Stem Cell Therapeutic Applications in Leukodystrophies

Ali Fatemi, MD

Director of Neurogenetics

Kennedy Krieger Institute

Johns Hopkins Medicine

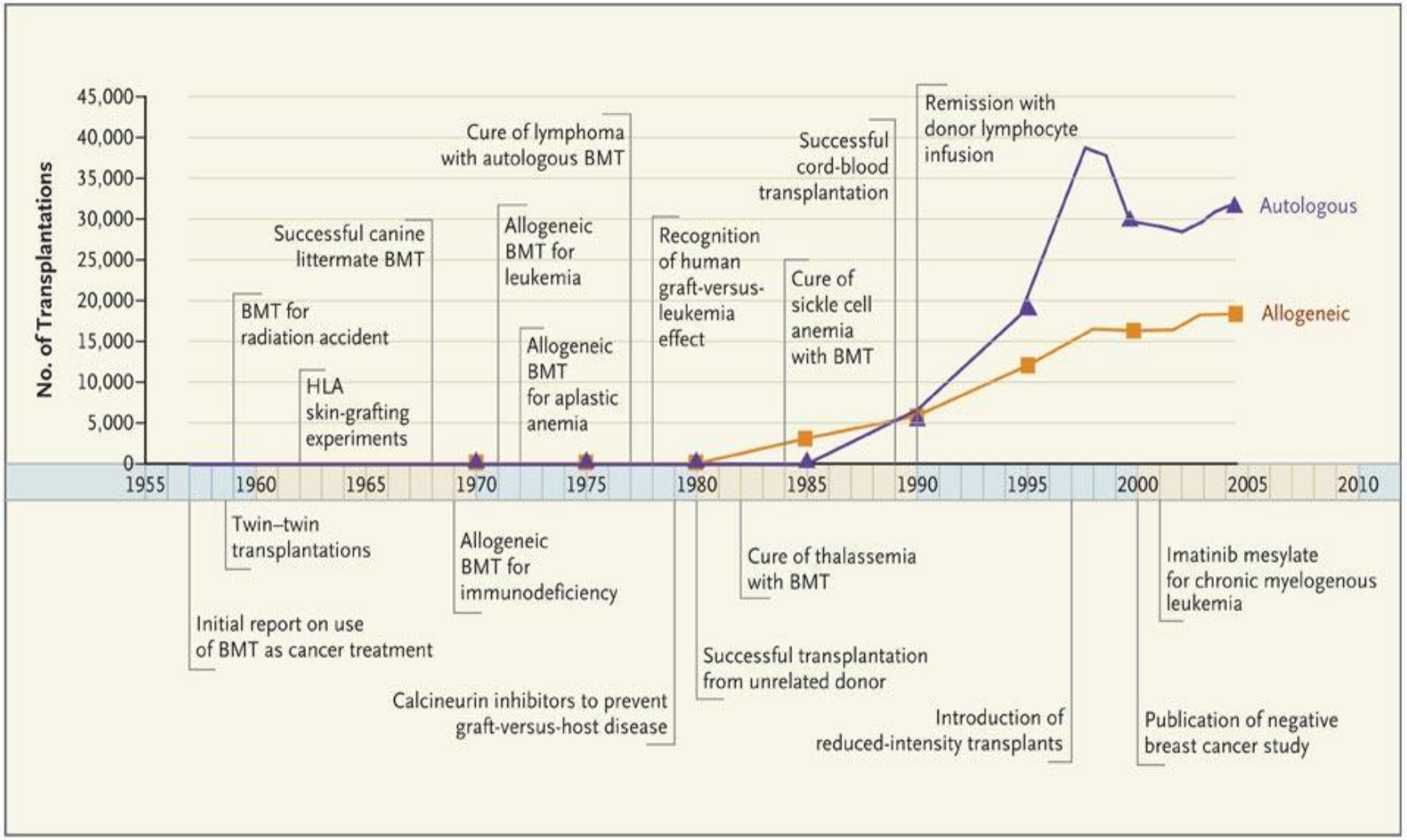
Kennedy Krieger Institute

JOHNS HOPKINS MEDICINE

Learning Objectives/Outline

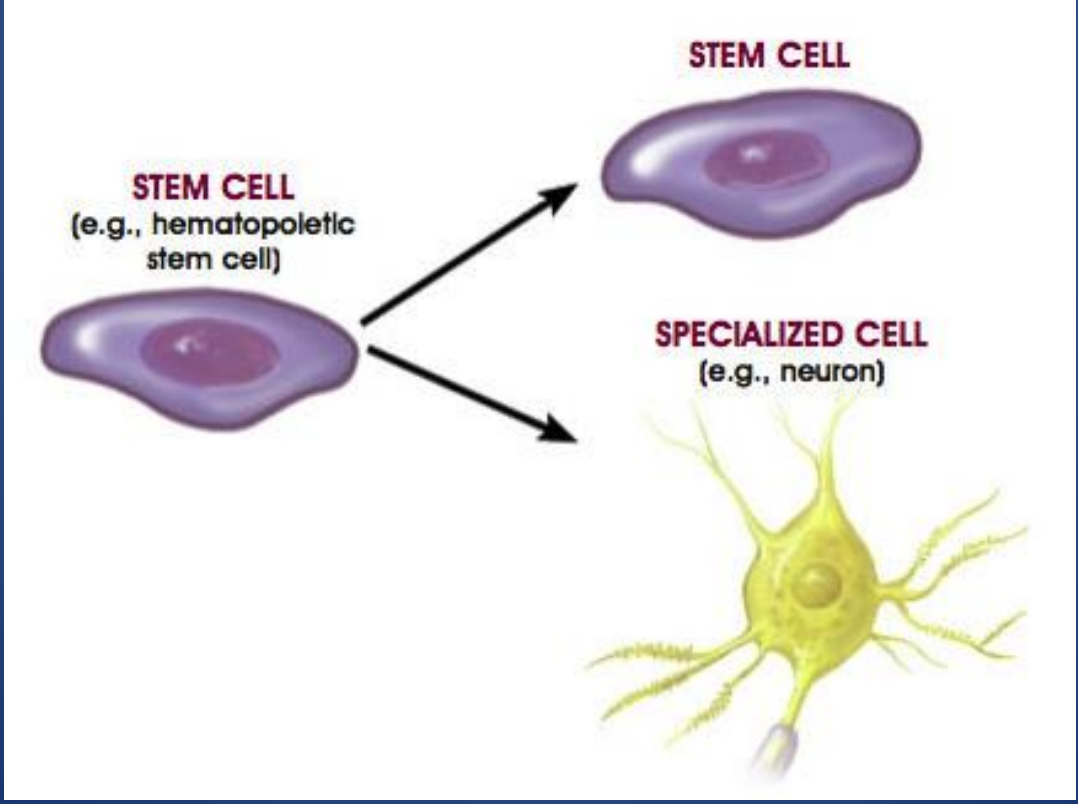
- **Define stem cells and different cell types**
- Review mechanisms of action in cell-based therapy
- Review current clinical trials
- Review potential adverse events

History of Stem Cell Transplantation



Defining Stem Cells

- Stem cell: unspecialized cell that is capable of replicating itself but also differentiate into specialized cells.



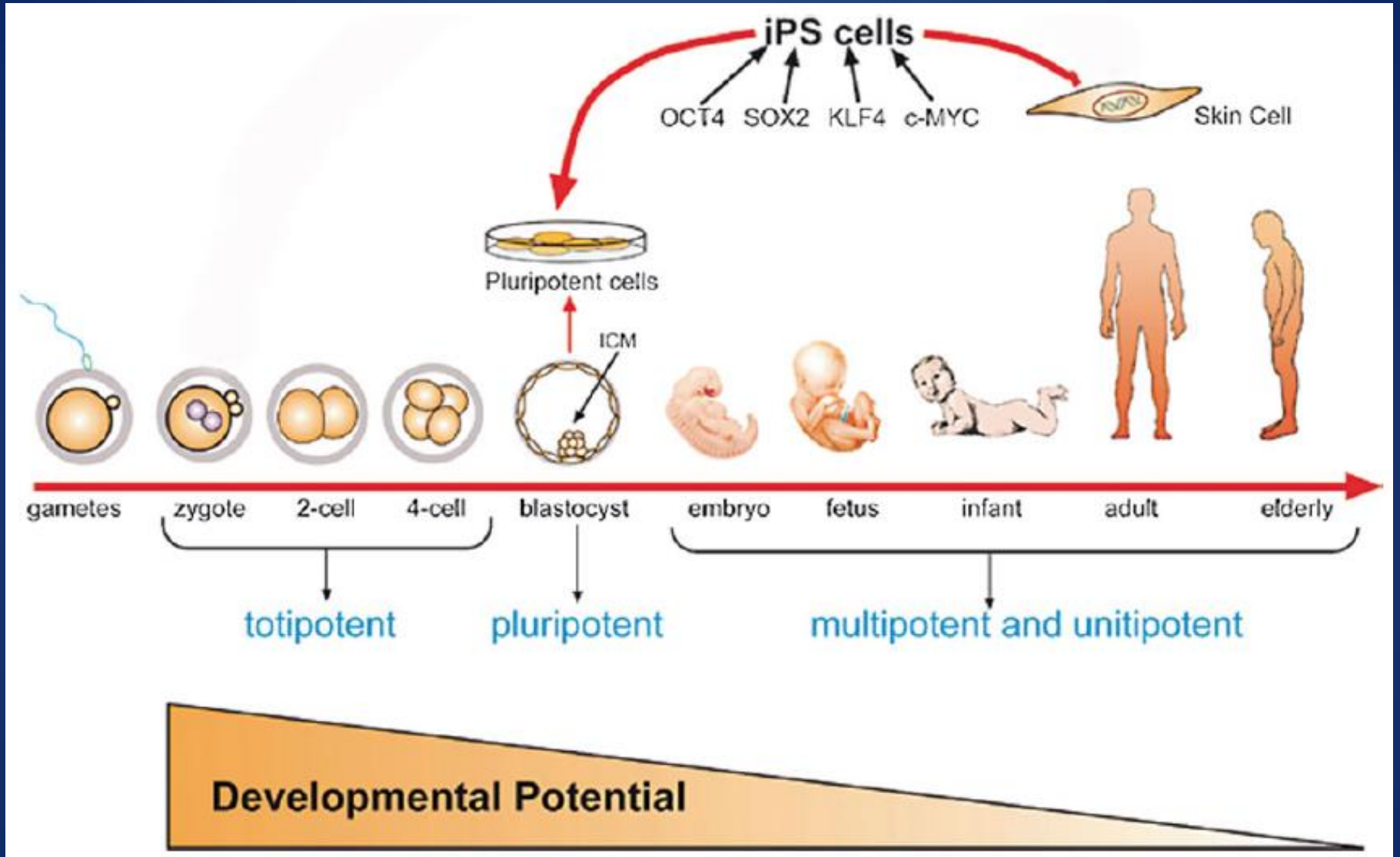


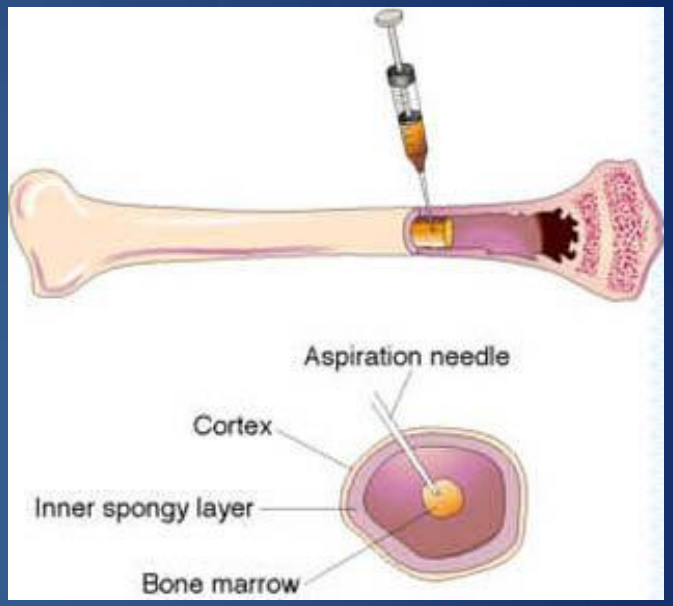
Fig. 1 Various types of stem cells. Adapted from Mitalipov and Wolf [22]

Myeloid Derived Stem Cells

- **Hematopoietic stem cells** - CD34+ cells can give rise to all blood cell types, few controversial reports that under certain conditions in-vitro these cells can become neurons.

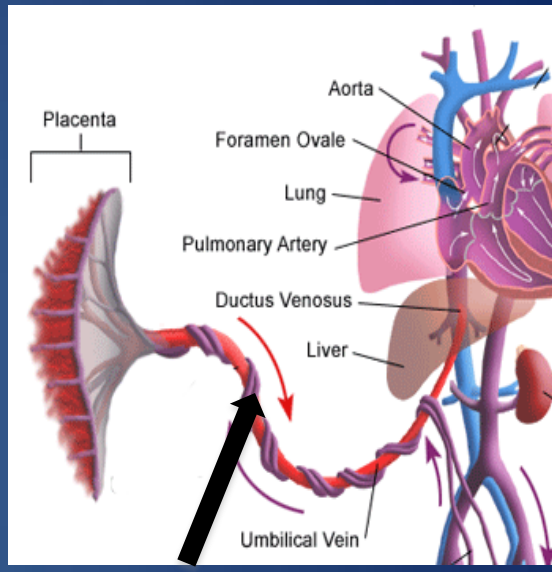
- **Mesenchymal stem cells** can be differentiated to a variety of different tissue cells in-vitro including neurons.

- 50,000 adult and pediatric patients/year worldwide have received bone marrow stem cells.



Umbilical Cord Blood Derived Stem Cells

Stem Cell Type	Definition	Putative mechanisms of action
Hematopoietic Stem Cells	Multipotent cells that can give rise to all blood cell types including myeloid and lymphoid lineages and are CD45 positive	- immunomodulation - neurotrophic effect on endogenous cells - differentiation into microglia that may release defective enzymes (in metabolic diseases)
Mesenchymal Stem Cells	Multipotent non-hematopoietic cells that differentiate into multiple mesenchymal lineages, and are CD34 negative and CD45 negative	- immunomodulation - neurotrophic effect of endogenous cells
Endothelial Progenitor Cells	Cells that are able to form vessels when transplanted in immune deficient mice, express CD34 but do not express CD45	- form new vessels in ischemic lesions
Aldehyde Dehydrogenase (ALDH) Positive Progenitor Cells	Cells enriched for both multipotent myeloid and endothelial colony-forming cells	- immunomodulation - release of growth factors - vessel formation
CD133+ Early Multipotent Stem Cells	Multipotent cells with ability to differentiate into various non-hematopoietic lineages (including neural and glial-like cells in vitro)	- promote axonal growth in - potential transdifferentiation into neural cells

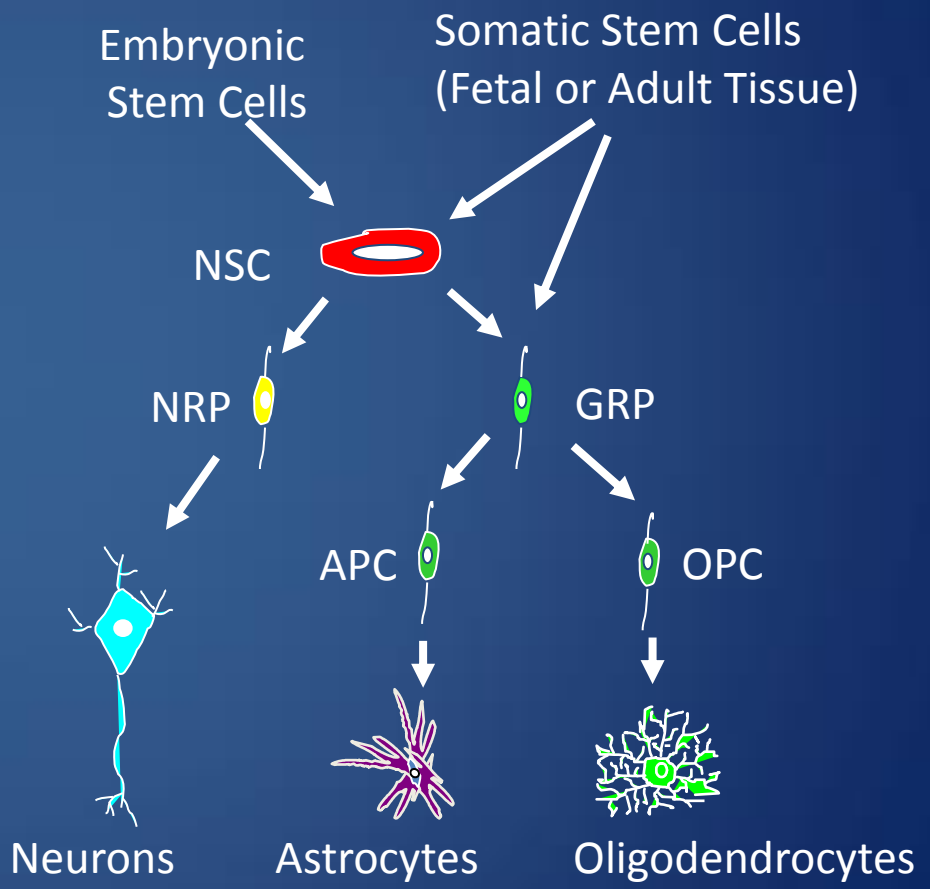


Umbilical cord

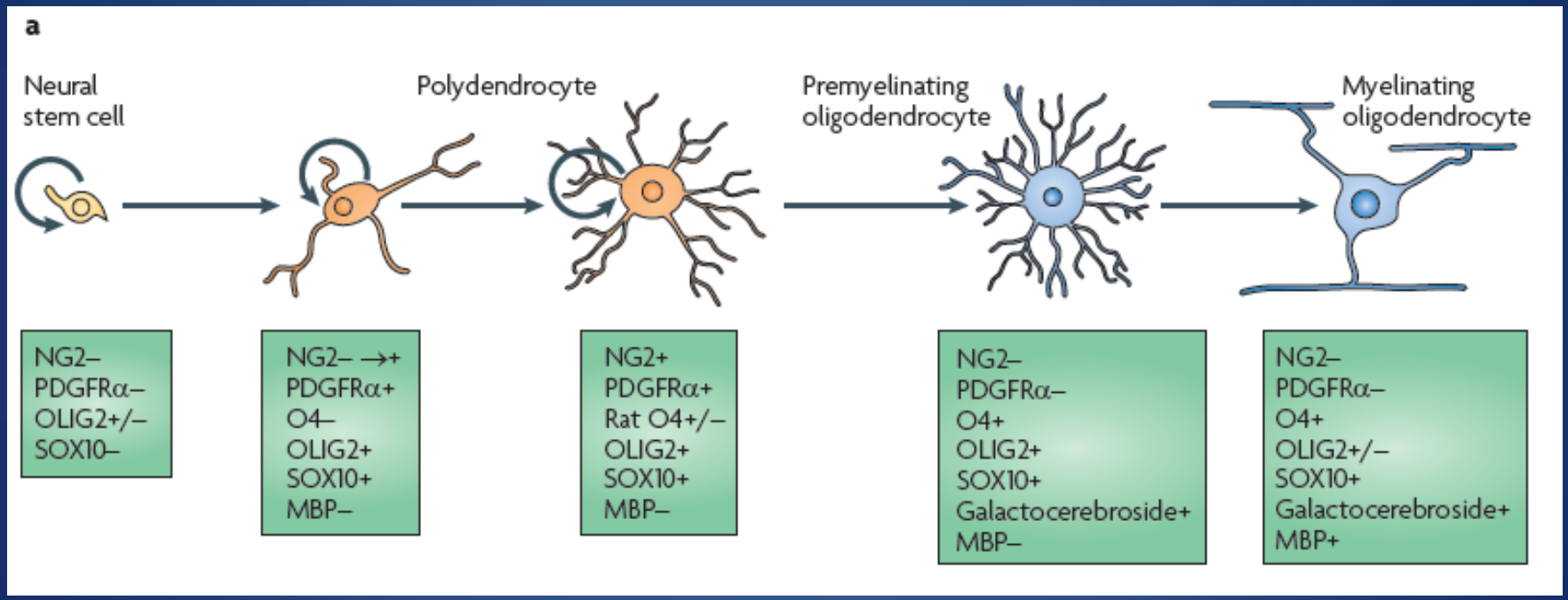
Verina T et al.
Pediatr Neurol 2013

Neural Stem Cells

- Neural stem cells can be derived from adult and fetal human cadavers.
- Mouse embryonic stem cells can be differentiated to neural stem cells in-vitro.
- Neural stem cells have the ability to become neurons, astrocytes, oligodendrocytes and endothelial cells.

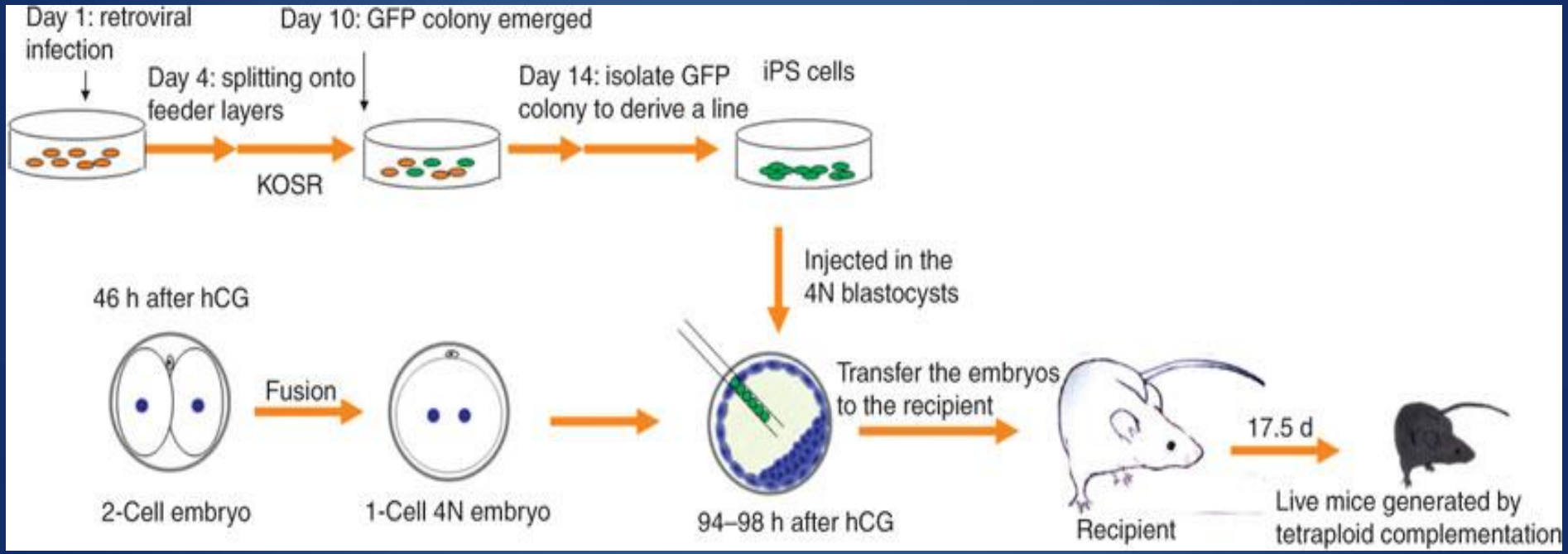


Glial Precursor Cells



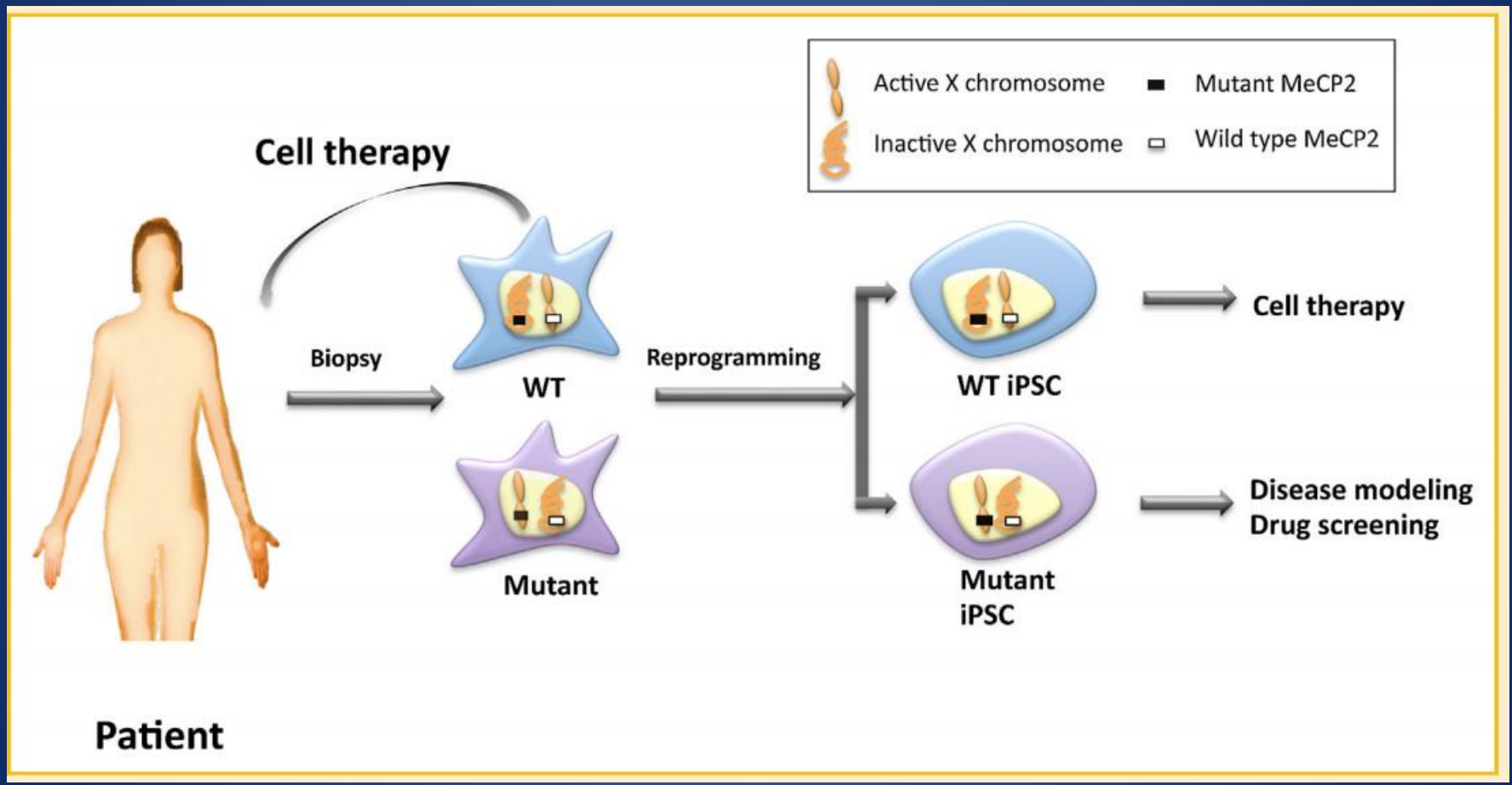
iPS Cells Make Viable Mice

Tetraploid Complementation Assay



From Zhao XY et al. Nature Protocols **5,-963 - 971 (2010)**

Using iPSCs to Study Disease
(example Rett syndrome)



Dajani R, Journal of Cellular Biochemistry 2013

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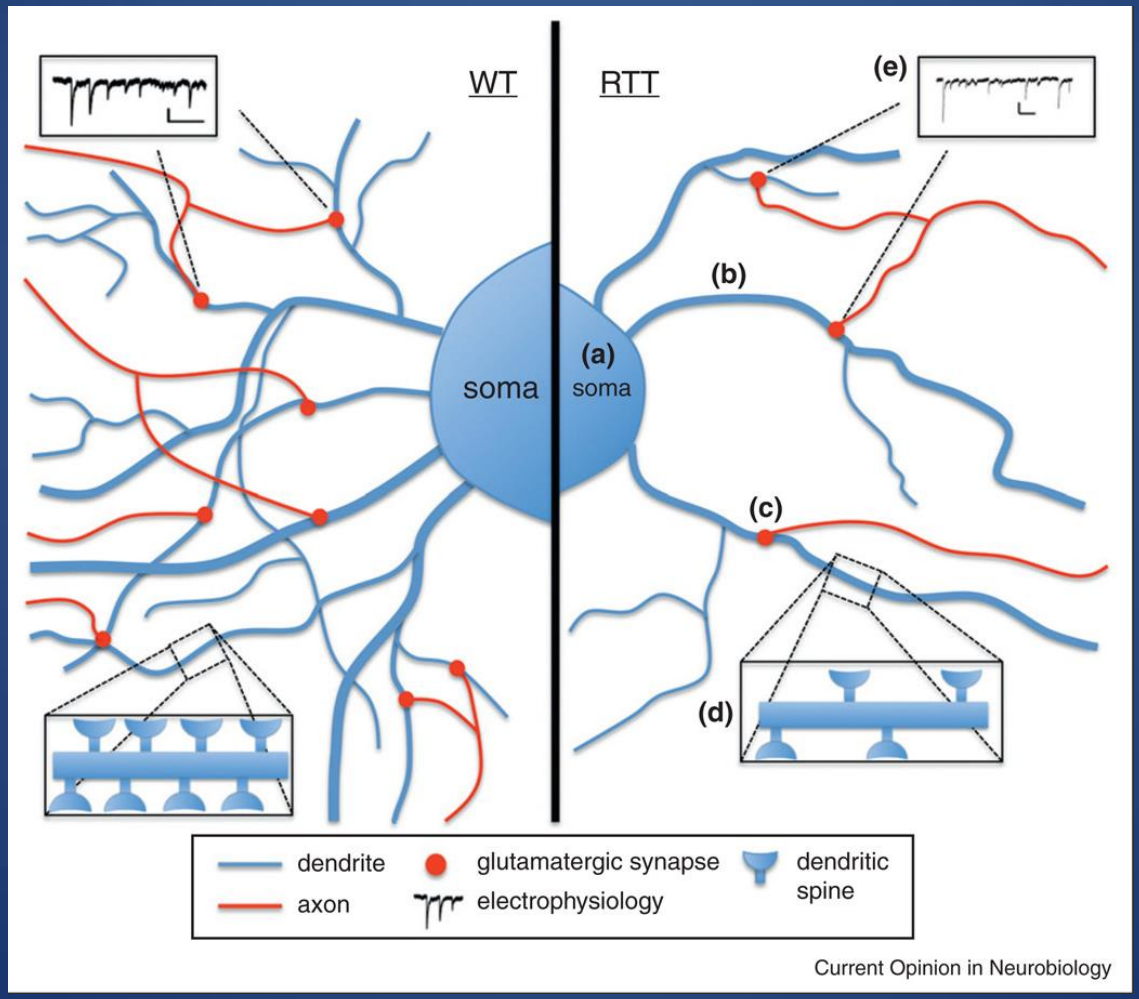
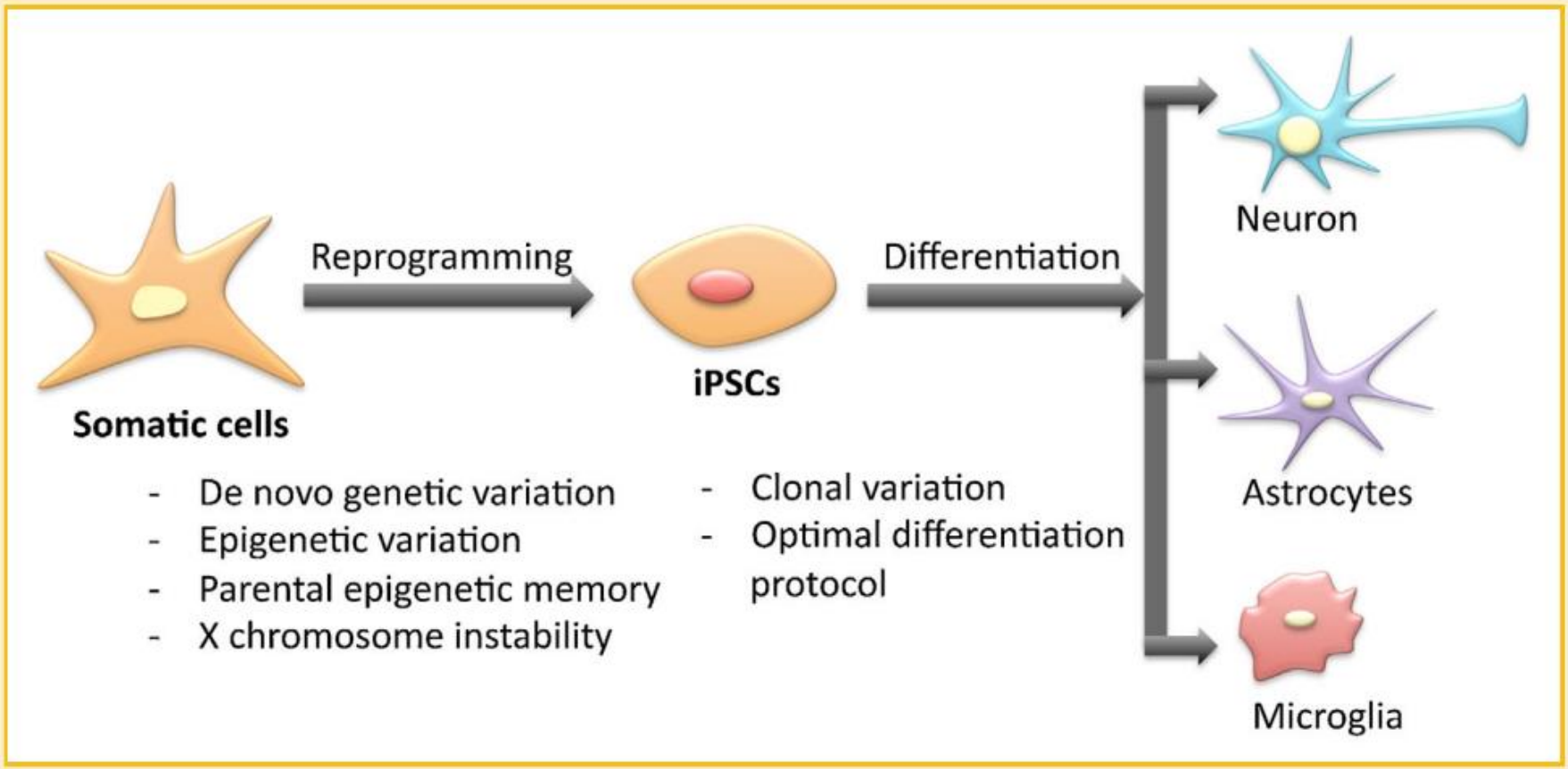


Issues with Reprogrammed Cells



Dajani R, Journal of Cellular Biochemistry 2013

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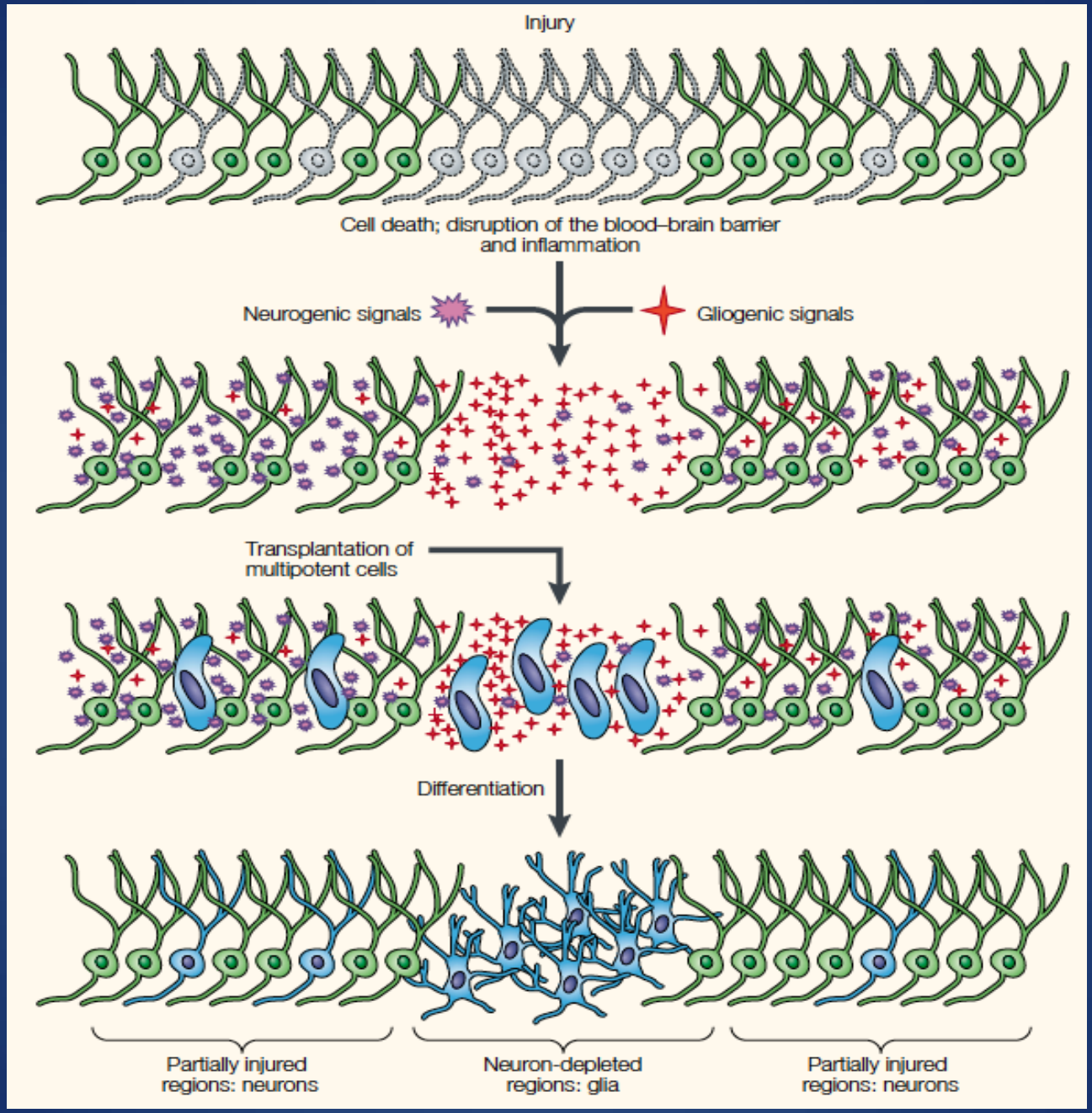
How Exogenous Cells May Help

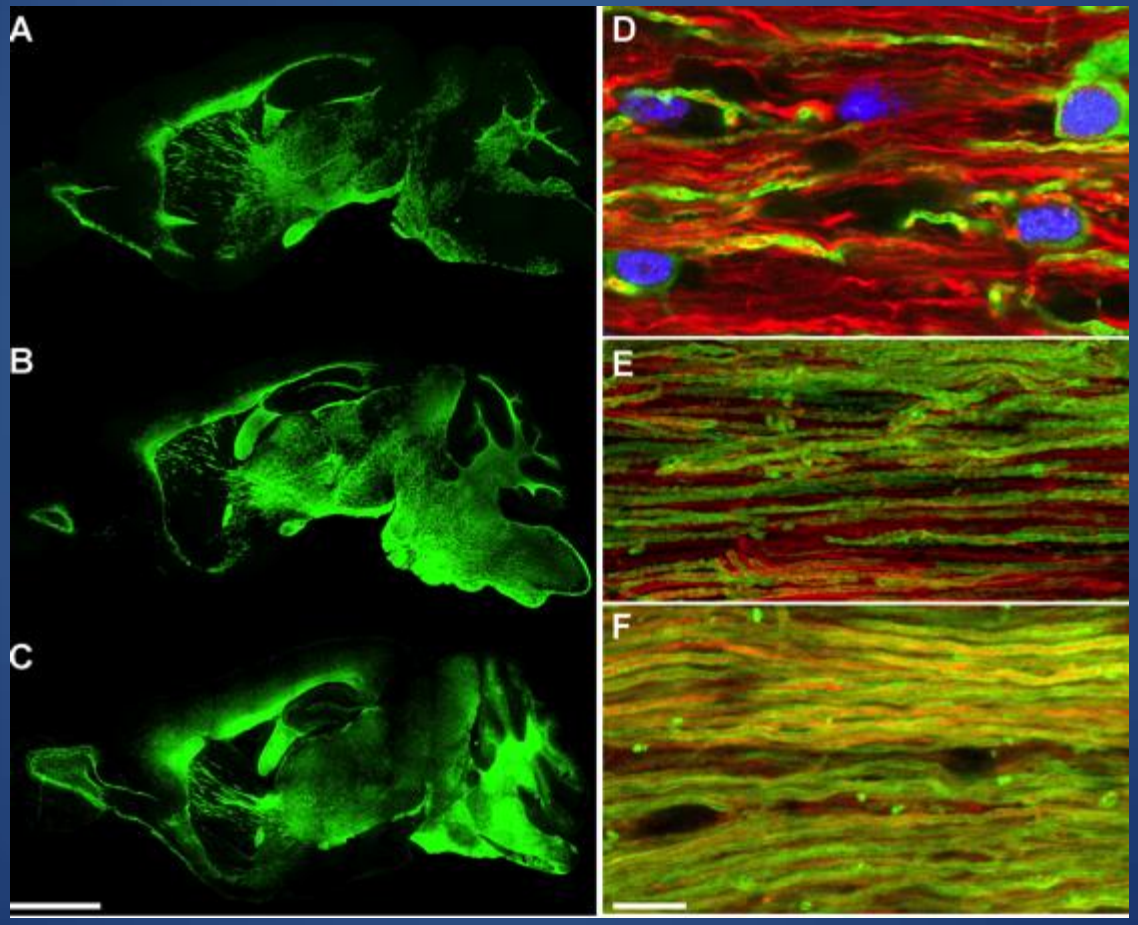
1. Integration into existing networks
2. Immunomodulation
3. Neuroprotection by trophic support
4. Cell-Based enzyme and gene delivery



Nature Reviews Neuroscience 2002, 3; 401

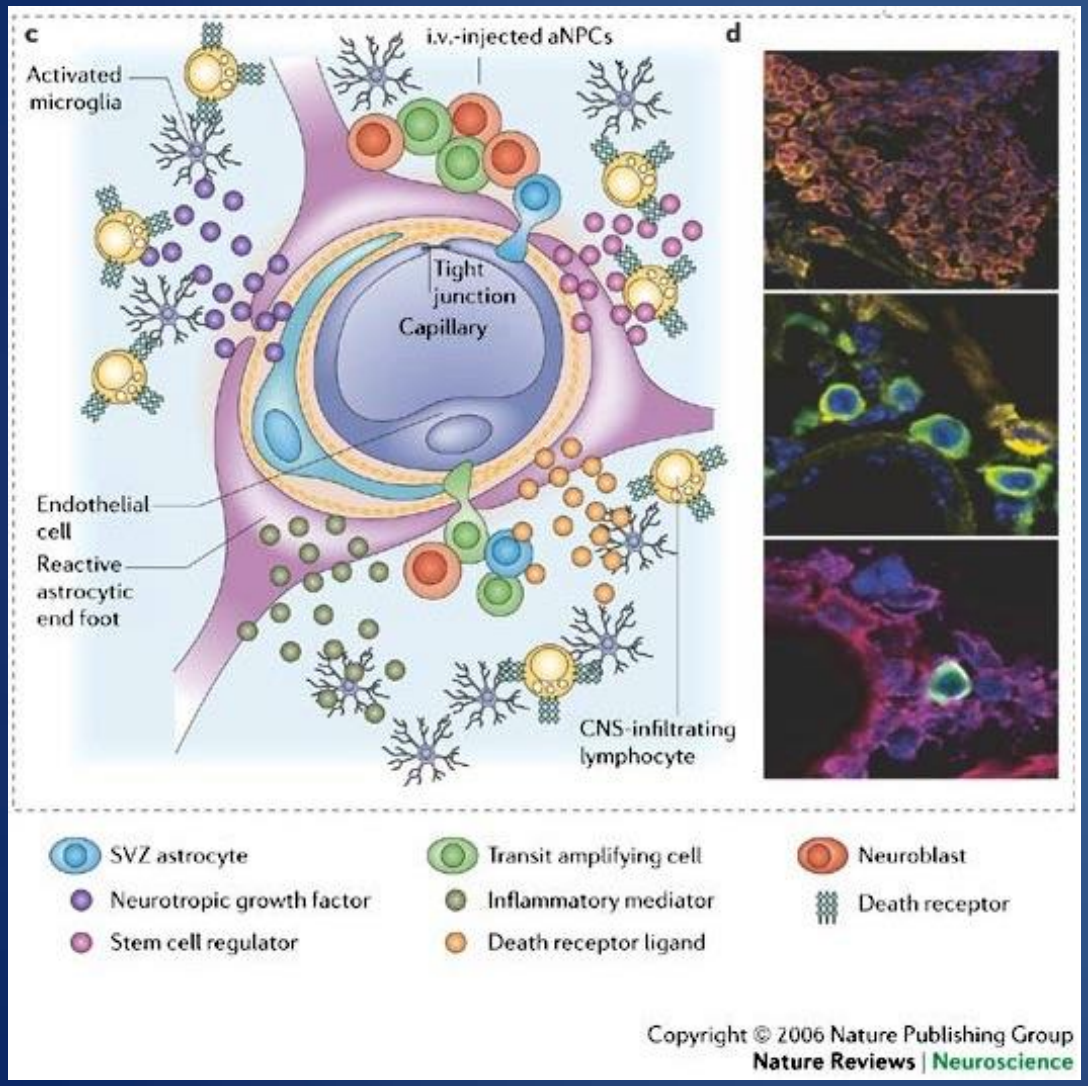
Integration Example

Human Glial Precursors remyeliante the shiverer



Windrem MS et al. *Nat Med* 2004

Immunomodulatory Effects



Martino *et al. Nature Reviews Neuroscience* **7,** 395–406 (May 2006)

Neural Spheres Migrate and Stimulate Endogenous Stem Cells

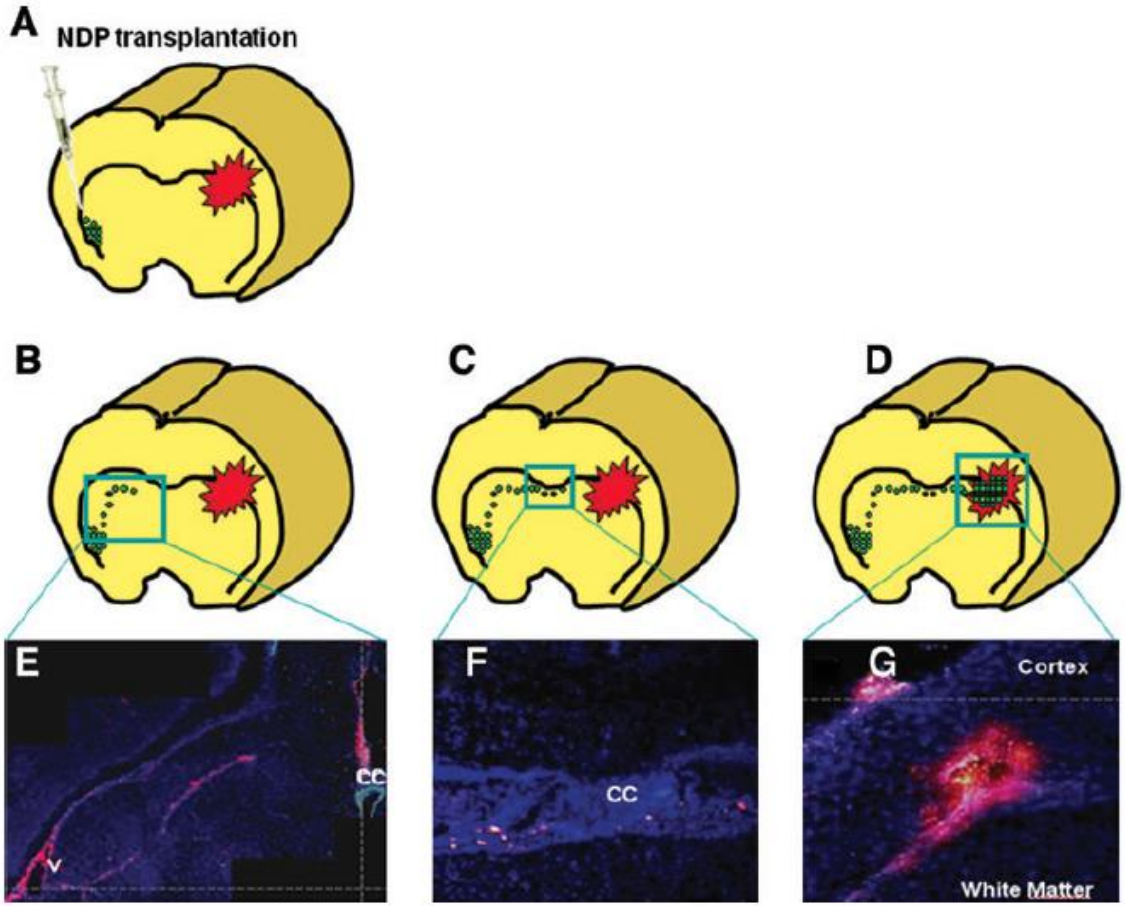
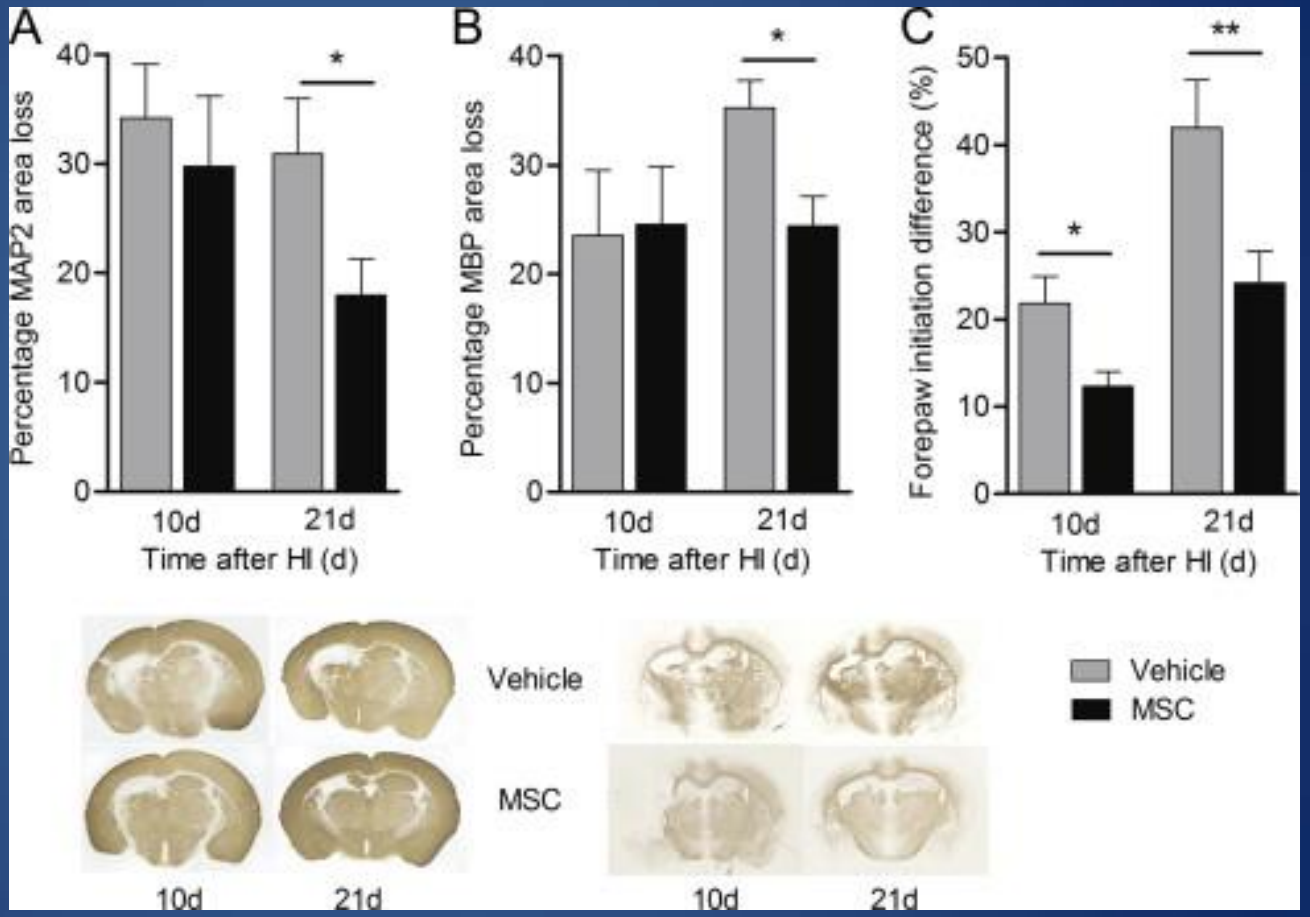


FIG. 2. In vivo fate of NDPs injected into ibotenate-lesioned brains. Injected NDPs migrate rapidly to the lesion site **(A–D)**. One day after ibotenate administration and NDP infusion, DiI-positive cells (red) are mostly located in the injected ventricle, and individual cells can be detected in the cerebrospinal fluid. Some NDPs are juxtaposed to the ventricular wall, whereas others are already migrating away from the injected ventricle. On day 2, DiI-positive cells migrate toward the lesion **(B, E)**. Migrating NDPs reach the corpus callosum on day 3 **(C, F)**. On day 4, DiI-positive cells are visible at the level of the lesion **(D, G)**. Blue staining, DAPI; red staining, DiI; V, ventricle; CC, corpus callosum. Color images available online at www.liebertonline.com/scd

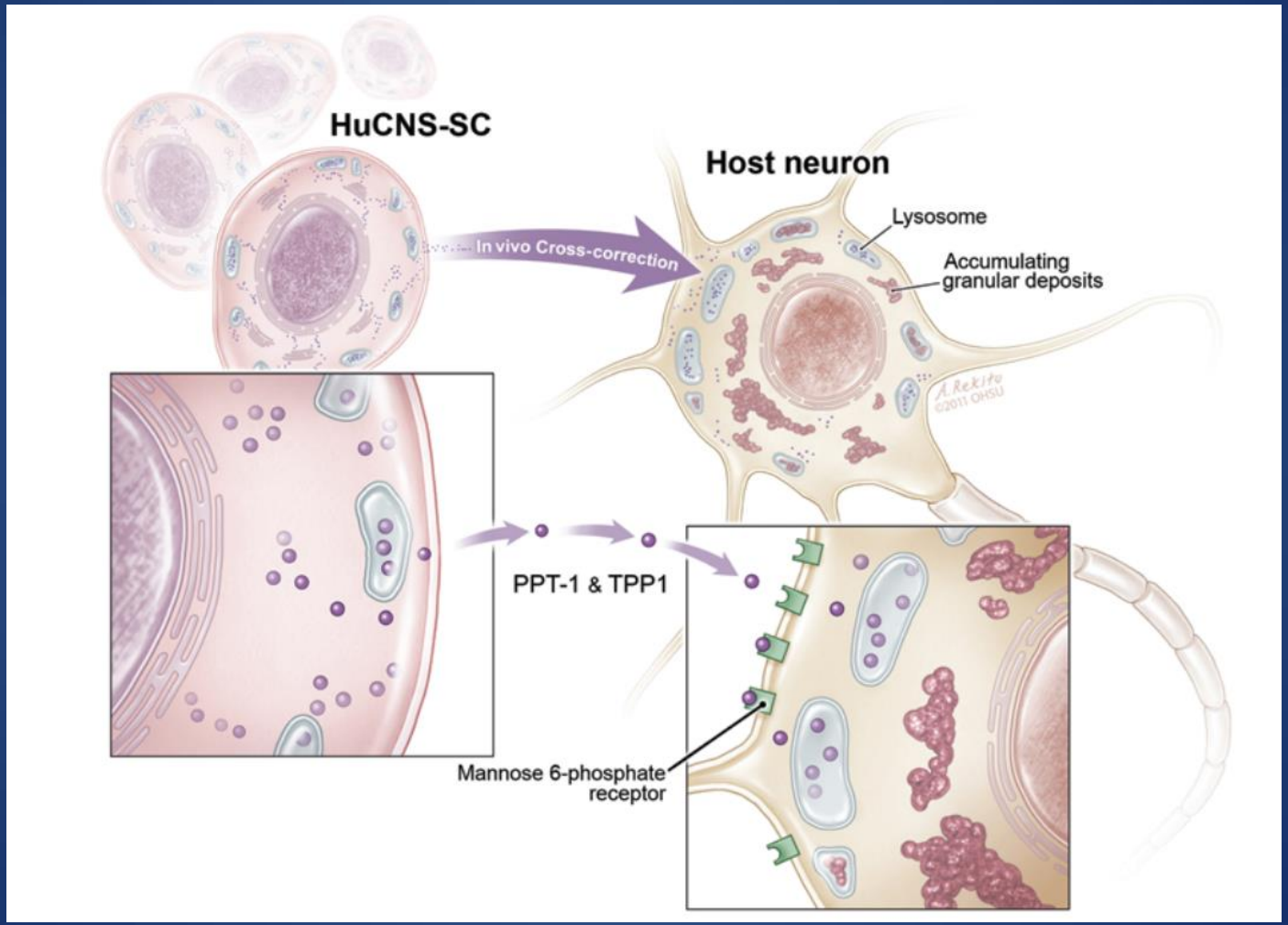
Mesenchymal Stem Cell Injection Improves Outcome in Mice with Neonatal Hypoxia-Ischemia

Cells injected into the brain 3 days after HI

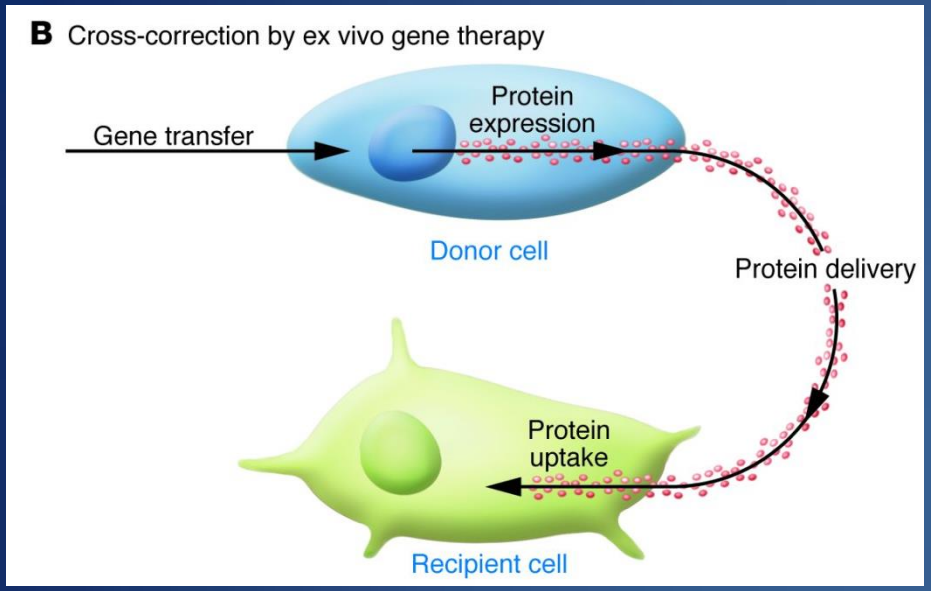


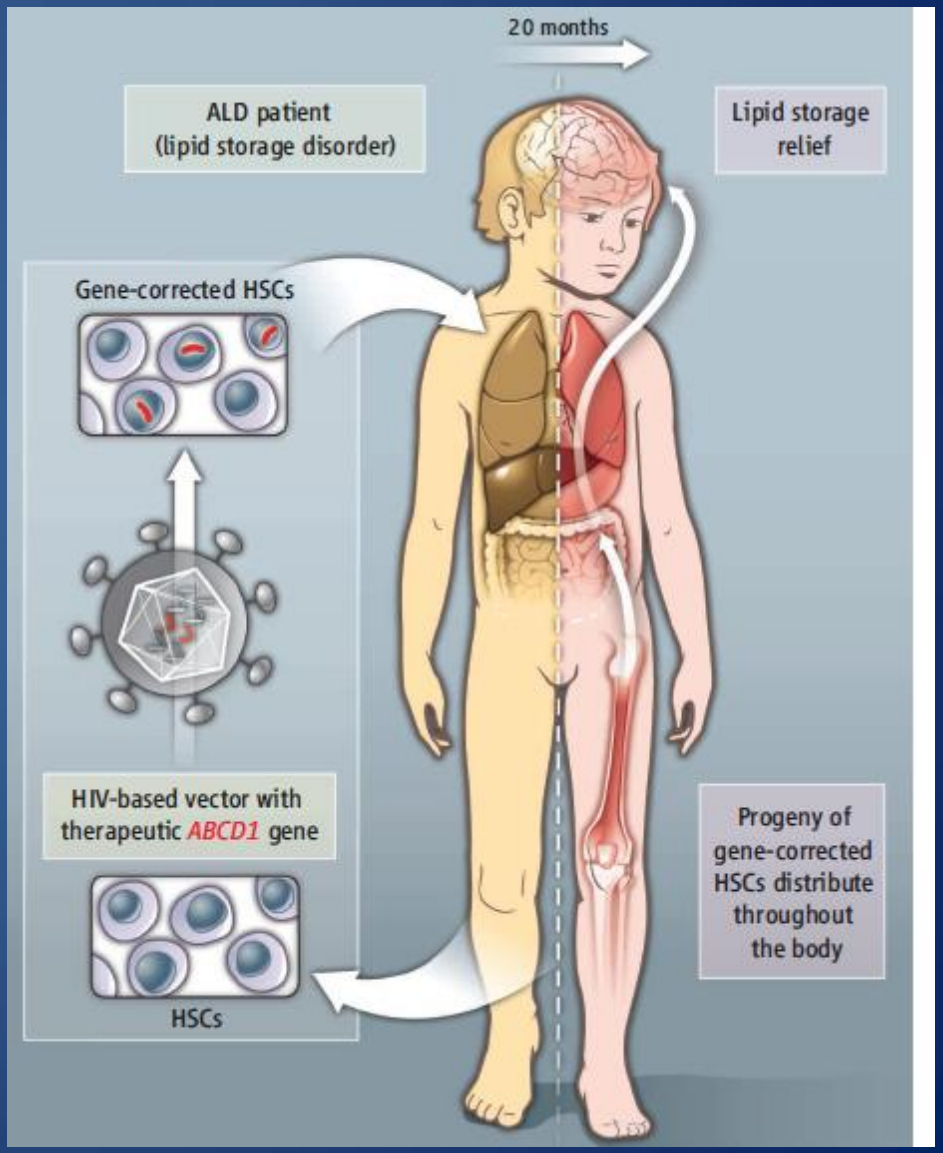
Van Velthoven et al. Brain, Behavior, and Immunity Volume 24, Issue 3, March 2010, Pages 387-393

Stem Cell-Based Enzyme Delivery



Stem Cell-Based Gene Delivery





Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 3996–4001, March 1998
Neurobiology

A tripotential glial precursor cell is present in the developing spinal cord

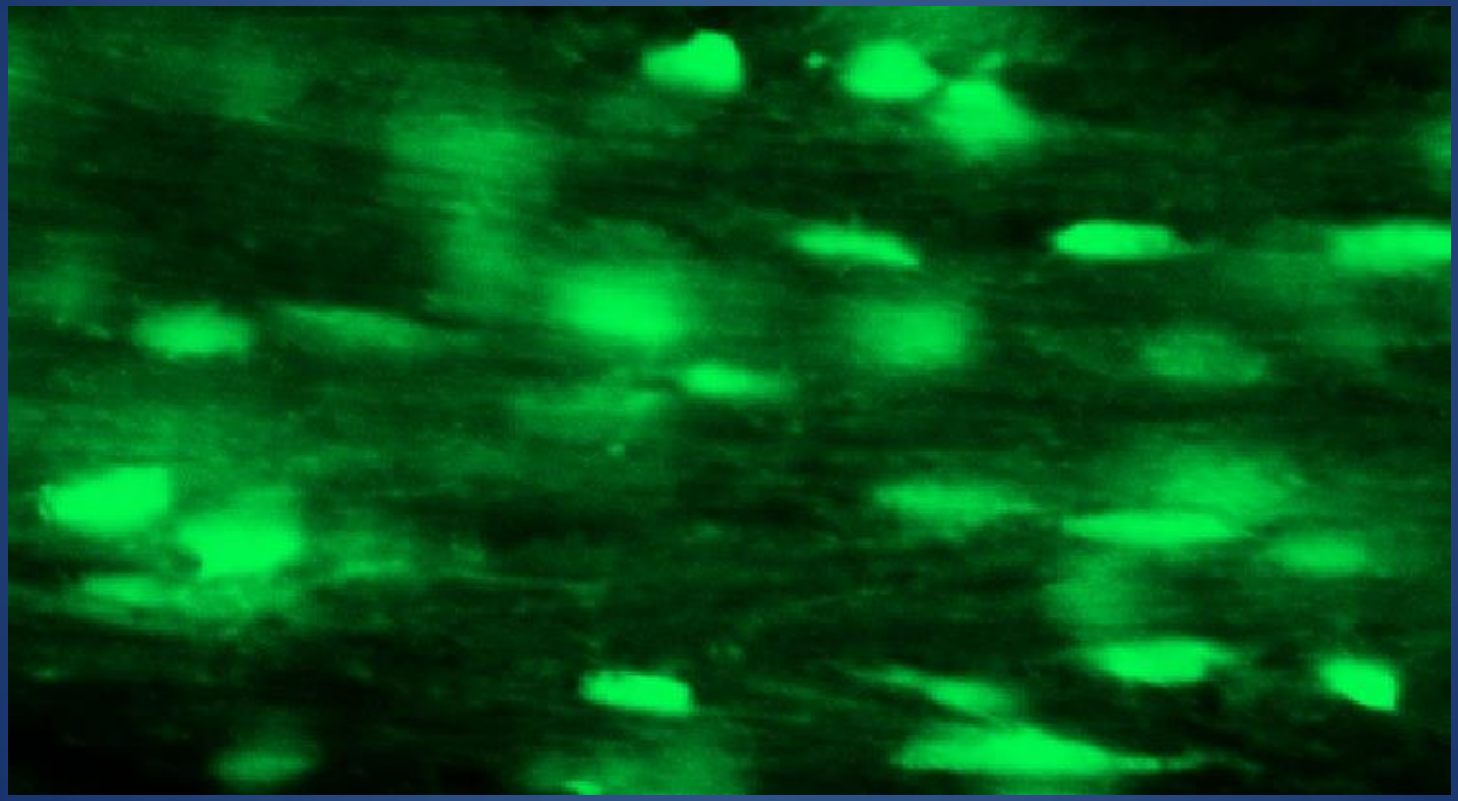
(stem cells/neuroepithelium/differentiation/development)

MAHENDRA S. RAO*, MARK NOBLE†, AND MARGOT MAYER-PRÖSCHEL†‡

†Huntsman Cancer Institute, Biopolymers Building 570, Room 410, University of Utah, Salt Lake City, UT 84112; and *Department of Neurobiology and Anatomy, University of Utah Medical School, 50 North Medical Drive, Salt Lake City, UT 84132

Communicated by Raymond L. White, University of Utah, Salt Lake City, UT, December 5, 1997 (received for review September 4, 1997)

Glial Precursors Migrate Along the White Matter



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Bone Marrow Stem Cell Transplantation

- Has improved outcome in some neurometabolic disease.
- High risk of mortality (5-30%) pending on patient's age, baseline disease and other factors.
- High morbidity due to chemotherapy and immunosuppressive treatment leading to infections and organ damage.

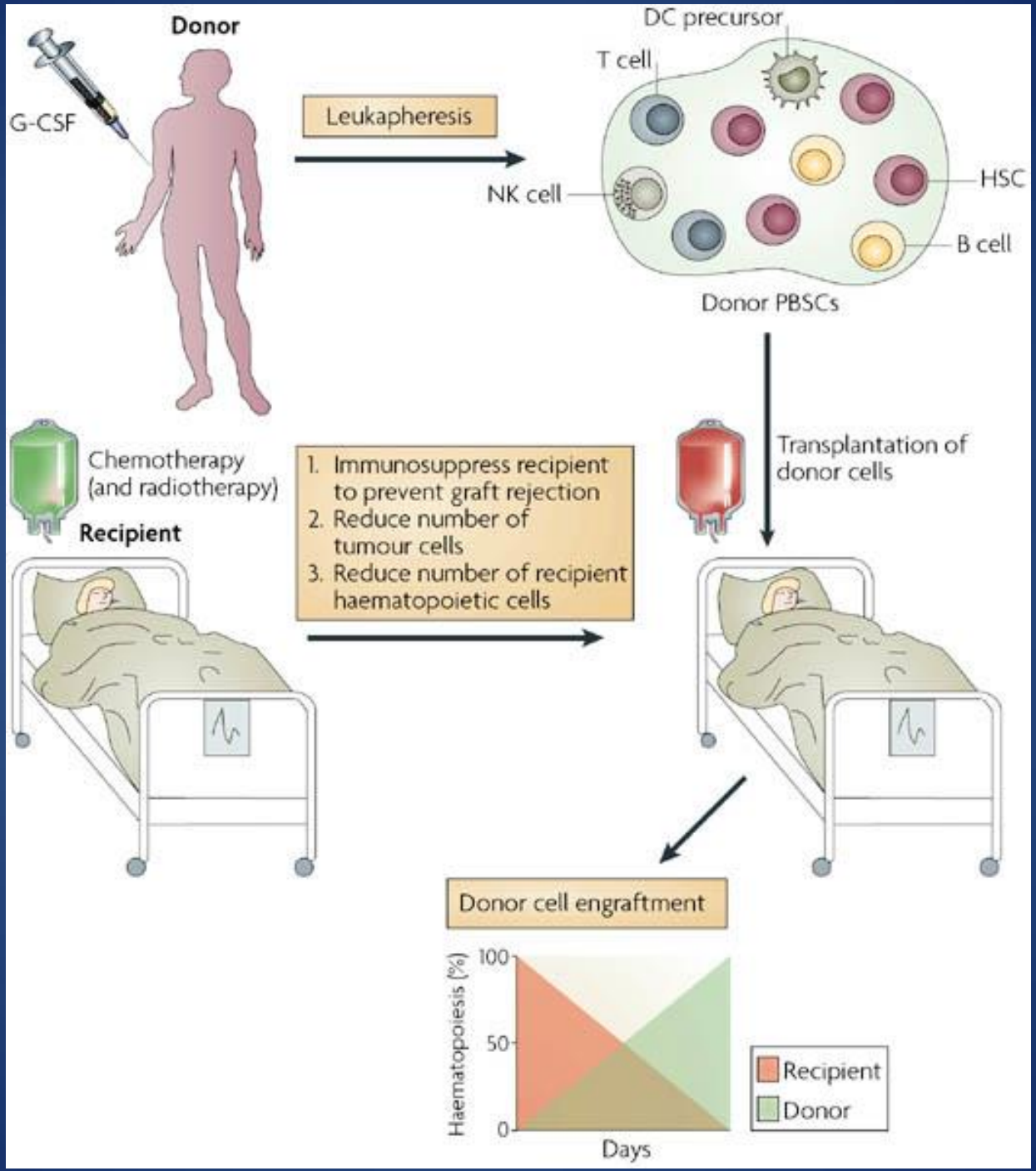

Donor
G-CSF
Leukapheresis
DC precursor
T cell
NK cell
HSC
B cell
Donor PBSCs
Chemotherapy
(and radiotherapy)
Recipient
1. Immunosuppress recipient to prevent graft rejection
2. Reduce number of tumour cells
3. Reduce number of recipient haematopoietic cells
Transplantation of donor cells
Donor cell engraftment
Haematopoiesis (%)
100
50
0
Days
Recipient
Donor

Table I. HSCT for various IMD: Reports from literature and our recommendations.

Category	Diagnosis	HSCT reported	Current status of HSCT
Mucopolysaccharidosis	MPS I, severe phenotype	BMT[1], UCBT[2]	Standard of care
	MPS II with CNS disease	BMT[3], UCBT[4]	Investigational
	MPS III A-D	BMT[5], UCBT[6]	Investigational
	MPS IV A-B	BMT[7]	Investigational
	MPS VI	BMT[8], UCBT[9]	If failed ERT
	MPS VII		Investigational
Glycoproteinosis	Aspartylglucosaminuria	BMT[10]	Standard of care
	Fucosidosis	BMT[11]	Standard of care
	Alpha-Mannosidosis	BMT[12], UCBT[13]	Standard of care
	Mucolipidosis II or I-cell disease	BMT[14], UCBT[15]	Standard of care
Sphingolipidosis	Fabry		Not indicated
	Farber	BMT[16]	Investigational
	Gaucher	BMT[17]	Investigational for CNS involvement
	GM1 gangliosidosis	BMT[18], UCBT[19]	Investigational
	Niemann-Pick disease A and B	BMT[20], UCBT[21]	Investigational
	Tay-Sachs disease	BMT[22], UCBT[23]	Investigational
	Sandhoff sisease	UCBT[24]	Investigational
	Globoid leucodystrophy	BMT[25], UCBT[26]	Standard of care
	Metachromatic leucodystrophy	BMT[27], UCBT[28]	Standard of care
Other lipidosis	Niemann-Pick disease C		Not Indicated
	Wolman disease	BMT[29]	Standard of care
	Ceroid lipofuscinosis	BMT[30]	Investigational
Glycogen storage disorders	GSD type II, early infantile	BMT[31]	Investigational
Peroxisomal storage disorders (PSD)	Adrenoleucodystrophy	BMT[32], UCBT[33]	Standard of care
	Adrenomyeloneuropathy	BMT, UCBT[34]	Investigational
Other	Pelizaeus-Merzbacher disease	UBCT[34]	Investigational
	Lesch-Nyhan	UCBT[34]	Investigational

'Standard of care' – Significant single institution or registry based studies demonstrating efficacy of HSCT. Each case should be evaluated for risk and benefits based on many factors including status of disease, functional status, donor availability, quality of graft amongst others.

Br J Haematol. 2010 Feb; 148 (3):356-72. Epub 2009 Nov 16.

Cord Blood Nucleated Cell Transplantation in Neurologic Diseases

- Recently used in neurometabolic diseases
- Associated with lower morbidity and mortality, easier to find a matched donor
- Role of autologous transplantation

Autologous Cord Blood Transplantation in Cerebral Palsy

- More than 170 children with diagnosis of cerebral palsy have received autologous CB units as compassionate care at Duke University
- Ongoing trial in USA, NCT01072370, Inclusion Criteria:
  - 1-12 years of age, placebo-controlled, FU after one year
  - Clinical evidence of a non-progressive motor disability due to brain dysfunction. The subjects will not have the ability to sit independently by one year of age or the ability to walk by 18 months of age.
- 2 other studies: Korea (allogeneic + Epo) and Iran (CD133+ autolog)

Autologous Cord Blood Transplantation in HIE

- Two ongoing trials listed at clinicaltrials.gov:
  NCT00593242 (Duke Univ. USA)
  - Term infants with moderate to severe encephalopathy that missed cooling receive autologous cord blood within first 14 days
  - Compared to historical controls
  - Outcome will be assessed at 9-12 months

  NCT01506258 (Mexico)
  - Term infants with HIE within the first 48h of life
  - Compared to controls who refuse therapy
  - Outcome at one year

Phase I (Safety) Trial of Neural Stem Cells in USA

J Neurosurg Pediatrics 11:643–652, 2013

Central nervous system stem cell transplantation for children with neuronal ceroid lipofuscinosis

Clinical article

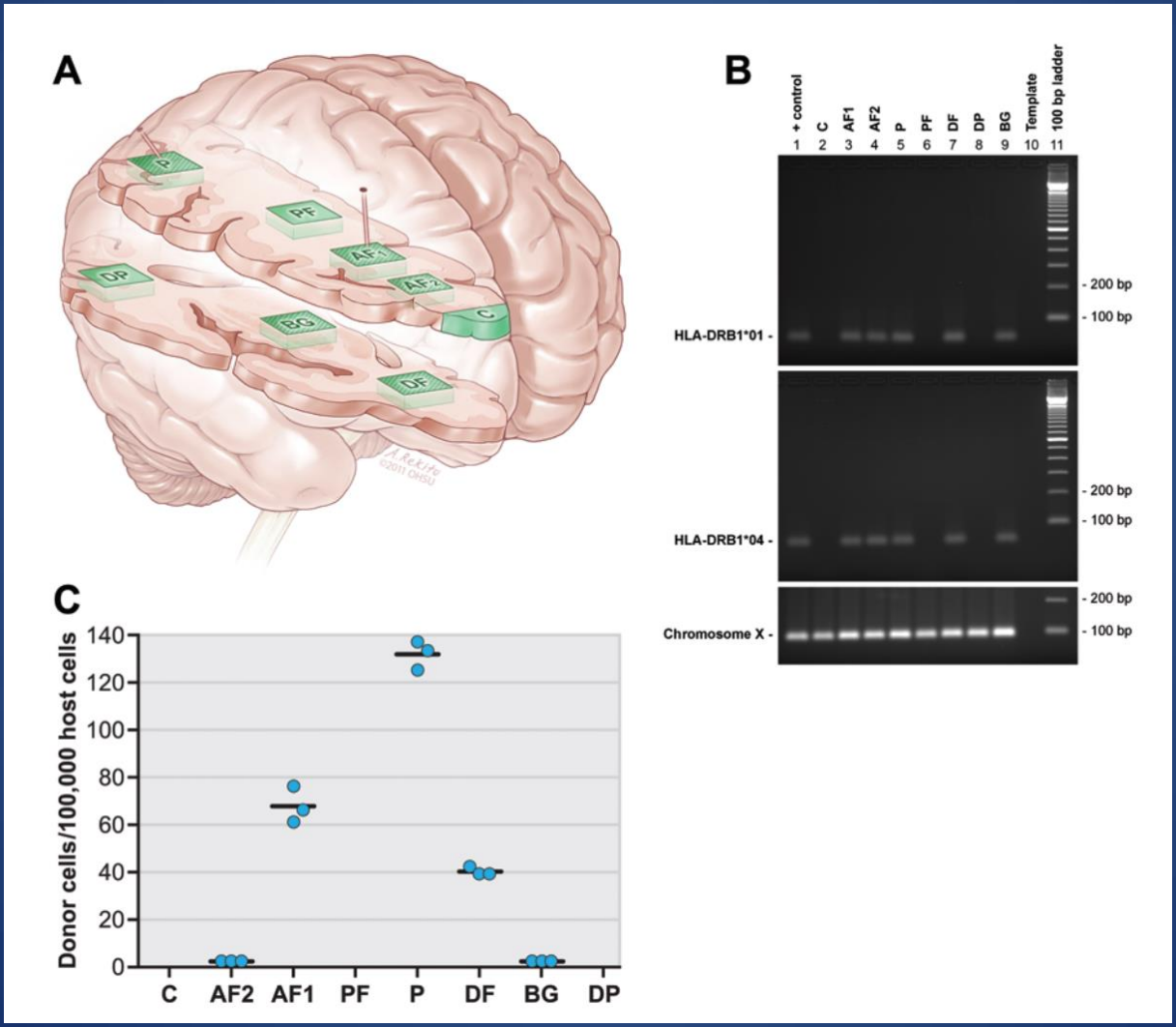
Nathan R. Selden, M.D., Ph.D.,[1,8] Amira Al-Uzri, M.D.,[2,8] Stephen L. Huhn, M.D.,[9] Thomas K. Koch, M.D.,[2,3] Darryn M. Sikora, Ph.D.,[2] Mina D. Nguyen-Driver, Psy. D.,[2] Daniel J. Guillaume, M.D., M.Sc.,[1,8] Jeffrey L. Koh, M.D.,[4] Sakir H. Gultekin, M.D.,[5] James C. Anderson, M.D.,[6] Hannes Vogel, M.D.,[10] Trenna L. Sutcliffe, M.D.,[11] Yakop Jacobs, Ph.D.,[9] and Robert D. Steiner, M.D.,[2,7,8]

Departments of [1]Neurological Surgery, [2]Pediatrics, [3]Neurology, [4]Anesthesiology and Peri-Operative Medicine, [5]Pathology, [6]Diagnostic Radiology, and [7]Molecular and Medical Genetics, Oregon Health & Science University; [8]Doernbecher Children's Hospital, Portland, Oregon; [9]StemCells, Inc., Newark; [10]Department of Pathology, Stanford University Medical School, Stanford; and [11]Department of Pediatrics Palo Alto Medical Foundation, Los Altos, California

HuNSC Tx in Batten Disease

- In six patients with advanced stages of infantile and late infantile Neuronal Ceroid Lipofuscinosis due to PPT1 deficiency.
- Cells directly transplanted into two different sites in each hemisphere via stereotaxic surgery, three patients got 500mil cells, three got 1bil cells
- Patients immunosuppressed for 12 months
- Monitored for four years, three patients all due to NCL disease progression
- Autopsy no evidence of malignancy

Evidence of Cell Migration in Autopsy Case



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News

Fetal Stem Cell Injections Create Brain Tumors in Israeli Boy

BY LIFESITENEWS.COM

Fri Feb 20, 2009 12:15 EST | Comments (0)

Complications of Hematopoeitic Cell Transplantation

- Acute and chronic graft versus host disease
- Engraftment syndrome
- Veno-occlusive disease
- Idiopathic pulmonary syndrome
- Immunosuppression associated infection
- Side effect of chemotherapeutics (preparative regimen)

Lessons Learned from Krabbe Disease

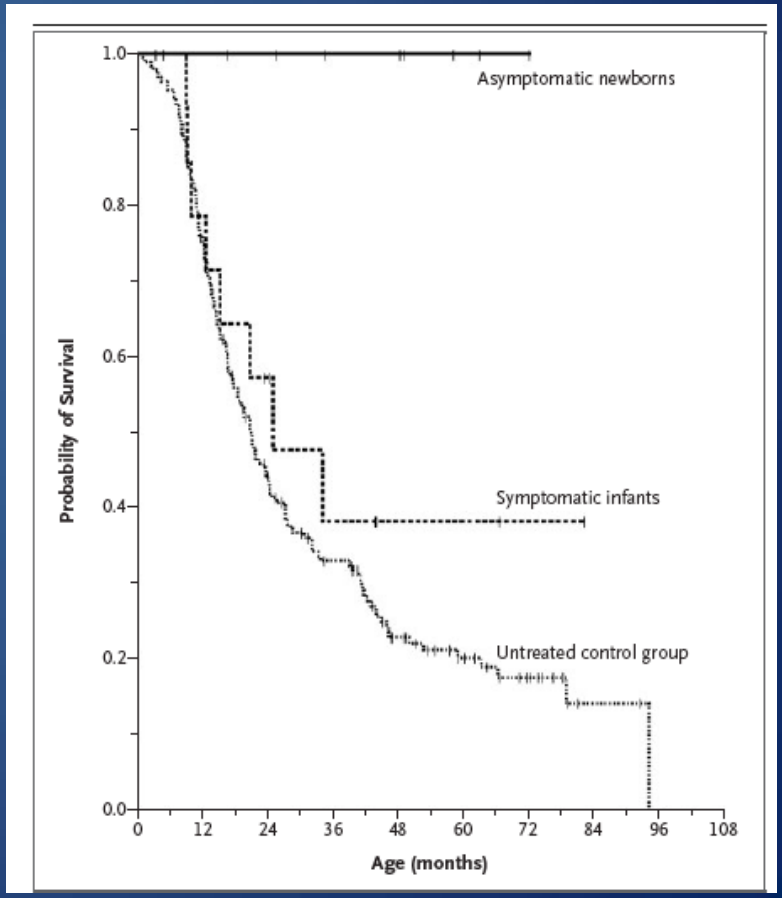
the 'big thing in 2005'

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transplantation of Umbilical-Cord Blood in Babies with Infantile Krabbe's Disease

Maria L. Escolar, M.D., Michele D. Poe, Ph.D., James M. Provenzale, M.D., Karen C. Richards, M.D., June Allison, R.N., Susan Wood, P.N.P., David A. Wenger, Ph.D., Daniel Pietryga, M.D., Donna Wall, M.D., Martin Champagne, M.D., Richard Morse, M.D., William Krivit, M.D., Ph.D., and Joanne Kurtzberg, M.D.



Long Term Follow Up Study of Same Cohort Published in 2009

- 16 presymptomatic children transplanted at Duke and elsewhere for early infantile Krabbe disease
- Two died
- All others spastic – three mild
- Five required gastostomies
- All were below 3% with height and weight
- All have abnormal expressive language
- 50% walk with assistive devices
- 25% don't walk

Duffner P et al. *Genetics in Medicine* (2009) 11, 450

Summary

- Currently ongoing cell based therapy for a number of neurometabolic conditions.
- Advanced cell engineering methods open the door to new therapeutic approaches.
- Expect to have many more trials to come within the next 5-10 years.
- Not all patients will be ideal candidates.
- Stem cell therapy can be harmful, very dangerous complications including death.
- Need for careful investigations to determine who will benefit and in whom it may be harmful.

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