LA GRANDE PROMESSA DELLE CELLULE STAMINALI PER LA RIPARAZIONE CEREBRALE: ILLUSIONE O REALTÀ?

MUSEO DI STORIA NATURALE
"GIACOMO DORIA"

SOCIETA' AMICI DEL MUSEO "G. DORIA"
In collaborazione con
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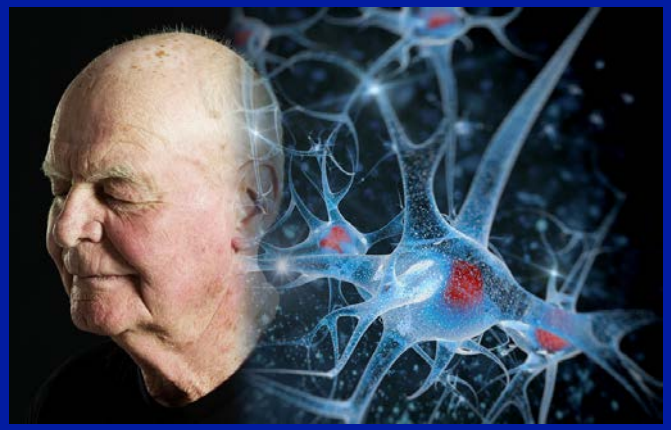
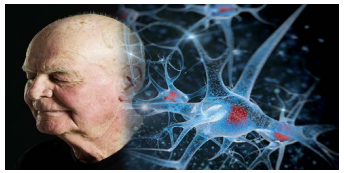


Maria Pia Abbracchio

Professore ordinario di Farmacologia
Laboratory of Molecular and Cellular Pharmacology of Purinergic Transmission
Department of Pharmacological and Biomolecular Sciences
University of Milan, Italy



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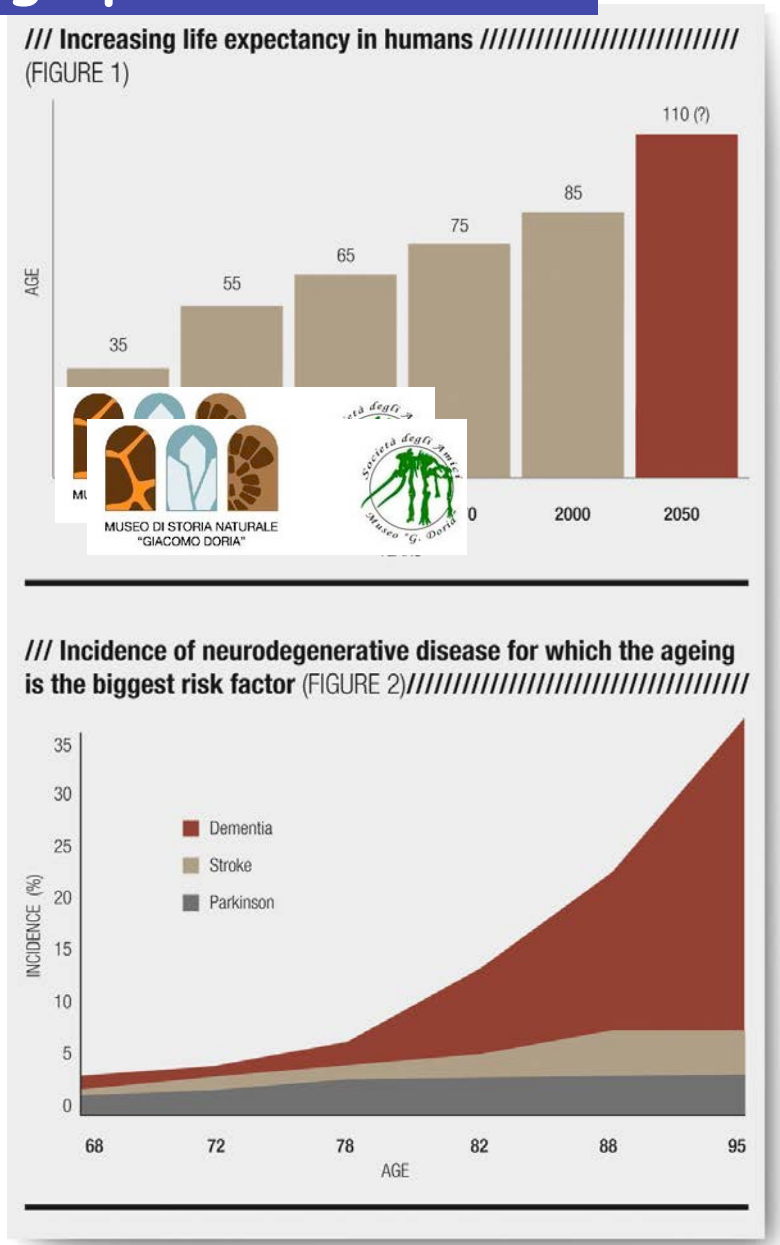
Aging, neurodegenerative diseases and the coming epidemic

Aging: the numbers

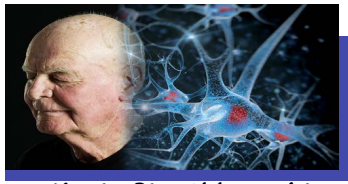
Globally, the 65-plus demographic is estimated to triple from 524 million in 2010 to about 1.5 billion by 2050

Aging associated-neuro degenerative diseases:

- Stroke
- Cerebral trauma
- Parkinson's disease
- Huntinghton's disease
- Alzheimer's disease
- Multiple Sclerosis
- Amiotrophic lateral sclerosis



From: Jesus Avila, R&D on Ageing: the Biomedical Viewpoint



Extent of the problem: the case of Alzheimer's disease

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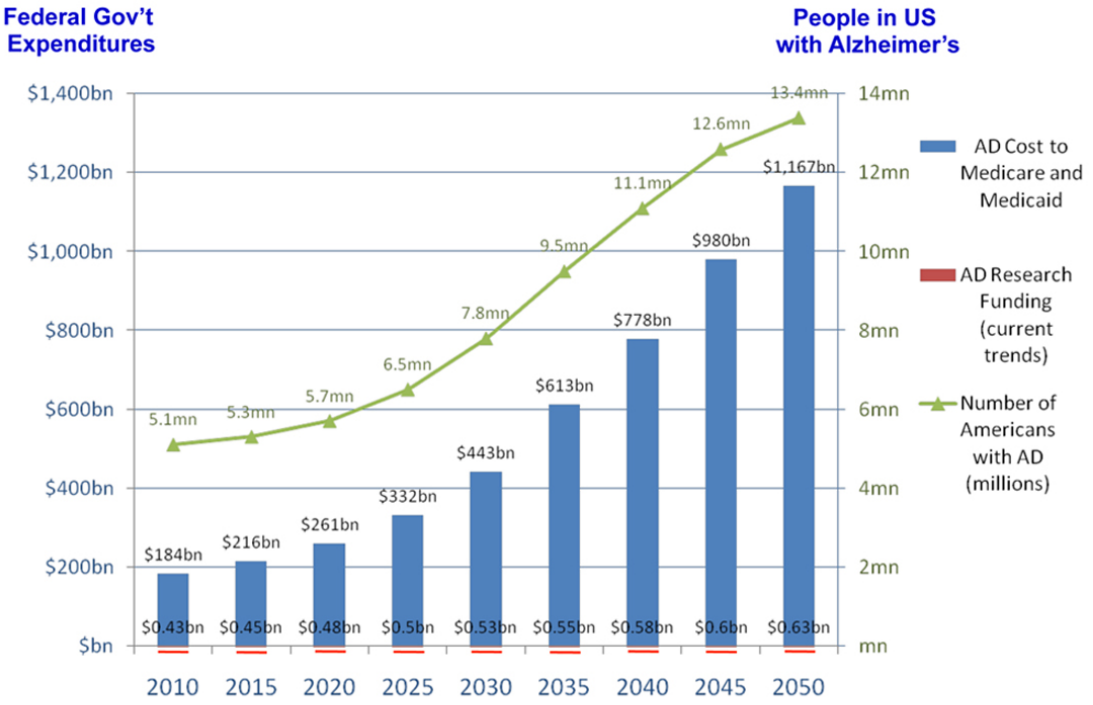
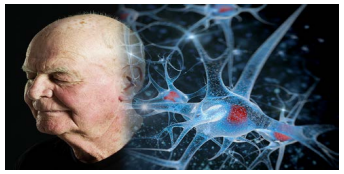


Sources: Alzheimer's Study Group, *A National Alzheimer's Strategic Plan: The Report of the Alzheimer's Study Group* (March 2009); Alzheimer's Association. *2009 Alzheimer's Disease Facts and Figures* (March 2009); National Institutes of Health Office of the Budget



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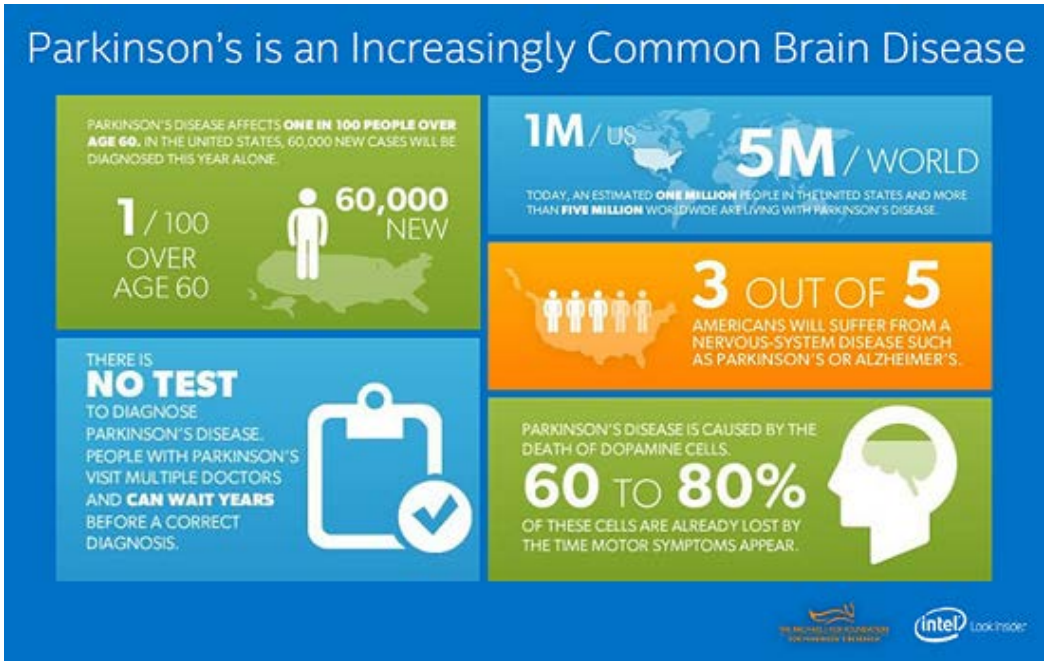
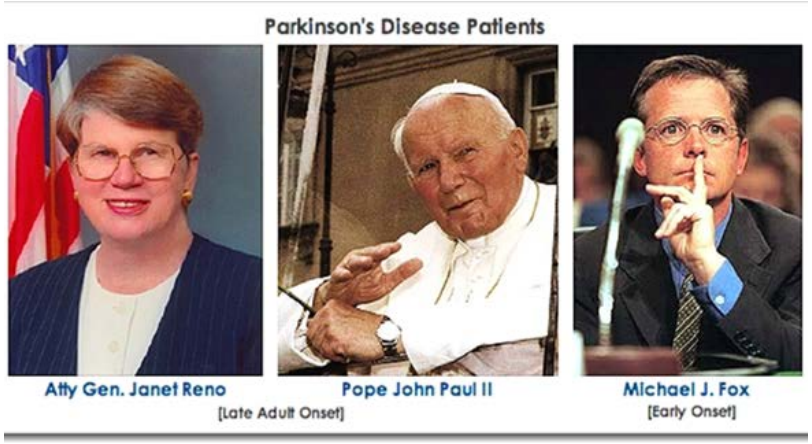
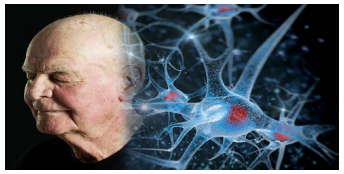
…not only Alzheimer's….







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…not only Alzheimer's….

Cognitive defects is a common hallmark of neurodegenerative diseases

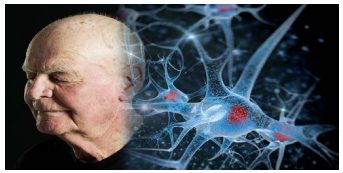
Parkinson's Disease Foundation

Not Just a Movement Disorder: Cognitive Changes in PD

By Laura Marsh, M.D.

Distractibility, disorganization, forgetfulness, and difficulties with planning: it frequently comes as a surprise to people with Parkinson's disease (PD) and their families that "cognitive changes" — alterations in memory, attention, and thinking — are often part of PD. After all, in 1817, when James Parkinson first described the "shaking palsy" he said that, "the senses and intellect were uninjured." While he was correct in most of his assertions, Dr. Parkinson did miss the mark with this claim.

THE DANA FOUNDATION



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Cognitive Impairment in Multiple Sclerosis: A Forgotten Disability Remembered

By Kristen Rahn, Ph.D., Barbara Slusher, M.B.A., Ph.D., and Adam Kaplin, M.D., Ph.D.

Editor's note: Physicians first noted the presence of cognitive impairment in patients with multiple sclerosis (MS) more than 160 years ago, yet it took clinicians until 2001 to codify a standard test to measure cognitive function. We now know that cognitive impairment occurs in up to 65 percent of people with MS and usually lessens their ability to remember previously learned information. So far, trials of drugs formulated to treat cognitive impairment have failed, but the authors remain optimistic that new approaches to diagnosis and drug development could lead to effective therapies in the future.

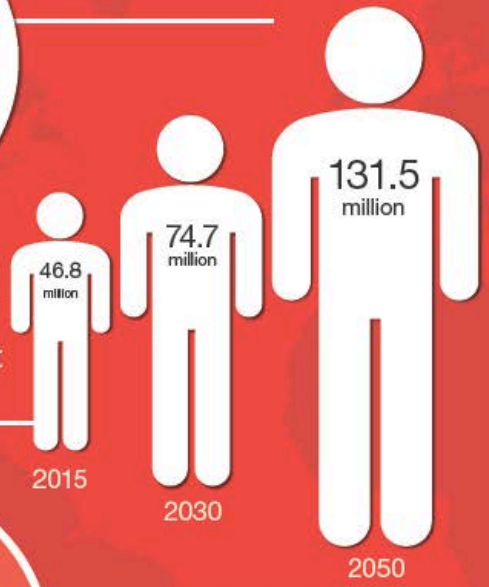
The global impact of dementia

Around the world, there will be 9.9 million new cases of dementia in 2015,

one every 3 seconds

46.8 million people worldwide are living with dementia in 2015.

This number will almost double every 20 years.



68% 2050

Much of the increase will take place in low and middle income countries (LMICs): in 2015, 58% of all people with dementia live in LMICs, rising to 63% in 2030 and 68% in 2050.

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The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to

US$ 2 trillion by 2030

If global dementia care were a country, it would be the

18th largest economy

in the world exceeding the market values of companies such as Apple and Google

(source: Forbes 2015 ranking).

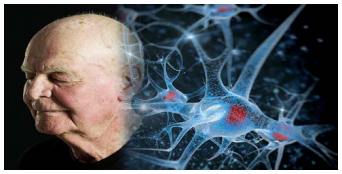
This map shows the estimated number of people living with dementia in each world region in 2015.

We must now involve more countries and regions in the global action on dementia.

The World Alzheimer Report 2015 was independently researched by King's College London and supported by Bupa.

Alzheimer's Disease International

The global voice on dementia



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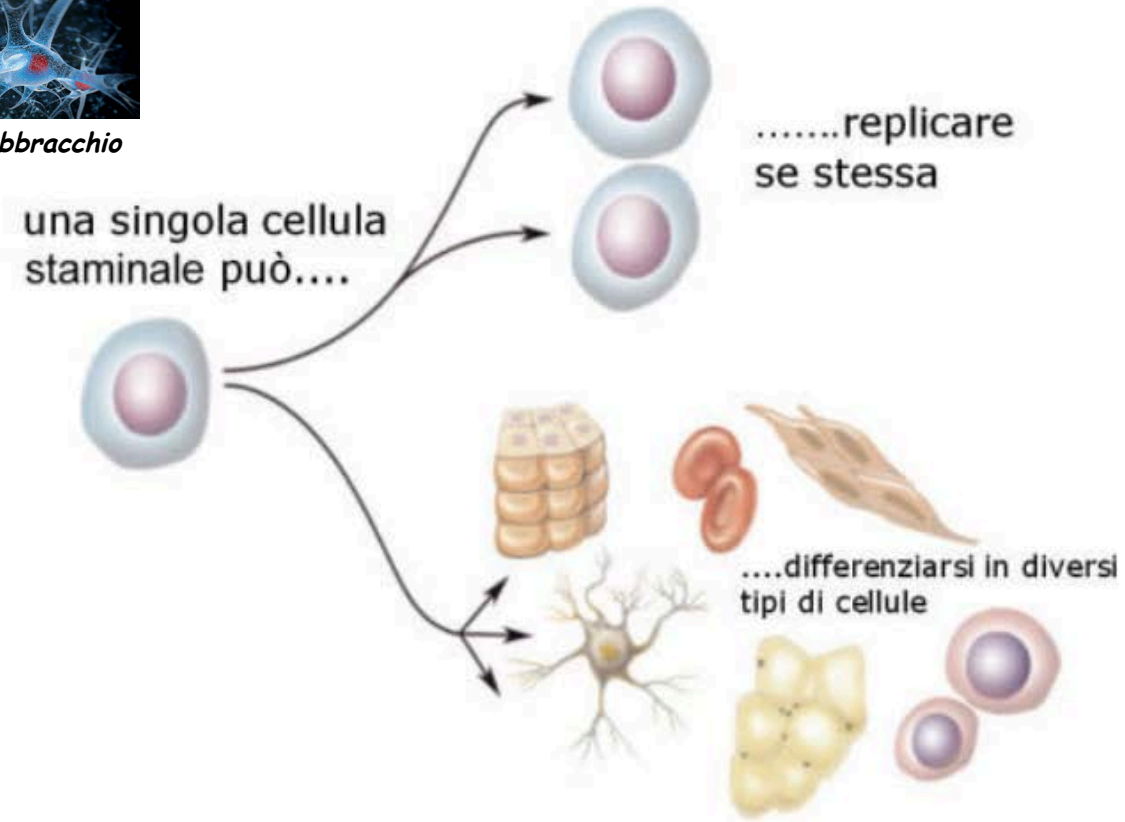
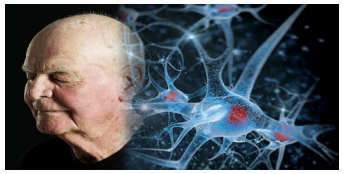


- **Cellula presente in embrione, feto o organismo adulto con la capacità di automantenersi proliferando indefinitamente ("self renewal")…**

- **…e capace, in determinate condizioni, di generare le cellule specializzate di organi e tessuti.**



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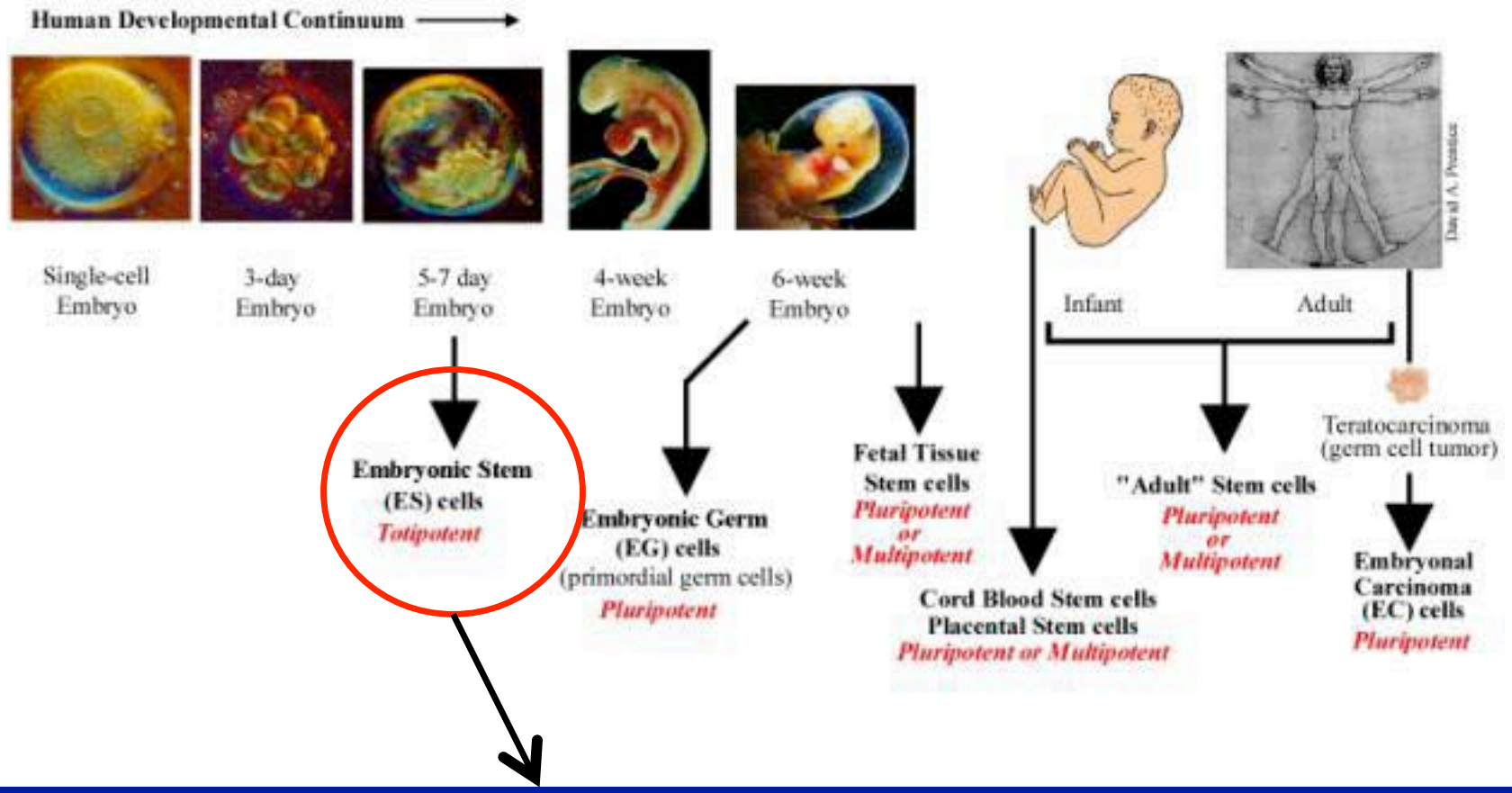
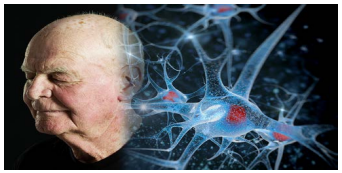
The promise of stem cells for neuro-rejenerative therapies

Stem Cells



Embryonic cells transplantation for cell substitution therapy in Parkinson's, Alzheimer's, multiple sclerosis, stroke…



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Cellule staminali embrionali

Vantaggi:

- Sono totipotenti
- Possono potenzialmente originare tutti i tipi di cellule presenti nel nostro corpo
- Applicabili teoricamente a tutte le malattie

Svantaggi/problemi:

- Generano risposte immunitarie
- Sono altamente proliferative e possono generare tumori
- Il loro uso comporta notevoli implicazioni etiche e legali

Razionale del trapianto

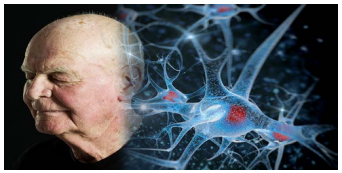
Trapiantare i neuroni nella sede della degenerazione

↓

Ricostruire la struttura nervosa ed i circuiti danneggiati

↓

Riparare il danno funzionale
(creare le condizioni per il recupero funzionale)



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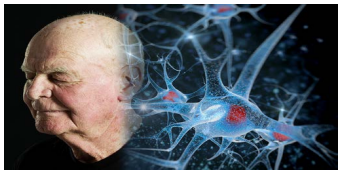

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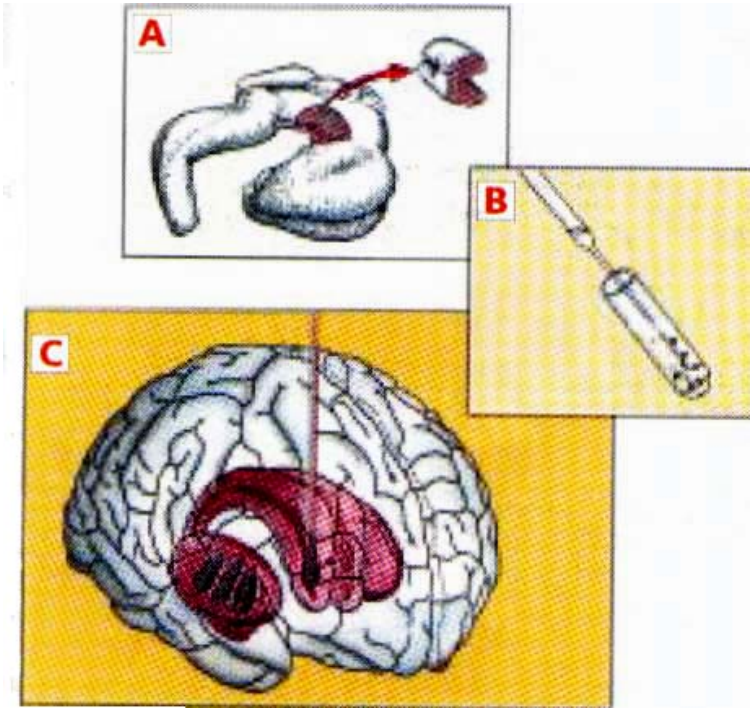
Embryonic stem cell transplantation in Parkinson's disease



- Many patients have experienced transplant rejection or dyskinesias
- Transplanted cells can differentiate to cells other than dopaminergic neurons
- In some cases, cells can generate tumors
- Transplanted cells can get sick !!

However….

Some patients have shown clear beneficial effects (disease amelioration, need for lower doses of medications, long term survival of transplanted cells)

Important proof-of-concept that cell substitution therapy could work!

Drugs Aging. 2001;18(10):773-85.

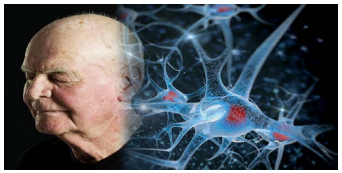
Fetal tissue transplantation for patients with Parkinson's disease: a database of published clinical results.

Clarkson ED.

Author information

Abstract

Over the past 13 years approximately 300 patients with Parkinson's disease have received transplants of human fetal dopamine cells in an attempt to reduce or control disease symptoms. Many of these patients have had improvements in their motor skills and a reduction in their daily levodopa administration. However, improvements are far from guaranteed and questions need to be answered before this technique can be widely applied. To help address some of these issues, a search of all the published results of patients with Parkinson's disease transplanted with human fetal tissue was conducted. This generated a database of 70 transplant recipients who had their levodopa administration and clinical benefit reported both prior to transplant and at least 6 months post-transplant. Furthermore, the number of years of disease onset prior to transplant was available for all recipients. This database was examined for motor improvement and reduction in levodopa dosage for up to 2 years post-transplant to determine the effects of time on transplant outcome. The database showed that most recipients had significant improvements in motor skills and levodopa administration, and that most benefits were observed in the first 6 months post-transplant. In addition, the database demonstrated that the number of years of disease onset prior to transplantation was not a predictor of patient outcome 1-year post-transplant. Current and future directions in fetal tissue transplantation research and replacements for fetal tissue are discussed.



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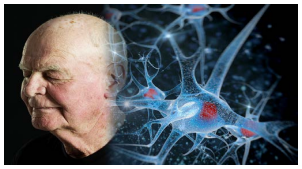

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Cellule staminali somatiche o adulte

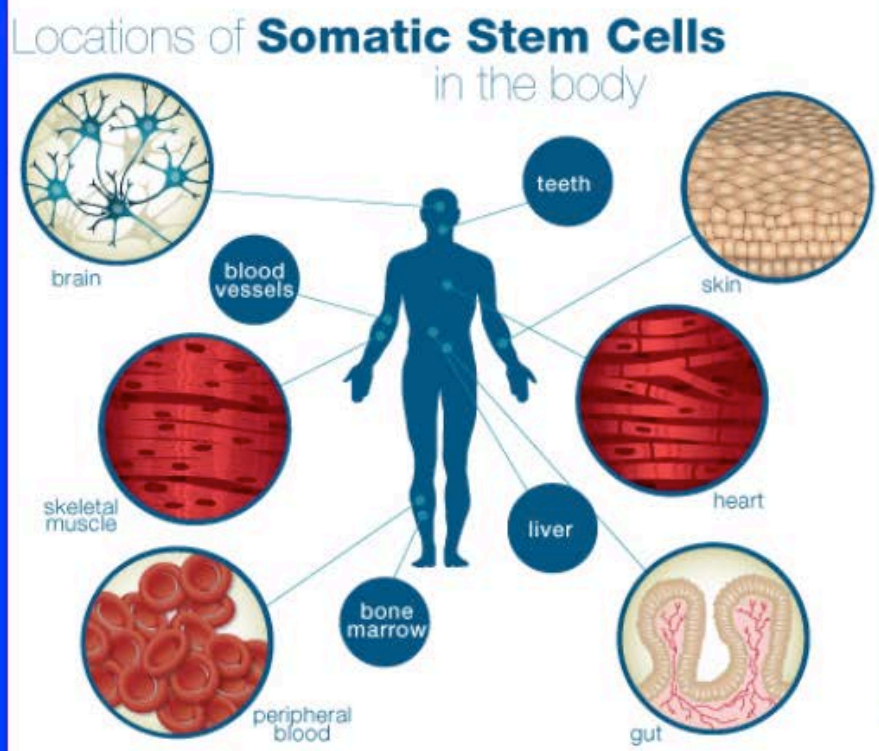
•Rappresentano una riserva per la riparazione dei tessuti adulti

•Quelle isolate dal sangue e del midollo osseo vengono usate per le malattie del sangue (es, leucemie, anemie)

Vantaggi:

•Non generano risposte immunitarie se usate in maniera autologa, perché possono essere isolate e reimpiantate nello stesso paziente

•Il loro uso non comporta alcun problema etico

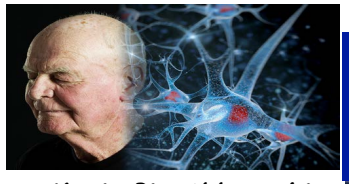


Svantaggi/problemi:

•Non sono totipotenti ma solo multipotenti

•Sono presenti in piccolissime quantità e a volte difficilmente accessibili

•Possono generare solo le cellule del tessuto a cui appartengono



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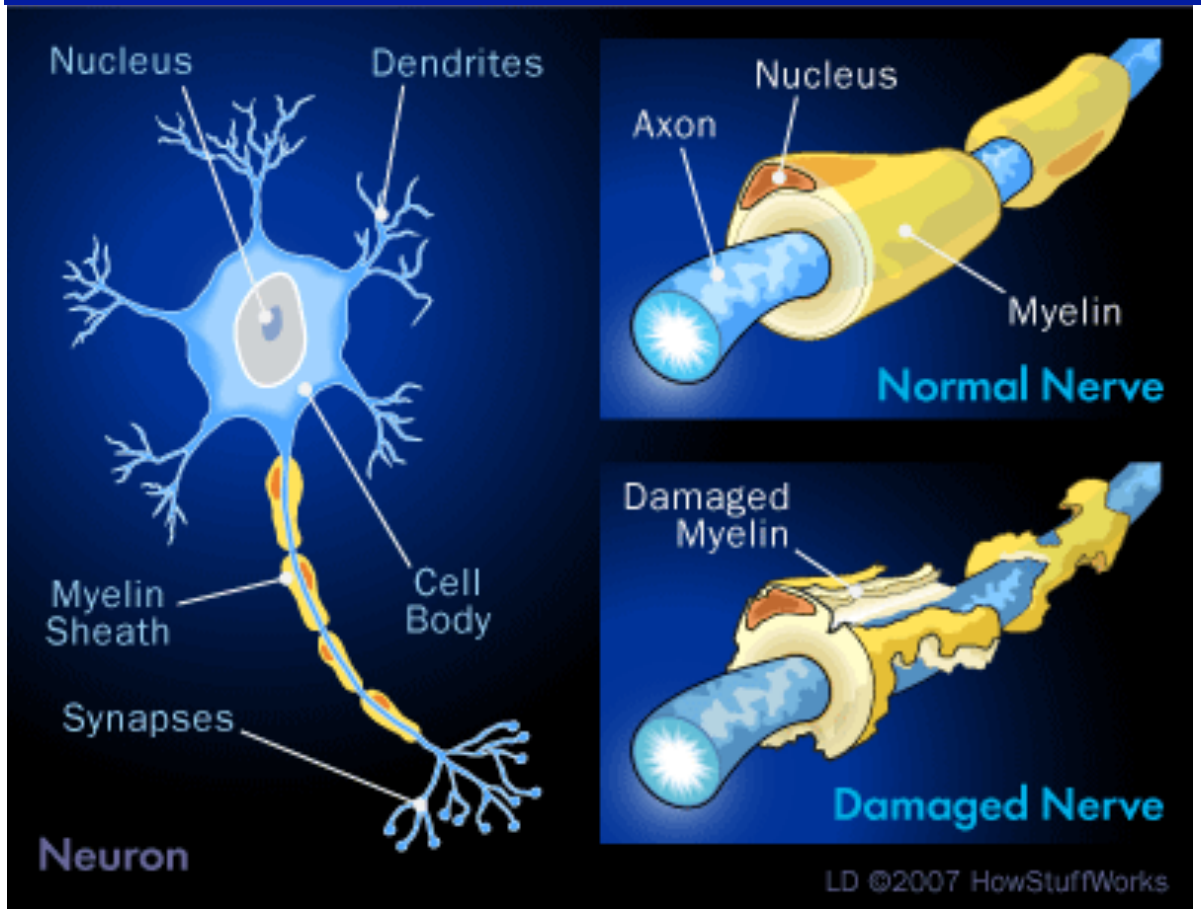
OLIGODENDROCYTES: CELLS ENABLING NERVE TRANSMISSION AND SUPPORTING AXONAL ENDINGS



DEMYELINATION: A CONDITION LEADING TO MYELIN DISRUPTION AND NEUROLOGICAL DISFUNCTION COMMON TO MULTIPLE SCLEROSIS AND SEVERAL OTHER NEURODEGENERATIVE AND NEUROPSYCHIATRIC CONDITIONS

Re-myelination matters….not only in Multiple Sclerosis!

Oligodendrocyte signals maintain axonal integrity and myelin repair fosters brain repair in neurodegenerative diseases

French Sciences Publishing Group

European Journal of BioMedical Research

www.frenchsciencespg.com

ISSN: 2428-5544

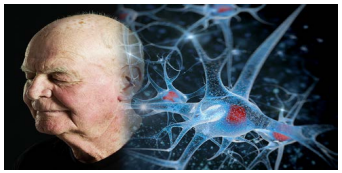
Remyelination is critical for white matter stroke recovery

Yaning Li

Neurosurgery Department, School of Medicine, Stanford University, CA, US

Mini Review

Parkinson's disease medication shows promise for myelin repair



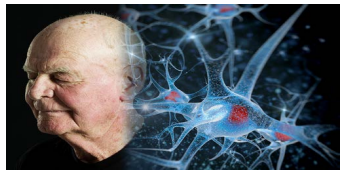
Maria Pia Abbracchio

ARTICLE

doi:10.1038/nature12647

A regenerative approach to the treatment of multiple sclerosis

Vishal A. Deshmukh[1], Virginie Tardif[2], Costas A. Lyssiotis[1]†, Chelsea C. Green[1], Bilal Kerman[3], Hyung Joon Kim[3], Krishnan Padmanabhan[3], Jonathan G. Swoboda[1], Insha Ahmad[1], Toru Kondo[4], Fred H. Gage[3], Argyrios N. Theofilopoulos[2], Brian R. Lawson[2]*, Peter G. Schultz[1,5]* & Luke L. Lairson[1,5]*



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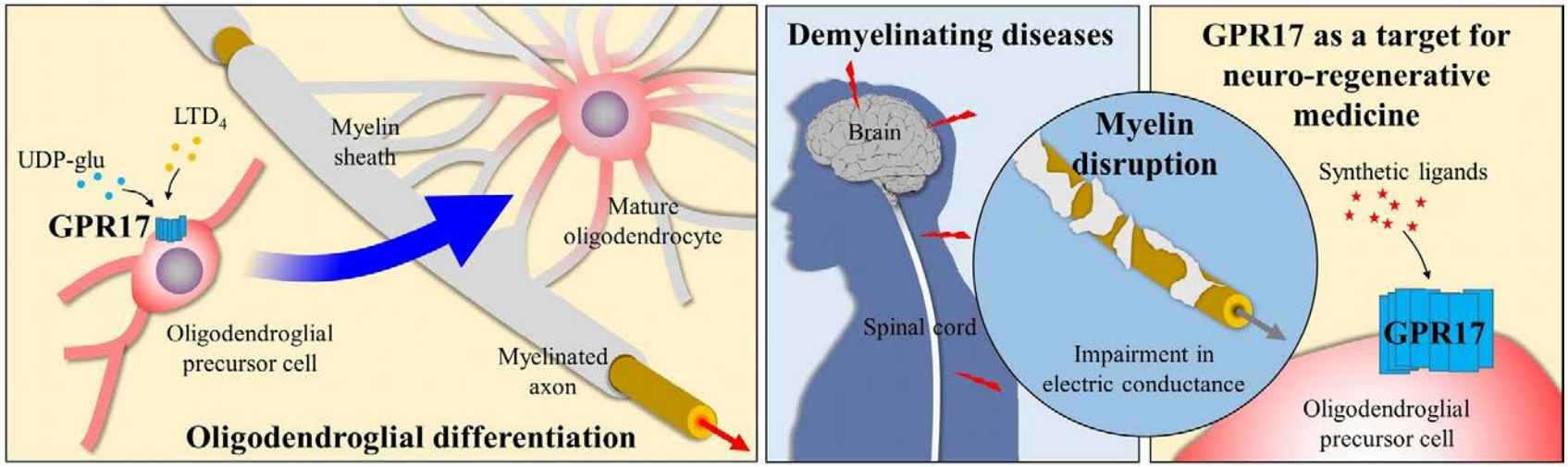
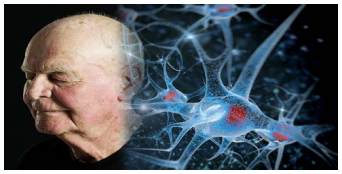
GPR17, a membrane receptor involved in OPC maturation and a new target for re-myelinating therapies



From Fumagalli M, Lecca D, Abbracchio MP, Neuropharmacology, 2015

The GPR17 ligand Montelukast significantly improves spontaneous re-myelination in the MCAo rodent model

Bruker Avancell 4.7T



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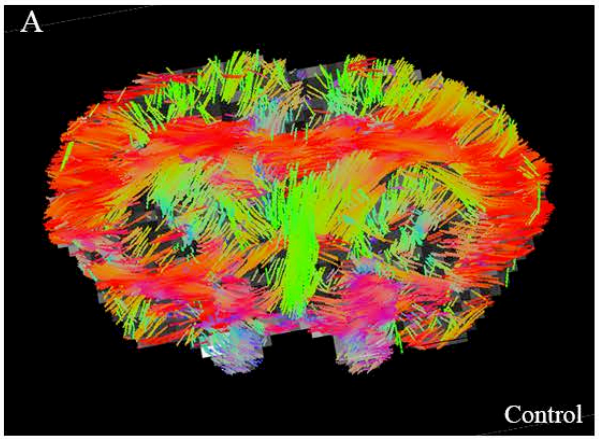
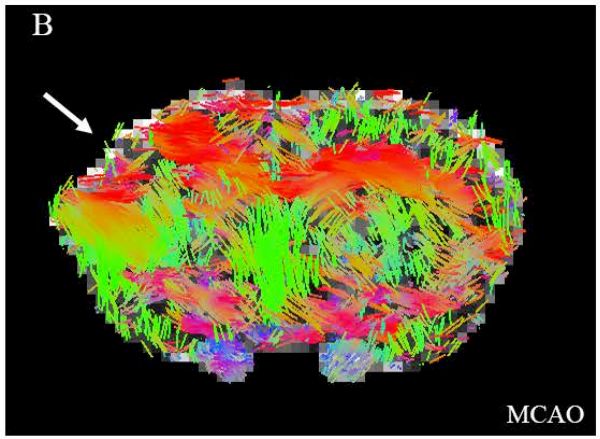
Vevo2100 VisualSonics





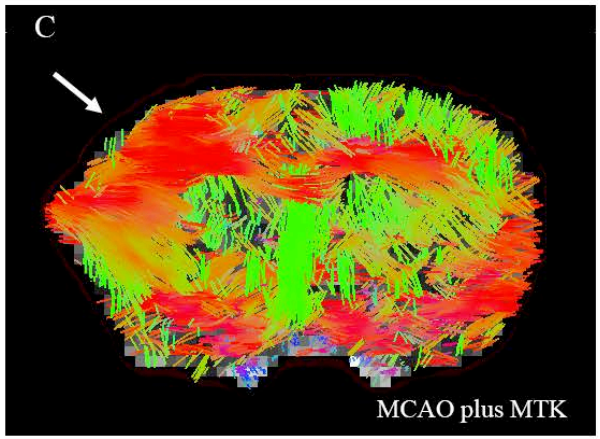
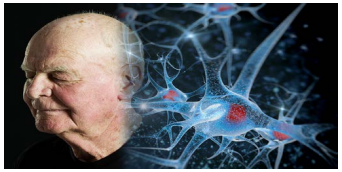


Figure 4. Mtk improves myelin reconstruction in MCAo, as assessed by DWI.

Gelosa P et al., submitted 2016

Adult neurogenic areas: the hippocampal dentate gyrus



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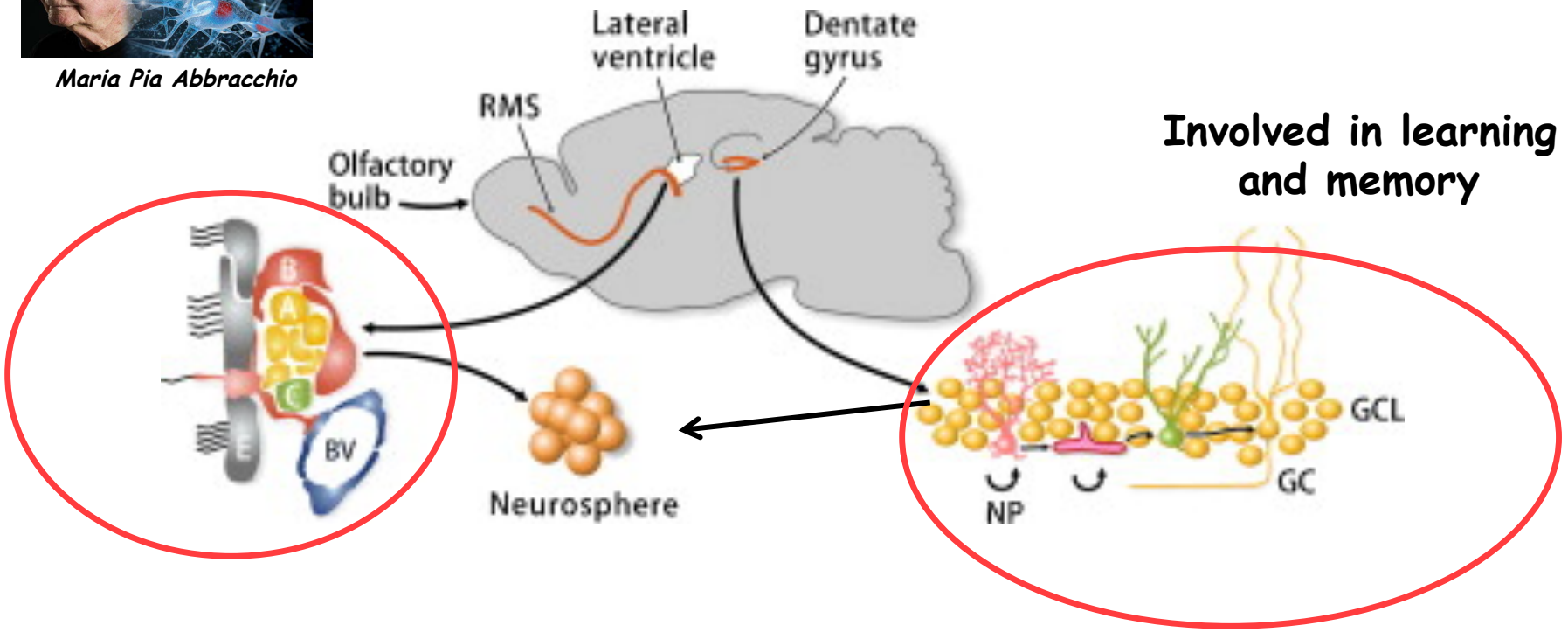
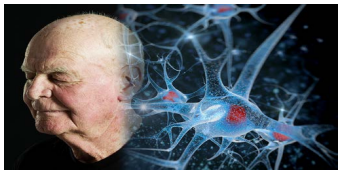


Modified from: Zimmermann, H. Purinergic signaling in neural development
Seminars in Cell & Developmental Biology 2011

Throughout adulthood, memories are consolidated via the formation of new neurons in the hippocampus



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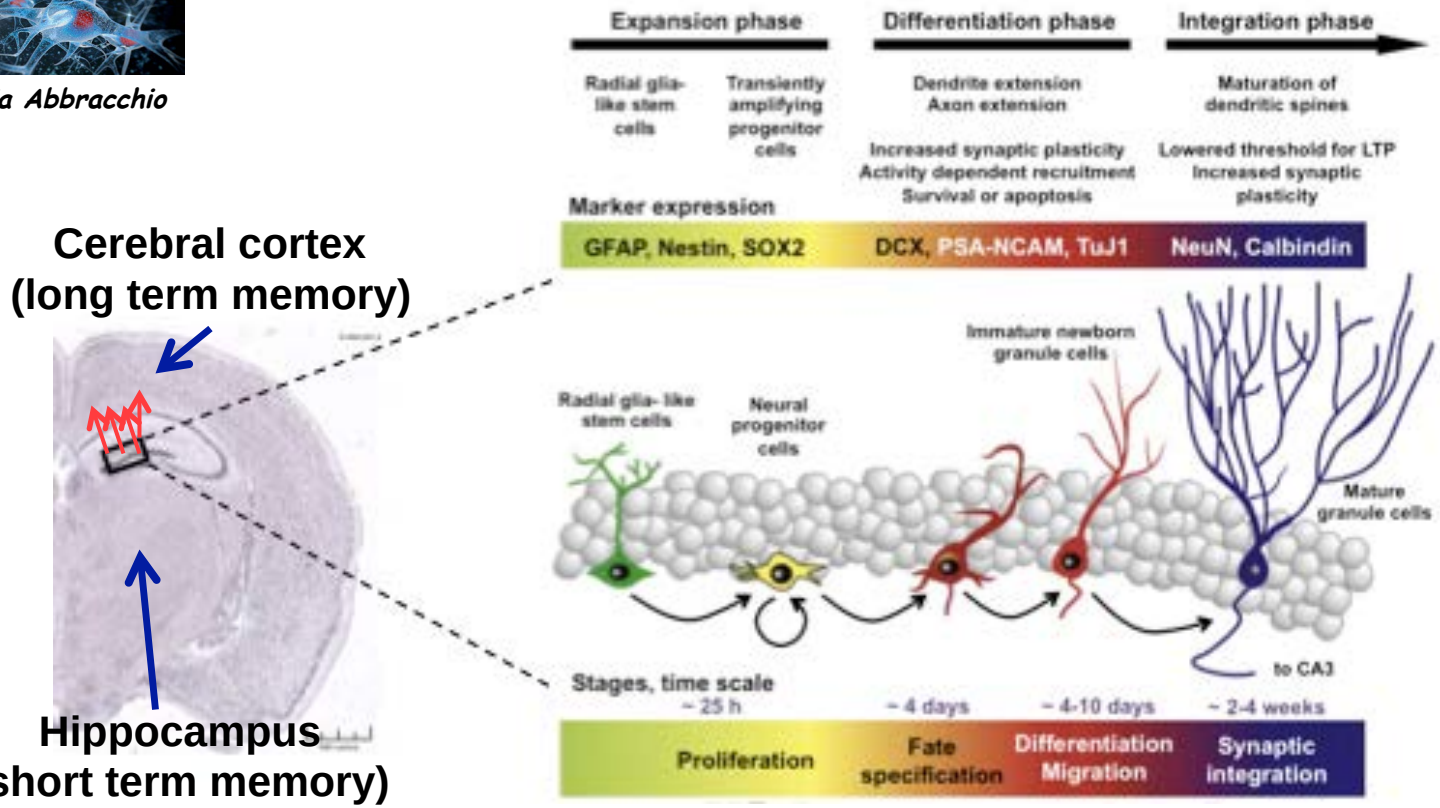
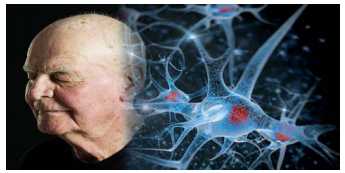


- Involved in normal learning and memory
- Progressively impaired function in aging associated learning decline and in pathological aging (e.g., Alzheimer's disease)
- A target for memory enhancing therapies? and/or in neurodegenerative conditions?



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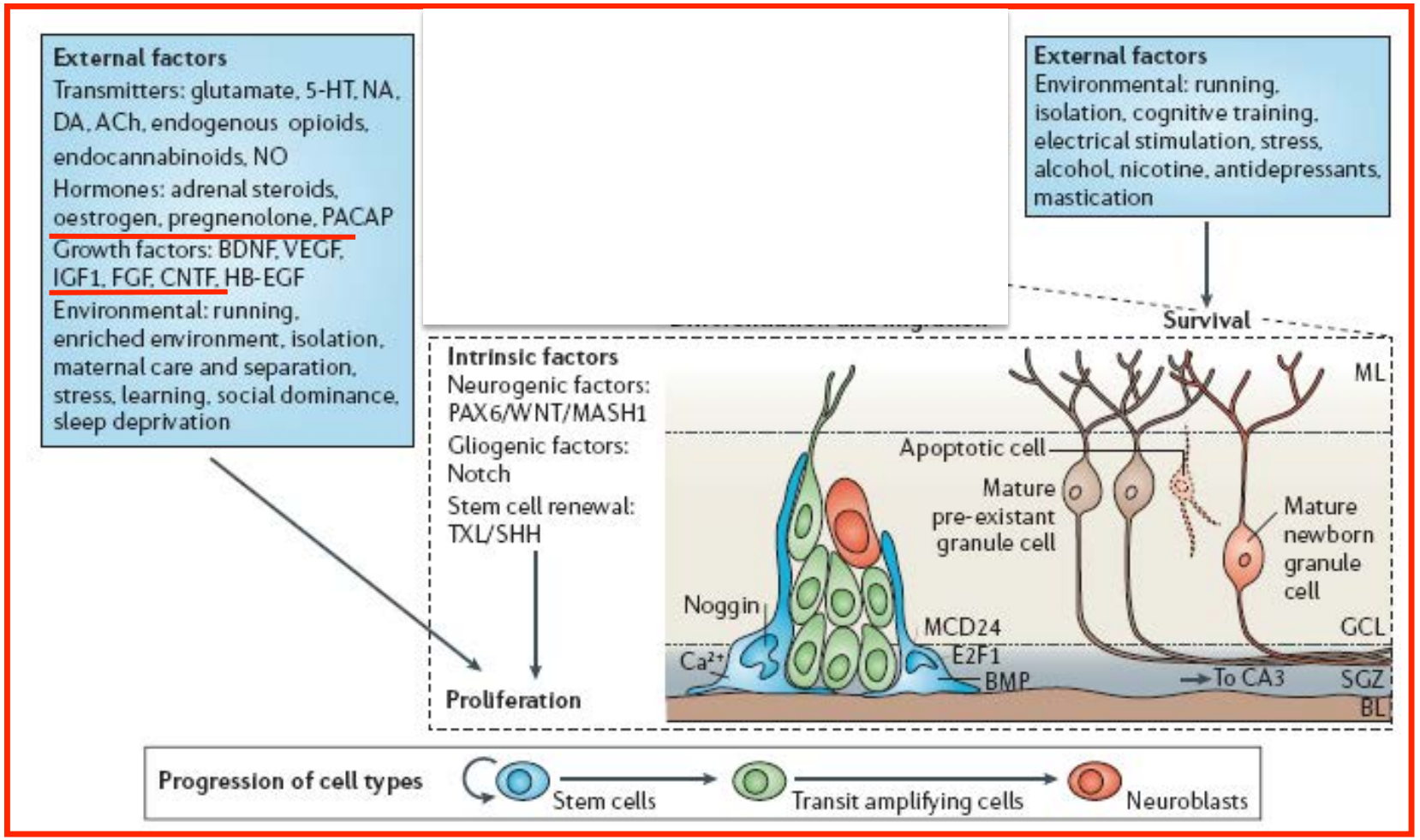
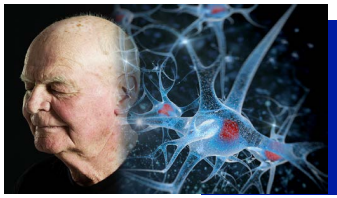
……the formation of these new neurons is greatly stimulated when we learn new things

(Bischofberger et al., Nat Neurosci 10:273-275, 2007)



Lledo et al., Nat Rev Neurosci 7:179-193 (2006)



Aging decreases the number of stem cells in hippocampus

Maria Abbracchio,
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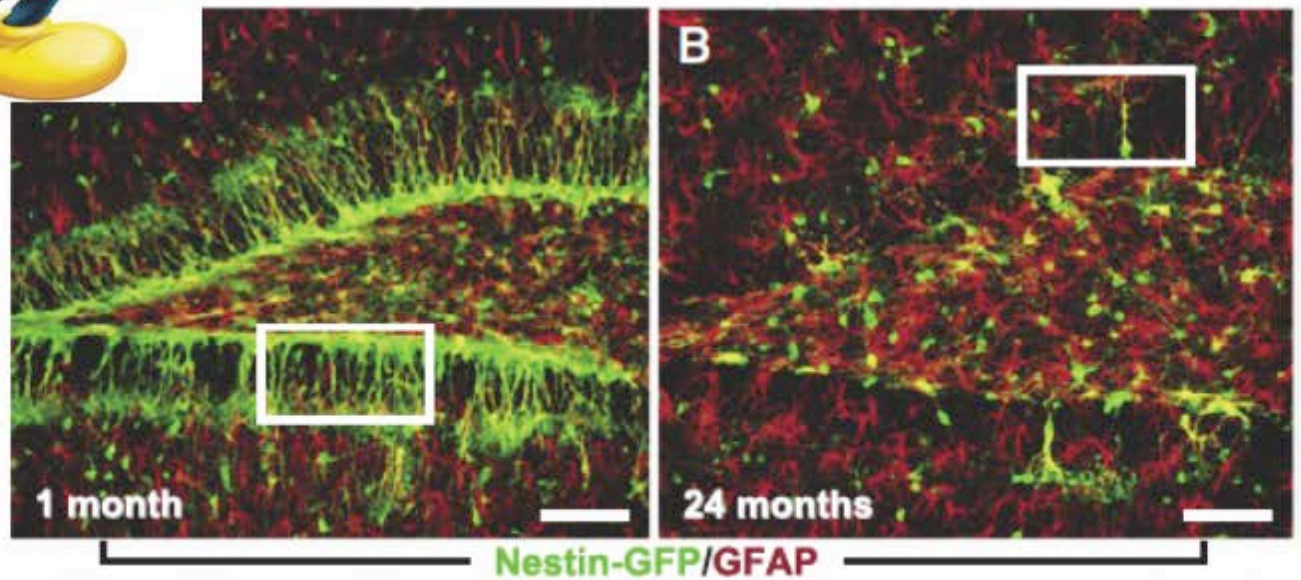
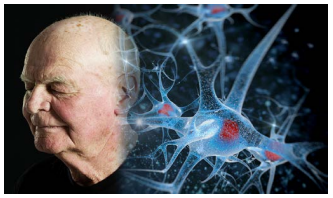


Cell Stem Cell *8*, 566–579, May 6, 2011 ©2011 Elsevier Inc.



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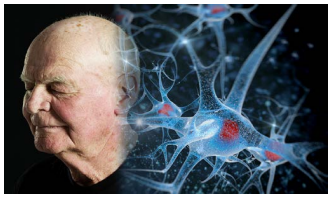
Is there a way to rejuvenate our hippocampus and help our hippocampal stem cells to generate more neurons, in order to restore cognitive functions in aging and neurodegenerative diseases characterized by learning and memory deficits?



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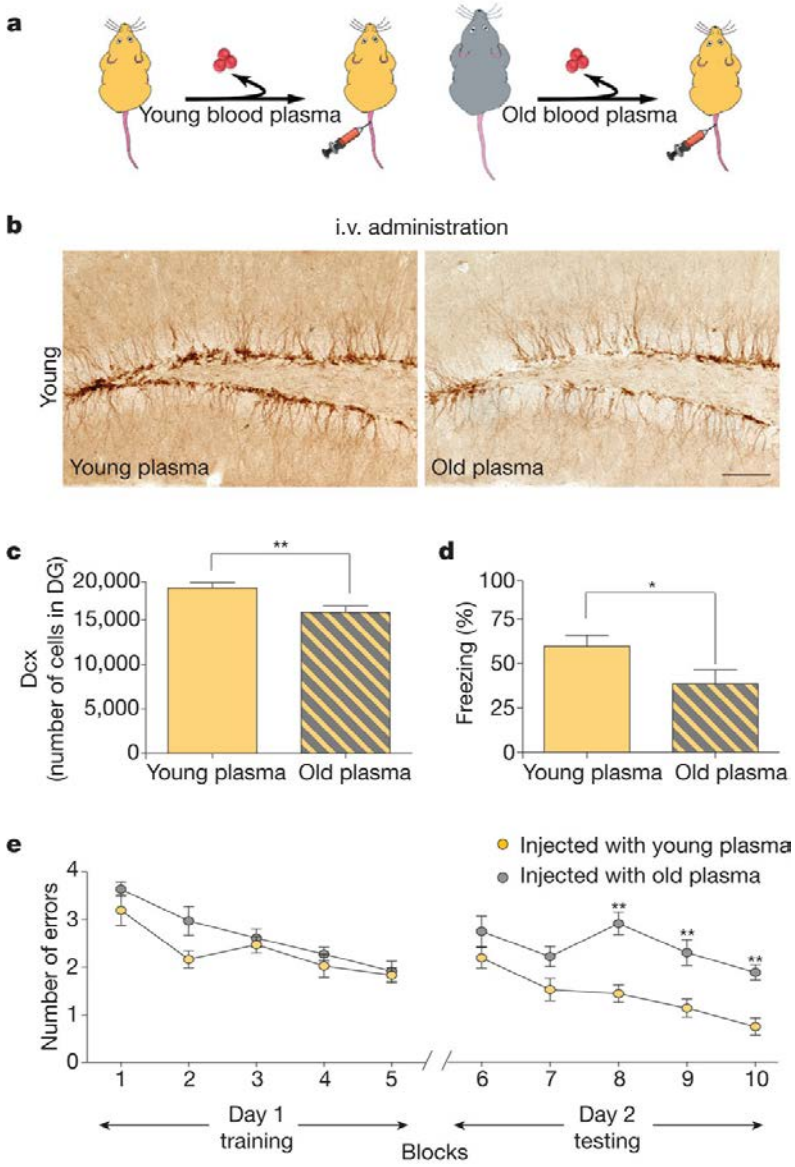
The blood of young individuals contains factors that restore hippocampal neurogenesis, while the blood of old individuals inhibits it!

SA Villeda *et al*. *Nature* 477, 90-94, 2011



….but, is there anyother way?

nature

nature COMMUNICATIONS

Received 9 Dec 2014 | Accepted 24 Aug 2015 | Published 27 Oct 2015

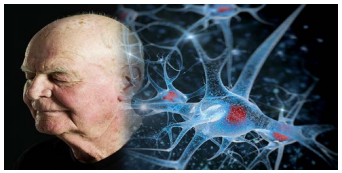
DOI: 10.1038/ncomms9466 OPEN

Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug

Julia Marschallinger[1,2], Iris Schäffner[3], Barbara Klein[1,2], Renate Gelfert[1,2], Francisco J. Rivera[1,2], Sebastian Illes[1,2], Lukas Grassner[1,2,4], Maximilian Janssen[1,2], Peter Rotheneichner[1,2,5], Claudia Schmuckermair[6], Roland Coras[7], Marta Boccazzi[8], Mansoor Chishty[9], Florian B. Lagler[10], Marija Renic[11], Hans-Christian Bauer[2,12], Nicolas Singewald[6], Ingmar Blümcke[7], Ulrich Bogdahn[13], Sebastien Couillard-Despres[2,5], D. Chichung Lie[3], Maria P. Abbracchio[8] & Ludwig Aigner[1,2]

Yes! With drugs!

As human life expectancy has improved rapidly in industrialized societies, age-related cognitive impairment presents an increasing challenge. Targeting histopathological processes that correlate with age-related cognitive declines, such as neuroinflammation, low levels of neurogenesis, disrupted blood–brain barrier and altered neuronal activity, might lead to structural and functional rejuvenation of the aged brain. Here we show that a 6-week treatment of young (4 months) and old (20 months) rats with montelukast, a marketed anti-asthmatic drug antagonizing leukotriene receptors, reduces neuroinflammation, elevates hippocampal neurogenesis and improves learning and memory in old animals. By using gene knockdown and knockout approaches, we demonstrate that the effect is mediated through inhibition of the GPR17 receptor. This work illustrates that inhibition of leukotriene receptor signalling might represent a safe and druggable target to restore cognitive functions in old individuals and paves the way for future clinical translation of leukotriene receptor inhibition for the treatment of dementias.



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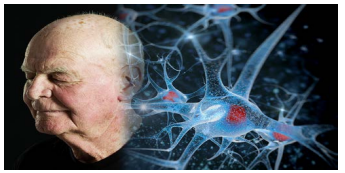
The P2Y-like GPR17 receptor is expressed in small subsets of cells of the hippocampal dentate gyrus



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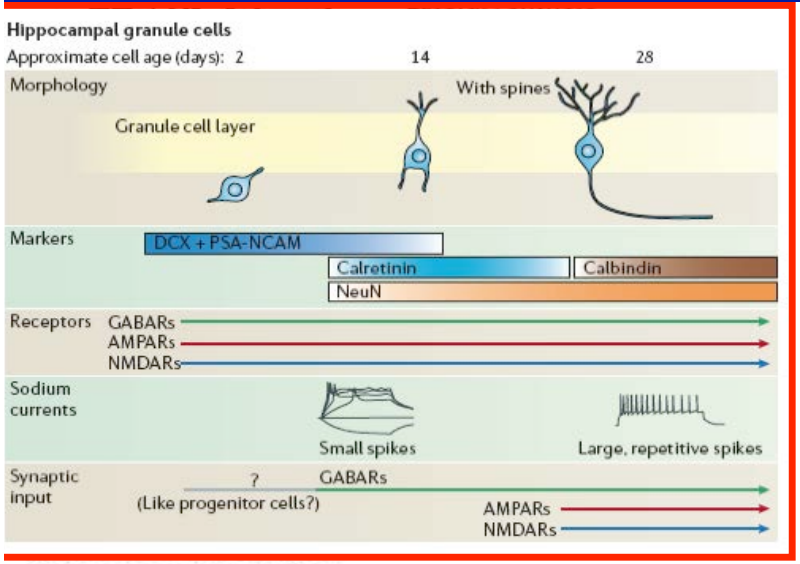
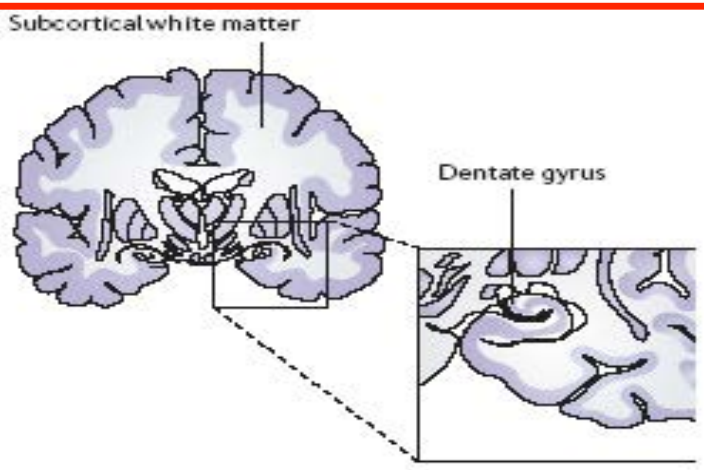
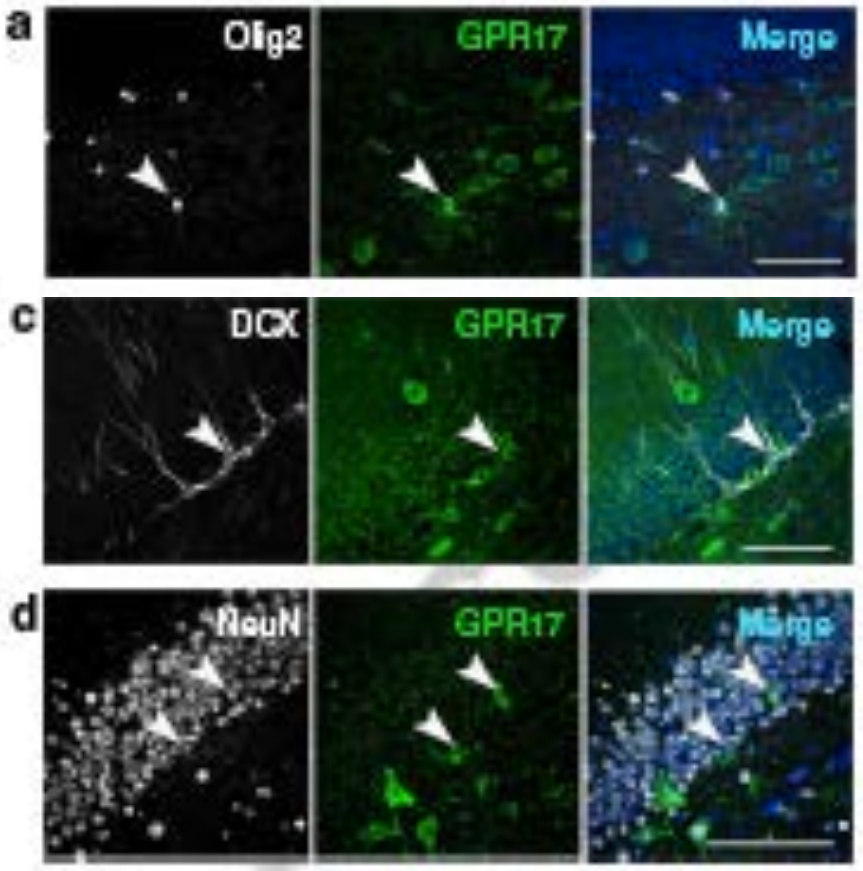
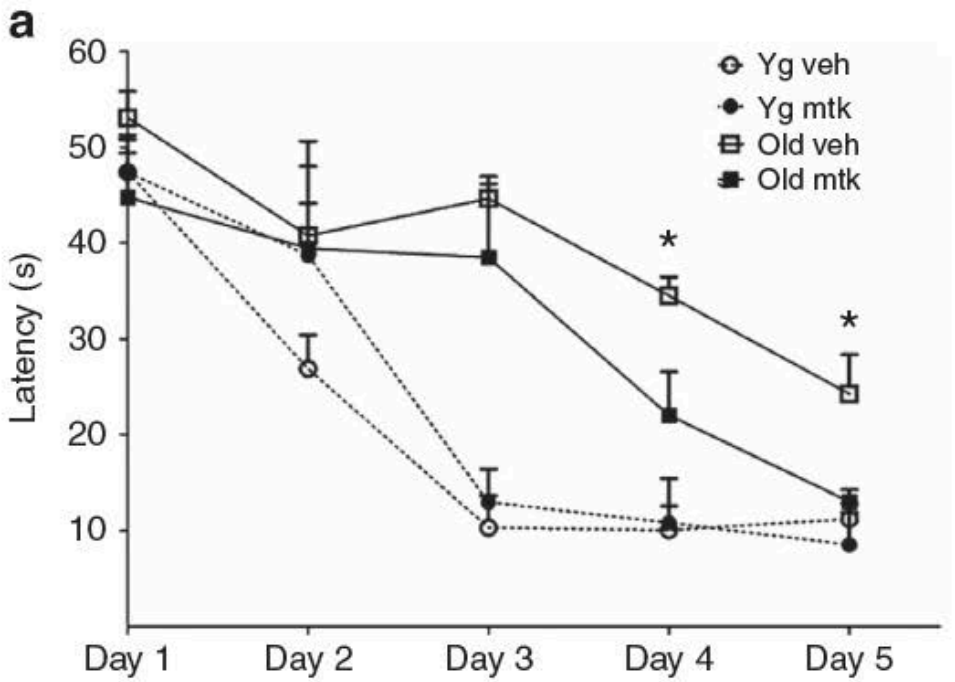


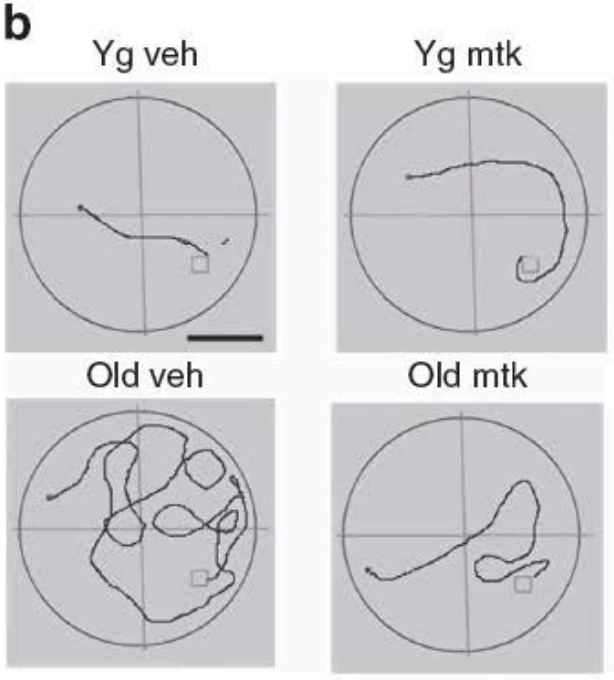


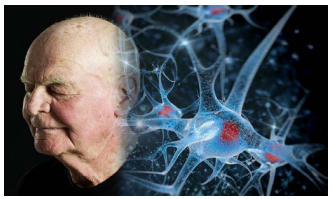


Marschallinger J et al., Nature Communications, 2015

Treatment of old rats with montelukast, a GPR17 antagonist, alleviates aging-associated learning and memory deficits





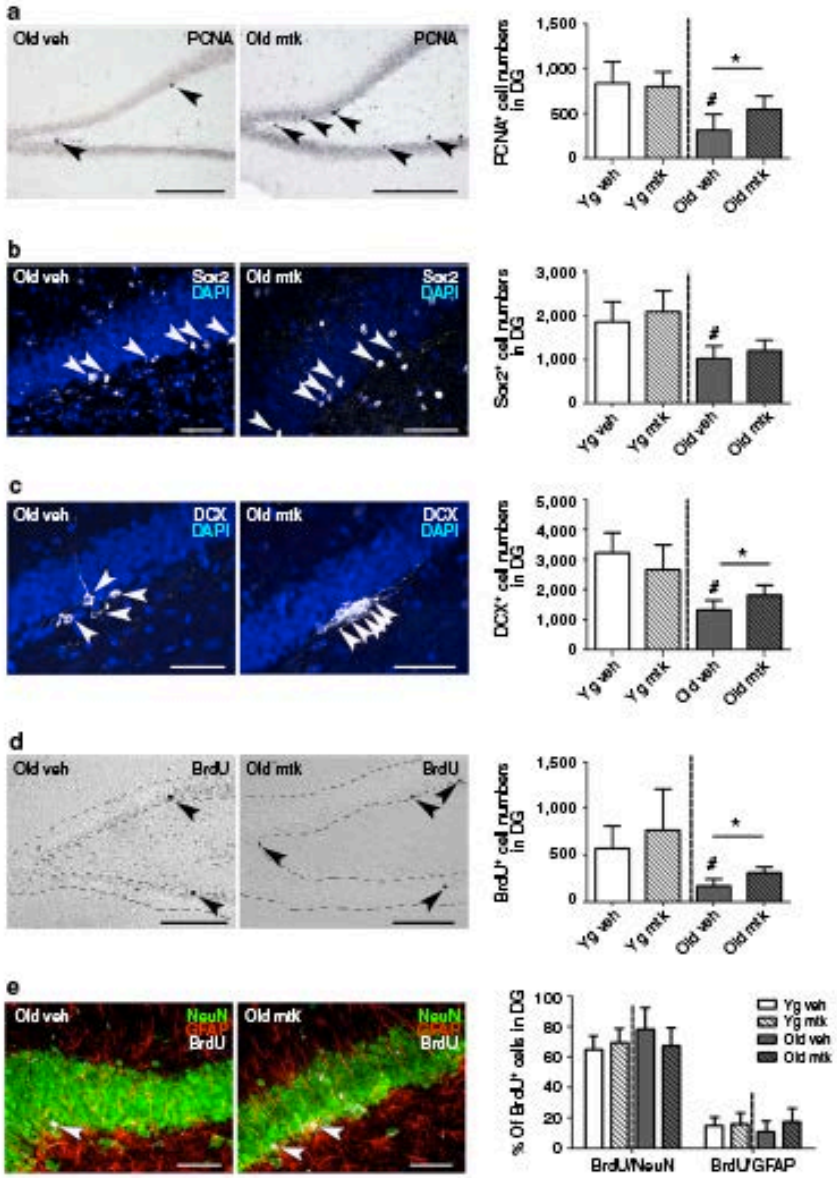


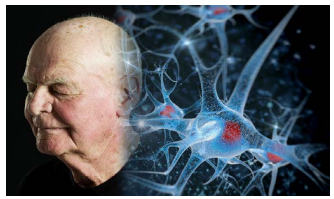
Maria Abbracchio,
La Real Academia Nacional de Farmacia, 2016

Marschallinger J et al., Nature Communications, 2015

Montelukast treatment increases dentate gyrus neurogenesis in the aged brain

ARTICLE NATURE COMMUNICATIONS | DOI: 10.1038/ncomms9466





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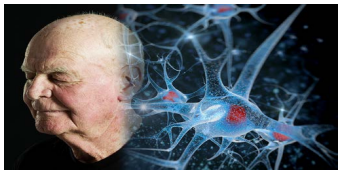
CONCLUSIONS



Maria Pia Abbracchio

"We know rejuvenation exists. Now we have to figure out the bare minimum of therapeutics or genetic tinkering necessary for it to be safely translated into a human."

Saul Villeda, PhD

E' possibile far regredire una cellula somatica ad una cellula staminale pluripotente?

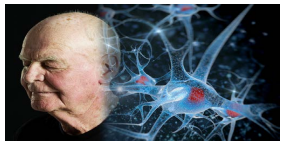
Cell *126*, 663–676, August 25, 2006

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]

Shinya Yamanaka

Strategia della
RIPROGRAMMAZIONE
molecolare



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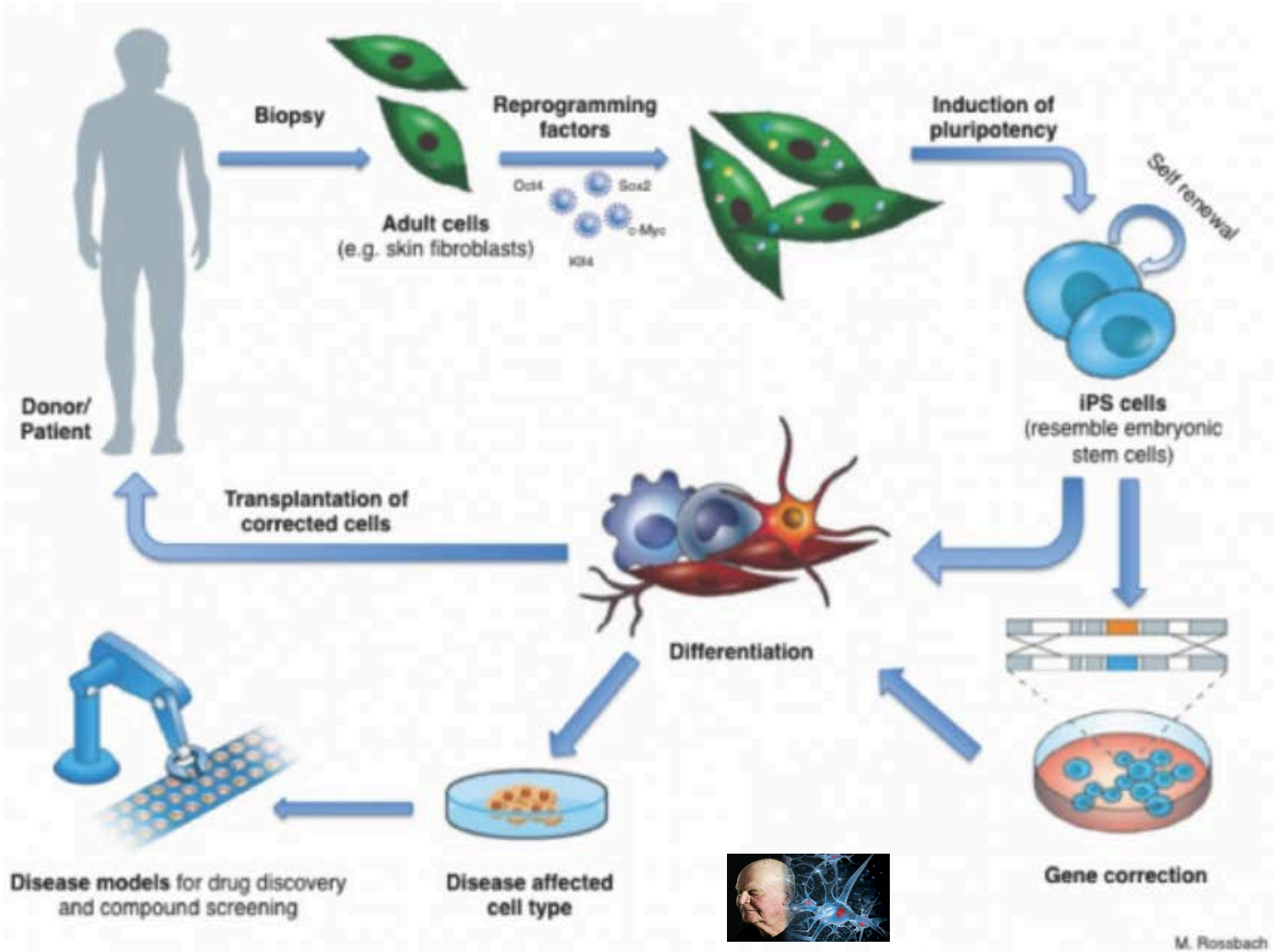
induced Pluripotent Stem Cells (iPS)



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TRANSLATIONAL AND CLINICAL RESEARCH

Neuronal Properties, In Vivo Effects, and Pathology of a Huntington's Disease Patient-Derived Induced Pluripotent Stem Cells

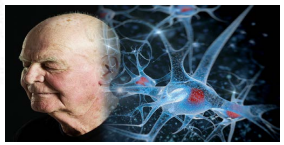
IKSOO JEON,[a] NAYEON LEE,[a] JIA-YI LI,[b,c] IN-HYUN PARK,[d,e] KYOUNG SUN PARK,[f] JISOOK MOON,[a] SUNG HAN SHIM,[a] CHUNGGAB CHOI,[a] DA-JEONG CHANG,[a] JIHYE KWON,[a] SEUNG-HUN OH,[a] DONG AH SHIN,[g] HYUN SOOK KIM,[a] JEONG TAE DO,[a] DONG RYUL LEE,[a] MANHO KIM,[h] KYUNG-SUN KANG,[i] GEORGE Q. DALEY,[d] PATRIK BRUNDIN,[b,j] JIHWAN SONG[a]

[a]CHA Stem Cell Institute, CHA University, Seoul, Korea; [b]Neuronal Survival Unit, and [c]Neural Plasticity and Repair Unit, Wallenberg Neuroscience Center, Lund University, Lund, Sweden; [d]Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, USA; [e]Department of Genetics, Yale University School of Medicine, New Haven, USA; [f]Division of Integrative Bioscience and Biotechnology, Pohang University of Science and Technology, Pohang, Korea; [i]Adult Stem Cell Research Center, College of Veterinary Medicine, Seoul National University, Seoul, Korea; [j]Department of Neurosurgery, Yonsei University College of Medicine, Seoul, Korea; [h]Department of Neurology, Seoul National University, College of Medicine; [g]Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, USA

Key Words. Huntington's disease • Induced pluripotent stem cells • GABAergic neurons • Quinolinic acid • Behavioral recovery • Aggregate formation

ABSTRACT

Induced pluripotent stem cells (iPSCs) generated from somatic cells of patients can be used to model different human diseases. They may also serve as sources of transplantable cells that can be used in novel cell therapies. Here, we analyzed neuronal properties of an iPSC line derived from a patient with a juvenile form of Huntington's disease (HD) carrying 72 CAG repeats (HD-iPSC). Although its initial neural inducing activity was lower than that of human embryonic stem cells, we found that HD-iPSC can give rise to GABAergic striatal neurons, the neuronal cell type that is most susceptible to degeneration in HD. We then transplanted HD-iPSC-derived neural precursors into a rat model of HD with a unilateral excitotoxic striatal lesion and observed a significant behavioral recovery in the grafted rats. Interestingly, during our in vitro culture and when the grafts were examined at 12 weeks after transplantation, no aggregate formation was detected. However, when the culture was treated with a proteasome inhibitor (MG132) or when the cells engrafted into neonatal brains were analyzed at 33 weeks, there were clear signs of HD pathology. Taken together, these results indicate that, although HD-iPSC carrying 72 CAG repeats can form GABAergic neurons and give rise to functional effects in vivo, without showing an overt HD phenotype, it is highly susceptible to proteasome inhibition and develops HD pathology at later stages of transplantation. These unique features of HD-iPSC will serve as useful tools to study HD pathology and develop novel therapeutics. Stem Cells *2012;30:2054–2062*



Laboratory of Cellular and Molecular Pharmacology of Purinergic Transmission

Dept Pharmacological and Biomolecular Sciences
University of Milan, Italy

Maria P. Abbracchio, *Professor and Lab Head*
Stefania Ceruti, *Assistant Professor*
Marta Fumagalli, *Assistant Professor*
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Giusy Coppolino, *PhD student*
Davide Marangon, *PhD student*
Giulia Magni, *Research Fellow*

Our patents:

US 2009156521, EP 1807701, IT/MI2010A002037, PCT/IB20 11/054865, E0084789 RD 2012 04 24

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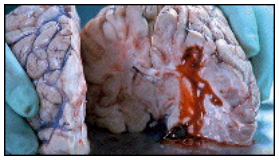

News
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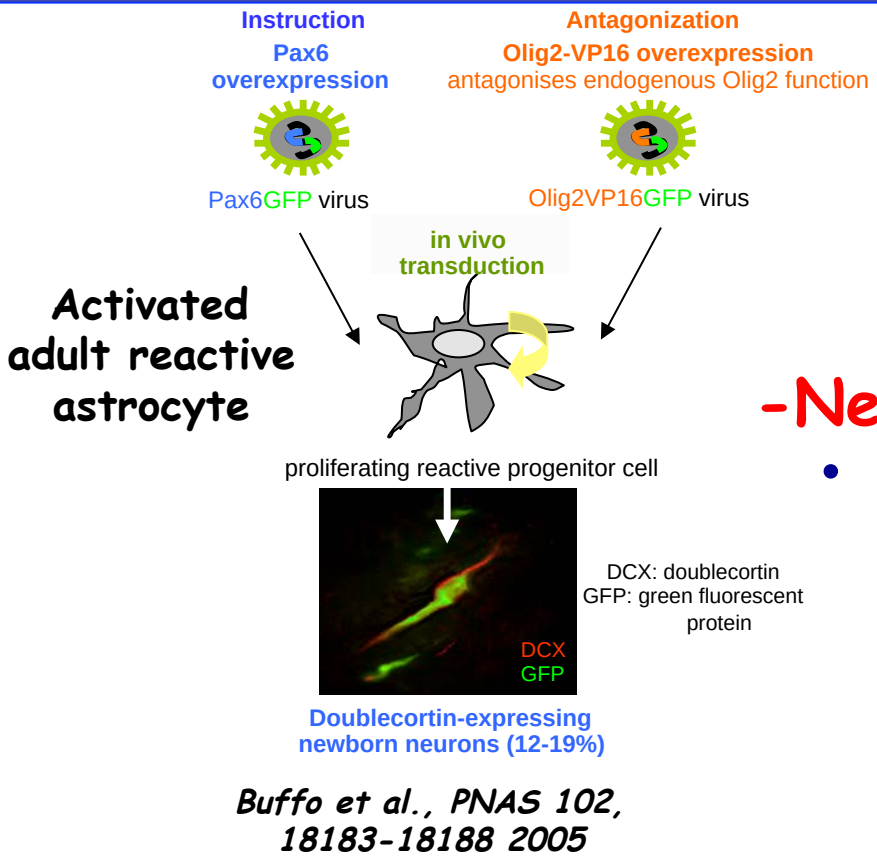
Reactive astrocytes as a source of new cells to regenerate the brain

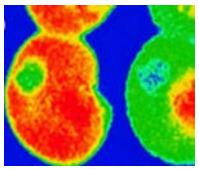


Buffo et al., PNAS 102, 18183-18188 2005

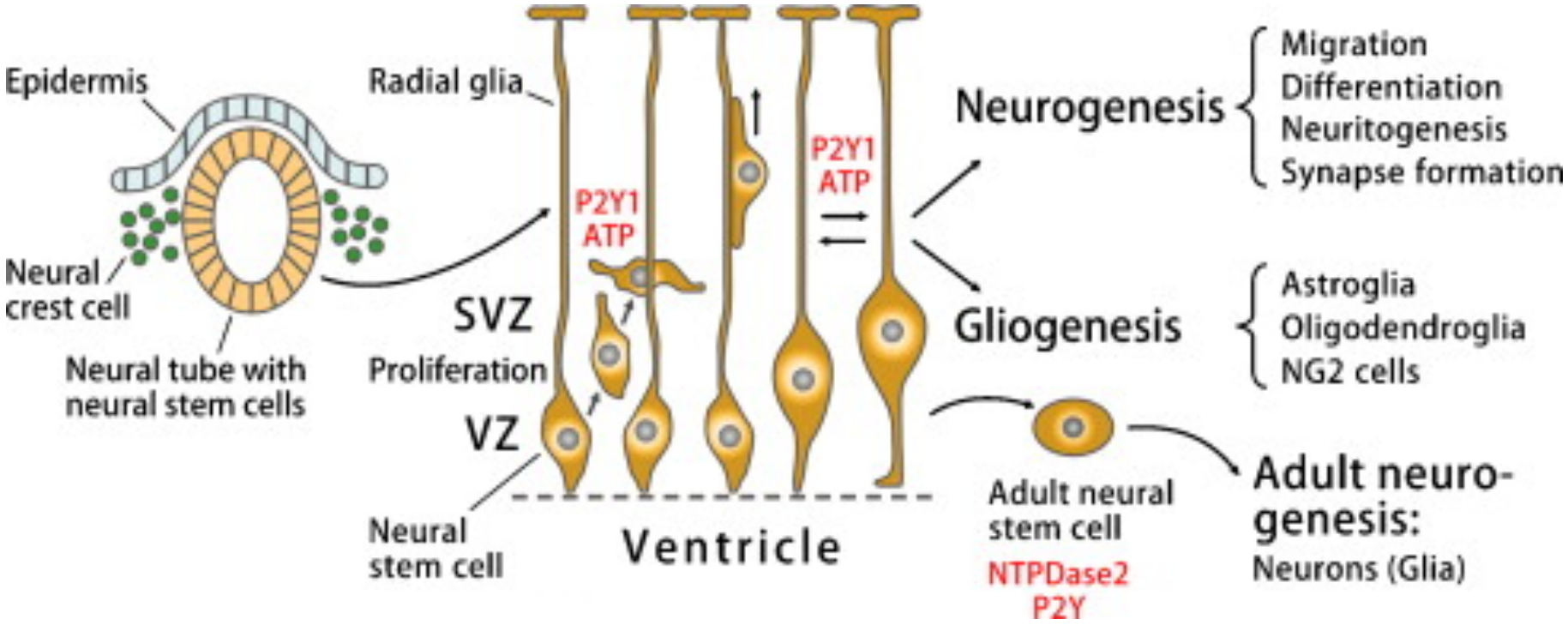
-Need for epigenetic reprogramming

- Transduction of neuronal/glial genes
- Growth factors, chondroitinase, riluzole, purinergic agents, etc.

-Need to favorably "condition" the extracellular milieu to foster NCS repairing abilities



Purinergic signalling plays a key role from the very beginning of life



From: Zimmermann, H. Purinergic signaling in neural development
Seminars in Cell & Developmental Biology 2011