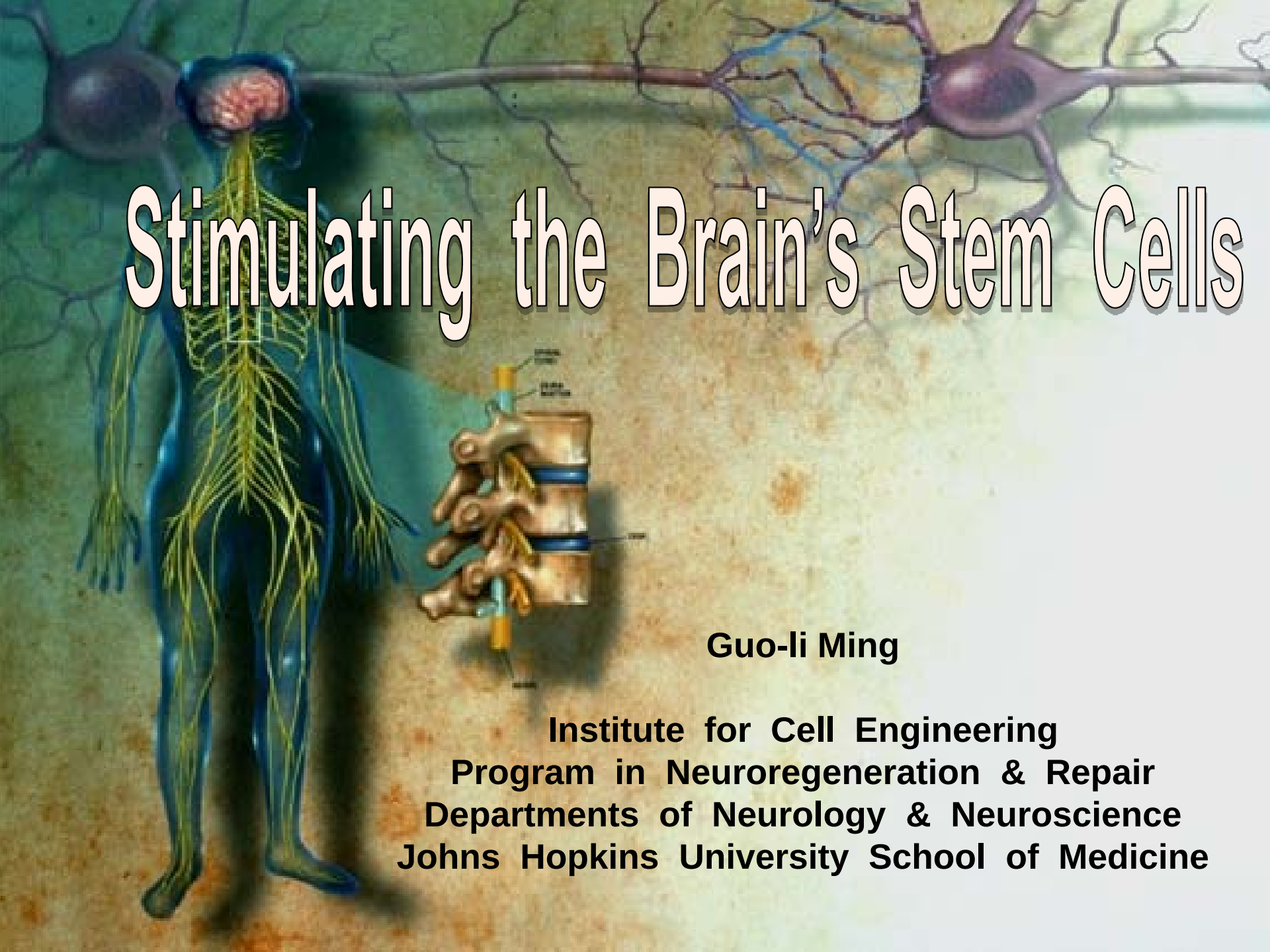
Stimulating the Brain's Stem Cells



Guo-li Ming

Institute for Cell Engineering
Program in Neuroregeneration & Repair
Departments of Neurology & Neuroscience
Johns Hopkins University School of Medicine

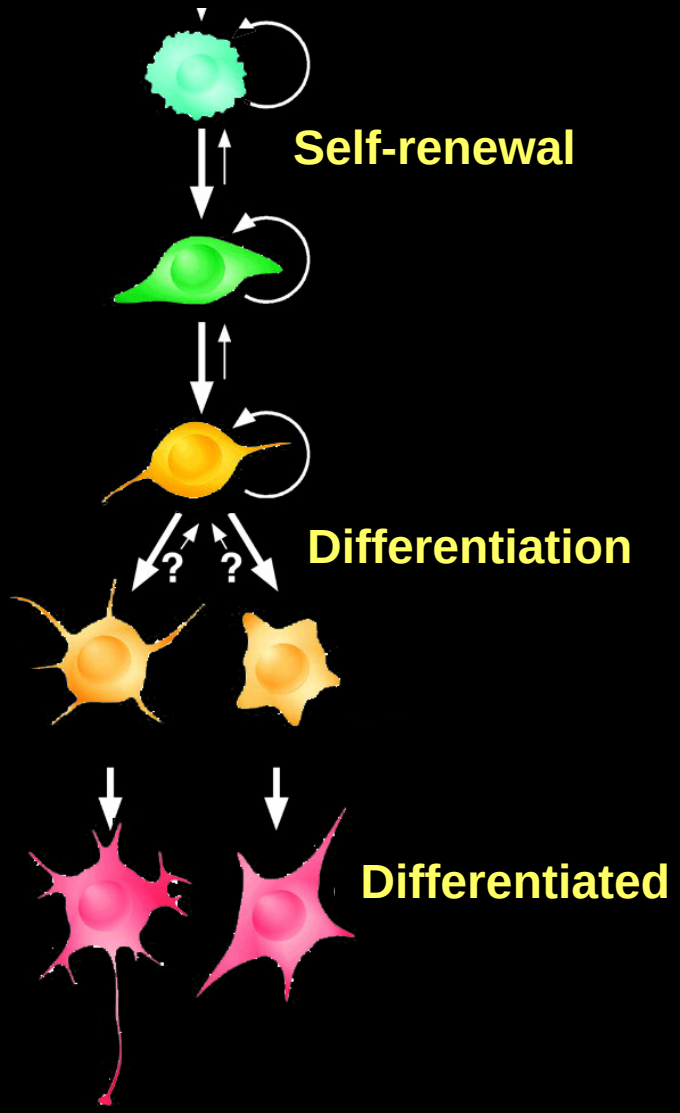
What are stem cells?

Rudolf Virchow (1858):

Omnis cellula e cellula

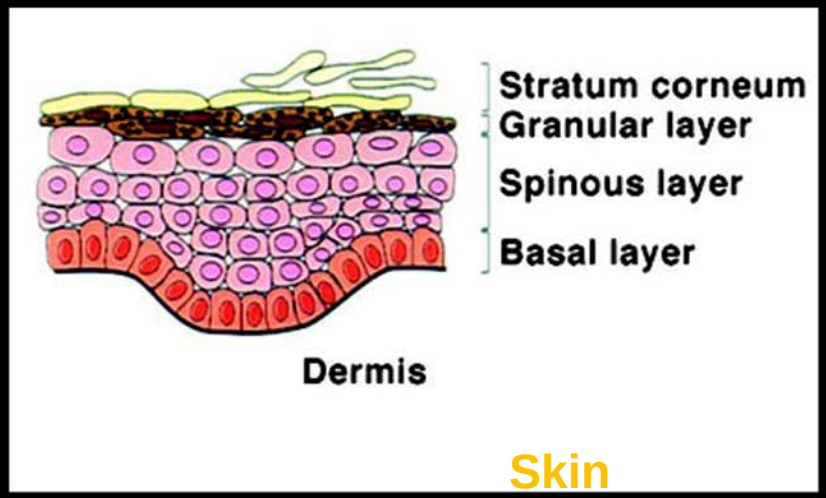
All cells only arise from pre-existing cells

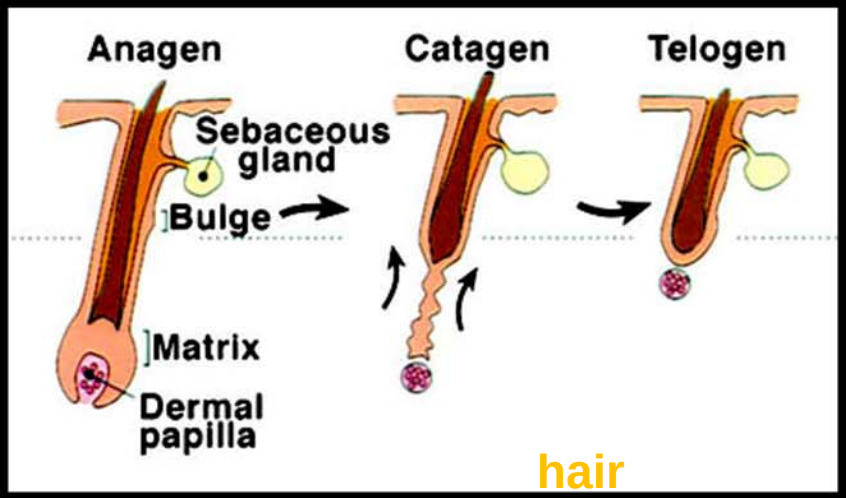
Stem cells are the foundation cells for every organ and tissue in the body. They are like a blank microchip that can ultimately be programmed to perform particular tasks.
Under proper conditions, stem cells begin to develop or 'differentiate' into specialized cells that carry out a specific function, such as in the skin, muscle or liver.
Additionally, stem cells can 'self-renew,' that is they can divide and give rise to more stem cells.

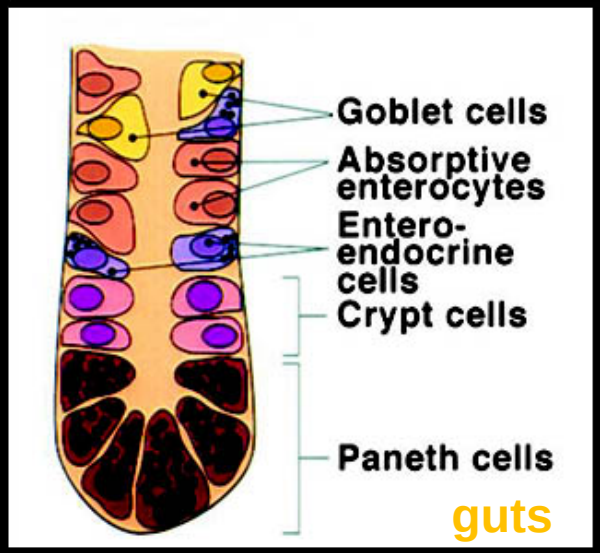


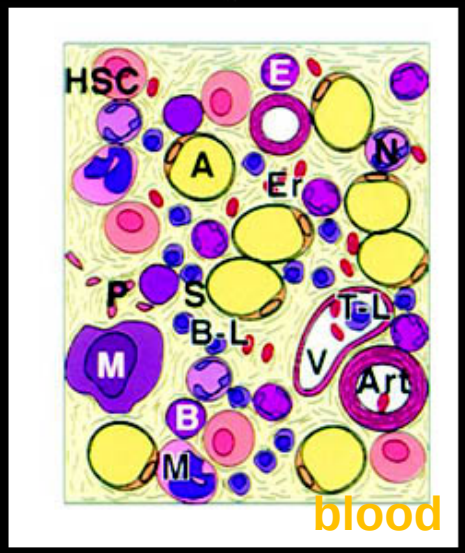
Stem cells in the adulthood

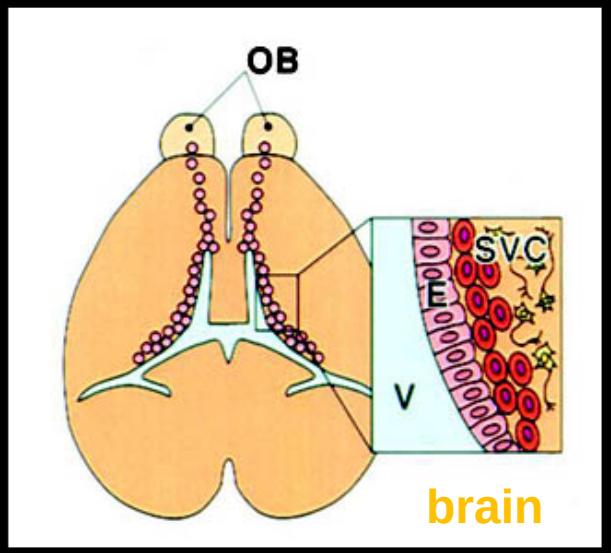
-- regenerating and repairing the mature tissue





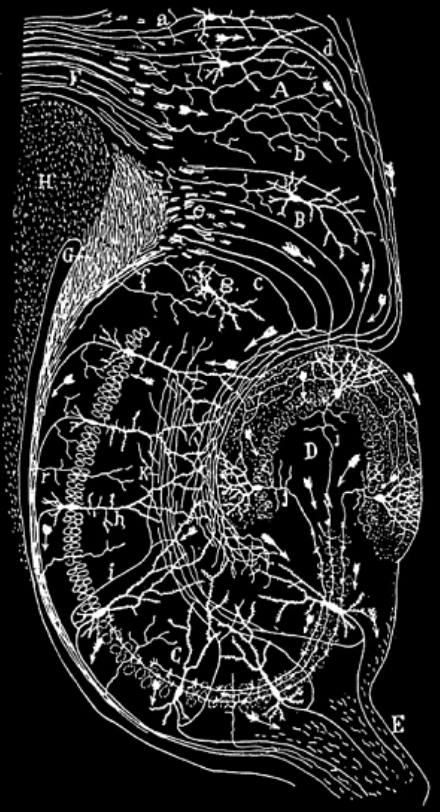


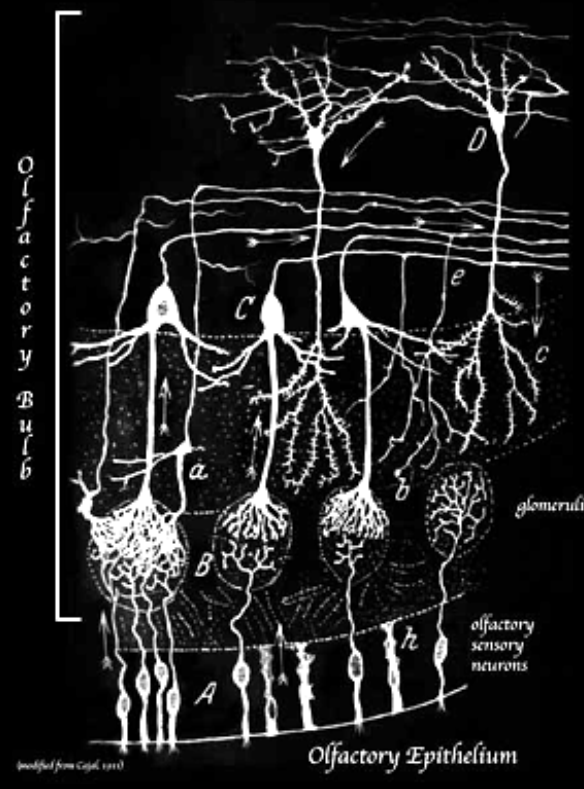




(Adapted from Fuchs & Segre, Cell 2000)

Do adult brain's stem cells exist?

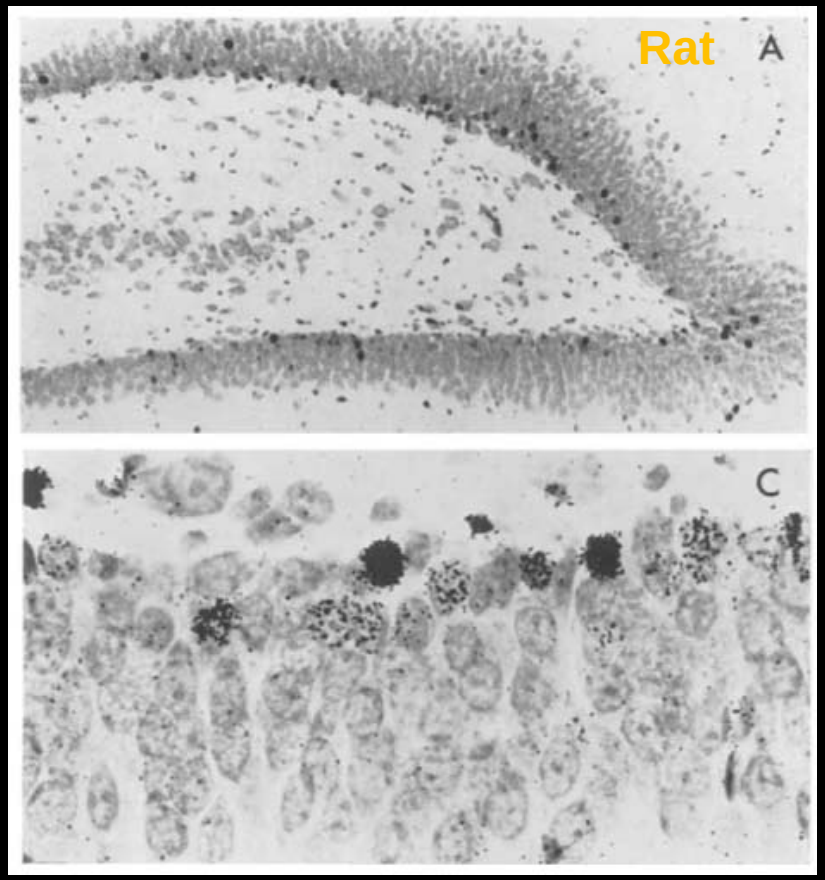




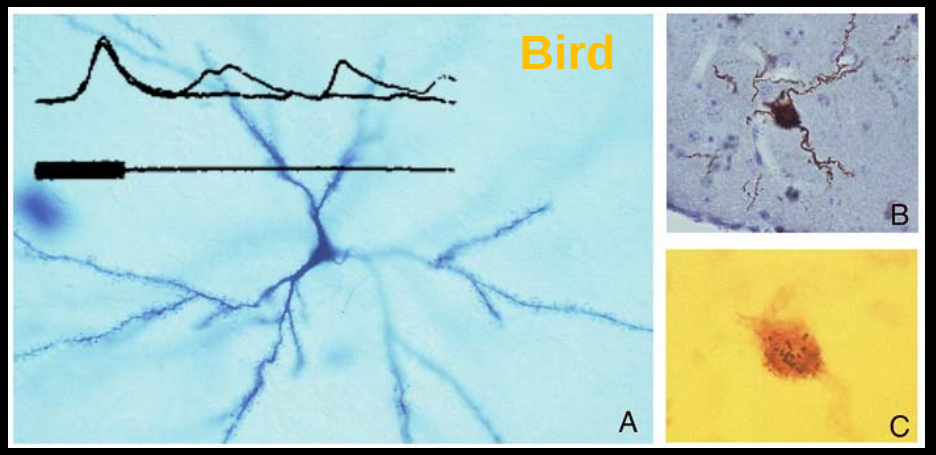
"In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree."
-- Ramon y Cajal (1913).

Stem cells in specific brain regions

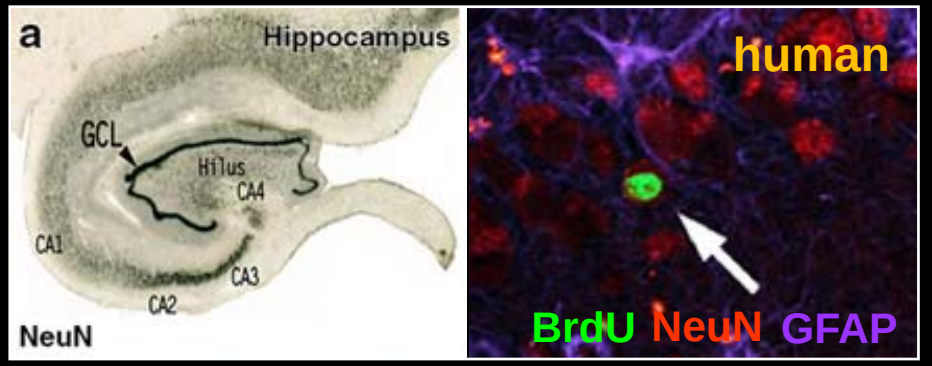
Altman and Das, J. Comp. Neurol. 1964



Paton and Nottebohm, Science 1984

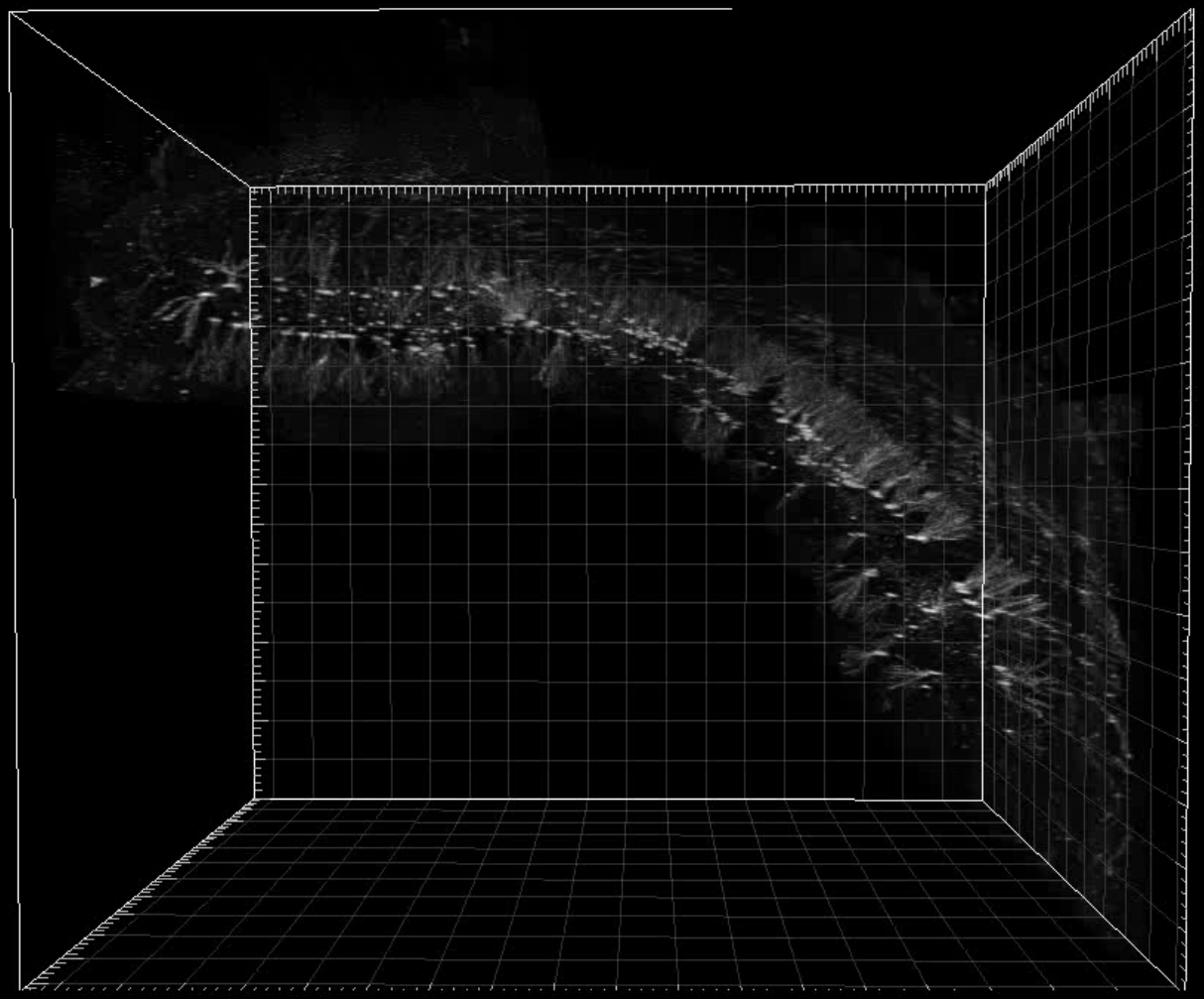


Eriksson, Gage et al. Nat. Med. 1998



- Mouse
- Rat
- Cat
- Birds
- Tree Shrew
- Marmoset
- Rhesus
- Human

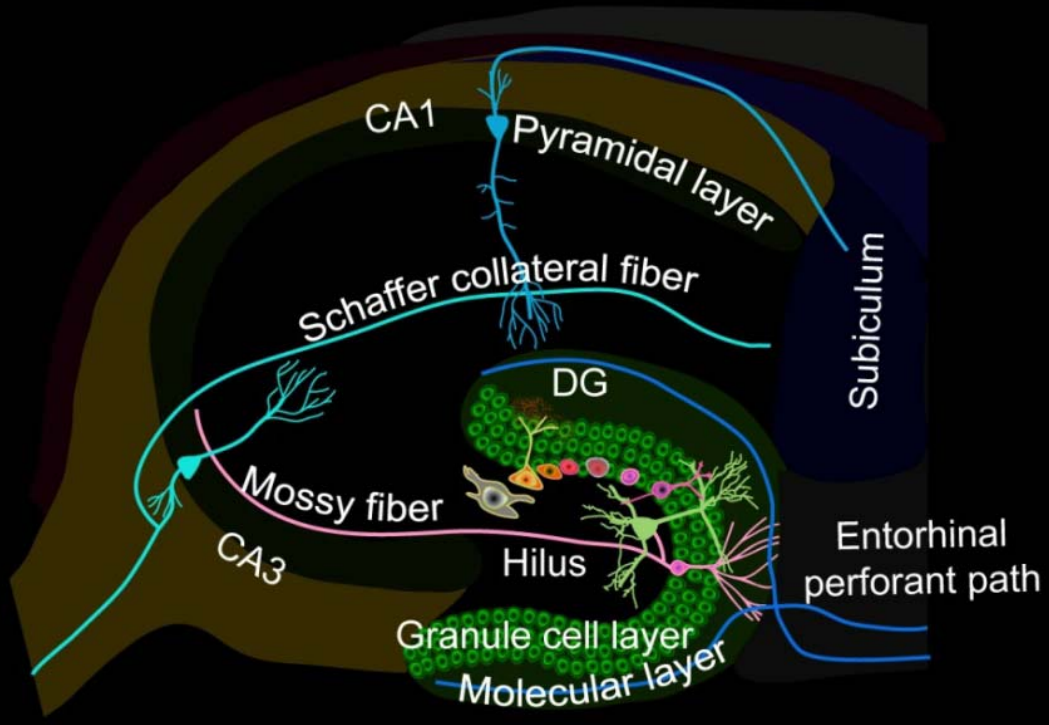
Brain's stem cells give rise to newborn nerve cells



(Gerry Sun)

What do the newborn nerve cells do?

In the hippocampus of young adult rats: 9,000 new cells each day; over 250,000/month 6% of total cell size of the granule cell population



Functions

- Cognitive (learning & memory)
- Affective (mood regulation)

Dysfunctions

- Epilepsy
- Brain disorders
- Brain tumors

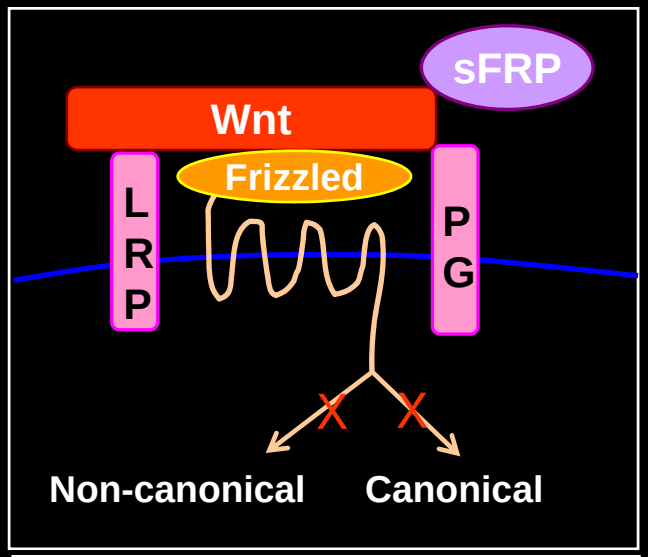
Regulators of brain's stem cells

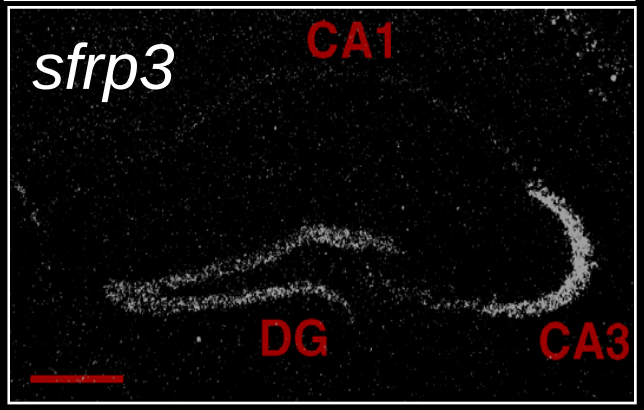
- Enriched environment
- Physical excise
- Learning
- Stress
- Aging
- Dietary restriction
- Hormones
- Neurotransmitters
- Degenerative neurological diseases
- Antidepressants
- Opiates, Methamphetamine
- Seizure
- Stroke
- inflammation

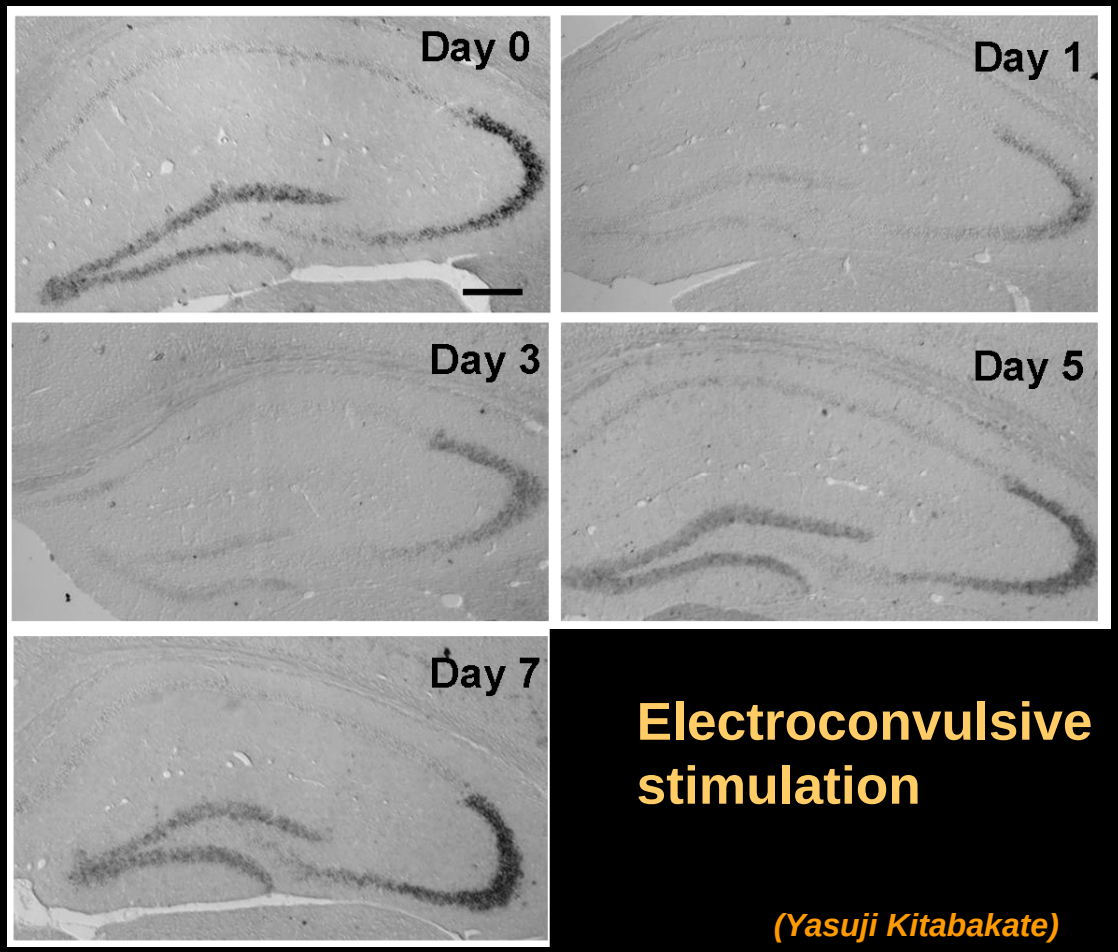
Brain's stem cells and antidepressants

- All clinical antidepressant treatments, including both chemical antidepressants (Prozac) and electroconvulsive therapy (ECT), stimulates brain's stem cells in the adult hippocampus in rodents, primates and humans.
- Antidepressant-induced behavioral responses in some rodent models requires brain's stem cells.
- Brain's stem cells has been used as a cellular model to search for novel antidepressants.

ECT reduces the expression of secreted Frizzled-related Protein 3 (sFRP3) - a Wnt inhibitor, in the adult hippocampus



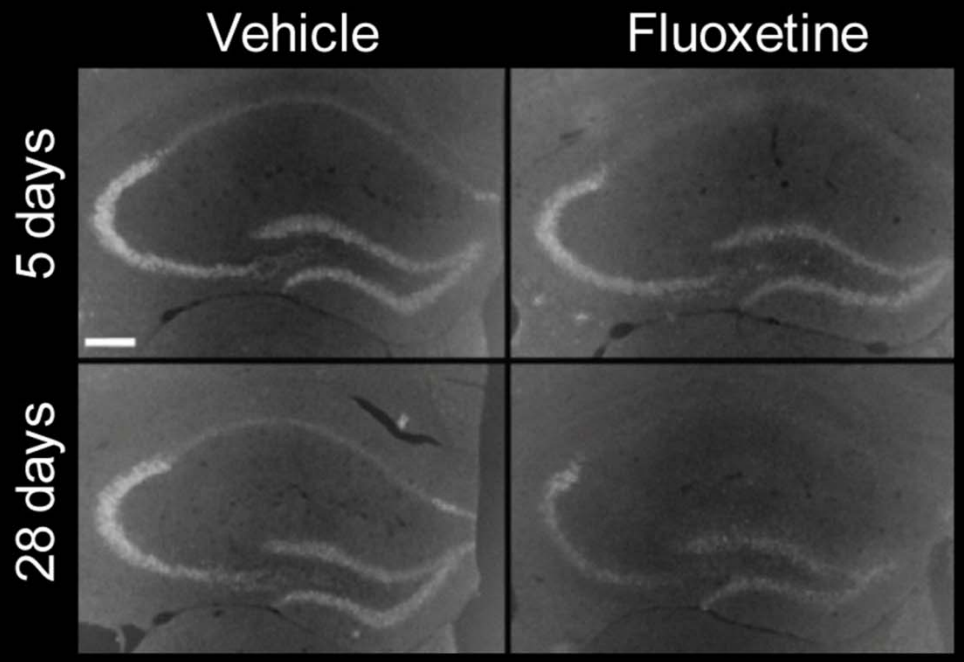


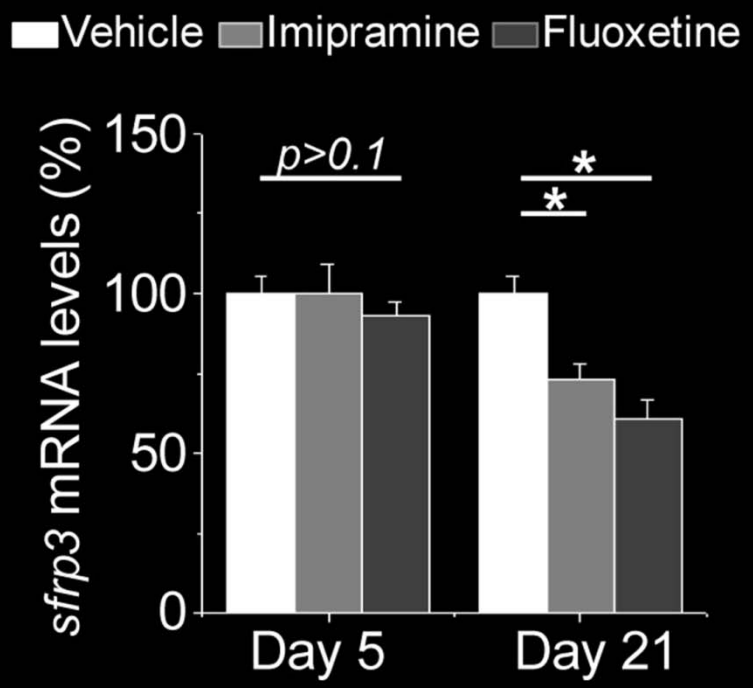


Electroconvulsive stimulation

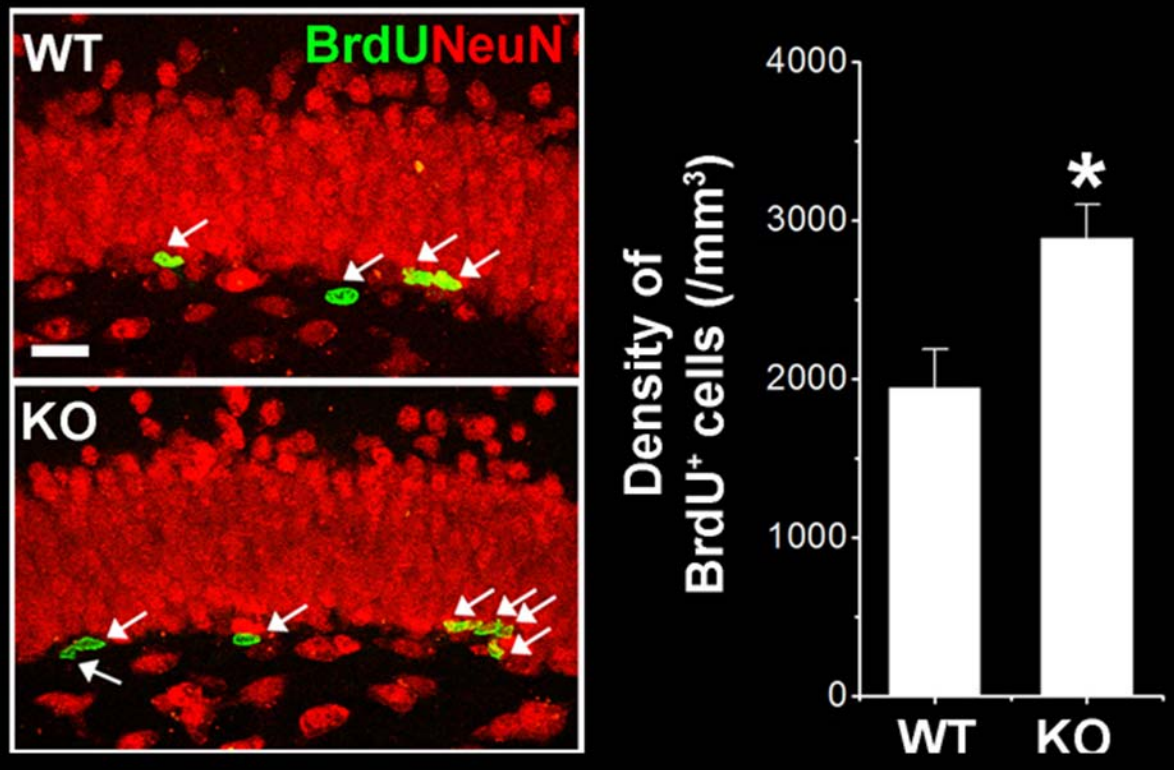
(Yasuji Kitabakate)

Chemical antidepressants suppress the expression of sFRP3



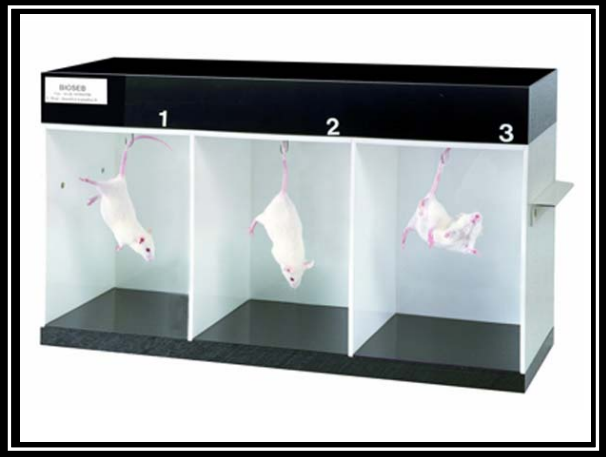


Wnt pathway stimulates brain stem cells



sFRP3 deletion mimics anti-depressant-induced behavioral effects

Tail Suspension Test

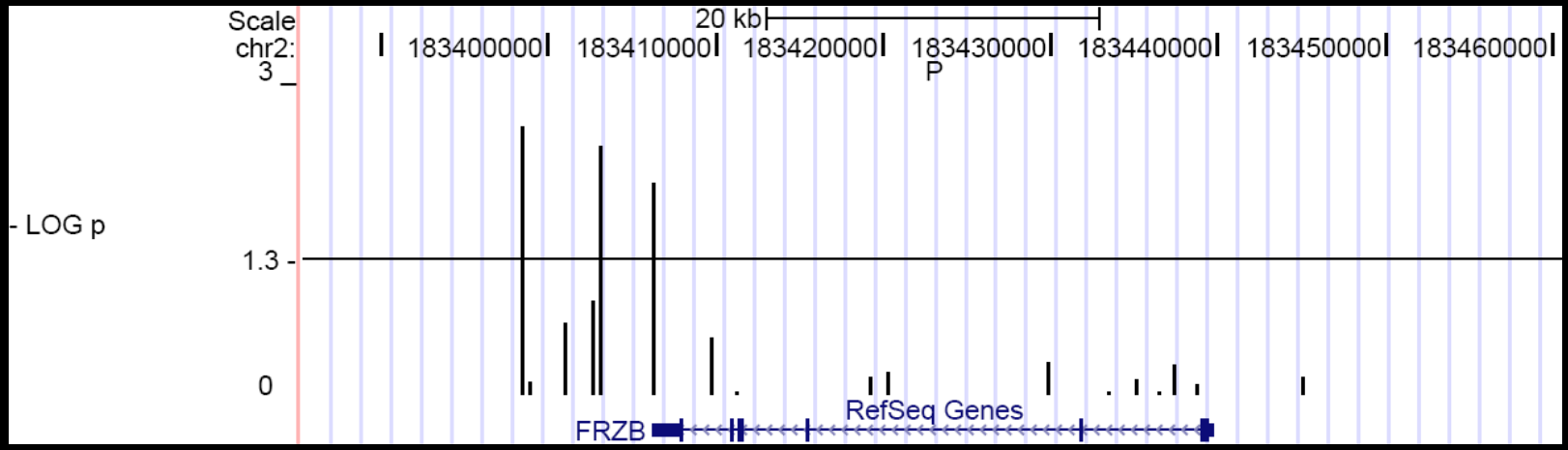


Forced Swimming Test

- Tail suspension test has been used to assay mood levels, it is the most widely used tests to assay the efficacy of antidepressants
- Forced swimming tests examines negative mood, also used to test the effect of antidepressants
- sFRP deletion mice are happy mice
- fluoxetine has no further effects on sFRP deletion mice

(Yasuji Kitabakate)

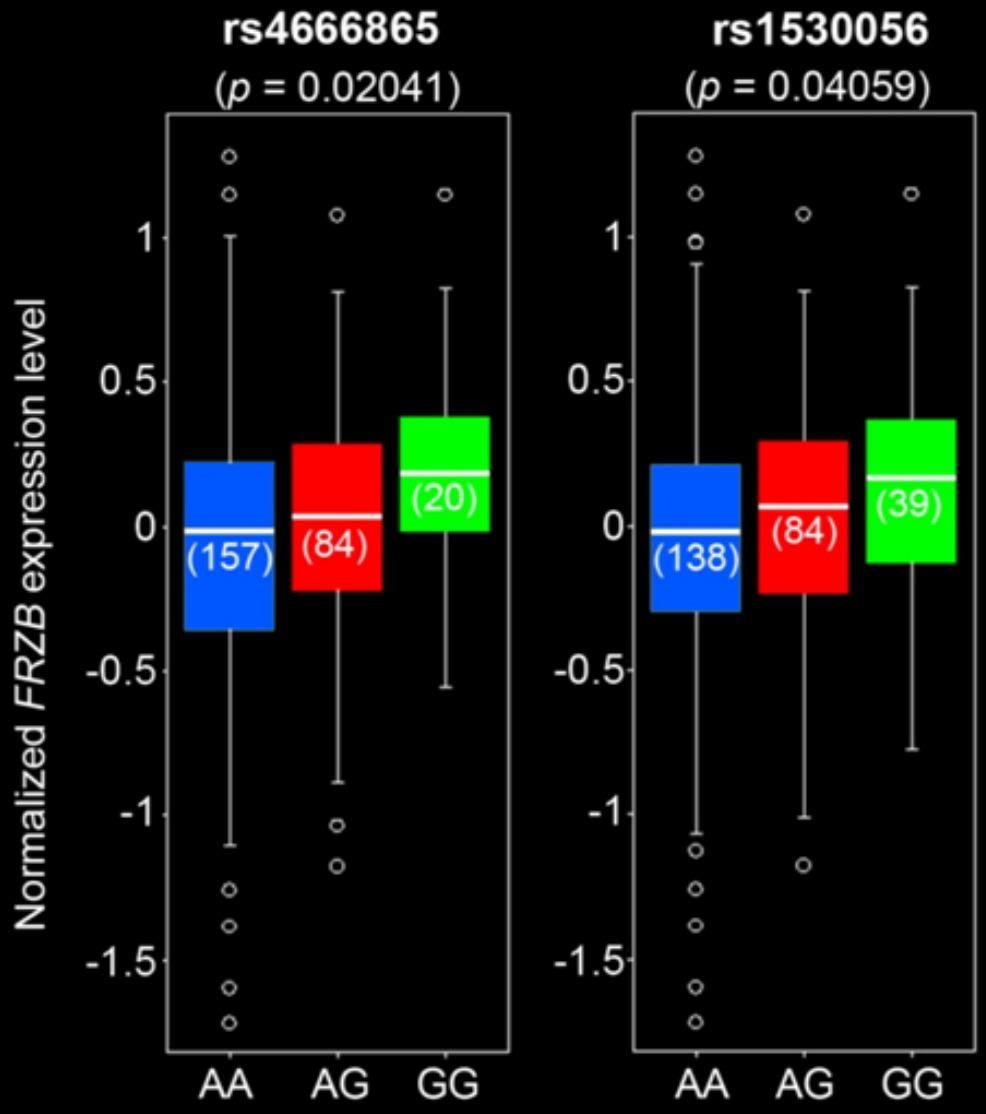
sFRP3 SNPs exhibit significant association with latency to partial responses in depression patients



SNP	*p*-value	Corrected *p*-value**
rs11902959	0.0028*	0.038*
rs1530056	0.0044*	0.038*
rs4666865	0.0097*	0.055

(Elisabeth Binder, Munich)

Same sFRP3 SNPs correlate with sFRP3 mRNA expression in the human brain



(Danny Weinberger, Lieber)

sFRP3 - potential target for novel treatment of depression

- Multiple antidepressant treatments alter sFRP3 gene expression
- sFRP3 KO mice show reduction in depressive-like behavior
- sFRP3 is a negative regulator of adult neurogenesis
- Enhanced adult neurogenesis correlates with efficacy of antidepressant treatment
- sFRP3 (*FRZB*) SNPs associate with latency to partial antidepressant response in patients