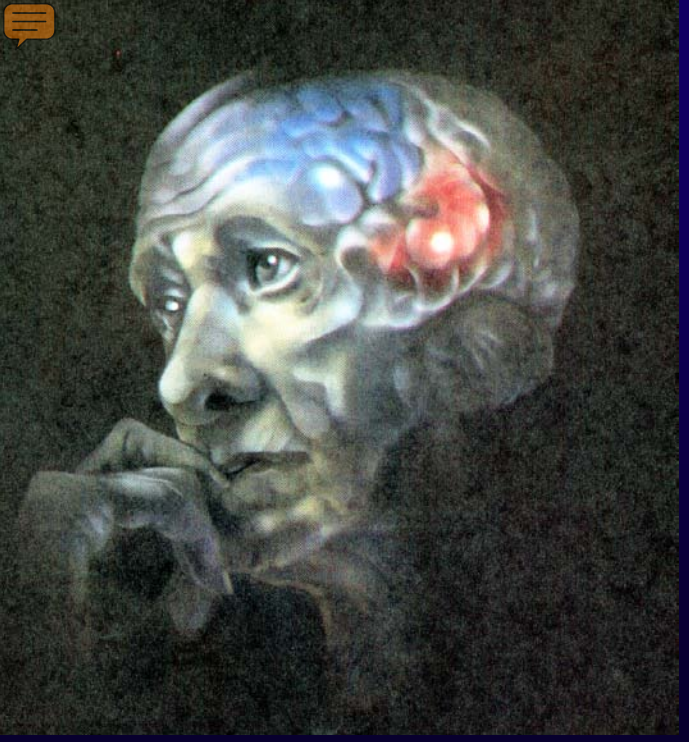


How is the brain influenced by radiation?

Amelia J. Eisch, Ph.D.
Department of Psychiatry, UT Southwestern
October 3, 2009

Bad news:
Radiation inhibits brain structure, function

- Overt cell loss
- Decreased learning and memory
- Decreased motor functioning
- Imaging abnormalities

- Clinical implications:
  - Better treatment for cancer results in deficits later in life
  - Enhanced susceptibility to neurodegenerative and neuropsychiatric disorders?

Radiation can decrease hippocampal function

Morris Water Maze

Test spatial memory

Craig Powell

Bad news:
Radiation inhibits brain structure, function

- Overt cell loss
- Decreased learning and memory
- Decreased motor functioning
- Imaging abnormalities

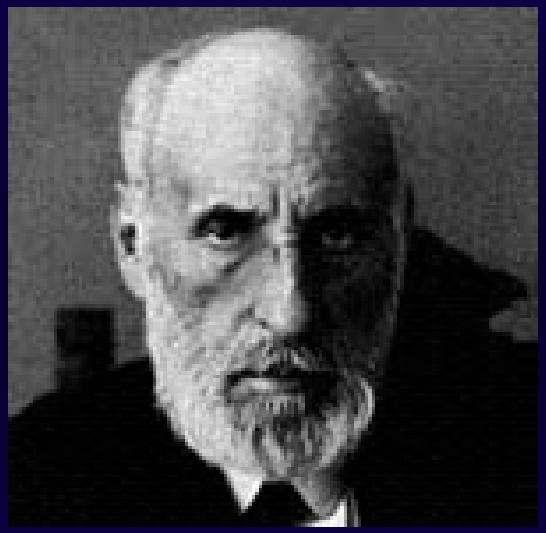
- Clinical implications:
  - Better treatment for cancer results in deficits later in life
  - Enhanced susceptibility to neurodegenerative and neuropsychiatric disorders?

Any good news?

- Can we prevent the damage?
  - \+ Shielding from space radiation
  - \- Missions will be long

- Can we diminish or repair the damage?
  - \+ Brain is remarkably resilient or “neuroplastic”
  - \+ Might be able to rebound from limited radiation exposure

  - \- What about extended radiation exposure?
  - \- Is there a non-invasive way to diminish or repair damage?

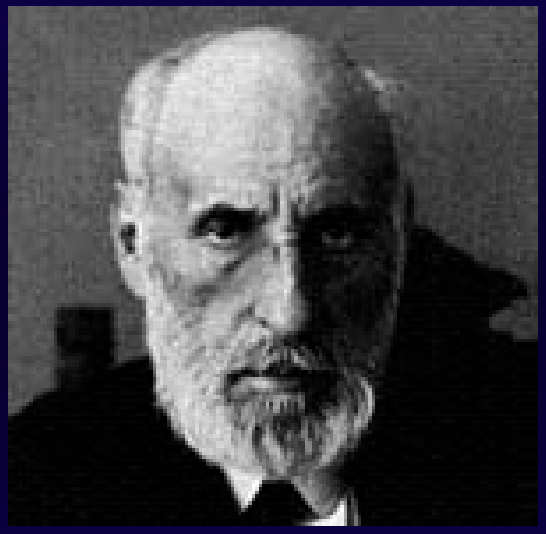


Santiago Ramon y Cajal

“…nerve paths are something fixed, ended, immutable.

Everything may die, nothing may be regenerated.”

The adult mammalian brain gives rise to new cells with neurogenic potential



Santiago Ramon y Cajal

- **Rat**
  - Altman & Das (*Nature* 1965)
  - Kaplan & Hinds (*Science* 1977)
- **Primate**
  - Gould et al. (*PNAS* 1998)
  - Kornack and Rakic (*PNAS* 1999)
- **Human**
  - Eriksson et al. (*Nat Med* 1998)

To harness adult neurogenesis for regenerative medicine, we have to understand it

EDITORIAL

nature medicine
VOLUME 4 • NUMBER 11 • NOVEMBER 1998

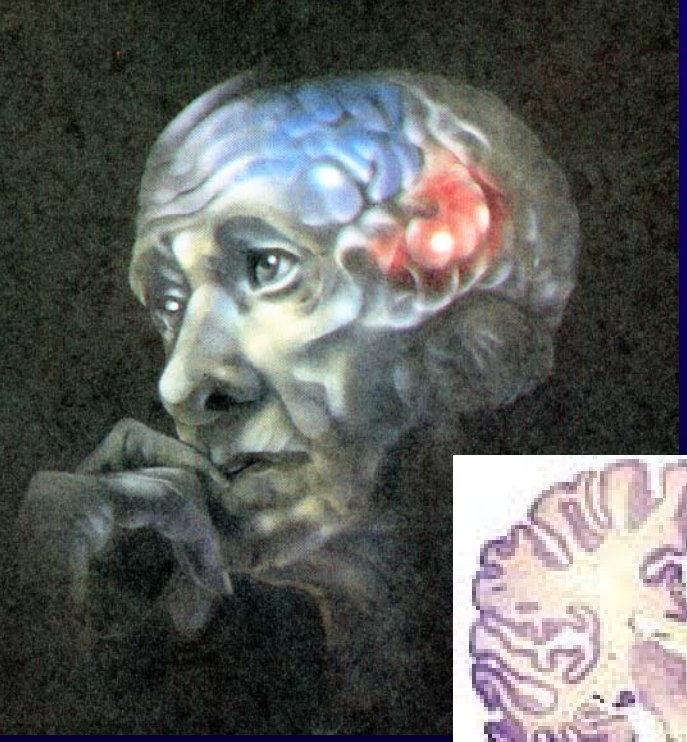
Take comfort in human neurogenesis

1999)

- **Human**
  - Eriksson et al. (*Nat Med* 1998)

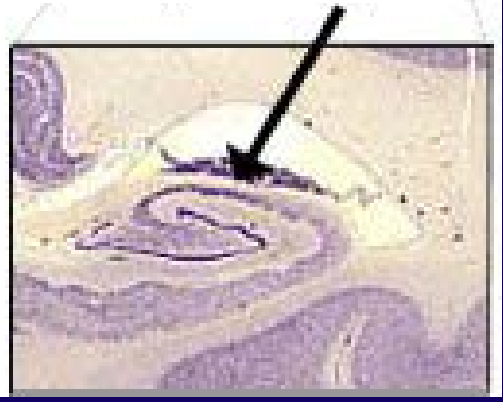
Adult neurogenesis = repair the injured brain, spinal cord?

- Regenerative medicine
  - Alzheimer's disease
  - Parkinson's disease
  - Spinal injuries

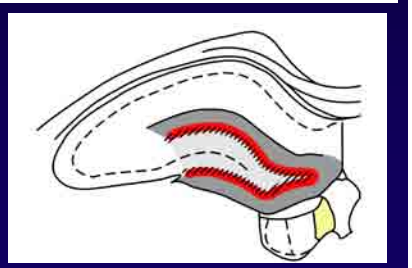


Adult neurogenesis = insight to memory?

Hippocampus



Subgranular zone (SGZ)



- **Regenerative medicine**
  - Alzheimer's disease
  - Parkinson's disease
  - Spinal injuries
- **Normal brain function**
  - Understanding memory

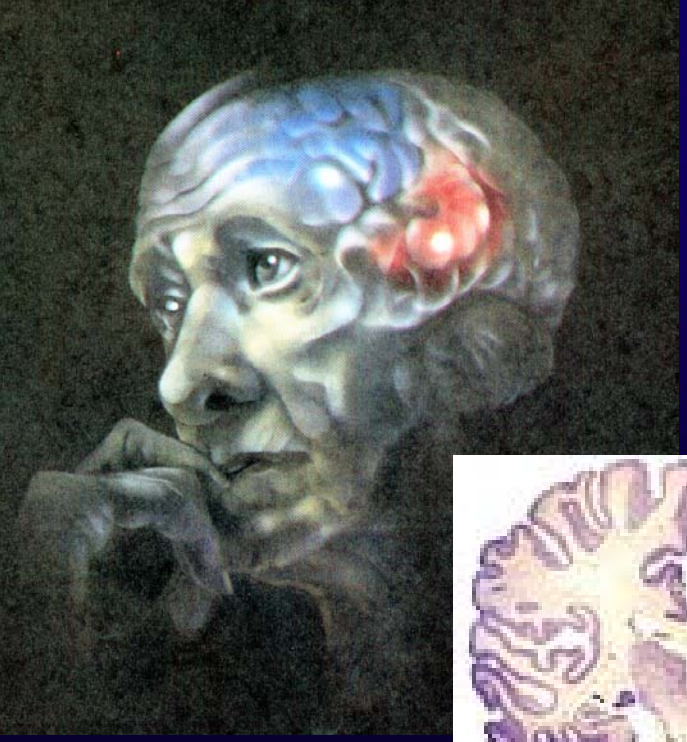
Radiation can decrease and spatial learning can increase hippocampal function, neurogenesis

Morris Water Maze

Test spatial memory

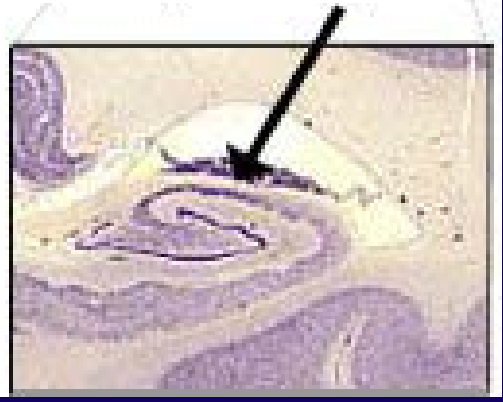
Correlative or causative?

Craig Powell

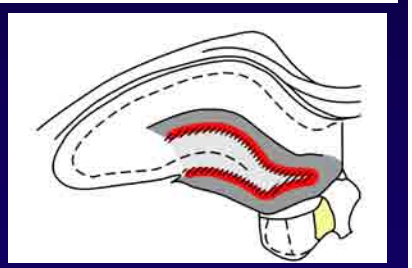


Adult neurogenesis = insight to mental illness?

Hippocampus



Subgranular zone (SGZ)



- **Regenerative medicine**
  - Alzheimer's disease
  - Parkinson's disease
  - Spinal injuries
- **Normal brain function**
  - Understanding memory
- **Neuropsychiatric disorders**
  - Depression, addiction, stress

Radiation and addiction both decrease adult hippocampal function, neurogenesis

Animal model of addiction: i.v. drug self-administration

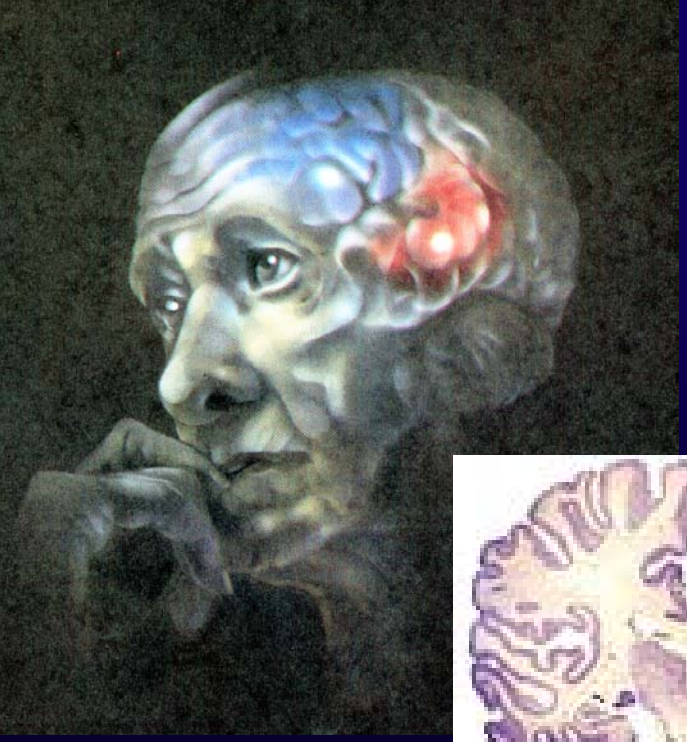
Drug-context associations

Active vs. inactive lever press

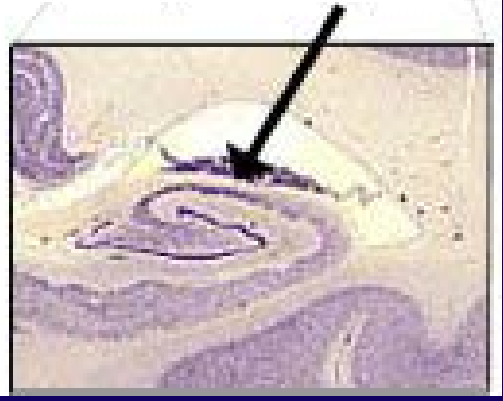
Compulsive drug taking

Intravenous cocaine
3 hr into 4 hr session
Back mount for i.v. catheter entry
Head mount for i.c.v. cannula

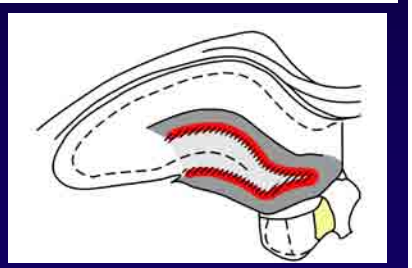
Diana Simmons



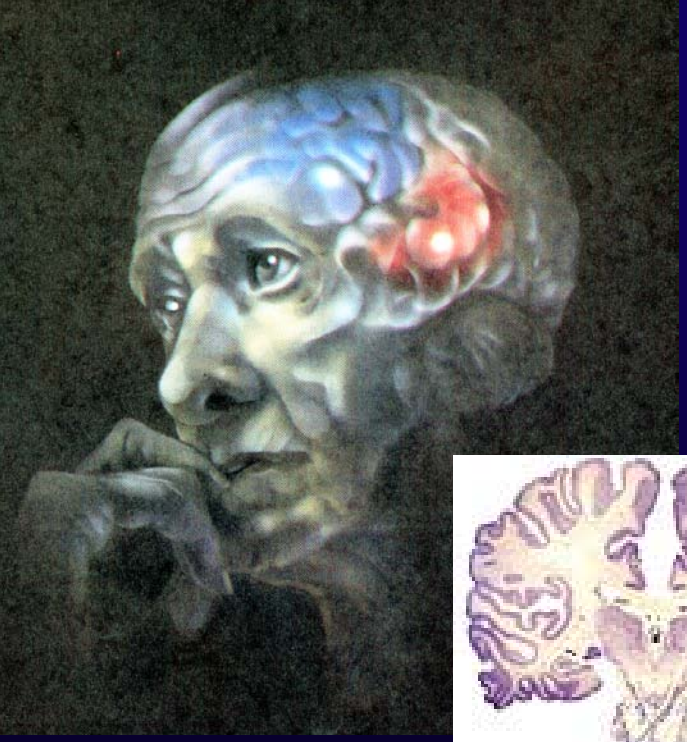
Hippocampus



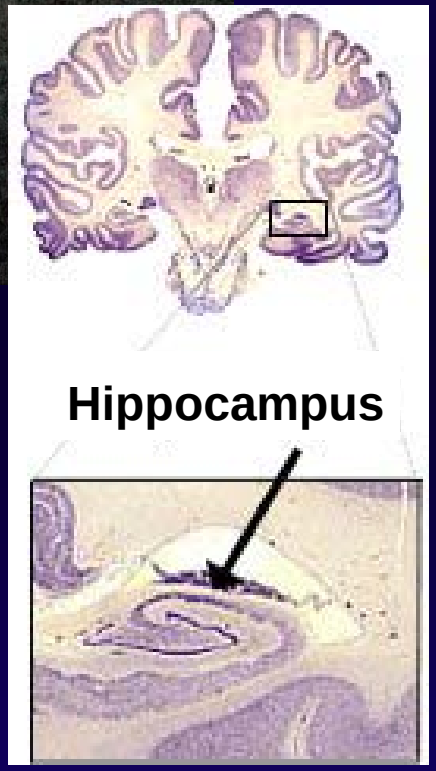
Subgranular zone (SGZ)

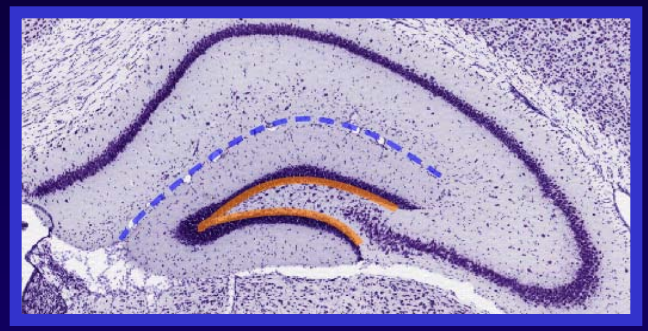


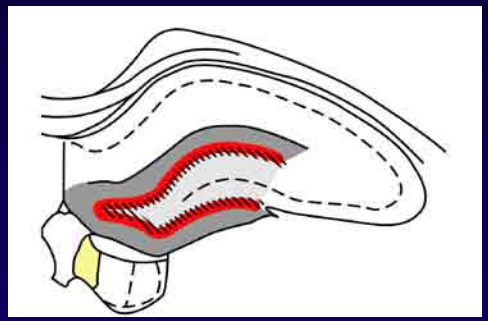
If we understand adult neurogenesis, we are better prepared to understand (and maybe repair or prevent) radiation-induced brain changes.



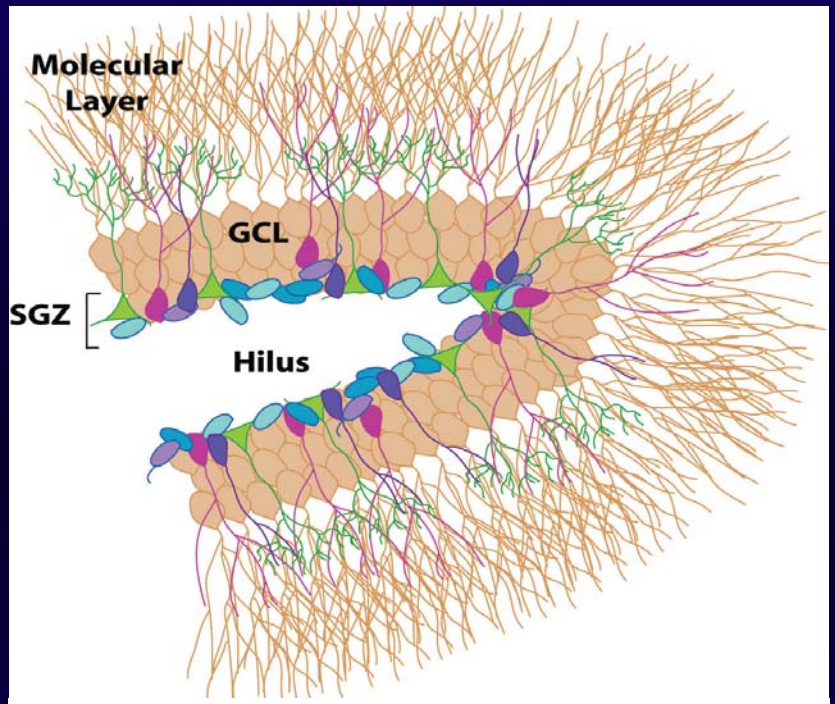
Subgranular zone (SGZ) of the hippocampus is one of two sites of adult neurogenesis

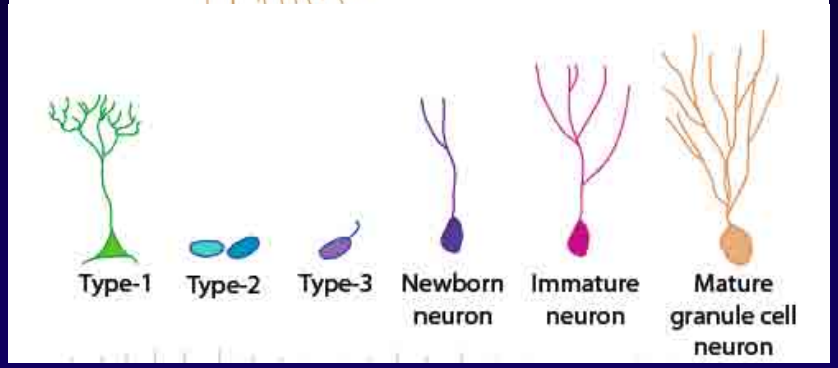


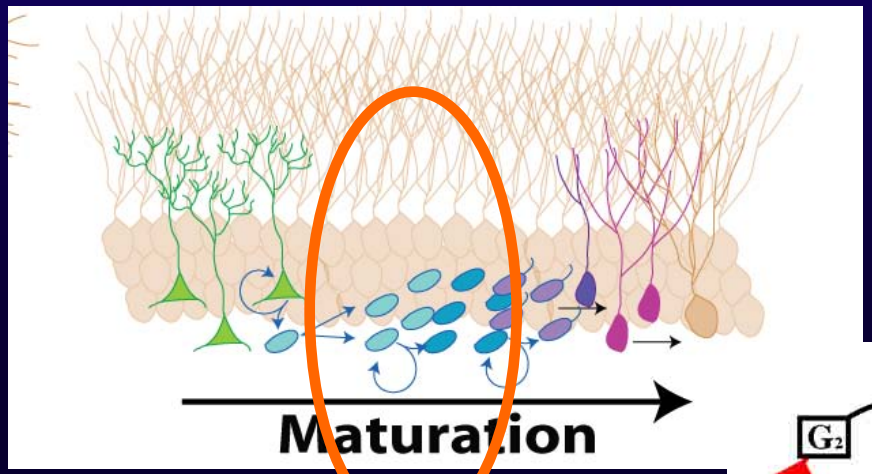


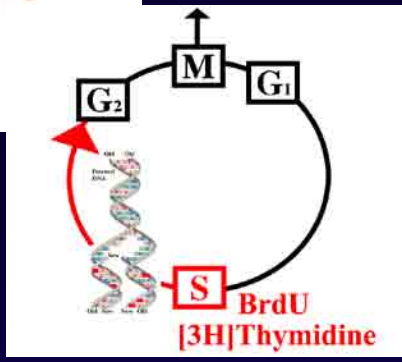


BrdU labels actively dividing SGZ cells

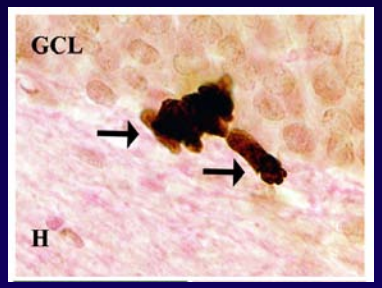




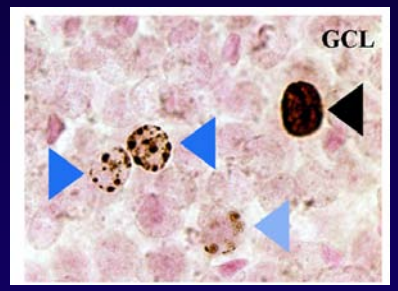




BrdU



Proliferation

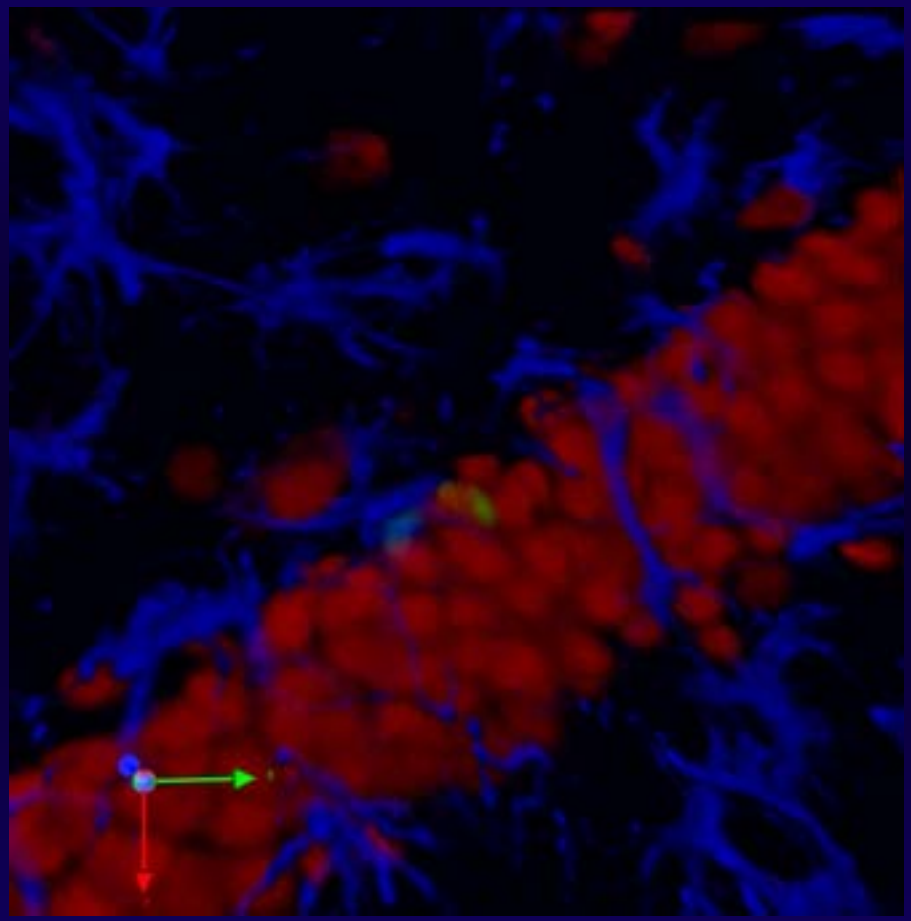


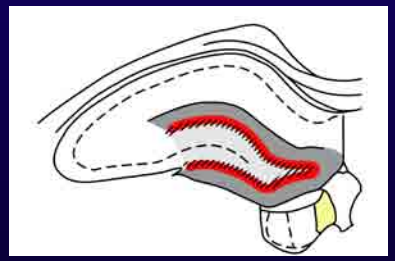
Survival

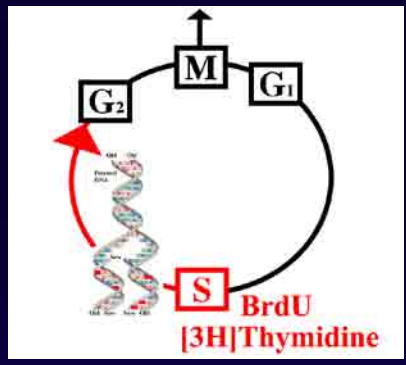
Eisch et al., J Neurosci, 2008

Visualization of adult hippocampal neurogenesis

Critical for allowing assessment of irradiation on SGZ neurogenesis *in vivo*



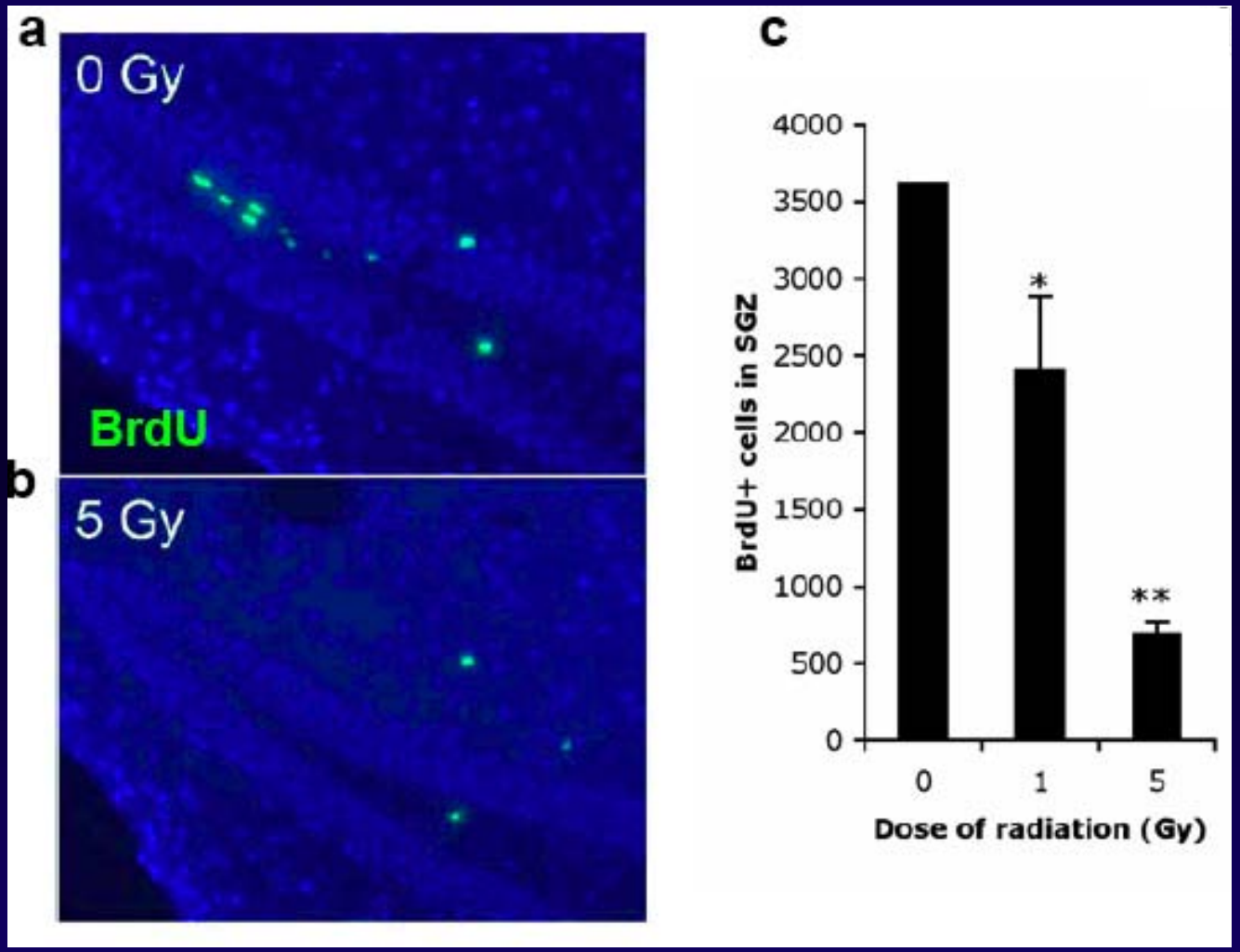




BrdU (labeled 4 weeks earlier)
NeuN (neuron)
GFAP (astrocyte)

Michael Donovan

X-irradiation decreases BrdU+ cells (SGZ proliferation)

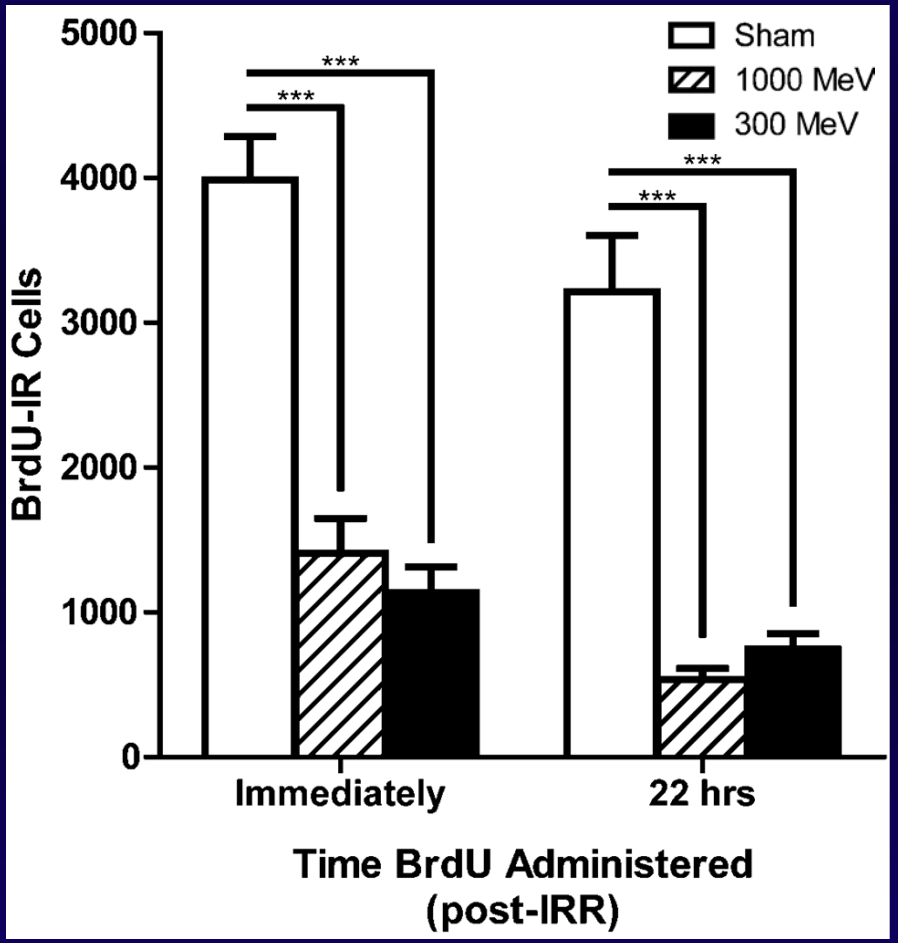


48h after exposure, 8-10 weeks of age at IR

What about space radiation?

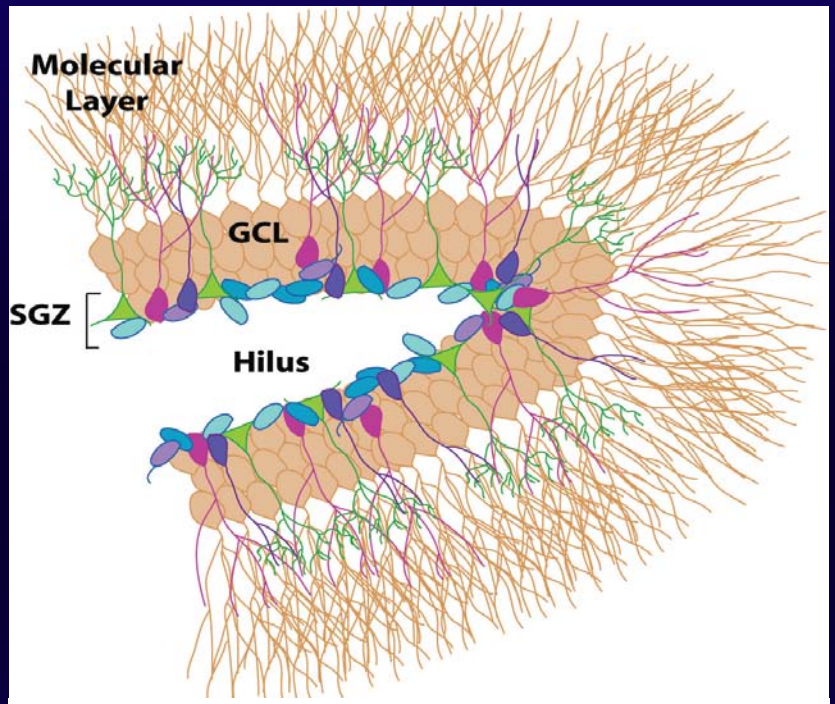
Nathan DeCarolis

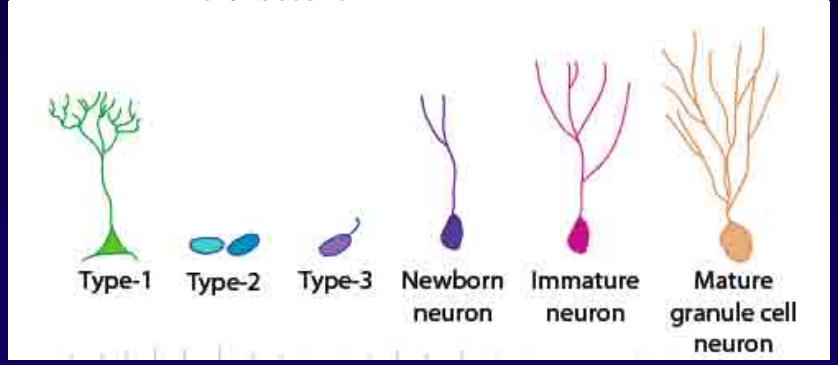
^{56}Fe particle irradiation (space radiation) decreases BrdU+ cells (SGZ proliferation)

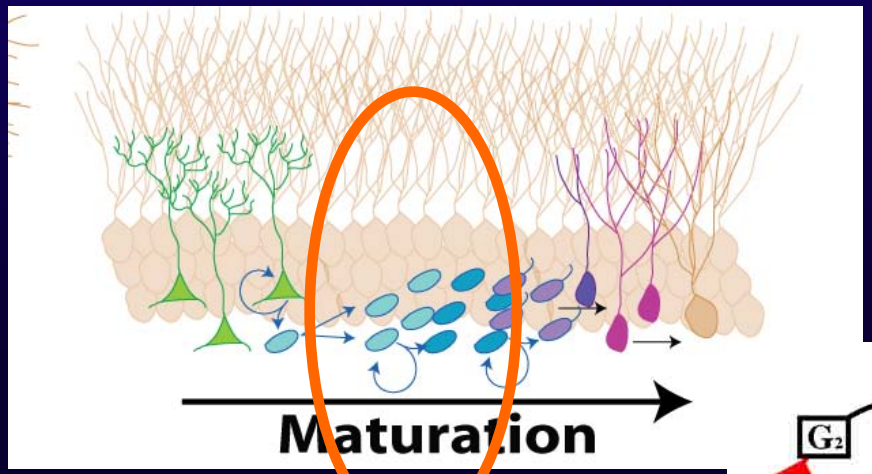


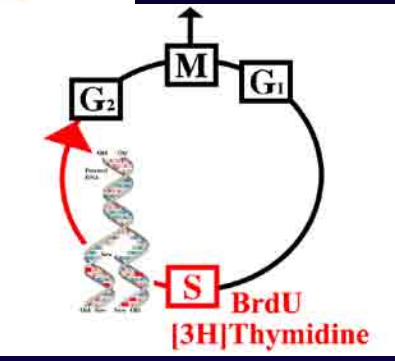
Nathan DeCarolis

To really measure the process of hippocampal neurogenesis, we need to move “beyond BrdU”

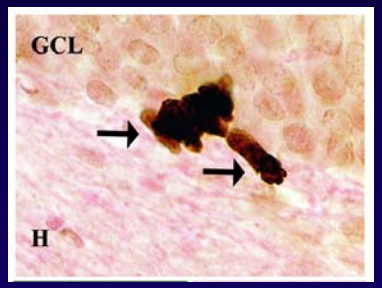








BrdU



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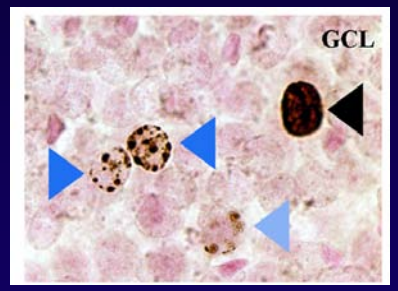
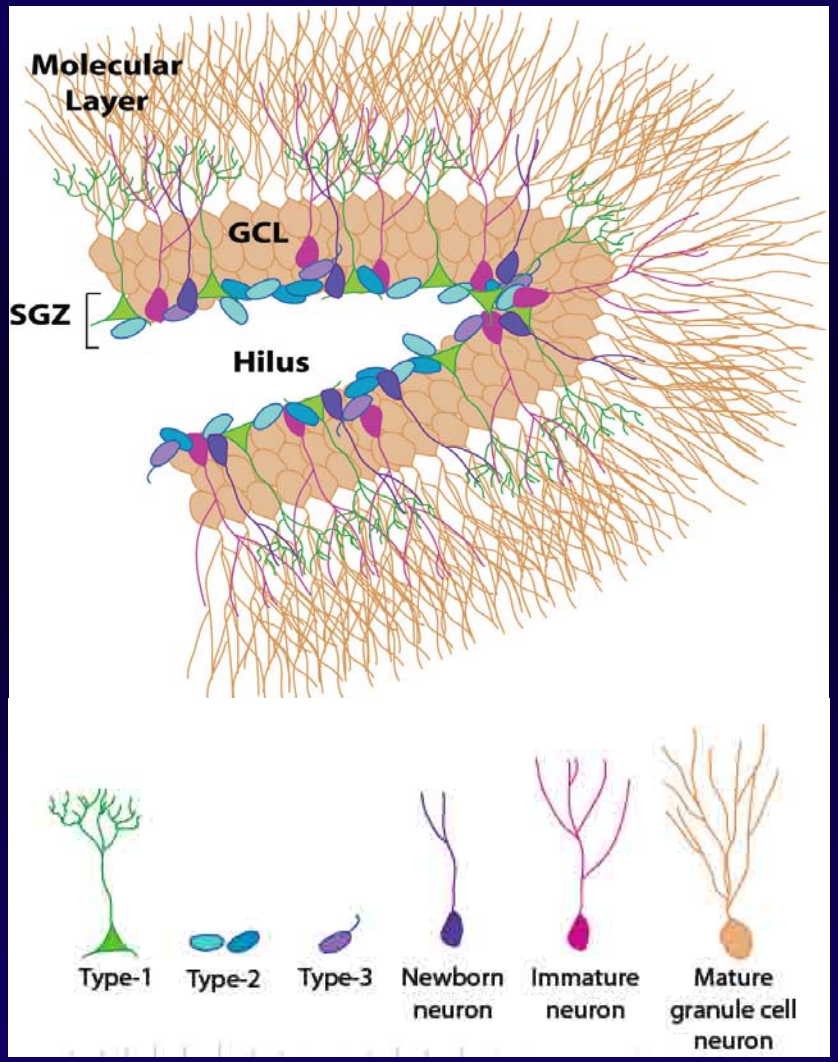
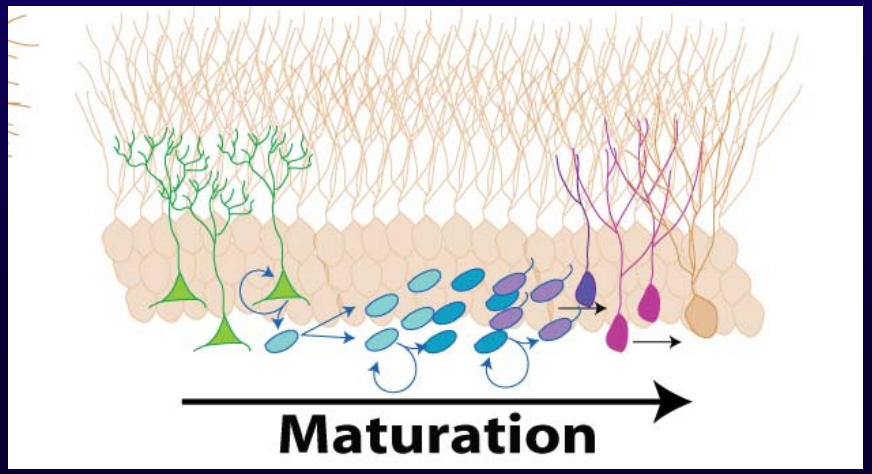


Survival

Eisch et al., J Neurosci, 2008

Utilize markers, morphology to identify different stages of neurogenesis





Nestin

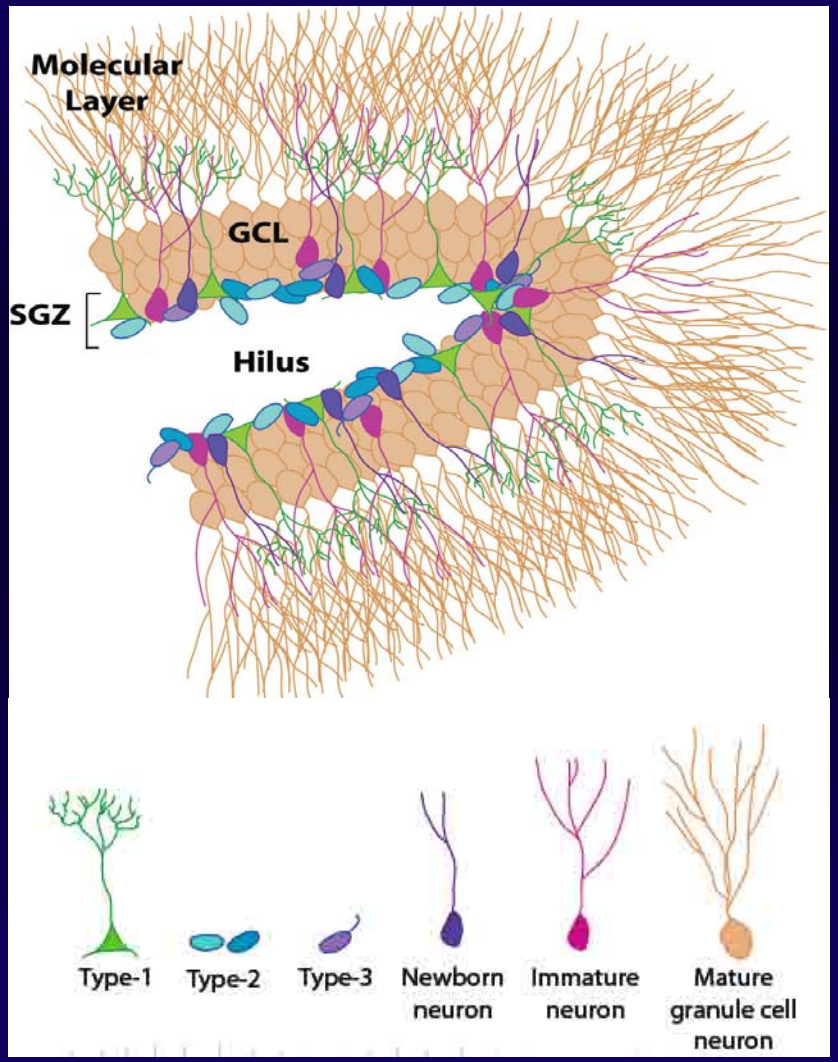
BrdU

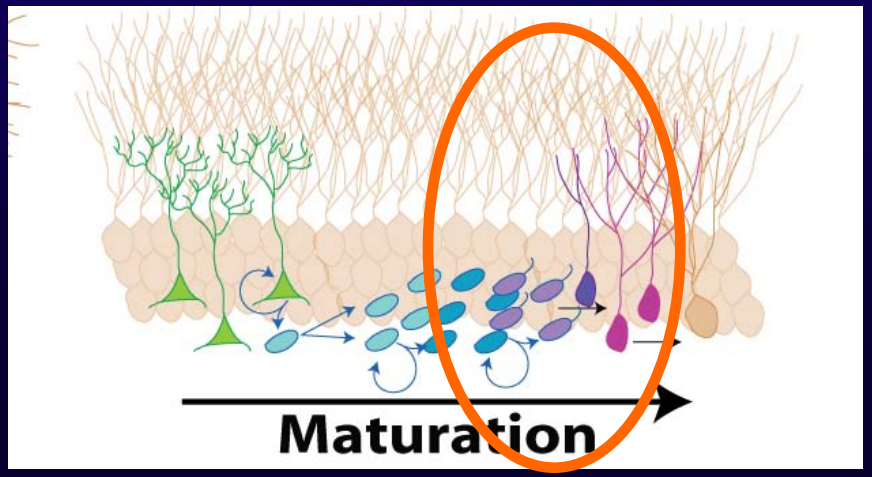
DCX (Doublecortin)

NeuN

Eisch et al., J Neurosci, 2008

How does radiation influence the process of neurogenesis?





Nestin

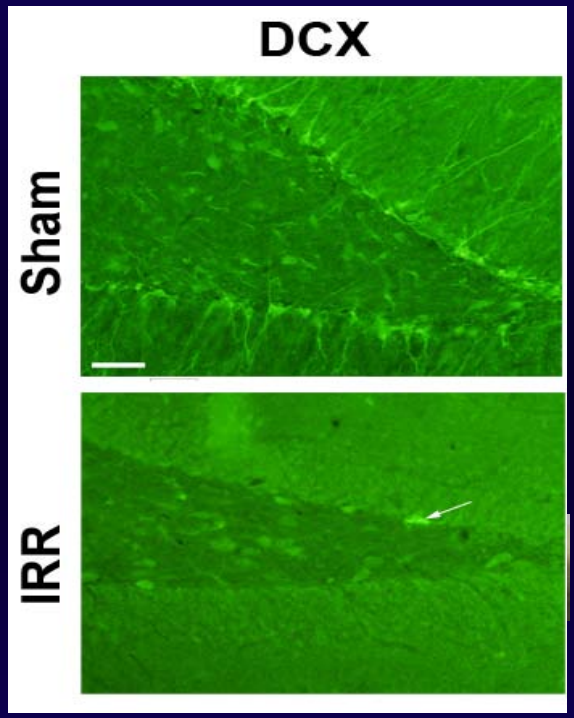
BrdU

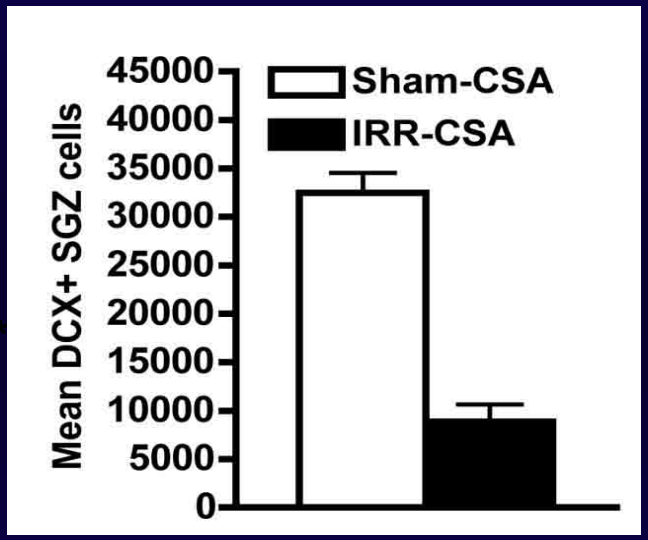
DCX (Doublecortin)

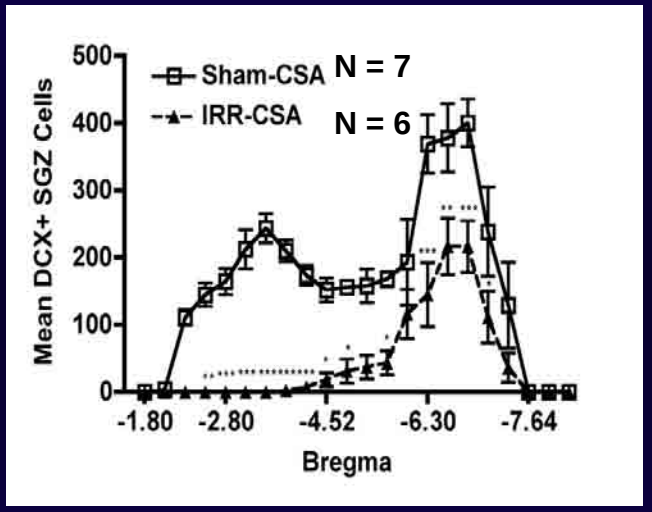
NeuN

Eisch et al., J Neurosci, 2008

Cranial X-ray irradiation inhibits neurogenesis in the adult rat hippocampus

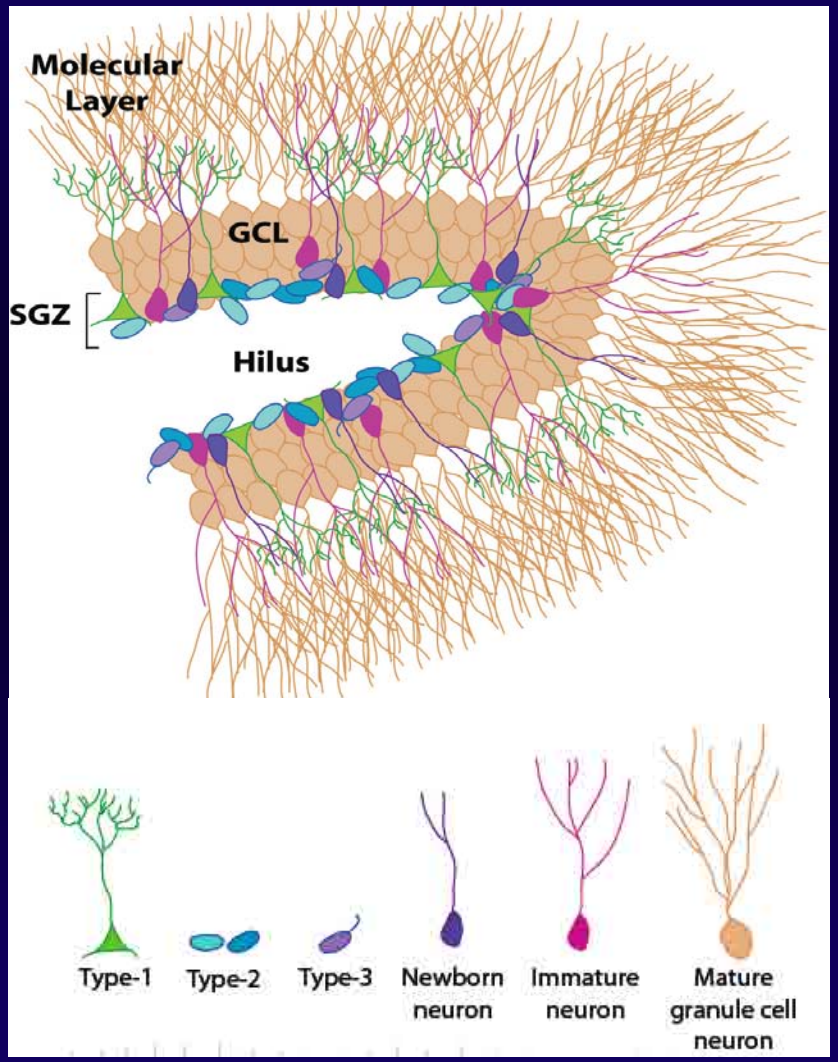


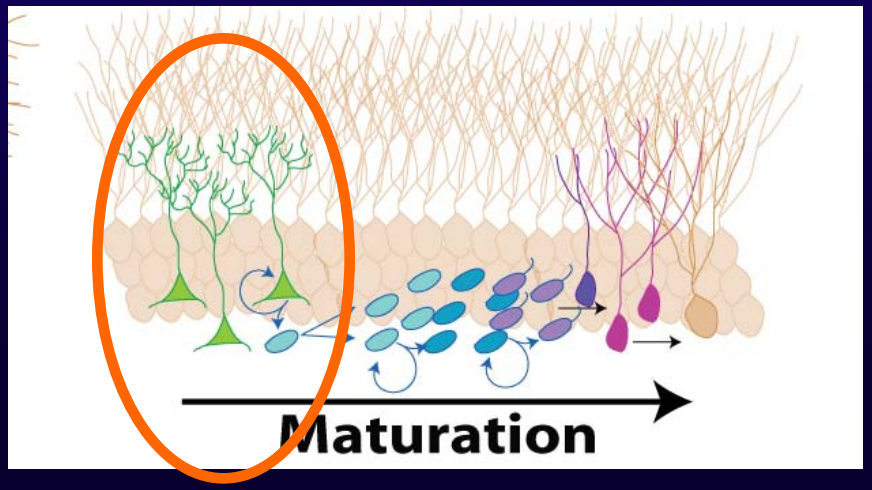




Michele Noonan

What about the stem cells?





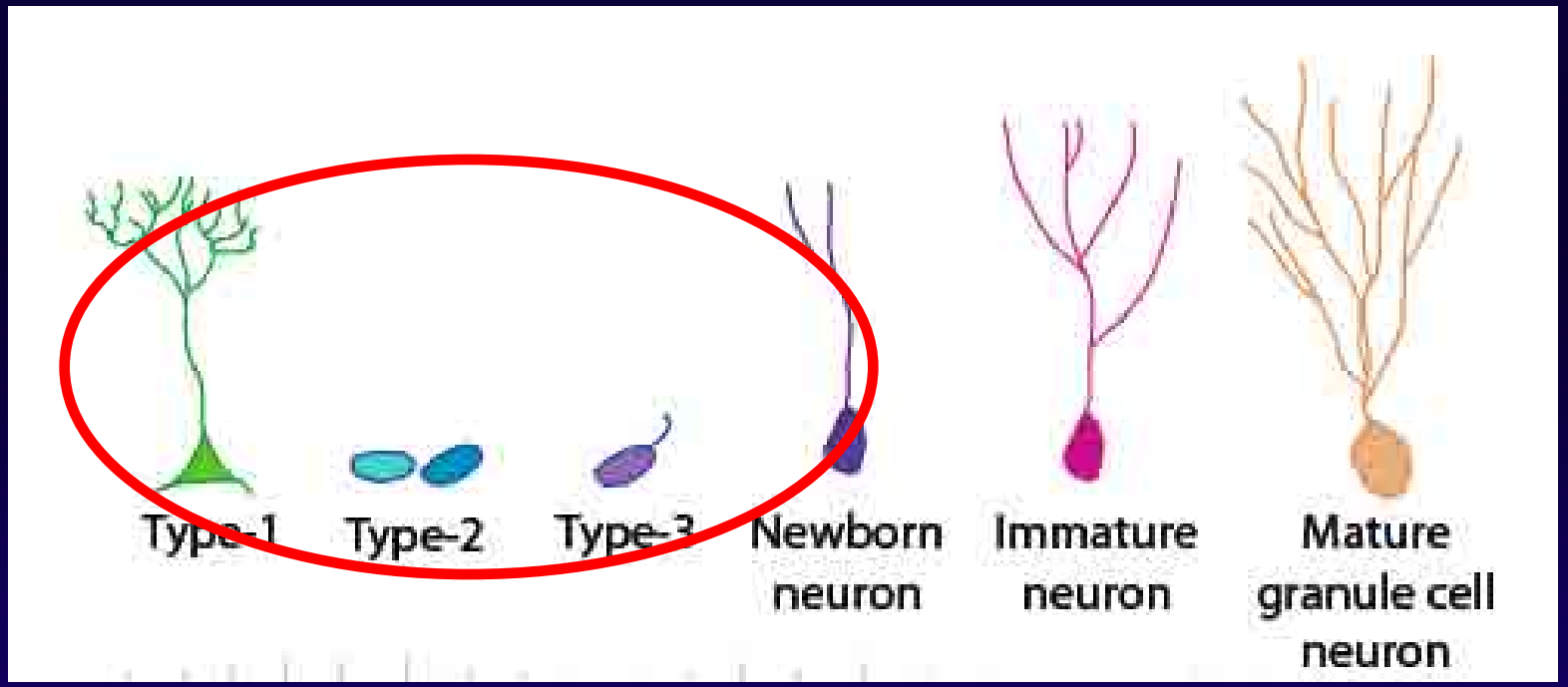
Nestin

Are neural stem cells susceptible to radiation *in vivo*?

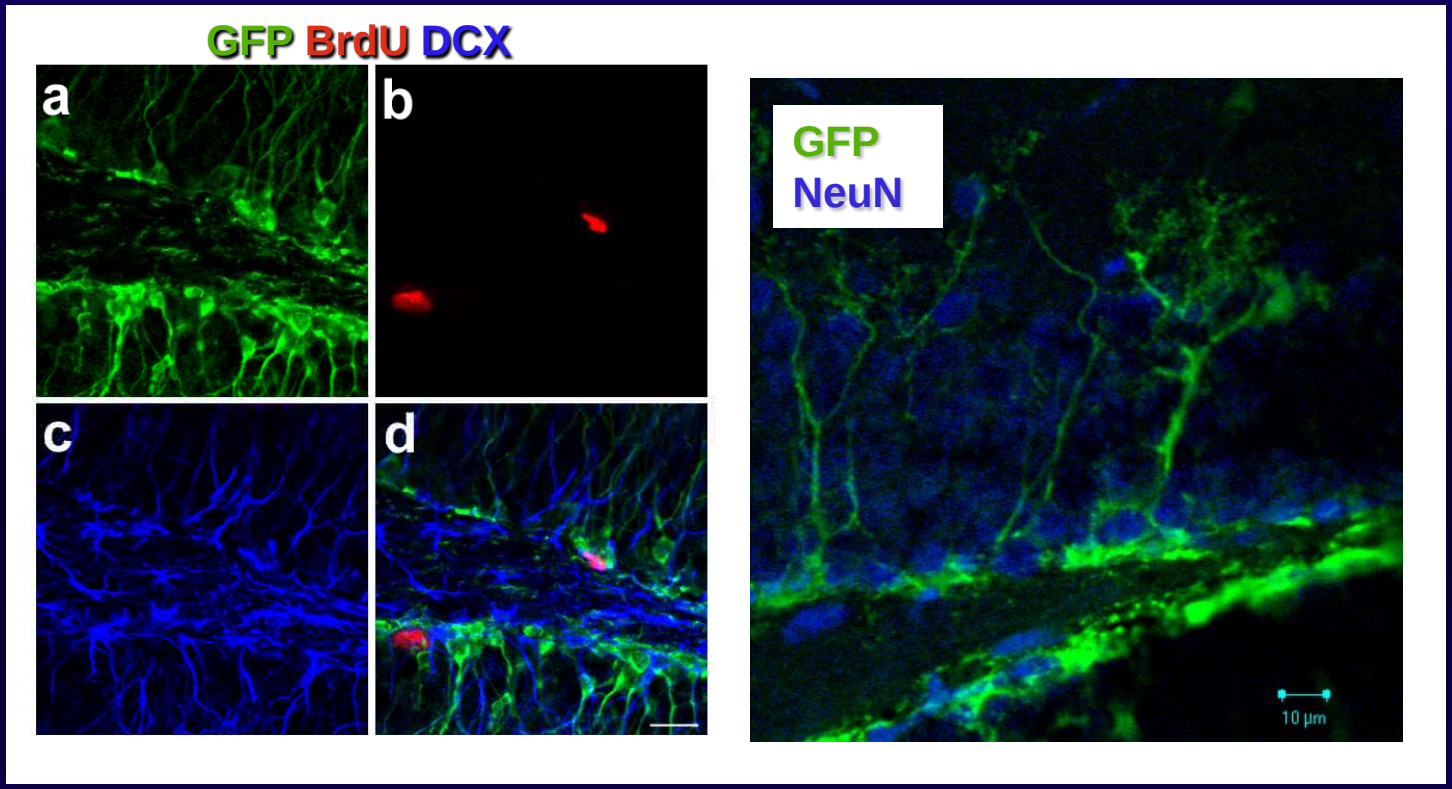
Eisch et al., J Neurosci, 2008

Visualize neural stem cells *in vivo:* nestin-GFP transgenic mouse

- Expresses Green Fluorescent Protein (GFP) constitutively under *nestin* promoter



Morphological analysis of Type 1 cells is critical

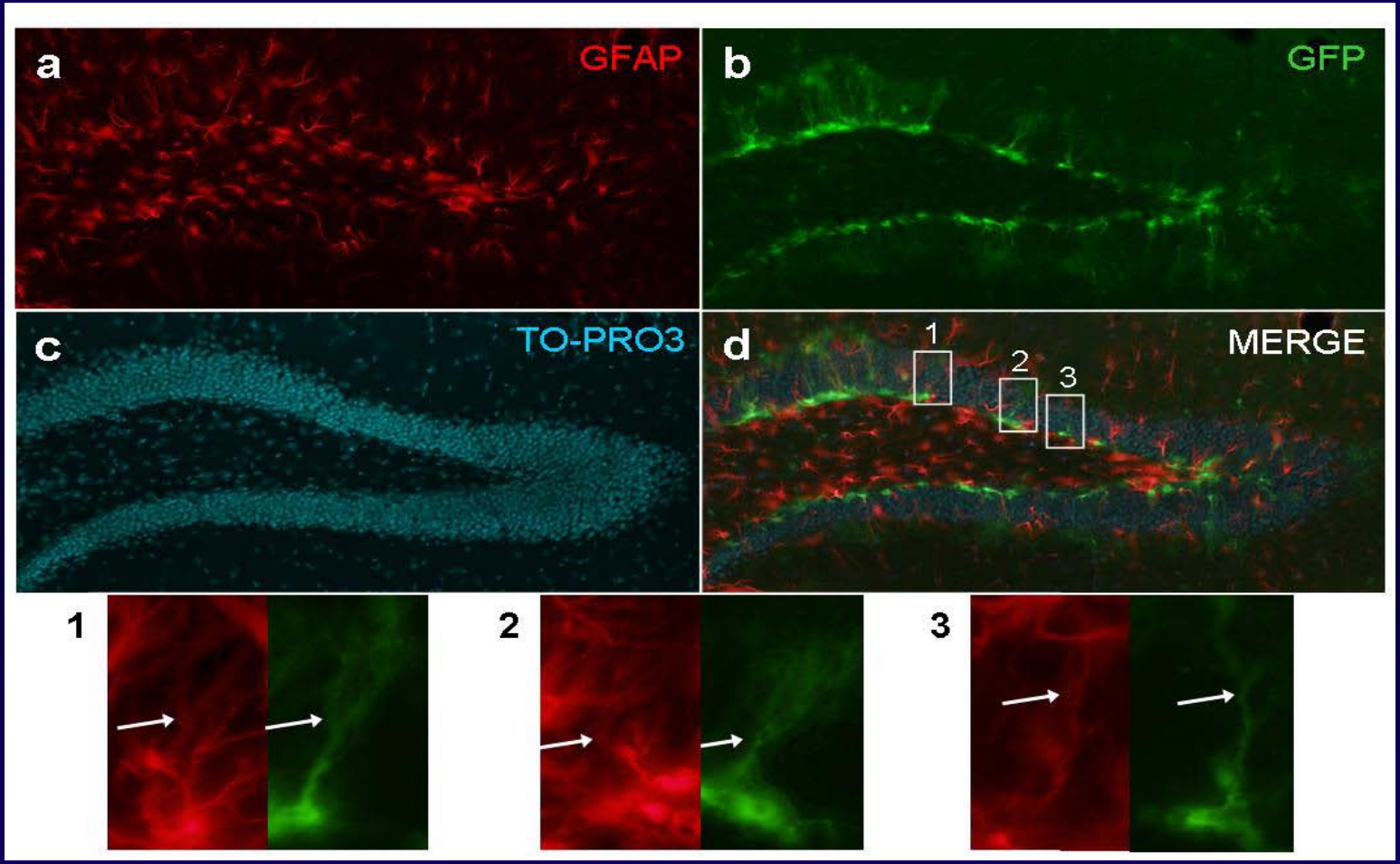


Morphology

Protein expression (GFP+ nestin, GFAP, mushashi, Sox2)

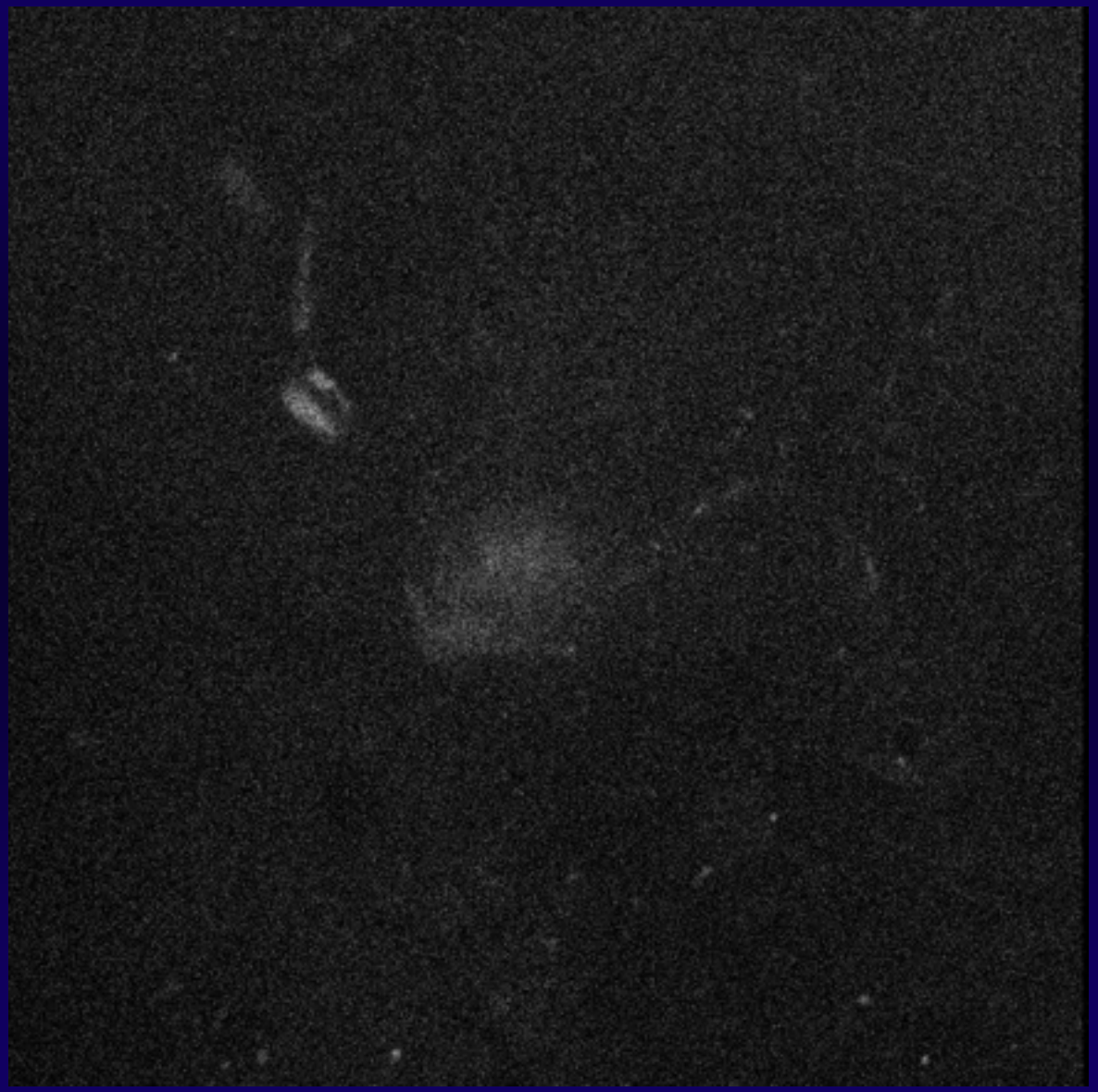
Diane Lagace

Visualization of Type 1 stem-like cells in the adult hippocampal SGZ



nestinGFP transgenic mouse

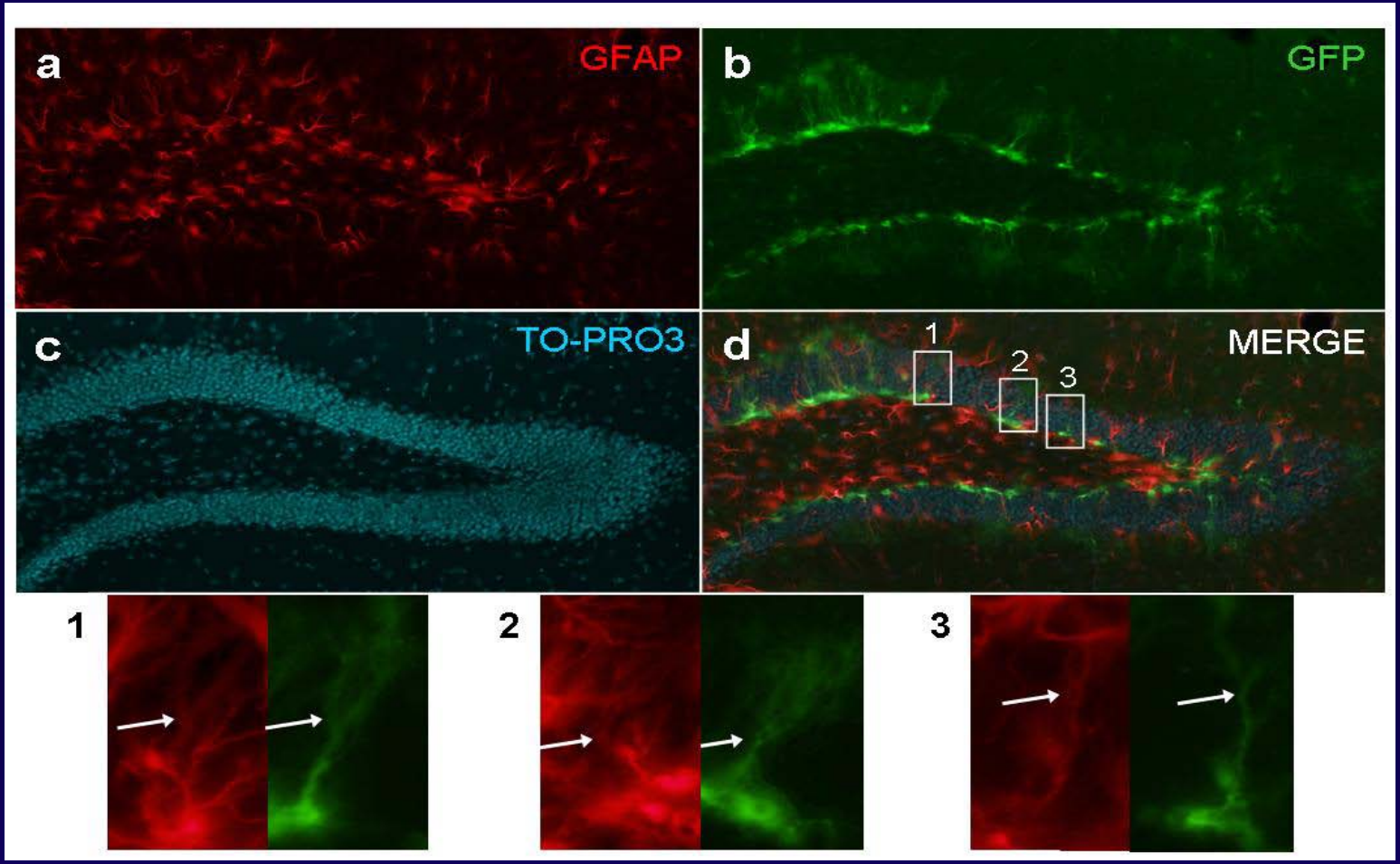
Nathan DeCarolis



Two-photon visualization of Type 1 stem-like cells in the adult mouse hippocampus

Juan Varela, David Petrik

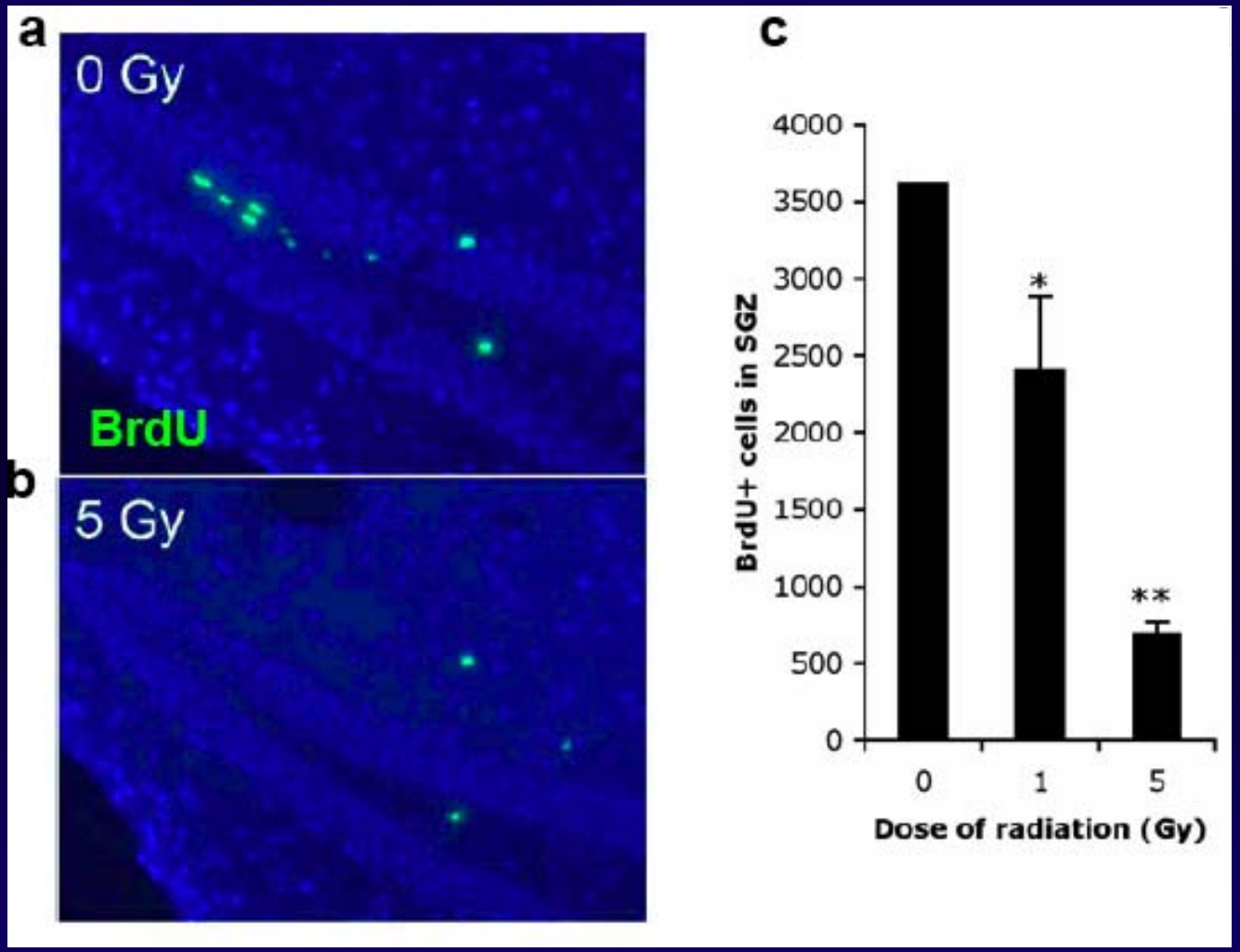
Are the number of Type 1 cells changed after X-ray irradiation?



nestinGFP transgenic mouse

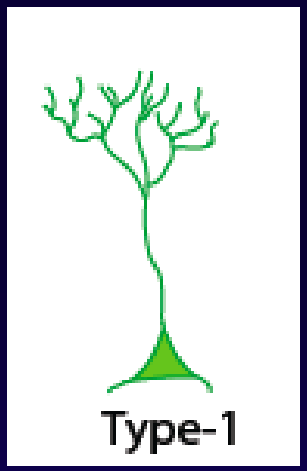
Nathan DeCarolis

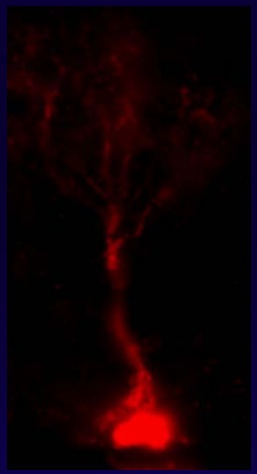
X-irradiation decreases BrdU+ cells (SGZ proliferation)



48h after exposure, 8-10 weeks of age at IR

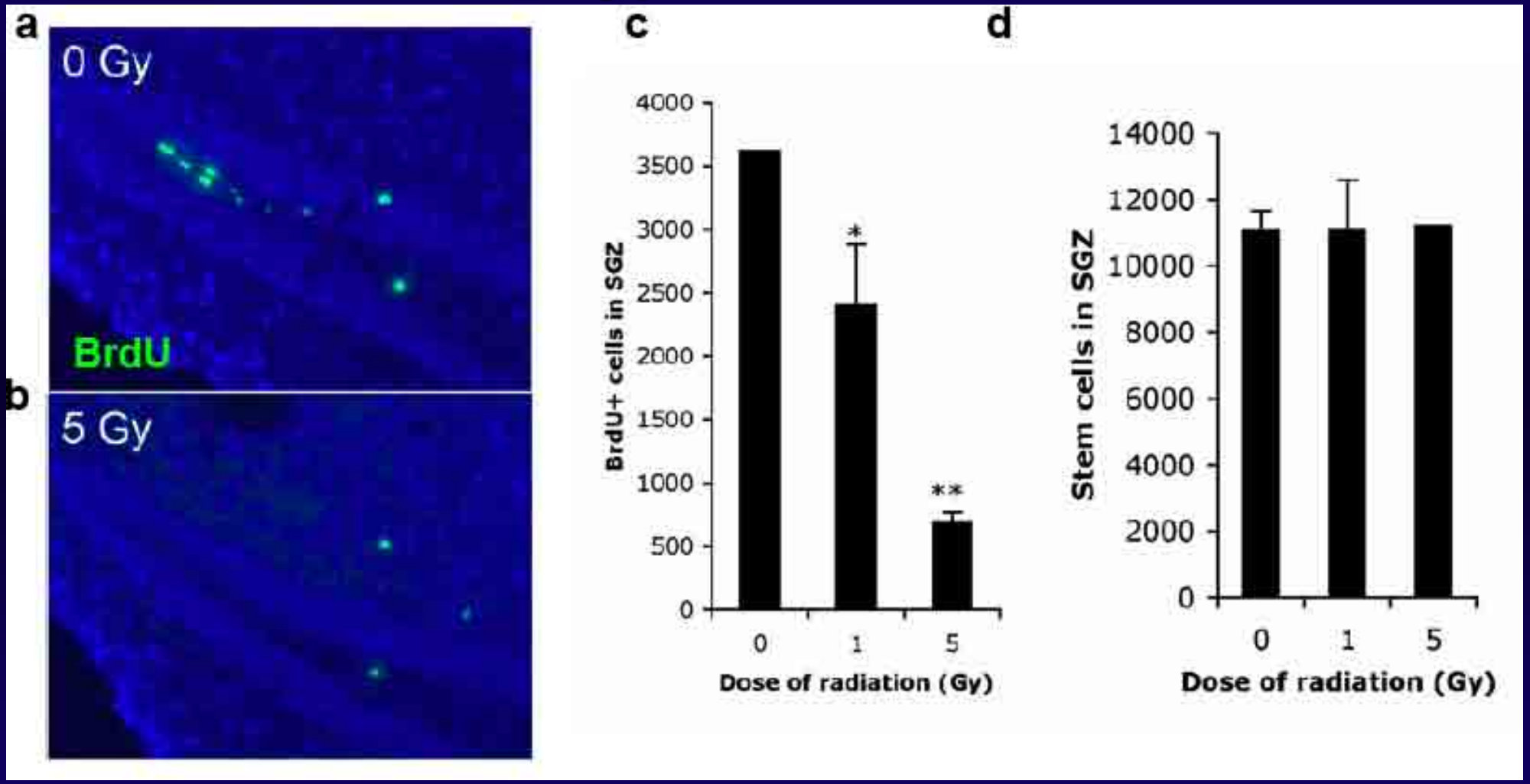
What about the stem cells?





Nathan DeCarolis

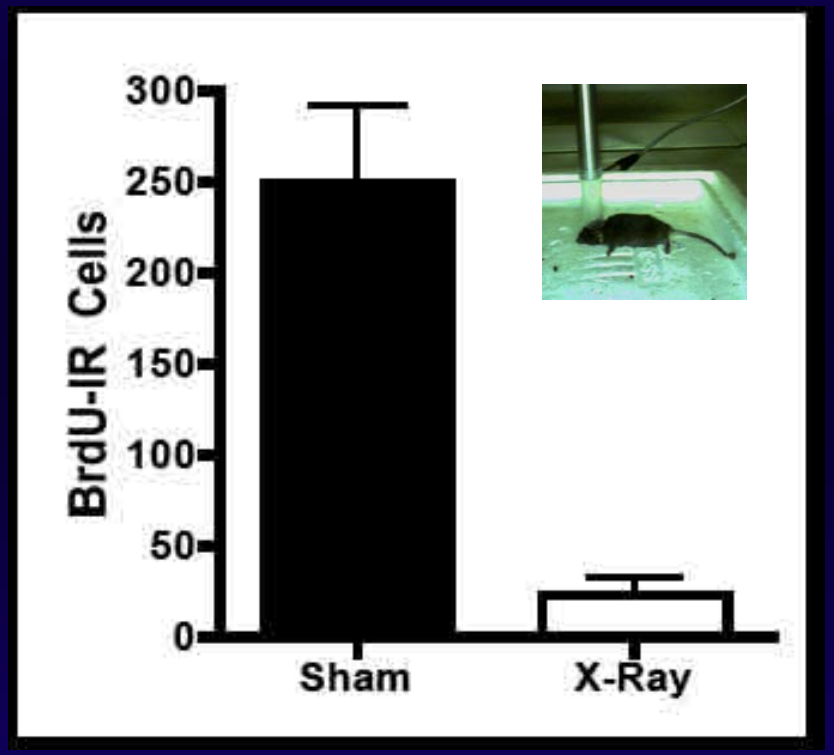
X-ray irradiation does not change the number of Type1 SGZ cells

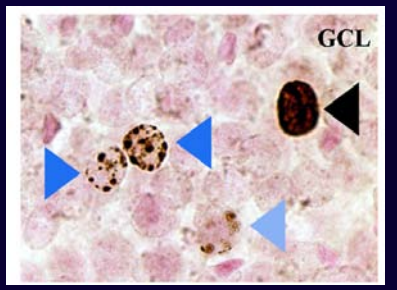


48h after exposure, 8-10 weeks of age at IR

Nathan DeCarolis

Long-lasting inhibition of BrdU-labeled cells in SGZ



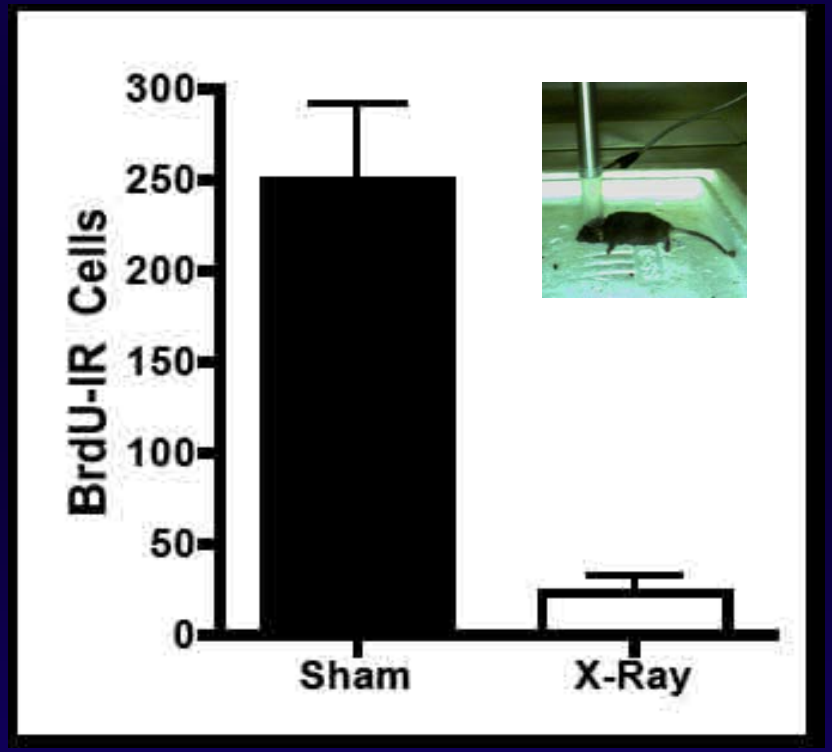


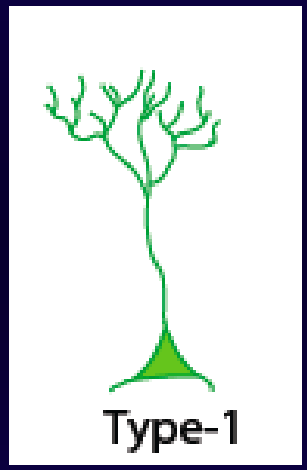
Survival

2 months after exposure, 5Gy

Nathan DeCarolis

What about Type 1 SGZ cells?

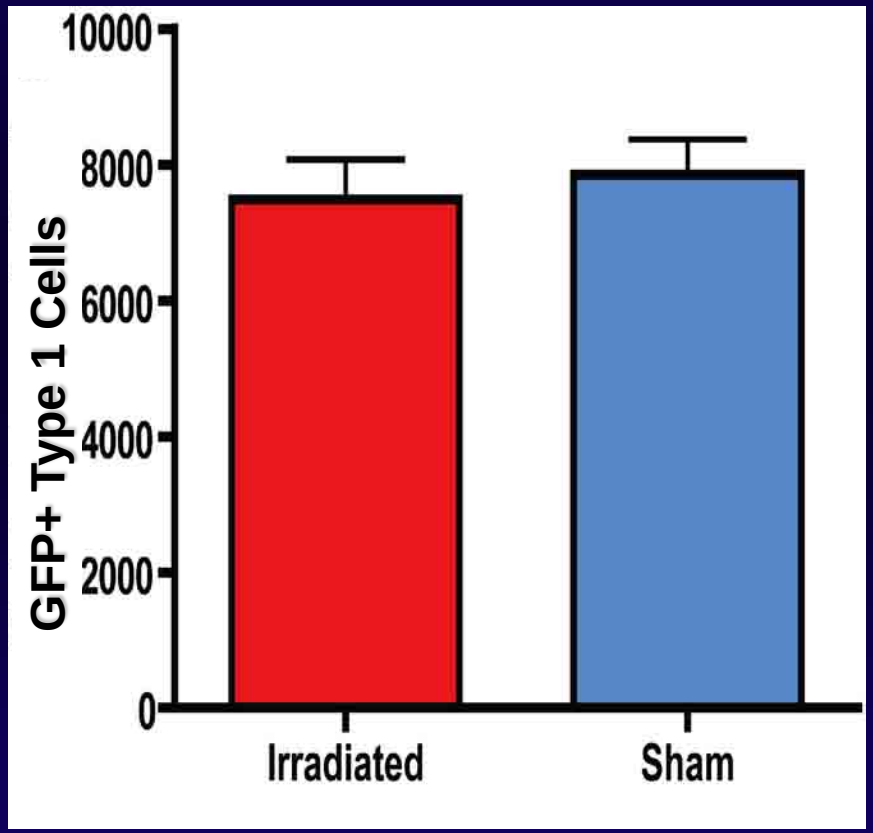


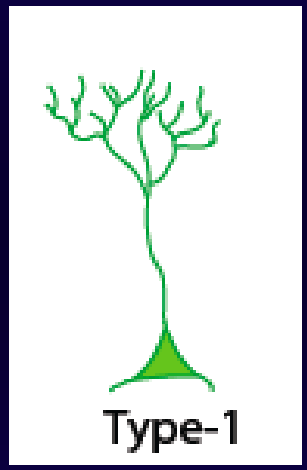


2 months after exposure, 5Gy

Nathan DeCarolis

Type 1 SGZ cell number is also unchanged 8 weeks post-irradiation

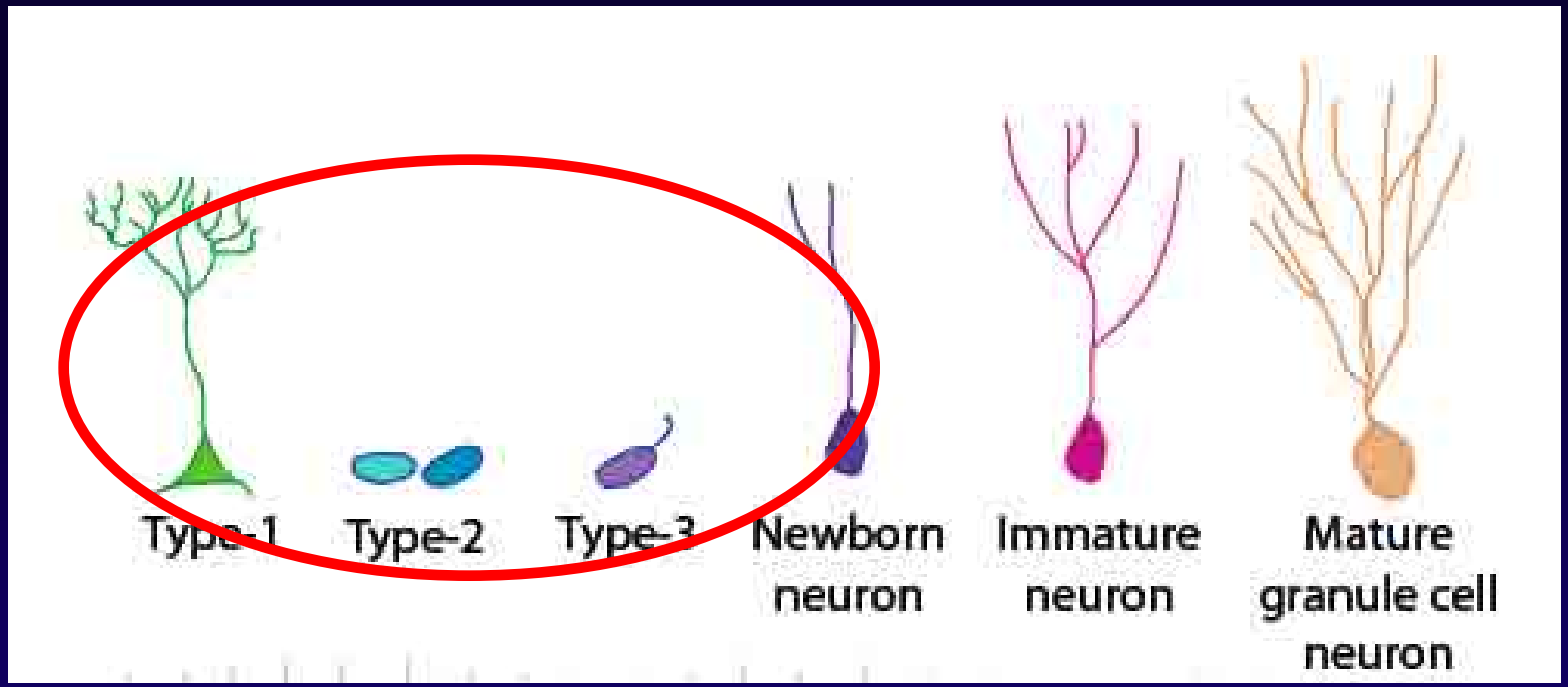




2 months after exposure, 5Gy

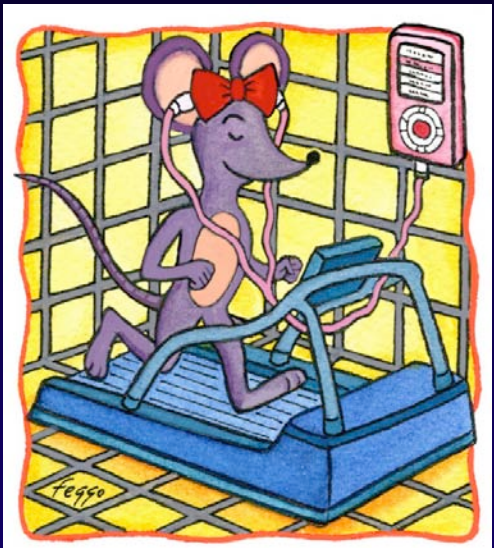
Nathan DeCarolis

If the Type 1 putative stem cells are there after irradiation, can they replace the depleted population of progenitors and restore neurogenesis?



If the Type 1 putative stem cells are there after irradiation, can they replace the depleted population of progenitors and restore neurogenesis?

Voluntary exercise stimulates neurogenesis



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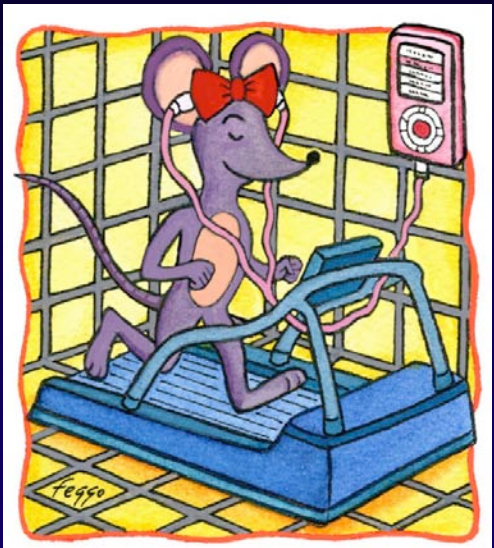
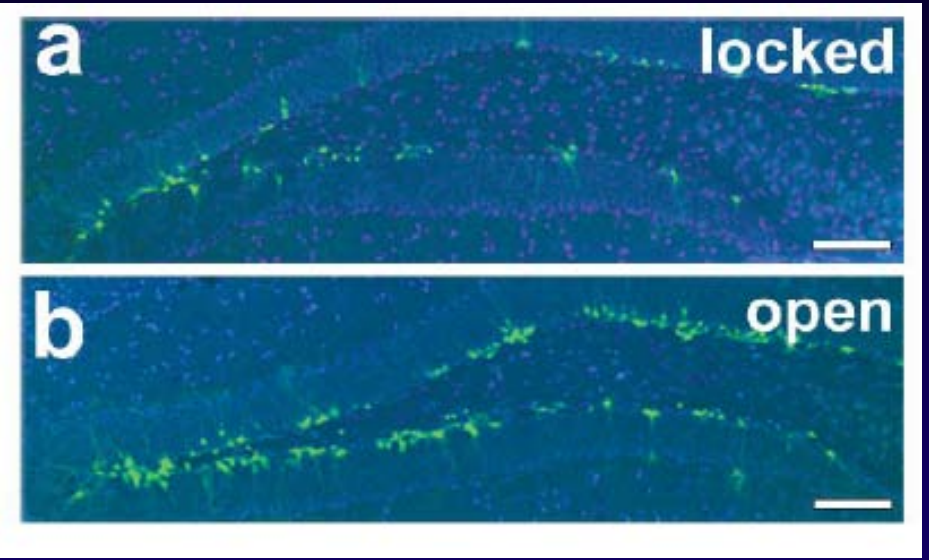
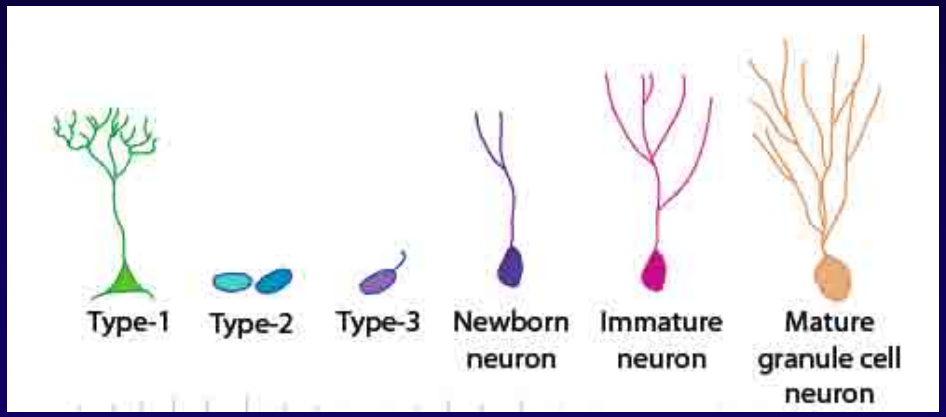
Voluntary exercise stimulates neurogenesis



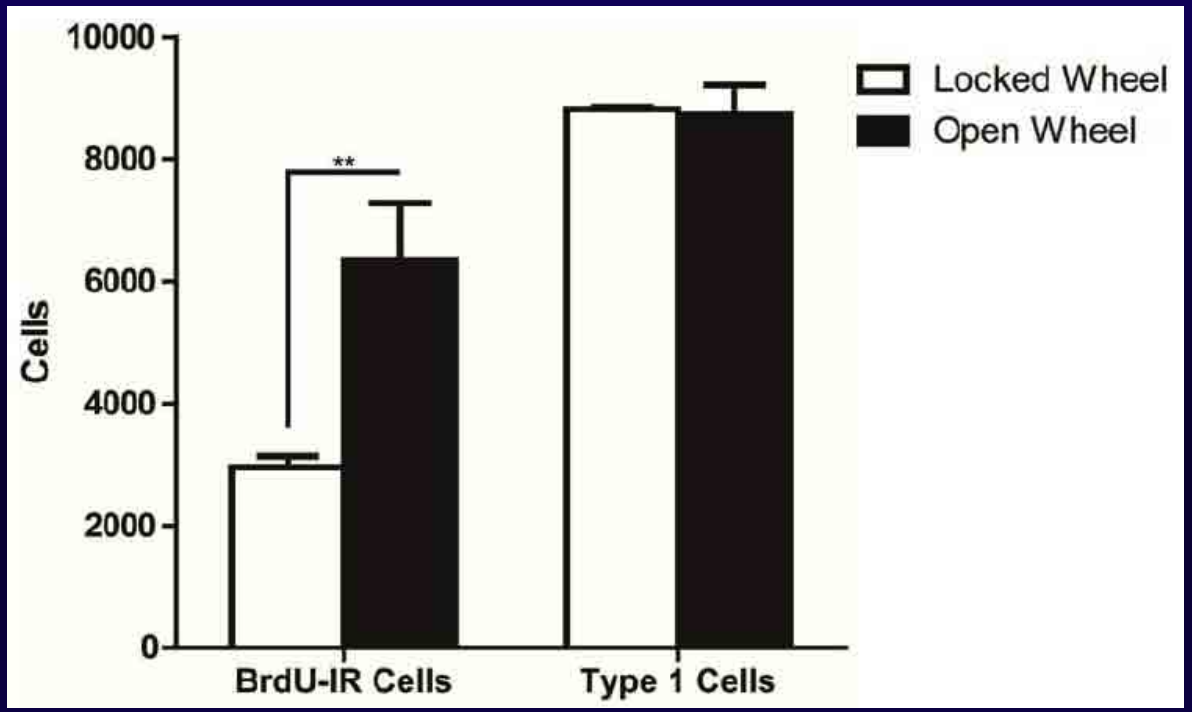


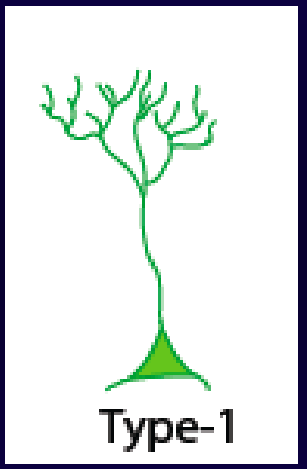
Lagace et al., 2007

Does voluntary exercise change Type 1 SGZ cell number?



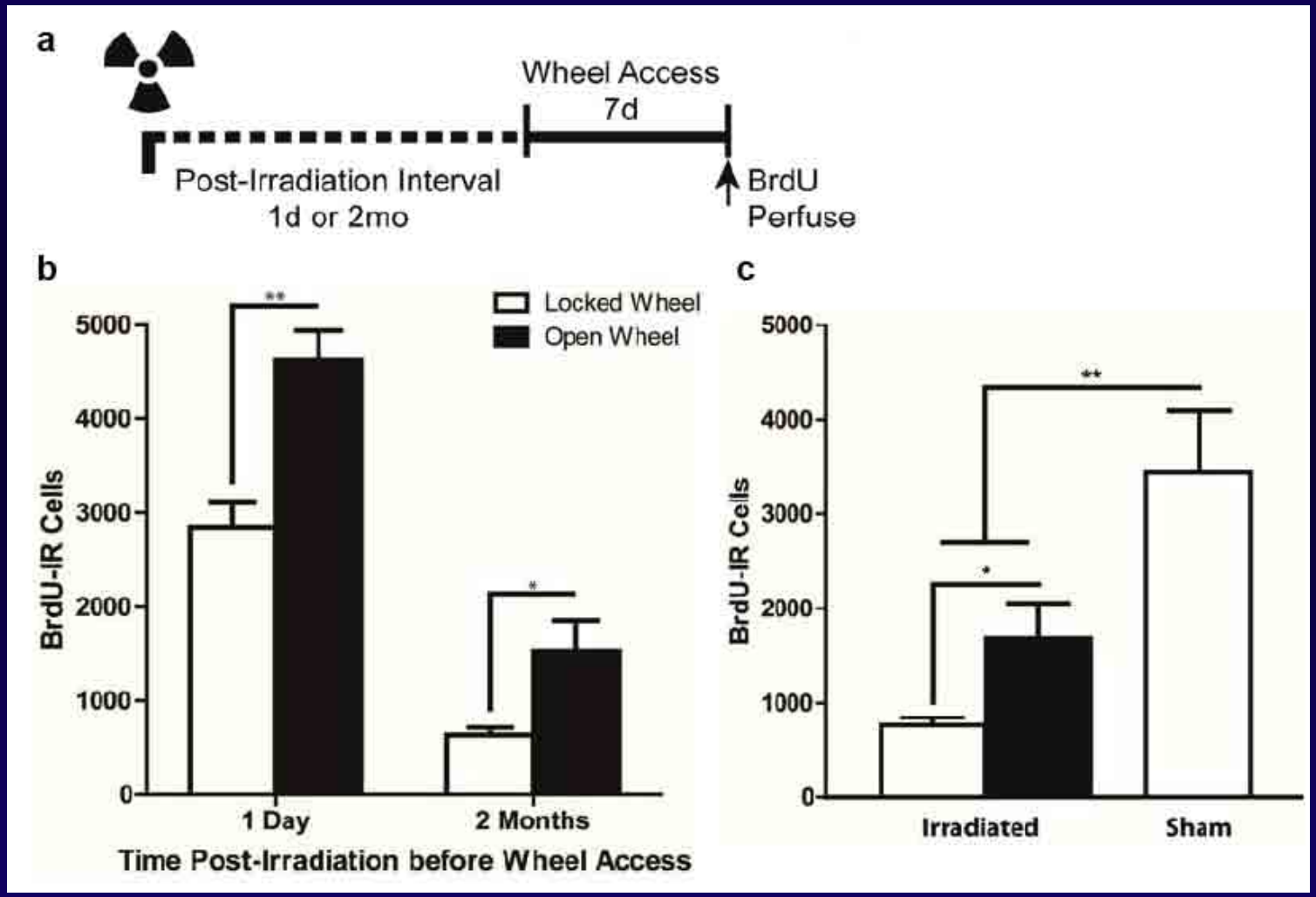
Voluntary running increases proliferation (BrdU+) but does not alter the number of Type 1 SGZ cells





Nathan DeCarolis, Jessica Ables

Running ameliorates the irradiation-induced proliferation deficit



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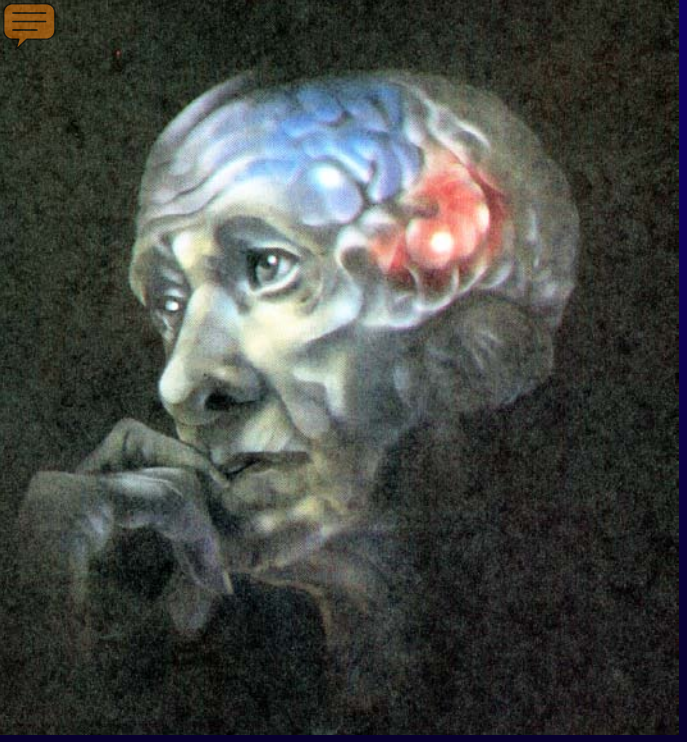
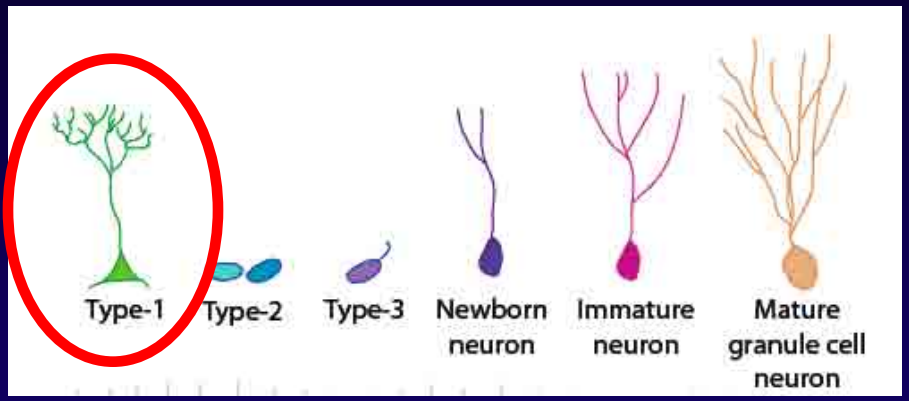


How is the brain influenced by radiation?

Decreased hippocampal neurogenesis
No change in hippocampal stem cells

…and what can we do about it?

Stimulate stem cell division?



Exercise

Hippocampal learning

Laboratory of Amelia Eisch

Wellington Amaral
Sarah Bulin
Adam Carlton
Nathan DeCarolis
Madeleine Johnson
Junie LeBlanc
Shveta Malhotra
Neal Melvin
David Petrik
Phil Rivera

Past Eisch Lab Members

Amy Arguello (Mt. Sinai)
Laure Farnbauch (Ohio)
Michele Noonan (Cal Tech)

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NIH
UT Southwestern

www3.utsouthwestern.edu/eisch
amelia.eisch@utsouthwestern.edu

Laboratory of Benjamin P.C. Chen

Shichuan Zhang
Eric Shih

Past Chen Lab Members

Francesca Ahn (Mt. Sinai)

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