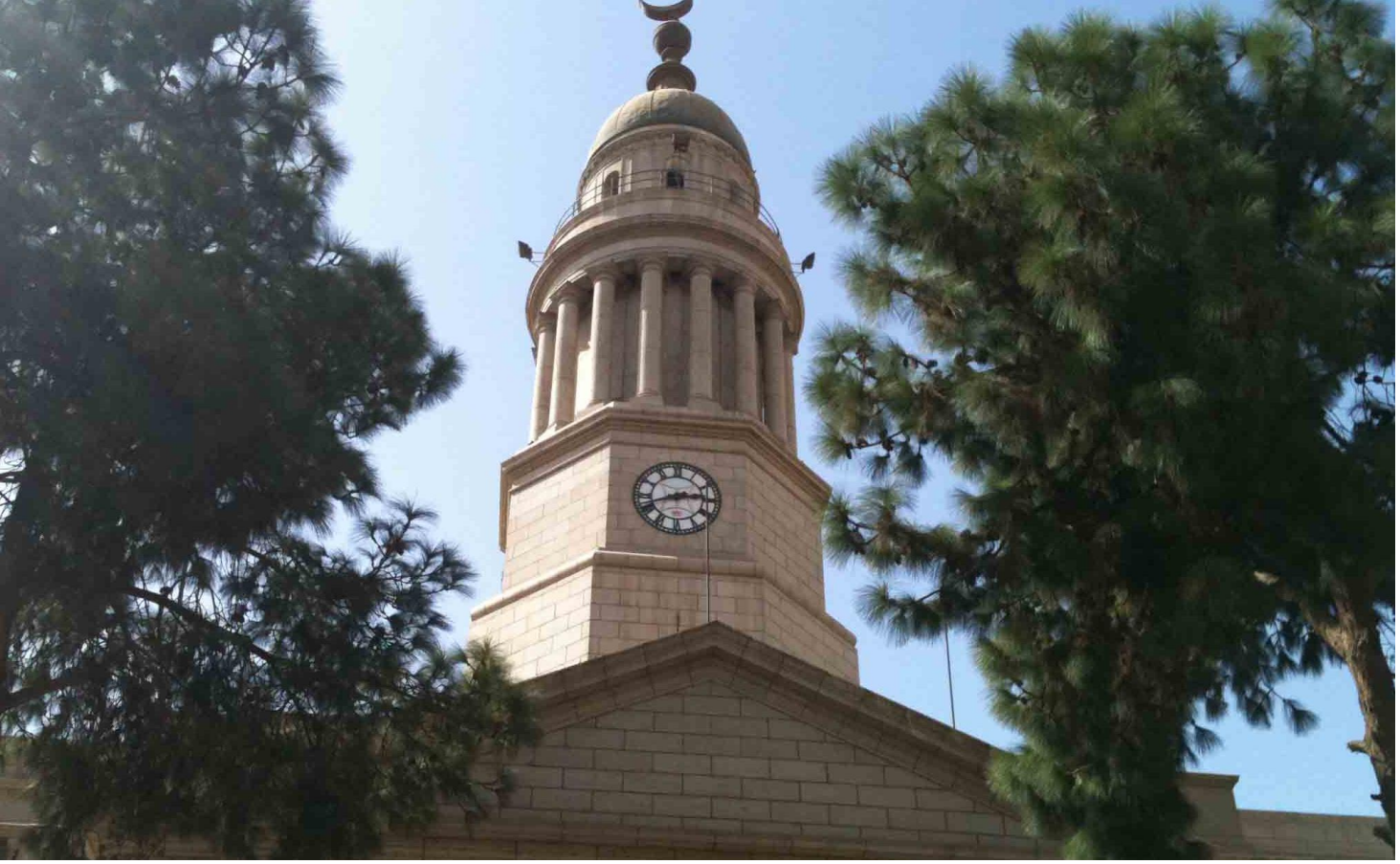


Stem Cell Therapy

In Pediatric Neurological Disorders

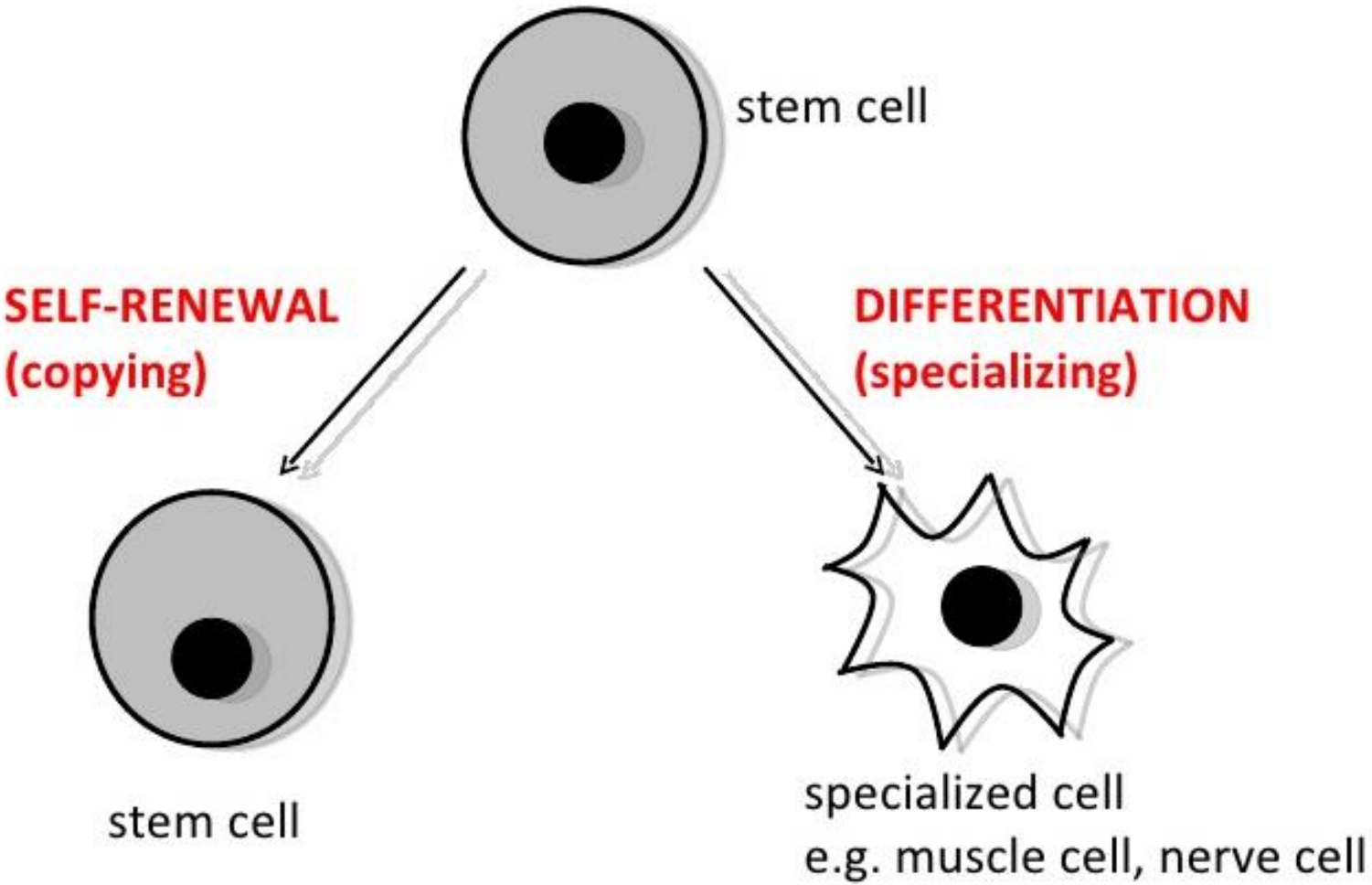
Amr Hasan, M.D.

Associate Professor of Neurology - Cairo University

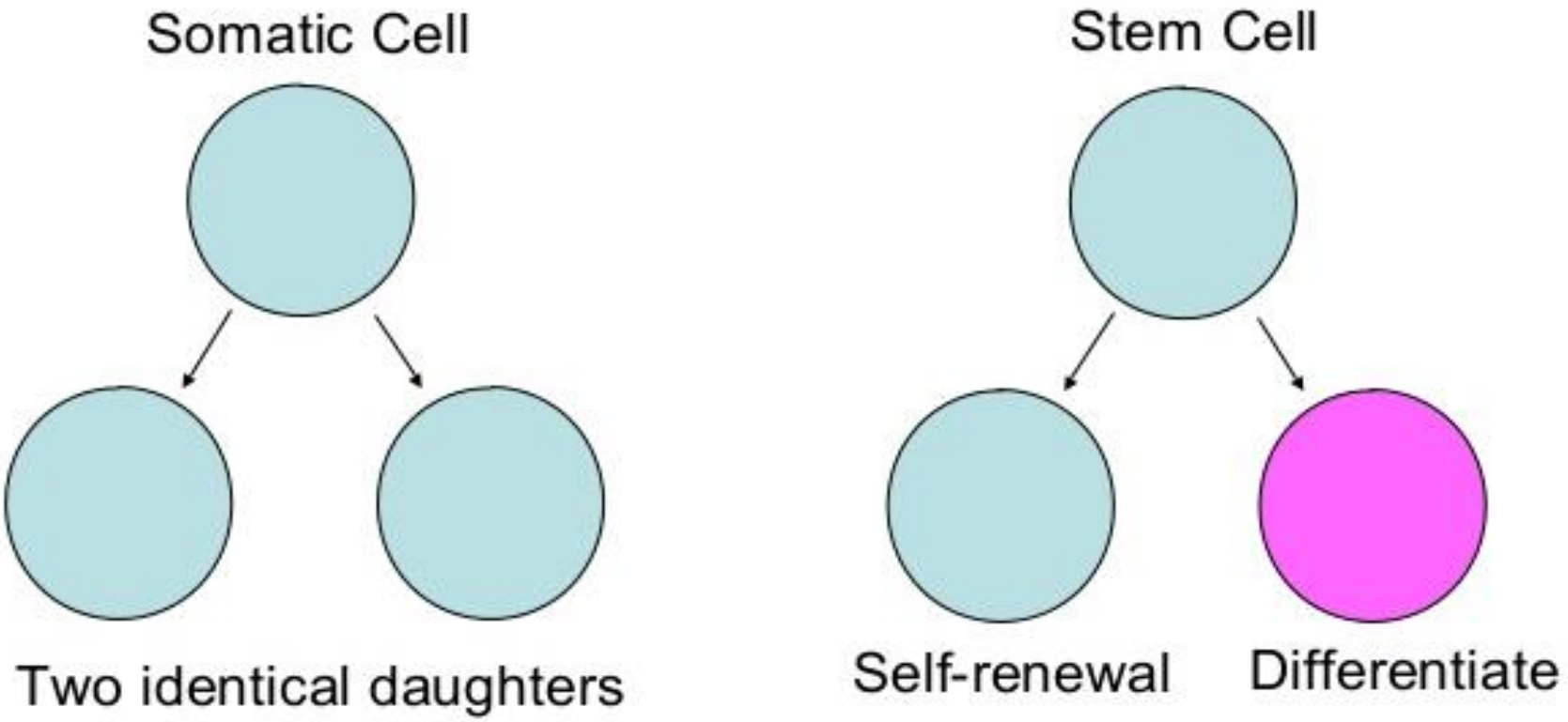
What is a stem cell?

" It is an undifferentiated cell that can produce daughter cells that can either remain a stem cell (a process called self-renewal) or commit to a pathway leading to differentiation"

What is a stem cell?



What is a stem cell?



Sources of stem cells

- Embryos
- Umbilical cord
- Adults

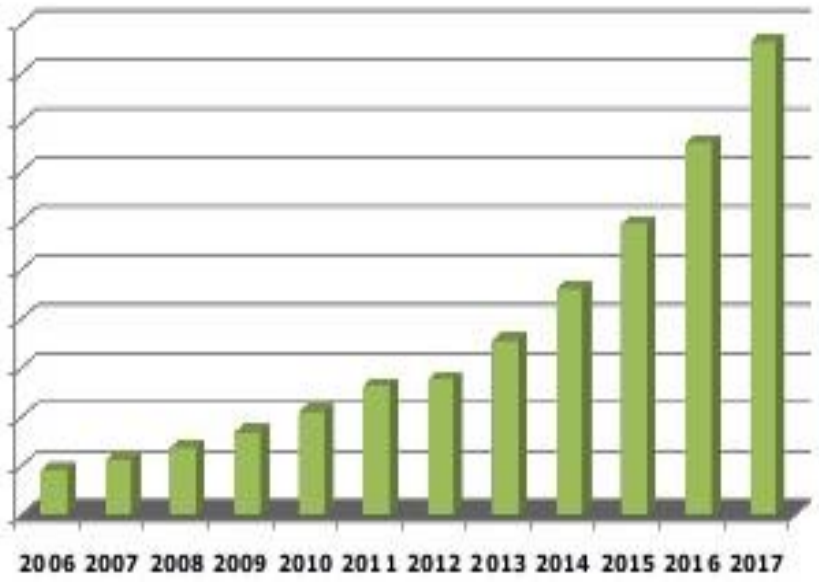
Embryonic stem cells

- These stem cells derived from the inner cell mass of the blastocyst at a stage before it would implant in the uterine wall

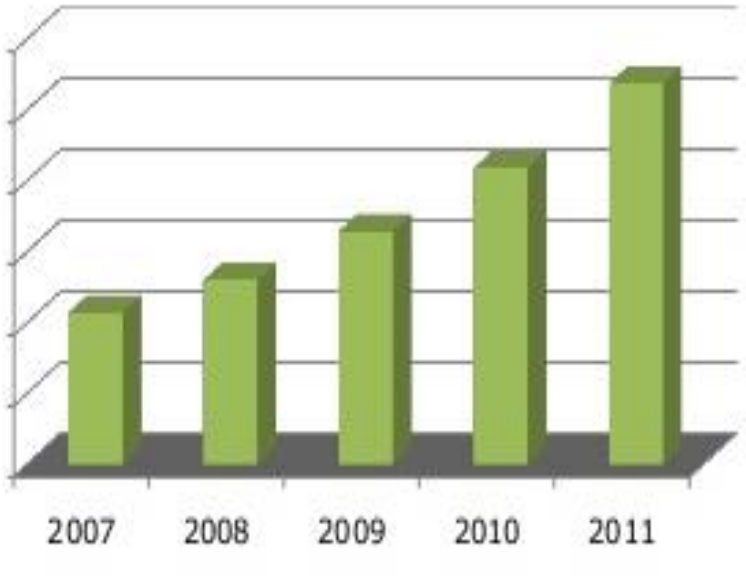
Umbilical cord stem cells

- These are cells harvested from the cord blood.
- Cord blood is rich in the stem cells
- It has both mesenchymal blood cell and haematopoietic stem cells
- 1st successful umbilical cord blood transplantationin1989in a patient with Fanconi's anaemia

Global Stem Cell Banking Market Size, 2006-2011 (US$ Billion)



Indian Stem Cell Banking Market Size, 2007-2011 (US$ Million)



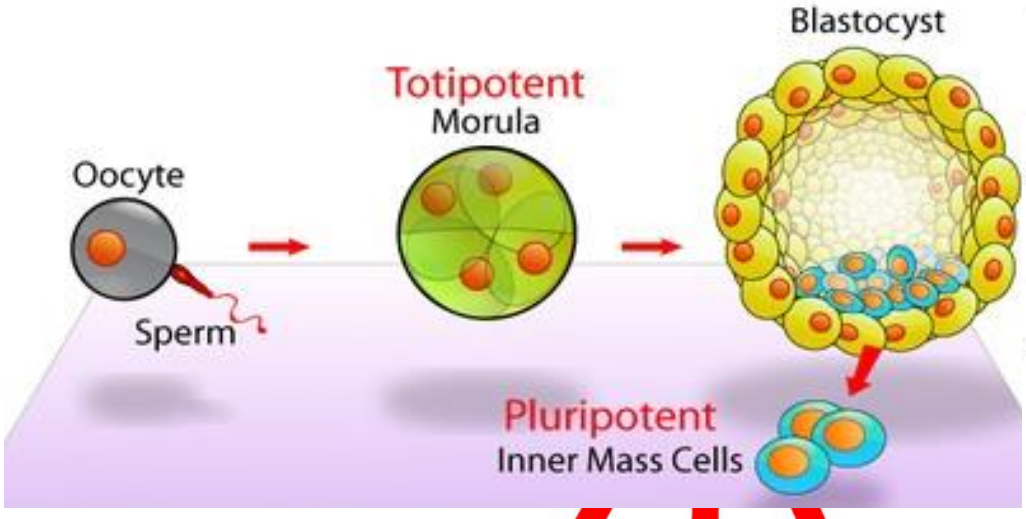
Adult stem cells

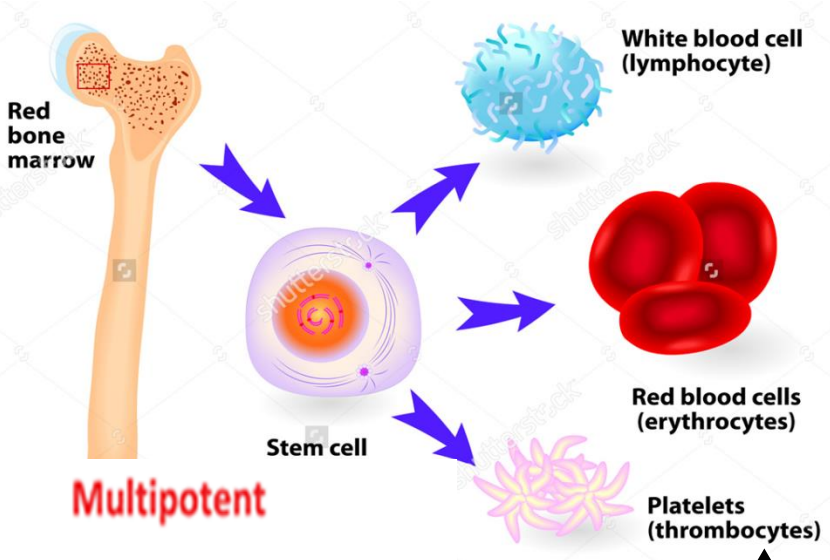
- Hematopoietic
- Mammary
- Mesenchymal
- Neural
- Endothelial
- Olfactory
- Neural crest
- Testicular

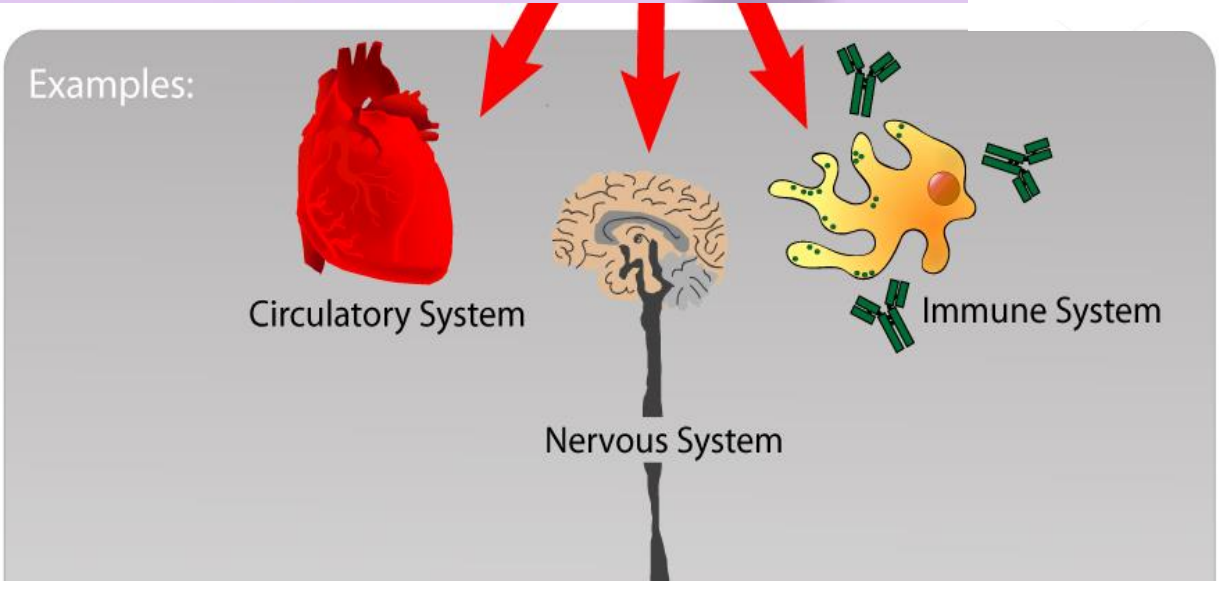
Thought to reside in a specific area of each tissue

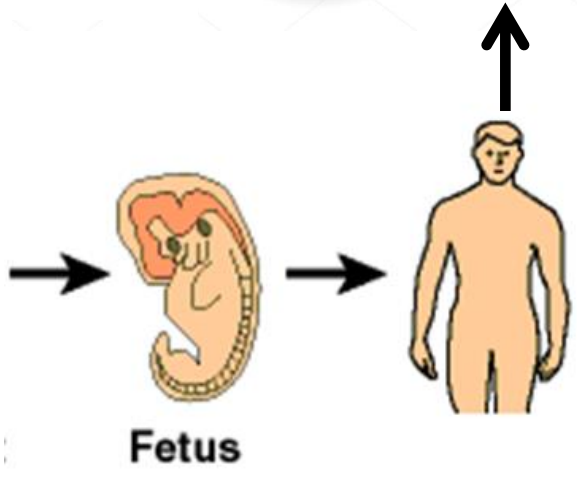
'stem cell niche'

Potency of stem cells

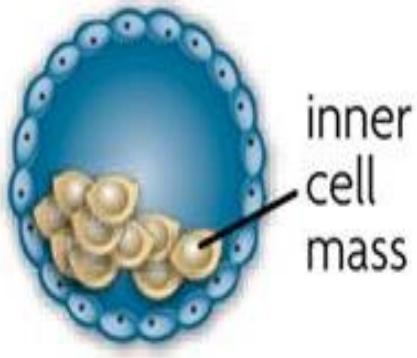




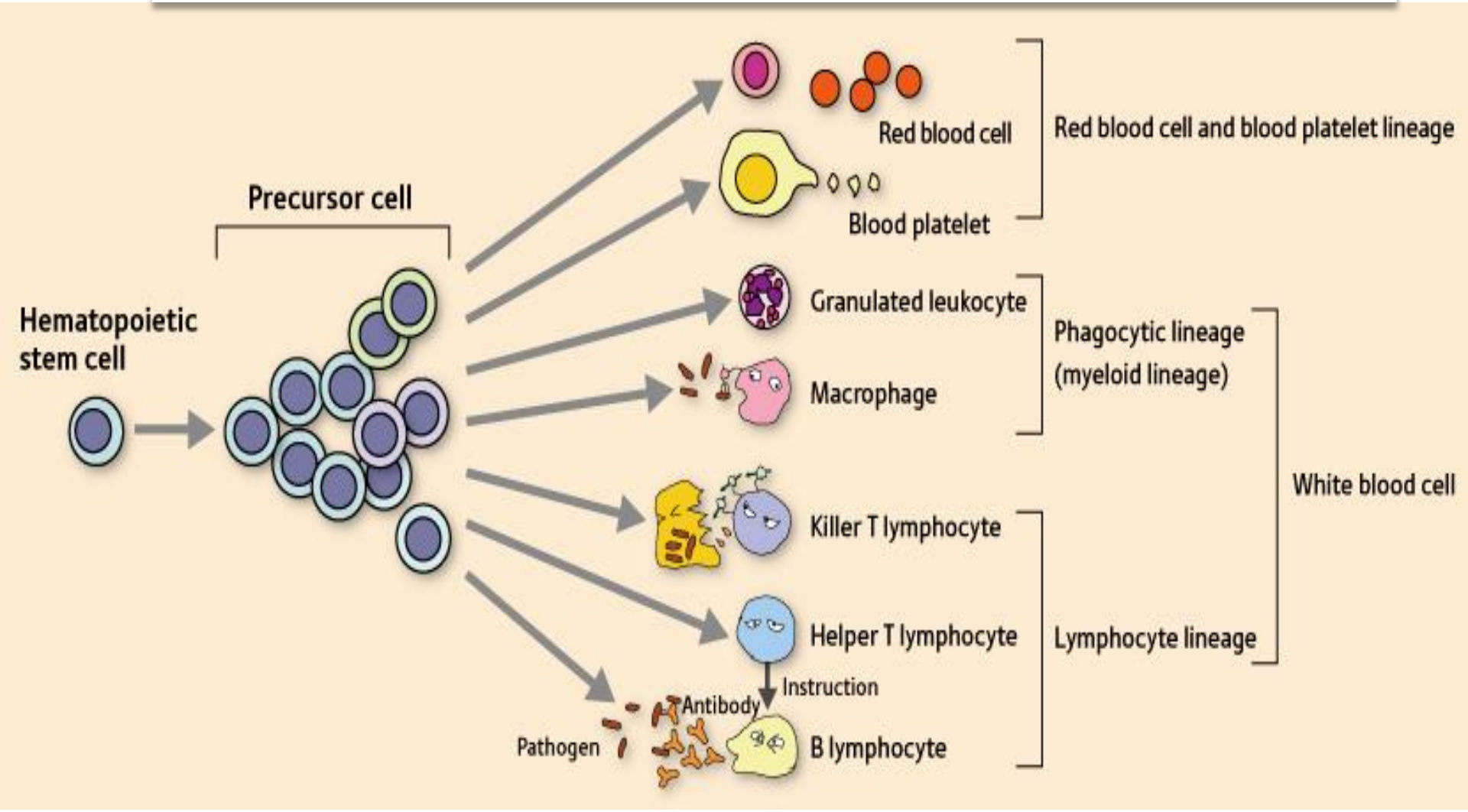




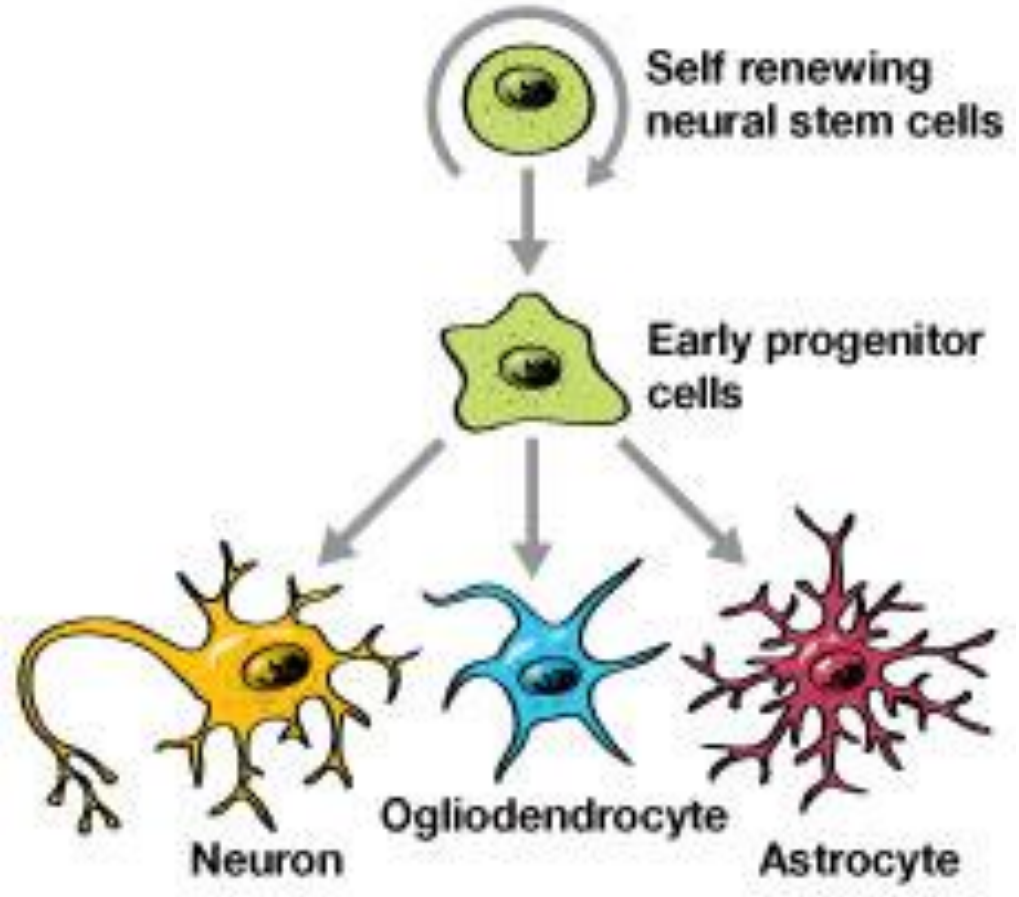
Potency of stem cells

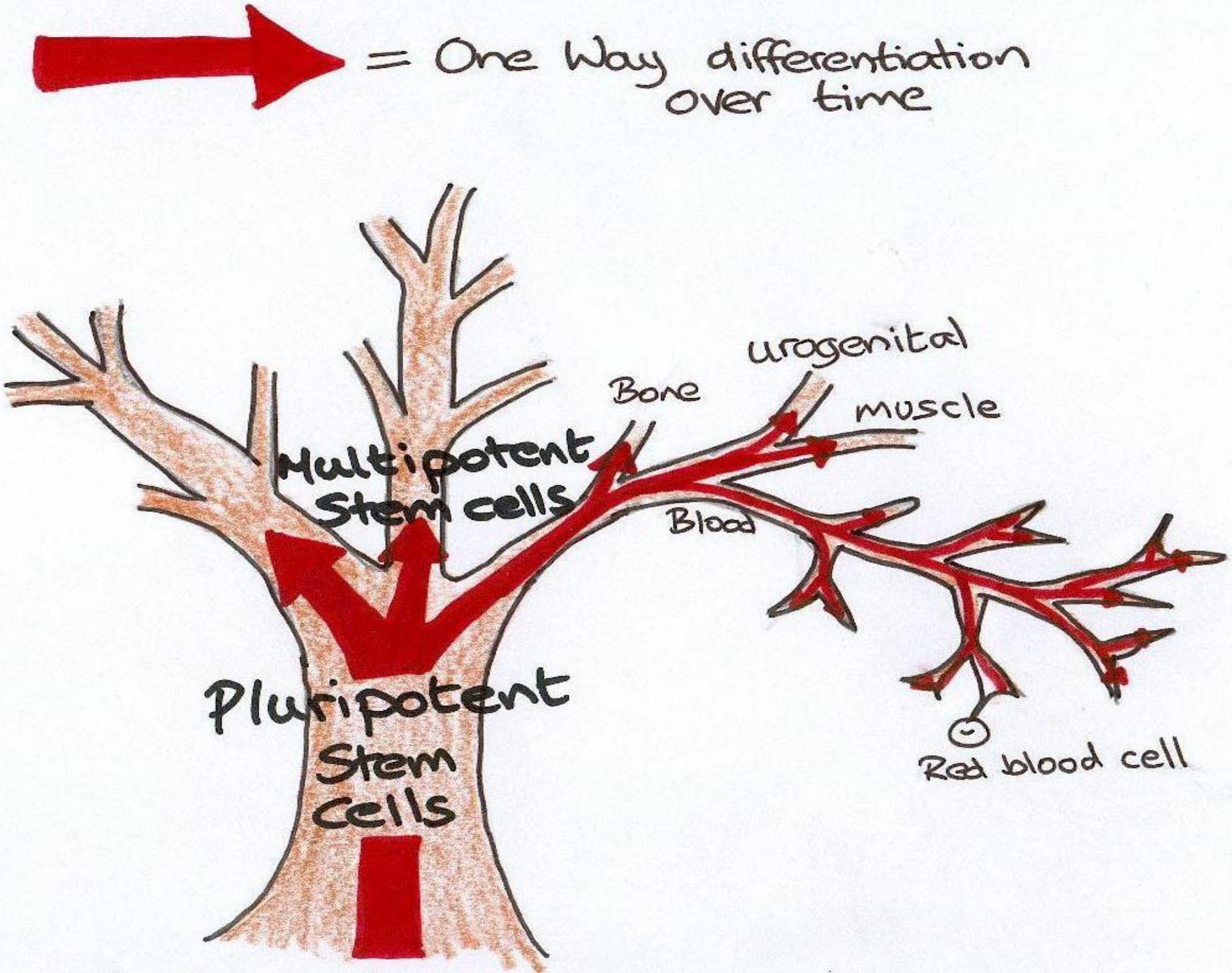
Class	totipotent	pluripotent	multipotent
Type of cell	fertilized egg 	embryonic stem cell 	adult stem cell (example from blood) 
Can give rise to	all cells	almost any cell	closely related cells
Example	new organism	neurons, skin, muscle, kidney, cartilage, bone, liver, pancreas	red blood cells, platelets, white blood cells

Adult stem cells: Haematopoietic stem cell

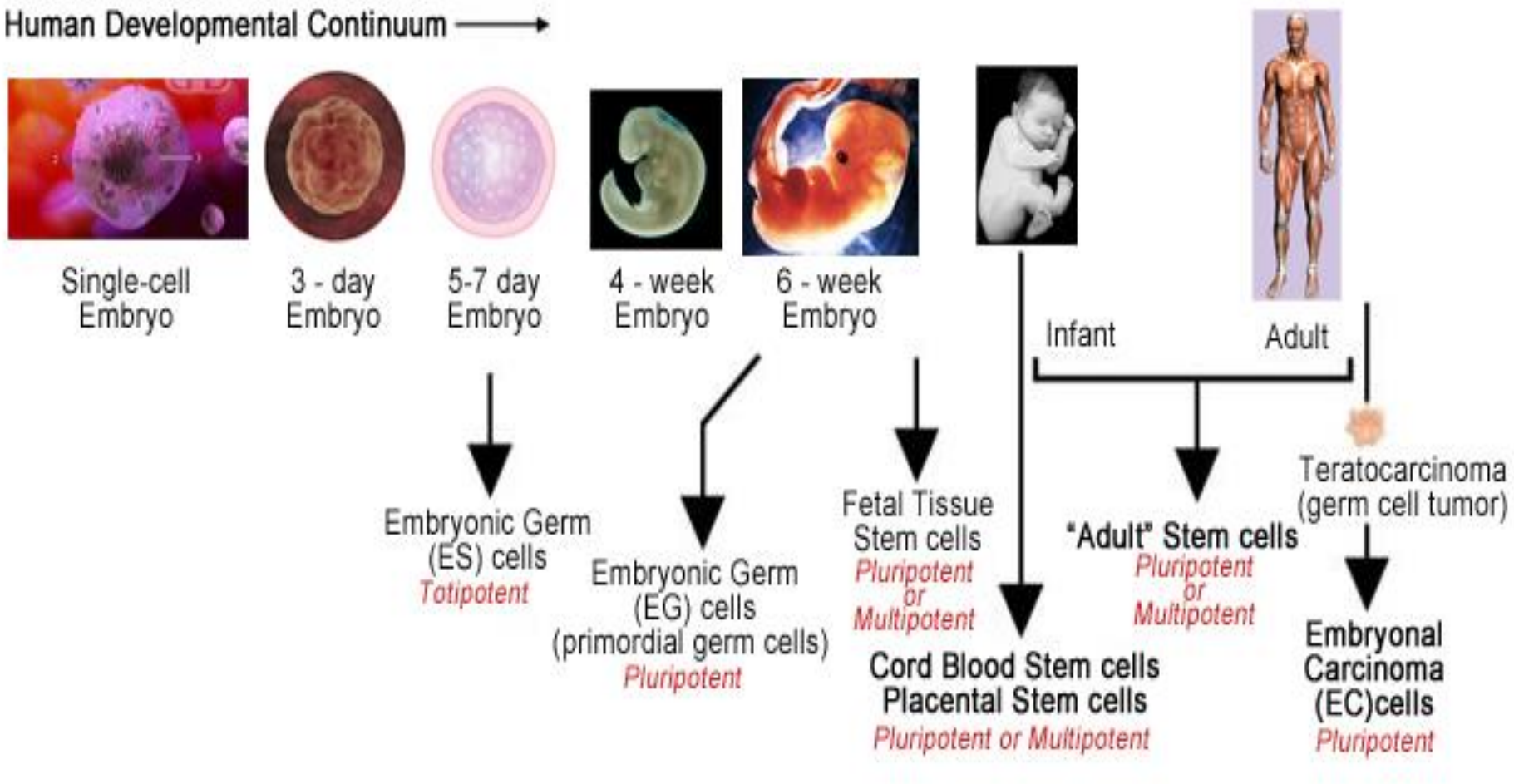


Adult stem cells : Neural stem cell

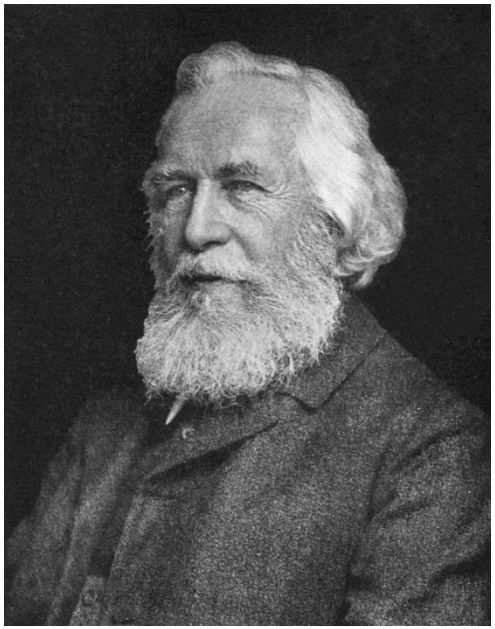



= One Way differentiation over time
Bone
urogenital
muscle
Multipotent Stem cells
Blood
Pluripotent Stem Cells
Red blood cell

Sources of stem cells



Stem cell timeline



Ernst Heinrich
(1834 -1919)
German biologist

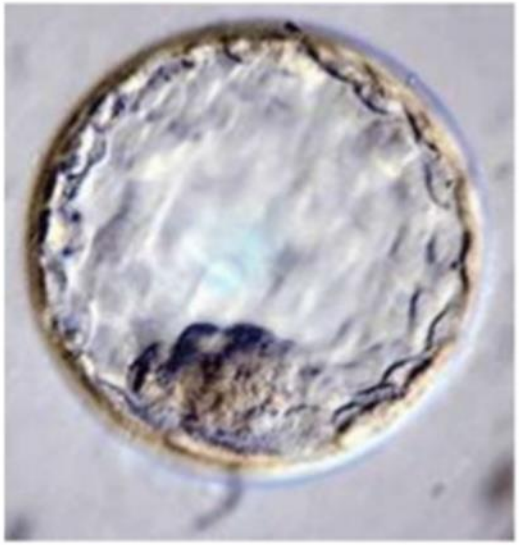
Edward Donnall Thomas
(1920-2012)
American physician

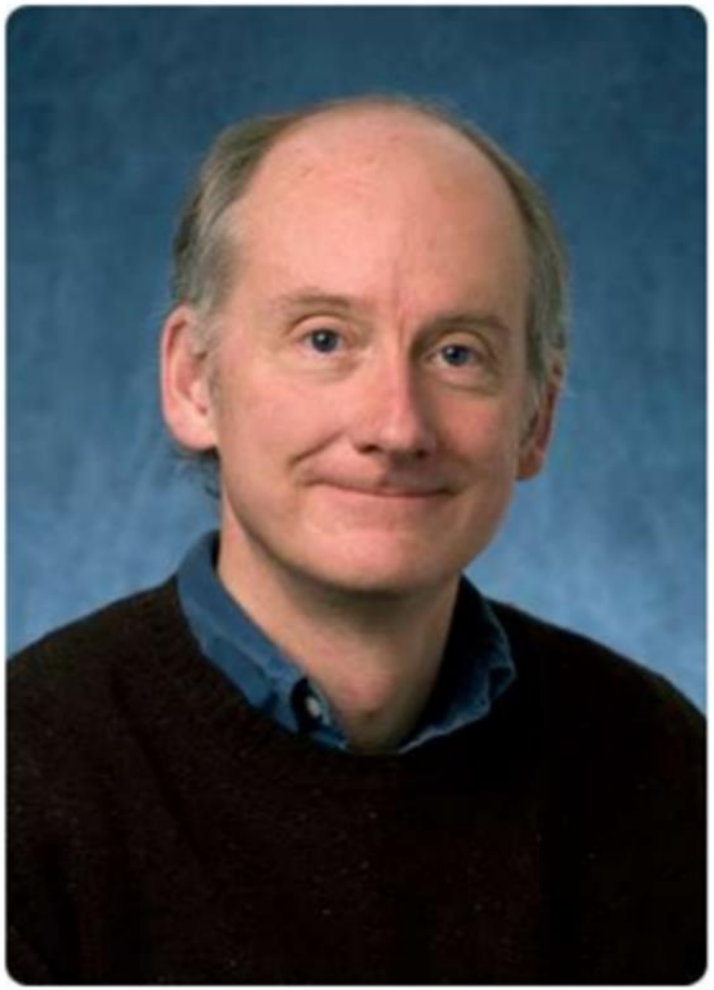
Stem cell timeline

1998, University of Wisconsin-Madison

- **James Thomson**

Isolated cells from the inner cell mass of the early embryo, and developed the first human embryonic stem cell lines.





Stem cell therapy

Stem cells are able to

- Renew themselves
- Differentiate into distinctive mature cell types

New tissue formation, repair, and regeneration

Regenerative medicine

Regenerative medicine

is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage or congenital defects ***(Mason and Dunnill, 2008).***

Essential properties of stem cell to be used in practice

Capable of clonal propagation in vitro to ensure homogeneity

Genetic stability at high passage

Integration within the host brain following transplantation

Connectivity within host circuits

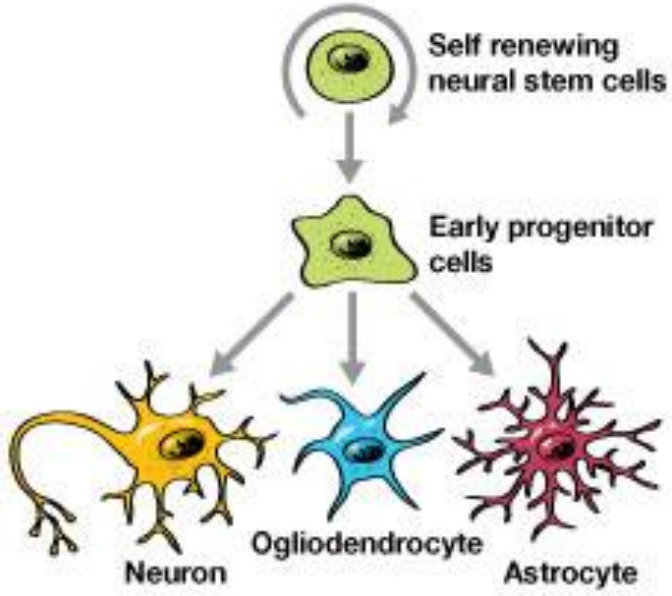
Migration and engraftment at sites of damage

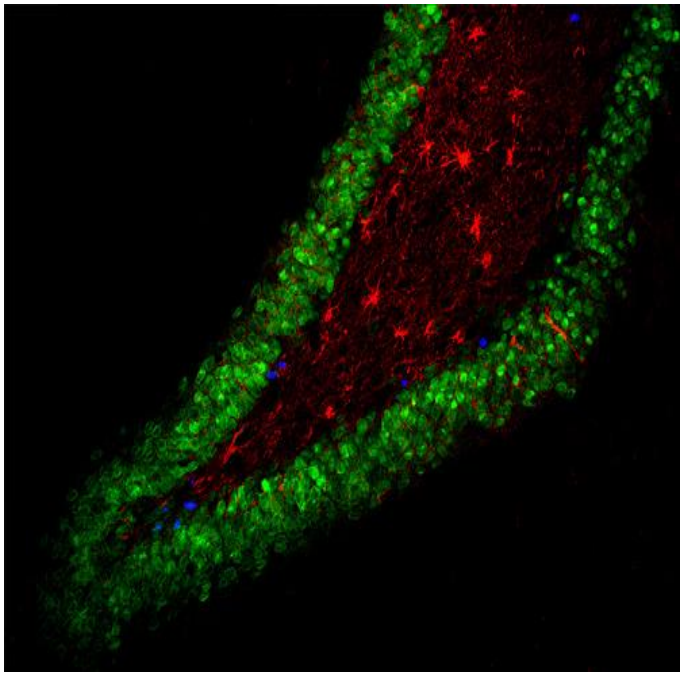
Correct differentiation into appropriate neural cell types

Functional benefits

Lack of side effects

Adult stem cells : Neural stem cell

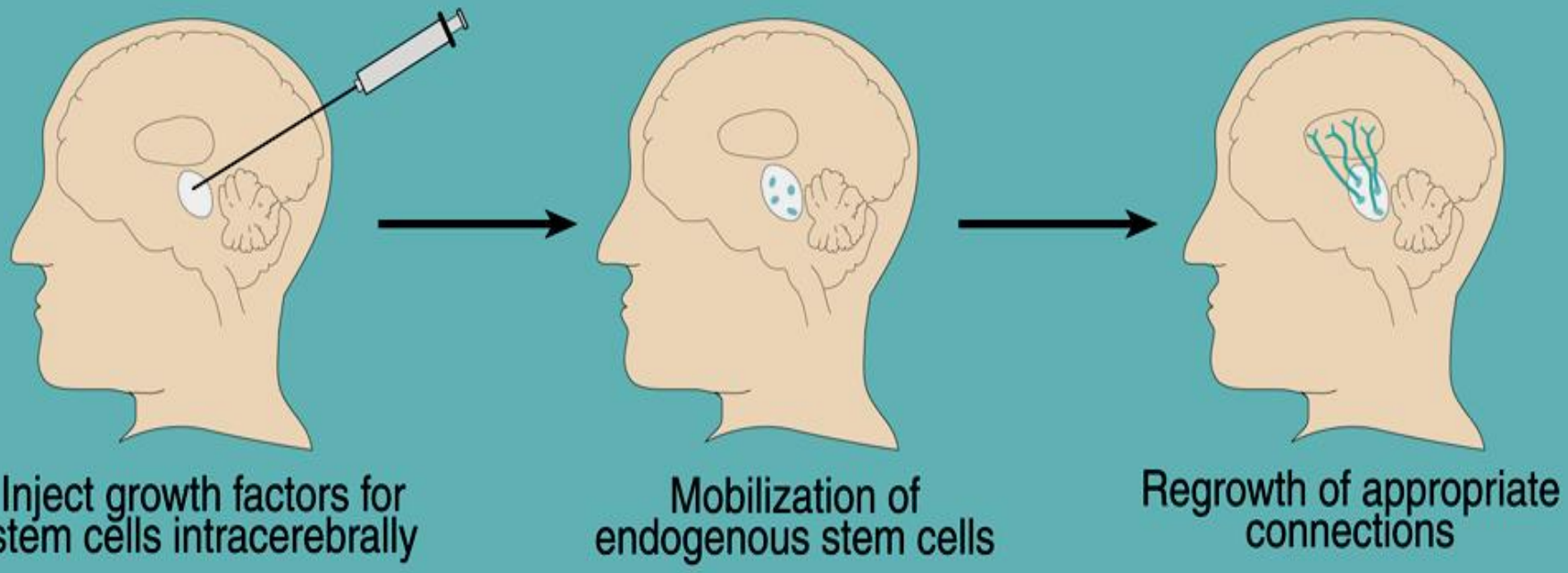




They are located in:

- ***Subventricular zone*** lining the lateral ventricles, where they give rise to newly-born neurons that migrate to the olfactory bulb via the rostral migratory stream.
- ***Subgranular zone***, part of the dentate gyrus of the hippocampus

In vivo mobilization of endogenous brain stem cells with growth factors



Advantages

- Access to fetal tissue not required
- No problems of immune rejection

Disadvantages

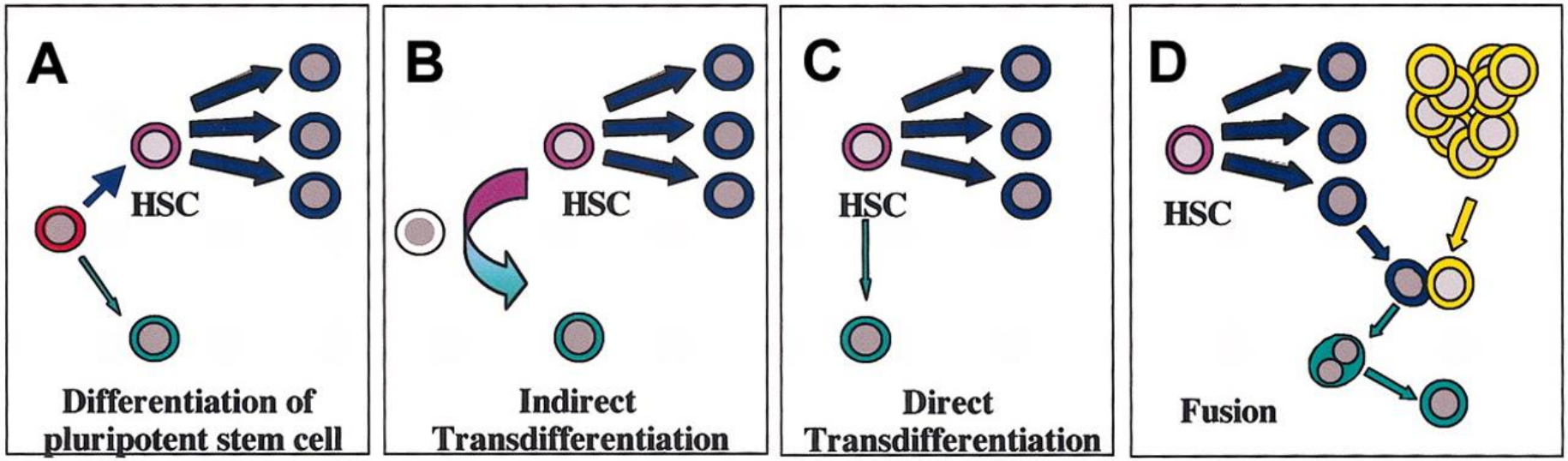
- Not all brain regions may respond to the factors

Stem cell plasticity

- Under special conditions tissue-specific adult stem cells can generate a whole spectrum of cell types of other tissues, even crossing germ layers.

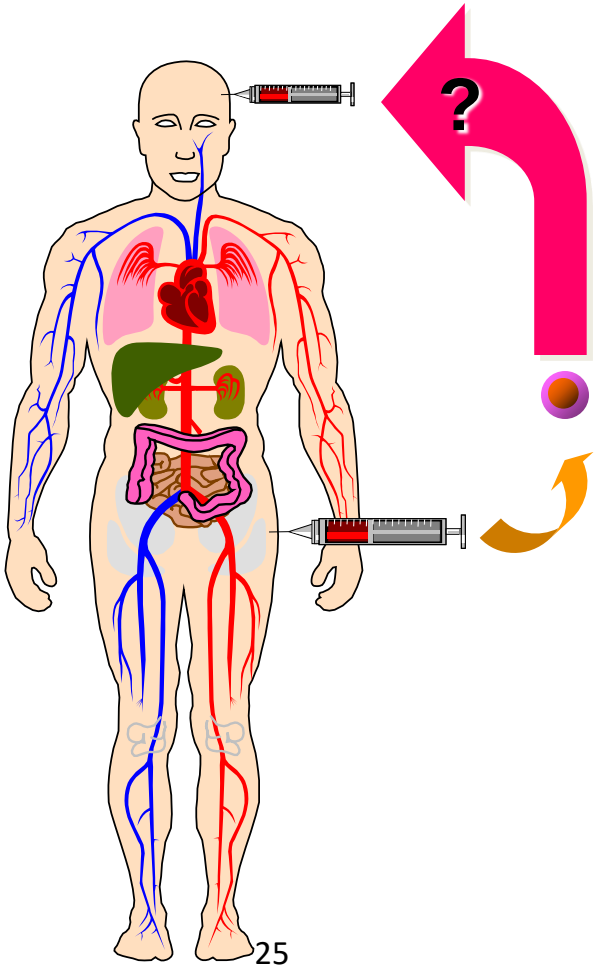
- It can be induced by modifying the growth medium when stem cells are cultured **in vitro** or transplanting them to an organ of the body different from the one they were originally isolated from (**in vivo**).

Stem cell plasticity : proposed mechanisms

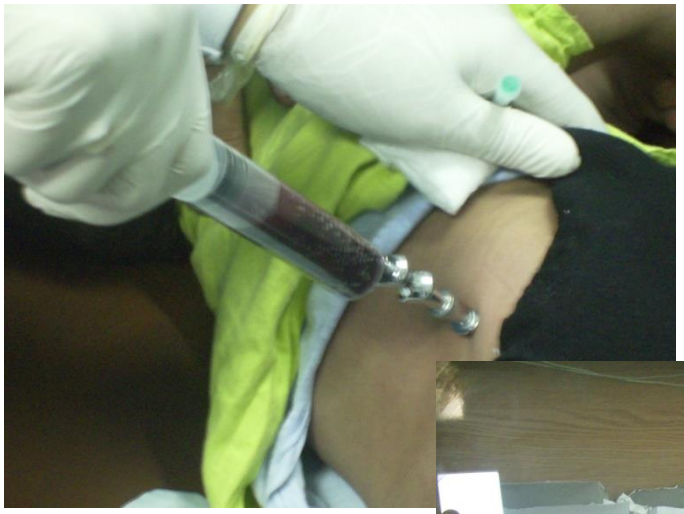


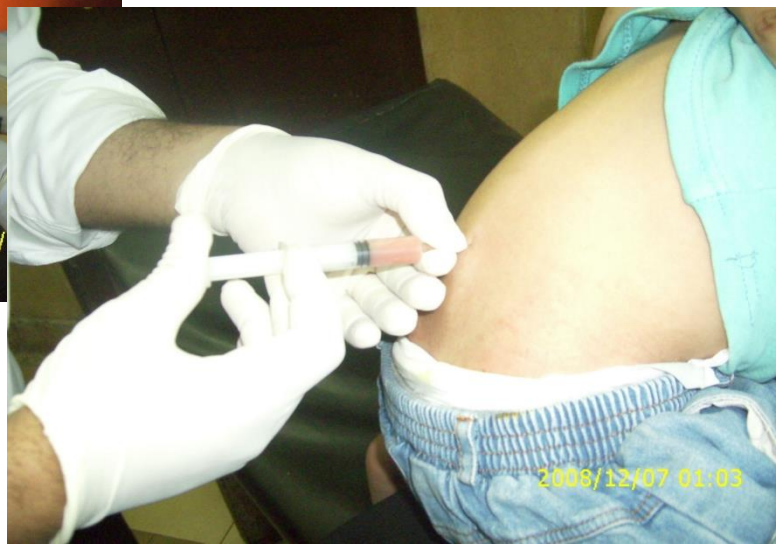
Stem cell plasticity

Bone Marrow-Derived Stem Cells for Brain Would Provide Stem Cell Therapy without Transplantation

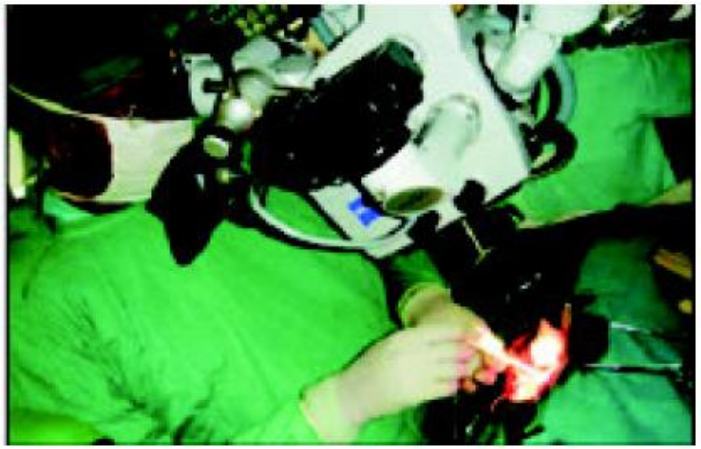


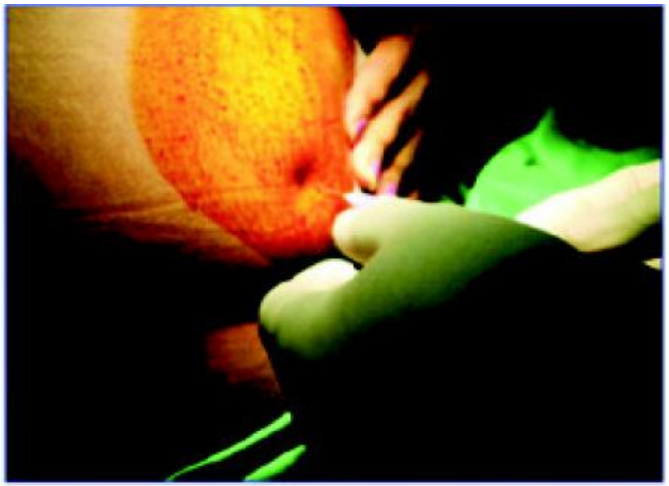
Stem cell transplantation

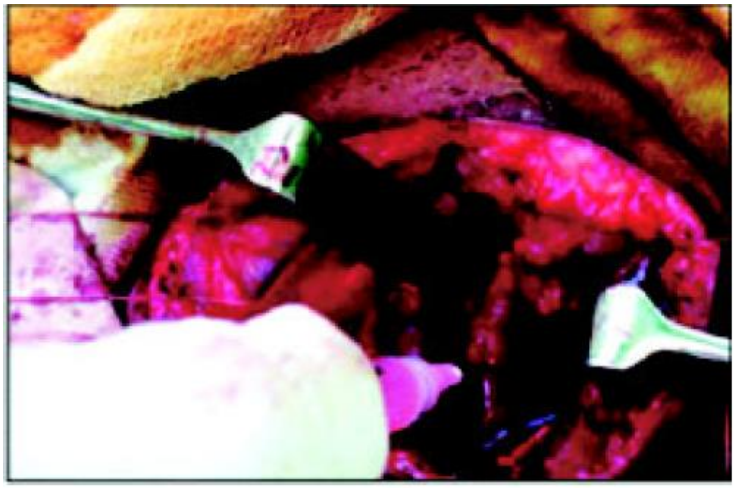


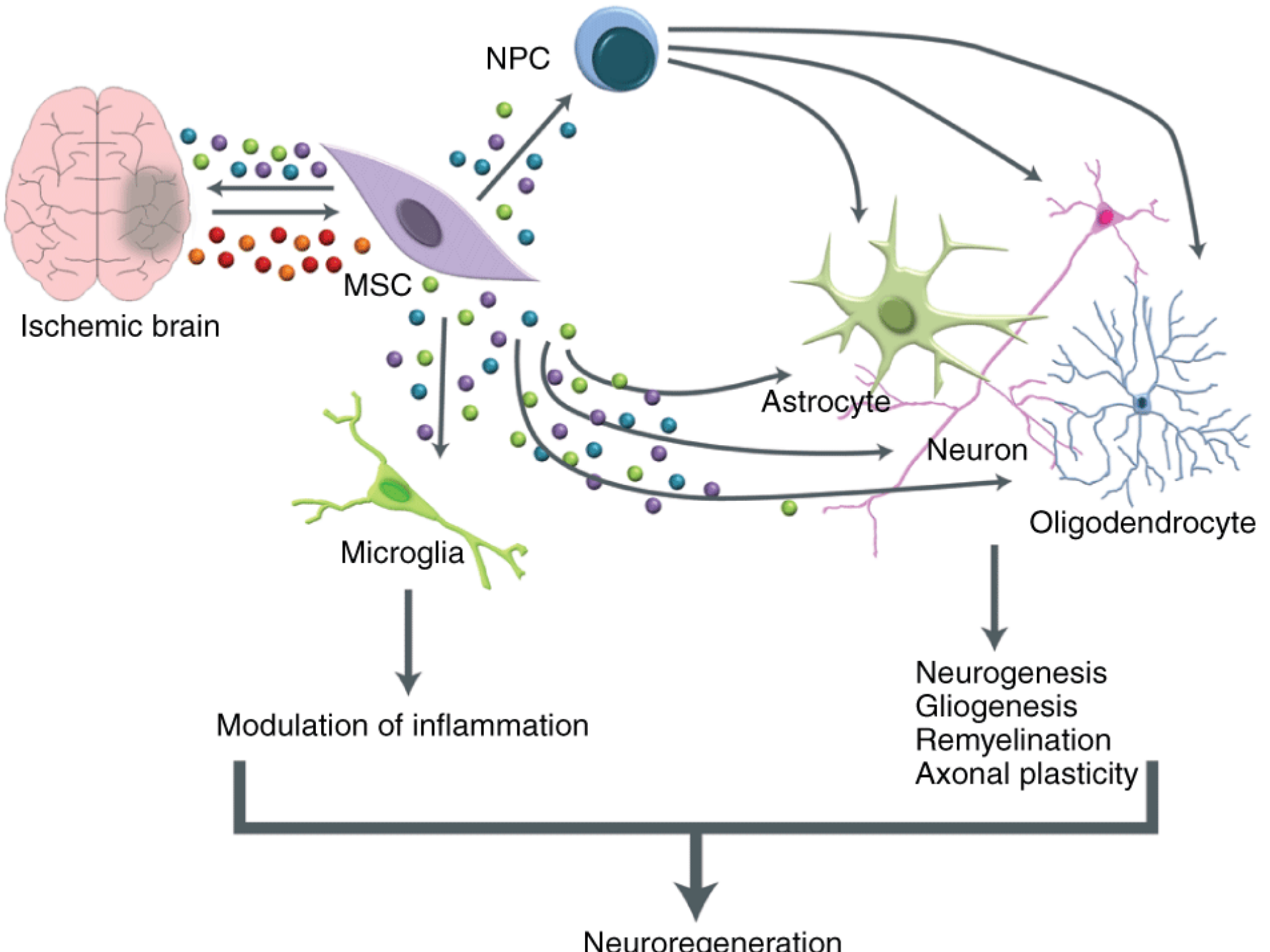


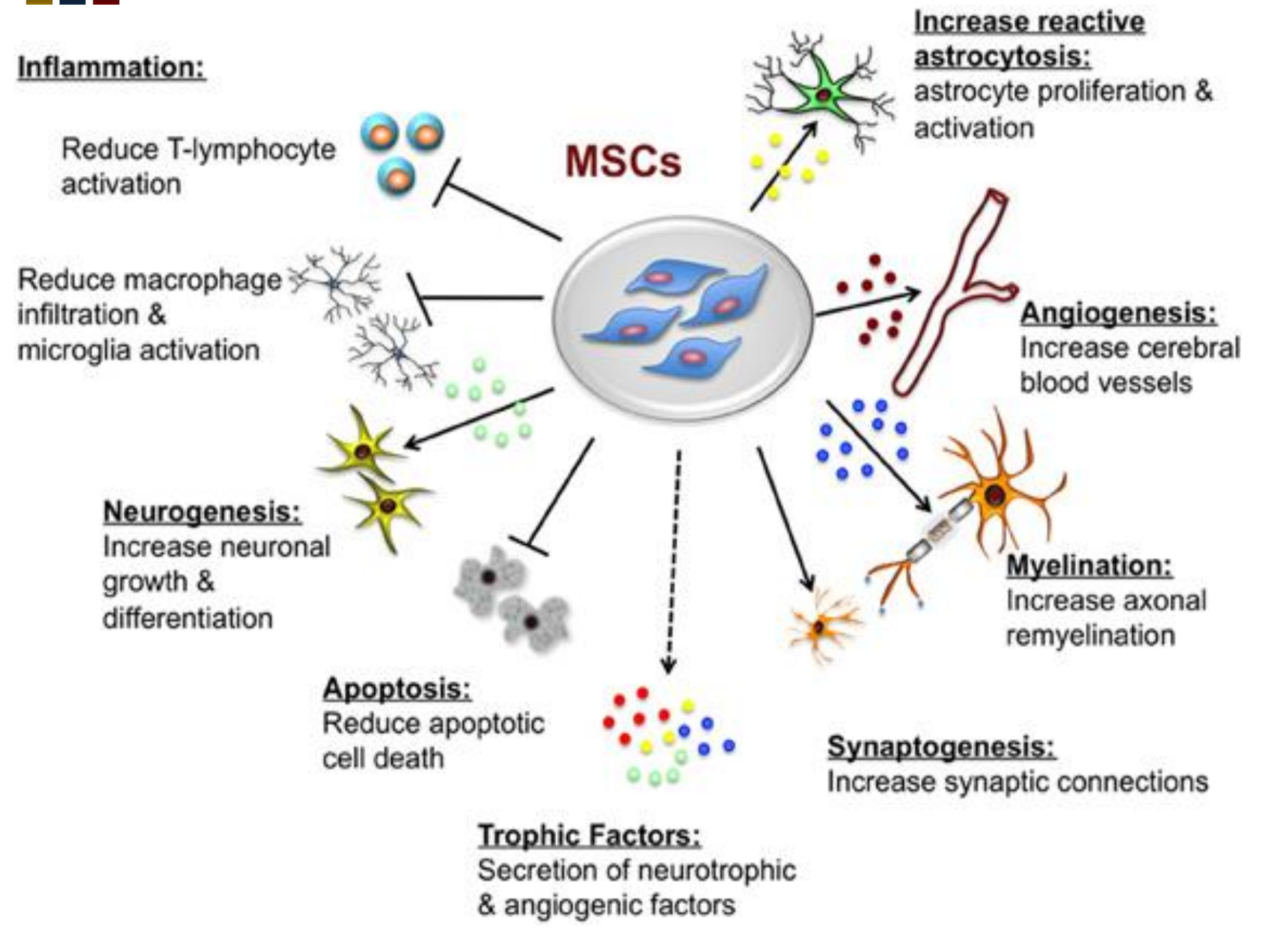
Stem cell transplantation

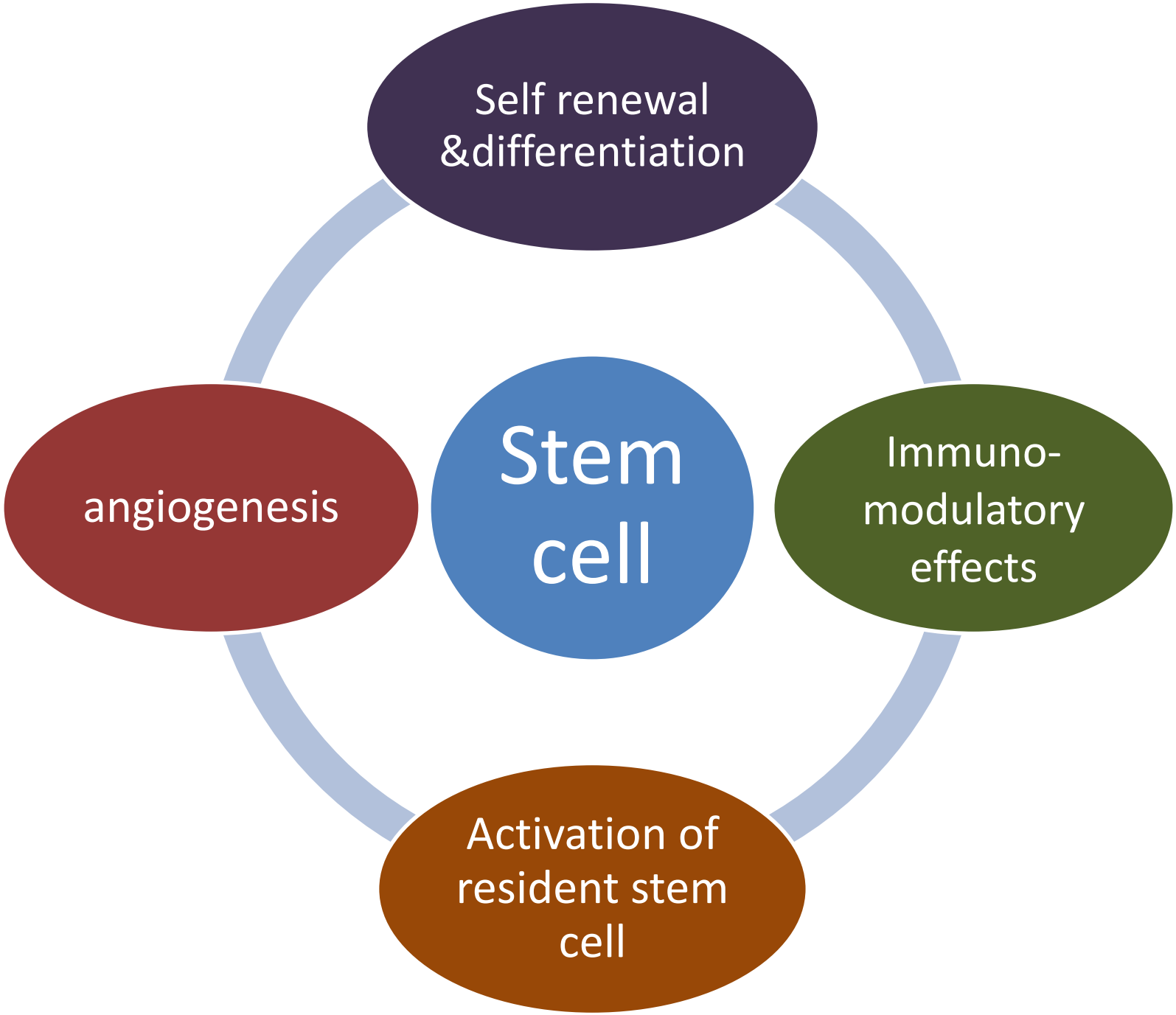


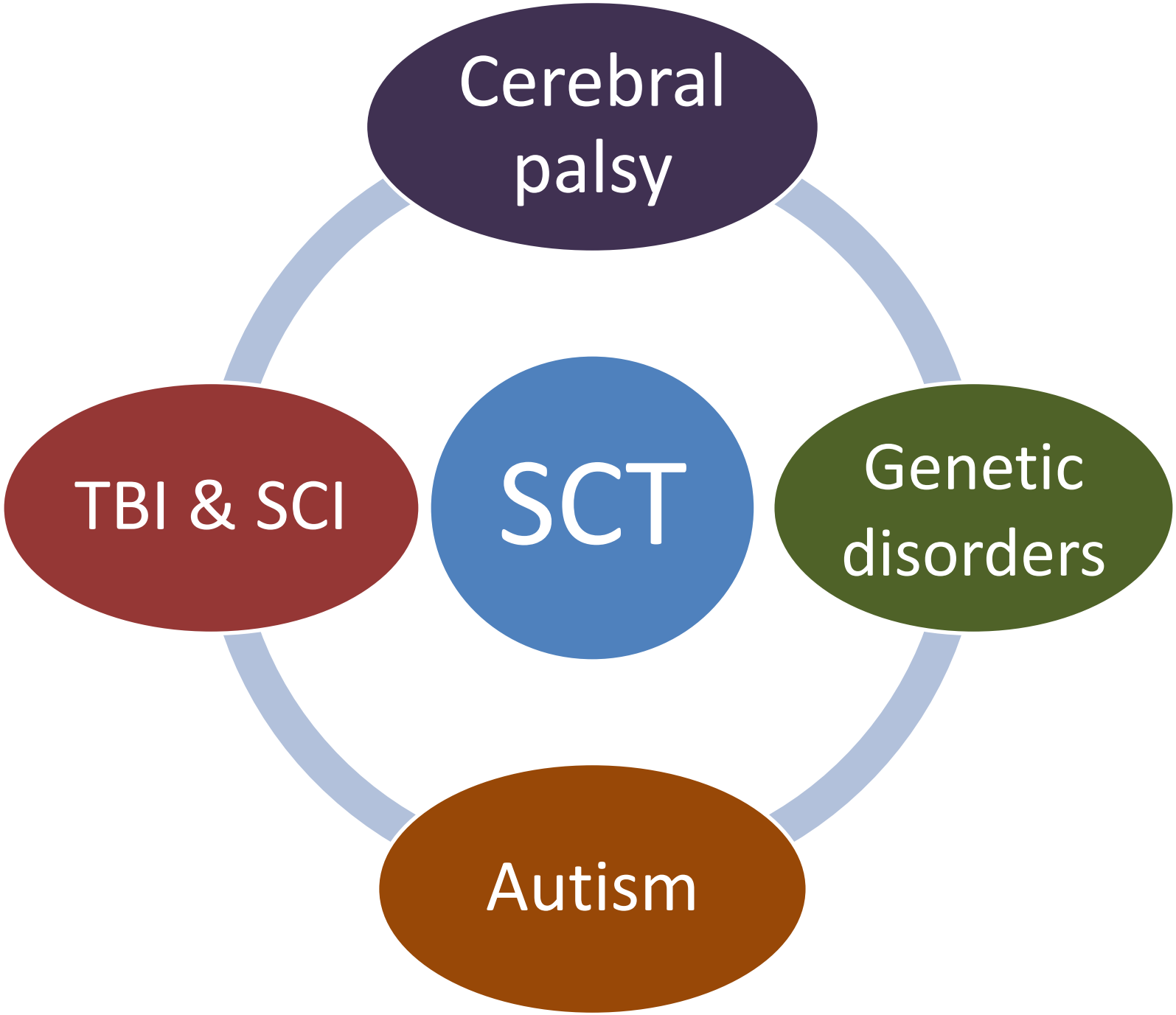





NPC
Ischemic brain
MSC
Astrocyte
Neuron
Oligodendrocyte
Microglia
Modulation of inflammation
Neurogenesis
Gliogenesis
Remyelination
Axonal plasticity
Neuroregeneration

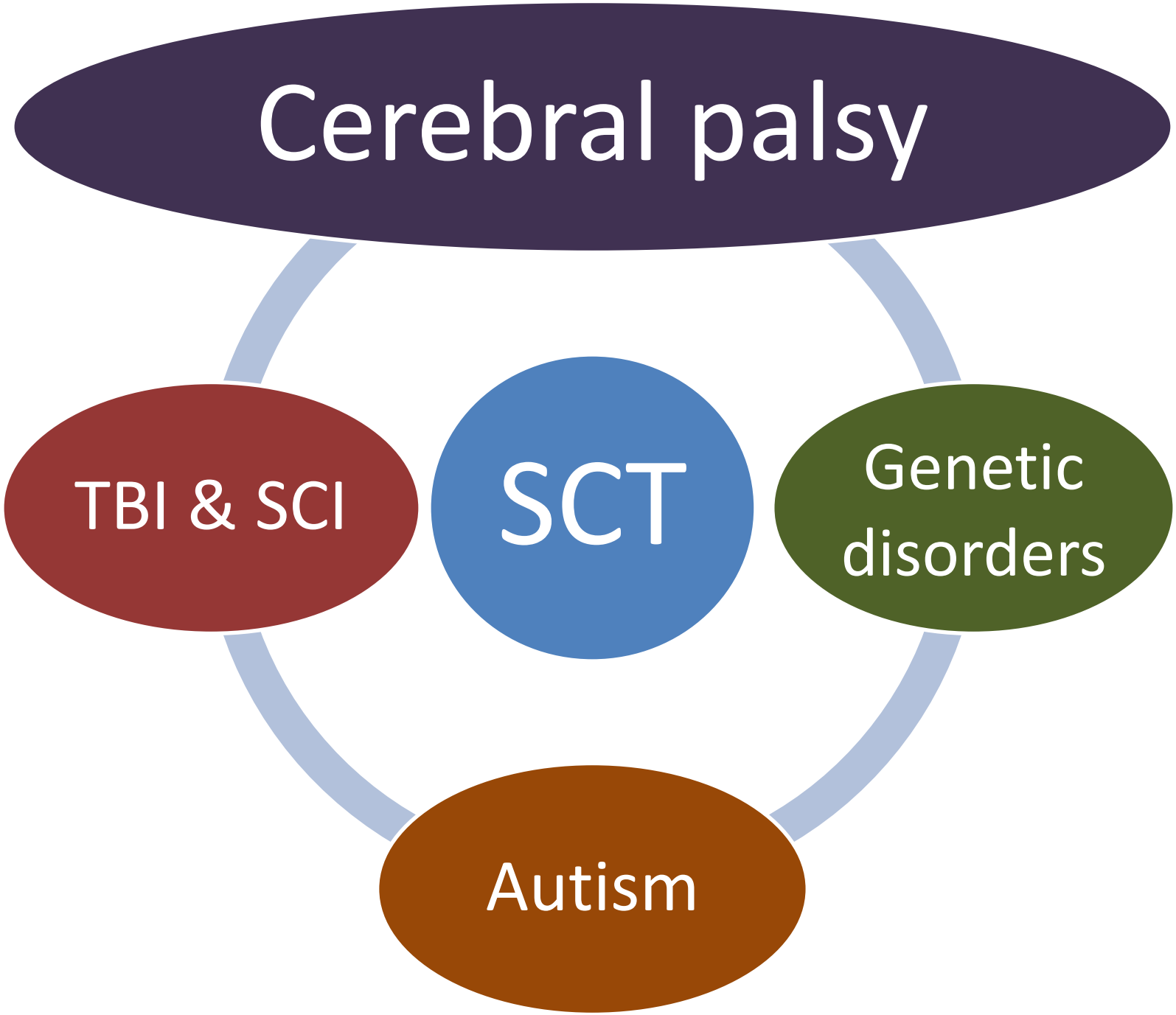

Inflammation:
Reduce T-lymphocyte activation
Reduce macrophage infiltration & microglia activation
MSCs
Increase reactive astrocytosis:
astrocyte proliferation & activation
Angiogenesis:
Increase cerebral blood vessels
Neurogenesis:
Increase neuronal growth & differentiation
Myelination:
Increase axonal remyelination
Apoptosis:
Reduce apoptotic cell death
Synaptogenesis:
Increase synaptic connections
Trophic Factors:
Secretion of neurotrophic & angiogenic factors


Self renewal &differentiation
Stem cell
angiogenesis
Immuno-modulatory effects
Activation of resident stem cell


Cerebral palsy
TBI & SCI
SCT
Genetic disorders
Autism

Limitations to stem cell therapy

- Isolation
- Type of cell
- Homing
- Integration
- Functional benefits
- Scientific evidence


Cerebral palsy
TBI & SCI
SCT
Genetic disorders
Autism

Stem cell used in cerebral palsy trials

- amnion epithelial cells (hAECs)
- CD34-expressing cells from umbilical cord blood
- embryonic stem (ES) cells
- fetal stem cells
- induced pluripotent stem cells (iPS cells)
- mesenchymal stem cells (MSCs)
- multipotent adult progenitor cells (MAPCs)
- neural stem cells (NSCs)
- olfactory ensheathing cells
- oligodendrocyte progenitor cells (OPCs)
- umbilical cord blood (UCB)/human UCB

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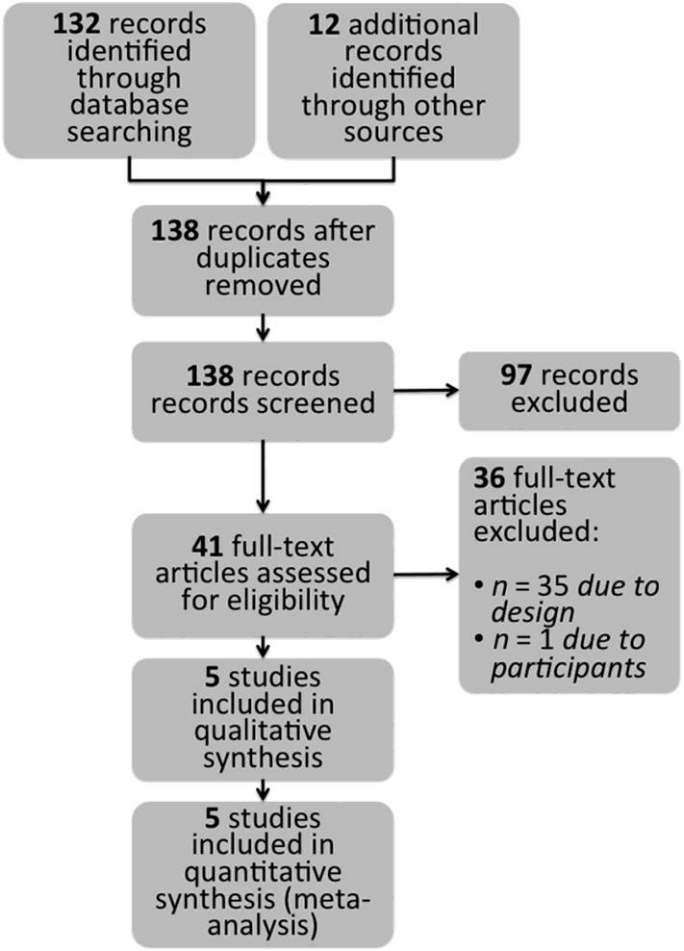
Stem Cells Transl Med. 2016 Aug;5(8):1014-25. doi: 10.5966/sctm.2015-0372. Epub 2016 May 31.

Concise Review: Stem Cell Interventions for People With Cerebral Palsy: Systematic Review With Meta-Analysis.

Novak I[1], Walker K[2], Hunt RW[3], Wallace EM[4], Fahey M[5], Badawi N[2].



Cell types and mechanisms of action, supporting evidence, and associated risks.

Citation	Cell types and description	Assumed mechanism of cell action for cerebral palsy	Preclinical evidence in cerebral palsy	Therapeutic evidence in cerebral palsy	Associated risks
Chen et al. [21]	OECs Description: OECs are macroglia found in the nervous system and support neurogenesis throughout life Source: Adult derived or fetal derived glial cells from nasal tissue	Mechanism unclear a. Regenerative: OECs ensheathe axons in the olfactory receptors, and it is hypothesized they might have this remyelination action in the brain [21] b. Anti-inflammatory: Assumed no c. Tropic: Assumed yes to promote tissue sparing and stimulate endogenous repair [21]	Unknown in cerebral palsy but spinal cord animal model data exist	One included clinical trial [21] reported short-term motor gains in children with cerebral palsy but high risk of bias existed	Safety in cerebral palsy unknown Neurosurgical and infection risks exist from the transplantation procedure Tumorigenic risks unknown and monitoring should occur using neuroimaging
Chen et al. [25] and Luan et al. [23]	NSCs and NPCs Description: NSCs are found in the brain and give rise to neurons, astrocytes, and oligodendrocytes Source: Fetal or adult derived adult multipotent cells	Mechanisms proposed to include a. Regenerative: NSCs make myelin and it is hypothesized they might remyelinate an injured brain or brain with arrested myelination from prematurity b. Anti-inflammatory: Assumed no c. Tropic: Assumed yes by stimulating other repair mechanisms	Rodent model: In the neonatal cerebral palsy stroke model and hypoxic-ischemic rat model NSCs reduce the severity of brain injury conferring neurobehavioral and motor gains [26]	Two included clinical trials [23, 25] reported short-term motor gains in children with cerebral palsy but high risk of bias existed	Neurosurgical and infection risks exist from the transplantation procedure Tumorigenic risks have not been observed in phase 1 trials using adult NSCs with immunosuppression but safety is unknown for NPCs or NSC-like cells and therefore monitoring should occur using neuroimaging
Kang et al. [22] and Min et al. [24]	UCB Description: UCB contains hematopoietic stem cells (HSCs) capable of making all types of blood cells, but also comprises a mixture of cells including MSCs (see row below for more information) and CD34 cells Source: Adult multipotent cells MSCs Description: Bone marrow stromal cells, composed of a mixture of cell types Source: Adult multipotent cells Comment: Umbilical cord blood contains MSCs	Mechanism unclear [10, 12] a. Regenerative: UCBs cannot replace damaged brain cells but might support regeneration b. Anti-inflammatory: Assumed yes given UCB contains MSCs c. Tropic: Assumed yes since UCBs home to injured tissue and provide paracrine effects that might support regeneration Mechanism unclear [10, 12] a. Regenerative: MSCs cannot replace damaged brain cells but might support regeneration b. Anti-inflammatory: Assumed yes c. Tropic: Assumed yes since MSCs home to injured tissue and provide paracrine effects that might support regeneration, e.g., by sparing intrinsic cells and secretion of growth factors that stimulate repair processes	Rodent model: In the neonatal cerebral palsy stroke model and hypoxic-ischemic rat model UCBs reduce the severity of brain injury conferring neurobehavioral and motor gains [10, 12] Sheep model: In the hypoxic-ischemic sheep model for cerebral palsy, UCB prevents neuronal apoptosis [27] Rodent model: In the neonatal cerebral palsy stroke model, intranasal delivery of MSCs significantly reduces infarct size and gray matter loss [28] Primate model: MSCs transplantation leads to upregulation of IL-10 expression, plus a decrease in neuronal apoptosis and astroglial activity in the periischemic area [10]	Two included clinical trials [22, 24] reported short-term motor gains in people with cerebral palsy from allogeneic UCB transfusion Cerebral palsy clinical trials using autologous UCB are under way but not yet complete Cerebral palsy clinical trials using MSCs are under way but not yet complete Comment: MSCs are more likely to be helpful for infants with cerebral palsy during the early acute and inflammatory brain injury phase, e.g., in neonatal stroke and hypoxic-ischemic encephalopathy causal pathways to cerebral palsy	Long-term safety in cerebral palsy unknown Autologous UCB assumed to be probably safe given the decades of long-term safety data in hematologic applications Allogeneic UCB appeared relatively safe in the two included clinical trials [22, 24] but the theoretical risk of graft-versus-host (GVH) disease exists, even though GVH is considered unlikely to occur in people with cerebral palsy with healthy immune systems Long-term safety in cerebral palsy is unknown Assumed to be low risk because they have historically been assumed to be immune privileged, although this knowledge is evolving

Abbreviations: MSC, mesenchymal stem cell; NPC, neural progenitor cell; NSC, neural stem cell-like; OEC, olfactory ensheathing cell; UCB, umbilical cord blood.

STEM CELLS TRANSLATIONAL MEDICINE

Risk of bias, methodological quality, and trial limitations.

Citation	Random sequence generation: selection bias	Allocation concealment: selection bias	Blinding of participants and personnel: performance bias	Blinding of outcome assessment: detection bias	Incomplete outcome data: attrition bias	Selective reporting: reporting bias	PEDro trial quality score	GRADE quality rating	Study limitations
Chen et al. [21]	Low risk	Low risk	Unclear risk	Unclear risk	High risk	High risk	5/10	Low	Sample: Large number of dropouts (n = 18/33); n = 7/33 of intended sample not recruited; wide age range studied Design and analysis: Small sample size
Chen et al. [25]	High risk	High risk	High risk	Low risk	Low risk	Low risk	5/10	Low	Design and analysis: Lack of randomization; small sample size Instruments: Validlity of Gessell data collected in children too old for the instrument; redundancy of collecting the GMFM-88 data, when GMFM-66 also collected
Kang et al. [22]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	8/10	High	Sample: Wide age range studied; placebo group median age is older and therefore may be less responsive to any intervention; unclear why n = 2 participants were excluded after randomization Design and analysis: Lack of rehabilitation protocol for both arms of the trial, when rehabilitation is standard of care (i.e., patients could have been worsening by natural history) Instruments: Manual muscle test validity in (a) 6-month-old children who cannot respond to commands and (b) people without the selective motor control to complete testing; validly of Bayley II, PEDI, weeFIM data collected in children and adults too old for the instrument's upper age range; use of Bayley II, not Bayley III Intervention: Use of i.v. and i.a. infusion in the same study, resulting in some data needing to be excluded; confounding use of cyclosporine as an immunosuppressant, since cyclosporine might also have neuroprotective effects
Luan et al. [23]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	High risk	6/10	Moderate	Design and analysis: Not stated if participants were blinded; no between-group analysis conducted for standardized measures Instruments: Use of an author-devised cognitive assessment test, which had unknown psychometric properties
Min et al. [24]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	9/10	High	Design and analysis: Lack of a UCB + rehabilitation group to allow examination of the effects of UCB; random sequence generation not described Instruments: Validly of Bayley II, PEDI, weeFIM data collected in children and adults too old for the instrument's upper age range; use of Bayley II, not Bayley III Intervention: Confounding use of cyclosporine as an immunosuppressant, since cyclosporine might also have neuroprotective effects

Abbreviations: GMFM, Gross Motor Function Measure; PEDI, Pediatric Evaluation of Disability Inventory; UCB, umbilical cord blood; WeeFIM = Wee Functional Independence Measure.

STEM CELLS TRANSLATIONAL MEDICINE

Forest plot.

Study	Stem Cell +/– Rehabilitation Mean	SD	Total	Rehabilitation/ Placebo Mean	SD	Total	Weight	Std. Mean Difference IV Random, 95% CI
2.1 Gross Motor Function Changes from Stem Cell Intervention | 6-month Effects								
Chen et al. 2010 [21]	26.67	25.33	6	19.0	20.0	8	18.1%	0.32 [–0.75, 1.39]
Chen et al. 2013 [25]	104.1	65.0	30	90.63	57.03	30	21.1%	0.22 [–0.29, 0.73]
Kang et al. 2015 [22]	36.37	2.04	13	33.25	0.91	17	19.1%	2.02 [1.11, 2.93]
Luan et al. 2012 [23]	5.69	2.91	45	3.92	2.33	49	21.5%	0.67 [0.25, 1.09]
Min et al. 2013 [24]	14.5	1.8	35	9.6	1.2	34	20.5%	3.16 [2.44, 3.88]
Total (95% CI)			**129**			**138**	**100%**	**1.27 [0.22, 2.33]**

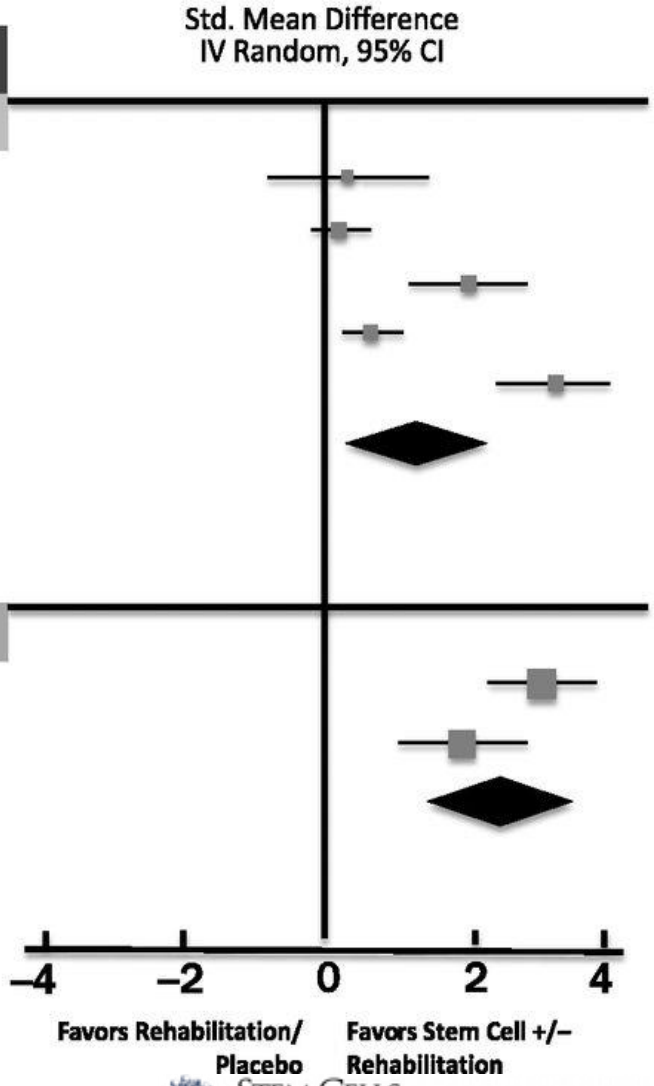
Heterogeneity: $Tau^2 = 1.30$ $Chi^2 = 52.57$ df = 4 ($p < .00001$); $I^2 = 92\%$

Test for overall effect: $Z = 2.36$ ($p = .02$).

2.2 Gross Motor Function Changes from Umbilical Cord Blood | 6-month Effects								
Min et al. 2013 [24]	14.5	1.8	35	9.6	1.2	34	53.1%	3.16 [2.44, 3.88]
Kang et al. 2015 [22]	36.37	2.04	13	33.25	0.91	17	46.9%	2.02 [1.11, 2.93]
Total (95% CI)			**48**			**51**	**100%**	**2.62 [1.51, 3.74]**

Heterogeneity: $Tau^2 = 0.47$ $Chi^2 = 3.71$, df = 1 ($p = .05$); $I^2 = 73\%$

Test for overall effect: $Z = 4.62$ ($p < .00001$).



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STEM CELLS TRANSLATIONAL MEDICINE

Rates of serious adverse events.

Citation	Serious adverse events			
	Event	Stem cell	Rehabilitation	Erythropoietin
Chen et al. [21]	Death	0/6	0/8	N/A
	Other serious adverse event	0/6	0/8	N/A
	Total (%)	**0/6 (0)**	**0/8 (0)**	**N/A**
Chen et al. [25]	Death	0/30	0/30	N/A
	Other serious adverse event	0/30	0/30	N/A
	Total (%)	**0/30 (0)**	**0/30 (0)**	**N/A**
Kang et al. [22]	Death	0/18	0/18	N/A
	Other serious adverse event	0/18	0/18	N/A
	Total (%)	0/18 **(0)**	0/18 **(0)**	**N/A**
Luan et al. [23]	Death	0/45	0/49	N/A
	Other serious adverse event	1/45	0/49	N/A
	Total (%)	**1/45 (2)**	**0/49 (0)**	**N/A**
Min et al. [24]	Death	1/35	0/34	0/34
	Other serious adverse event	2/35	3/34	3/34
	Total (%)	**3/36 (8)**	**3/34 (9)**	**3/36 (8)**
Total (%)		**4/135 (3)**	**3/139 (2)**	**3/36 (8)**

Abbreviation: N/A, not applicable.

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Effects of Neural Progenitor Cell Transplantation in Children With Severe Cerebral Palsy

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Umbilical Cord Blood Therapy Potentiated with Erythropoietin for Children with Cerebral Palsy: A Double-blind, Randomized, Placebo-controlled Trial

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Key words. Umbilical cord blood • Erythropoietin • Cerebral palsy • Clinical trial • Function

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Brief Communication

Intracranial Transplant of Olfactory Ensheathing Cells in Children and Adolescents With Cerebral Palsy: A Randomized Controlled Clinical Trial

Lin Chen,*† Hongyun Huang,*† Haitao Xi,*† Zihang Xie,* Ruiwen Liu,* Zhao Jiang,* Feng Zhang,* Yancheng Liu,* Di Chen,* Qingmiao Wang,* Hongmei Wang,*† Yushui Ren,† and Changman Zhou†‡

*Center for Neurorestoratology, Beijing Rehabilitation Center, Beijing, P.R. China
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‡Department of Anatomy and Embryology, Peking University Health Science Center, Beijing, P.R. China

Stem Cells Dev. 2015 Oct 1;24(19):2259-68. doi: 10.1089/scd.2015.0074. Epub 2015 Jul 2.

Involvement of Immune Responses in the Efficacy of Cord Blood Cell Therapy for Cerebral Palsy.

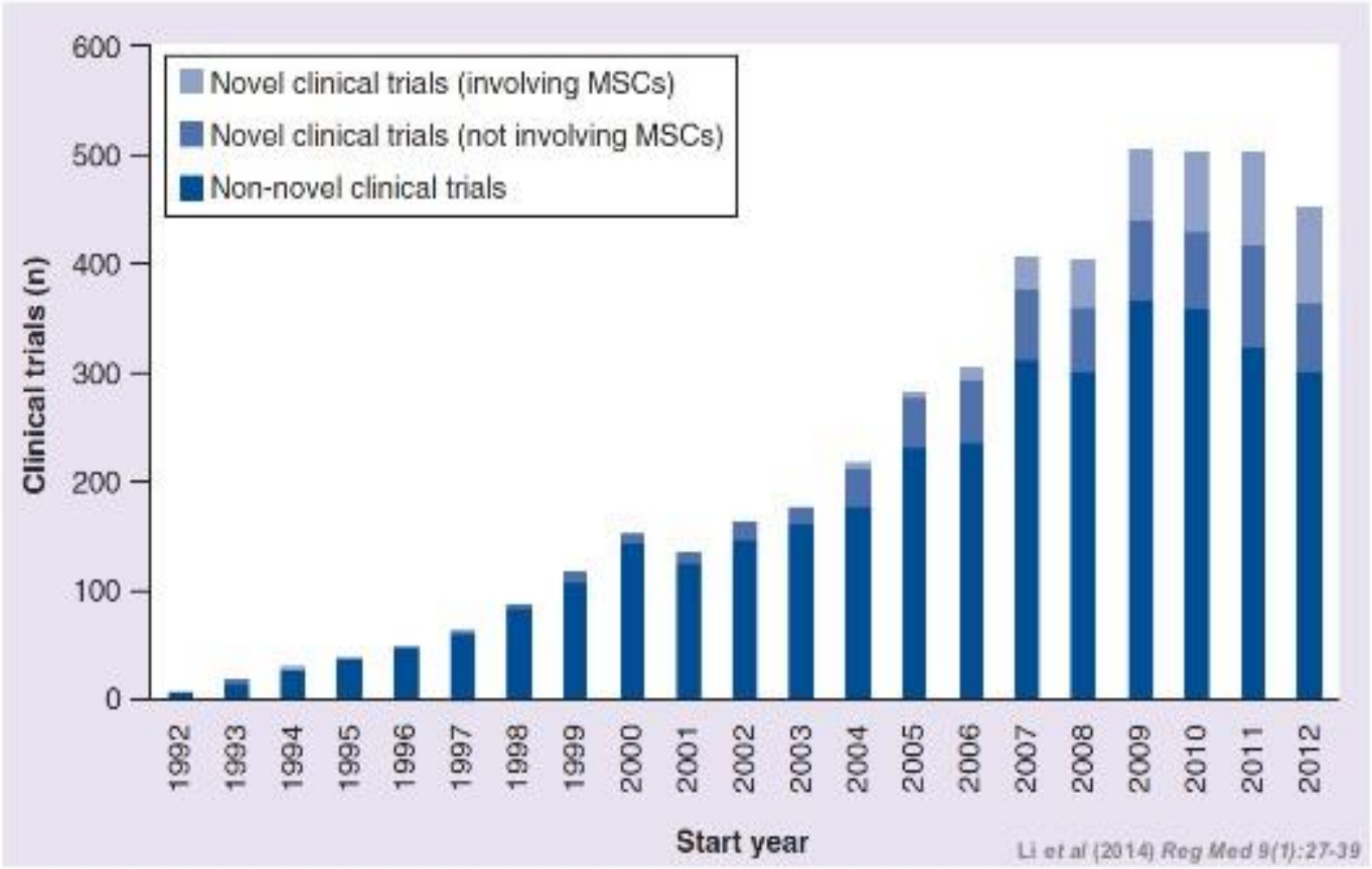
Kang M[1], Min K[2], Jang J[2], Kim SC[1], Kang MS[3], Jang SJ[4], Lee JY[4], Kim SH[5], Kim MK[6], An SA[1], Kim M[2].

J Transl Med. 2013 Jan 26;11:21. doi: 10.1186/1479-5876-11-21.

Neural stem cell-like cells derived from autologous bone mesenchymal stem cells for the treatment of patients with cerebral palsy.

Chen G[1], Wang Y, Xu Z, Fang F, Xu R, Wang Y, Hu X, Fan L, Liu H.

Growth in 'novel' applications stem cells




NUMBER OF TRIALS
120
100
80
60
40
20
0
1
1
9
7
12
30
30
51
66
85
76
93
114
2001
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
YEAR

Stem cell tourism

China

India

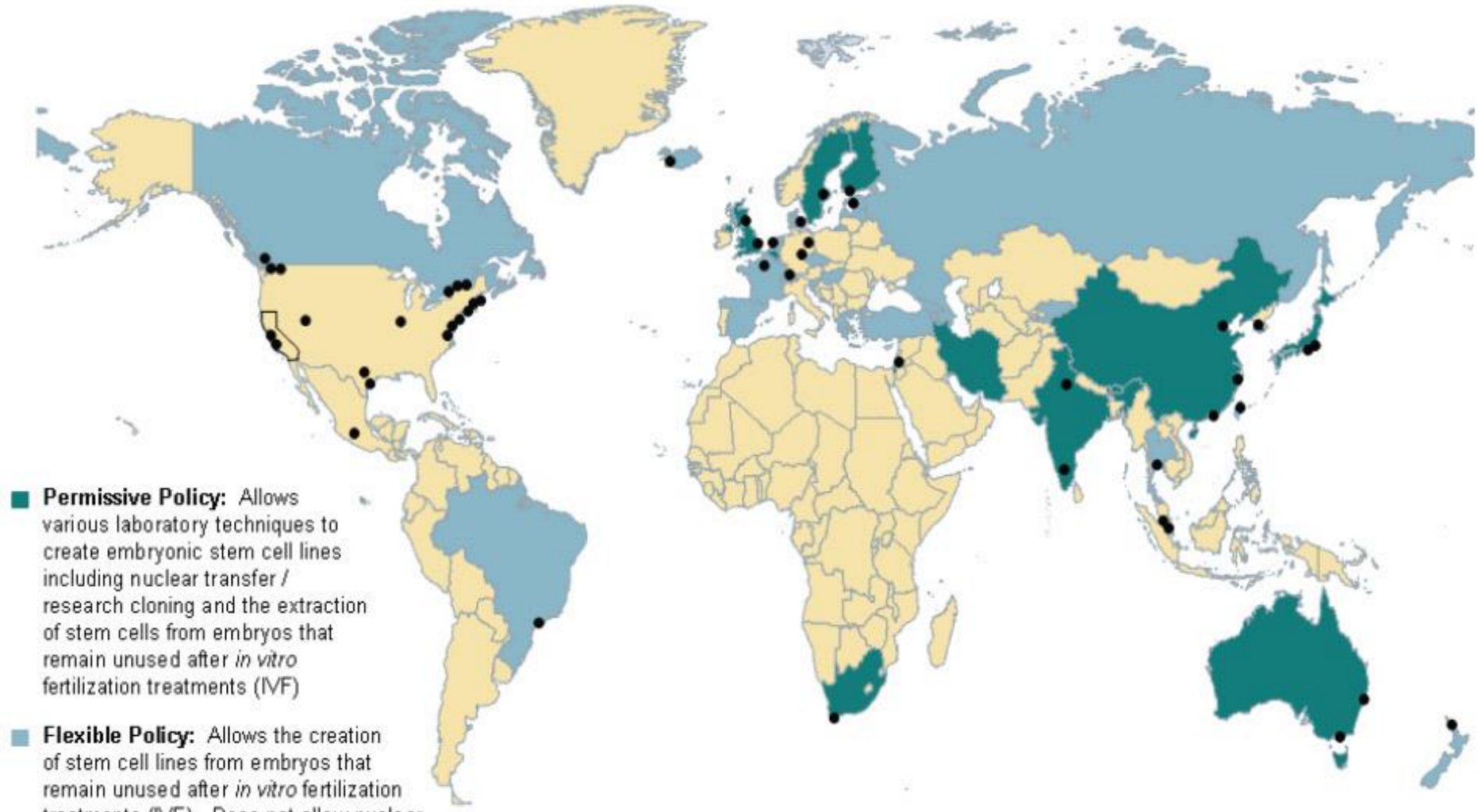
The Caribbean

Latin America

Nations of the former Soviet Union

Even in the US

World Stem Cell Policy



- **Permissive Policy:** Allows various laboratory techniques to create embryonic stem cell lines including nuclear transfer / research cloning and the extraction of stem cells from embryos that remain unused after *in vitro* fertilization treatments (IVF)
- **Flexible Policy:** Allows the creation of stem cell lines from embryos that remain unused after *in vitro* fertilization treatments (IVF). Does not allow nuclear transfer / research cloning
- **Restrictive Policy or No Established Policy**
- Genome Sequencing Research Centers.
- California supports embryonic stem cell research through Proposition 71

Source: William Hoffman, MBBNet, University of Minnesota. For more detail, see: http://www.mbbnet.umn.edu/scmap.html
Published by the Monitor Company Group, Cambridge, Massachusetts, USA

SPRING, 2011

ON THE uptake

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Neuroscience Program
UTNP

CURRENT STATUS OF STEM CELL TREATMENTS FOR CEREBRAL PALSY:
A GUIDE FOR PATIENTS, FAMILIES AND CAREGIVERS

Potential Pitfalls:

- Once stem cells are put in, they can never be removed.
- There are no proven stem cell treatments available for patients right now, and it will take a number of years for safe and effective therapies to make it to the clinic.
- Unregulated clinics outside North America are offering stem cell transplants; however, these clinics have shown no scientific proof that their procedures offer any effect beyond placebo effects and/or normal development.
- Stem cell transplantation would probably have to be performed within the window of time between the first appearance of injury and irreparable loss of neurons.

Stem Cell Patient Bill of Rights

Article One, The Right to Truly Informed Consent.

Article Two, The Right to Treatment by a Trained Provider.

Article Three, The Right to Have Your Stem Cells Be Prepared in a GMP Facility.

Article Four, The Right to Continuing Follow Up by the Provider.

Article Five, The Right to Ownership of Your Stem Cells.

Article Six, The Right to Expanded Compassionate Use For Fatal Diseases.

Article Seven, The Right to be in a Clinical Trial for Experimental Procedures.

Article Eight, The Right to Not to be Charged for Clinical Trial Participation.

Article Nine, The Right to Full Disclosure of Anticipated Costs.

Active Ten, The Right to be Treated Regardless of Socioeconomic Status.

Paul Knoepfler




THANK YOU

amrhasanneuro@kasralainy.edu.eg