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

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.
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

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

Human Hippocampal Neurogenesis Persists throughout Aging
Adult hippocampal neurogenesis in humans

**Human Adult Neurogenesis: Evidence and Remaining Questions**

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: Learning and Memory

- 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

Adult Hippocampal Neurogenesis emerging as Target of choice?
Our hippocampal neurogenesis Lines of Research

- Environmental and Molecular mechanisms controlling hippocampal neurogenesis in health and disease
- Healthy Aging
- Alzheimer's Disease
- Mood and Depression

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

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

Egeland et al. Translational Psychiatry 2017

Human Hippocampal Stem Cell line – Controlled Environment

Identification and validation of new genes and miRNAs und the role of environmental factors on hippocampal neurogenesis.
Human Hippocampal Stem Cell line – Stress Model

Identification of the mode of action of antidepressants
Powel et al. 2017a, b

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

AHN: A Target for intervention
HEALTH
DISEASE
PREDICTION
MONITORING

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

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Human Serum
Semi-automated cell profiling platform
Cellular read-out, stem cellness, proliferation, differentiation, cell morphology, etc. The platform allows to analyze over 100,000 single cells per experiment.

Human Serous
Human Hippocampal Progenitor cell line
Why using serum?

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

(ii) 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**

The ageing systemic milieu negatively regulates neurogenesis and cognitive function

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**In vitro Parabiosis assay**

**Healthy Young donors**

(n=27, Mean age: 29.7)

**Healthy Old donors**

(n=35, Mean age: 77.7)

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Older donor serum increases apoptotic hippocampal stem cell death

*Unpublished data
Shown live at the meeting*
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

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

Older donor serum induces a molecular ageing phenotype in hippocampal stem cells
Old/Young in vitro parabiosis recapitulates some molecular hallmarks of ageing.

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 vs. biological age.

Hippocampal neurogenesis in Alzheimer’s Disease (rodent models)

Systematic comparison needed with:
- Age
- Gender
- Genetic background
- Neuropathology stage
- Methods of neurogenesis detection

Hippocampal neurogenesis in Alzheimer’s Disease (human postmortem tissues)

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

- Gatt et al. 2014

Mu & Gage, 2011

Maruszak et al. 2013

Systematic comparison needed with:
- Age
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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

Aleksandra Maruszak et al., bioRxiv 175604; doi: https://doi.org/10.1101/175604
Can we monitor AD progression?

**Signatures of disease progression**

**Signatures of conversion to AD (proliferation assay)**

**Signatures of conversion to AD (differentiation assay)**

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

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

Who will convert to AD?
Who will convert to AD?

Baseline serum sample data
• Disparate logistic regression
  ➤ Model predicting conversion from MCI to AD with an accuracy of 96.75%

- 96.75% chance of correct classification

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

OR \[ P > z \]

Education (years)

Ki67 (proliferation) 1.35 0.038
CC3 (differentiation) 3.49 0.016
Intercept 1.68e-15 0.012

\( p = 0.0001 \), \( \text{Pseudo } R^2 = 0.6672 \)

Hosmer-Lemeshow chi\(^2\) (8) = 9.22
Prob > chi\(^2\) = 0.3244

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.

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

Who will convert to AD: Machine Learning Cross-validation

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, \( \text{AUC} = 0.94 \), Sensitivity: 91.65%, Specificity: 81.68%.

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

- 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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