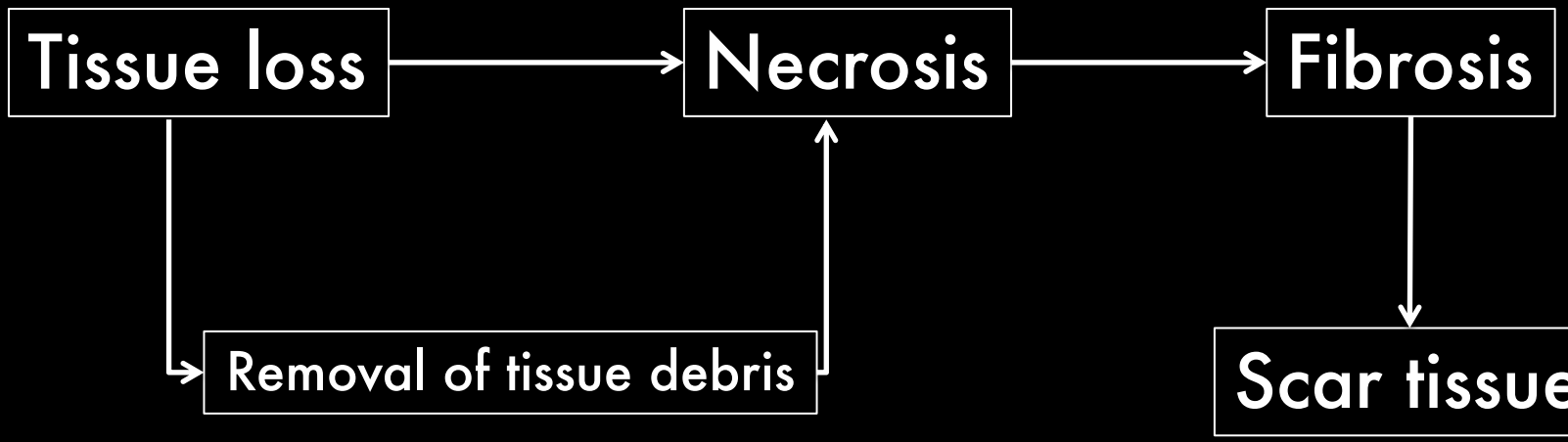
In Biology;

Regeneration = Renewal of cells and tissue to some extent often by a stimulus

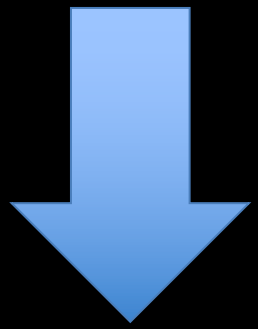
Rejuvenation = Process by which some organisms replace or restore the lost or amputated body parts

- Every organism (from bacteria to human) show some degree of regeneration
- Regeneration may be "complete (hair, nail grow)" or "incomplete (wound healing)"

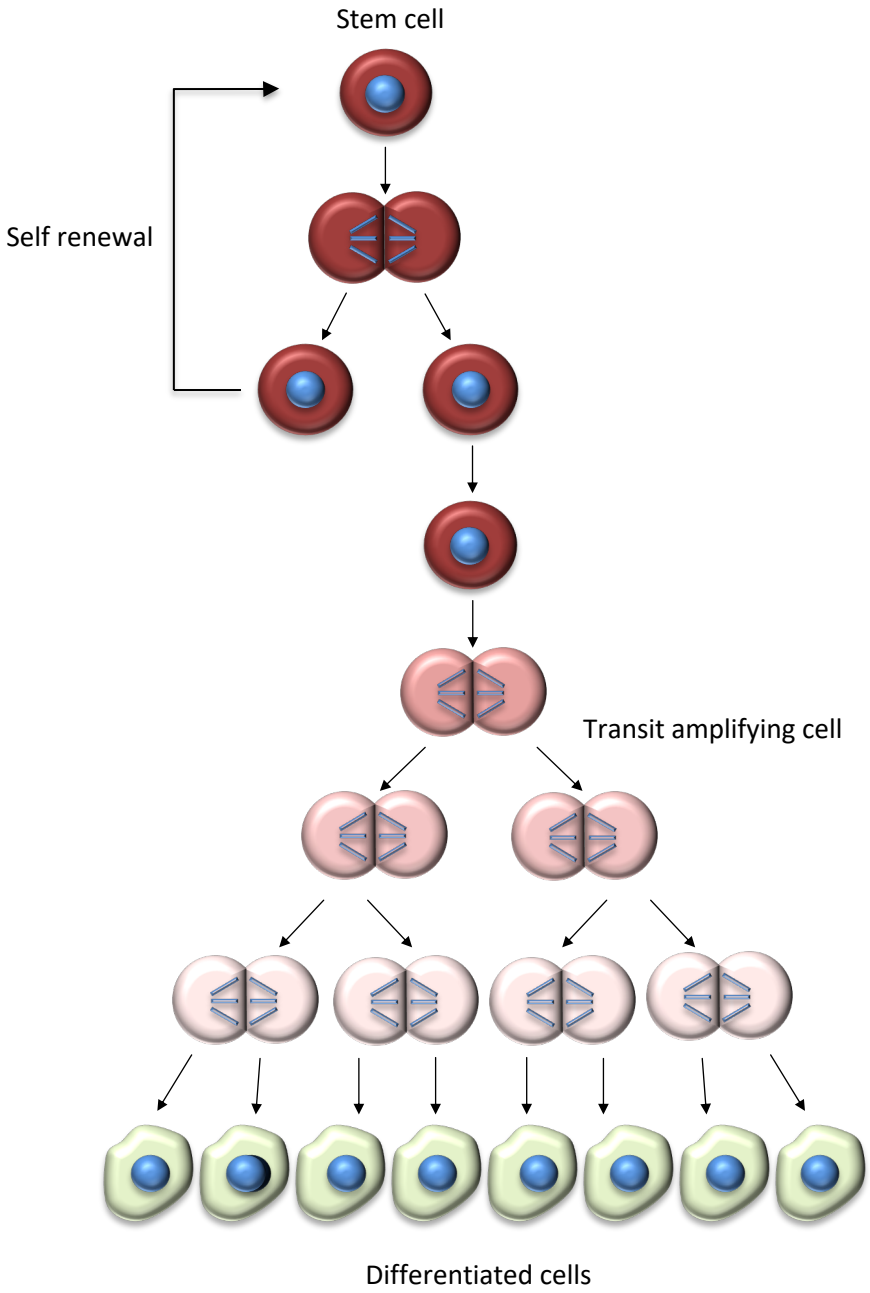


General Strategy in Regeneration

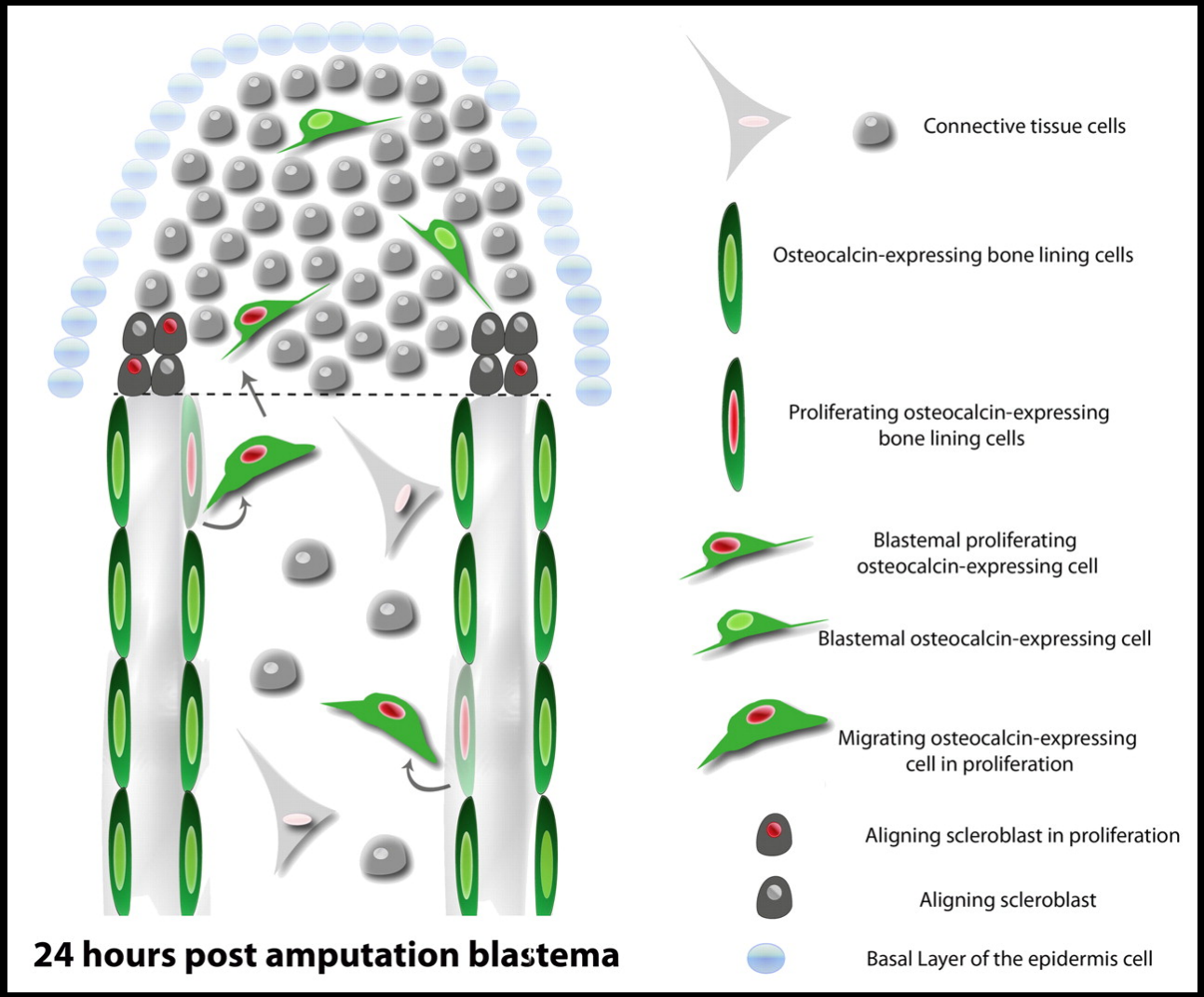
To use the existing cells and tissues
(stem cells, progenitor cells and somatic cells)



To gain shape, polarity and function
of the tissue/organ


Stem cell
Self renewal
Transit amplifying cell
Differentiated cells

Formation of Blastema



Migration ⟶ Dedifferantiation ⟶ Proliferation ⟶ Redifferantiation

Leader Organisms in Rejuvenation (adaptive regeneration models)

- Amphibia (salamander, frog etc.)
- Fishes (zebrafish)
- Echinoderms (sea stars, sea cucumbers etc.)

Cardiomyocyte Regeneration in Lower Organisms

- Amphibians
  - Frog
  - Salamander

- Amphibians regenerate heart after major injury through the reactivation of the mitotic cycle in differentiated cardiomyocytes

- Zebra Fish
  - Most robust and best characterized cardiac regenerative responses among all nonmammalian vertebrate
  - Cardiac muscle regeneration is primarily achieved by preexisting cardimyocyte, not from the cardiomyogenic precursors in the zebrafish heart (Xiagn, 2016)

Regeneration Sites and Speed in Human

- Skin, Hair, Nail
  - Epidermis layer of the skin 3-4 weeks
  - Hair 6-7 years (avr. growth rate 0.5 mm/day)
  - Body hairs 0.27 mm/day
  - Eyebrow hairs 64 days
  - Hand nails 3.5 mm/month
  - Toe nails 1.6 mm/month
- Cornea epithelium (7-layer specialized epithelium)
  - 5-7 days
  - Retina pigment epithelium does not regenerate
- Adipose (Fat) Tissue
  - Fat cells (adipocytes) 10 years
  - 10% of body fat is replaced every 10 years
- Intestine epithelium
  - 3-4 days
  - Paneth cells 6-8 week

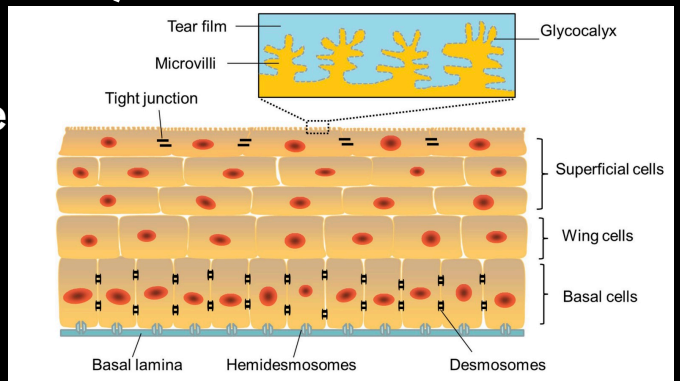


Figure 2. Cross-sectional schema of the corneal epithelium.

Regeneration Sites and Speed in Human

- Taste buds on the tongue
  - 10 days
- Endometrium (inner lining of the uterus)
  - 28 days
- Tip of the fingers and toes
  - Few months in infants
- Lungs
  - Respiratory epithelium 4-5 weeks
  - Air conducting duct epithelium 4-5 weeks
- Liver
  - Hepatocytes 300-500 days
  - Due to their extraordinary regeneration capicity, 70% loss can be recovered in 3-4 months
- Heart
  - 1% per year from the age of 25, to 0.45% per year at the age of 75)
  - Only 30-50% of all cardiomyocytes are replaced during the entire lifespan
- Spinal & Peripheral Nerves
  - 3-4 mm/days upon injury
- Erythrocytes
  - 100-120 days
- Striated Muscle Cell
  - 15 year
- Bones
  - Continuous regeneration of osteocytes by bone ling cells
  - Long bones are totally regerated over 10 years

Internal Regulatory Molecules of Regeneration

- Stem & Progenitor Cells
- Growth Factors (regional/systemic)
- Small Molecules (secreted by the cells)
- Debris Scavengers / Tissue Remodelers
  - Macrophages / Neutrophils
  - MMP, TPA, TNF-alpha

Genes Involved in Limb Development and Proteins

Gene family	Example	Role	Area of action
Fibroblast growth factors	FGF-4 and FGF-8	Growth factors	AER
Hedgehog	Sonic hedgehog (Shh)	Binds Ptc to release Smo and promotes expression of BMP, WNT, HOX, & Gli	ZPA
Patched (tumour suppressor gene) and smoothened	Ptc and Smo	Ptc is an Shh receptor. Smo is released when Shh binds Ptc.	Cell surface mesenchyme
Bone morphogenic proteins	BMP-2 BMP-7	Osteoblast differentiation Chondrocyte condensation and differentiation	Mesenchyme and AER
WNT	Wnt-7a	Dorsalising gene. Turns on LMX-1. Repressed by engrailed-1. Promotes Shh expression	AER
Fringe	Radical fringe	Limits the AER to the tip of the limb bud	Dorsal AER
Homeobox (HOXA, B, C, D)	Hox-b8	Controls limb positioning and patterning in developing zeugopod, autopod and stylopod	Overlapped pattern in lateral plate mesoderm and limb bud
T-box	Tbx4 Tbx5	Transcription factors, turned on by BMP2, BMP4 or Wnt, control limb identity	Early stages of limb outgrowth
SOX	SOX9	Condensation and differentiation of chondroblasts	Early skeleton