
بسم الله الرحمن الرحيم

Regenerative Medicine & stem cell therapy for the Elderly

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Regenerative Medicine

The term regenerative medicine has been used to describe a relatively new branch of medicine whose focus is the restoration of normal function in tissues that are damaged or lost due to age, disease, injury, or congenital defects. Regenerative medicine efforts have shown promise in the treatment of both acute injuries and chronic disease across multiple organ systems.

Stem Cell – Definition

- A cell that has the ability to continuously divide and differentiate (develop) into various other kind(s) of cells/tissues

Stem Cell Characteristics

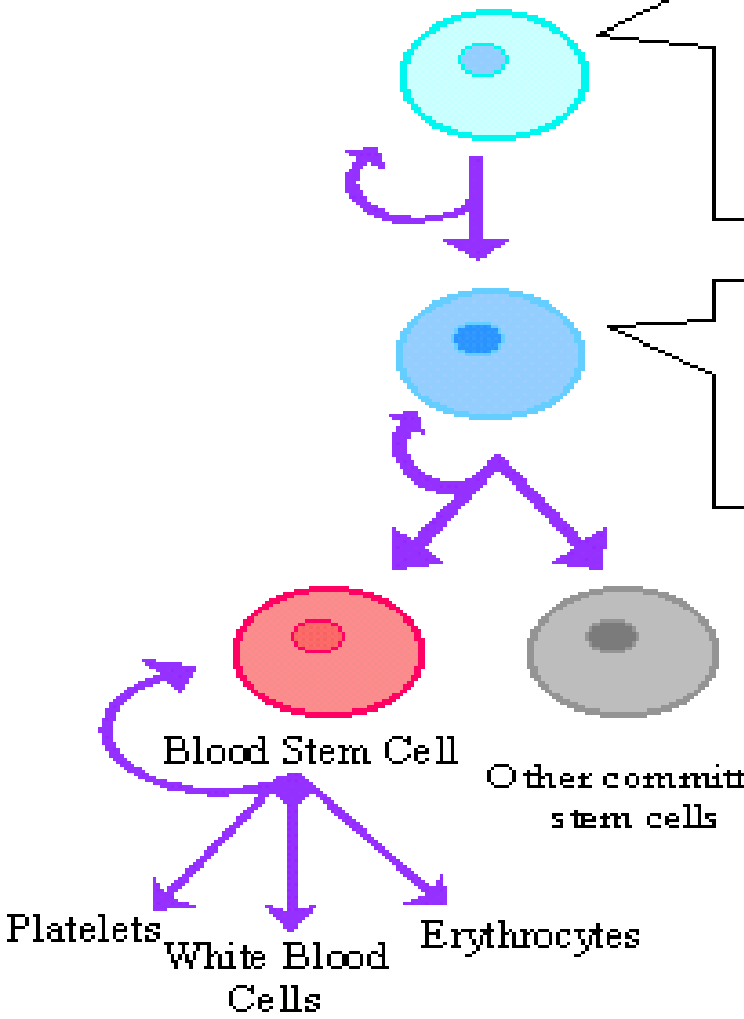
- **‘Blank cells’ (unspecialized)**
- **Capable of dividing and renewing themselves for long periods of time (proliferation and renewal)**
- **Have the potential to give rise to specialized cell types (differentiation)**

- Self renewable: a cell that has the ability to continuously divide
- Pluripotent: ability to develop into several different kinds of cells/tissues
- Repair: ability to return function to damaged cells in the living organism

Kinds of Stem Cells

Stem cell type	Description	Examples
Totipotent	Each cell can develop into a new individual	Cells from early (1-3 days) embryos
Pluripotent	Cells can form any (over 200) cell types	Some cells of blastocyst (5 to 14 days)
Multipotent	Cells differentiated, but can form a number of other tissues	Fetal tissue, cord blood, and adult stem cells

Stem Cell Differentiation



Totipotent Stem Cell
These cells have unlimited capability, and have the ability to form extraembryonic membranes and tissues, the embryo itself, and all postembryonic tissues and organs. An example is an embryo

Pluripotent Stem Cell
These cells are capable of giving rise to most, but not all, tissues of an organism. An example is inner mass cells

Multipotent Stem Cell
These cells are committed to give rise to cells that have a specific function. An example is blood stem cells

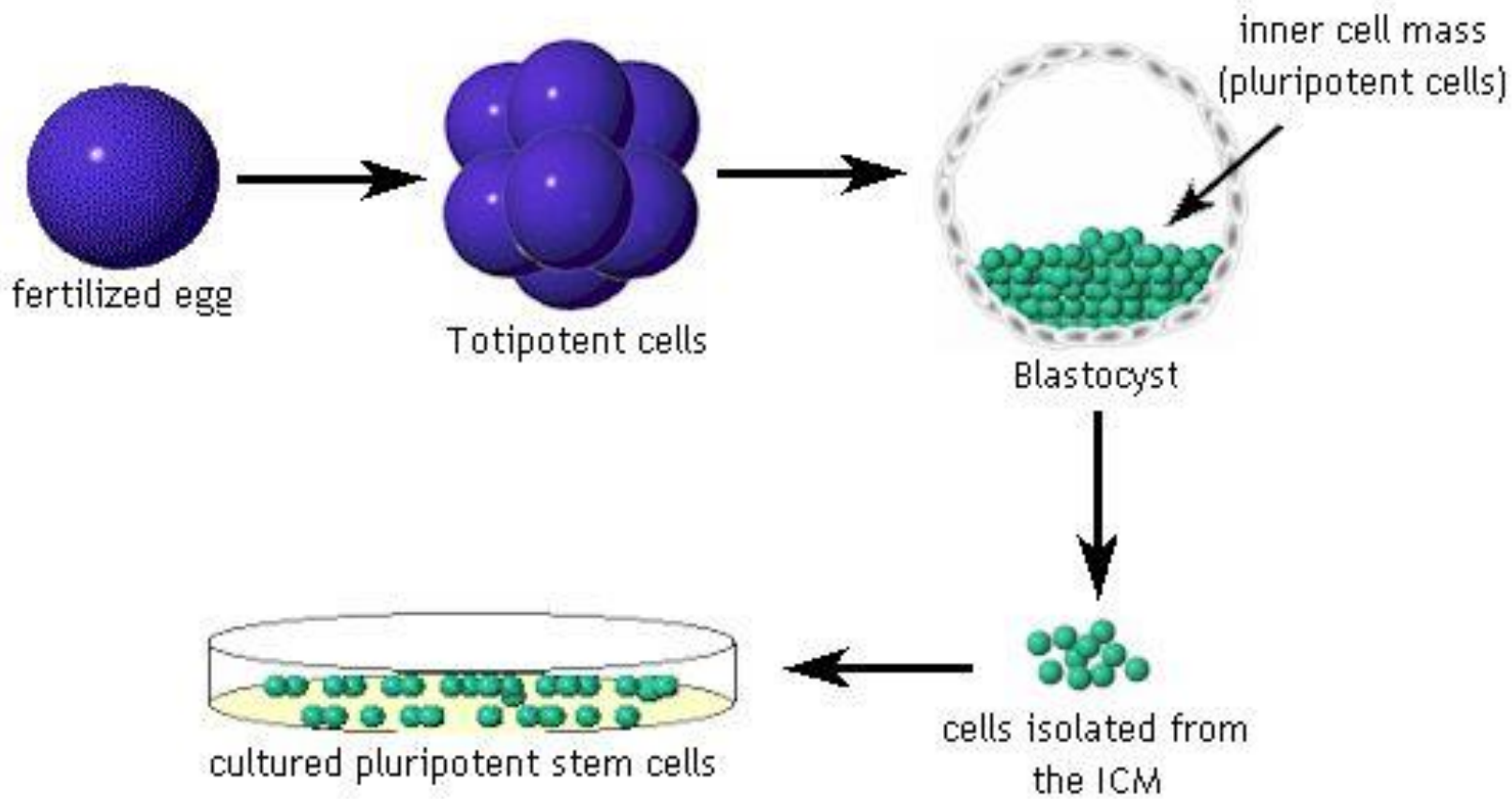
Kinds of Stem Cells

Embryonic stem cells come from a five to six-day-old embryo. They have the ability to form virtually any type of cell found in the human body.

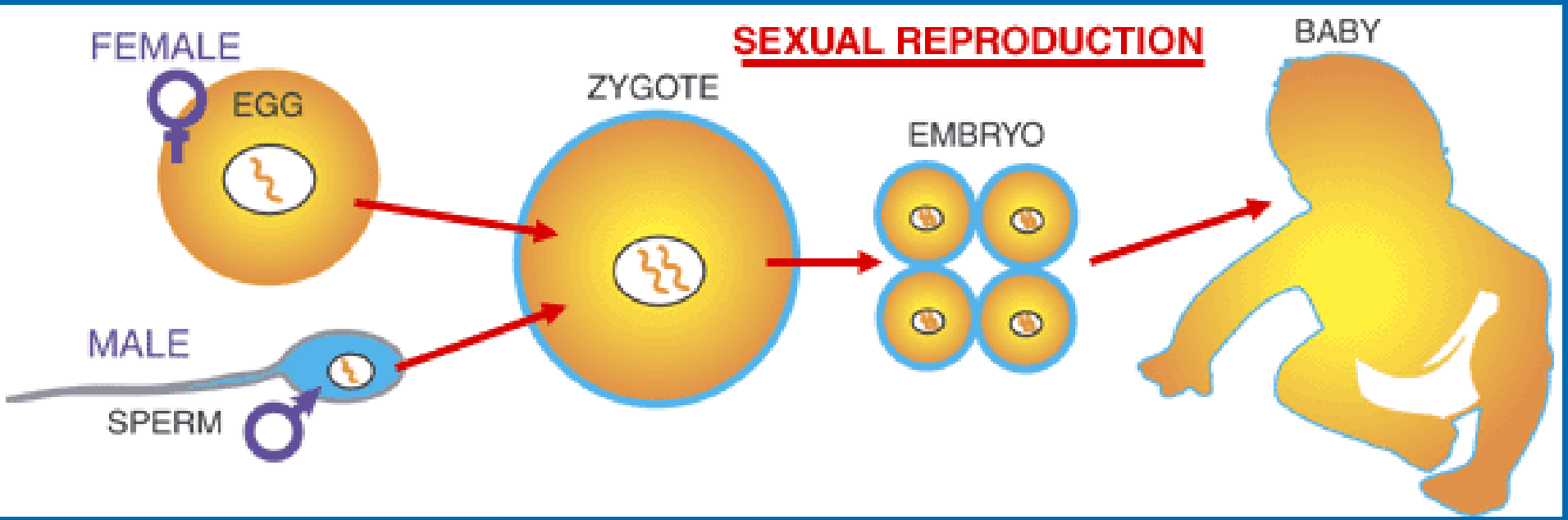
Embryonic germ cells are derived from the part of a human embryo or fetus that will ultimately produce eggs or sperm (gametes).

Adult stem cells are undifferentiated cells found among specialized or differentiated cells in a tissue or organ after birth. Based on current research they appear to have a more restricted ability to produce different cell types and to self-renew.

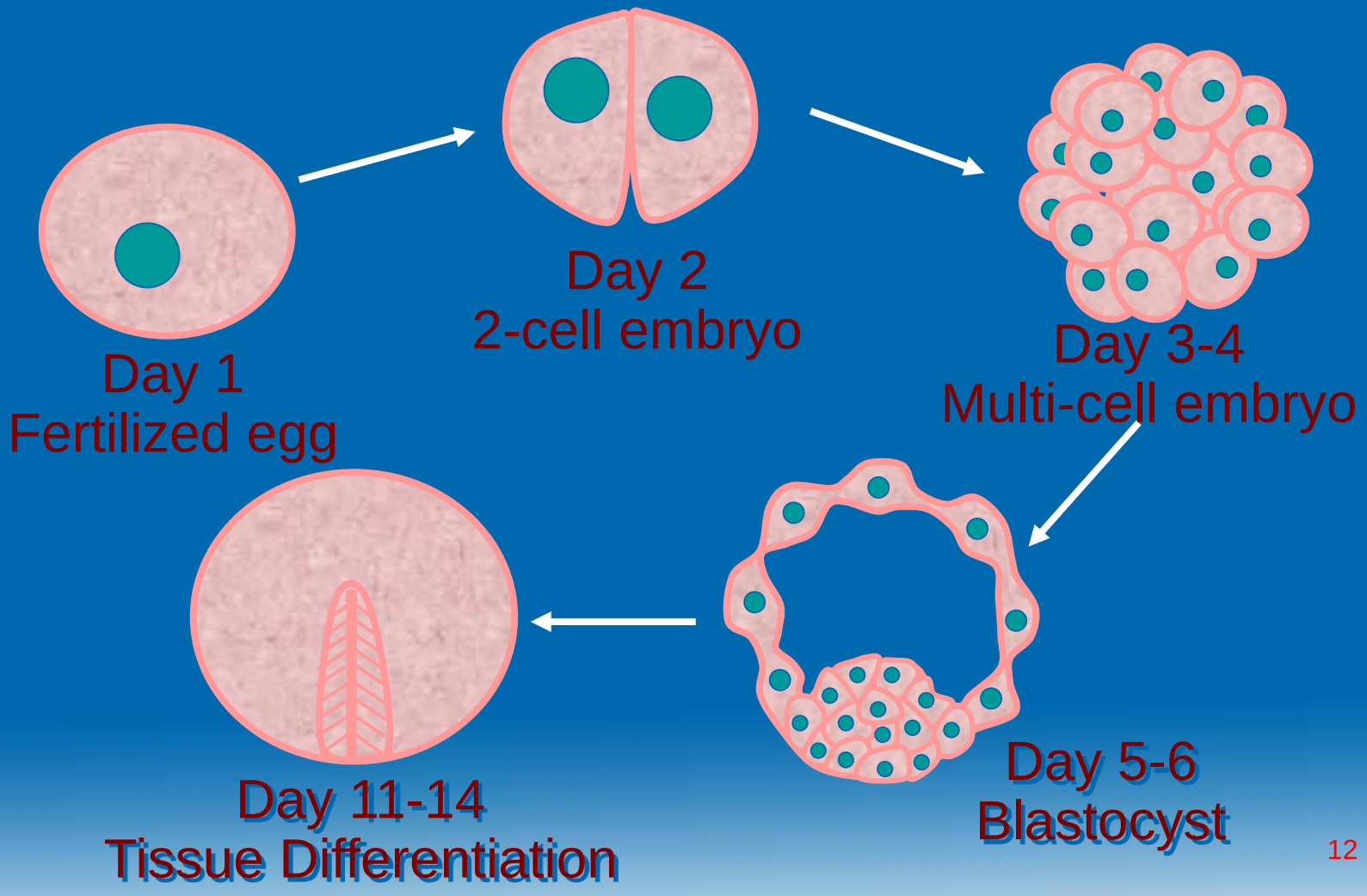
Blastocyst Diagram



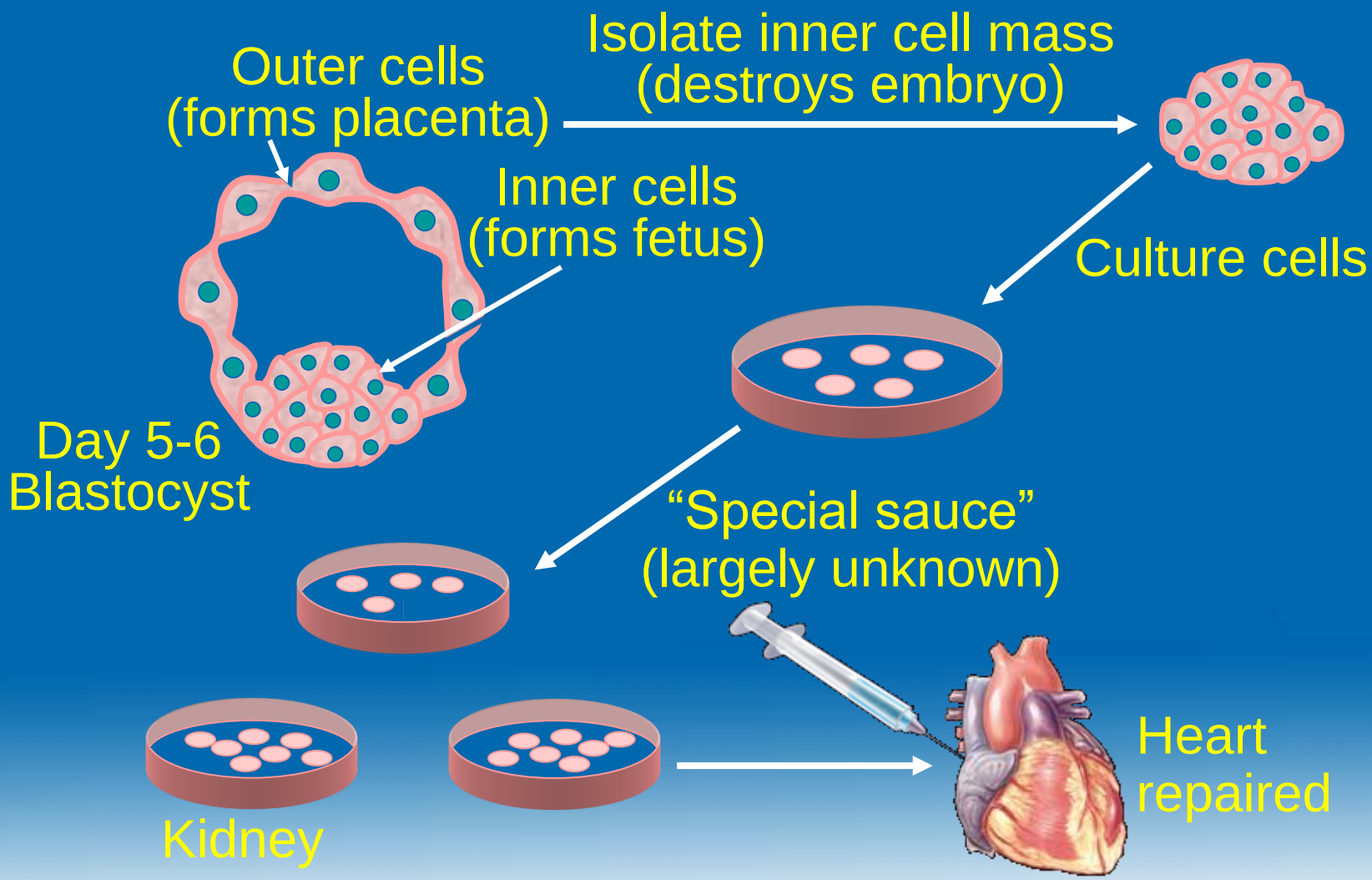
Sexual Reproduction

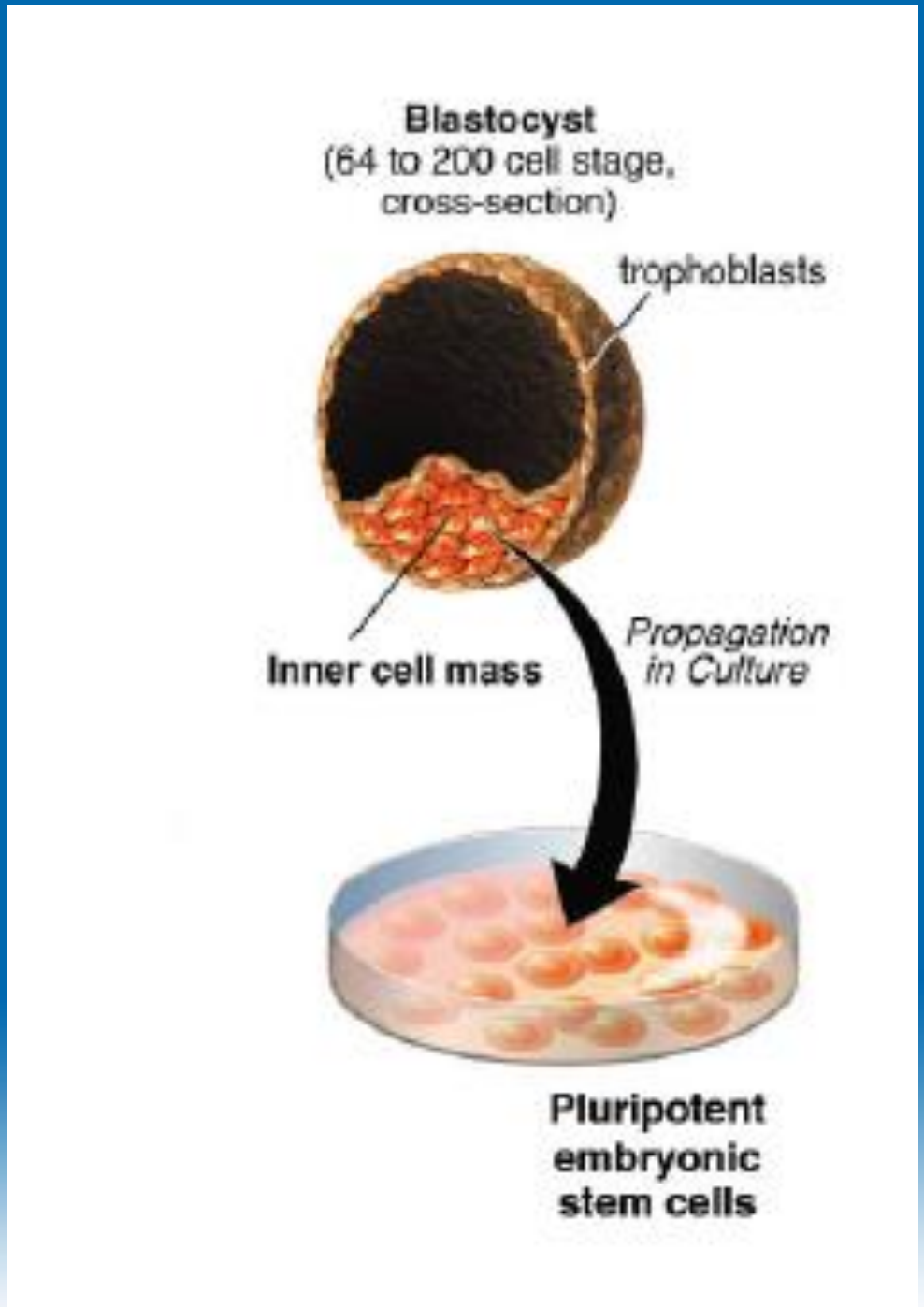


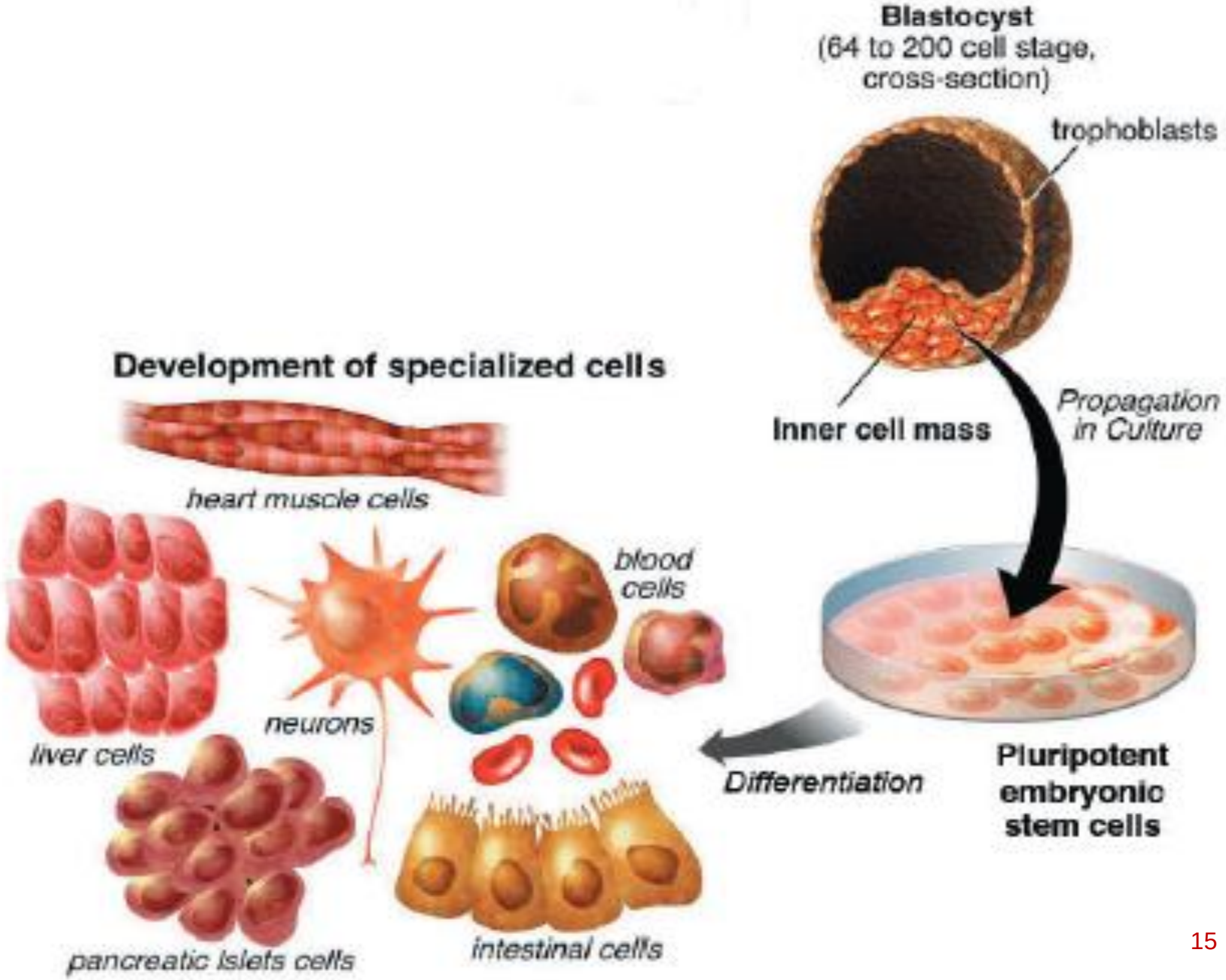
Stages of Embryogenesis

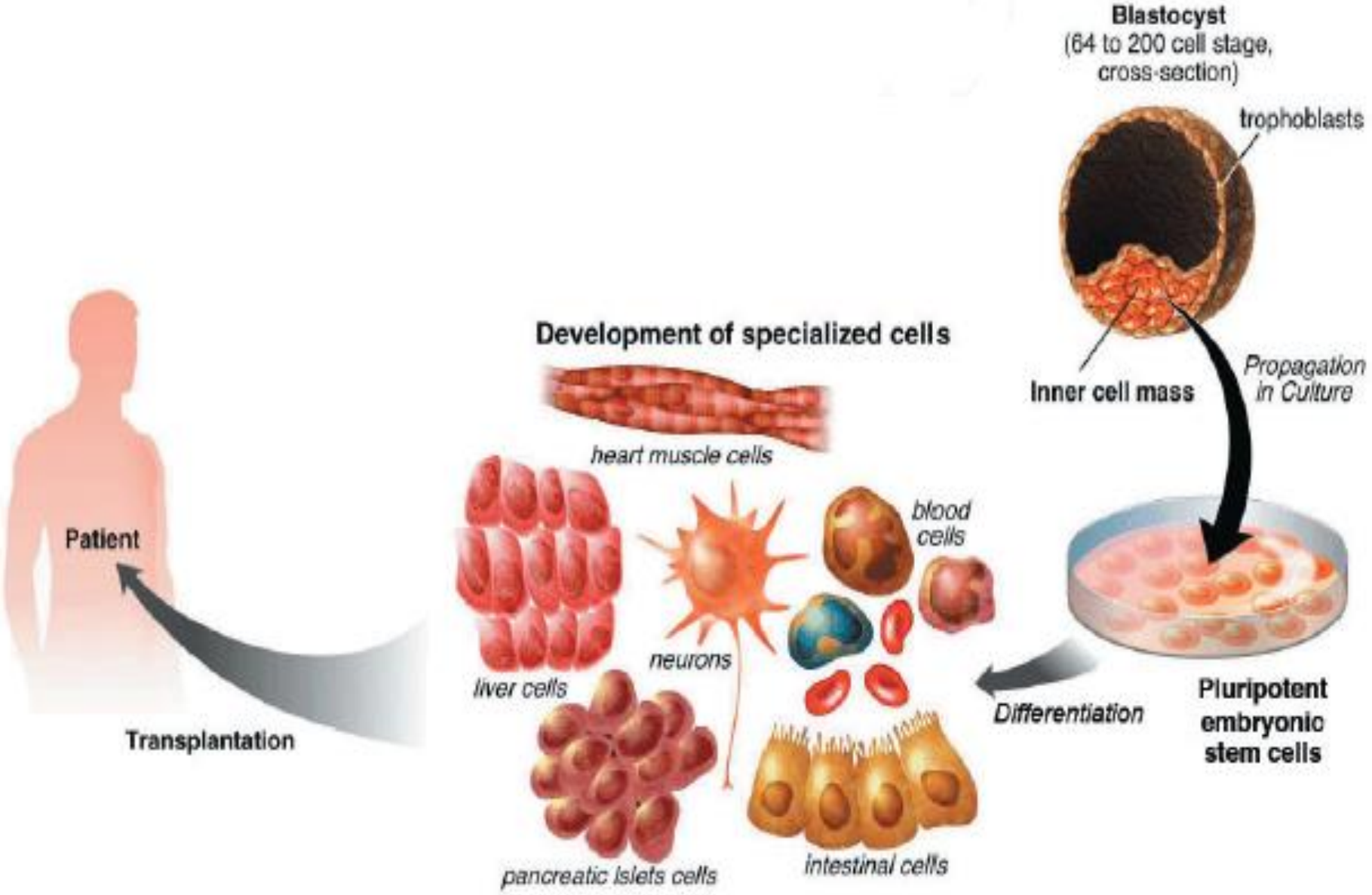


Derivation and use of Embryonic Stem Cell Lines

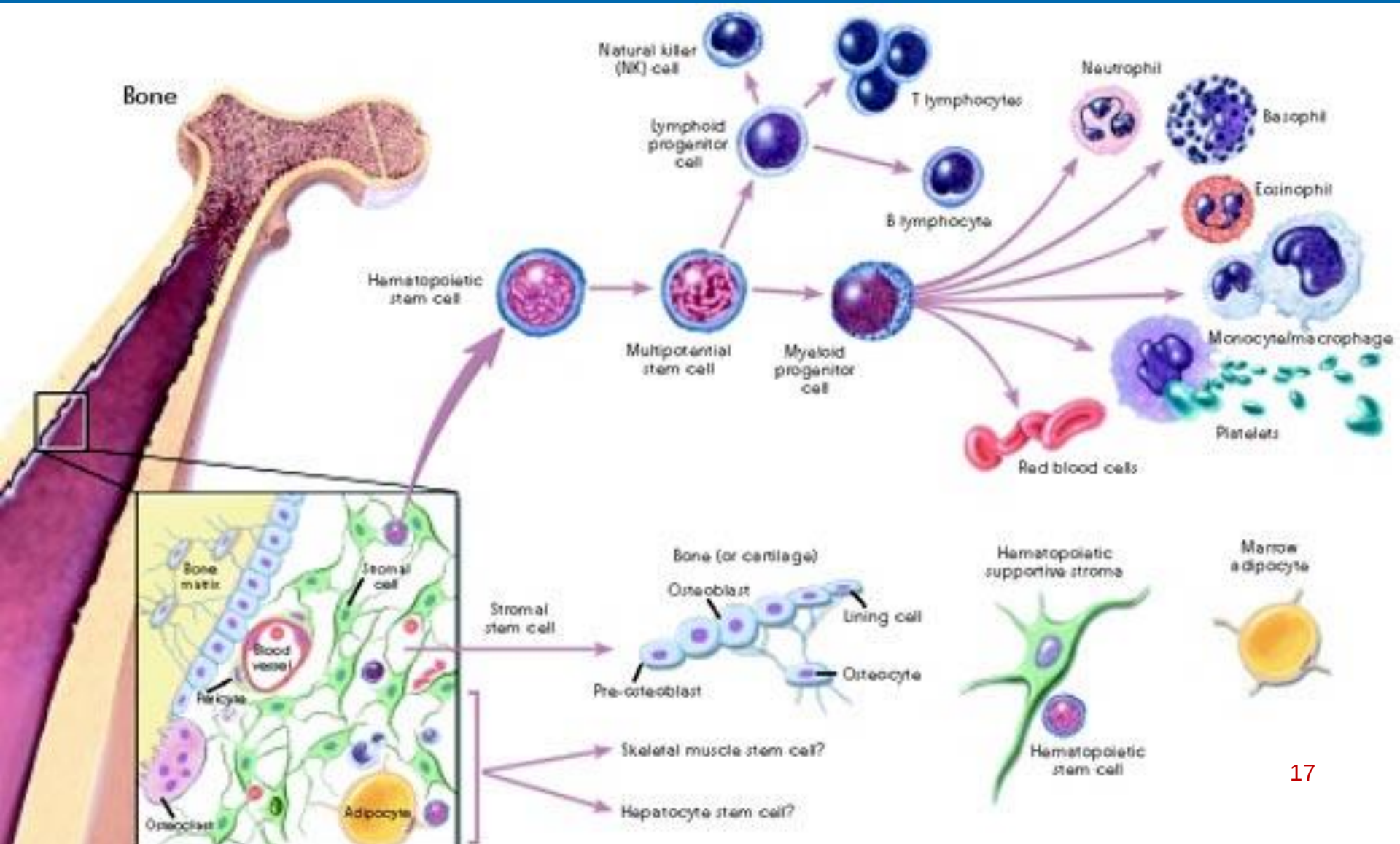


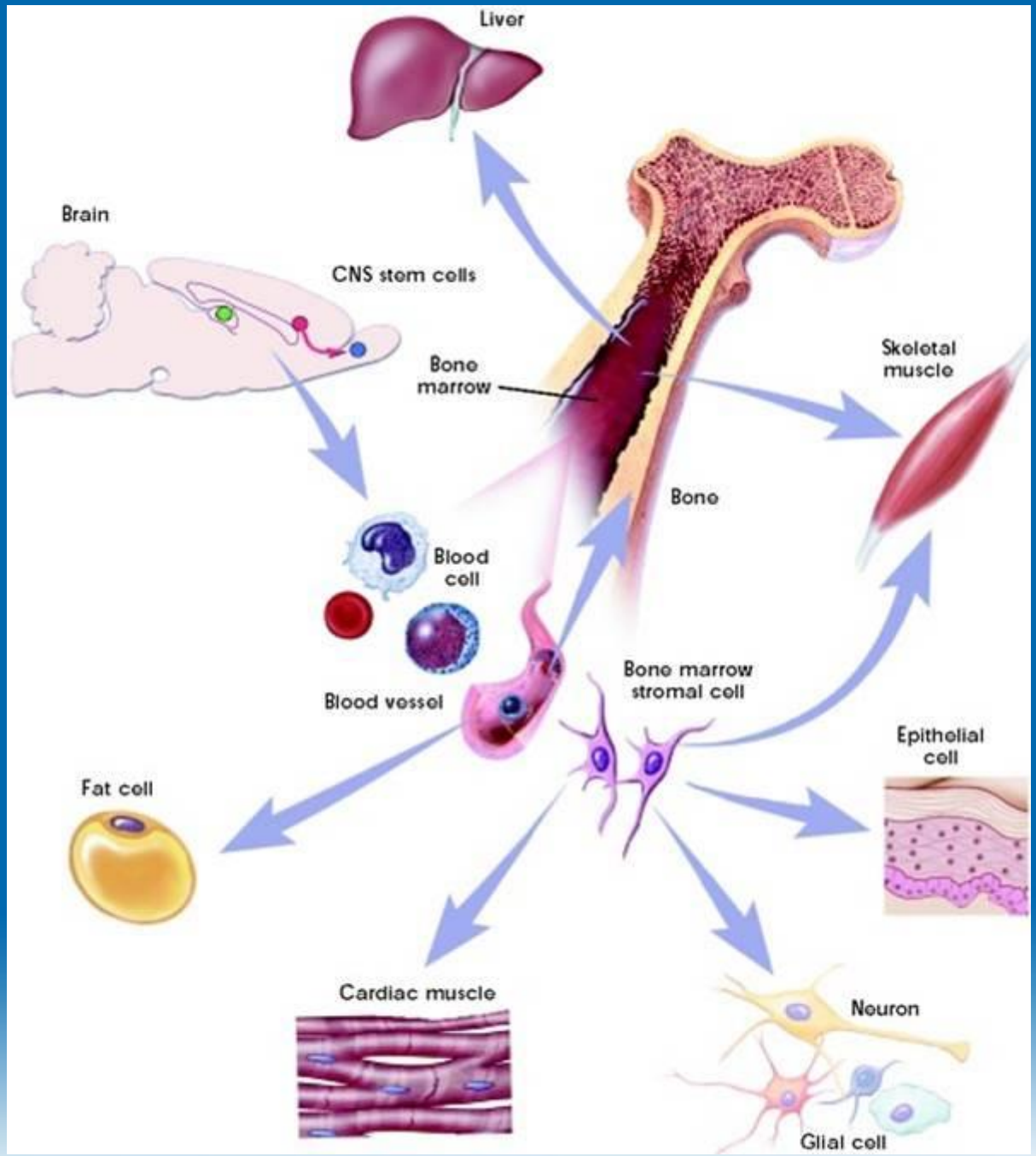

Blastocyst
(64 to 200 cell stage,
cross-section)
trophoblasts
Inner cell mass
Propagation
in Culture
Pluripotent
embryonic
stem cells


Blastocyst
(64 to 200 cell stage,
cross-section)
trophoblasts
Inner cell mass
Propagation
in Culture
Development of specialized cells
heart muscle cells
blood
cells
neurons
liver cells
Differentiation
Pluripotent
embryonic
stem cells
pancreatic islets cells
intestinal cells


Blastocyst
(64 to 200 cell stage, cross-section)
trophoblasts
Inner cell mass
Propagation in Culture
Pluripotent embryonic stem cells
Differentiation
Development of specialized cells
heart muscle cells
blood cells
neurons
liver cells
pancreatic islets cells
intestinal cells
Patient
Transplantation

Adult stem cells




Liver
Brain
CNS stem cells
Bone marrow
Skeletal muscle
Bone
Blood cell
Blood vessel
Bone marrow stromal cell
Epithelial cell
Fat cell
Cardiac muscle
Neuron
Glial cell

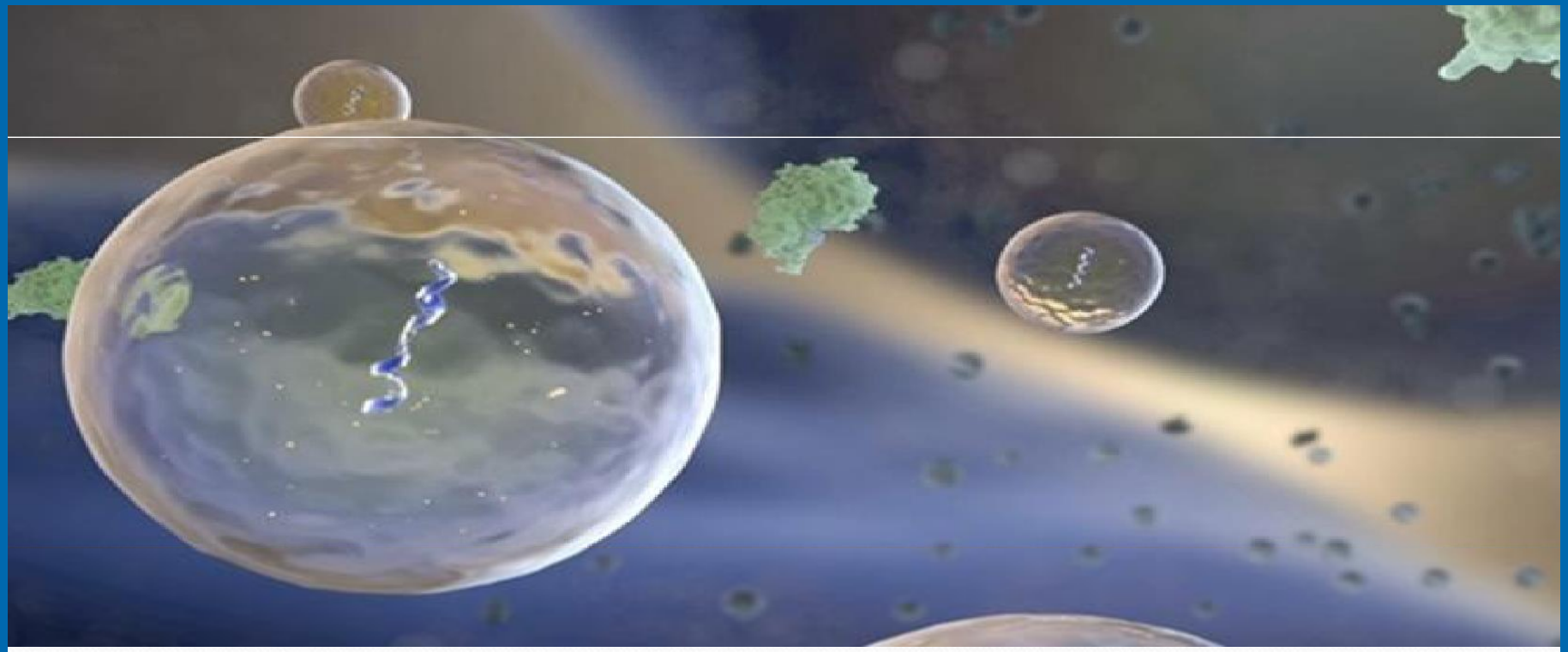
- Isolate individual stem cell populations
- Ensure that cells retain their functionality and potential to differentiate

- Characterize & track stem cell populations
- Ensure that cells are "transplant" ready

- Culture stem cell lines in a stable, multi- or pluri-potent state, free from mutations & to sufficient quantity
- Enable Economical expansion to make cell-therapy a reality

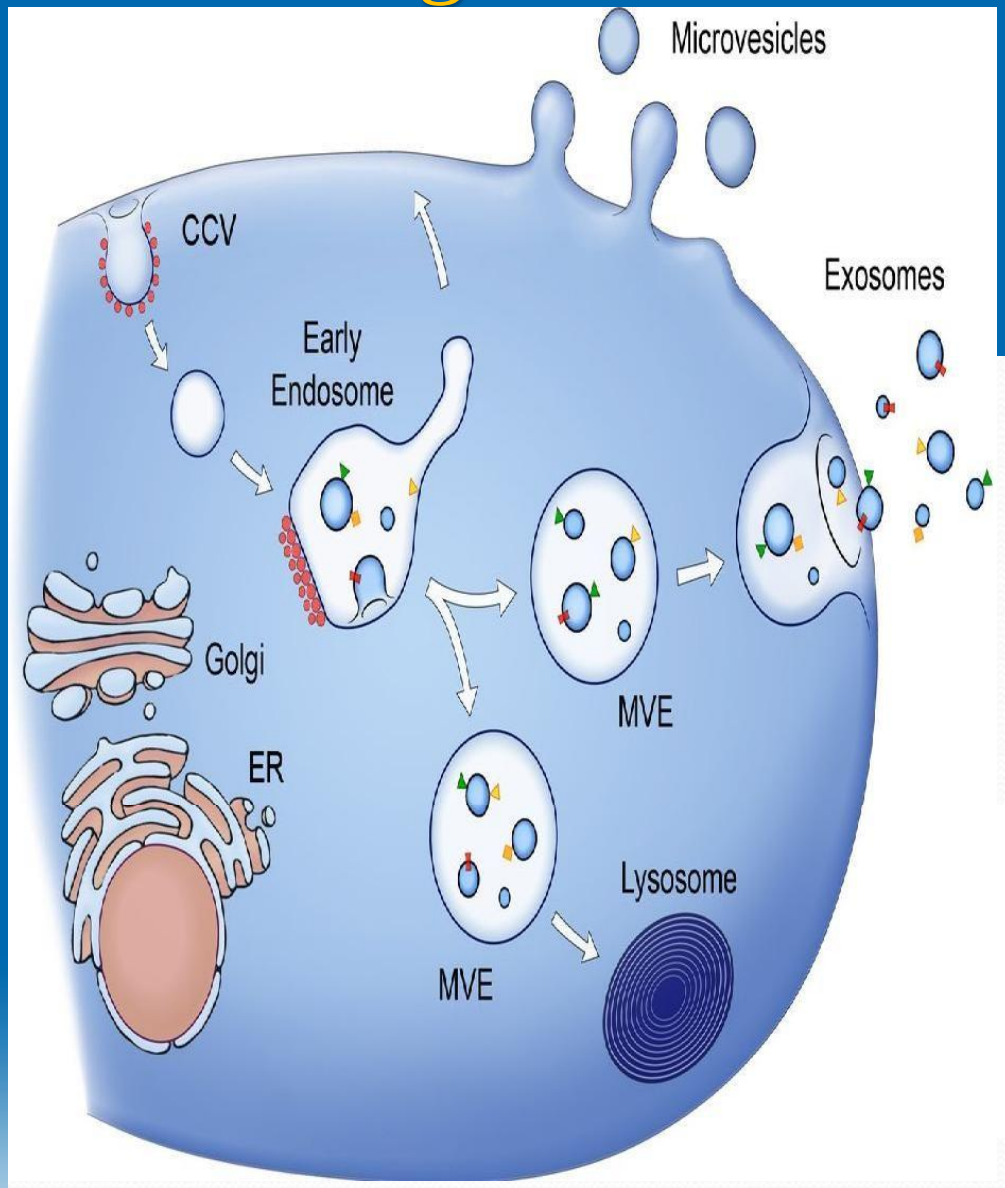
- Control & activate stem cell differentiation to desired lineages
- Functionally active differentiated cells

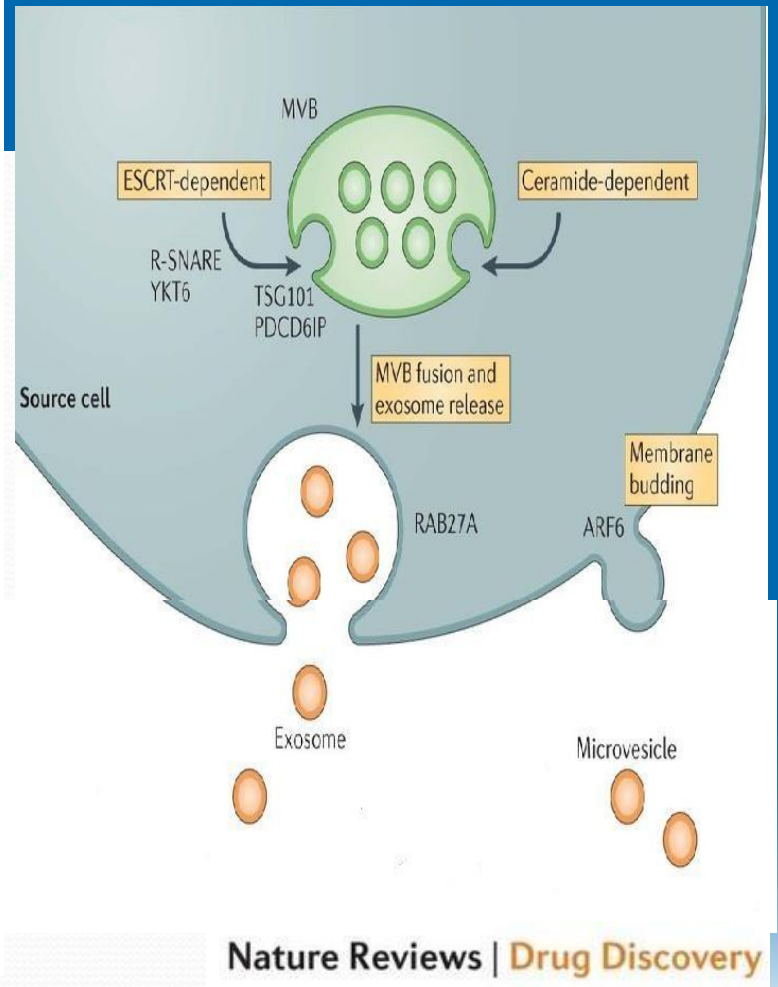
Exosome Origins: Why the Cell Source Matter



Kamran Mansouri
Associate Professor of Molecular Medicine

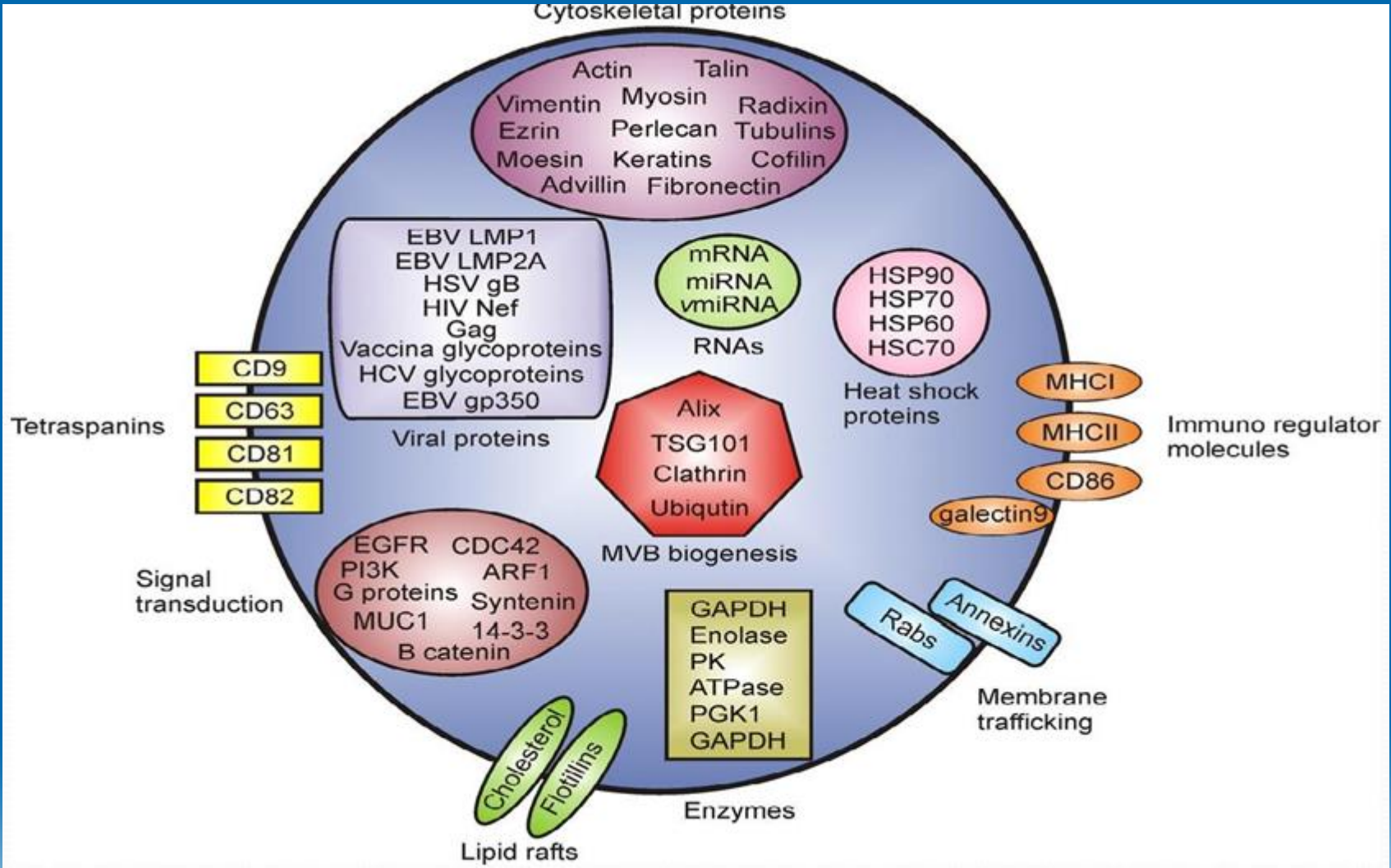
Biogenesis and Release of EMV





JCB 2013;200:373-383

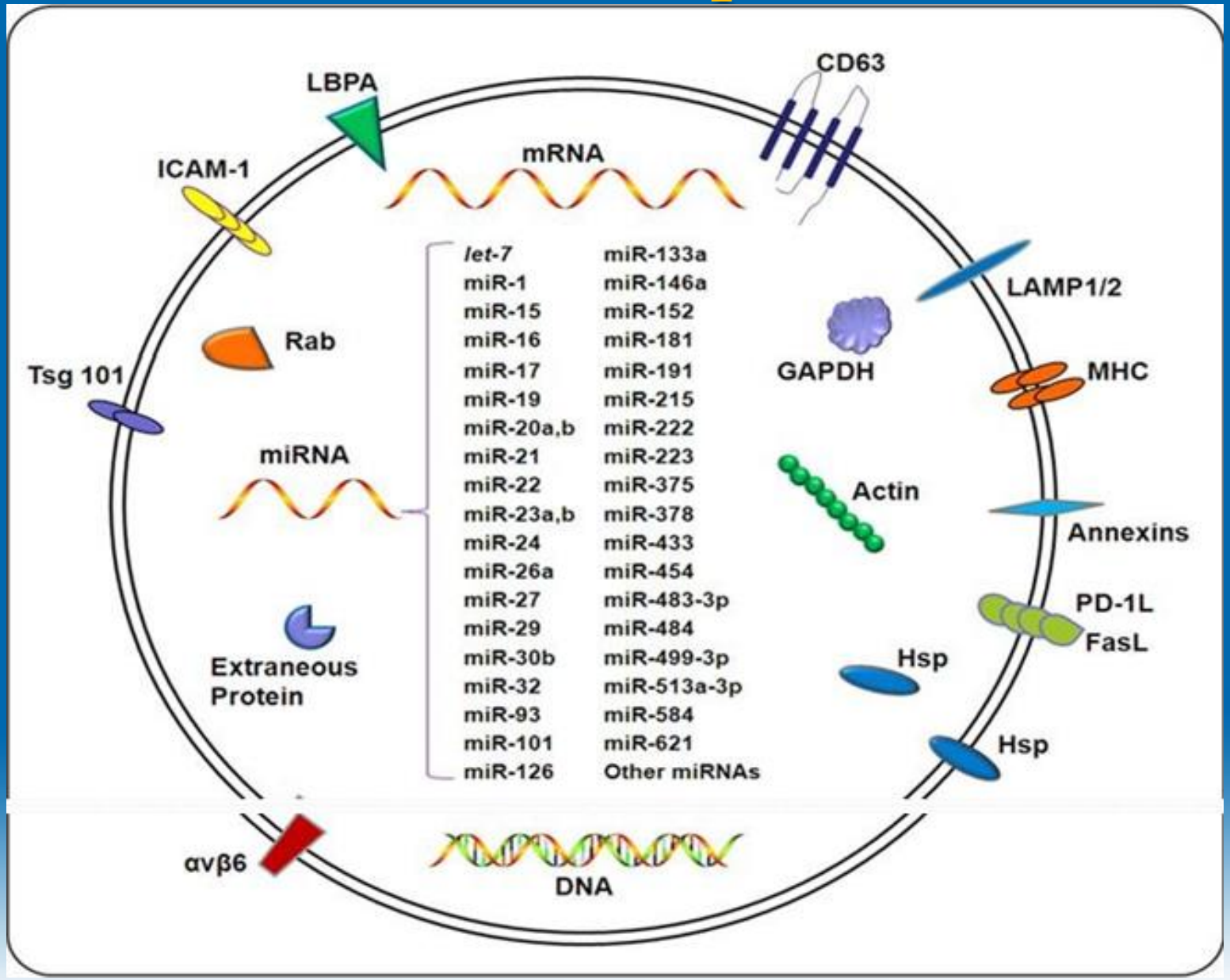
Exosome composition



A complete database of exosomal proteins can be found at ExoCarta (exocarta.ludwig.edu.au/) (Mathivanan et al., .(2012)

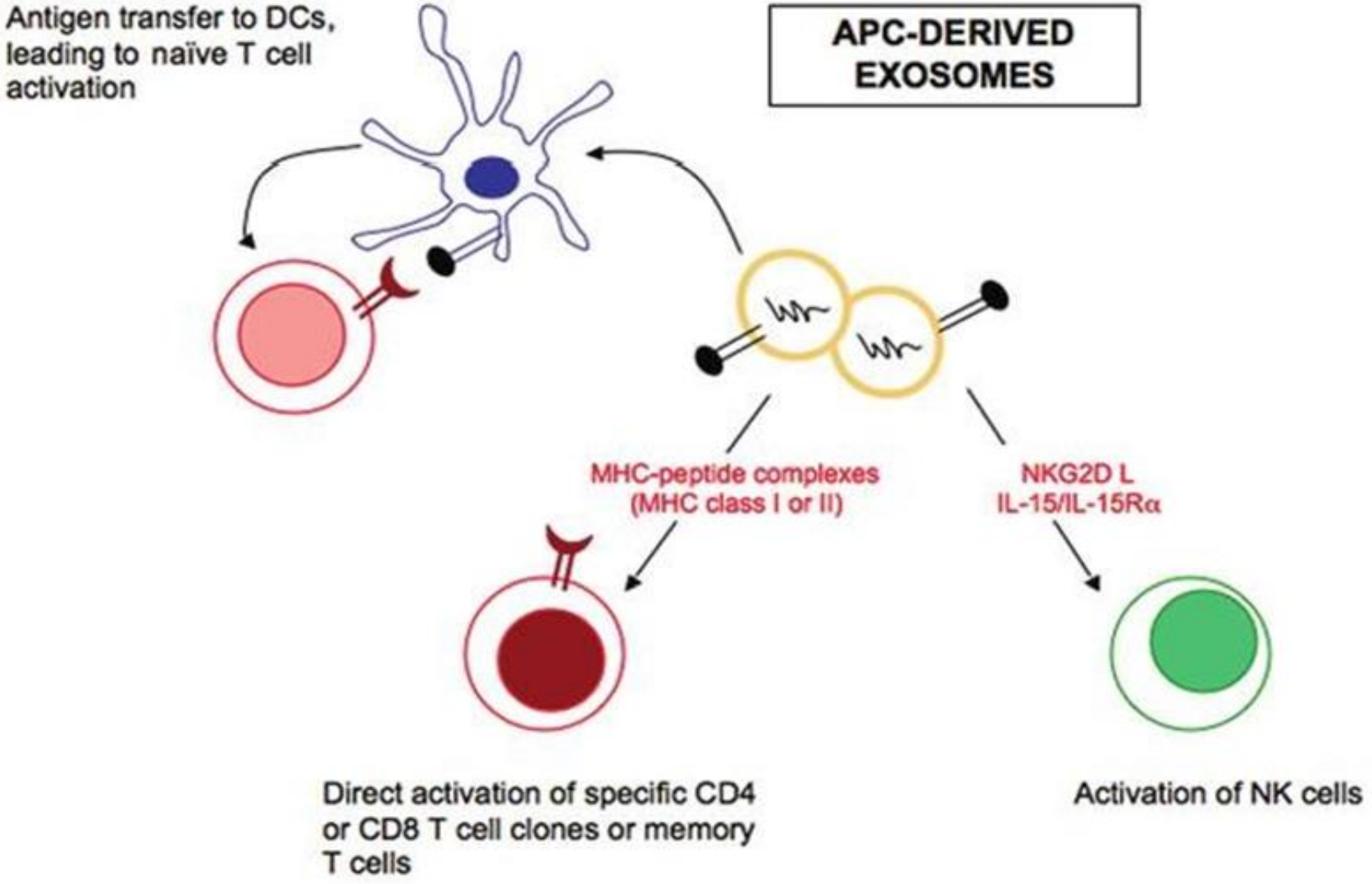
Virol. 2011;85:12844-12854

Exosome composition



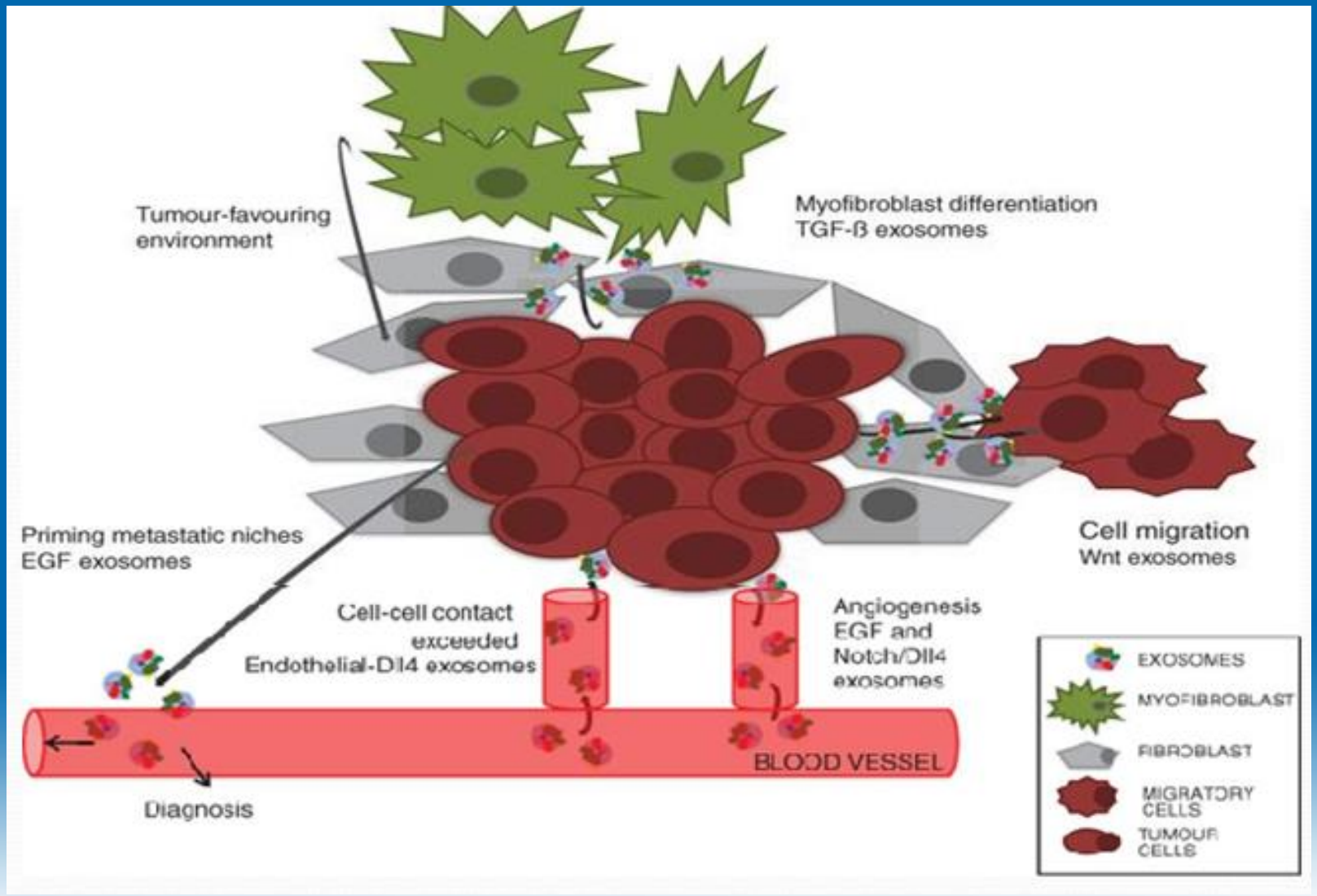
Exosomes as intercellular communicators

Proposed antigen presentingfunctions of exosomes



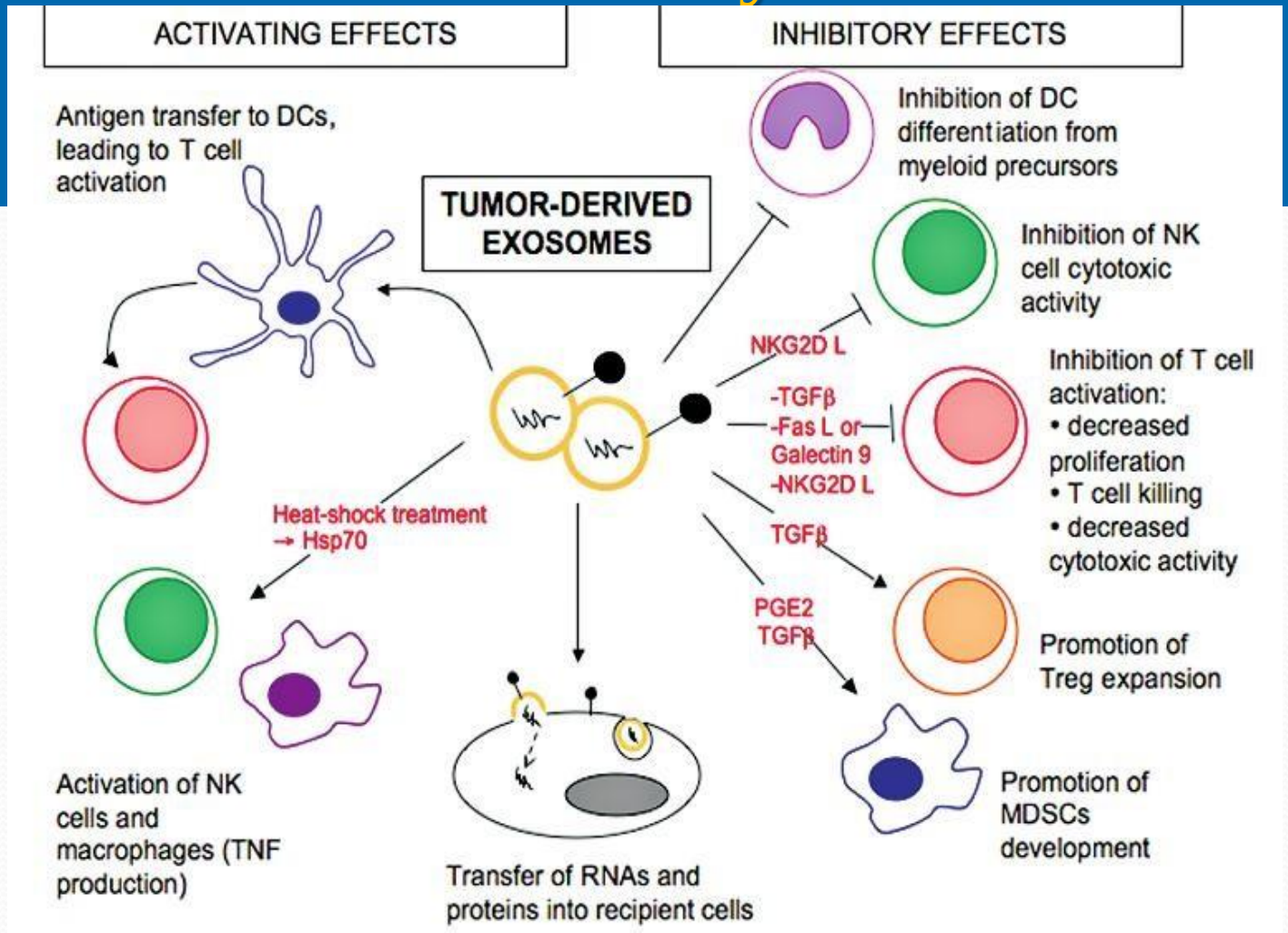
Traffic 2011; 12: 1659–1668

Cell communication through cell-fate signals carrying exosomes in tumor microenvironment



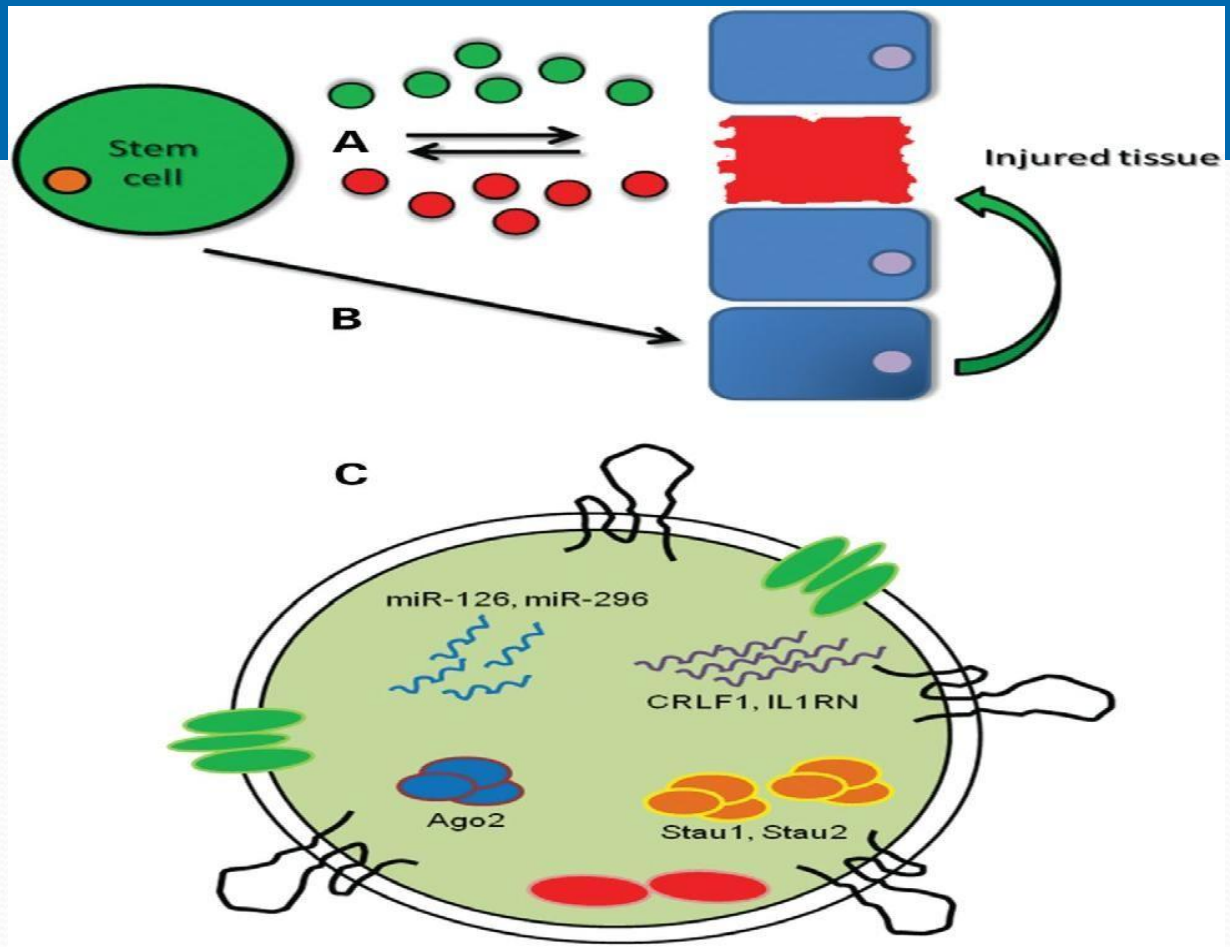
vesicles. Vol 2013 ; 2

Proposed immunological functions of exosomes secreted by tumors



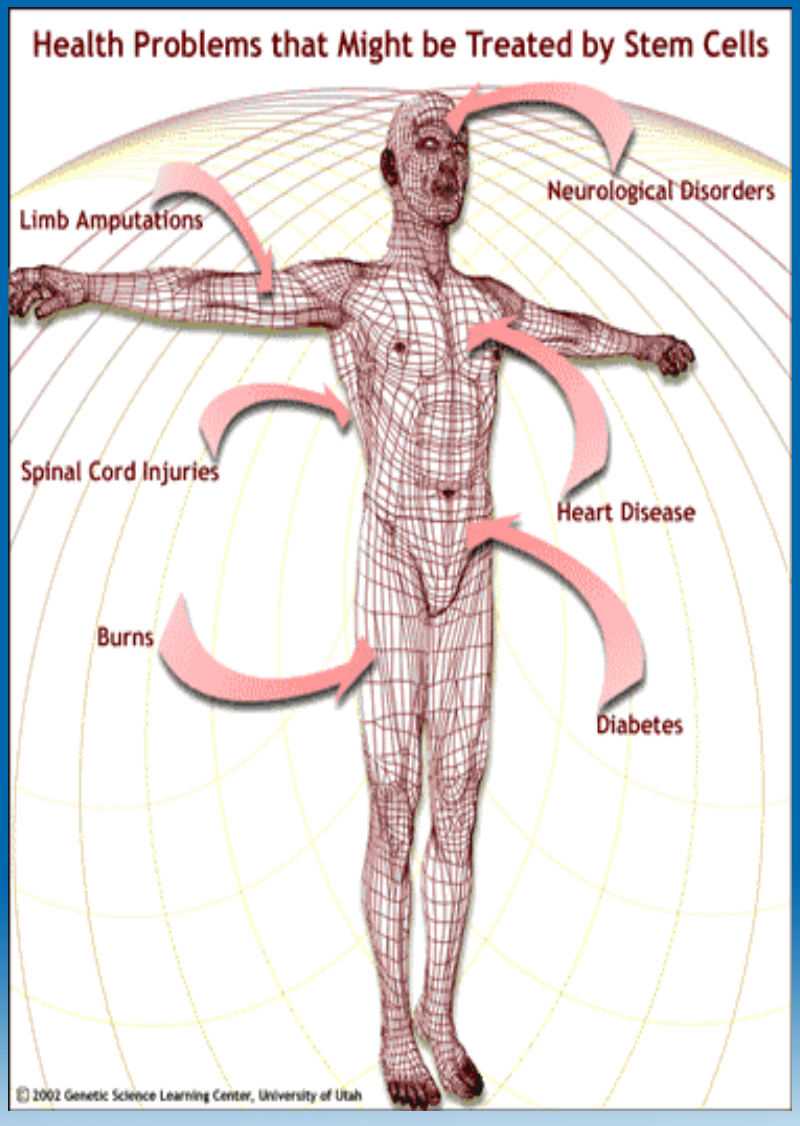
Traffic 2011; 12: 1659–1668

The mechanisms of stem cell exosome/ microvesicle-mediated regeneration of injured tissues



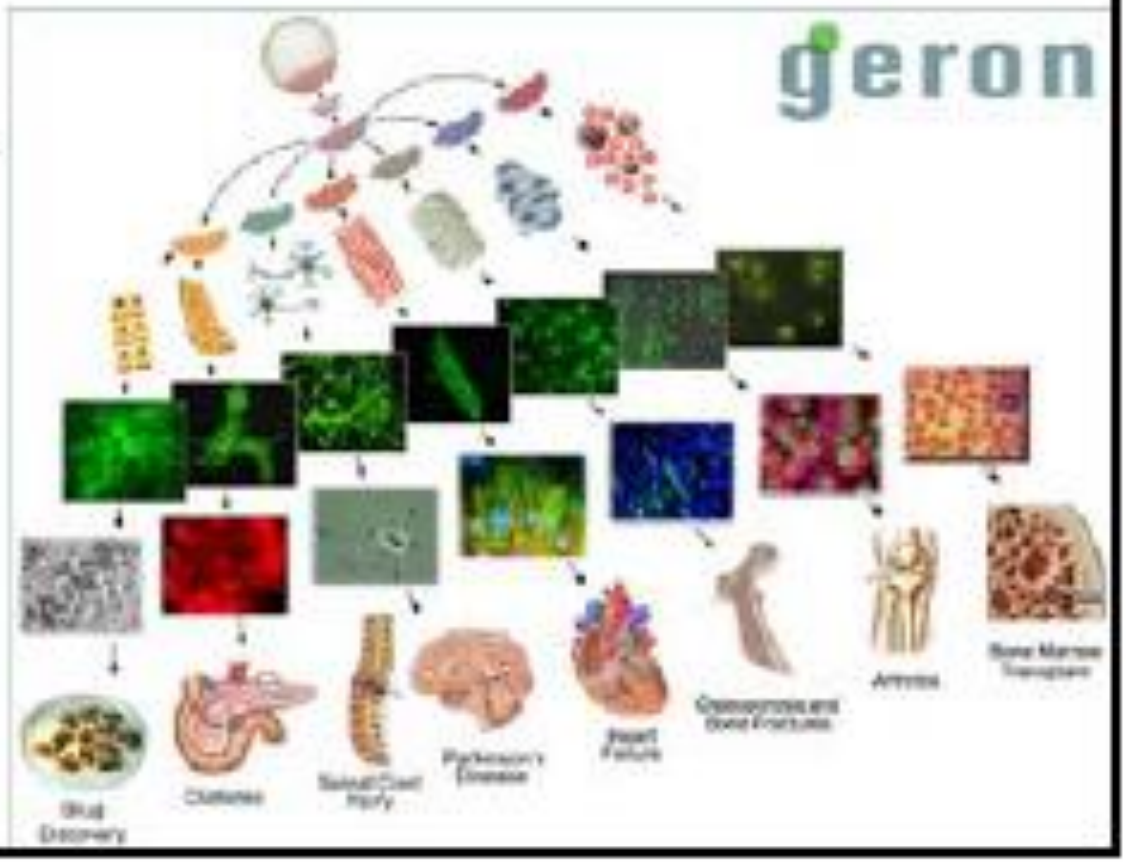
Applications

- **Disease**
  - **Diabetes, Spinal cord injury, Parkinson's disease, heart disease**
- **Genetic based Disease**
  - **Cystic fibrosis, Huntington's**



How they could treat certain types of diseases?

-Tissue repair
-Heart Disease
-Cancer
-Arthritis
-Parkisons disease
-Diabetes

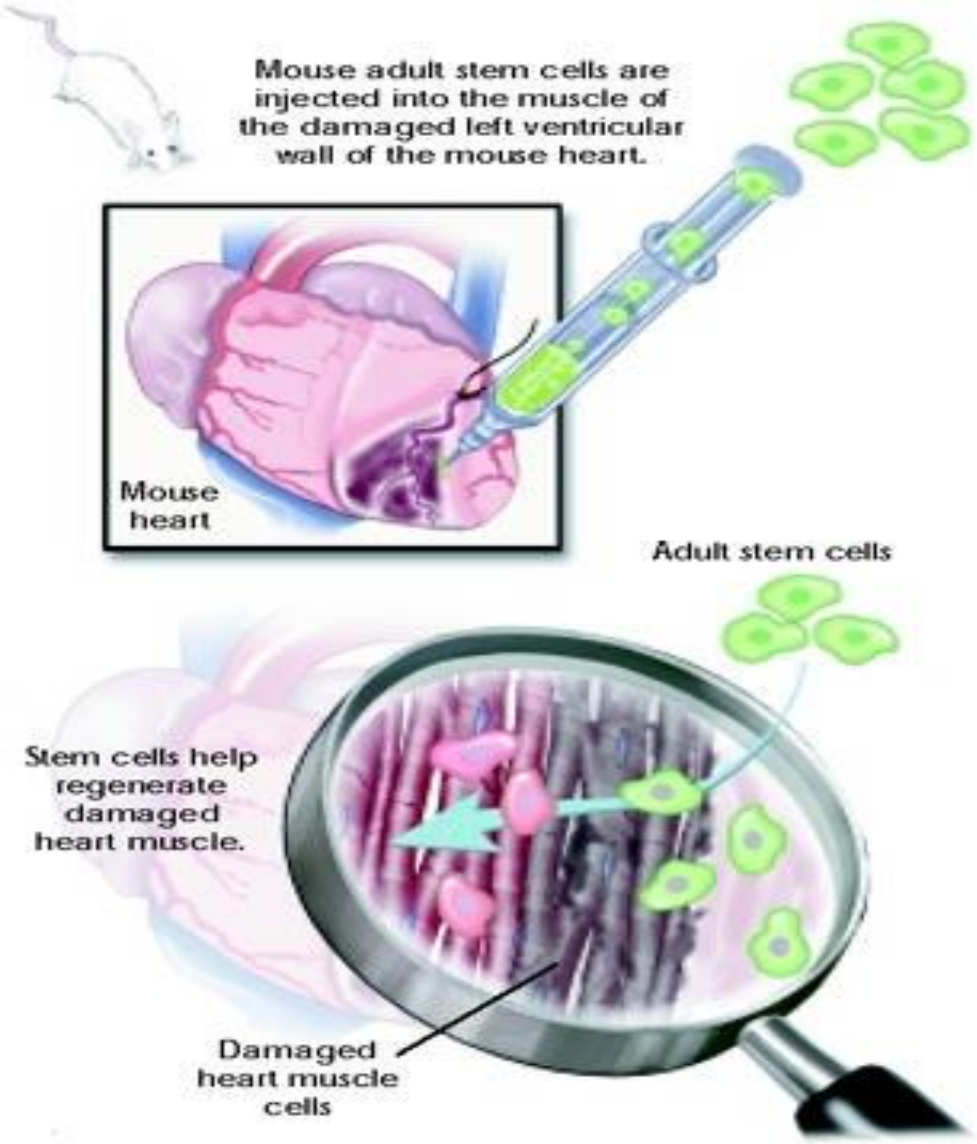


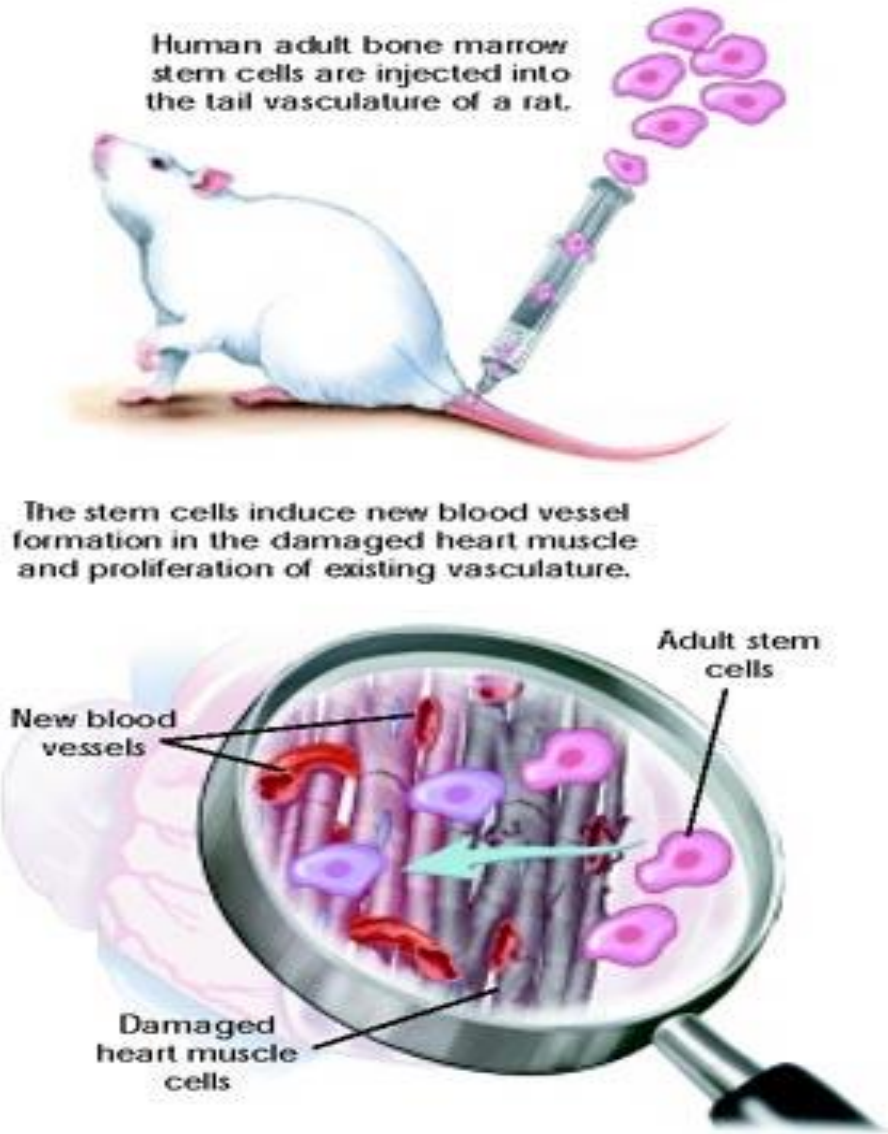
Tissue Repair

- Regenerate spinal cord, heart tissue or any other major tissue in the body.

Heart Disease

- Adult bone marrow stem cells injected into the hearts arteries are believed to improve cardiac function in victims of heart failure or heart attack.


Mouse adult stem cells are injected into the muscle of the damaged left ventricular wall of the mouse heart.
Mouse heart
Adult stem cells
Stem cells help regenerate damaged heart muscle.
Damaged heart muscle cells


Human adult bone marrow stem cells are injected into the tail vasculature of a rat.
The stem cells induce new blood vessel formation in the damaged heart muscle and proliferation of existing vasculature.
Adult stem cells
New blood vessels
Damaged heart muscle cells

Leukemia and Cancer

- Studies show leukemia patients treated with stem cells emerge free of disease.
- Injections of stem cells have also reduced pancreatic cancers in some patients.

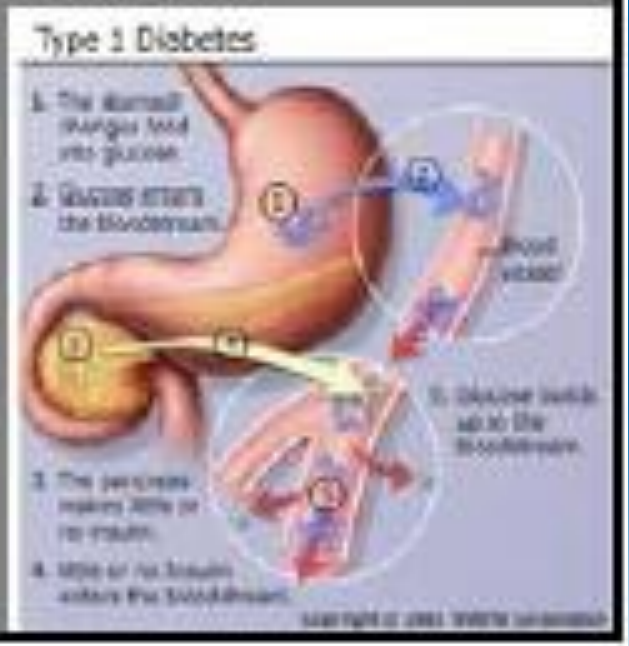
Rheumatoid Arthritis

- Adult stem cells may be helpful in jumpstarting repair of eroded cartilage.

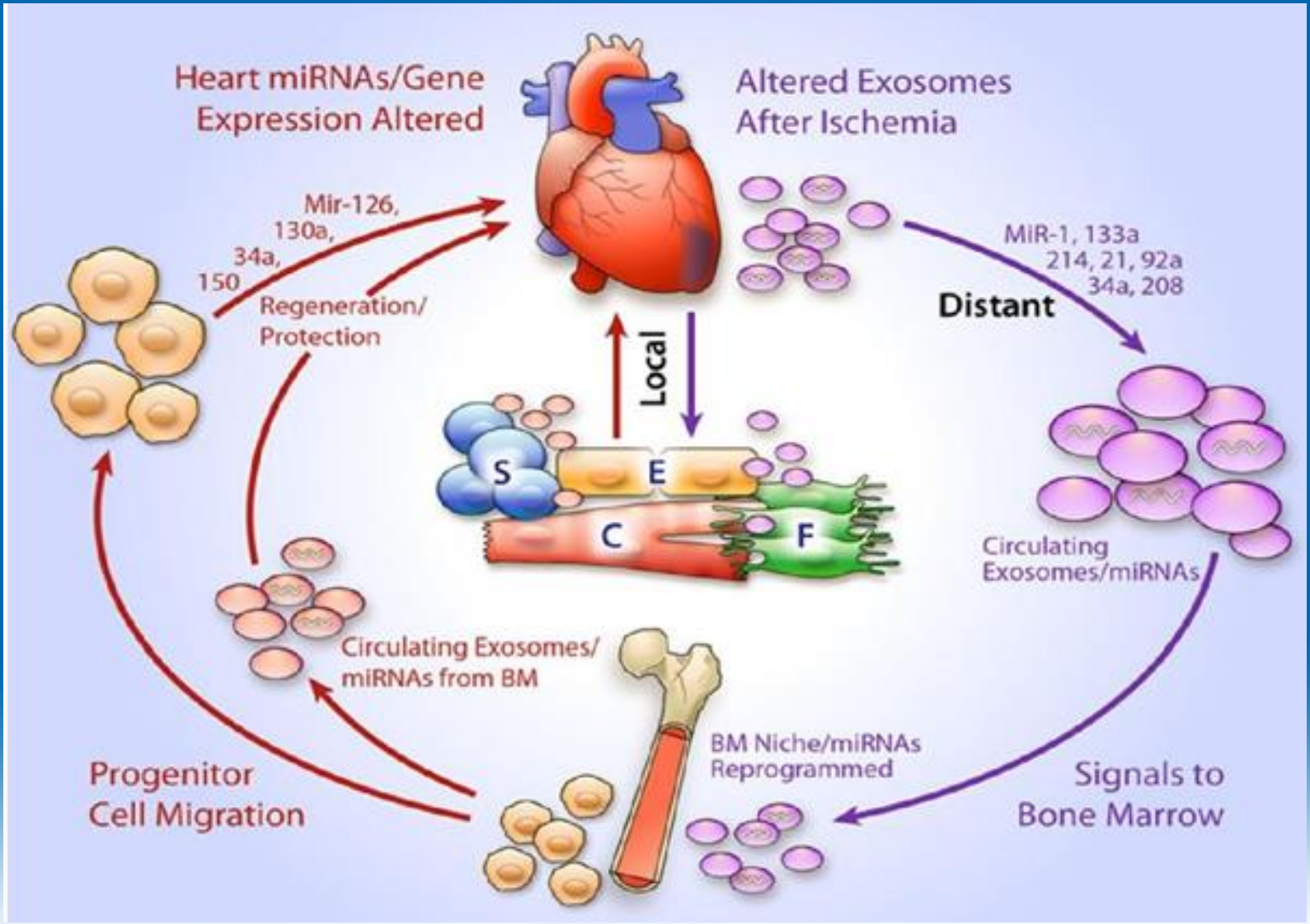
A foot with painful, advanced rheumatoid arthritis

Type I Diabetes

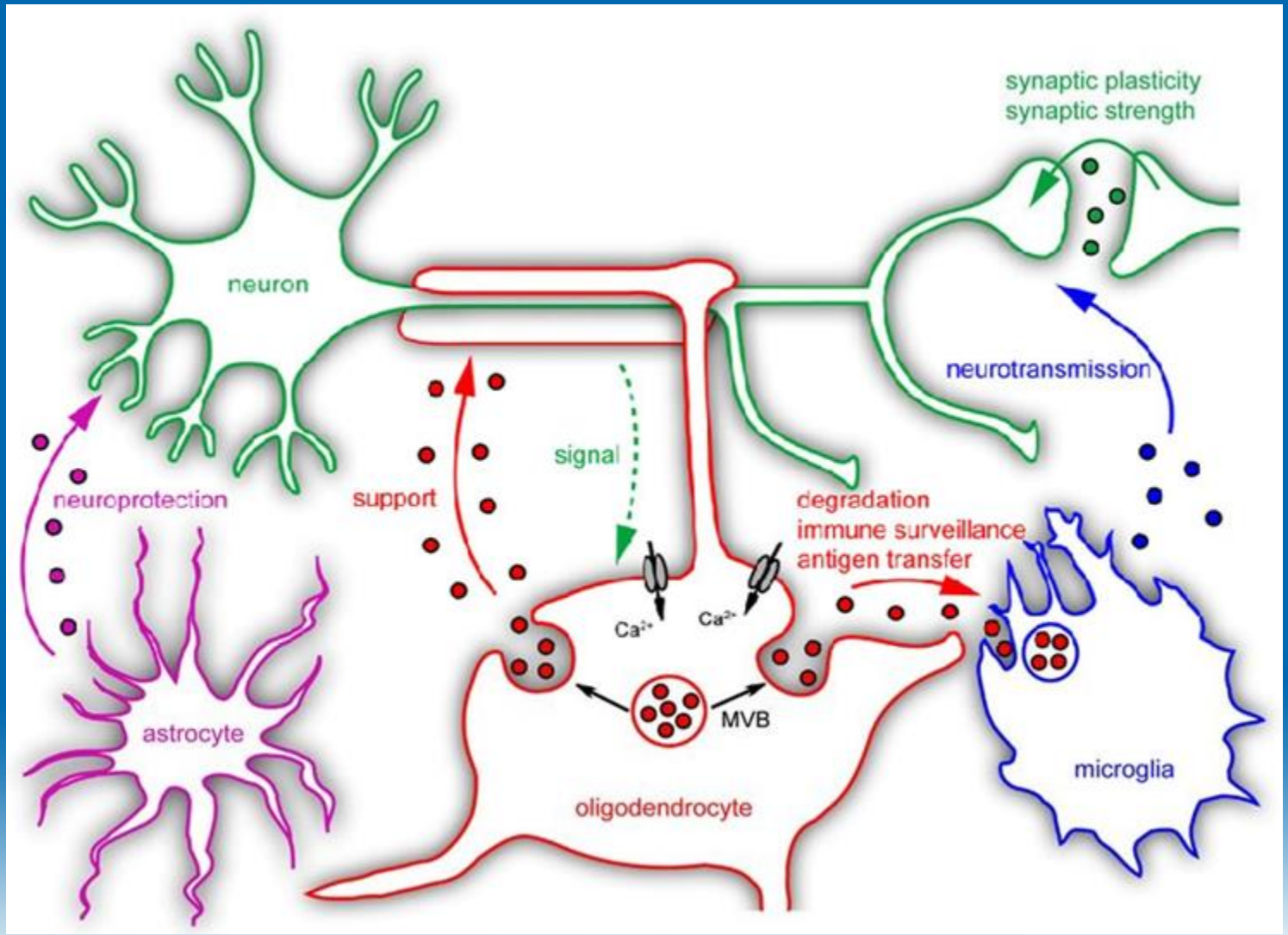
- Pancreatic cells do not produce insulin.
- Basic research focused on understanding how embryonic stem cells might be trained to become pancreatic islets cells needed to secrete insulin.



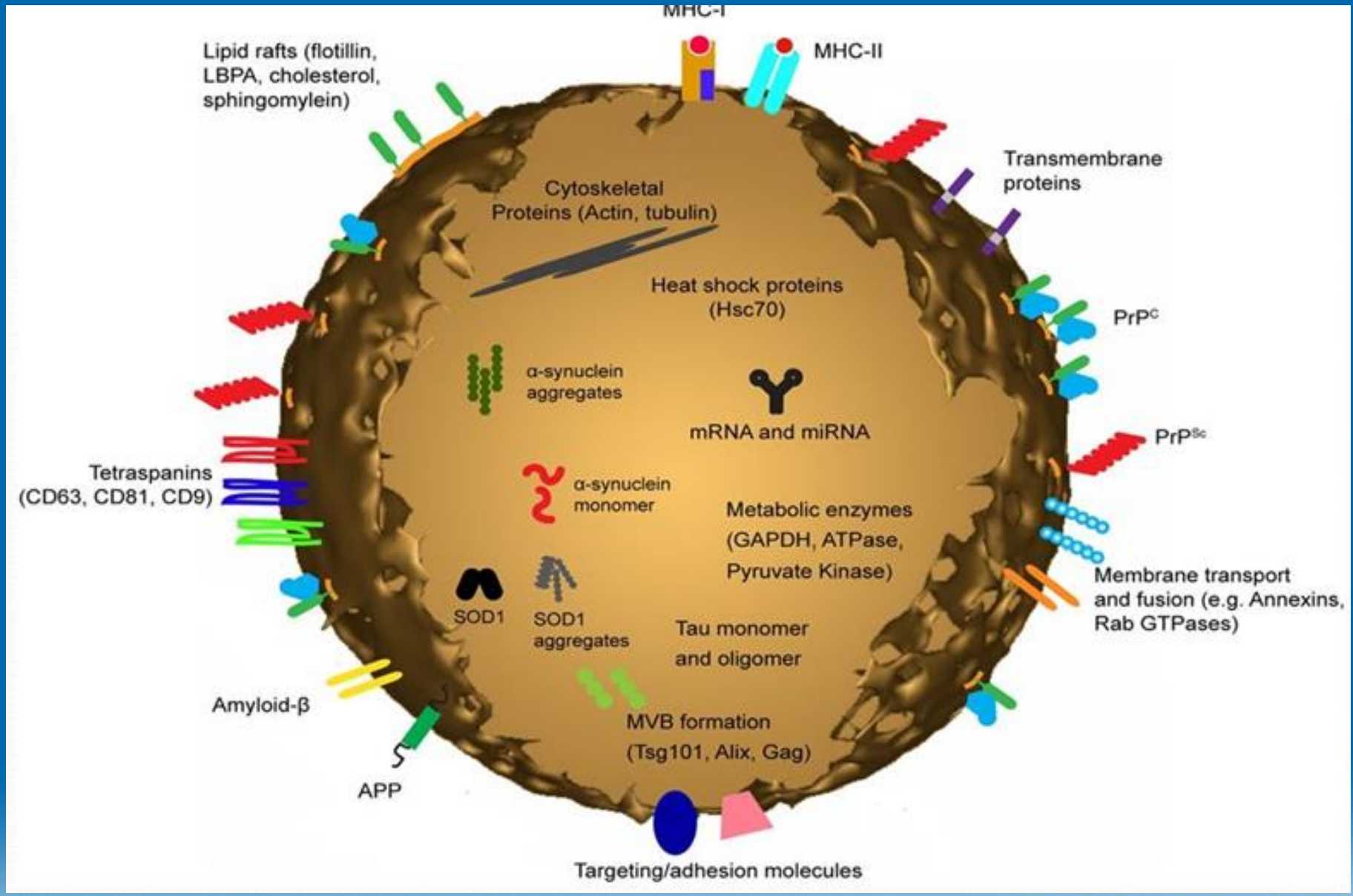
A suggested hypothesis on the role of exosomes released from a damaged heart as a potential intercellular communicator



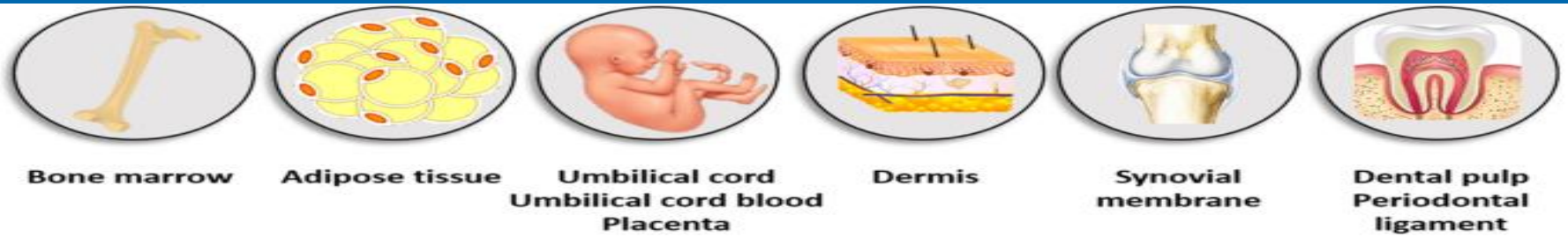
Postulated roles of exosomes/microvesicles in neural cell communication

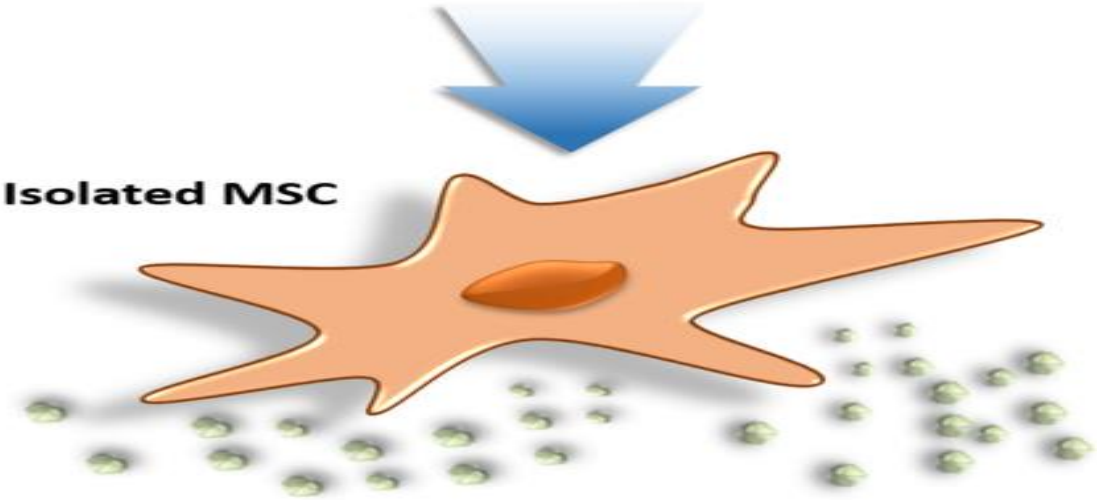


Front. Physiol., 30 April



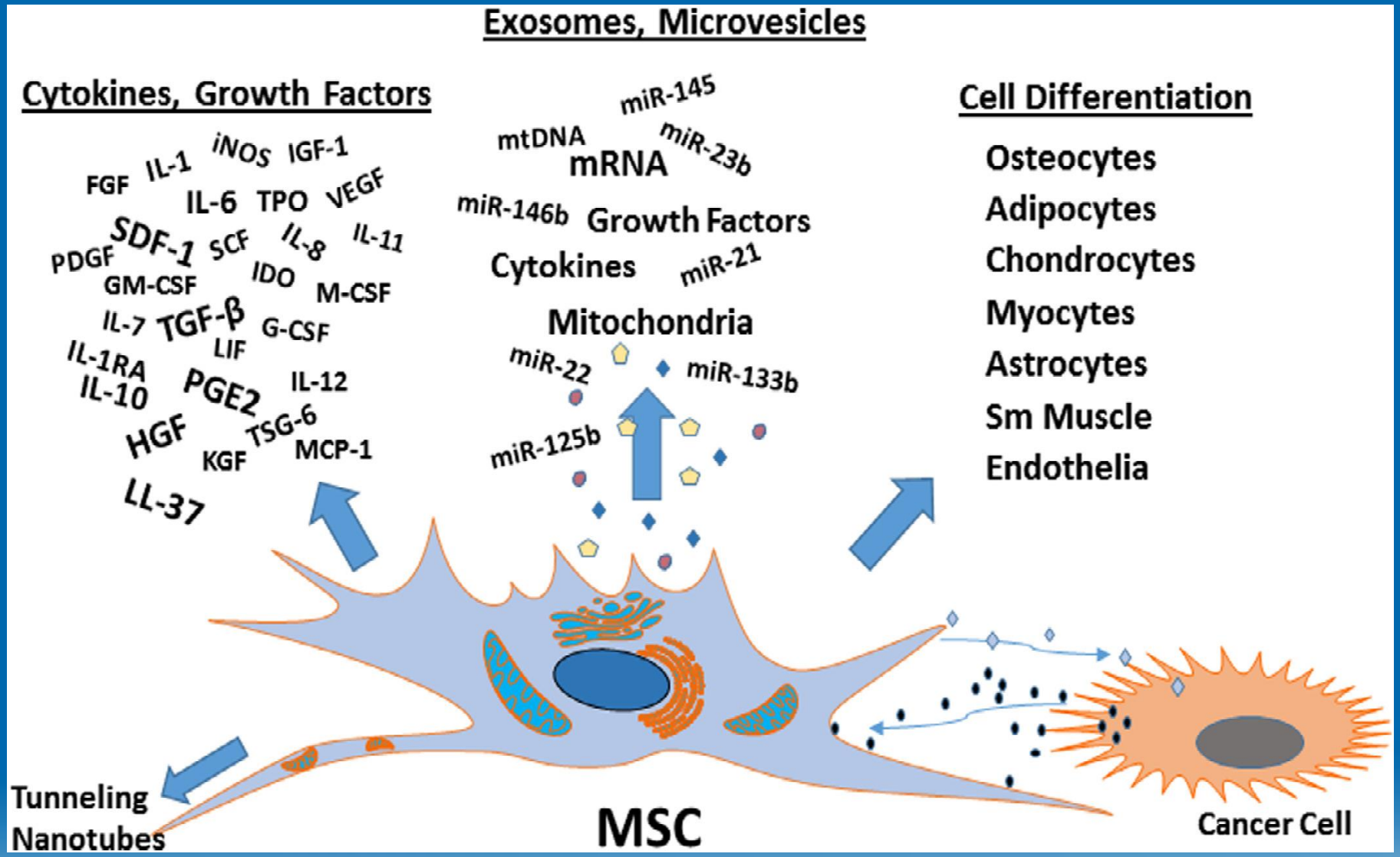
Frontiers in physiology published: 03 May 2012

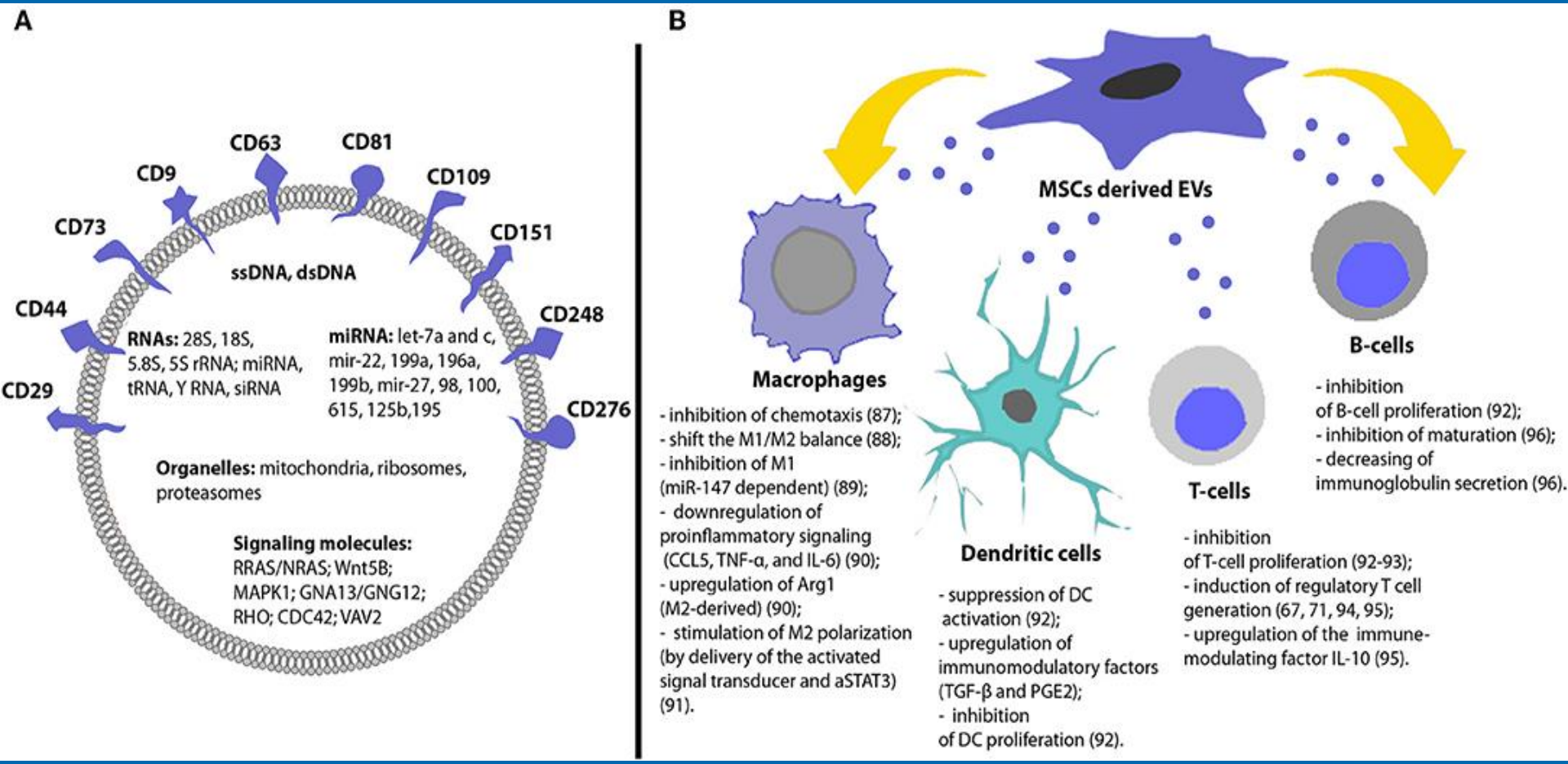


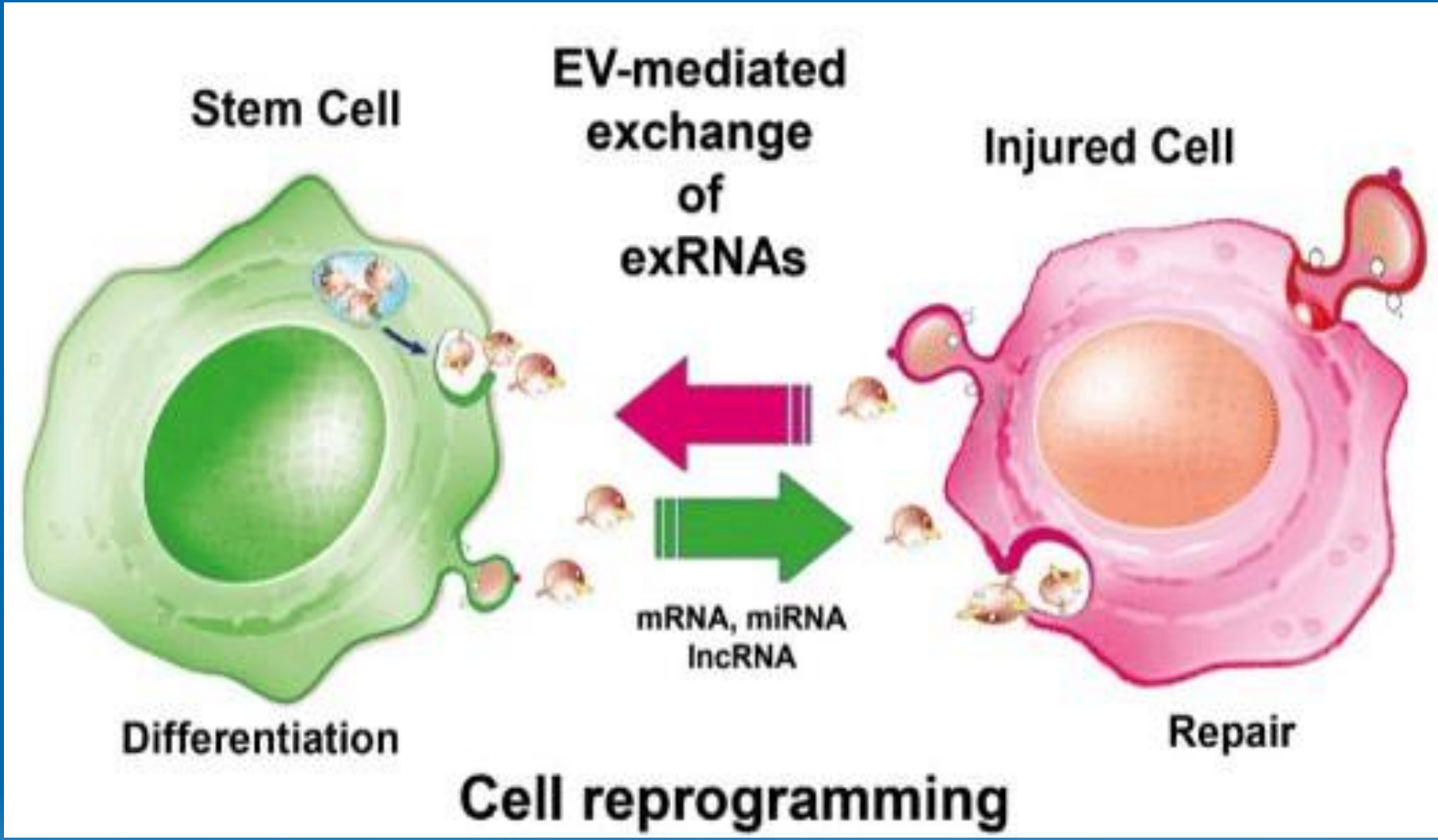


Immunomodulation	Engraftment	Angiogenesis
PGE_2 IDO iNOS HGF TGF-β1 LIF	SDF-1/CXCL12 CXCR4 MCP-1	VEGF IGF-1 MCP-1 bFGF IL-6

Wound healing	Anti-apoptosis	Chemoattraction
EGF KGF IL-1β Angiopoietin-2	VEGF TGF-β IGF-1 HGF bFGF GM-CSF	CCL2 CCL5 CX3CL1 CXCL2 CXCL12


Exosomes, Microvesicles
Cytokines, Growth Factors
FGF
IL-1
iNOS
IGF-1
IL-6
TPO
VEGF
SDF-1
SCF
IL-8
IL-11
PDGF
GM-CSF
IDO
M-CSF
IL-7
TGF-β
G-CSF
LIF
IL-1RA
IL-10
PGE2
IL-12
HGF
TSG-6
KGF
MCP-1
LL-37
miR-145
mtDNA
miR-23b
mRNA
miR-146b
Growth Factors
Cytokines
miR-21
Mitochondria
miR-22
miR-133b
miR-125b
Cell Differentiation
Osteocytes
Adipocytes
Chondrocytes
Myocytes
Astrocytes
Sm Muscle
Endothelia
Tunneling
Nanotubes
MSC
Cancer Cell


A
CD63
CD81
CD9
CD109
CD73
CD151
ssDNA, dsDNA
CD44
CD248
RNAs: 28S, 18S, 5.8S, 5S rRNA; miRNA, tRNA, Y RNA, siRNA
miRNA: let-7a and c, mir-22, 199a, 196a, 199b, mir-27, 98, 100, 615, 125b,195
CD29
CD276
Organelles: mitochondria, ribosomes, proteasomes
Signaling molecules: RRAS/NRAS; Wnt5B; MAPK1; GNA13/GNG12; RHO; CDC42; VAV2
B
MSCs derived EVs
Macrophages
- inhibition of chemotaxis (87);
- shift the M1/M2 balance (88);
- inhibition of M1 (miR-147 dependent) (89);
- downregulation of proinflammatory signaling (CCL5, TNF-α, and IL-6) (90);
- upregulation of Arg1 (M2-derived) (90);
- stimulation of M2 polarization (by delivery of the activated signal transducer and aSTAT3) (91).
Dendritic cells
- suppression of DC activation (92);
- upregulation of immunomodulatory factors (TGF-β and PGE2);
- inhibition of DC proliferation (92).
T-cells
- inhibition of T-cell proliferation (92-93);
- induction of regulatory T cell generation (67, 71, 94, 95);
- upregulation of the immune-modulating factor IL-10 (95).
B-cells
- inhibition of B-cell proliferation (92);
- inhibition of maturation (96);
- decreasing of immunoglobulin secretion (96).


Stem Cell
EV-mediated exchange of exRNAs
Injured Cell
mRNA, miRNA
lncRNA
Differentiation
Repair
Cell reprogramming


با تشکر از حسن توجه شما