Human induced pluripotent stem as *in vitro* models to study the etiology of Alzheimer's disease

Prof. James Adjaye

Institute for Stem Cell Research and Regenerative Medicine,

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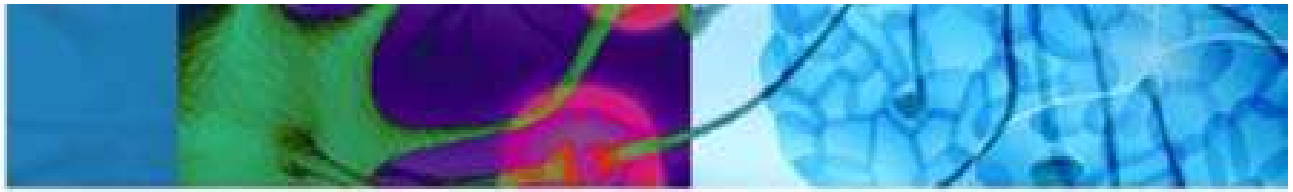
Duesseldorf, Germany

BIOMED 21

A HUMAN PATHWAYS APPROACH TO DISEASE RESEARCH

8-9 December 2015 | Crowne Plaza Hotel, Brussels



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SEVENTH FRAMEWORK PROGRAMME

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

Paris, 19 March 2013

Communiqué de presse

AgedBrainSYSBIO, a research initiative against neurodegenerative diseases

A European group of academic laboratories and industrial scientists from SMEs will combine integrative systems biology & comparative genomics for studying human brain ageing and/or most common age-related diseases with a special emphasis on late-onset Alzheimer Disease for identifying and validating new molecular targets and biomarkers. This four-year research programme is coordinated by Inserm (Pr Michel Simonneau).

Country	Participant organisation legal name		Principal Investigator
France	Inserm	Institut National de la santé et de la recherche clinique (Inserm)	Michel Simonneau
	Institut Pasteur de Lille	Institut Pasteur de Lille (IPL)	Jean-Charles Lambert
	CS	Centre Européen de Recherche en Biologie et Médecine (CERBM-GIE)	Yann Herault
	HYBRIGENICS	HYBRIGENICS SA	Jean-Christophe Rain
	InsermTransfert	Inserm Transfert SA (IT)	Christiane Dascher-Nadel
Belgium	VIB	VIB	Christine van Broeckhoven
	reMYND	reMYND NV	Dick Terwel
Germany	Heinrich Heine University of Düsseldorf	Heinrich Heine Universität Düsseldorf (UDUS)	James Adjaye
	GENE BRIDGES	Gene Bridges GmbH	Harald Kranz
	EMBL-EBI	European Molecular Biology Laboratory - European Bioinformatics Institute (EMBL-EBI)	Henning Hermjakob
Israel	אוניברסיטת תל-אביב TEL AVIV UNIVERSITY	Tel-Aviv University (TAU)	Tal Pupko
Estonia	QureTEC	OU QURETEC	Jaak Vilo
Switzerland	SIB Swiss Institute of Bioinformatics	Swiss Institute of Bioinformatics (SIB)	Ioannis Xenarios
United Kingdom	Babraham Institute	The Babraham Institute (BI)	Nicolas Le Novère

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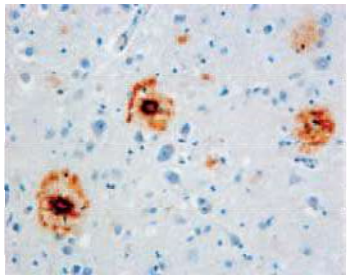
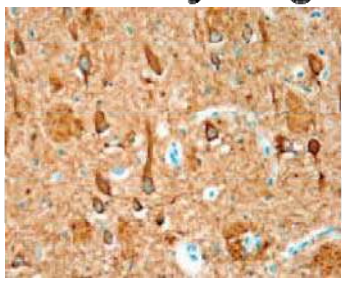
- Leading cause of dementia (26 million affected)
- Protein aggregation disease
  - Amyloid beta Plaques
  - Tau (hyperphosphorylated) Tangles
- Genetic risk
  - Early onset (1%) autosomal dominant
  - Late onset Apoe4 increases risk
- No disease modifying therapies available

Pathology Hallmarks

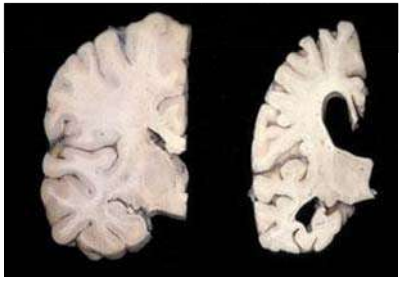
Amyloid Plaques - Aβ



Neurofibrillary tangles - tau



Atrophy



Biochemical Pharmacology 85 (2013) 289–305

Contents lists available at SciVerse ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Alzheimer's therapeutics: Continued clinical failures question the validity of the amyloid hypothesis—but what lies beyond?

Kevin Mullane [a], Michael Williams [b,*]

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[b] Department of Molecular Pharmacology and Biological Chemistry, Feinberg School of Medicine, Northwestern University, Chicago, IL, United States

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Amyloid
Tau
GWAS
Clinical trial failures

ABSTRACT

The worldwide incidence of Alzheimer's disease (AD) is increasing with estimates that 115 million individuals will have AD by 2050, creating an unsustainable healthcare challenge due to a lack of effective treatment options highlighted by multiple clinical failures of agents designed to reduce the brain amyloid burden considered synonymous with the disease.

The amyloid hypothesis that has been the overarching focus of AD research efforts for more than two decades has been questioned in terms of its causality but has not been unequivocally disproven despite multiple clinical failures. This is due to issues related to the quality of compounds advanced to late stage clinical trials and the lack of validated biomarkers that allow the recruitment of AD patients into trials before they are at a sufficiently advanced stage in the disease where therapeutic intervention is deemed futile.

Pursuit of a linear, reductionistic amyloidocentric approach to AD research, which some have compared to a religious faith, has resulted in other, equally plausible but as yet unvalidated AD hypotheses being underfunded leading to a disastrous roadblock in the search for urgently needed AD therapeutics. Genetic evidence supporting amyloid causality in AD is reviewed in the context of the clinical failures, and progress in tau-based and alternative approaches to AD, where an evolving modus operandi in biomedical research fosters excessive optimism and a preoccupation with unproven, and often ephemeral, biomarker/genome-based approaches that override transparency, objectivity and data-driven decision making, resulting in low probability environments where data are subordinate to self propagating hypotheses.

Journal of Alzheimer's Disease 47 (2015) 857–868
DOI 10.3233/JAD-150281
IOS Press

Hypothesis

A Human-Based Integrated Framework for Alzheimer's Disease Research

Francesca Pistollato*, Sarah E. Cavanaugh and P. Charukeshi Chandrasekera
Physicians Committee for Responsible Medicine, Washington, DC, USA

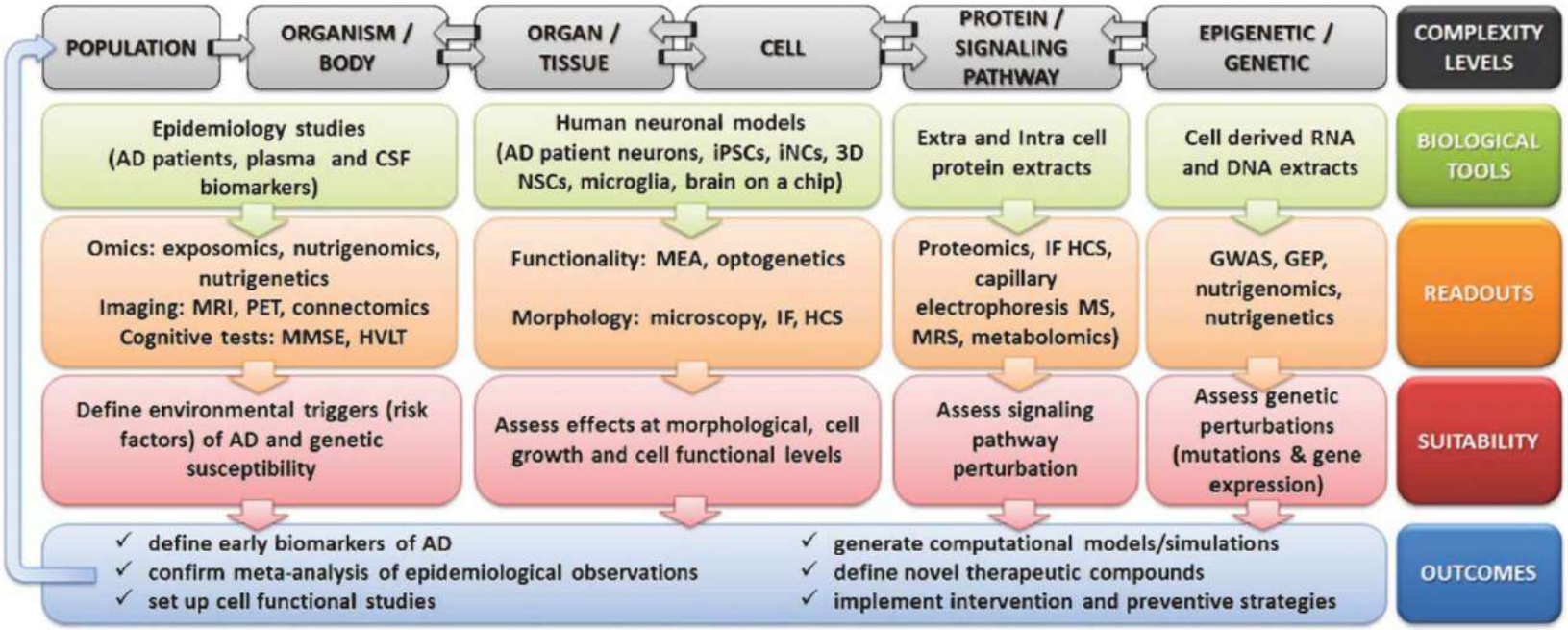

Fig. 1. Overview of the novel available tools and readouts applicable to design human-oriented AD research, accounting for multiple levels of complexity. CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography; MMSE, Mini-Mental State Examination; HVLT, Hopkins verbal learning test; iPSCs, induced pluripotent stem cells; iNCs, induced neuronal cells; NSCs, neural stem cells; MEA, microelectrode array; IF HCS, immunofluorescence-high content screening; MS, mass spectrometry; MRS, magnetic resonance spectroscopy; GWAS, genome-wide association studies; GEP, gene expression profiling.

Journal of Alzheimer's Disease 47 (2015) 857–868
DOI 10.3233/JAD-150281

Genome Wide Association Studies

- Genome-wide association studies are a way for scientists to identify genes involved in human disease.

- This method searches the genome for small variations, called single nucleotide polymorphisms or SNPs (pronounced “snips”), that occur more frequently in people with a particular disease than in people without the disease.

http://ghr.nlm.nih.gov/handbook/genomicresearch/gwastudies

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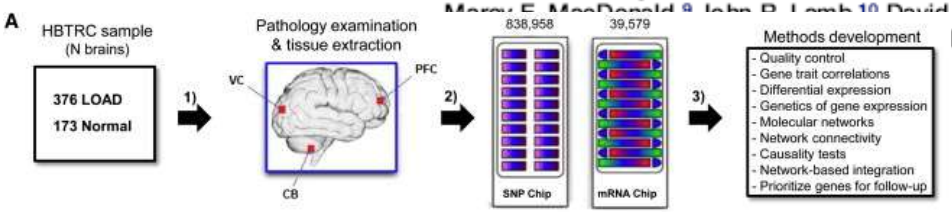
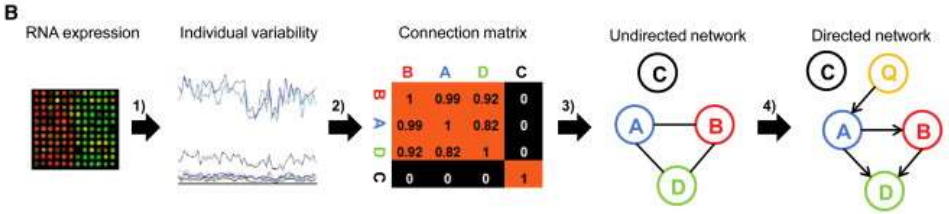
Resource

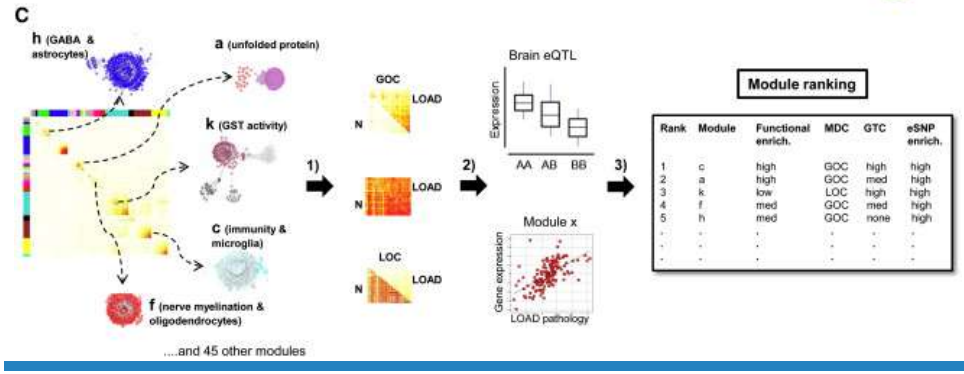
Cell

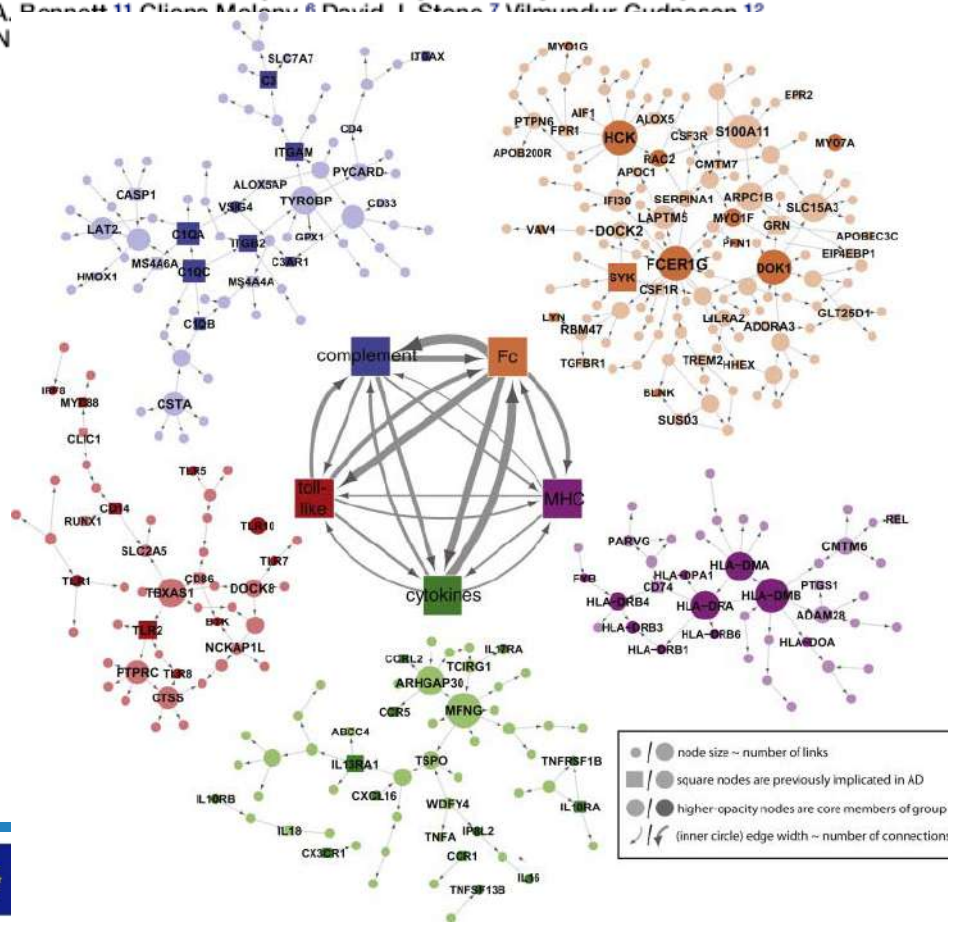
Integrated Systems Approach Identifies Genetic Nodes and Networks in Late-Onset Alzheimer's Disease

Bin Zhang,[1,2,3,4,14,*] Chris Gaiteri,[4,14] Liviu-Gabriel Bodea,[5,14] Zhi Wang,[4] Joshua McElwee,[6] Alexei A. Podtelezhnikov,[7] Chunsheng Zhang,[6] Tao Xie,[6] Linh Tran,[4] Radu Dobrin,[6] Eugene Fluder,[6] Bruce Clurman,[8] Stacey Melquist,[6] Manikandan Narayanan,[6] Christine Suver,[4] Hardik Shah,[1,2] Milind Mahajan,[1,2,3] Tammy Gillis,[9] Jayalakshmi Mysore,[9]

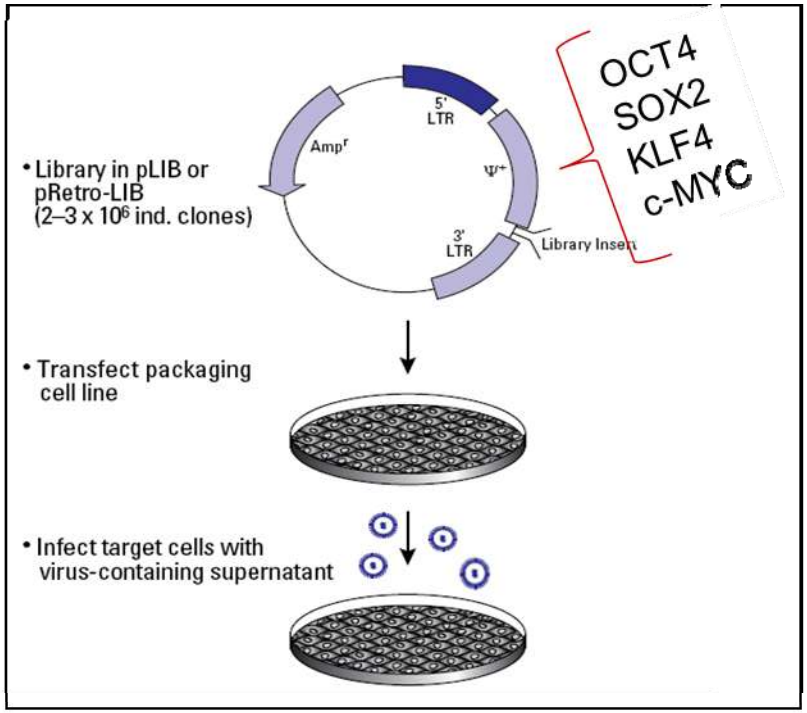








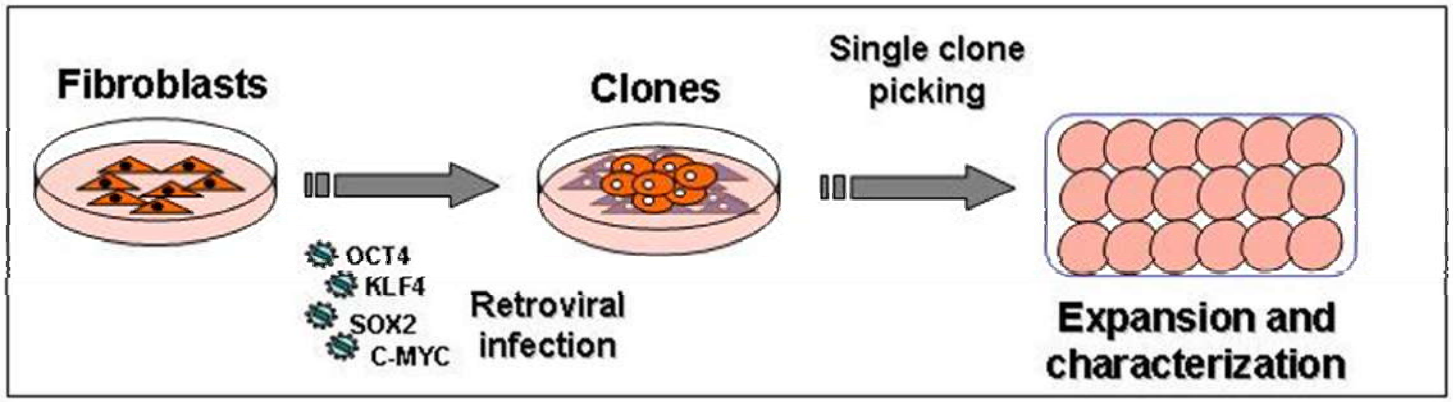
Protocol for cellular reprogramming



Yamanaka cocktail
OCT4, SOX2, KLF4, c-MYC

Thomson cocktail
OCT4, SOX2, NANOG, LIN28

1) Viral production



2) Transduction and generation of iPS clones

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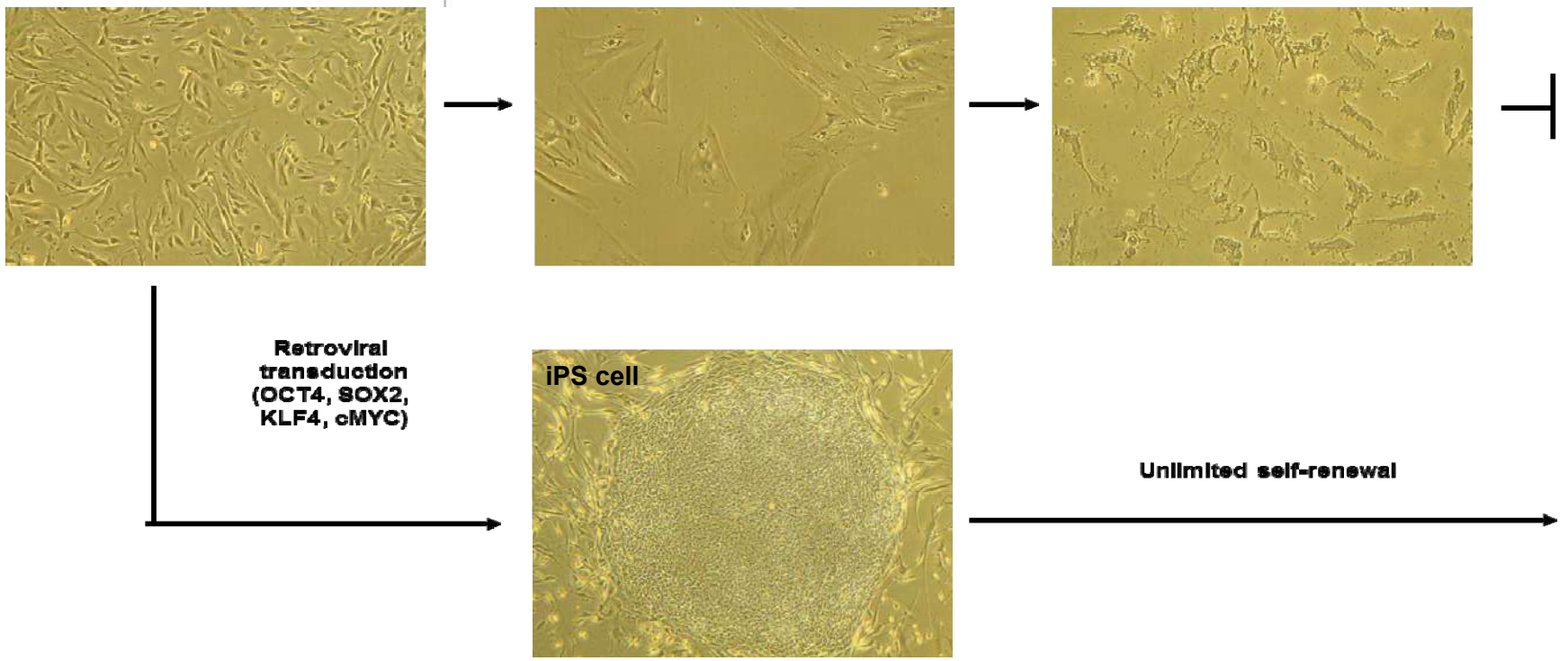
STEM CELLS

EMBRYONIC STEM CELLS/INDUCED PLURIPOTENT STEM CELLS

The Senescence-Related Mitochondrial/Oxidative Stress Pathway is Repressed in Human Induced Pluripotent Stem Cells

ALESSANDRO PRIGIONE,[a] BEATRIX FAULER,[b] RUDI LURZ,[b] HANS LEHRACH,[a] JAMES ADJAYE[a]

[a]Department of Vertebrate Genomics, Molecular Embryology and Aging Group, [b]Electron Microscopy Group, Max Planck Institute for Molecular Genetics, Ihnestrasse 73, D-14195 Berlin, Germany



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Cell Stem Cell

Short Article

Modeling Alzheimer's Disease with iPSCs Reveals Stress Phenotypes Associated with Intracellular Aβ and Differential Drug Responsiveness

Takayuki Kondo,[1,2,7] Masashi Asai,[7,9,10] Kayoko Tsukita,[1,7] Yumiko Kutoku,[11] Yutaka Ohsawa,[11] Yoshihide Sunada,[11] Keiko Imamura,[1] Naohiro Egawa,[1] Naoki Yahata,[1,7] Keisuke Okita,[1] Kazutoshi Takahashi,[1] Isao Asaka,[1] Takashi Aoi,[1] Akira Watanabe,[1] Kaori Watanabe,[7,10] Chie Kadoya,[7,10] Rie Nakano,[7,10] Dai Watanabe,[3] Kei Maruyama,[9] Osamu Hori,[12] Satoshi Hibino,[13] Tominari Choshi,[13] Tatsutoshi Nakahata,[1] Hiroyuki Hioki,[4] Takeshi Kaneko,[4] Motoko Naitoh,[5] Katsuhiro Yoshikawa,[5] Satoko Yamawaki,[5] Shigehiko Suzuki,[5] Ryuji Hata,[14] Shu-ichi Ueno,[15] Tsuneyoshi Seki,[16] Kazuhiro Kobayashi,[16] Tatsushi Toda,[16] Kazuma Murakami,[6] Kazuhiro Irie,[6] William L. Klein,[17] Hiroshi Mori,[18] Takashi Asada,[19] Ryosuke Takahashi,[2] Nobuhisa Iwata,[7,10,*] Shinya Yamanaka,[1,8] and Haruhisa Inoue[1,7,8,*]

LETTER

doi:10.1038/nature1082

Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells

Mason A. Israel[1,2], Shauna H. Yuan[1,3], Cedric Bardy[4], Sol M. Reyna[1,2], Yangling Mu[4], Cheryl Herrera[1], Michael P. Hefferan[5], Sebastiaan Van Gorp[6], Kristopher L. Nazor[7], Francesca S. Boscolo[8], Christian T. Carson[9], Louise C. Laurent[8], Martin Marsala[5,10], Fred H. Gage[4], Anne M. Remes[11], Edward H. Koo[3] & Lawrence S. B. Goldstein[1,3]

Israel and Goldstein *Genome Medicine* 2011, 3:49
http://genomemedicine.com/content/3/7/49

Genome Medicine

REVIEW

Capturing Alzheimer's disease genomes with induced pluripotent stem cells: prospects and challenges

Mason A Israel* and Lawrence SB Goldstein*

Hossini *et al. BMC Genomics* (2015) 16:84
DOI 10.1186/s12864-015-1262-5

BMC Genomics

RESEARCH ARTICLE Open Access

Induced pluripotent stem cell-derived neuronal cells from a sporadic Alzheimer's disease donor as a model for investigating AD-associated gene regulatory networks

Amir M Hossini[1†], Matthias Megges[2,5,6†], Alessandro Prigione[2,8], Bjoern Lichtner[2], Mohammad R Toliat[3], Wasco Wruck[5], Friederike Schröter[5], Peter Nuernberg[3], Hartmut Kroll[4], Eugenia Makrantonaki[1,7], Christos C Zouboulis[1] and James Adjaye[2,5*]

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Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Part of the Special Issue: Alzheimer's Disease – Amyloid, Tau and Beyond

TREM2 and the neuroimmunology of Alzheimer's disease

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ABSTRACT

Late-onset Alzheimer's disease (AD) is a sporadic disorder with increasing prevalence in aging. The ε4 allele of Apolipoprotein E(ApoEε4) was the only known major risk factor for late onset AD. Recently, two groups of investigators independently identified variants of the *TREM2* gene, encoding triggering receptor expressed on myeloid cells 2 as causing increased susceptibility to late onset AD with an odds ratio similar to that of ApoEε4. *TREM2* is a receptor expressed on innate immune cells. Using a novel technology called Direct RNA Sequencing wedetermined the quantitative transcriptome of microglia, the principal innate neuroimmune cells and confirmed that *TREM2* is a major microglia-specific gene in the central nervous system. Over the past several years we have shown that microglia play a dichotomous role in AD. Microglia can be protective and promote phagocytosis, degradation and ultimately clearance of Aβ, the pathogenic protein deposited in the brains of Alzheimer's patients. However, with disease progression, microglia become dysfunctional, release neurotoxins, lose their ability to clear Aβ and produce pro-inflammatory cytokines that promote Aβ production and accumulation. *TREM2* has been shown to regulate the phagocytic ability of myeloid cells and their inflammatory response. Here we propose that the mechanism(s) by which *TREM2* variants cause Alzheimer's disease are via down regulation of the Aβ phagocytic ability of microglia and by dysregulation of the pro-inflammatory response of these cells. Based on our discussion we propose that TREM2 is a potential therapeutic target for stopping ordelaying progression of AD.

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Investigating the role of rare heterozygous *TREM2* variants in Alzheimer's disease and frontotemporal dementia

Elise Cuyvers[a,b], Karolien Bettens[a,b], Stéphanie Philtjens[a,b], Tim Van Langenhove[a,b,c], Ilse Gijselinck[a,b], Julie van der Zee[a,b], Sebastiaan Engelborghs[b,d], Mathieu Vandenbulcke[e], Jasper Van Dongen[a,b], Nathalie Geerts[a,b], Githa Maes[a,b], Maria Mattheijssens[a,b], Karin Peeters[a,b], Patrick Cras[b,c], Rik Vandenberghe[f,g], Peter P. De Deyn[b,d,h], Christine Van Broeckhoven[a,b], Marc Cruts[a,b], Kristel Sleegers[a,b,*], on behalf of the BELNEU consortium

[a] Neurodegenerative Brain Diseases group, Department of Molecular Genetics, VIB, Antwerp, Belgium
[b] Institute Born-Bunge, University of Antwerp, Antwerp, Belgium
[c] Department of Neurology, Antwerp University Hospital, Edegem, Belgium
[d] Department of Neurology and Memory Clinic, Hospital Network Antwerp, Middelheim and Hoge Beuken, Antwerp, Belgium
[e] Department of Psychiatry and Memory Clinic, University Hospitals Leuven, Leuven, Belgium
[f] Department of Neurology and Memory Clinic, University Hospitals Leuven, Leuven, Belgium
[g] Laboratory for Cognitive Neurology, Department of Neurology, University of Leuven, Leuven, Belgium
[h] Department of Neurology and Alzheimer Research Center, University Medical Center Groningen, Groningen, the Netherlands

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Frontotemporal dementia
Rare variants
Meta-analysis
IgV-set domain

ABSTRACT

Homozygous mutations in exon 2 of *TREM2*, a gene involved in Nasu-Hakola disease, can cause frontotemporal dementia (FTD). Moreover, a rare *TREM2* exon 2 variant (p.R47H) was reported to increase the risk of Alzheimer's disease (AD) with an odds ratio as strong as that for *APOEε4*. We systematically screened the *TREM2* coding region within a Belgian study on neurodegenerative brain diseases (1216 AD patients, 357 FTD patients, and 1094 controls). We observed an enrichment of rare variants across *TREM2* in both AD and FTD patients compared to controls, most notably in the extracellular IgV-set domain (relative risk = 3.84 [95% confidence interval = 1.29–11.44]; $p = 0.009$ for AD; relative risk = 6.19 [95% confidence interval = 1.86–20.61]; $p = 0.0007$ for FTD). None of the rare variants individually reached significant association, but the frequency of p.R47H was increased ~3-fold in both AD and FTD patients compared to controls, in line with previous reports. Meta-analysis including 11 previously screened AD cohorts confirmed the association of p.R47H with AD ($p = 2.93 \times 10^{-17}$). Our data corroborate and extend previous findings to include an increased frequency of rare heterozygous *TREM2* variations in AD and FTD, and show that *TREM2* variants may play a role in neurodegenerative diseases in general.

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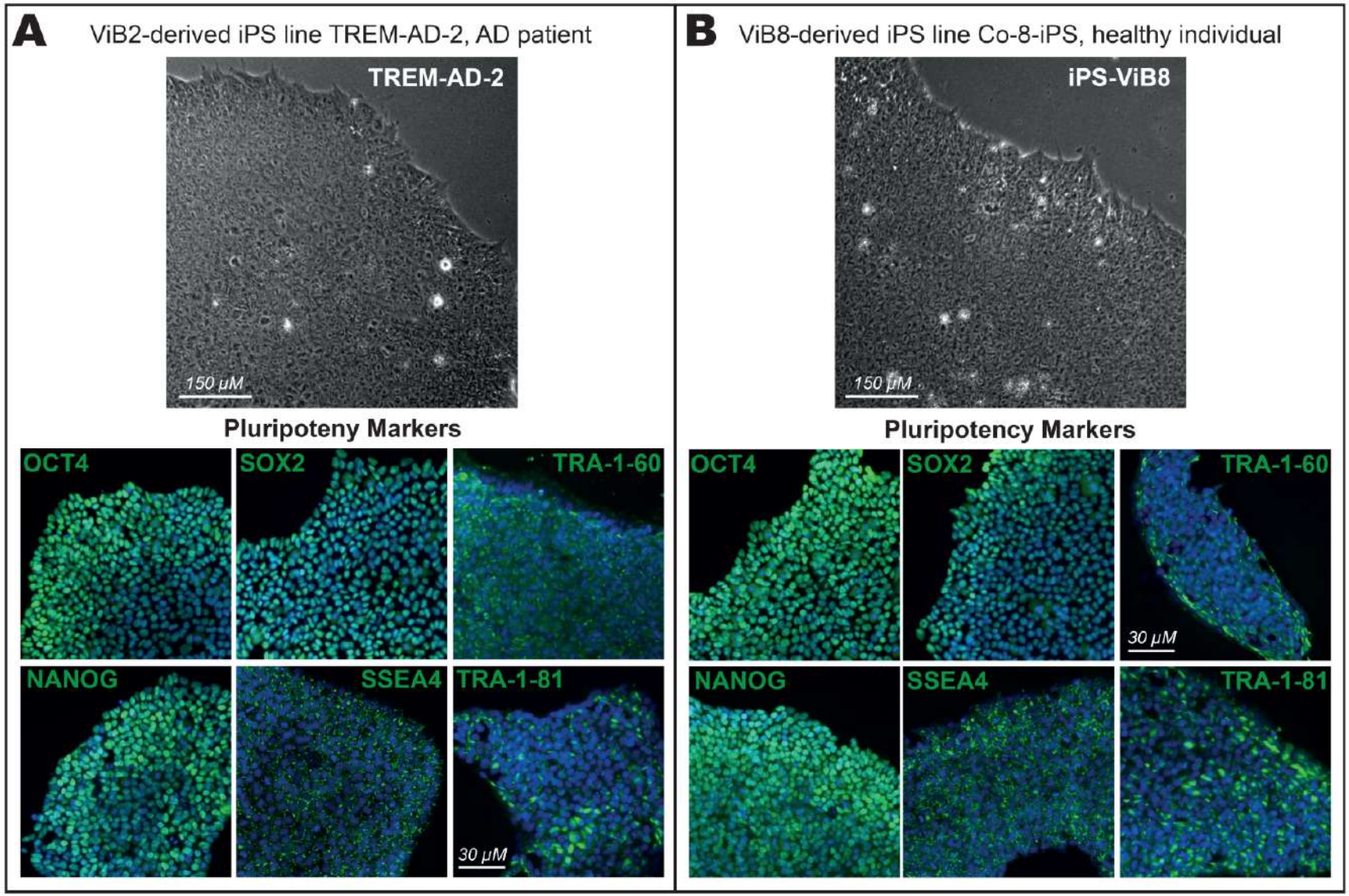
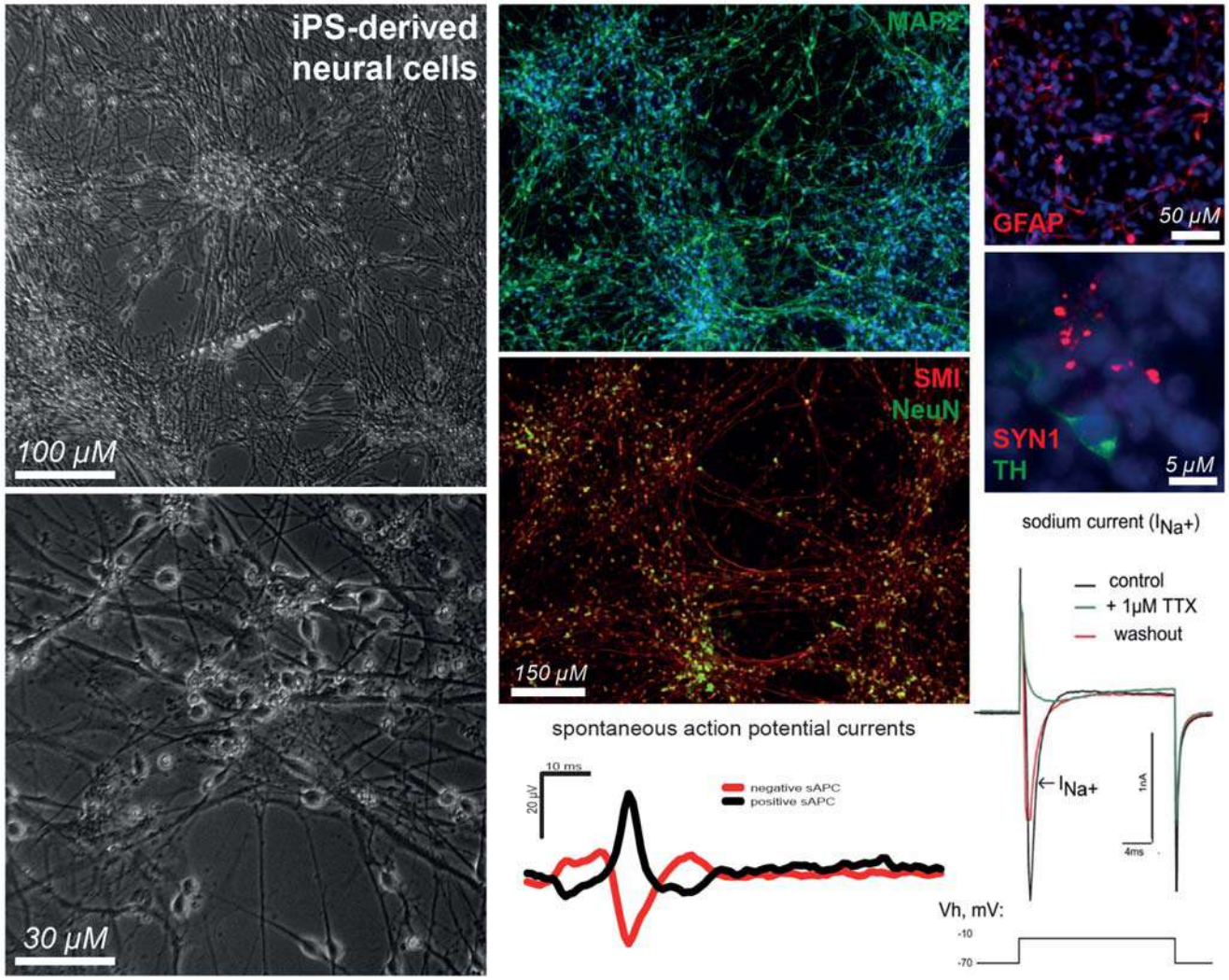
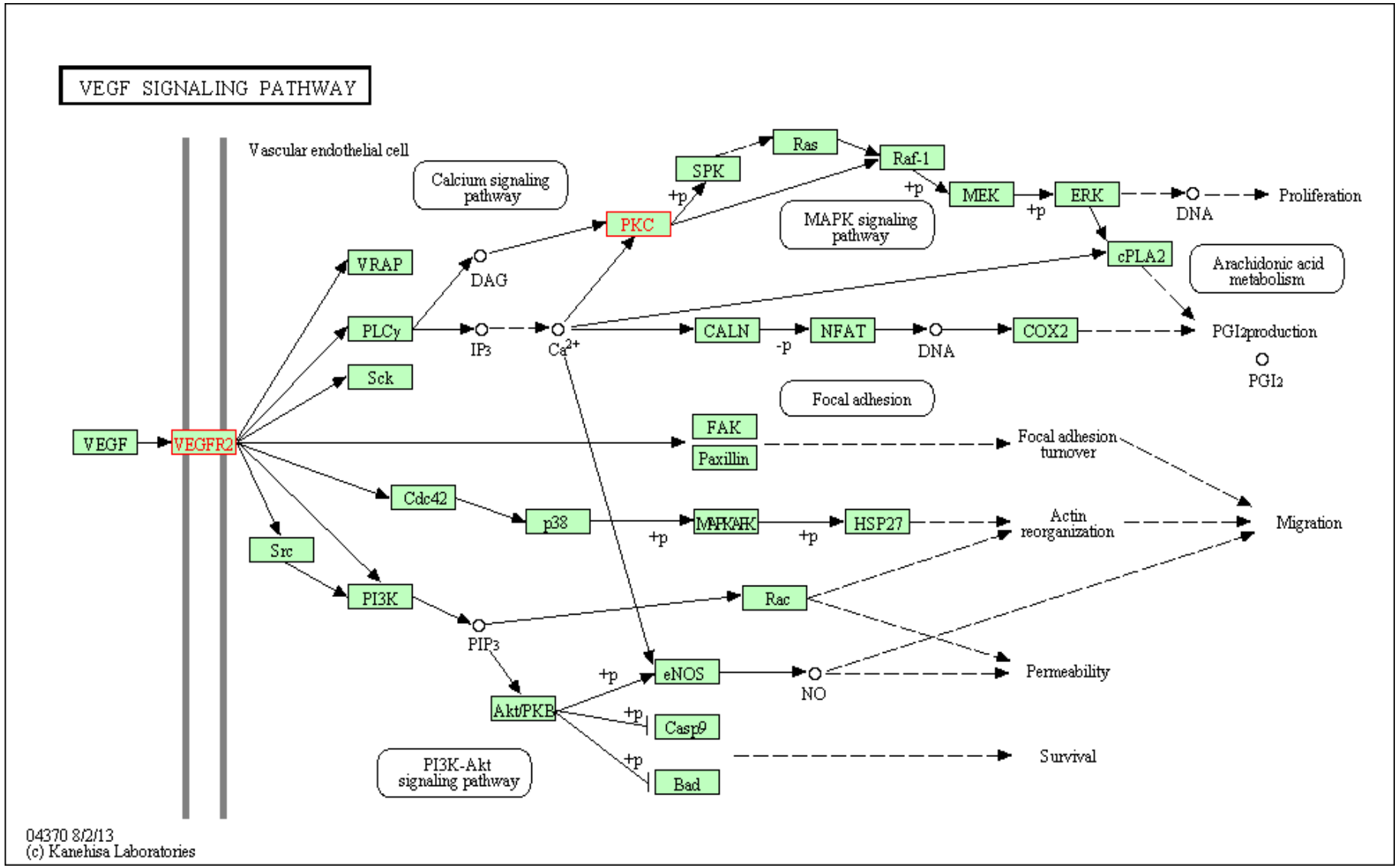
Derivation and characterisation of iPS cells derived from an AD patient bearing the TREM2 / R47H variant



Studying Alzheimer´s Disease in a dish



Vascular endothelial growth factor signalling pathway is over-represented in AD-TREM2 (R47H) neuronal cells



VEGF signalling pathway is over-represented in AD-TREM2 (R47H) neuronal cells

ELSEVIER

Neurobiology of Aging 27 (2006) 1212–1215

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Brief communication

Association study of the vascular endothelial growth factor gene with the risk of developing Alzheimer's disease

Julien Chapuis [a], Jinzhou Tian [b,d], Jing Shi [b,d], Faiza Bensemain [a], Dominique Cottel [a], Corinne Lendon [c], Philippe Amouyel [a], David Mann [b], Jean-Charles Lambert [a,*]

Int. J. Devl Neuroscience 27 (2009) 517–523

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

journal homepage: www.elsevier.com/locate/ijdevneu

ELSEVIER

Vascular endothelial growth factor (VEGF) affects processing of amyloid precursor protein and β-amyloidogenesis in brain slice cultures derived from transgenic Tg2576 mouse brain

Susanne Bürger [a], Monika Noack [a], Ludmil P. Kirazov [c], Evgeni P. Kirazov [c], Cyrill L. Naydenov [d], Elena Kouznetsova [a], Yousef Yafai [b], Reinhard Schliebs [a,*]

[a] Paul Flechsig Institute for Brain Research, University of Leipzig, Germany
[b] Department of Eye Clinics, University Hospital, University of Leipzig, Germany
[c] Institute of Experimental Morphology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia, Bulgaria
[d] Department of Chemistry and Biochemistry, Medical University Sofia, Bulgaria

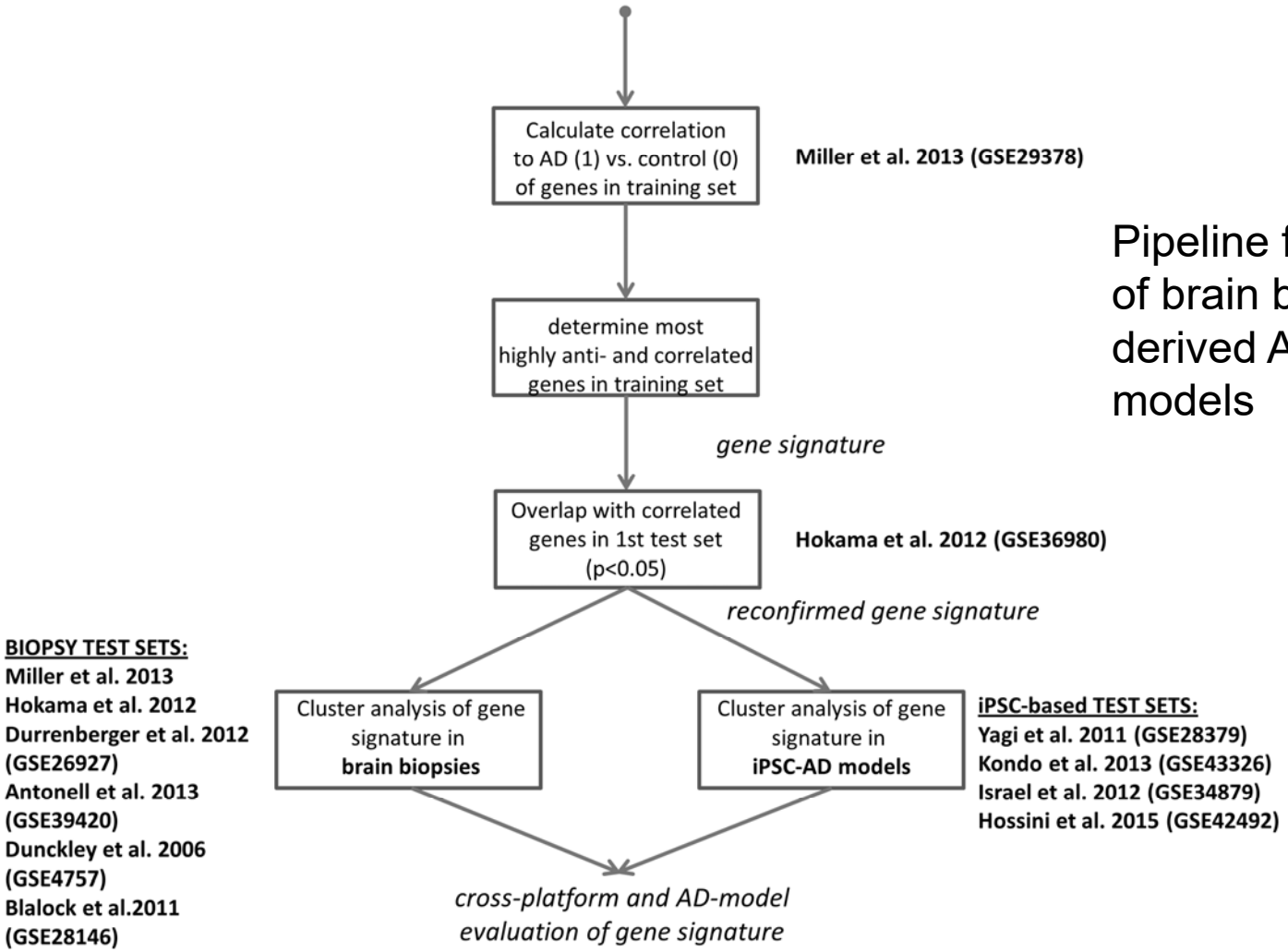
Meta-analysis of AD-associated gene expression datasets

Journal of Alzheimer's Disease

Wruck W, Schröter F and Adjaye J

Meta-analysis of transcriptome data related to hippocampus biopsies and iPSC-derived neuronal cells from Alzheimer disease patients reveals an association with FOXA1 and FOXA2 gene regulatory networks.
In Press

Experimental design



Pipeline for the meta-analysis of brain biopsies and iPSC-derived Alzheimer‘s disease models

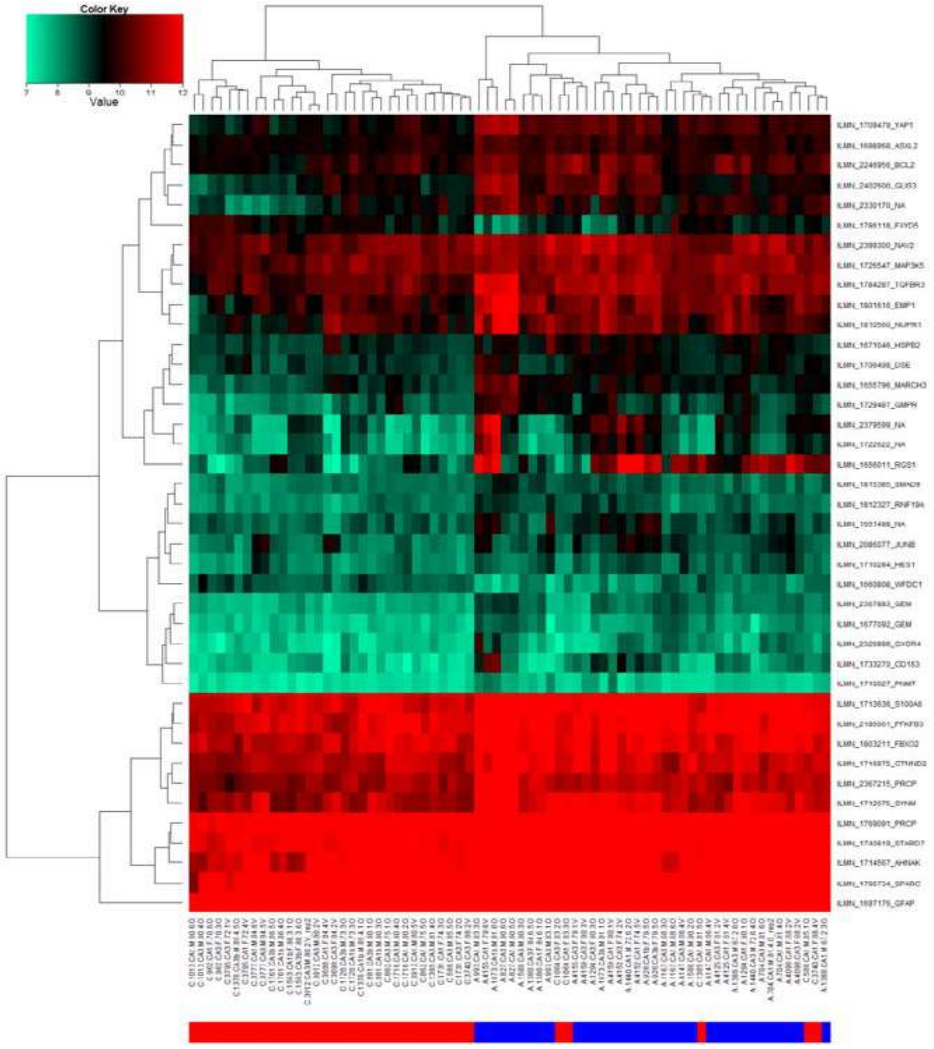
[Wruck W, Schröter F and Adjaye J. Meta-analysis of transcriptome data related to hippocampus biopsies and iPSC-derived neuronal cells from Alzheimer disease patients reveals an association with FOXA1 and FOXA2 gene regulatory networks. *Journal of Alzheimer’s Disease. in press*.]

AD-associated gene signature

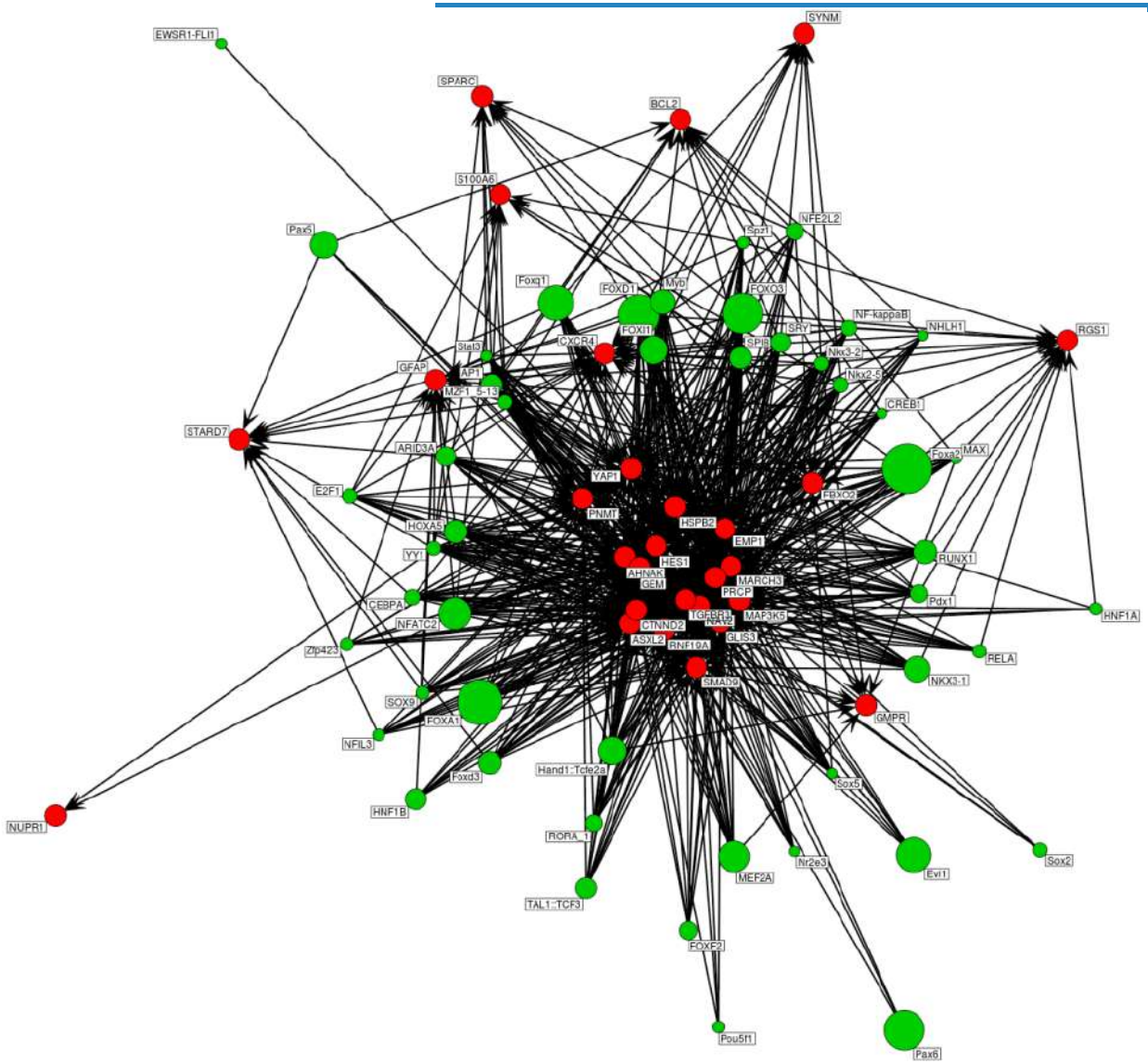
The AD gene signature was extracted from genes with highest correlation to the Alzheimer‘s disease phenotype in brain biopsies
[*Miller et al. Genes and pathways underlying regional and cell type changes in Alzheimer’s disease. Genome Med. 5, 48*.]

Red bar: Healthy controls

Blue bar: AD patients



Transcription factor analysis of the gene signature reveals Forkhead-family members as regulators of AD



Transcription factor analysis with the oPOSSUM-3 tool was performed with genes from the AD gene signature.

Red circles denote genes Green circles denote transcription factors with a size corresponding to their significance (z-score).

Factors from the Forkhead family (FOXA1,FOXA2, FOXD1, FOXO3, FOXQ1, FOXI1) have the highest significance.

Pathways and gene ontologies

GOID	Pvalue	Term	genes
0014015	0.00003	positive regulation of gliogenesis	CXCR4,GFAP,HES1
0008283	0.00008	cell proliferation	BCL2,CXCR4,EMP1,GFAP,HES1,NUPR1,S100A6,SPARC,TGFBR3,WFDC1,YAP1
0035295	0.00016	tube development	BCL2,CXCR4,HES1,SMAD9,SPARC,YAP1
0023056	0.00020	positive regulation of signaling	ASXL2,BCL2,CXCR4,GFAP,HES1,MAP3K5,TGFBR3,YAP1
0014013	0.00020	regulation of gliogenesis	CXCR4,GFAP,HES1
0010647	0.00020	positive regulation of cell communication	ASXL2,BCL2,CXCR4,GFAP,HES1,MAP3K5,TGFBR3,YAP1
0010720	0.00024	positive regulation of cell development	BCL2,CXCR4,GFAP,HES1
0021783	0.00026	preganglionic parasympathetic nervous system development	HES1,NAV2
0042127	0.00028	regulation of cell proliferation	BCL2,GFAP,HES1,NUPR1,S100A6,SPARC,TGFBR3,WFDC1,YAP1
0045597	0.00035	positive regulation of cell differentiation	ASXL2,BCL2,CXCR4,GFAP,HES1,SMAD9
0048486	0.00035	parasympathetic nervous system development	HES1,NAV2
0060251	0.00041	regulation of glial cell proliferation	GFAP,HES1
0002320	0.00046	lymphoid progenitor cell differentiation	BCL2,HES1
0016049	0.00064	cell growth	BCL2,EMP1,NUPR1,TGFBR3,WFDC1
0030856	0.00065	regulation of epithelial cell differentiation	BCL2,HES1,YAP1
0014009	0.00070	glial cell proliferation	GFAP,HES1
0035265	0.00072	organ growth	BCL2,TGFBR3,YAP1
0045595	0.00075	regulation of cell differentiation	ASXL2,BCL2,CXCR4,GFAP,HES1,SMAD9,TGFBR3,YAP1
0009628	0.00084	response to abiotic stimulus	BCL2,CXCR4,GMPR,SMAD9,SPARC,TGFBR3,YAP1
0048713	0.00085	regulation of oligodendrocyte differentiation	CXCR4,HES1

The 20 most significant terms from **gene ontology** over-representation analysis of the AD gene signature point to a major role of regulation of glial cells and development of the nervous system

KEGG pathway analysis of the AD gene signature

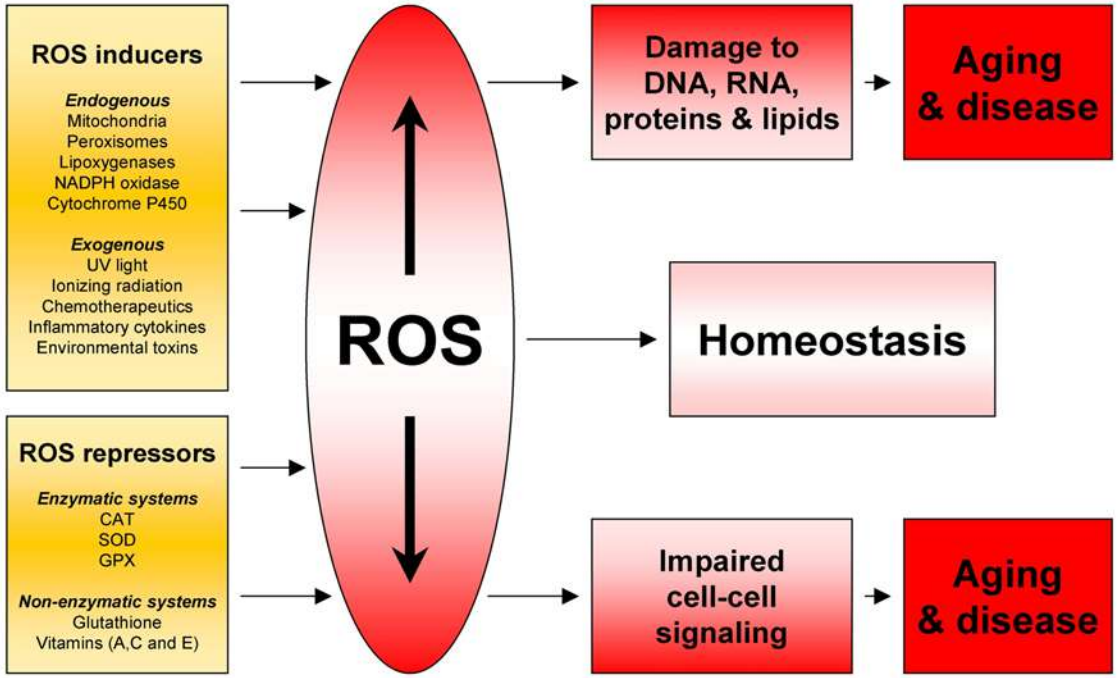
keggid	kegg_name	p	q	genes
hsa04141	Protein processing in endoplasmic reticulum	0.0017	0.3285	FBXO2,MAP3K5,BCL2
hsa05014	Amyotrophic lateral sclerosis (ALS)	0.0029	0.3285	MAP3K5,BCL2
hsa04722	Neurotrophin signaling pathway	0.0151	1.0000	MAP3K5,BCL2
hsa04950	Maturity onset diabetes of the young	0.0377	1.0000	HES1

AD-associated metabolic pathways

dataset	Literature	dataset_description	kegg_name	p	FDR
GSE36980	Hokama et al., 2012	hippocampus	Glycolysis / Gluconeogenesis	0.09	0.27
GSE43326	Kondo et al., 2013	iPSC AD model fAD: APP	Glycolysis / Gluconeogenesis	0.16	0.45
GSE42492	Hossini et al., 2015	iPSC AD model LOAD, sAD	Glycolysis / Gluconeogenesis	1	1
GSE28146	Blalock et al., 2011	hippocampus	Citrate cycle (TCA cycle)	0.18	0.65
GSE36980	Hokama et al., 2012	hippocampus	Citrate cycle (TCA cycle)	1.20E-05	4.50E-04
GSE42492	Hossini et al., 2015	iPSC AD model LOAD, sAD	Citrate cycle (TCA cycle)	1	1
GSE28146	Blalock et al., 2011	hippocampus	Oxidative phosphorylation	0.03	0.2
GSE36980	Hokama et al., 2012	hippocampus	Oxidative phosphorylation	1.20E-06	6.90E-05
GSE42492	Hossini et al., 2015	iPSC AD model LOAD, sAD	Oxidative phosphorylation	0.65	1
GSE36980	Hokama et al., 2012	hippocampus	Insulin signaling pathway	1.20E-05	4.50E-04
GSE43326	Kondo et al., 2013	iPSC AD model fAD: APP	Insulin signaling pathway	2.20E-04	7.30E-03
GSE42492	Hossini et al., 2015	iPSC AD model LOAD, sAD	Insulin signaling pathway	0.67	1

Metabolic pathways are significantly over-represented in several datasets (red:p,q < 0.05)

Metabolic Stability Theory of Aging



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RESEARCH ARTICLE

Age-related transcriptional changes in gene expression in different organs of mice support the metabolic stability theory of aging

Thore C. Brink · Lloyd Demetrius · Hans Lehrach · James Adjaye

The capacity of a cell to maintain production rates of ROS within certain bounds (ROS homeostasis)
may play a critical role in preventing damage to the cell and hence promote healthy aging

Summary

- Research on AD should expand beyond the focus on β-amyloid plaques and should embrace inflammatory and metabolic processes.
- We should embrace aging research and central mechanisms that promote healthy lifespan.
- A paradigm shift towards human-based, rather than animal-based research is paramount in view of the increasing prevalence of AD.
- Human induced pluripotent stem cell derived *in vitro* models, coupled with high-throughput ('omics') readouts, computational models, together with data obtained from meta-analysis of epidemiological and interventional studies, are among the ideal tools needed for elucidating etiopathological aspects of AD.

CAUTION!

- iPSC-based *in vitro* models are still "work in progress"
- How do we study LOAD based on a few months of "disease in a dish"

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