Sandrine Thuret, PhD

Generation of New Hippocampal Neurons in the Adult Brain: Implication for Mental Health

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Disclosure Statement of Financial Interest

I, (Sandrine Thuret),

DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

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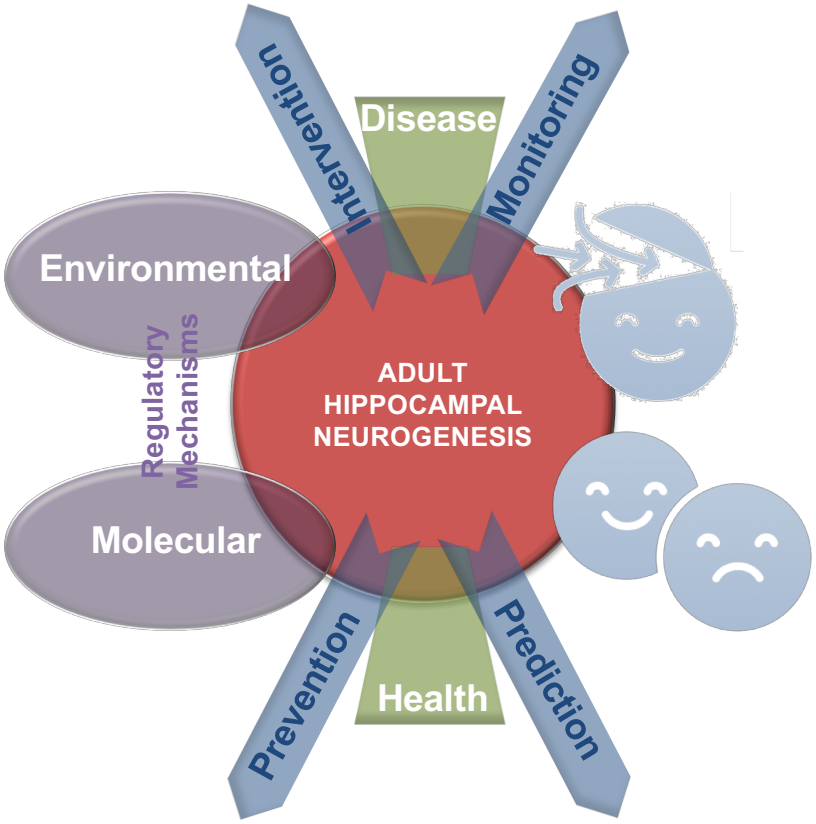

Intervention
Disease
Monitoring
Environmental
Regulatory Mechanisms
ADULT HIPPOCAMPAL NEUROGENESIS
Molecular
Prevention
Health
Prediction

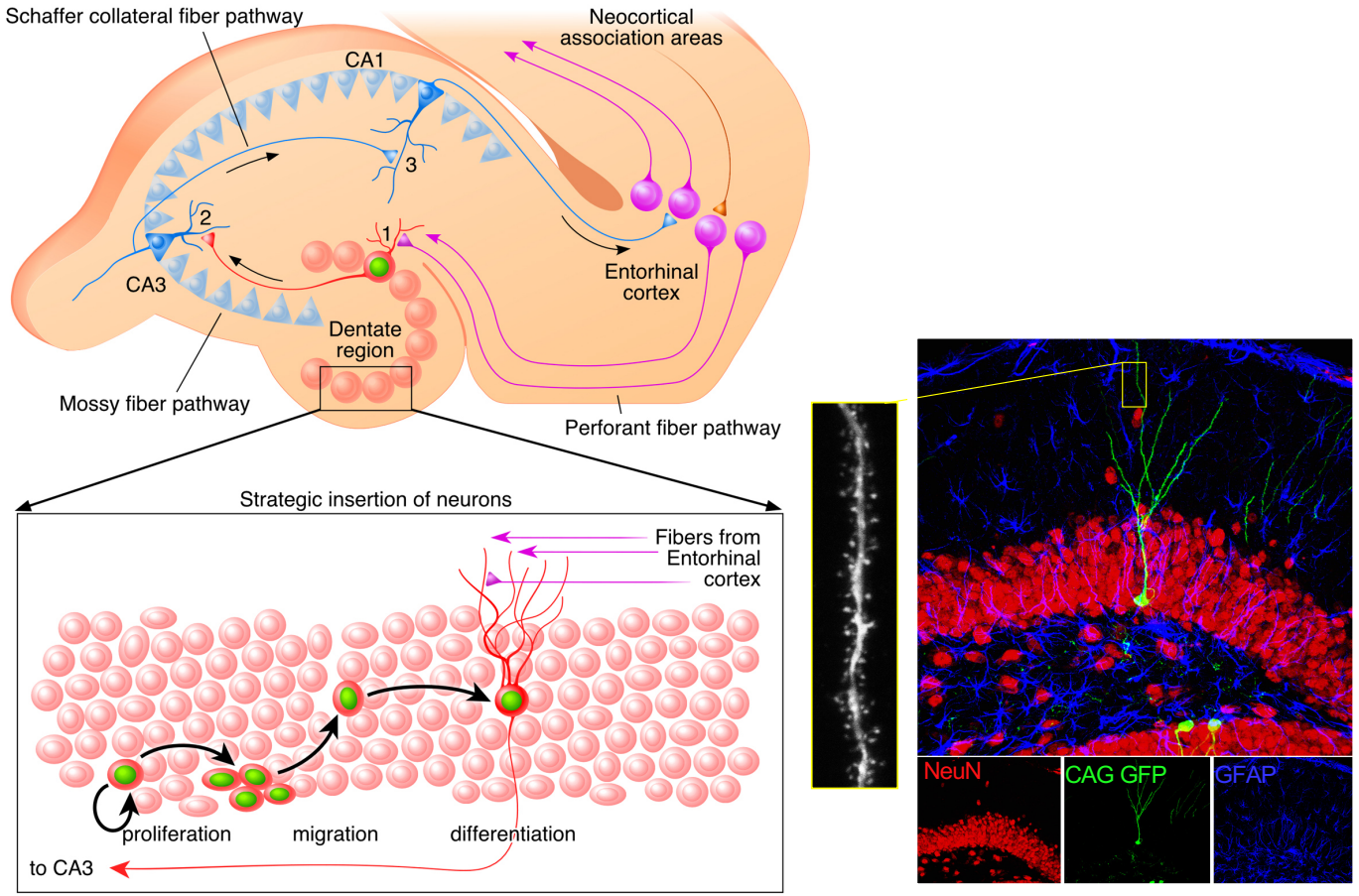
"Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, and immutable: everything may die, nothing may be regenerated."

Santiago Ramon y Cajal, 1928

Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats.

Altman & Das, 1965

Adult hippocampal neurogenesis

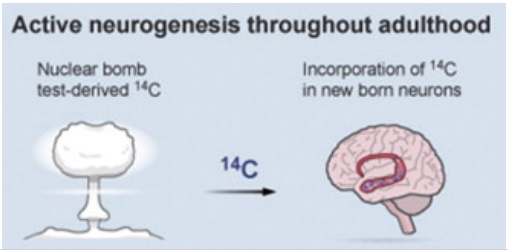


Adult hippocampal neurogenesis in **humans**

Dynamics of Hippocampal Neurogenesis in Adult Humans

Cell 153, 1219–1227, June 6, 2013 ©2013 Elsevier Inc. 1219

Kirsty L. Spalding,[1,8] Olaf Bergmann,[1,8] Kanar Alkass,[1,2] Samuel Bernard,[3] Mehran Salehpour,[4] Hagen B. Huttner,[1,5] Emil Boström,[1] Isabelle Westerlund,[1] Céline Vial,[3] Bruce A. Buchholz,[6] Göran Possnert,[4] Deborah C. Mash,[7] Henrik Druid,[2] and Jonas Frisén[1,*]



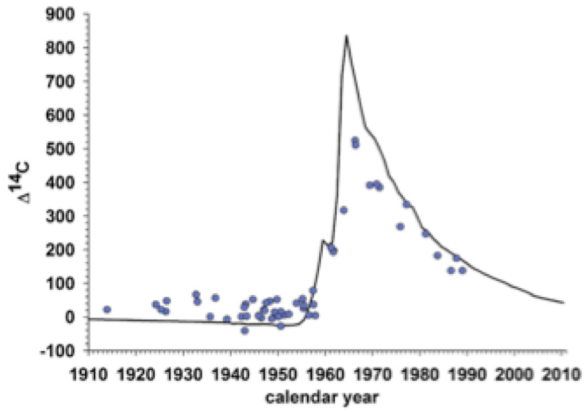


Figure 3. Hippocampal Neurogenesis in Adult Humans

^{14}C concentrations in hippocampal neuron genomic DNA correspond to a time after the date of birth of the individual, demonstrating neurogenesis throughout life.

LETTER

doi:10.1038/nature25975

Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults

Shawn F. Sorrells[1,2]*, Mercedes F. Paredes[1,3]*, Arantxa Cebrian-Silla[4], Kadellyn Sandoval[1,3], Dashi Qi[5], Kevin W. Kelley[1], David James[1], Simone Mayer[1,3], Julia Chang[6], Kurtis I. Auguste[2], Edward F. Chang[2], Antonio J. Gutierrez[7], Arnold R. Kriegstein[1,3], Gary W. Mathern[8,9], Michael C. Oldham[1,2], Eric J. Huang[10], Jose Manuel Garcia-Verdugo[4], Zhengang Yang[5] & Arturo Alvarez-Buylla[1,2]

Human Hippocampal Neurogenesis Persists throughout Aging

Maura Boldrini,[1,5,9,10,*] Camille A. Fulmore,[5] Alexandria N. Tartt,[5] Laika R. Simeon,[5] Ina Pavlova,[6] Verica Poposka,[8] Gorazd B. Rosoklija,[1,5,7] Aleksandar Stankov,[8] Victoria Arango,[1,5] Andrew J. Dwork,[1,2,5,7] René Hen,[1,3,4,6] and J. John Mann[1,5]

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[2]Department of Pathology and Cell Biology, Columbia University, New York, NY 10032, USA
[3]Department of Neuroscience, Columbia University, New York, NY 10032, USA
[4]Department of Pharmacology, Columbia University, New York, NY 10032, USA
[5]Division of Molecular Imaging and Neuropathology, NYS Psychiatric Institute, New York, NY 10032, USA
[6]Division of Integrative Neuroscience, NYS Psychiatric Institute, New York, NY 10032, USA
[7]Macedonian Academy of Sciences & Arts, 2, Ss. Cyril & Methodius University, Skopje 1000, Republic of Macedonia
[8]Institute for Forensic Medicine, Ss. Cyril & Methodius University, Skopje 1000, Republic of Macedonia
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*Correspondence: mb928@cumc.columbia.edu
https://doi.org/10.1016/j.stem.2018.03.015

Adult hippocampal neurogenesis in **humans**

Cell Stem Cell

Minireview

Human Adult Neurogenesis: Evidence and Remaining Questions

Gerd Kempermann,[1,*] Fred H. Gage,[2,*] Ludwig Aigner,[3] Hongjun Song,[4] Maurice A. Curtis,[5] Sandrine Thuret,[6] H. Georg Kuhn,[7,8] Sebastian Jessberger,[9] Paul W. Frankland,[10] Heather A. Cameron,[11] Elizabeth Gould,[12] Rene Hen,[13] D. Nora Abrous,[14] Nicolas Toni,[15] Alejandro F. Schinder,[16] Xinyu Zhao,[17] Paul J. Lucassen,[18] and Jonas Frisén[19,*]

Renewed discussion about whether or not adult neurogenesis exists in the human hippocampus, and the nature and strength of the supporting evidence, has been reignited by two prominently published reports with opposite conclusions. Here, we summarize the state of the field and argue that there is currently no reason to abandon the idea that adult-generated neurons make important functional contributions to neural plasticity and cognition across the human lifespan.

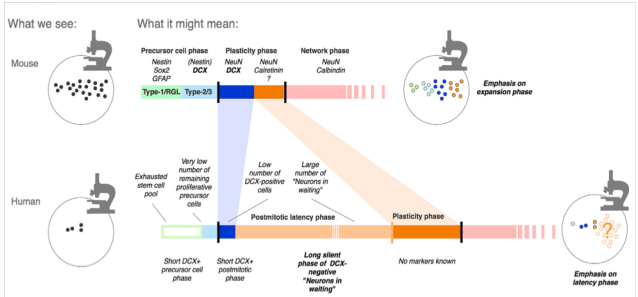


Figure 2. Consequences of Species Differences in the Course of Neurogenesis
Besides methodological considerations, a hypothetical concept of a temporal decoupling of the stages of adult neurogenesis and species differences in marker expression, although largely speculative at this time, might explain part of the discrepancies between rodent and human data. The point is that alternative hypotheses that are consistent with the available data are possible.

Trends in Molecular Medicine

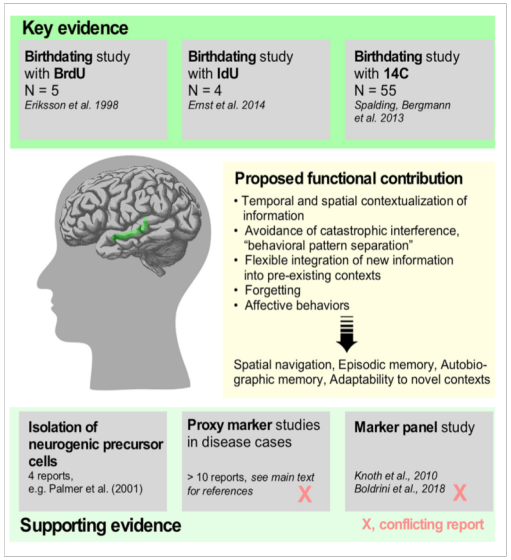
CellPress

Spotlight

Adult Human Hippocampal Neurogenesis: Controversy and Evidence

Hyunah Lee[1] and Sandrine Thuret[1,*]

The hippocampus has been described as one of the few sites in the mammalian brain capable of generating new cells continuously throughout life. Two recent studies that report contradicting findings on adult human hippocampal neurogenesis, however, reminds us of the caveats and challenges of studying this phenomenon in post-mortem tissues.



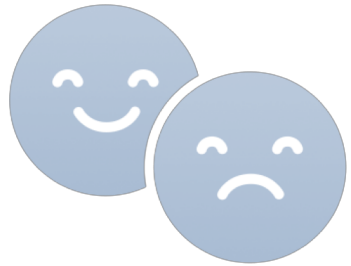
New Dentate Gyrus granule cells:

- Increase spatial memory capacity
- Reduce interference between memories (pattern separation)
- Add information about time to memories
- Are involved in forgetting of established context-memories.

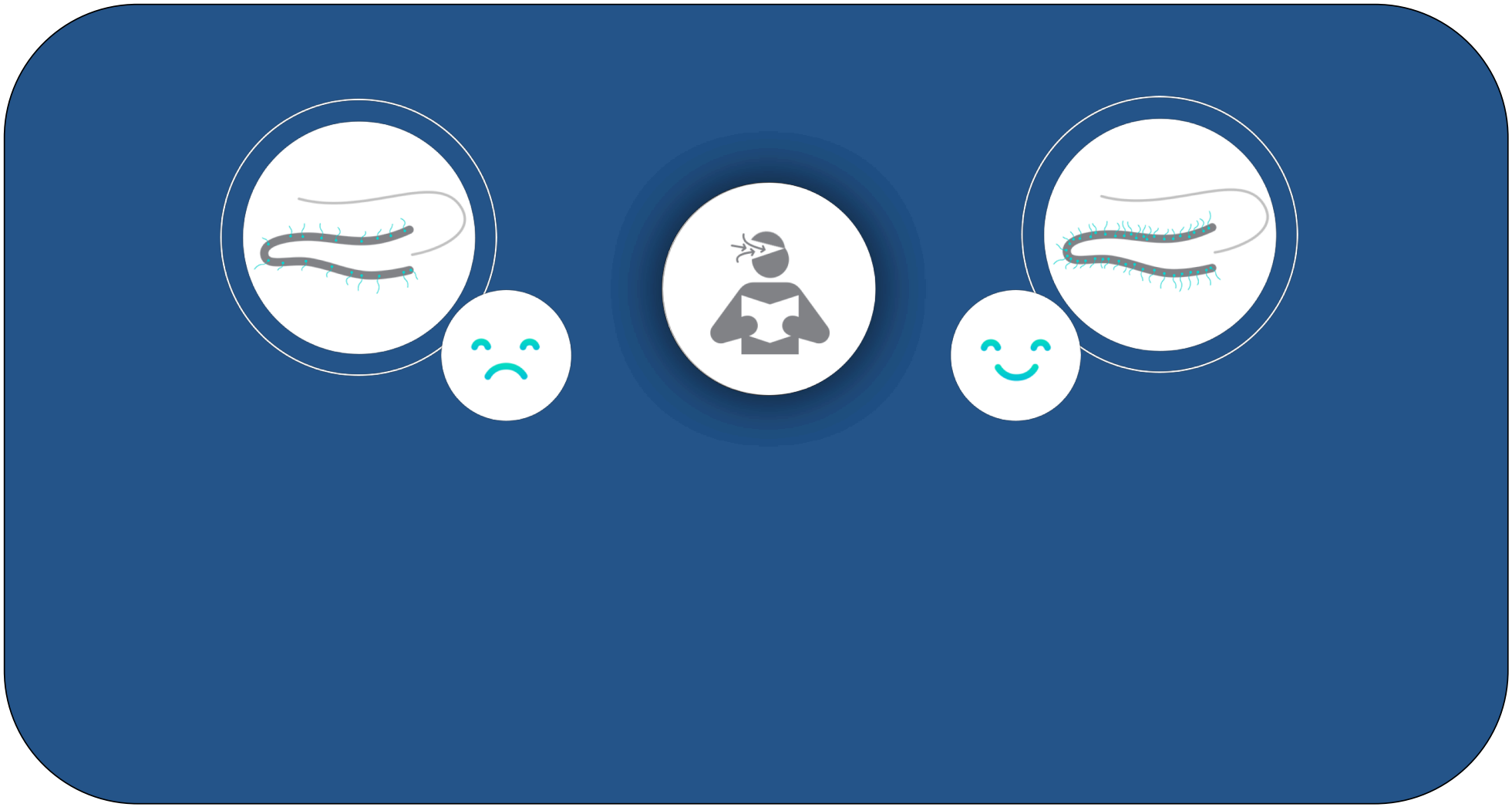
Functional Relevance of Adult Hippocampal Neurogenesis: **Mood**

- Adult Hippocampal Neurogenesis is reduced in some animal models of depression.

- Many treatments for depression promote Adult Hippocampal Neurogenesis and/or are dependent on functional neurogenesis.



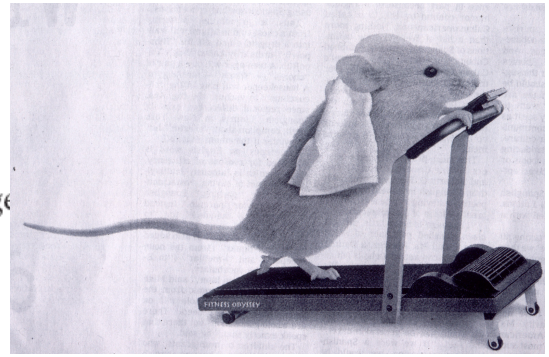
Adult Hippocampal Neurogenesis: **Regulated by environmental influences**

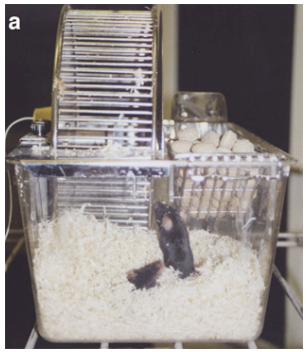


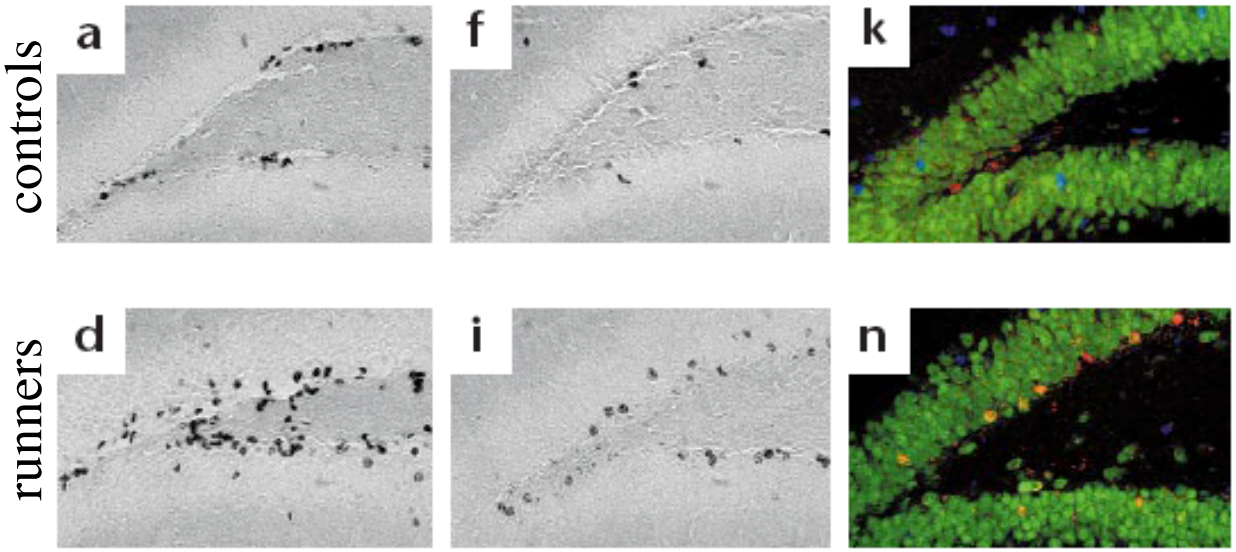
Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus

nature *neuroscience* • volume 2 no 3 • march 1999

Henriette van Praag[1], Gerd Kempermann[1,2] and Fred H. Gage

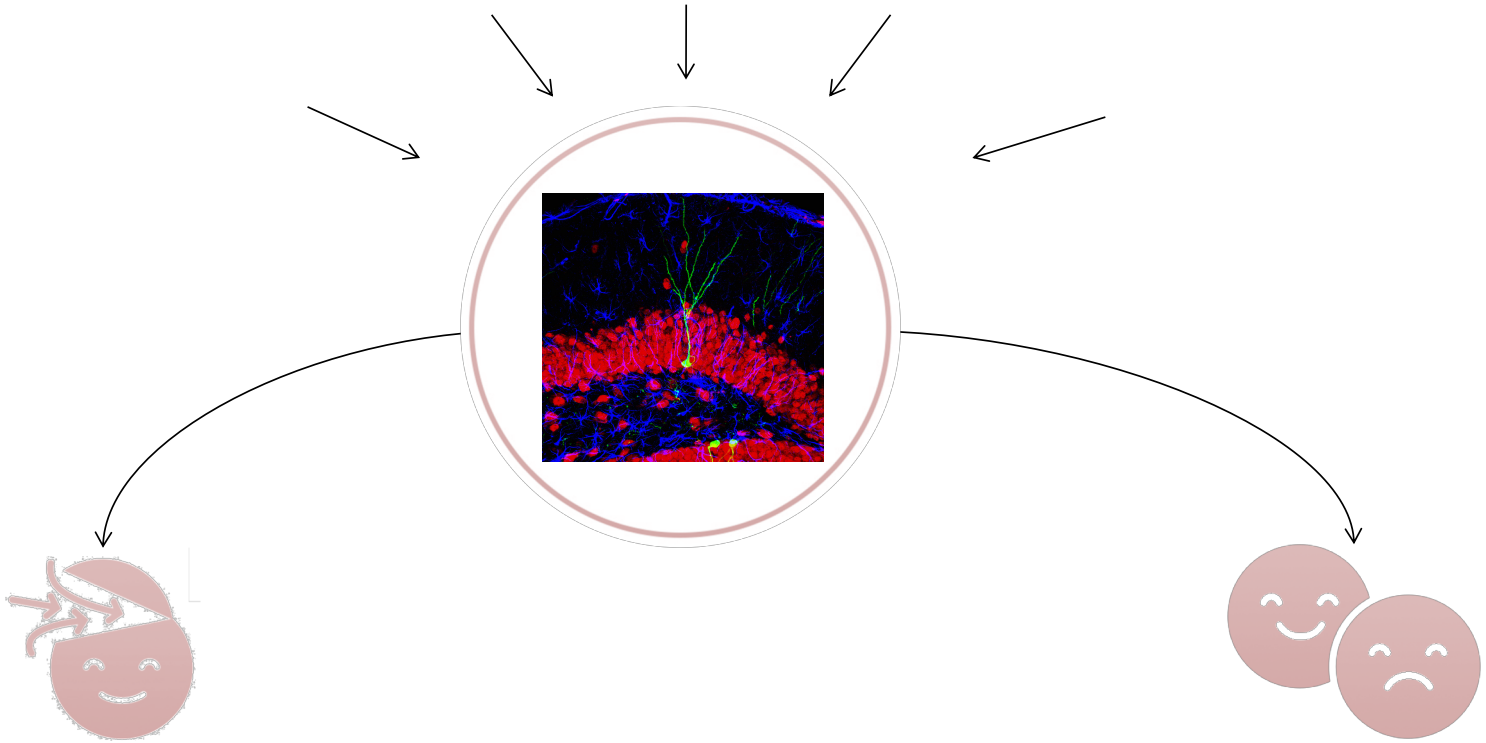




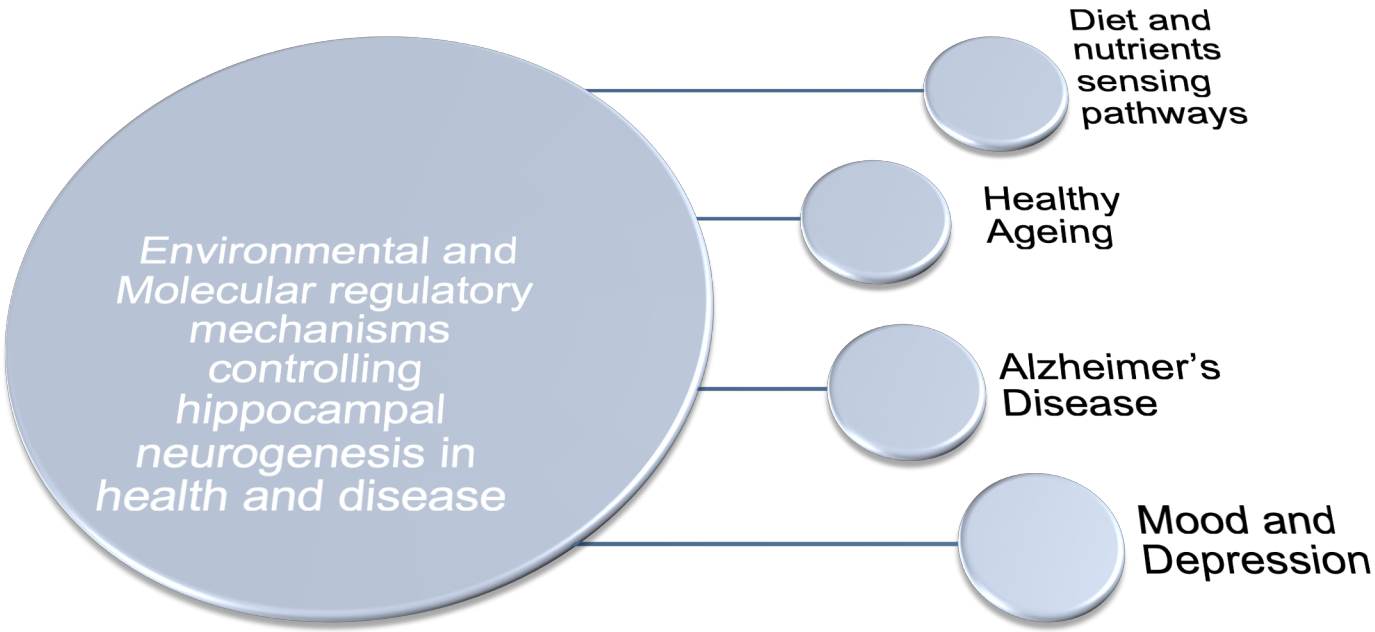


	Control	Runner
Proliferation, 1day	4393 (607)	6773 (971)***
Survival, 4 weeks	1880 (251)	3791 (715)**
Survival (%), 4 weeks	43 (5.7)	56 (10.6)
Phenotypes:		
Neuron (%)	76.8 (3.2)	88.3 (1)*
Astrocyte (%)	7 (2.1)	3.3 (0.6)
Other (%)	16.3 (1.7)	9 (1.3)*
Volume (mm^3)	0.43 (0.02)	0.42 (0.02)

Adult Hippocampal Neurogenesis emerging as **Target of choice**?



Our hippocampal neurogenesis Lines of Research

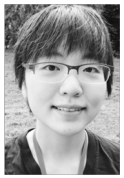


Andrea Du Preez 

Curie Kim 

Chiara de Lucia 

Edina Silajdzic 

Hyun-ah Lee 

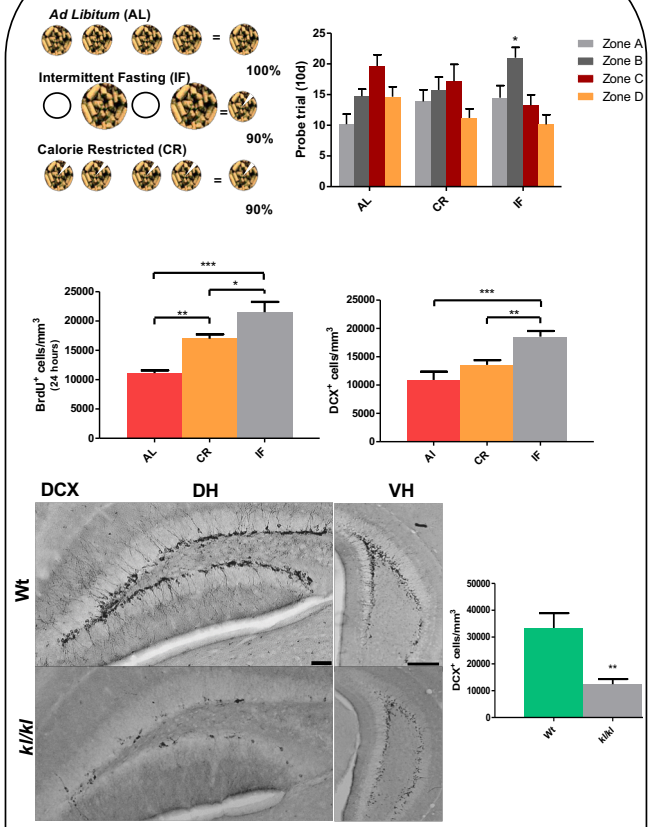
Thomas Berger 

Demelza Smeeth 

Amina McDiarmid 

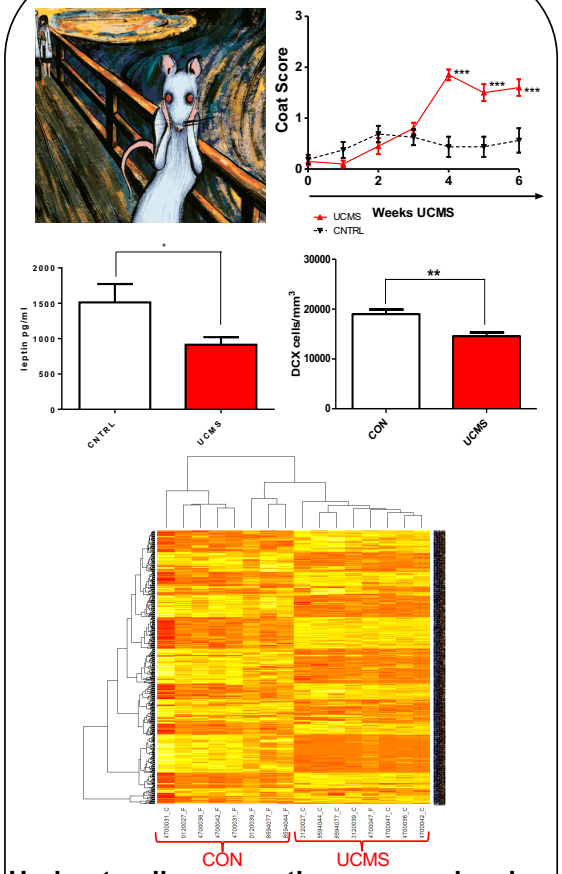
Alish Palmos 

Animal Models



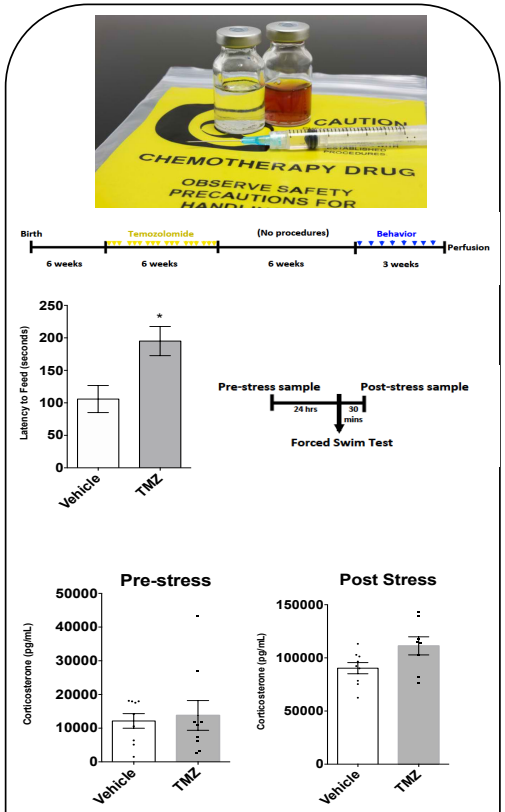
Intermittent fasting enhances recognition memory and adult hippocampal neurogenesis via the longevity gene Klotho and miR-497.

Dias et al. in preparation



Understanding the molecular neurobiology of depression.

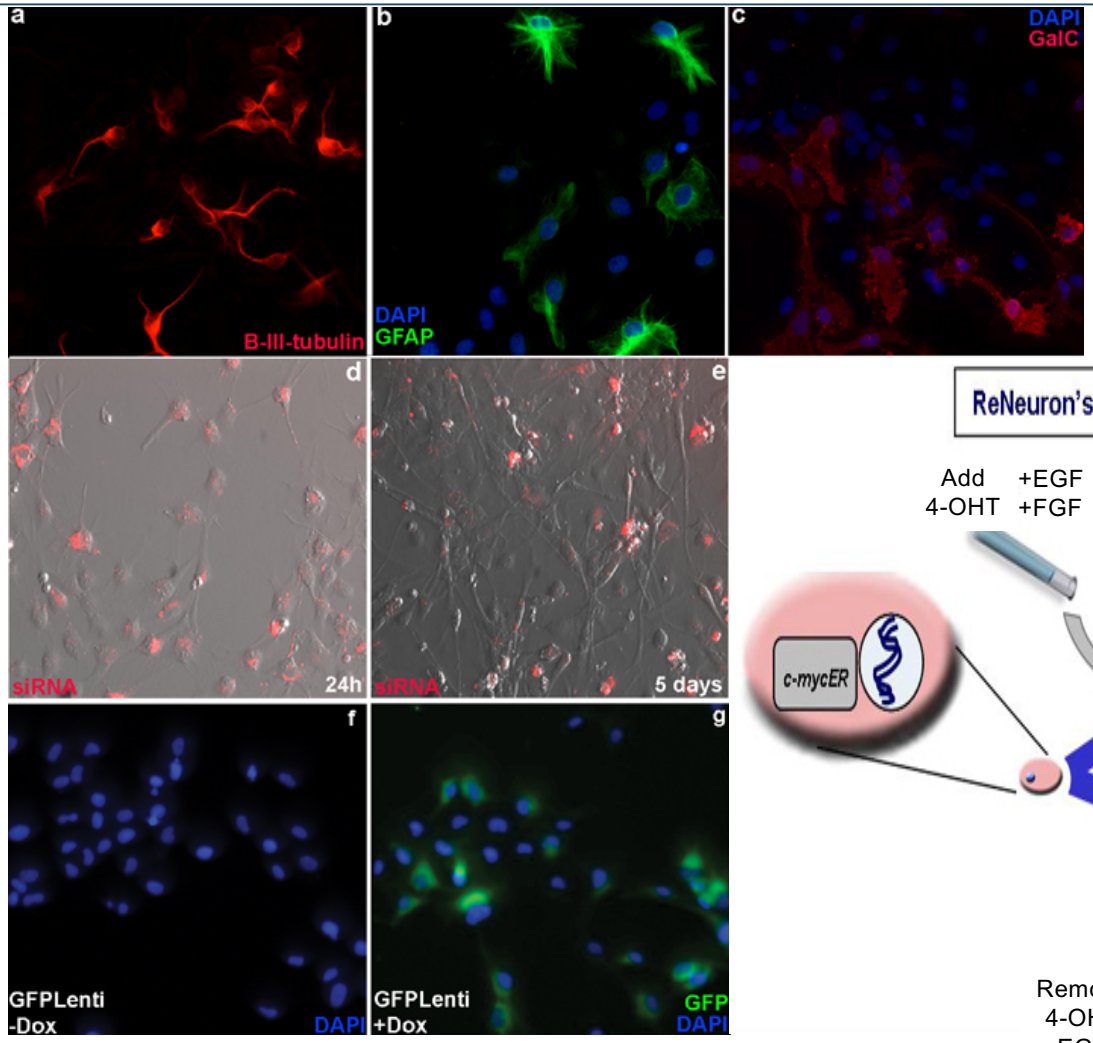
Musaelyan et al. 2018 and in preparation



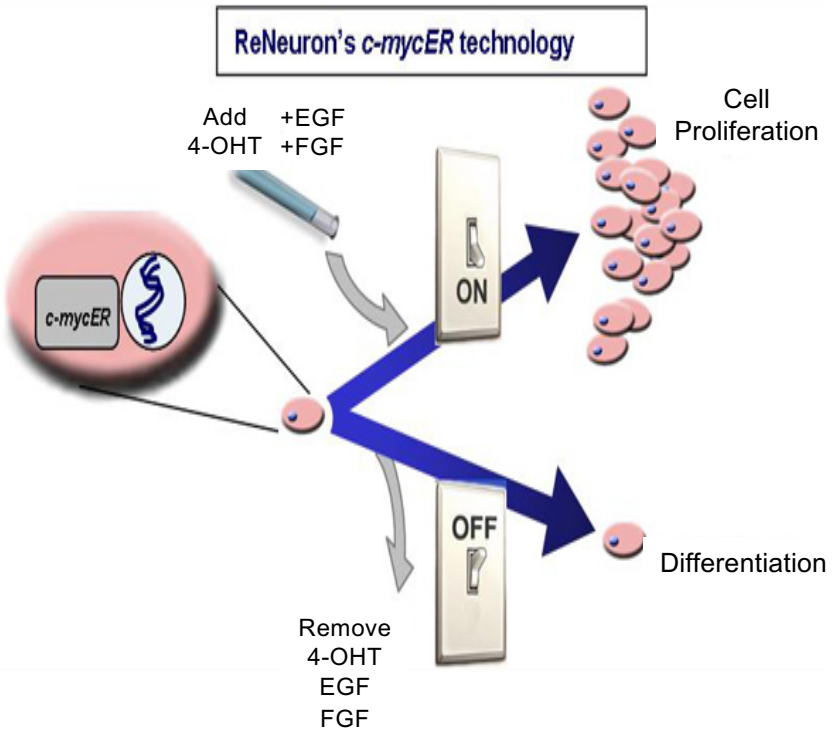
Neurogenesis depletion using anti-mitotic drug Temozolomide causes changes in affective behaviour in mice.

Egeland et al. Translational Psychiatry 2017

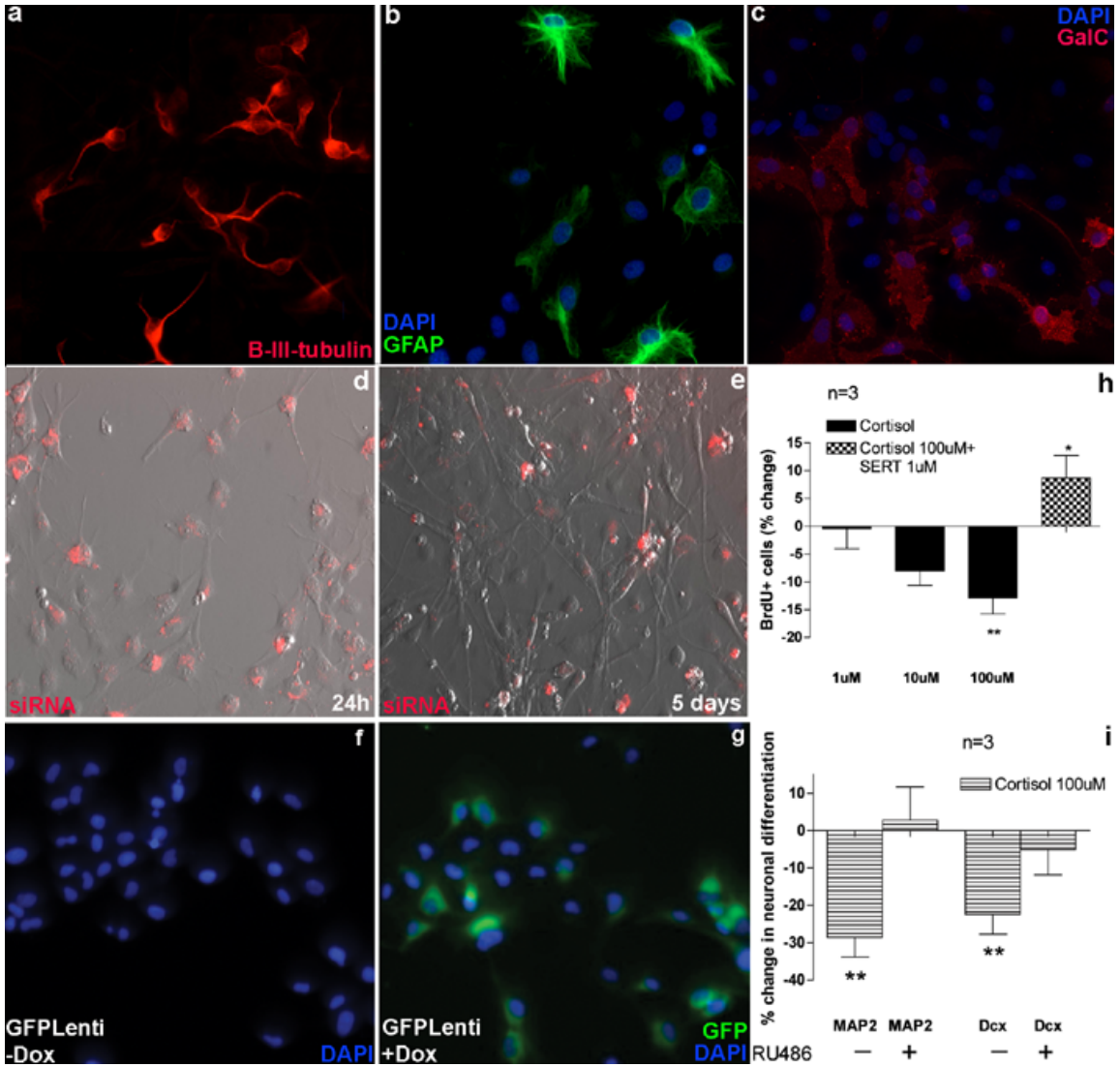
Human Hippocampal Stem Cell line – Controlled Environment



Identification and validation of new genes and microRNAs involved in Proliferation and/or Neuronal Differentiation



Human Hippocampal Stem Cell line – Stress Model



Identification of the mode of action of antidepressants

Anacker et al., 2011, 2013a, 2013b

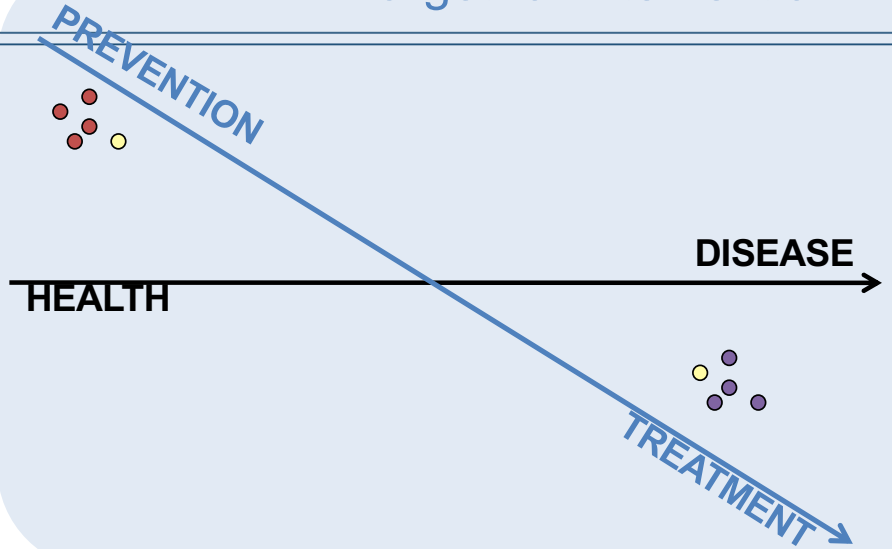
Identification of nutrient-derived bioactives preventing stress-induced decrease of neurogenesis

Stangl et al. in preparation

Identification of drugs for repositioning as new antidepressants

Powel et al. 2017a, b

AHN: A Target for intervention



The Role of Dietary Polyphenols on Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavioural Effects on Depression and Anxiety

Gisele Pereira Dias,[1,2,3] Nicole Cavegn,[1] Alina Nix,[1] Mário Cesar do Nascimento Bevilaqua,[2] Doris Stangl,[1] Muhammad Syahrul Anwar Zainuddin,[1] Antonio Egidio Nardi,[3] Patricia Franca Gardino,[2] and Sandrine Thuret[1]

Hippocampal Neurogenesis in Alzheimer's Disease: Is There a Role for Dietary Modulation?

Aleksandra Maruszak, Adam Pilarski, Tytus Murphy, Nicholas Branch and Sandrine Thuret*

Department of Neuroscience, Institute of Psychiatry, King's College London, London, United Kingdom

Nutrition, adult hippocampal neurogenesis and mental health

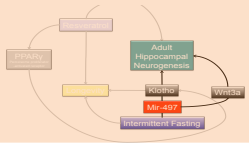
Muhammad Syahrul Anwar Zainuddin and Sandrine Thuret*

Effects of Diet on Brain Plasticity in Animal and Human Studies: Mind the Gap

Tytus Murphy, Gisele Pereira Dias, and Sandrine Thuret

Modulation of Adult Hippocampal Neurogenesis by Early-Life Environmental Challenges Triggering Immune Activation

Ksenia Musaelyan,[1,2,3] Martin Egeland,[1,2] Cathy Fernandes,[3] Carmine M. Pariante,[1,2] Patricia A. Zunszain,[1,2] and Sandrine Thuret[1]



Interleukin-1β: A New Regulator of the Kynurenine Pathway Affecting Human Hippocampal Neurogenesis

Patricia A Zunszain[1], Christoph Anacker[1], Annamaria Cattaneo[1], Shanas Choudhury[1], Ksenia Musaelyan[1], Aye Mu Myint[2], Sandrine Thuret[1], Jack Price[3] and Carmine M Pariante*[1]

Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor

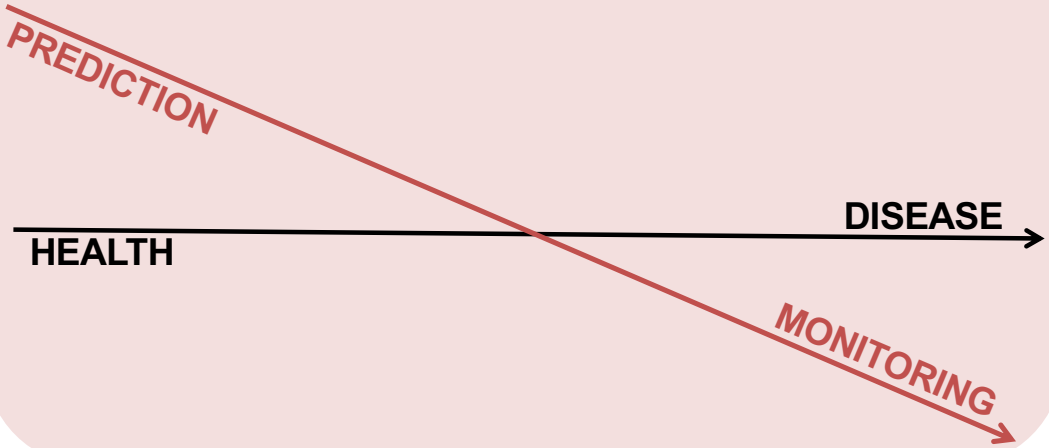
Molecular Psychiatry (2011) 16, 738–750
© 2011 Macmillan Publishers Limited All rights reserved 1359-4184/11
www.nature.com/mp

Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis

Christoph Anacker[a,b,c,1], Annamaria Cattaneo[b,d], Ksenia Musaelyan[b], Patricia A. Zunszain[b], Mark Horowitz[b], Raffaella Molteni[e], Alessia Luoni[e], Francesca Calabrese[e], Katherine Tansey[f], Massimo Gennarelli[d,g], Sandrine Thuret[h], Jack Price[a], Rudolf Uher[a,b], Marco A. Riva[e], and Carmine M. Pariante[a,b]

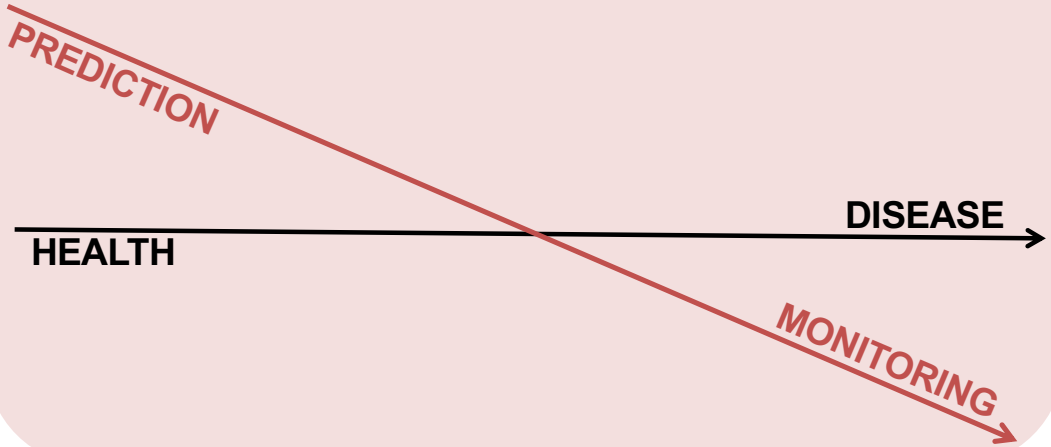
8708–8713 | PNAS | May 21, 2013 | vol. 110 | no. 21

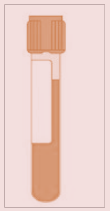
AHN: A Biomarker for Health status, disease prediction and monitoring



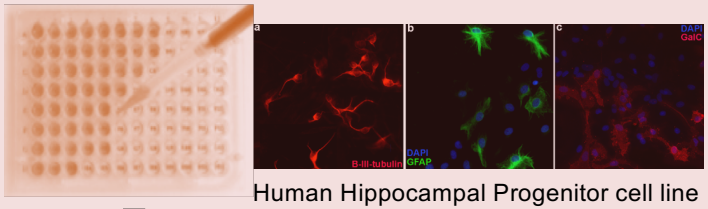
AHN: A Biomarker for Health status, disease prediction and monitoring

AHN: A Biomarker for Health status, disease prediction and monitoring

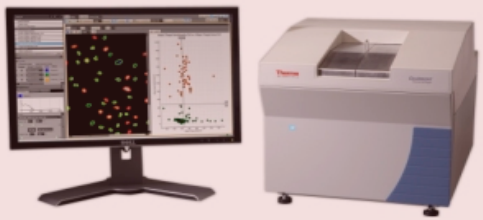




Human Serum



Human Hippocampal Progenitor cell line



Semi-automated cell profiling platform

Cellular read-out: Stem cellness- Proliferation- Differentiation (inc. neurogenesis)- Neurite outgrowth – Senescence- Cell death…

Aleksandra Maruszak et al., bioRxiv
Murphy et al. in preparation

Why using serum?

(i) The neurogenic niche is localized around blood vessels allowing for potential communication with the systemic environment.

(i) Cognitive/mood impairments and adult hippocampal neurogenesis can be ameliorated through systemic perturbations such as exercise and diet.

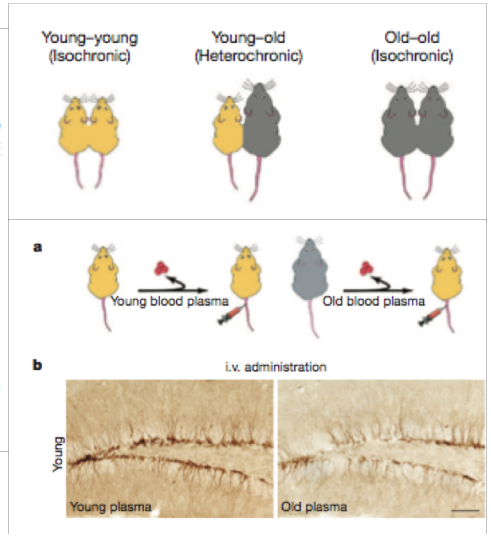
(iii) The systemic milieu can inhibit or promote adult neurogenesis in an age-dependent fashion in mice.

LETTER

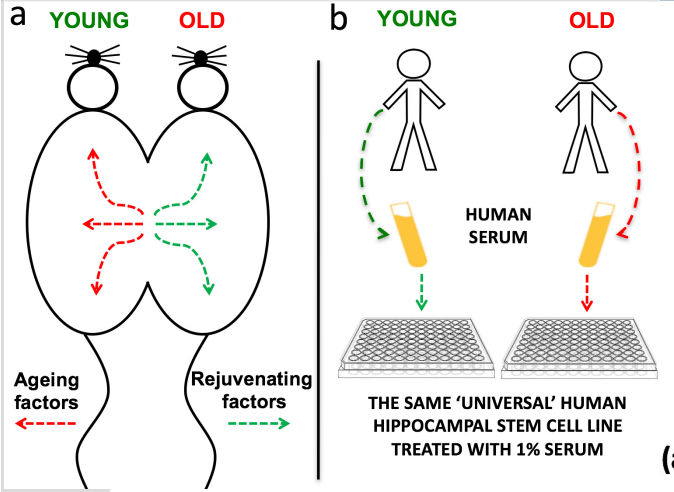
doi:10.1038/nature10357

The ageing systemic milieu negatively regulates neurogenesis and cognitive function

Saul A. Villeda[1,2], Jian Luo[1], Kira I. Mosher[1,2], Bende Zou[3], Markus Britschgi[1]†, Gregor Bieri[1,4], Trisha M. Stan[1,5], Nina Fainberg[1], Zhaoqing Ding[1,5], Alexander Eggel[1], Kurt M. Lucin[1], Eva Czirr[1], Jeong-Soo Park[1]†, Sebastien Couillard-Després[6], Ludwig Aigner[6], Ge Li[7], Elaine R. Peskind[7,8], Jeffrey A. Kaye[9], Joseph F. Quinn[9], Douglas R. Galasko[10], Xinmin S. Xie[3], Thomas A. Rando[1,11,12] & Tony Wyss-Coray[1,2,5,11]



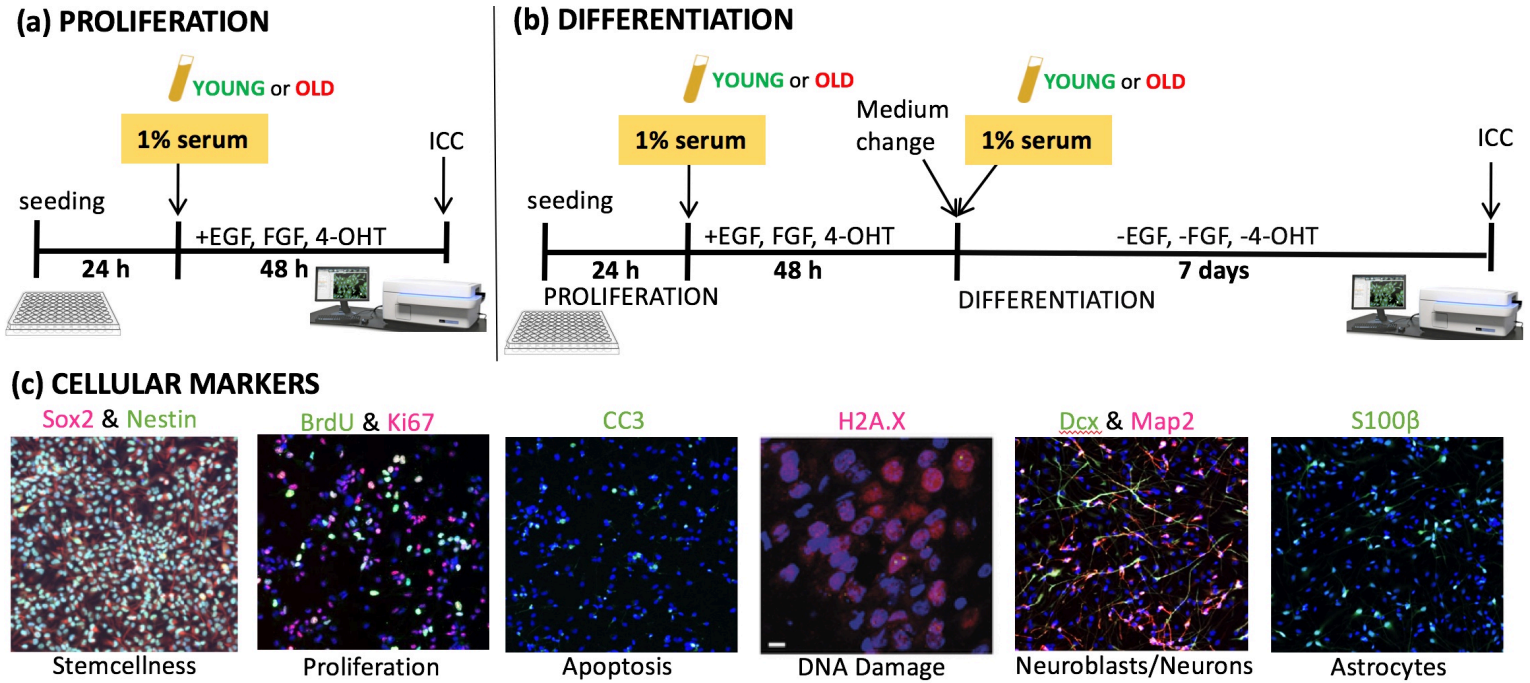
In vitro Parabiosis assay



Healthy Young donors
(n=27, Mean age: 29.7)

Healthy Old donors
(n=35, Mean age: 77.7)

Tytus Murphy et al. in preparation



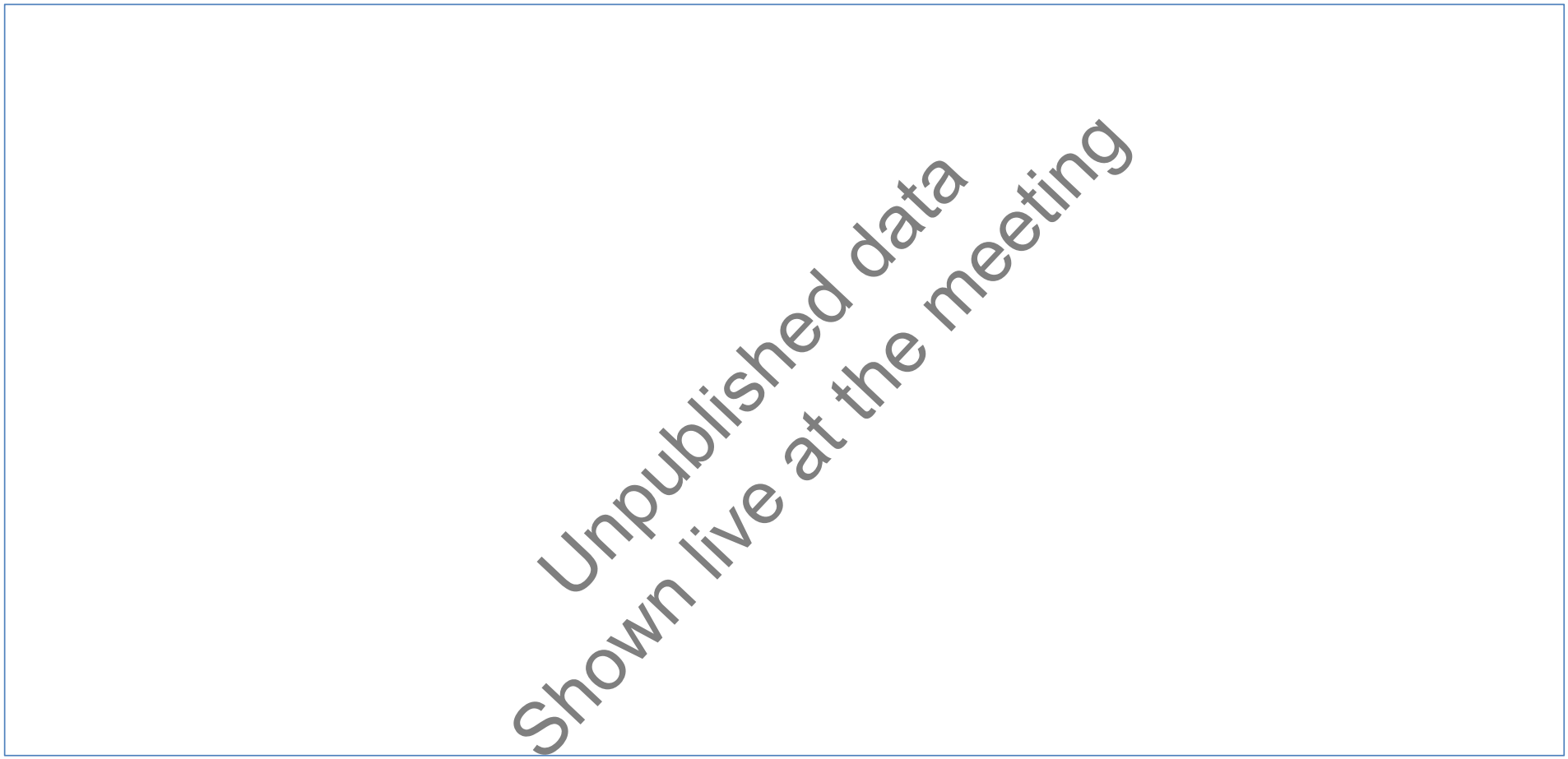
Older donor serum increases apoptotic hippocampal **stem cell death**

Age of Donor serum alone is not linked to hippocampal stem cell proliferation and differentiation

Hippocampal and DG volumes are correlated with the percentage of **Neuroblasts**

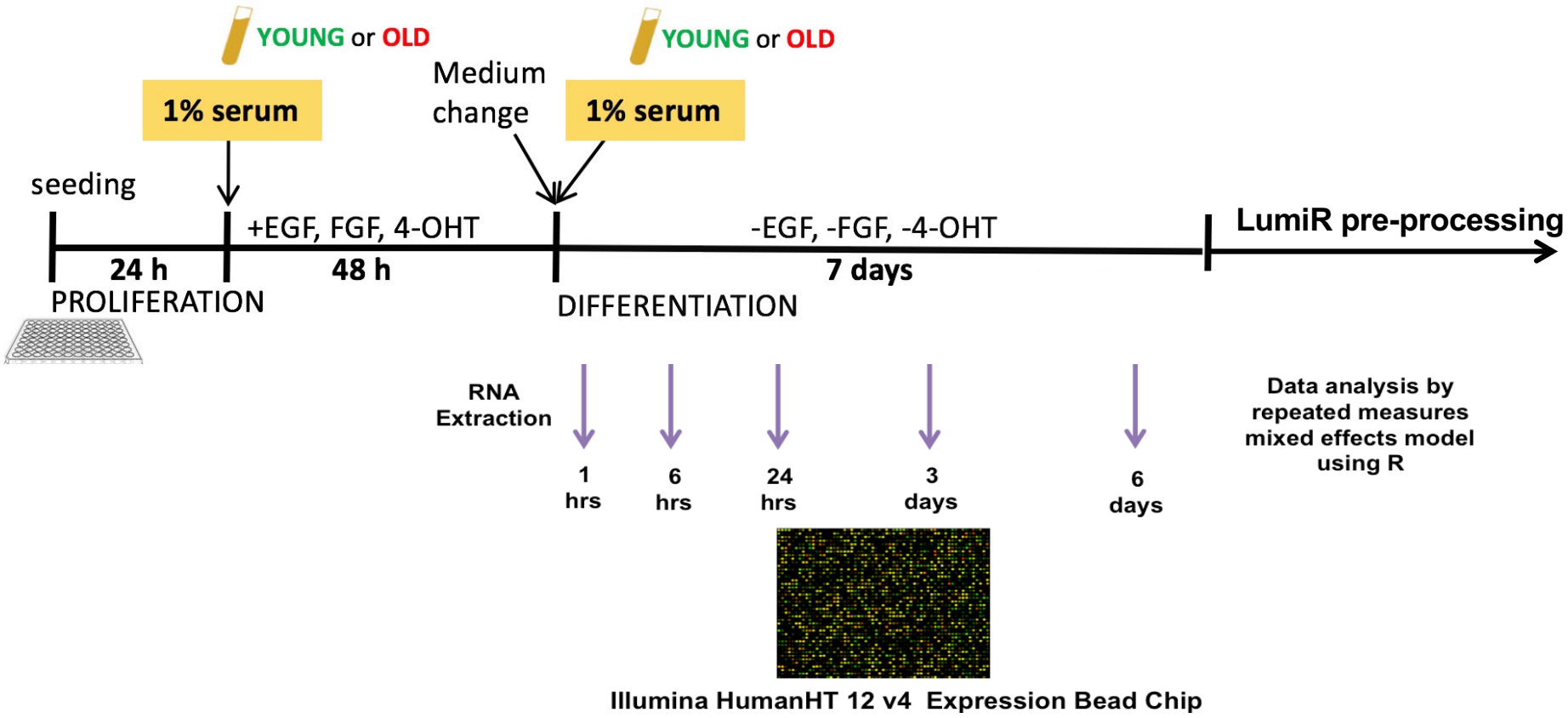
Chiara de Lucia, unpublished data, in preparation

Cognitive Decline is linked to lower percentage of **Neurons**



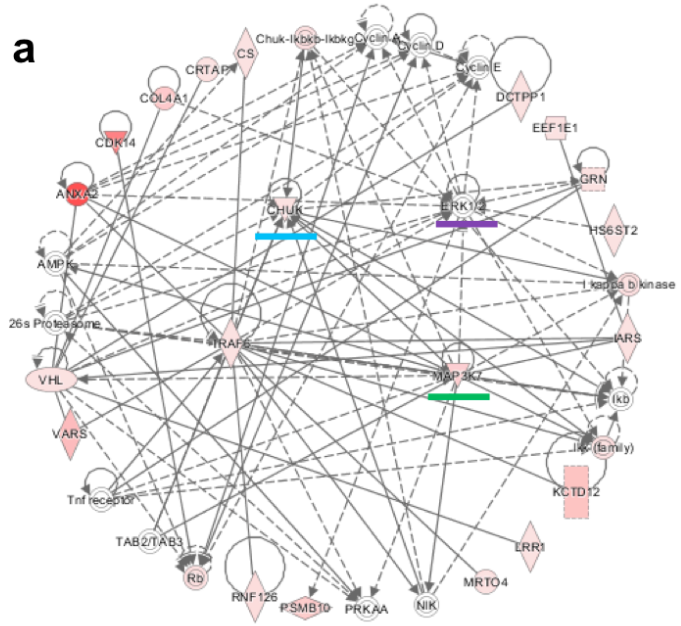
Chronological age alone does not correspond to biological age when investigating neurogenesis

Does older donor serum induces a molecular ageing phenotype?



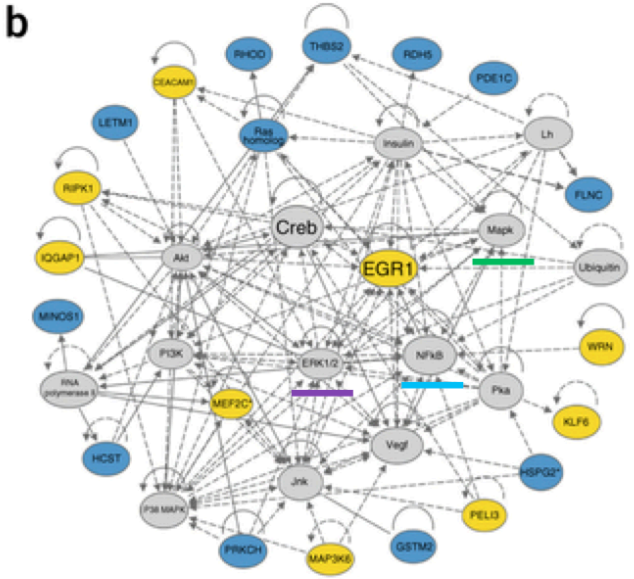
Functional network analysis reveals conserved **ageing molecular signature**

Human hippocampal progenitors cultured with young vs. old human serum



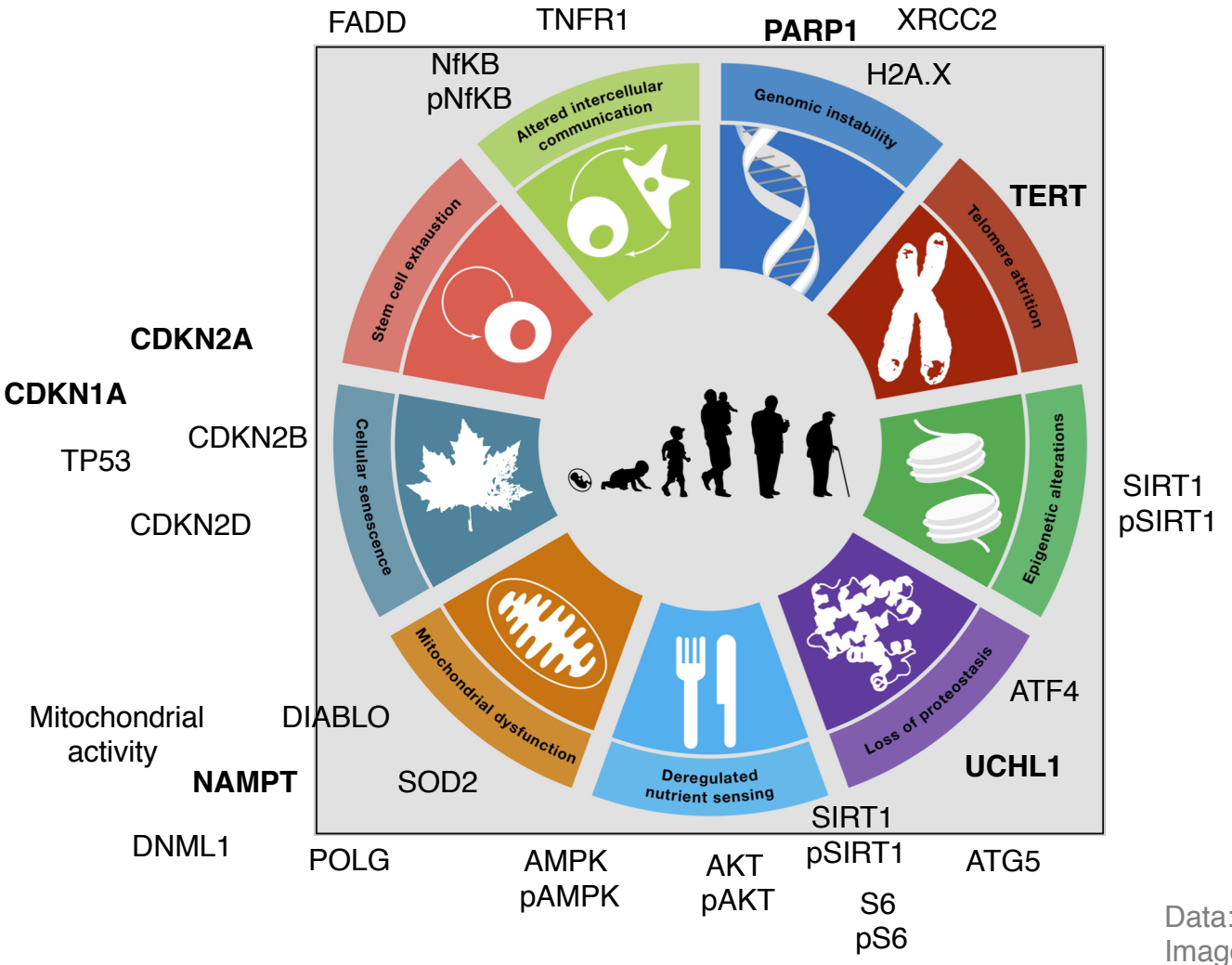
Murphy et al. in preparation

Old mouse heterochronic parabionts vs. old isochronic parabionts



Villeda et al., 2014

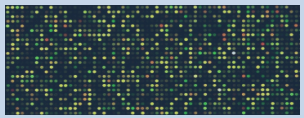
Older donor serum induces a molecular ageing phenotype in hippocampal stem cells

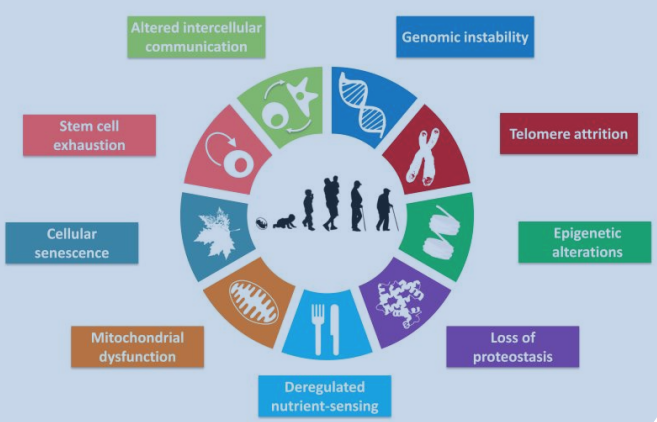


Data: Tytus Murphy and Chiara de Lucia
Image from Lopez-Otin et al., 2013

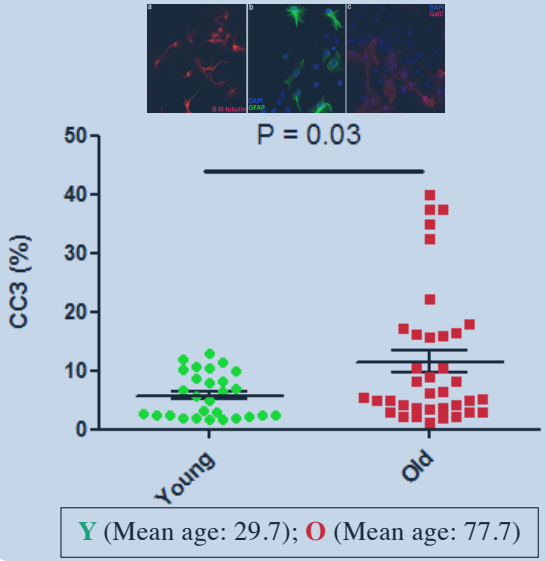
Old_Young *in vitro* parabiosis recapitulates some molecular hallmarks of Ageing

Ageing expression profile of hippocampal stem cells exposed to Old v. Young serum





Ageing Cellular profile of hippocampal stem cells exposed to Old v. Young serum



Y (Mean age: 29.7); O (Mean age: 77.7)

The systemic environment is a major determinant of hippocampal stem cell biology during ageing.

Age is associated with increased heterogeneity:
Reflecting a lifetime of **unequal exposure** to changing environments / **different life styles e.g. diet** → **Chronological age ≠ biological age**

Hippocampal neurogenesis in **Alzheimer's Disease (rodent models)**

Table 1 Summary of neurogenesis changes in transgenic mouse models of AD

Genetic Manipulation	Strain Name	Genotype	Promoter	Age (mon)	Pathology (Aβ deposition)	Neurogenesis assessment	Effect	Reference
Knock-in		mo PS1M146V/-		3		BrdU injection twice daily (2 hr apart) for 4 consecutive days	Decreased proliferation and differentiation	[36]
		hu ApoE4		3, 6-7, 12-13		BrdU injection twice (6 hr apart)	Diminished neuronal maturation	[41]
		mo APPswe/ PS1ΔE9		8-9 18-24	post	DCX, MCM2 immunostaining	Decreased proliferation	[42]
Transgenic		hu PS1P117L	NSE	3-4		one BrdU injection per day for 12 consecutive days	Decreased survival	[37]
		hu PS1ΔE9, hu PS1M146L	PrP	3		single injection of BrdU	Decreased proliferation and differentiation	[38]
	Tg2576	chimeric mo-hu APPswe	PrP	12-14	pre	five daily injections of BrdU	Decreased proliferation, survival and differentiation	[39]
	PDAPP	hu APPind	PDGF	2 12	pre post	one i.p. injection of BrdU	Decreased proliferation and survival	[40]
	APP/ PS1	chimeric mo-hu APPswe/ hu PS1ΔE9	PrP	6	pre, post	BrdU injection once daily for 12 consecutive days	Decreased survival	[43]
	APP/ PS1	chimeric mo-hu APPswe/ hu PS1ΔE9	PrP	2	pre	BrdU injection every 12 hr for 3 days	Decreased proliferation and differentiation	[44]
	3xTg-AD	hu APPswe/ PS1M146V/ tauP301L	Thy-1.2	4, 9			Decreased proliferation	[45]
	J20	hu APPswe, ind	PDGF	3, 12	pre, post	BrdU injection twice daily (8 hr apart) for 3 consecutive days	Increased proliferation and differentiation	[46]
	J20	hu APPswe, ind	PDGF	3, 5, 9, 11	pre, post	daily injection of BrdU for 5 days	Increased proliferation and differentiation	[47]
	J20	hu APPswe, ind	PDGF	2-3	pre	BrdU injection for 3 days	Accelarated early development but impaired late maturation of newborn neurons	[48]
Knock-out		ApoE		3, 6-7, 12-13		BrdU injection twice (6 hr apart)	Reduced neurogenesis but increased astrogenesis	[41]
		PS1/PS2 forebrain KO		7-9 18-20		single dose injection of BrdU	Enhanced cell proliferation at early stages of neurodegeneration but impaired survival at late stages	[49]

Systematic comparison needed with same:

-Age
-gender
-genetic background
-neuropathology stage
-methods of neurogenesis detection

Mu & Gage, 2011
Maruszak et al. 2013

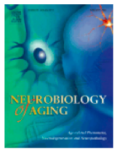
Hippocampal neurogenesis in **Alzheimer's Disease (human postmortem tissues)**

ELSEVIER

Neurobiology of Aging

Available online 8 January 2019

In Press, Accepted Manuscript



Expression of neurogenic markers in Alzheimer's disease: A systematic review and meta-transcriptional analysis

Ariana Gatt [1], Hyunah Lee [1], Gareth Williams [1], Sandrine Thuret [1], Clive Ballard [1, 2]

Show more

https://doi.org/10.1016/j.neurobiolaging.2018.12.016

Highlights

- The role of adult neurogenesis in Alzheimer's disease (AD) is not well elucidated.
- We systematically review post-mortem and transcriptional AD studies on neurogenesis.
- Expression of neural progenitor is transcriptionally upregulated in AD.
- New neurons might fail to mature and integrate in the neurogenic niches in AD.
- Neurogenesis is reduced in the later stages of AD.

Gatt et al. 2018

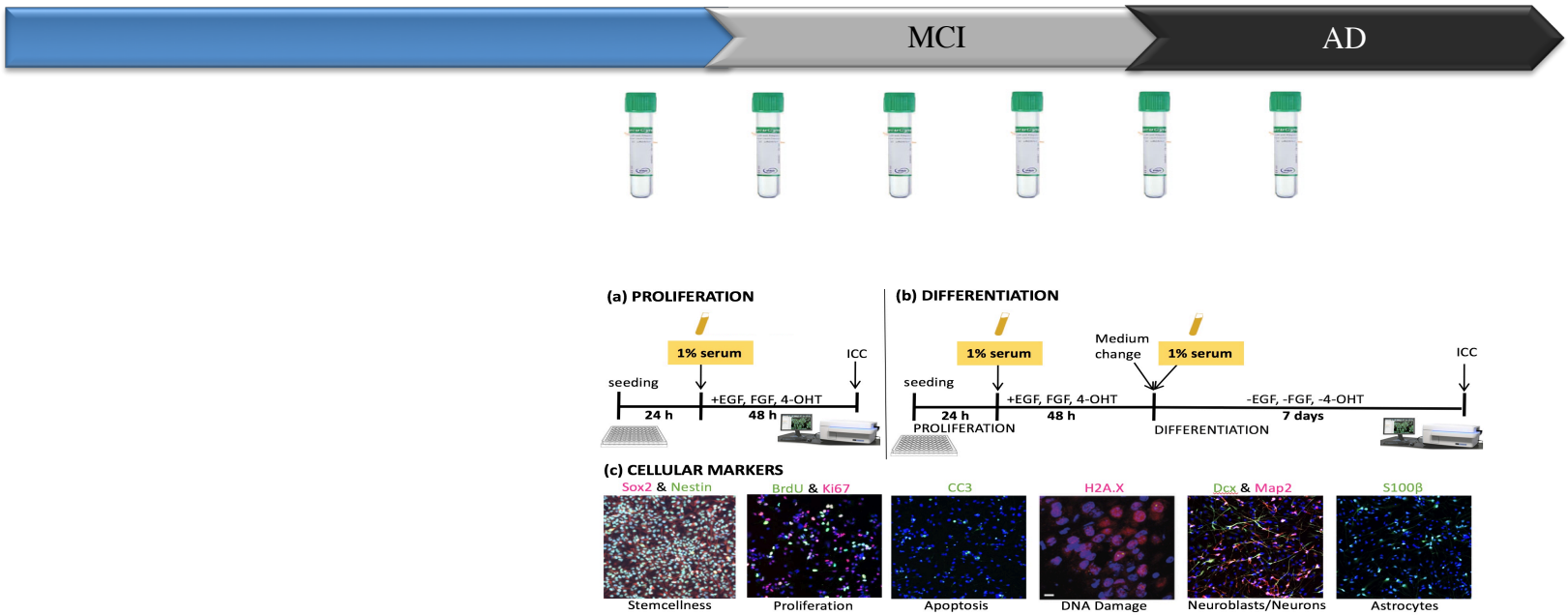
Hippocampal neurogenesis in **Alzheimer's Disease**

Alterations in AHN occur at the very early stage of AD progression

Prior to processes that may secondarily affect neurogenesis (neuronal loss, amyloid deposition and inflammation).

AHN= An integral part of AD pathology

Longitudinal patients serum samples

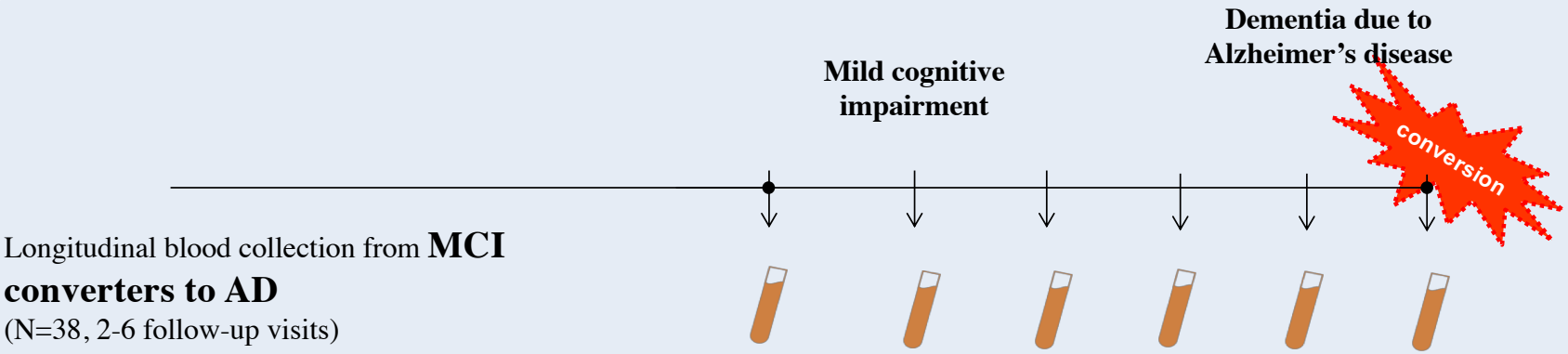


-Can we clarify the longitudinal changes in hippocampal neurogenesis during AD progression?

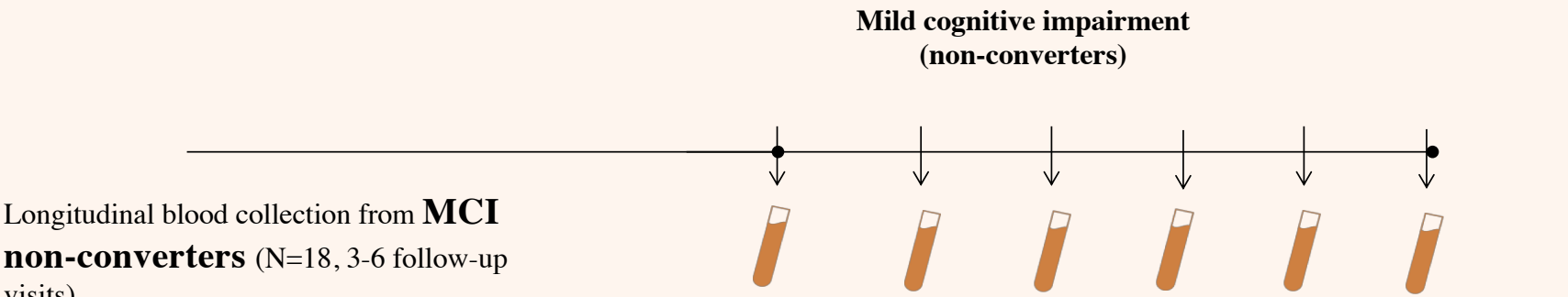
-Can we predict AD conversion from Mild Cognitive Impairment (MCI)?

Longitudinal serum samples

AddNeuroMed and KHP-DCR cohorts



Longitudinal blood collection from **MCI converters to AD** (N=38, 2-6 follow-up visits)

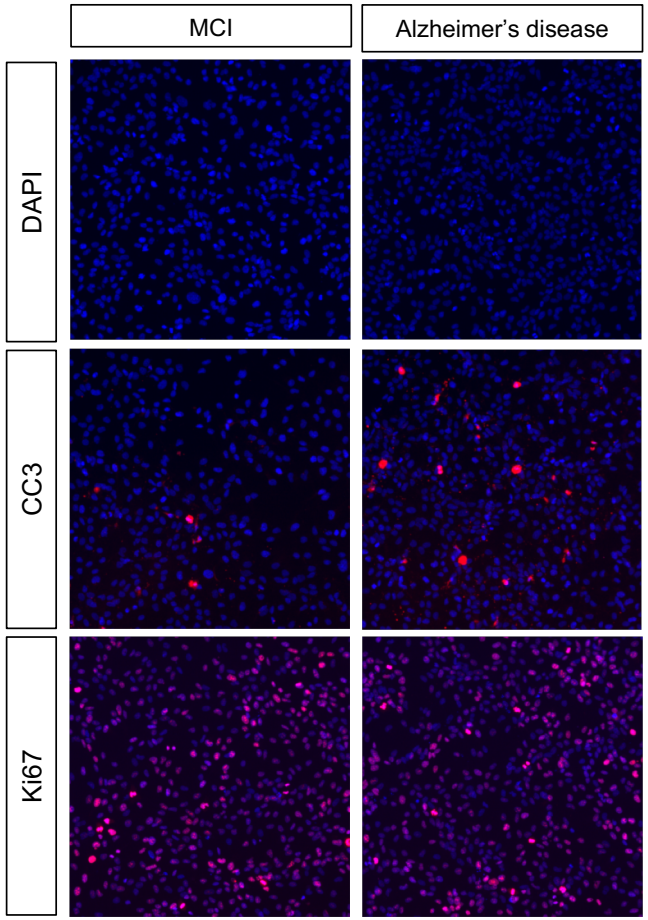


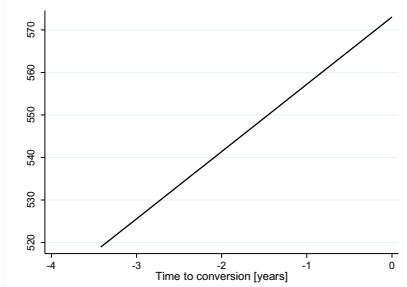
Longitudinal blood collection from **MCI non-converters** (N=18, 3-6 follow-up visits)

Aleksandra Maruszak et al.,
bioRxiv 175604; doi: https://doi.org/10.1101/175604

Can we monitor **AD progression**?

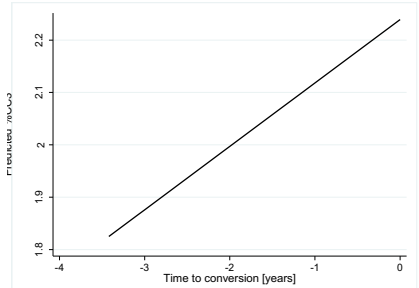
Signatures of conversion to AD (proliferation assay)





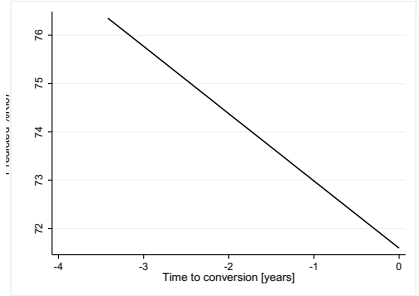
Increased cell count

p=0.002



Increased apoptotic cell death

p=0.023



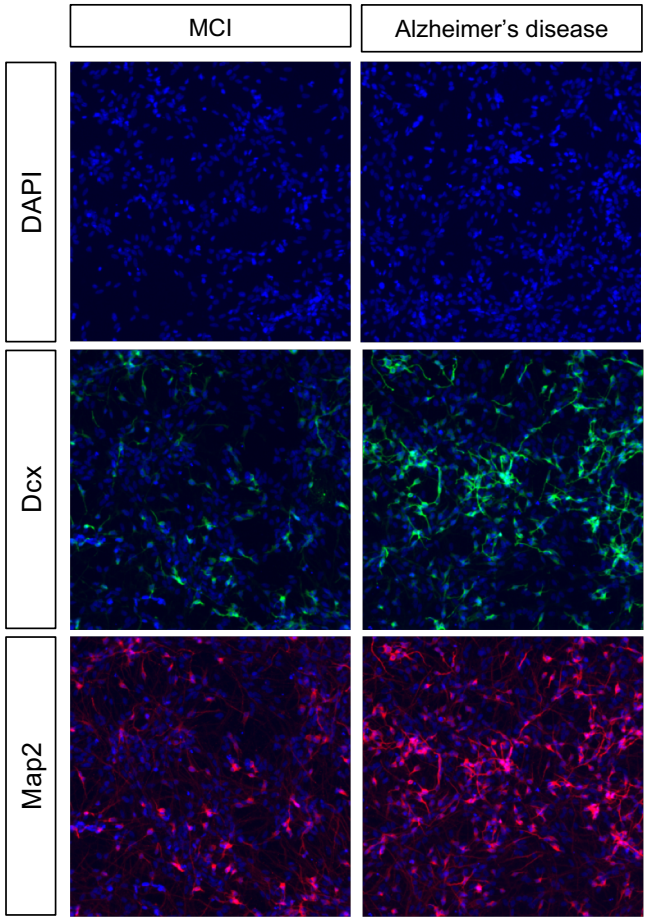
Decreased proliferation

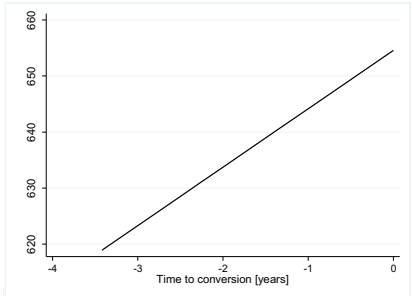
p<0.0001

Mixed effects regression models for repeated measures
P-values represent significance of the fitted model.

Aleksandra Maruszak et al.,
bioRxiv 175604; doi: https://doi.org/10.1101/175604

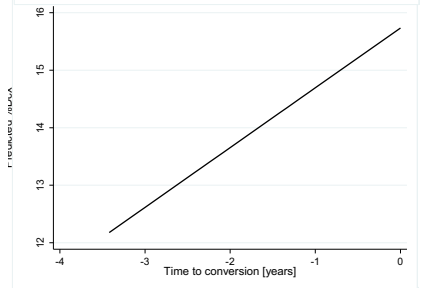
Signatures of conversion to AD (differentiation assay)





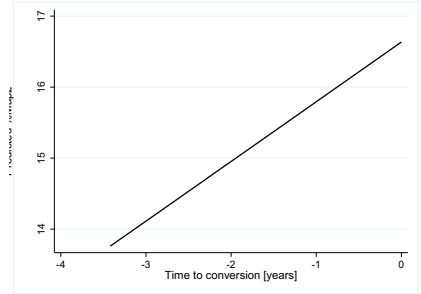
Increased cell count

p=0.037



Increased number of neuroblasts

p=0.021



Increased number of neurons

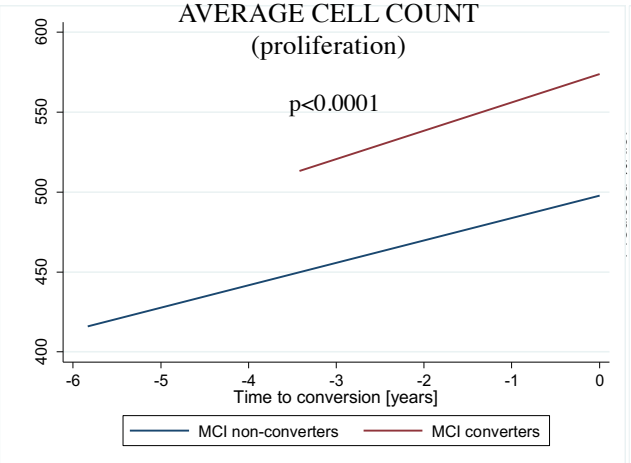
p=0.044

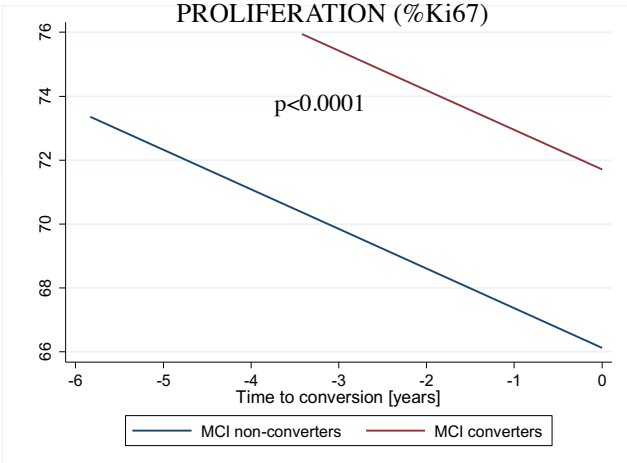
Mixed effects regression models for repeated measures
P-values represent significance of the fitted model.

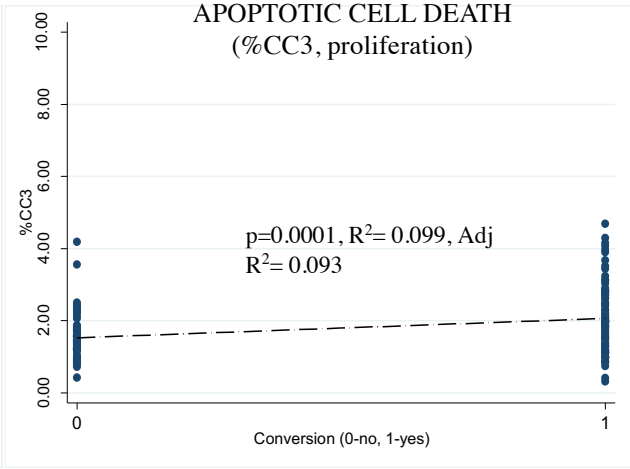
Aleksandra Maruszak et al.,
bioRxiv 175604; doi: https://doi.org/10.1101/175604

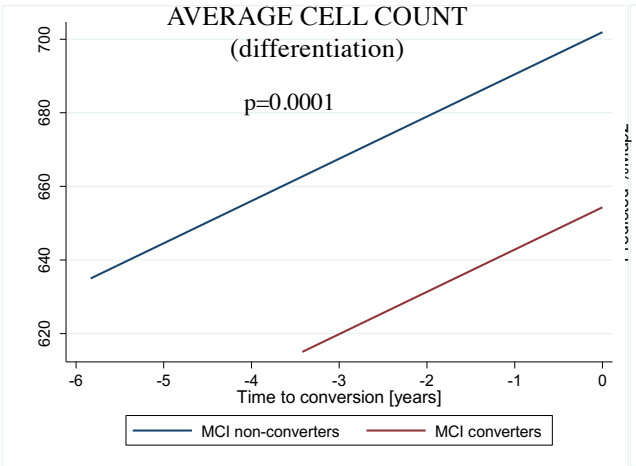
Can we distinguish **MCI converters** from **MCI non-converters**?

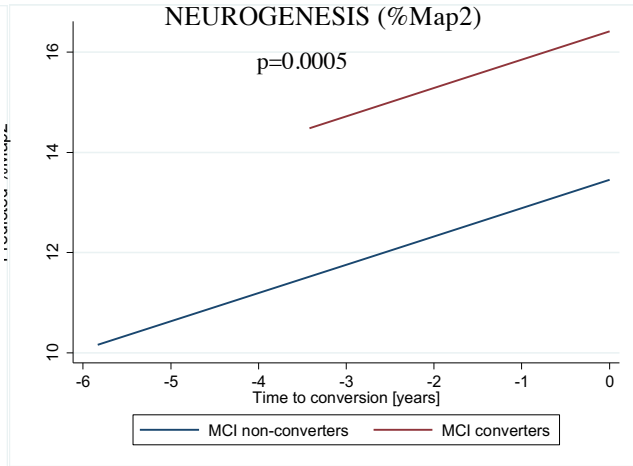
MCI converters and non-converters have a different cellular profile

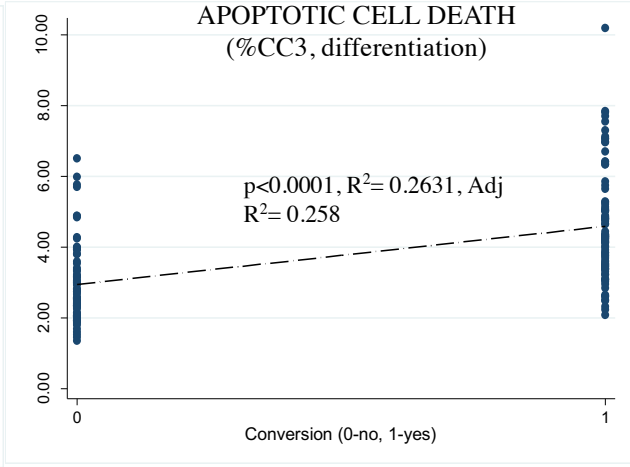












Mixed effects regression models for repeated measures
P-values represent significance of the fitted model.

Aleksandra Maruszak et al.,
bioRxiv 175604; doi: https://doi.org/10.1101/175604

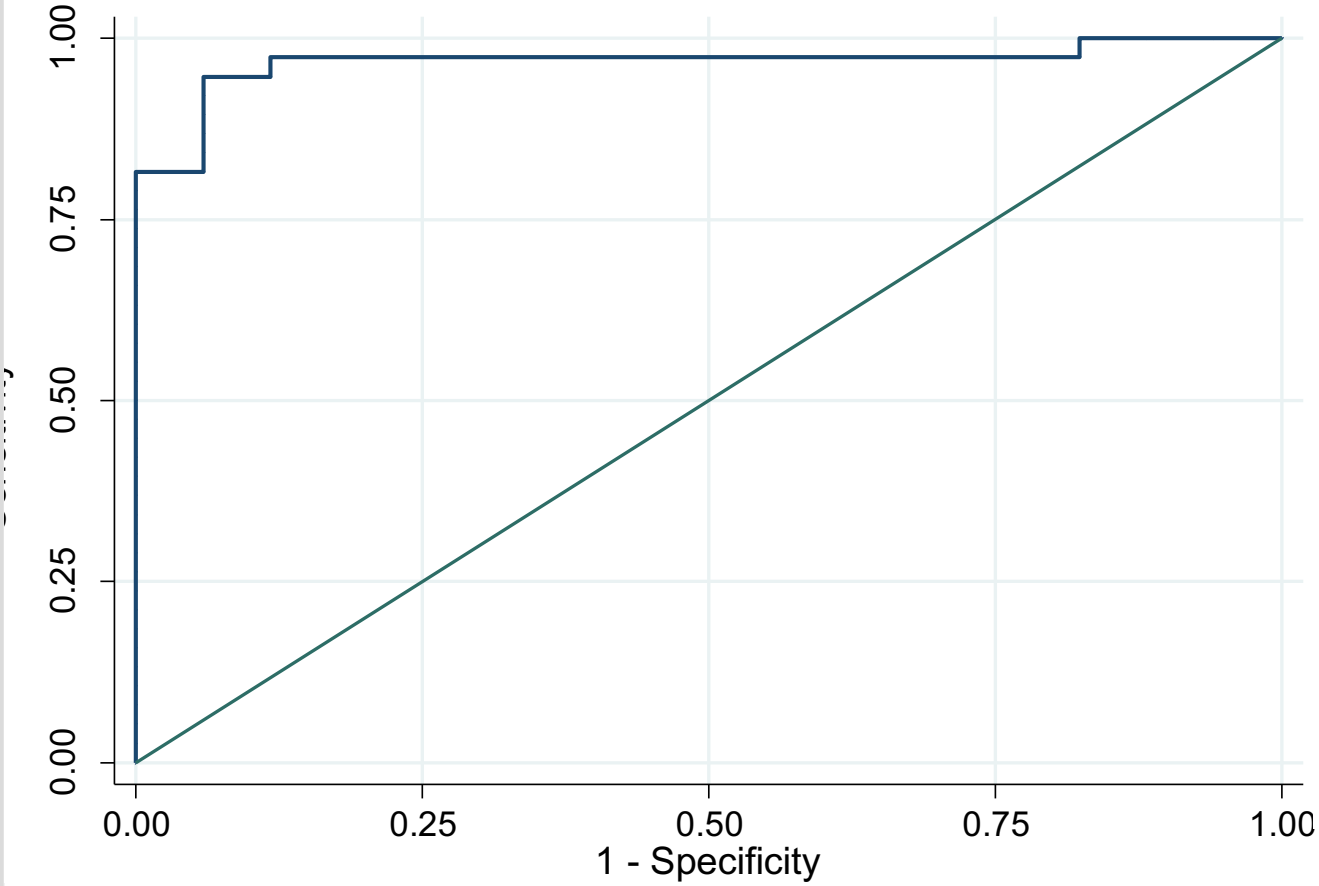
Who will **convert to AD**?

Who will convert to AD?

- Baseline serum sample data
- Stepwise logistic regression

➔Model predicting conversion from MCI to AD with an accuracy of 96.75%

96.75% chance of correct classification



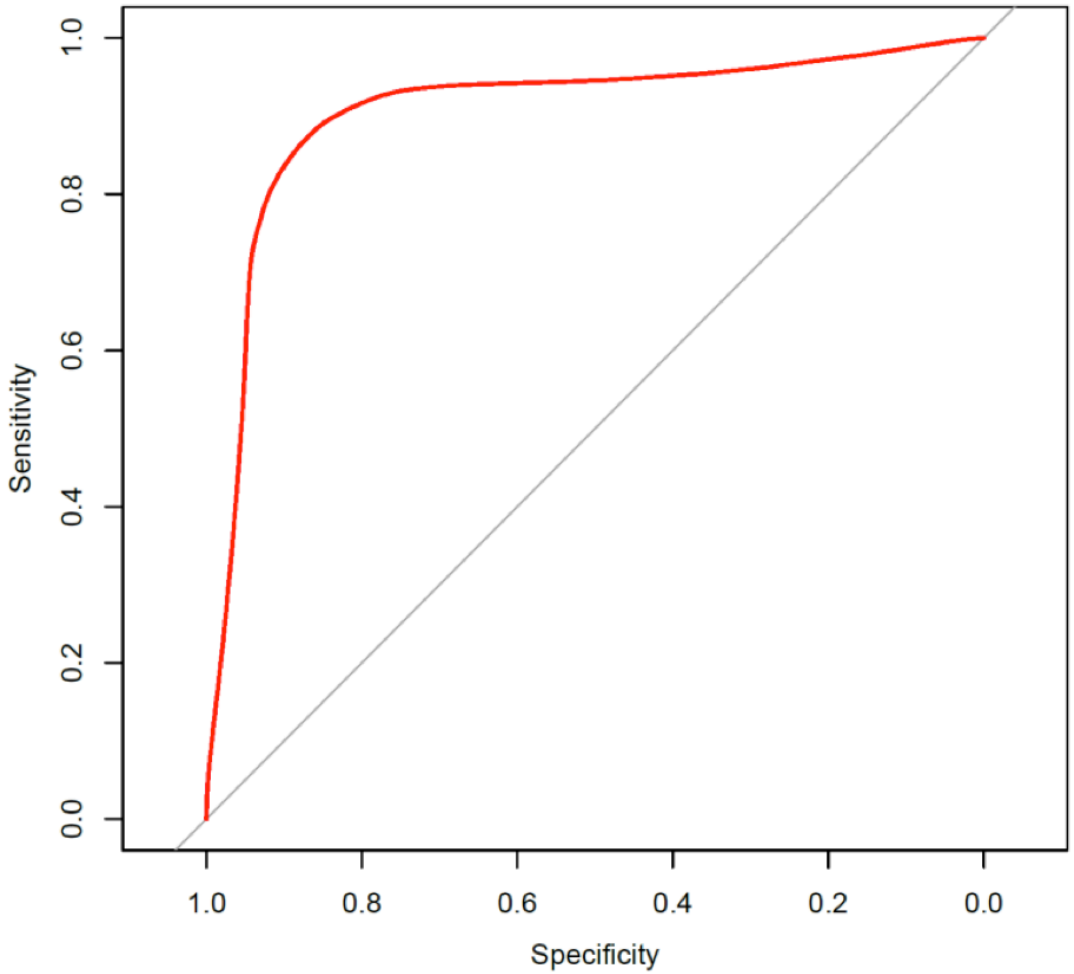
	OR	P>z
Education (years)	0.72	0.040
Av cell count (proliferation)	1.03	0.001
Ki67 (proliferation)	1.35	0.038
CC3 (differentiation)	3.49	0.016
Intercept	1.68e-15	0.012

p=0.0001, Pseudo R2=0.6672
Hosmer-Lemeshow chi2(8) = 9.22
Prob > chi2 = 0.3244

Area under the Receiver Operating Characteristic (ROC) curve: 0.9675 - Sensitivity cut-off: 72%

Aleksandra Maruszak et al.,
bioRxiv 175604; doi: https://doi.org/10.1101/175604

Who will convert to AD: Machine Learning Cross-validation



Support Vector Machine Classifiers using the Radial-Based Kernel were trained to predict conversion status.

Performance of the classifier was assessed using 1000 repeats of 5-fold cross-validation

Education (years)
Av cell count (proliferation)
Ki67 (proliferation)
CC3 (differentiation)

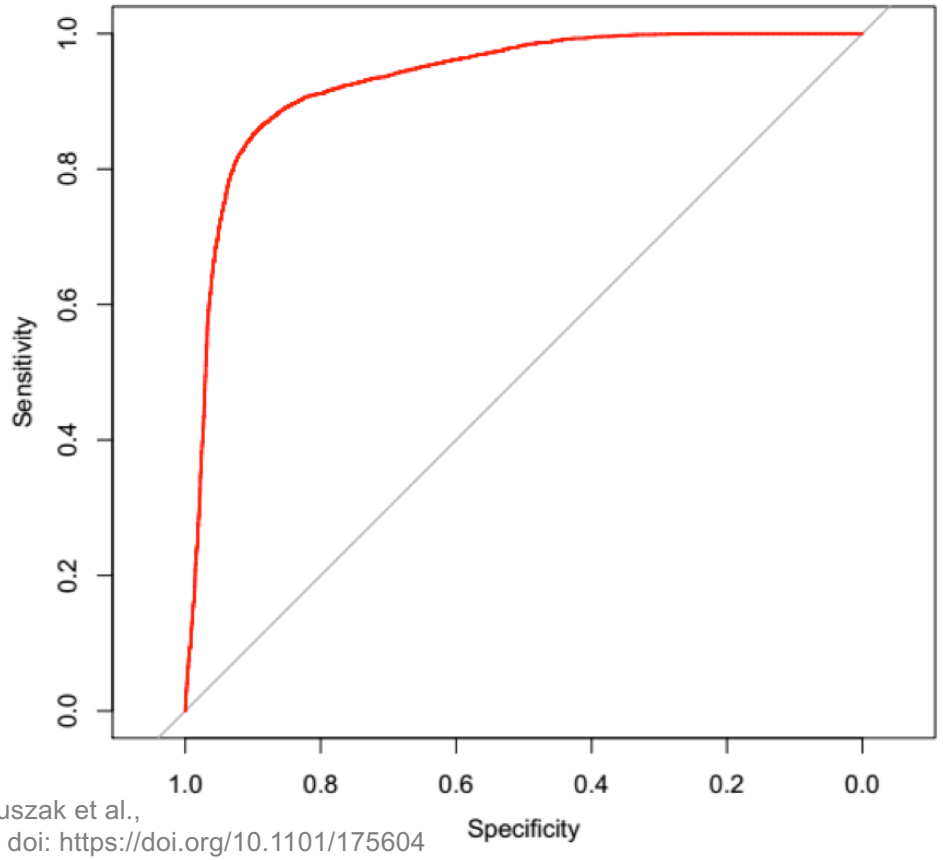
Area under the Receiver Operating Characteristic (ROC) curve: **0.93** - Sensitivity 90.3%, Specificity 79.0%.

Aleksandra Maruszak et al.,
bioRxiv 175604; doi: https://doi.org/10.1101/175604

Ben Liu, Alejo J Nevado-Holgado
Simon Lovestone [Oxford University, UK]

Who will convert to AD: Proteomics

SOMAScan assay on baseline serum samples of MCI converters and non-converters: **4006 different protein epitopes.**



Receiver-operator characteristic-curve for predicting conversion to Alzheimer's disease using **a panel of 207 proteins.** Area under the curve, **AUC=0.94** Sensitivity= 91.65%, Specificity= 81.68%.

Aleksandra Maruszak et al.,
bioRxiv 175604; doi: https://doi.org/10.1101/175604

Ben Liu, Alejo J Nevado-Holgado
Simon Lovestone [Oxford University, UK]

1- Can we monitor AD progression? ✓

Conversion to AD is significantly associated with changes in hippocampal progenitor cell count, proliferation, cell death and neurogenesis.

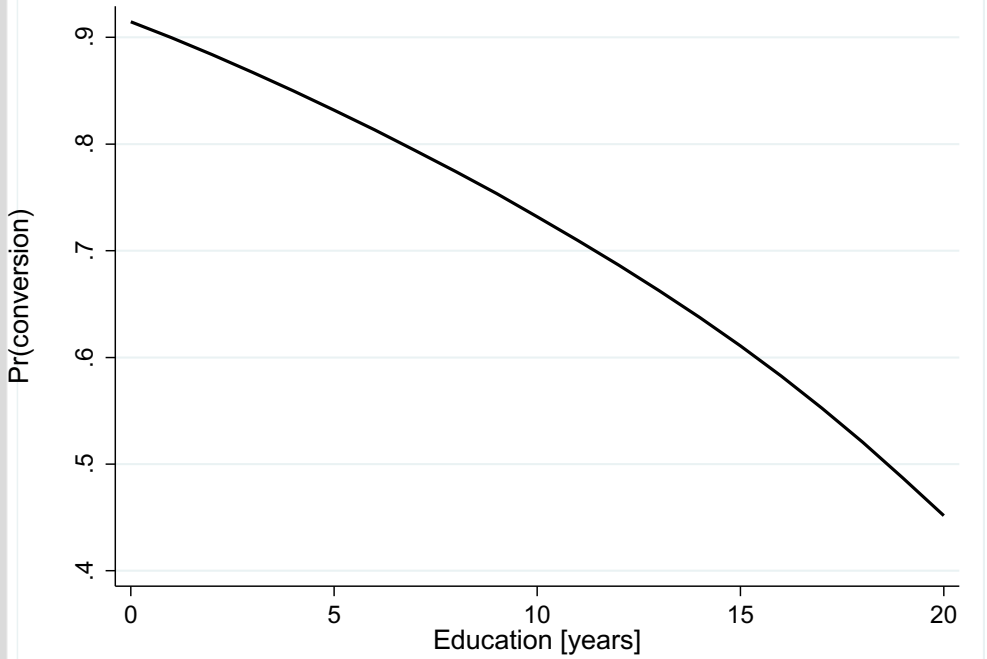
2- Can we distinguish MCI converters from MCI non-converters? ✓

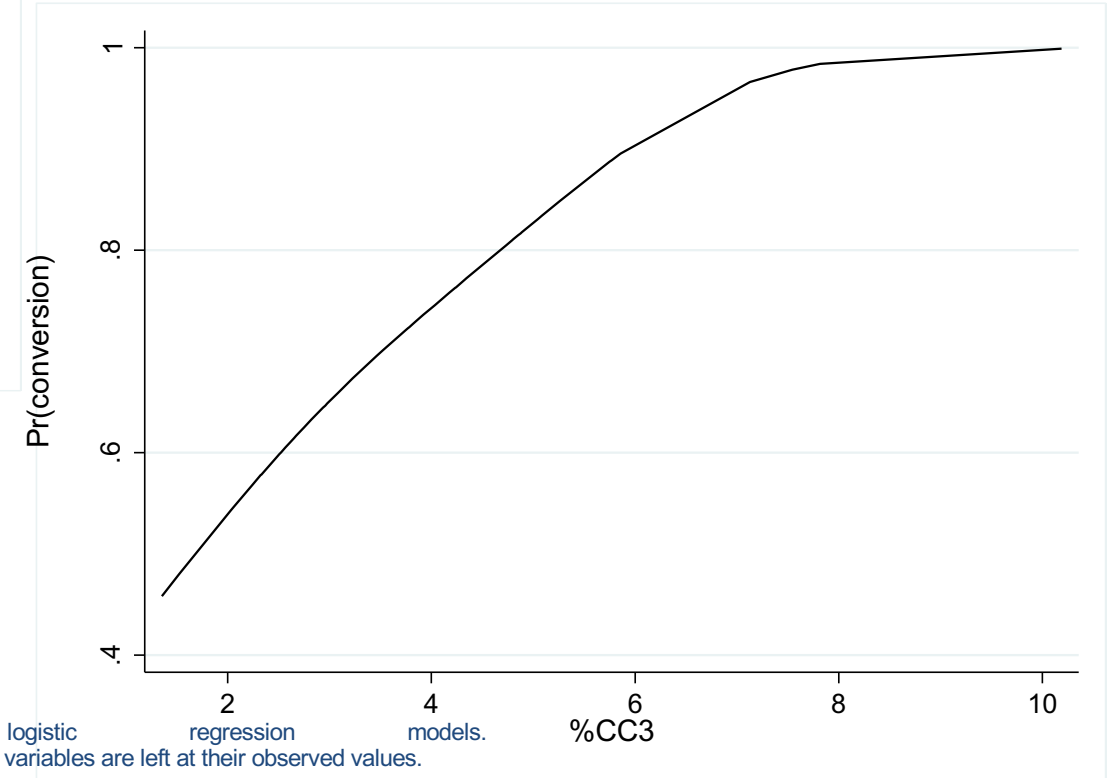
MCI converters can be distinguished from MCI non-converters using markers of proliferation, neurogenesis and cell death.

3- Can we predict AD conversion? ✓

Education and baseline assay readouts on hippocampal progenitor cell count, proliferation and cell death predict conversion to AD with high accuracy.

Can we modify the probability to convert from MCI to AD?





mcp (*marginsconplot*) after STATA fitting logistic regression models.
Average adjusted prediction for each of the observed values for education or CC3, while other variables are left at their observed values.

- Validation study has started.
- Up to 3.5 years for intervention to delay AD conversion/ for stratification in clinical trials.
- Assay for testing candidate molecules to rescue the conversion cellular phenotype.
- Assay for monitoring interventions/disease progression.

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Doris Stangl

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MRC Medical Research Council

The Psychiatry Research Trust

Collaborators:
Simon Lovestone [Oxford University, UK]
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