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REVIEW

Modelling mitochondrial dysfunction in Alzheimer's disease using human induced pluripotent stem cells

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Abstract

Alzheimer's disease (AD) is the most common form of dementia. To date, only five pharmacological agents have been approved by the Food and Drug Administration for clinical use in AD, all of which target the symptoms of the disease rather than the cause. Increasing our understanding of the underlying pathophysiology of AD will facilitate the development of new therapeutic strategies. Over the years, the major hypotheses of AD etiology have focused on deposition of amyloid beta and mitochondrial dysfunction. In this review we highlight the potential of experimental model systems based on human induced pluripotent stem cells (iPSCs) to provide novel insights into the cellular pathophysiology underlying neurodegeneration in AD. Whilst Down syndrome and familial AD iPSC models faithfully reproduce features of AD such as accumulation of Aβ and tau, oxidative stress and mitochondrial dysfunction, sporadic AD is much more difficult to model in this way due to its complex etiology. Nevertheless, iPSC-based modelling of AD has provided invaluable insights into the underlying pathophysiology of the disease, and has a huge potential for use as a platform for drug discovery.

Key words: Induced pluripotent stem cells; Alzheimer's disease; Mitochondria

Core tip: Alzheimer's disease (AD) is a huge burden on the healthcare system and on society. At present, there are no therapeutic approaches that address the underlying causes of this devastating disease, largely because we lack understanding of the underlying molecular mechanisms. Induced pluripotent stem cells (iPSCs) from AD or Down syndrome patients can be used to elucidate these molecular mechanisms, therefore presenting a novel approach to this problem. In this review, we focus on the ability of iPSC models to gain insight into the mitochondrial dysfunction that occurs during AD and therefore identify novel drug targets.

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HYPOTHESES OF CAUSATION: THE AMYLOID HYPOTHESIS *VS* THE MITOCHONDRIAL CASCADE HYPOTHESIS

Alzheimer's disease (AD) is characterized by the presence of tangles of hyper-phosphorylated tau and plaques of beta-amyloid (Aβ) in the central nervous system (CNS). However, it is not clear whether the tangles and plaques drive the pathophysiology of AD or whether they are symptomatic, caused by a common underlying process. The vast majority of people with AD present at 65 or older with "sporadic" AD (sAD). Around 1% of subjects present with atypical early onset familial AD (fAD), generally diagnosed between the ages of 30-60[1,2]. Despite this, most research has focused on fAD since its etiology is the most straightforward to model. fAD is most frequently caused by mutations in the genes encoding the three components of the amyloid precursor protein (APP) processing pathway (Figure 1), the γ-secretase-component, encoding the genes presenilin (PSEN)-1 and PSEN-2, or the APP gene itself, whereas a growing consensus suggests that sAD is more likely to be caused by impaired clearance of Aβ[3-7].

The genetic basis of fAD suggests that the accumulation of Aβ in plaques is one, if not the only, cause of the disease, as was suggested by the "amyloid hypothesis" of AD[8]. The amyloid hypothesis has evolved over the years and the most recent version distinguishes between soluble forms of Aβ, which are likely to accumulate in cells early in AD and be highly toxic, and insoluble fibrillary Aβ which is deposited later in the disease and is less toxic (reviewed in[9-12]) (Figure 2). Interestingly, tau tangles are generally no longer posited as a primary cause for AD, despite being a major cause of neuronal death, since mutations in the tau gene (*MAPT*) do not cause AD (reviewed in[13]), instead leading to frontotemporal dementia and parkinsonism. MAPT knockout mice are also relatively normal[14]. Instead Aβ accumulation is thought to cause accumulation of tau tangles[15], since treatment of AD neurons *in vitro* with Aβ-specific antibodies reverses the tau accumulation phenotype[16], although the mechanism for this association is currently unknown[17]. In support of the amyloid hypothesis, exposure of astrocytes and neurons to exogenous Aβ causes mitochondrial dysfunction, impaired glucose uptake and ultimately cell death[18,19] whilst injecting $Aβ_{42}$ into the CNS of healthy rats[20] and primates[21] causes impaired memory. In addition, APP duplications cause fAD[22] and the incidence of AD-like dementia is almost universal in ageing Down's syndrome (DS) subjects, who have three copies of chromosome 21 and therefore of the APP gene[23]. Approximately two thirds of people with DS will develop a dementia by the age of 60[23], compared to an incidence closer to 1 in 10 in the general population at a similar age. Furthermore, Prasher *et al*[24] described a 78-year-old woman with DS but without AD, in which the distal segment of chromosome 21 was translocated so that the APP gene, amongst others, was not triplicated[24]. Despite extensive evidence for the role of Aβ in AD aetiology, various anti-amyloid drugs have failed in clinical trials[25,26], as have anti-tangle drugs, which have also all failed phase II clinical trials[27]. This, along with the observations that sAD patients do not harbor APP or PSEN mutations[28], that many ageing individuals also have plaques and tangles at post mortem without signs of dementia[29,30], and that triplication of all genes on chromosome 21 except APP in mice still leads to Aβ deposition and cognitive deficits in mice[31], suggests that the pathophysiology underlying AD progression likely to be more complex. Thus, the search for the underlying mechanisms driving the pathophysiology of sAD and identification of novel candidate drug targets is urgent.

Swerdlow and Khan[32] proposed the mitochondrial cascade hypothesis, suggesting that AD develops as a consequence of an individual's baseline mitochondrial function coupled with a decline in mitochondrial function with age[33,34]. This might explain the role of ageing in the aetiology of sAD and is supported by various forms of experimental evidence. For example, evidence of oxidative stress can precede plaque formation in the brain[35], AD has a strong maternal genetic contribution[36,37] and cybrid cells, in which platelets from AD patients were fused with neuro-blastoma/teratocarcinoma cell lines lacking mtDNA, develop molecular features of

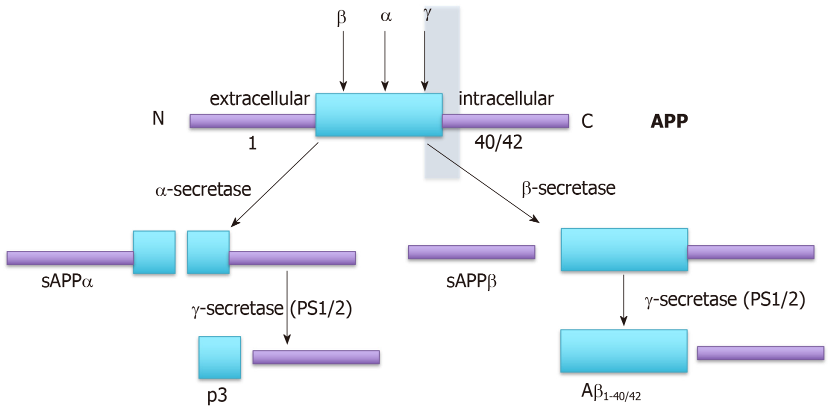

Figure 1 Amyloid precursor protein processing. Adapted from[80].

AD including Aβ production[38]. Exposure of HEK293 cells to the mitochondrial respiratory chain inhibitor antimycin A was associated with increased reactive oxygen species (ROS) generation, Aβ deposition and toxicity and this was reduced by expression of the alternative oxidase, which prevents antimycin A-induced ROS production[39]. Furthermore, normal astrocytes exhibit intracellular accumulation of Aβ similar to that observed in DS astrocytes when mitochondrial metabolism is prevented by the treatment with the uncoupler carbonyl cyanide mchlorophenyl-hydrazone (CCCP)[40].

The role of Aβ in AD remains controversial since, despite its toxicity, it can also protect cells, perhaps by virtue of an antioxidant role (reviewed in[41,42]). This role, evidenced by the ability of aggregated $Aβ_{42}$ peptide to abolish ROS formation in rat mitochondria exposed to $FeSO_4$ and ascorbate, has been proposed to be mediated by metal chelation by the peptide[43]. In addition, soluble (s)APPα, generated by the non-amyloidogenic processing of APP (Figure 1), has been shown to be neuroprotective[44]. It has been suggested that accumulation of $Aβ_{40}$ and $Aβ_{42}$ in AD may be a protective response to the oxidative damage caused by mitochondrial dysfunction[45], consistent with the mitochondrial cascade theory. This idea is supported by the observation that the survival of DS neurons was increased by recombinant or astrocyte-produced Aβ[40]. It seems plausible that ageing (or premature ageing in DS[46,47]) causes both Aβ accumulation, as a result of neurodegeneration, and mitochondrial dysfunction/oxidative stress and therefore that a vicious cycle develops whereby accumulation of Aβ into plaques causes oxidative stress which in turn increases the amyloidogenic processing of APP and Aβ deposition[45]. Interestingly, tau phosphorylation also increases in response to disruption of mitochondrial function through inhibition of the electron transport chain[48-50]. Both hypotheses are therefore likely to be correct at least to some extent.

MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS IN AD: MECHANISTIC INSIGHT

Various mechanisms by which Aβ plaques may cause oxidative stress have been proposed. For example, it has long been suggested that Aβ generates oxygen radicals directly in solution[51], since Aβ coordinates with iron and copper, which can generate ROS[52,53]. Aβ also has the capacity to form Ca^{2+}-permeant channels in lipid bilayers[54,55]. This property is dependent on the membrane cholesterol content of the bilayer[56,57], leading to the selective generation of Ca^{2+} signals in astrocytes, but not neurons after exposure to Aβ, reflecting differences in membrane cholesterol content between the two cell types[58]. This phenomenon may explain our previous observations, detailed below, in which we described mitochondrial dysfunction in astrocytes in response to Aβ, followed only later by the death of neurons. Interestingly, reactive astrocytes have been shown to actively induce neuronal death in the context of many neurodegenerative diseases, including AD[59,60].

We have previously shown that exogenous Aβ-mediated Ca^{2+} influx into rat astrocytes activate the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which generates superoxide. This results in DNA damage and large transient depolarizations of the mitochondrial membrane potential, driven by Ca^{2+} signals and opening of the mitochondrial permeability transition pore (mPTP)[18,19,61]. We showed

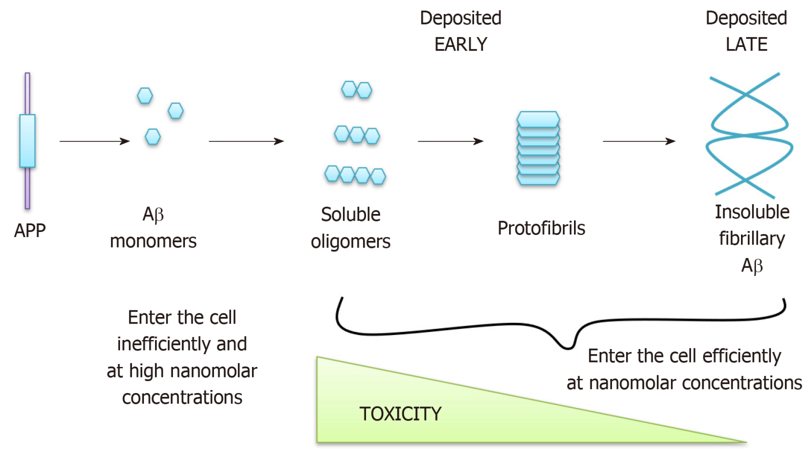

Figure 2 The different forms of Aβ. Adapted from[178] with additional information from[84].

that overactivation of Poly (ADP-ribose) polymerase (PARP)-1 in astrocytes and neurons in response to superoxide-driven DNA damage caused NAD+ depletion, failure of glycolysis in neurons and neuronal death. Neurons were rescued by inhibition of each step of this pathway - by NADPH oxidase inhibitors, PARP-1 inhibitors and by supply of metabolic substrates that bypass glycolysis, such as supplementation with methyl succinate or pyruvate[18] (Figure 3). That these mechanisms are not simply an artefact of the experimental design and operate in the intact AD nervous system is suggested by a number of observations. For example, intercellular Ca^{2+} waves passing between astrocytes and initiated at Aβ plaques were described *in vivo* in a double transgenic mouse model of AD expressing APP and mutant PSEN[62] and we found evidence for increased activation of the NADPH oxidase in the hippocampus of a triple transgenic AD mouse model[18]. Similarly, Love *et al*[63] reported evidence of increased PARP activity in post-mortem AD brains.

Impaired mitochondrial substrate supply may be exacerbated by decreased glucose uptake, a feature of the AD brain[64], likely due to Aβ exposure, which impairs glucose uptake in astrocytes[18]. This effect has been modelled in stem cell-derived neurons and astrocytes upon exposure to Aβ, which resulted in decreased levels of glucose uptake[65]. Interestingly, glucose levels have been shown in some studies to increase in the AD brain[66], which has been proposed to lead to decreased glucose uptake as an adaptive response. Whilst the mechanisms remain uncertain, Liu *et al*[67] demonstrated decreased expression of the glucose transporters GLUT-1 (the blood-brain barrier and astrocytic glucose transporter) and GLUT-3 in the AD brain and Prapong *et al*[68] have shown that Aβ inhibits neuronal glucose uptake by preventing the fusion of GLUT-3-containing vesicles with the plasma membrane.

Mitochondrial dysfunction in AD is well-established (reviewed in[69]) and respiratory capacity is generally decreased across AD models[70,71]. Mitochondrial dynamics also appear to be dysregulated in AD. Expression of the proteins mitofusin-1 and -2 and optic atrophy-1, which are involved in mitochondrial fusion, and dynamin-like protein-1, which mediates fission, are all downregulated in pyramidal neurons of AD patients[72,73]. In addition, genes associated with autophagy and mitophagy are downregulated in fibroblasts derived from sAD patients[73]. Despite this, Birnbaum *et al*[74] demonstrated an upregulation of mitochondrial complex protein expression. Mechanistically, PTEN-induced putative kinase (PINK)1, which promotes removal of damaged mitochondria by mitophagy, is downregulated in AD and restoring its expression decreases Aβ production, oxidative stress and mitochondrial dysfunction in APP-overexpressing mouse brains[75]. PINK1 mutations are associated with Parkinson's disease (reviewed in[76,77]), highlighting the common mechanisms underlying the various neurodegenerative disorders.

A ROLE FOR THE MITOCHONDRIAL mPTP IN AD

Supraphysiological increases in intra-mitochondrial Ca^{2+} can trigger opening of the mPTP, causing mitochondrial depolarization and cell death, especially if the Ca^{2+} signal is coincident with oxidative stress[18,78-81]. It has been suggested that Aβ may directly contribute to the formation of the mPTP by binding cyclophilin D, the major regulator of mPTP opening, resident in the mitochondrial matrix[82]. Alternatively, it

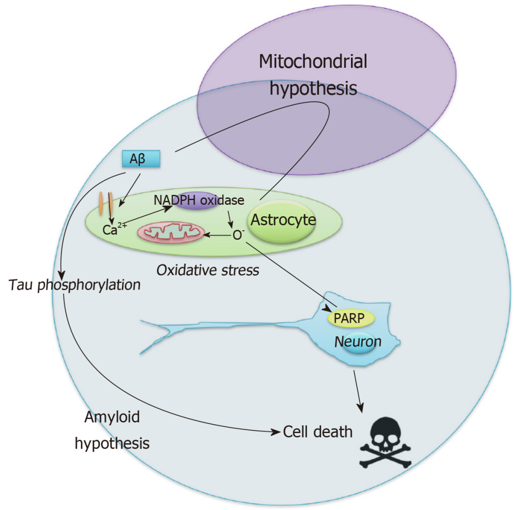

Figure 3 A proposed mechanism for the role of Aβ in neuronal death. Showing the intersection of the amyloid and mitochondrial hypotheses.

has been suggested that Aβ upregulates another putative regulator of mPTP opening, the voltage-dependent anion-selective channel-1[83]. The concept that Aβ can be internalized into the cell was recently supported by a study which visualized its uptake using confocal microscopy[84]. Interestingly, mitochondria in DS astrocytes were described as shorter, consistent with mitochondrial fragmentation and, possibly, mitochondrial swelling due to mPTP formation[85]. Furthermore, a double transgenic AD mouse model crossed with a cyclophilin D knockout mouse (in which mPTP opening is suppressed), performed significantly better in various cognitive tasks[82,86]. Aβ can also disrupt the mitochondrial respiratory chain directly through the inhibition of complex IV[87-89], complex V (reviewed in[42]) and/or by binding to Aβ-binding alcohol dehydrogenase[88,90-94], all of which would contribute to mitochondrial dysfunction and potentially to increased ROS production[95]. Moreover, deregulation of complex I has been shown to be regulated by tau[96].

THE NEED FOR BETTER MODEL SYSTEMS

Much insight has been gained through animal models. However, the lack of effective disease modifying drugs for AD largely reflects the failure of these studies to translate to efficacy in humans[97]. Reasons for this failure remain unclear, but certainly, the anatomy and genetics of the brain in rodents differ significantly from that of the human[1]. sAD is especially difficult to model, as we know so little about the underlying mechanisms, and mouse models have been generated through genetic manipulation and are therefore representative of fAD than sAD[98], with the hope that these will give insights into mechanisms of sAD. Even in the case of fAD they do not accurately mimic AD progression, for example by exhibiting full tau tangle pathology[99]. Animal models do have the unique advantage of being able to model systemic physiological factors such as diet, obesity and hypertension, all of which play important roles in sAD (reviewed in[100]). Mouse models also cannot realistically lend themselves to drug screens. Postmortem brain tissue from AD patients has also been used as a research tool. However, this is difficult to obtain[101] and the ability to generate neural cultures from postmortem tissue is highly dependent on the quality of the tissue, which is often compromised during the later stages of the disease[102].

Adding Aβ exogenously to cell cultures has been widely employed as a strategy and may have generated interesting data on the mechanisms of Aβ toxicity, but is also fraught with interpretational difficulties. It is difficult to know whether the levels or forms of Aβ that are used experimentally are (patho) physiologically relevant. In addition, various groups have added pre-aggregated tau fibrils to induced pluripotent stem cell (iPSC)-derived neurons to model AD, demonstrating that these fibrils efficiently enter the neurons[103], are propagated intracellularly[104] and that the tau aggregation phenotype that they induce can be rescued by treatment with autophagy inducers[105]. The advantages and disadvantages of the different model systems are summarized in Table 1.

Table 1 Advantages and disadvantages of different systems for modelling Alzheimer's disease[178]

Model system	Advantages	Disadvantages
Animal models	Can be used to model physiological factors such as diet, obesity and hypertension	Findings may not be able to be directly extrapolated to humans
Postmortem tissue	Human-derived	Difficult to obtain; May be of poor quality due to the destructive effects of AD in its later stages
iPSC-based models	Human-derived; More easily obtained than post-mortem tissue	Cannot be used to model physiological or epigenetic factors; Large variation between sAD iPSC lines (may not exhibit phenotype); Neuronal derivatives may be akin to 'younger' neurons

AD: Alzheimer's disease; iPSC: Induced pluripotent stem cells.

MODELLING AD USING IPSCS

The use of patient-derived iPSCs may be able to address many of these challenges, since they are derived from human subjects and are easier to obtain than postmortem tissue. In addition, tau phosphorylation has been demonstrated both in AD patient iPSC-derived neurons[106,107] and cerebral organoids generated from these cells[108] while GSK3β, a major tau kinase, has been shown to be upregulated in AD iPSC-derived neurons[17,107].

iPSCs were first generated from mouse[109] and human[110] fibroblasts in 2006 and 2007 respectively. The pioneering work of Prof. Yamanaka's group in Japan demonstrated that pluripotency, the ability to give rise to the three germ layers, could be induced in these cells through the forced expression of four key "Yamanaka factors", OCT4, SOX2, KLF4 and cMYC. The original Yamanaka factors are still in use today, with the optional addition of LIN28, p53 shRNA and NANOG to increase efficacy and the substitution of LMYC in the place of cMYC. The substitution of the latter factor is for safety reasons, since cMYC is a known oncogene[111]. In addition, pTAT-mcMYC[112] or fluorescence-activated cell sorting for differentiation markers[102] can be used to prevent uncontrolled proliferation.

Importantly, the epigenetic landscape is largely reset by the reprogramming process[113]. This will inevitably limit the use of iPSC-derived neurons to study the role of epigenetic factors in AD. Despite this phenomenon, some iPSC lines have been shown to exhibit an "epigenetic memory" of their cell type of origin[114]. This observation, along with the high degree of variability between iPSC clones (reviewed in[115]), may mean that they exhibit differing abilities to differentiate down a particular lineage, which should be taken into account when using iPSCs in this way. To address these issues, various groups have published protocols for the direct conversion of fibroblasts into induced neural precursor cells (iNPCs[116]) and induced neuronal cells (iNs[117]), in which case the epigenetic changes a cell has obtained over the lifespan of the individual are maintained. The choice of whether to use iPSC-derived neurons or iNPCs/iNs will depend on whether the researchers intend to study the genetic basis of the disease only or both genetic and epigenetic factors. However, the cell type of origin, usually fibroblasts, may still be an issue depending to what extent this cell type is affected by the disease and ageing in comparison to the neurons and astrocytes of the brain that are directly affected by the disease in the patient.

Since their original discovery a decade ago, iPSCs have proven to be an invaluable tool for studying disease progression "in a dish". Diseases that have been modelled in this way include amyotrophic lateral sclerosis[118], familial dysautonomia[119], Rett syndrome[120], schizophrenia[121], spinal muscular atrophy[122,123], DS[124], Huntingdon's disease[125], Duchenne muscular dystrophy, Parkinson's disease, AD, type 1 diabetes[126] and Gaucher disease[125]. These diseases all have a genetic basis, which is necessary to allow recapitulation of the disease phenotype in iPSCs and their derivatives.

sAD may be included in this category to some degree since it is linked to SNP variants in particular genes in 60%-80% of cases[102] (reviewed in[127]). Interestingly, in two recent studies only one of two sAD patient lines studied demonstrated an AD phenotype in the iPSC-derived neurons, including altered APP expression and Aβ secretion[17,53], demonstrating the high variability of results obtained using sAD patient-derived iPSCs. This variability is likely to reflect the different genetic backgrounds of the two different patients and highlights the importance of maximising the number of cell lines used, particularly in the case of sAD where phenotypes are so variable. The maximum number of cell lines used in the studies described here is Young *et al*[128] who use seven lines. However, studies of other diseases have been identified that use almost 30 disease lines to ensure that the statistical power of their findings is sufficient[129]. These types of studies will be important, at least initially, to identify subtypes of patients with similar phenotypes and therefore to potentially allow particular therapies to be targeted to these subtypes. Variations in the neural differentiation protocols used are also likely to represent another potential source of variation between studies. This may lead to different neural cell phenotypes and therefore possibly to different mechanistic findings.

Encouragingly, however, Hossini *et al*[130] have demonstrated AD-like gene expression profiles in sAD patient iPSC-derived neurons, including alterations in the response to oxidative stress. In addition, AD-associated phenotypes such as the presence of large RAB5+ early endosomes, which indicate impaired autophagy, increased susceptibility to cell death, abnormal calcium influx and altered axonal transport have all been observed in cells derived from patients with both fAD and sAD[17,53,131,132], reinforcing the validity of iPSC sAD models.

Many groups have modelled AD using fAD[15-17,53,98,101,108,131,133-140], sAD[17,53,98,128,129,136,141] or DS[15,124,142-147] iPSCs (Table 2). Indeed, fAD iPSC-derived neurons appear to faithfully reproduce the Aβ overproduction/tau hyperphosphorylation phenotype[15,16]. Interestingly, AD iPSCs differentiate into NPCs with indistinguishable growth rate and morphology to control cells and show a comparable efficacy of terminal differentiation into neurons[98], as do DS iPSCs[124].

Neural differentiation of iPSCs also presents the unique opportunity to model disease progression from an early stage. For example, it has been shown that Aβ secretion increases throughout neural differentiation of both fAD patient and control iPSCs[16]. Moreover, DS iPSC-derived neurons are electrophysiologically active; DS and control cell lines show no significant differences in this respect[144] and neural cultures develop AD-like pathologies after relatively short periods in culture. Despite this, iPSC-derived neurons have been shown to be more similar to late fetal neurons than late adult neurons which may limit the expression of tau isoforms[148]. In addition, iPSC-derived astrocytes from both sAD and fAD patients exhibited defective localization of astroglial markers in comparison to control cell lines[98] and fAD iPSC-derived astrocytes exhibited increased Aβ production, dysregulated calcium homeostasis and were more inflammatory, producing more ROS[98,149]. Birnbaum *et al*[74] also showed oxidative stress in iPSC-derived neurons from sAD patients, even in the absence of Aβ and tau pathology, providing support for the mitochondrial cascade hypothesis. Hibaoui *et al*[143] showed that DS iPSC-derived neurospheres contained a reduced number of NPCs, likely related to the observation that NPC proliferation was decreased and levels of apoptosis increased in the patient-derived cells. Upon neural maturation, they observed decreased expression of neuronal markers and increased expression of astroglial markers in DS cells in comparison to isogenic controls. These defects could be rescued by inhibition of dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A, suggesting that its triplication in DS is responsible for the phenotypes observed.

AD MODELLING IN 3D CULTURE SYSTEMS

In addition to 2D disease modelling, various groups are attempting to model AD in 3D cultures, in order to recreate the interactions between neurons and glia in the brain[99,108,141]. Lancaster *et al*[150] were the first to generate cerebral organoids, paving the way for 3D studies by demonstrating that these "mini brains" recapitulate the development of the fetal brain and can be used to model diseases such as microcephaly. 3D culture may have benefits over 2D culture. For example, Choi *et al*[99] describe accelerated Aβ and tau pathologies in 3D compared to 2D cultures, arguing that Aβ aggregates get "trapped" in the 3D structure rather than being released into the culture medium as they would in 2D and therefore that 3D cultures more accurately model the disease. This assumes that aggregated extracellular species are the toxic entity as opposed to soluble oligomers or intracellular accumulation. However, current drawbacks of 3D modeling include their heterogeneity and lack of developmental maturity[150-152]. Jorfi *et al*[153] have recently addressed the heterogeneity issue by demonstrating the derivation of more uniform neurospheroids which may be of use in future studies.

DRUG TESTING USING AD IPSCS

One of the major potential applications of AD derived iPSCs is in drug discovery. This

Table 2 List of studies that have used induced pluripotent stem cells to model Alzheimer's disease

Study	Disease	Key findings	Advantages	Disadvantages
Yagi *et al*[133], 2011	fAD	Relevant expression of APP and secretase subunits in iPSC-derived neurons	Obvious AD phenotype observed	fAD only represents ~ 5% patients
Shi *et al*[124], 2012a	DS	AD pathology (such as aberrant Aβ production and hyperphosphorylated Tau) developed over months in culture, as opposed to years in vivo	Show tau (advanced) phenotype	Findings may not be able to be extrapolated to AD
Israel *et al*[17], 2012	fAD, sAD	fAD neurons and one out of two sAD neurons exhibit altered APP expression and Aβ secretion and swollen endosomes	Comparison of fAD and sAD, in essence using fAD lines as positive control	High levels of variation between cell lines
Koch *et al*[101], 2012	fAD	Key steps in proteolytic APP processing are recapitulated in hES and iPSC-derived neurons	Obvious AD phenotype observed	High levels of variation between cell lines
Maclean *et al*[146], 2012	DS	Disturbance of multilineage myeloid haematopoiesis in T21 at fetal liver stage	Reproducible phenotype because clear genetic link	Findings may not be able to be extrapolated to AD
Kondo *et al*[53], 2013	fAD, sAD	Aβ oligomers accumulated in iPSC-derived neurons and astrocytes in fAD and one out of two sAD patients, also observed ROS	Comparison of fAD and sAD, in essence using fAD lines as positive control	High variation between sAD cell lines
Xu *et al*[66], 2013	Exogenous Aβ	Cell cycle re-entry in iPSC-derived neurons treated with Aβ	Used pharmacological inhibitors to demonstrate rescue of phenotype	May not be physiologically relevant
Weick *et al*[142], 2013	DS	Compensatory responses to oxidative stress in T21 neurons, also reduced synaptic activity	Reproducible phenotype because clear genetic link	Findings may not be able to be extrapolated to AD
Woodruff *et al*[139], 2013	fAD	PSEN1 mutations impair γ-secretase activity but do not disrupt γ-secretase-independent functions	Obvious AD phenotype observed	fAD only represents ~5% patients
Hibaoui *et al*[143], 2014	DS	Abnormal neural differentiation, likely caused by DYRK1A on chromosome 21	Used fetal fibroblasts to generate iPSCs (less acquired mutations)	Findings may not be able to be extrapolated to AD
Muratore *et al*[16], 2014	fAD	iPSC-derived neurons have increased Aβ42 and Aβ38, along with increased levels of both tau and phosphorylated tau	Obvious AD phenotype observed	fAD only represents ~5% patients
Mahairaki *et al*[134], 2014	fAD	Increased Aβ42:Aβ40 ratio in fAD iPSC-derived neurons	Obvious AD phenotype observed	fAD only represents ~5% patients
Sproul *et al*[135], 2014	fAD	Identified 14 genes that are differentially regulates in *PSEN1* mutant NPCs relative to controls	Obvious AD phenotype observed	fAD only represents ~5% patients
Duan *et al*[131], 2014	fAD	iPSC-derived neurons with ApoE3/4 mutations showed typical AD features	Obvious AD phenotype observed	fAD only represents ~5% patients
Liu *et al*[67], 2014	fAD	Treatment with NSAID reduced Aβ42:Aβ40 ratio	Obvious AD phenotype observed	fAD only represents ~5% patients
Young *et al*[128], 2015	sAD	Human neurons with SORL1 mutations associated with sAD show a reduced response to BDNF, at the level of both SORL1 expression and APP processing	Many cell lines used (n = 7)	Only one type of sAD mutation examined; unlikely to be able to be extrapolated to a large patient cohort

Hossini *et al*[130], 2015	sAD	Genes associated with AD expressed in sAD iPSC-derived neurons (including oxidative stress response). Treatment with a γ-secretase inhibitor reduced levels of Tau.	Show AD-like gene expression patterns	Only one patient line used (*n* = 1)
Chang *et al*[147], 2015	DS	Tau mislocalisation	Show advanced (tau) phenotype	Findings may not be able to be extrapolated to AD
Murray *et al*[144], 2015	DS	Slower proliferation of NPCs, increased Aβ production, a decrease in mitochondrial membrane potential and increased no. and abnormal appearance of mitochondria, also increased no. of ds DNA breaks in T21 neurons	Reproducible phenotype because clear genetic link	Findings may not be able to be extrapolated to AD
Moore *et al*[15], 2015	fAD, DS	APP mutations increase levels of tau and phosphorylated tau whereas PSEN mutations do not	Obvious AD phenotype observed	Tested drugs (β-secretase and -secretase inhibitors) that have failed clinical trials
Tubsuwan *et al*[177], 2016	fAD	Description of model	Obvious AD phenotype observed	fAD only represents ~5% patients
Raja *et al*[108], 2016	fAD	Brain organoids from AD patients exhibit amyloid aggregation, pTau and endosome abnormalities, treatment with β and γ-secretase inhibitors reduced this pathology	Obvious AD phenotype observed	fAD only represents ~5% patients
Li *et al*[140], 2016	fAD	Characterisation of an iPSC line	Obvious AD phenotype observed	fAD only represents ~5% patients
Lee *et al*[119], 2016	sAD	Secretase inhibtors decreased Aβ generation but less potency in 3D	High number of sAD lines used (*n* = 5)	Tested generic drugs (BACE1 and -secretase inhibitors) that have failed clinical trials
Yang *et al*[136], 2017	fAD	Premature neuronal differentiation with decreased proliferation and increased apoptosis in AD-NPCs, Wnt-Notch pathway involvement	Obvious AD phenotype observed	fAD only represents ~5% patients
Dashinimaev *et al*[145], 2017	DS	Increased Aβ secretion and upregulation of *APP* gene, also increased *BACE2*, *RCAN1*, *ETS2*, *TMED10* expression in T21 neural cells compared to controls	Reproducible phenotype because clear genetic link	Findings may not be able to be extrapolated to AD
Jones *et al*[98], 2017	fAD, sAD	Astrocytes derived from iPSCs from both fAD and sAD patients exhibit a pronounced pathological phenotype	Comparison of fAD and sAD, in essence using fAD lines as positive control	Only one line each fAD and sAD used (*n* = 1)
Armijo *et al*[137], 2017	fAD, sAD	fAD neurons have increased susceptibility to Aβ in comparison to sAD (and control) neurons	Comparison of fAD and sAD, in essence using fAD lines as positive control	Only one line each fAD and sAD used (*n* = 1)
Ochalek *et al*[107], 2018	fAD, sAD	sAD iPSC-derived neurons reveal elevated tau hyperphosphorylation, increased amyloid levels and GSK3β activation	Show tau (advanced) phenotype	Differentiation protocol requires 10 weeks at least
Birnbaum *et al*[74], 2018	sAD	sAD iPSC-derived neurons display oxidative stress and increased mitochondrial protein expression which doesn't correlate with Aβ/tau	Occurs in ~95% of AD cases	Hard to explain why the oxidative stress and increased mitochondrial protein expression don't correlate with Aβ/tau

AD: Alzheimer's disease; iPSC: Induced pluripotent stem cells; DS: Down's syndrome; APP: Amyloid precursor protein; NPC: Neural precursor cells; Aβ: Beta-amyloid.

relies on the establishment of a reliable and robust readout that associates unequivocally with AD pathophysiology that is suitable for screening on high throughput platforms. Various groups have used AD iPSC-derived neurons to test γ-secretase inhibitors, with some efficacy[16,132,154]. Additional drugs that have been tested in this way include docosahexaenoic acid (DHA), which reduces ROS production by an unknown mechanism. Interestingly, treatment with this drug increased the survival time of AD iPSC-derived neurons[53]. Since Aβ-induced toxicity has been linked to aberrant cell cycle re-entry, CDK2 inhibitors[155] and avermectins[156] have also been shown to be effective blockers of Aβ-induced toxicity in AD iPSC-derived neuronal models, although the mechanism of action of avermectins is unknown other than they increase the relative production of shorter Aβ peptides and that this action is unrelated to γ-secretase activity[156]. In addition, a combinatorial approach may be useful. For example, Kondo *et al*[154] have used human iPSC-derived neurons to identify three drugs (bromocriptine, cromolyn and topiramate) from a screen of 1258 compounds that had the most potent Aβ-reducing effects in both fAD and sAD iPSC-derived neurons.

FUTURE AVENUES OF RESEARCH AND THERAPY

One particular benefit of iPSC technology is the ability to model the heterogeneity of sAD. Many AD-linked SNPs have been identified by genome-wide association studies[157], and so use of iPSCs may allow particular treatments to be targeted to groups of individuals based on the SNPs they harbor. This field of personalized medicine, known as pharmacogenomics, may mean that drugs that have failed in clinical trials of large cohorts may be effective when applied to specific patient groups (as discussed in[158]).

Human cell models, including those based on iPSCs, are the most appropriate for modelling the human genetic variation underlying sAD since they are derived directly from sAD patient cells. Despite this, disease phenotypes are not observed in all sAD iPSC lines[17,53]. Moreover, some cell lines exhibit extracellular Aβ accumulation whereas other lines exhibit intracellular Aβ and only the latter were responsive to DHA treatment[53], suggesting an additional parameter that should be considered when designing personalized treatments. Part of the issue here understands which of these readouts most reliably reflects meaningful AD pathophysiology. The lack of a "disease phenotype" observed in some cell lines is likely due to the "rejuvenation" of markers of ageing that occurs during iPSC reprogramming and includes not only epigenetic signatures but also telomere length, mitochondrial function and the levels of oxidative stress[159-161]. To address this challenge it has been suggested that "ageing" could be accelerated in cell cultures by exposure to toxins including hydrogen peroxide or compounds that trigger mitochondrial stress such as CCCP or rotenone[162,163]. Interestingly, it has been suggested that rotenone (an inhibitor of complex I of the respiratory chain) treatment may mimic Parkinson's disease (PD)[164], again showing similar molecular mechanisms underlying neurodegeneration between AD and PD. Alternatively, the epigenetic signature could be maintained by generating iNs instead of iPSCs as described previously[117,165,166]. Importantly, Mertens *et al*[167] showed that iNs from donors aged 0-89 retained ageing-associated molecular signatures whereas iPSCs did not. Another potential approach to combat this problem is to overexpress Progerin which re-establishes age-related markers in iPSC-derived fibroblasts and neurons[159].

Despite the huge promise of personalized medicine, therapeutics with wider applicability will be more cost-efficient. Due to the widespread mitochondrial dysfunction observed not only across sAD and fAD but also across various different neurodegenerative disorders it is likely that mitochondrial disease targets may constitute a more global approach.

CONCLUSION

Recent advances in iPSC technology have highlighted the importance of metabolic dysfunction in the progression of AD. Our hope and expectation is that understanding the molecular mechanisms underlying this metabolic dysfunction will reveal novel therapeutic targets for this devastating disease[168-177].

REFERENCES

1 **Sullivan SE**, Young-Pearse TL. Induced pluripotent stem cells as a discovery tool for Alzheimer's disease. *Brain Res* 2017; **1656**: 98-106 [PMID: 26459988 DOI: 10.1016/j.brainres.2015.10.005]

2 **Contreras L**, Drago I, Zampese E, Pozzan T. Mitochondria: the calcium connection. *Biochim Biophys Acta* 2010; **1797**: 607-618 [PMID: 20470749 DOI: 10.1016/j.bbabio.2010.05.005]

3 **Wavrant-DeVrièze F**, Lambert JC, Stas L, Crook R, Cottel D, Pasquier F, Frigard B, Lambrechts M, Thiry E, Amouyel P, Tur JP, Chartier-Harlin MC, Hardy J, Van Leuven F. Association between coding variability in the LRP gene and the risk of late-onset Alzheimer's disease. *Hum Genet* 1999; **104**: 432-434 [PMID: 10394937 DOI: 10.1007/s004390050980]

4 **Myers A**, Holmans P, Marshall H, Kwon J, Meyer D, Ramic D, Shears S, Booth J, DeVrieze FW, Crook R, Hamshere M, Abraham R, Tunstall N, Rice F, Carty S, Lillystone S, Kehoe P, Rudrasingham V, Jones L, Lovestone S, Perez-Tur J, Williams J, Owen MJ, Hardy J, Goate AM. Susceptibility locus for Alzheimer's disease on chromosome 10. *Science* 2000; **290**: 2304-2305 [PMID: 11125144 DOI: 10.1126/science.290.5500.2304]

5 **Ertekin-Taner N**, Graff-Radford N, Younkin LH, Eckman C, Baker M, Adamson J, Ronald J, Blangero J, Hutton M, Younkin SG. Linkage of plasma Abeta42 to a quantitative locus on chromosome 10 in late-onset Alzheimer's disease pedigrees. *Science* 2000; **290**: 2303-2304 [PMID: 11125143 DOI: 10.1126/science.290.5500.2303]

6 **Bertram L**, Blacker D, Mullin K, Keeney D, Jones J, Basu S, Yhu S, McInnis MG, Go RC, Vekrellis K, Selkoe DJ, Saunders AJ, Tanzi RE. Evidence for genetic linkage of Alzheimer's disease to chromosome 10q. *Science* 2000; **290**: 2302-2303 [PMID: 11125142 DOI: 10.1126/science.290.5500.2302]

7 **Olson JM**, Goddard KA, Dudek DM. The amyloid precursor protein locus and very-late-onset Alzheimer disease. *Am J Hum Genet* 2001; **69**: 895-899 [PMID: 11500807 DOI: 10.1086/323472]

8 **Hardy J**, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci* 1991; **12**: 383-388 [PMID: 1763432 DOI: 10.1016/0165-6147(91)90609-V]

9 **Sengupta U**, Nilson AN, Kayed R. The Role of Amyloid-β Oligomers in Toxicity, Propagation, and Immunotherapy. *EBioMedicine* 2016; **6**: 42-49 [PMID: 27211547 DOI: 10.1016/j.ebiom.2016.03.035]

10 **Hardy J**, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002; **297**: 353-356 [PMID: 12130773 DOI: 10.1126/science.1072994]

11 **Hardy J**. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. *J Neurochem* 2009; **110**: 1129-1134 [PMID: 19457065 DOI: 10.1111/j.1471-4159.2009.06181.x]

12 **Selkoe DJ**, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* 2016; **8**: 595-608 [PMID: 27025652 DOI: 10.15252/emmm.201606210]

13 **Pittman AM**, Fung HC, de Silva R. Untangling the tau gene association with neurodegenerative disorders. *Hum Mol Genet* 2006; **15** Spec No 2: R188-R195 [PMID: 16987883 DOI: 10.1093/hmg/ddl190]

14 **Šimić G**, Babić Leko M, Wray S, Harrington CR, Delalle I, Jovanov-Milošević N, Bažadona D, Buée L, de Silva R, Di Giovanni G, Wischik CM, Hof PR. Monoaminergic neuropathology in Alzheimer's disease. *Prog Neurobiol* 2017; **151**: 101-138 [PMID: 27084356 DOI: 10.1016/j.pneurobio.2016.04.001]

15 **Moore S**, Evans LD, Andersson T, Portelius E, Smith J, Dias TB, Saurat N, McGlade A, Kirwan P, Blennow K, Hardy J, Zetterberg H, Livesey FJ. APP metabolism regulates tau proteostasis in human cerebral cortex neurons. *Cell Rep* 2015; **11**: 689-696 [PMID: 25921538 DOI: 10.1016/j.celrep.2015.03.068]

16 **Muratore CR**, Rice HC, Srikanth P, Callahan DG, Shin T, Benjamin LN, Walsh DM, Selkoe DJ, Young-Pearse TL. The familial Alzheimer's disease APPV717I mutation alters APP processing and Tau expression in iPSC-derived neurons. *Hum Mol Genet* 2014; **23**: 3523-3536 [PMID: 24524897 DOI: 10.1093/hmg/ddu064]

17 **Israel MA**, Yuan SH, Bardy C, Reyna SM, Mu Y, Herrera C, Hefferan MP, Van Gorp S, Nazor KL, Boscolo FS, Carson CT, Laurent LC, Marsala M, Gage FH, Remes AM, Koo EH, Goldstein LS. Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. *Nature* 2012; **482**: 216-220 [PMID: 22278060 DOI: 10.1038/nature10821]

18 **Abeti R**, Abramov AY, Duchen MR. Beta-amyloid activates PARP causing astrocytic metabolic failure and neuronal death. *Brain* 2011; **134**: 1658-1672 [PMID: 21616968 DOI: 10.1093/brain/awr104]

19 **Abramov AY**, Canevari L, Duchen MR. Beta-amyloid peptides induce mitochondrial dysfunction and oxidative stress in astrocytes and death of neurons through activation of NADPH oxidase. *J Neurosci* 2004; **24**: 565-575 [PMID: 14724257 DOI: 10.1523/JNEUROSCI.4042-03.2004]

20 **Jin M**, Shepardson N, Yang T, Chen G, Walsh D, Selkoe DJ. Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. *Proc Natl Acad Sci U S A* 2011; **108**: 5819-5824 [PMID: 21421841 DOI: 10.1073/pnas.1017033108]

21 **Baker HF**, Ridley RM, Duchen LW, Crow TJ, Bruton CJ. Induction of beta (A4)-amyloid in primates by injection of Alzheimer's disease brain homogenate. Comparison with transmission of spongiform encephalopathy. *Mol Neurobiol* 1994; **8**: 25-39 [PMID: 8086126 DOI: 10.1007/BF02778005]

22 **Rovelet-Lecrux A**, Hannequin D, Raux G, Le Meur N, Laquerrière A, Vital A, Dumanchin C, Feuillette S, Brice A, Vercelletto M, Dubas F, Frebourg T, Campion D. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet* 2006; **38**: 24-26 [PMID: 16369530 DOI: 10.1038/ng1718]

23 **Wiseman FK**, Al-Janabi T, Hardy J, Karmiloff-Smith A, Nizetic D, Tybulewicz VL, Fisher EM, Strydom A. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. *Nat Rev Neurosci* 2015; **16**: 564-574 [PMID: 26243569 DOI: 10.1038/nrn3983]

24 **Prasher VP**, Farrer MJ, Kessling AM, Fisher EM, West RJ, Barber PC, Butler AC. Molecular mapping of Alzheimer-type dementia in Down's syndrome. *Ann Neurol* 1998; **43**: 380-383 [PMID: 9506555 DOI: 10.1002/ana.410430316]

25 **Smith AD**. Why are drug trials in Alzheimer's disease failing? *Lancet* 2010; **376**: 1466 [PMID: 21036274 DOI: 10.1016/S0140-6736(10)61994-0]

26 **Wan HI**, Jacobsen JS, Rutkowski JL, Feuerstein GZ. Translational medicine lessons from flurizan's failure in Alzheimer's disease (AD) trial: Implication for future drug discovery and development for AD. *Clin Transl Sci* 2009; **2**: 242-247 [PMID: 20443898 DOI: 10.1111/j.1752-8062.2009.00121.x]

27 **Navarrete LP**, Pérez P, Morales I, Maccioni RB. Novel drugs affecting tau behavior in the treatment of Alzheimer's disease and tauopathies. *Curr Alzheimer Res* 2011; **8**: 678-685 [PMID: 21605038]

28 **Swerdlow RH**. Pathogenesis of Alzheimer's disease. *Clin Interv Aging* 2007; **2**: 347-359 [PMID: 18044185]

29 **Swerdlow RH**. Is aging part of Alzheimer's disease, or is Alzheimer's disease part of aging? *Neurobiol Aging* 2007; **28**: 1465-1480 [PMID: 16876913 DOI: 10.1016/j.neurobiolaging.2006.06.021]

30 **Savva GM**, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C; Medical Research Council Cognitive Function and Ageing Study. Age, neuropathology, and dementia. *N Engl J Med* 2009; **360**:

2302-2309 [PMID: 19474427 DOI: 10.1056/NEJMoa0806142]
31 **Wiseman FK**, Pulford LJ, Barkus C, Liao F, Portelius E, Webb R, Chávez-Gutiérrez L, Cleverley K, Noy S, Sheppard O, Collins T, Powell C, Sarell CJ, Rickman M, Choong X, Tosh JL, Siganporia C, Whittaker HT, Stewart F, Szaruga M; London Down syndrome consortium, Murphy MP, Blennow K, de Strooper B, Zetterberg H, Bannerman D, Holtzman DM, Tybulewicz VLJ, Fisher EMC; LonDownS Consortium. Trisomy of human chromosome 21 enhances amyloid-β deposition independently of an extra copy of APP. *Brain* 2018; **141**: 2457-2474 [PMID: 29945247 DOI: 10.1093/brain/awy159]
32 **Swerdlow RH**, Khan SM. A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. *Med Hypotheses* 2004; **63**: 8-20 [PMID: 15193340 DOI: 10.1016/j.mehy.2003.12.045]
33 **Navarro A**, Boveris A. The mitochondrial energy transduction system and the aging process. *Am J Physiol Cell Physiol* 2007; **292**: C670-C686 [PMID: 17020935 DOI: 10.1152/ajpcell.00213.2006]
34 **Trifunovic A**, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, Bohlooly-Y M, Gidlöf S, Oldfors A, Wibom R, Törnell J, Jacobs HT, Larsson NG. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* 2004; **429**: 417-423 [PMID: 15164064 DOI: 10.1038/nature02517]
35 **Moreira PI**, Carvalho C, Zhu X, Smith MA, Perry G. Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. *Biochim Biophys Acta* 2010; **1802**: 2-10 [PMID: 19853658 DOI: 10.1016/j.bbadis.2009.10.006]
36 **Edland SD**, Silverman JM, Peskind ER, Tsuang D, Wijsman E, Morris JC. Increased risk of dementia in mothers of Alzheimer's disease cases: evidence for maternal inheritance. *Neurology* 1996; **47**: 254-256 [PMID: 8710088 DOI: 10.1212/WNL.47.1.254]
37 **Duara R**, Lopez-Alberola RF, Barker WW, Loewenstein DA, Zatinsky M, Eisdorfer CE, Weinberg GB. A comparison of familial and sporadic Alzheimer's disease. *Neurology* 1993; **43**: 1377-1384 [PMID: 8327141 DOI: 10.1212/WNL.43.7.1377]
38 **Swerdlow RH**. Mitochondria in cybrids containing mtDNA from persons with mitochondriopathies. *J Neurosci Res* 2007; **85**: 3416-3428 [PMID: 17243174 DOI: 10.1002/jnr.21167]
39 **El-Khoury R**, Kaulio E, Lassila KA, Crowther DC, Jacobs HT, Rustin P. Expression of the alternative oxidase mitigates beta-amyloid production and toxicity in model systems. *Free Radic Biol Med* 2016; **96**: 57-66 [PMID: 27094492 DOI: 10.1016/j.freeradbiomed.2016.04.006]
40 **Atwood CS**, Obrenovich ME, Liu T, Chan H, Perry G, Smith MA, Martins RN. Amyloid-beta: a chameleon walking in two worlds: a review of the trophic and toxic properties of amyloid-beta. *Brain Res Brain Res Rev* 2003; **43**: 1-16 [PMID: 14499458 DOI: 10.1016/S0165-0173(03)00174-7]
41 **Carrillo-Mora P**, Luna R, Colín-Barenque L. Amyloid beta: multiple mechanisms of toxicity and only some protective effects? *Oxid Med Cell Longev* 2014; **2014**: 795375 [PMID: 24683437 DOI: 10.1155/2014/795375]
42 **Sinha M**, Bhowmick P, Banerjee A, Chakrabarti S. Antioxidant role of amyloid β protein in cell-free and biological systems: implication for the pathogenesis of Alzheimer disease. *Free Radic Biol Med* 2013; **56**: 184-192 [PMID: 23041348 DOI: 10.1016/j.freeradbiomed.2012.09.036]
43 **Barger SW**, Harmon AD. Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E. *Nature* 1997; **388**: 878-881 [PMID: 9278049 DOI: 10.1038/42257]
44 **Smith MA**, Drew KL, Nunomura A, Takeda A, Hirai K, Zhu X, Atwood CS, Raina AK, Rottkamp CA, Sayre LM, Friedland RP, Perry G. Amyloid-beta, tau alterations and mitochondrial dysfunction in Alzheimer disease: the chickens or the eggs? *Neurochem Int* 2002; **40**: 527-531 [PMID: 11850109 DOI: 10.1016/S0197-0186(01)00123-1]
45 **Busciglio J**, Pelsman A, Wong C, Pigino G, Yuan M, Mori H, Yankner BA. Altered metabolism of the amyloid beta precursor protein is associated with mitochondrial dysfunction in Down's syndrome. *Neuron* 2002; **33**: 677-688 [PMID: 11879646 DOI: 10.1016/S0896-6273(02)00604-9]
46 **Horvath S**, Garagnani P, Bacalini MG, Pirazzini C, Salvioli S, Gentilini D, Di Blasio AM, Giuliani C, Tung S, Vinters HV, Franceschi C. Accelerated epigenetic aging in Down syndrome. *Aging Cell* 2015; **14**: 491-495 [PMID: 25678027 DOI: 10.1111/acel.12325]
47 **Roth GM**, Sun B, Greensite FS, Lott IT, Dietrich RB. Premature aging in persons with Down syndrome: MR findings. *AJNR Am J Neuroradiol* 1996; **17**: 1283-1289 [PMID: 8871713]
48 **Escobar-Khondiker M**, Höllerhage M, Muriel MP, Champy P, Bach A, Depienne C, Respondek G, Yamada ES, Lannuzel A, Yagi T, Hirsch EC, Oertel WH, Jacob R, Michel PP, Ruberg M, Höglinger GU. Annonacin, a natural mitochondrial complex I inhibitor, causes tau pathology in cultured neurons. *J Neurosci* 2007; **27**: 7827-7837 [PMID: 17634376 DOI: 10.1523/JNEUROSCI.1644-07.2007]
49 **Höglinger GU**, Lannuzel A, Khondiker ME, Michel PP, Duyckaerts C, Féger J, Champy P, Prigent A, Medja F, Lombes A, Oertel WH, Ruberg M, Hirsch EC. The mitochondrial complex I inhibitor rotenone triggers a cerebral tauopathy. *J Neurochem* 2005; **95**: 930-939 [PMID: 16219024 DOI: 10.1111/j.1471-4159.2005.03493.x]
50 **Szabados T**, Dul C, Majtényi K, Hargitai J, Pénzes Z, Urbanics R. A chronic Alzheimer's model evoked by mitochondrial poison sodium azide for pharmacological investigations. *Behav Brain Res* 2004; **154**: 31-40 [PMID: 15302108 DOI: 10.1016/j.bbr.2004.01.016]
51 **Varadarajan S**, Yatin S, Aksenova M, Butterfield DA. Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. *J Struct Biol* 2000; **130**: 184-208 [PMID: 10940225 DOI: 10.1006/jsbi.2000.4274]
52 **Huang X**, Atwood CS, Hartshorn MA, Multhaup G, Goldstein LE, Scarpa RC, Cuajungco MP, Gray DN, Lim J, Moir RD, Tanzi RE, Bush AI. The A beta peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. *Biochemistry* 1999; **38**: 7609-7616 [PMID: 10386999 DOI: 10.1021/bi990438f]
53 **Kondo T**, Asai M, Tsukita K, Kutoku Y, Ohsawa Y, Sunada Y, Imamura K, Egawa N, Yahata N, Okita K, Takahashi K, Asaka I, Aoi T, Watanabe A, Watanabe K, Kadoya C, Nakano R, Watanabe D, Maruyama K, Hori O, Hibino S, Choshi T, Nakahata T, Hioki H, Kaneko T, Naitoh M, Yoshikawa K, Yamawaki S, Suzuki S, Hata R, Ueno S, Seki T, Kobayashi K, Toda T, Murakami K, Irie K, Klein WL, Mori H, Asada T, Takahashi R, Iwata N, Yamanaka S, Inoue H. Modeling Alzheimer's disease with iPSCs reveals stress phenotypes associated with intracellular Aβ and differential drug responsiveness. *Cell Stem Cell* 2013; **12**: 487-496 [PMID: 23434393 DOI: 10.1016/j.stem.2013.01.009]
54 **Arispe N**, Pollard HB, Rojas E. Giant multilevel cation channels formed by Alzheimer disease amyloid beta-protein [A beta P-(1-40)] in bilayer membranes. *Proc Natl Acad Sci U S A* 1993; **90**: 10573-10577 [PMID: 7504270 DOI: 10.1096/fj.02-0829com]
55 **Kagan BL**, Azimov R, Azimova R. Amyloid peptide channels. *J Membr Biol* 2004; **202**: 1-10 [PMID:

15702375 DOI: 10.1007/s00232-004-0709-4]
56 **Arispe N**, Doh M. Plasma membrane cholesterol controls the cytotoxicity of Alzheimer's disease AbetaP (1-40) and (1-42) peptides. *FASEB J* 2002; **16**: 1526-1536 [PMID: 12374775]
57 **Kawahara M**, Kuroda Y, Arispe N, Rojas E. Alzheimer's beta-amyloid, human islet amylin, and prion protein fragment evoke intracellular free calcium elevations by a common mechanism in a hypothalamic GnRH neuronal cell line. *J Biol Chem* 2000; **275**: 14077-14083 [PMID: 10799482 DOI: 10.1074/jbc.275.19.14077]
58 **Abramov AY**, Ionov M, Pavlov E, Duchen MR. Membrane cholesterol content plays a key role in the neurotoxicity of β-amyloid: implications for Alzheimer's disease. *Aging Cell* 2011; **10**: 595-603 [PMID: 21332922 DOI: 10.1111/j.1474-9726.2011.00685.x]
59 **Liddelow SA**, Barres BA. Reactive Astrocytes: Production, Function, and Therapeutic Potential. *Immunity* 2017; **46**: 957-967 [PMID: 28636962 DOI: 10.1016/j.immuni.2017.06.006]
60 **Liddelow SA**, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, Wilton DK, Frouin A, Napier BA, Panicker N, Kumar M, Buckwalter MS, Rowitch DH, Dawson VL, Dawson TM, Stevens B, Barres BA. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 2017; **541**: 481-487 [PMID: 28099414 DOI: 10.1038/nature21029]
61 **Abramov AY**, Jacobson J, Wientjes F, Hothersall J, Canevari L, Duchen MR. Expression and modulation of an NADPH oxidase in mammalian astrocytes. *J Neurosci* 2005; **25**: 9176-9184 [PMID: 16207877 DOI: 10.1523/JNEUROSCI.1632-05.2005]
62 **Kuchibhotla KV**, Lattarulo CR, Hyman BT, Bacskai BJ. Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. *Science* 2009; **323**: 1211-1215 [PMID: 19251629 DOI: 10.1126/science.1169096]
63 **Love S**, Barber R, Wilcock GK. Increased poly(ADP-ribosyl)ation of nuclear proteins in Alzheimer's disease. *Brain* 1999; **122**: 247-253 [PMID: 10071053 DOI: 10.1093/brain/122.2.247]
64 **Jagust WJ**, Seab JP, Huesman RH, Valk PE, Mathis CA, Reed BR, Coxson PG, Budinger TF. Diminished glucose transport in Alzheimer's disease: dynamic PET studies. *J Cereb Blood Flow Metab* 1991; **11**: 323-330 [PMID: 1997504 DOI: 10.1038/jcbfm.1991.65]
65 **Tarczyluk MA**, Nagel DA, Rhein Parri H, Tse EH, Brown JE, Coleman MD, Hill EJ. Amyloid β 1-42 induces hypometabolism in human stem cell-derived neuron and astrocyte networks. *J Cereb Blood Flow Metab* 2015; **35**: 1348-1357 [PMID: 25853906 DOI: 10.1038/jcbfm.2015.58]
66 **Xu J**, Begley P, Church SJ, Patassini S, McHarg S, Kureishy N, Hollywood KA, Waldvogel HJ, Liu H, Zhang S, Lin W, Herholz K, Turner C, Synek BJ, Curtis MA, Rivers-Auty J, Lawrence CB, Kellett KA, Hooper NM, Vardy ER, Wu D, Unwin RD, Faull RL, Dowsey AW, Cooper GJ. Elevation of brain glucose and polyol-pathway intermediates with accompanying brain-copper deficiency in patients with Alzheimer's disease: metabolic basis for dementia. *Sci Rep* 2016; **6**: 27524 [PMID: 27276998 DOI: 10.1038/srep27524]
67 **Liu Y**, Liu F, Iqbal K, Grundke-Iqbal I, Gong CX. Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. *FEBS Lett* 2008; **582**: 359-364 [PMID: 18174027 DOI: 10.1016/j.febslet.2007.12.035]
68 **Prapong T**, Buss J, Hsu WH, Heine P, West Greenlee H, Uemura E. Amyloid beta-peptide decreases neuronal glucose uptake despite causing increase in GLUT3 mRNA transcription and GLUT3 translocation to the plasma membrane. *Exp Neurol* 2002; **174**: 253-258 [PMID: 11922666 DOI: 10.1006/exnr.2001.7861]
69 **Swerdlow RH**. Mitochondria and Mitochondrial Cascades in Alzheimer's Disease. *J Alzheimers Dis* 2018; **62**: 1403-1416 [PMID: 29036828 DOI: 10.3233/JAD-170585]
70 **Sorrentino V**, Romani M, Mouchiroud L, Beck JS, Zhang H, D'Amico D, Moullan N, Potenza F, Schmid AW, Rietsch S, Counts SE, Auwerx J. Enhancing mitochondrial proteostasis reduces amyloid-β proteotoxicity. *Nature* 2017; **552**: 187-193 [PMID: 29211722 DOI: 10.1038/nature25143]
71 **Sonntag KC**, Ryu WI, Amirault KM, Healy RA, Siegel AJ, McPhie DL, Forester B, Cohen BM. Late-onset Alzheimer's disease is associated with inherent changes in bioenergetics profiles. *Sci Rep* 2017; **7**: 14038 [PMID: 29070876 DOI: 10.1038/s41598-017-14420-x]
72 **Wang X**, Su B, Lee HG, Li X, Perry G, Smith MA, Zhu X. Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. *J Neurosci* 2009; **29**: 9090-9103 [PMID: 19605646 DOI: 10.1523/JNEUROSCI.1357-09.2009]
73 **Martín-Maestro P**, Gargini R, García E, Perry G, Avila J, García-Escudero V. Slower Dynamics and Aged Mitochondria in Sporadic Alzheimer's Disease. *Oxid Med Cell Longev* 2017; **2017**: 9302761 [PMID: 29201274 DOI: 10.1155/2017/9302761]
74 **Birnbaum JH**, Wanner D, Gietl AF, Saake A, Kündig TM, Hock C, Nitsch RM, Tackenberg C. Oxidative stress and altered mitochondrial protein expression in the absence of amyloid-β and tau pathology in iPSC-derived neurons from sporadic Alzheimer's disease patients. *Stem Cell Res* 2018; **27**: 121-130 [PMID: 29414602 DOI: 10.1016/j.scr.2018.01.019]
75 **Du F**, Yu Q, Yan S, Hu G, Lue LF, Walker DG, Wu L, Yan SF, Tieu K, Yan SS. PINK1 signalling rescues amyloid pathology and mitochondrial dysfunction in Alzheimer's disease. *Brain* 2017; **140**: 3233-3251 [PMID: 29077793 DOI: 10.1093/brain/awx258]
76 **Pickrell AM**, Youle RJ. The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron* 2015; **85**: 257-273 [PMID: 25611507 DOI: 10.1016/j.neuron.2014.12.007]
77 **Kumar A**, Tamjar J, Waddell AD, Woodroof HI, Raimi OG, Shaw AM, Peggie M, Muqit MM, van Aalten DM. Structure of PINK1 and mechanisms of Parkinson's disease-associated mutations. *Elife* 2017; 6 [PMID: 28980524 DOI: 10.7554/eLife.29985]
78 **Abeti R**, Duchen MR. Activation of PARP by oxidative stress induced by β-amyloid: implications for Alzheimer's disease. *Neurochem Res* 2012; **37**: 2589-2596 [PMID: 23076628 DOI: 10.1007/s11064-012-0895-x]
79 **Briston T**, Roberts M, Lewis S, Powney B, M Staddon J, Szabadkai G, Duchen MR. Mitochondrial permeability transition pore: sensitivity to opening and mechanistic dependence on substrate availability. *Sci Rep* 2017; **7**: 10492 [PMID: 28874733 DOI: 10.1038/s41598-017-10673-8]
80 **Canevari L**, Abramov AY, Duchen MR. Toxicity of amyloid beta peptide: tales of calcium, mitochondria, and oxidative stress. *Neurochem Res* 2004; **29**: 637-650 [PMID: 15038611 DOI: 10.1023/B:NERE.0000014834.06405.af]
81 **Briston T**, Selwood DL, Szabadkai G, Duchen MR. Mitochondrial Permeability Transition: A Molecular Lesion with Multiple Drug Targets. *Trends Pharmacol Sci* 2019; **40**: 50-70 [PMID: 30527591 DOI: 10.1016/j.tips.2018.11.004]

82 **Du H**, Guo L, Fang F, Chen D, Sosunov AA, McKhann GM, Yan Y, Wang C, Zhang H, Molkentin JD, Gunn-Moore FJ, Vonsattel JP, Arancio O, Chen JX, Yan SD. Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. *Nat Med* 2008; **14**: 1097-1105 [PMID: 18806802 DOI: 10.1038/nm.1868]

83 **Smilansky A**, Dangoor L, Nakdimon I, Ben-Hail D, Mizrachi D, Shoshan-Barmatz V. The Voltage-dependent Anion Channel 1 Mediates Amyloid β Toxicity and Represents a Potential Target for Alzheimer Disease Therapy. *J Biol Chem* 2015; **290**: 30670-30683 [PMID: 26542804 DOI: 10.1074/jbc.M115.691493]

84 **Jin S**, Kedia N, Illes-Toth E, Haralampiev I, Prisner S, Herrmann A, Wanker EE, Bieschke J. Amyloid-β(1-42) Aggregation Initiates Its Cellular Uptake and Cytotoxicity. *J Biol Chem* 2016; **291**: 19590-19606 [PMID: 27458018 DOI: 10.1074/jbc.M115.691840]

85 **Helguera P**, Seiglie J, Rodriguez J, Hanna M, Helguera G, Busciglio J. Adaptive downregulation of mitochondrial function in down syndrome. *Cell Metab* 2013; **17**: 132-140 [PMID: 23312288 DOI: 10.1016/j.cmet.2012.12.005]

86 **Du H**, Guo L, Zhang W, Rydzewska M, Yan S. Cyclophilin D deficiency improves mitochondrial function and learning/memory in aging Alzheimer disease mouse model. *Neurobiol Aging* 2011; **32**: 398-406 [PMID: 19362755 DOI: 10.1016/j.neurobiolaging.2009.03.003]

87 **Aliev G**, Smith MA, de la Torre JC, Perry G. Mitochondria as a primary target for vascular hypoperfusion and oxidative stress in Alzheimer's disease. *Mitochondrion* 2004; **4**: 649-663 [PMID: 16120422 DOI: 10.1016/j.mito.2004.07.018]

88 **Canevari L**, Clark JB, Bates TE. beta-Amyloid fragment 25-35 selectively decreases complex IV activity in isolated mitochondria. *FEBS Lett* 1999; **457**: 131-134 [PMID: 10486579 DOI: 10.1016/S0014-5793(99)01028-5]

89 **Readnower RD**, Sauerbeck AD, Sullivan PG. Mitochondria, Amyloid β, and Alzheimer's Disease. *Int J Alzheimers Dis* 2011; **2011**: 104545 [PMID: 21547208 DOI: 10.4061/2011/104545]

90 **Caspersen C**, Wang N, Yao J, Sosunov A, Chen X, Lustbader JW, Xu HW, Stern D, McKhann G, Yan SD. Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *FASEB J* 2005; **19**: 2040-2041 [PMID: 16210396 DOI: 10.1096/fj.05-3735fje]

91 **Gibson GE**, Karuppagounder SS, Shi Q. Oxidant-induced changes in mitochondria and calcium dynamics in the pathophysiology of Alzheimer's disease. *Ann N Y Acad Sci* 2008; **1147**: 221-232 [PMID: 19076444 DOI: 10.1196/annals.1427.038]

92 **Lustbader JW**, Cirilli M, Lin C, Xu HW, Takuma K, Wang N, Caspersen C, Chen X, Pollak S, Chaney M, Trinchese F, Liu S, Gunn-Moore F, Lue LF, Walker DG, Kuppusamy P, Zewier ZL, Arancio O, Stern D, Yan SS, Wu H. ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. *Science* 2004; **304**: 448-452 [PMID: 15087549 DOI: 10.1126/science.1091230]

93 **Takuma K**, Yao J, Huang J, Xu H, Chen X, Luddy J, Trillat AC, Stern DM, Arancio O, Yan SS. ABAD enhances Abeta-induced cell stress via mitochondrial dysfunction. *FASEB J* 2005; **19**: 597-598 [PMID: 15665036 DOI: 10.1096/fj.04-2582fje]

94 **Yan SD**, Stern DM. Mitochondrial dysfunction and Alzheimer's disease: role of amyloid-beta peptide alcohol dehydrogenase (ABAD). *Int J Exp Pathol* 2005; **86**: 161-171 [PMID: 15910550 DOI: 10.1111/j.0959-9673.2005.00427.x]

95 **Izzo A**, Nitti M, Mollo N, Paladino S, Procaccini C, Faicchia D, Calì G, Genesio R, Bonfiglio F, Cicatiello R, Polishchuk E, Polishchuk R, Pinton P, Matarese G, Conti A, Nitsch L. Metformin restores the mitochondrial network and reverses mitochondrial dysfunction in Down syndrome cells. *Hum Mol Genet* 2017; **26**: 1056-1069 [PMID: 28087733 DOI: 10.1093/hmg/ddx016]

96 **Rhein V**, Song X, Wiesner A, Ittner LM, Baysang G, Meier F, Ozmen L, Bluethmann H, Dröse S, Brandt U, Savaskan E, Czech C, Götz J, Eckert A. Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. *Proc Natl Acad Sci U S A* 2009; **106**: 20057-20062 [PMID: 19897719 DOI: 10.1073/pnas.0905529106]

97 **Duncan T**, Valenzuela M. Alzheimer's disease, dementia, and stem cell therapy. *Stem Cell Res Ther* 2017; **8**: 111 [PMID: 28494803 DOI: 10.1186/s13287-017-0567-5]

98 **Jones VC**, Atkinson-Dell R, Verkhratsky A, Mohamet L. Aberrant iPSC-derived human astrocytes in Alzheimer's disease. *Cell Death Dis* 2017; **8**: e2696 [PMID: 28333144 DOI: 10.1038/cddis.2017.89]

99 **Choi SH**, Kim YH, Hebisch M, Sliwinski C, Lee S, D'Avanzo C, Chen H, Hooli B, Asselin C, Muffat J, Klee JB, Zhang C, Wainger BJ, Peitz M, Kovacs DM, Woolf CJ, Wagner SL, Tanzi RE, Kim DY. A three-dimensional human neural cell culture model of Alzheimer's disease. *Nature* 2014; **515**: 274-278 [PMID: 25307057 DOI: 10.1038/nature13800]

100 **Businaro R**, Ippoliti F, Ricci S, Canitano N, Fuso A. Alzheimer's disease promotion by obesity: induced mechanisms-molecular links and perspectives. *Curr Gerontol Geriatr Res* 2012; **2012**: 986823 [PMID: 22701480 DOI: 10.1155/2012/986823]

101 **Koch P**, Tamboli IY, Mertens J, Wunderlich P, Ladewig J, Stüber K, Esselmann H, Wiltfang J, Brüstle O, Walter J. Presenilin-1 L166P mutant human pluripotent stem cell-derived neurons exhibit partial loss of γ-secretase activity in endogenous amyloid-β generation. *Am J Pathol* 2012; **180**: 2404-2416 [PMID: 22510327 DOI: 10.1016/j.ajpath.2012.02.012]

102 **Mungenast AE**, Siegert S, Tsai LH. Modeling Alzheimer's disease with human induced pluripotent stem (iPS) cells. *Mol Cell Neurosci* 2016; **73**: 13-31 [PMID: 26657644 DOI: 10.1016/j.mcn.2015.11.010]

103 **Evans LD**, Wassmer T, Fraser G, Smith J, Perkinton M, Billinton A, Livesey FJ. Extracellular Monomeric and Aggregated Tau Efficiently Enter Human Neurons through Overlapping but Distinct Pathways. *Cell Rep* 2018; **22**: 3612-3624 [PMID: 29590627 DOI: 10.1016/j.celrep.2018.03.021]

104 **Karikari TK**, Nagel DA, Grainger A, Clarke-Bland C, Hill EJ, Moffat KG. Preparation of stable tau oligomers for cellular and biochemical studies. *Anal Biochem* 2019; **566**: 67-74 [PMID: 30315761]

105 **Verheyen A**, Diels A, Dijkmans J, Oyelami T, Meneghello G, Mertens L, Versweyveld S, Borgers M, Buist A, Peeters P, Cik M. Using Human iPSC-Derived Neurons to Model TAU Aggregation. *PLoS One* 2015; **10**: e0146127 [PMID: 26720731 DOI: 10.1371/journal.pone.0146127]

106 **Shi Y**, Kirwan P, Smith J, Robinson HP, Livesey FJ. Human cerebral cortex development from pluripotent stem cells to functional excitatory synapses. *Nat Neurosci* 2012; **15**: 477-486, S1 [PMID: 22306606 DOI: 10.1038/nn.3041]

107 **Ochalek A**, Mihalik B, Avci HX, Chandrasekaran A, Téglási A, Bock I, Giudice ML, Táncos Z, Molnár K, László L, Nielsen JE, Holst B, Freude K, Hyttel P, Kobolák J, Dinnyés A. Neurons derived from sporadic Alzheimer's disease iPSCs reveal elevated TAU hyperphosphorylation, increased amyloid levels, and GSK3B activation. *Alzheimers Res Ther* 2017; **9**: 90 [PMID: 29191219 DOI:

10.1186/s13195-017-0317-z]
108 **Raja WK**, Mungenast AE, Lin YT, Ko T, Abdurrob F, Seo J, Tsai LH. Self-Organizing 3D Human Neural Tissue Derived from Induced Pluripotent Stem Cells Recapitulate Alzheimer's Disease Phenotypes. *PLoS One* 2016; **11**: e0161969 [PMID: 27622770 DOI: 10.1371/journal.pone.0161969]
109 **Takahashi K**, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; **126**: 663-676 [PMID: 16904174 DOI: 10.1016/j.cell.2006.07.024]
110 **Takahashi K**, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; **131**: 861-872 [PMID: 18035408 DOI: 10.1016/j.cell.2007.11.019]
111 **Nakagawa M**, Taniguchi Y, Senda S, Takizawa N, Ichisaka T, Asano K, Morizane A, Doi D, Takahashi J, Nishizawa M, Yoshida Y, Toyoda T, Osafune K, Sekiguchi K, Yamanaka S. A novel efficient feeder-free culture system for the derivation of human induced pluripotent stem cells. *Sci Rep* 2014; **4**: 3594 [PMID: 24399248 DOI: 10.1038/srep03594]
112 **Devineni A**, Tohme S, Kody MT, Cowley RA, Harris BT. Stepping back to move forward: a current review of iPSCs in the fight against Alzheimer's disease. *Am J Stem Cells* 2016; **5**: 99-106 [PMID: 27853631]
113 **Frobel J**, Hemeda H, Lenz M, Abagnale G, Joussen S, Denecke B, Sarić T, Zenke M, Wagner W. Epigenetic rejuvenation of mesenchymal stromal cells derived from induced pluripotent stem cells. *Stem Cell Reports* 2014; **3**: 414-422 [PMID: 25241740 DOI: 10.1016/j.stemcr.2014.07.003]
114 **Rouhani F**, Kumasaka N, de Brito MC, Bradley A, Vallier L, Gaffney D. Genetic background drives transcriptional variation in human induced pluripotent stem cells. *PLoS Genet* 2014; **10**: e1004432 [PMID: 24901476 DOI: 10.1371/journal.pgen.1004432]
115 **Cahan P**, Daley GQ. Origins and implications of pluripotent stem cell variability and heterogeneity. *Nat Rev Mol Cell Biol* 2013; **14**: 357-368 [PMID: 23673969 DOI: 10.1038/nrm3584]
116 **Kim J**, Efe JA, Zhu S, Talantova M, Yuan X, Wang S, Lipton SA, Zhang K, Ding S. Direct reprogramming of mouse fibroblasts to neural progenitors. *Proc Natl Acad Sci U S A* 2011; **108**: 7838-7843 [PMID: 21521790 DOI: 10.1073/pnas.1103113108]
117 **Vierbuchen T**, Ostermeier A, Pang ZP, Kokubu Y, Südhof TC, Wernig M. Direct conversion of fibroblasts to functional neurons by defined factors. *Nature* 2010; **463**: 1035-1041 [PMID: 20107439 DOI: 10.1038/nature08797]
118 **Dimos JT**, Rodolfa KT, Niakan KK, Weisenthal LM, Mitsumoto H, Chung W, Croft GF, Saphier G, Leibel R, Goland R, Wichterle H, Henderson CE, Eggan K. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. *Science* 2008; **321**: 1218-1221 [PMID: 18669821 DOI: 10.1126/science.1158799]
119 **Lee G**, Papapetrou EP, Kim H, Chambers SM, Tomishima MJ, Fasano CA, Ganat YM, Menon J, Shimizu F, Viale A, Tabar V, Sadelain M, Studer L. Modelling pathogenesis and treatment of familial dysautonomia using patient-specific iPSCs. *Nature* 2009; **461**: 402-406 [PMID: 19693009 DOI: 10.1038/nature08320]
120 **Marchetto MC**, Carromeu C, Acab A, Yu D, Yeo GW, Mu Y, Chen G, Gage FH, Muotri AR. A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. *Cell* 2010; **143**: 527-539 [PMID: 21074045 DOI: 10.1016/j.cell.2010.10.016]
121 **Brennand KJ**, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S, Li Y, Mu Y, Chen G, Yu D, McCarthy S, Sebat J, Gage FH. Modelling schizophrenia using human induced pluripotent stem cells. *Nature* 2011; **473**: 221-225 [PMID: 21490598 DOI: 10.1038/nature09915]
122 **Ebert AD**, Yu J, Rose FF, Mattis VB, Lorson CL, Thomson JA, Svendsen CN. Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature* 2009; **457**: 277-280 [PMID: 19098894 DOI: 10.1038/nature07677]
123 **Yoshida M**, Kitaoka S, Egawa N, Yamane M, Ikeda R, Tsukita K, Amano N, Watanabe A, Morimoto M, Takahashi J, Hosoi H, Nakahata T, Inoue H, Saito MK. Modeling the early phenotype at the neuromuscular junction of spinal muscular atrophy using patient-derived iPSCs. *Stem Cell Reports* 2015; **4**: 561-568 [PMID: 25801509 DOI: 10.1016/j.stemcr.2015.02.010]
124 **Shi Y**, Kirwan P, Smith J, MacLean G, Orkin SH, Livesey FJ. A human stem cell model of early Alzheimer's disease pathology in Down syndrome. *Sci Transl Med* 2012; **4**: 124ra29 [PMID: 22344463 DOI: 10.1126/scitranslmed.3003771]
125 **Park IH**, Arora N, Huo H, Maherali N, Ahfeldt T, Shimamura A, Lensch MW, Cowan C, Hochedlinger K, Daley GQ. Disease-specific induced pluripotent stem cells. *Cell* 2008; **134**: 877-886 [PMID: 18691744 DOI: 10.1016/j.cell.2008.07.041]
126 **Jang J**, Yoo JE, Lee JA, Lee DR, Kim JY, Huh YJ, Kim DS, Park CY, Hwang DY, Kim HS, Kang HC, Kim DW. Disease-specific induced pluripotent stem cells: a platform for human disease modeling and drug discovery. *Exp Mol Med* 2012; **44**: 202-213 [PMID: 22179105 DOI: 10.3858/emm.2012.44.3.015]
127 **Chouraki V**, Seshadri S. Genetics of Alzheimer's disease. *Adv Genet* 2014; **87**: 245-294 [PMID: 25311924 DOI: 10.1016/B978-0-12-800149-3.00005-6]
128 **Young JE**, Boulanger-Weill J, Williams DA, Woodruff G, Buen F, Revilla AC, Herrera C, Israel MA, Yuan SH, Edland SD, Goldstein LS. Elucidating molecular phenotypes caused by the SORL1 Alzheimer's disease genetic risk factor using human induced pluripotent stem cells. *Cell Stem Cell* 2015; **16**: 373-385 [PMID: 25772071 DOI: 10.1016/j.stem.2015.02.004]
129 **Cook CN**, Hejna MJ, Magnuson DJ, Lee JM. Expression of calcipressin1, an inhibitor of the phosphatase calcineurin, is altered with aging and Alzheimer's disease. *J Alzheimers Dis* 2005; **8**: 63-73 [PMID: 16155351 DOI: 10.3233/JAD-2005-8108]
130 **Hossini AM**, Megges M, Prigione A, Lichtner B, Toliat MR, Wruck W, Schröter F, Nuernberg P, Kroll H, Makrantonaki E, Zouboulis CC, Adjaye J. Induced pluripotent stem cell-derived neuronal cells from a sporadic Alzheimer's disease donor as a model for investigating AD-associated gene regulatory networks. *BMC Genomics* 2015; **16**: 84 [PMID: 25765079 DOI: 10.1186/s12864-015-1262-5]
131 **Duan L**, Bhattacharyya BJ, Belmadani A, Pan L, Miller RJ, Kessler JA. Stem cell derived basal forebrain cholinergic neurons from Alzheimer's disease patients are more susceptible to cell death. *Mol Neurodegener* 2014; 9: 3 [PMID: 24401693 DOI: 10.1186/1750-1326-9-3]
132 **Lacovich V**, Espindola SL, Alloatti M, Pozo Devoto V, Cromberg LE, Čarná ME, Forte G, Gallo JM, Bruno L, Stokin GB, Avale ME, Falzone TL. Tau Isoforms Imbalance Impairs the Axonal Transport of the Amyloid Precursor Protein in Human Neurons. *J Neurosci* 2017; **37**: 58-69 [PMID: 28053030 DOI: 10.1523/JNEUROSCI.2305-16.2016]

133 **Yagi T**, Ito D, Okada Y, Akamatsu W, Nihei Y, Yoshizaki T, Yamanaka S, Okano H, Suzuki N. Modeling familial Alzheimer's disease with induced pluripotent stem cells. *Hum Mol Genet* 2011; **20**: 4530-4539 [PMID: 21900357 DOI: 10.1093/hmg/ddr394]

134 **Mahairaki V**, Ryu J, Peters A, Chang Q, Li T, Park TS, Burridge PW, Talbot CC, Asnaghi L, Martin LJ, Zambidis ET, Koliatsos VE. Induced pluripotent stem cells from familial Alzheimer's disease patients differentiate into mature neurons with amyloidogenic properties. *Stem Cells Dev* 2014; **23**: 2996-3010 [PMID: 25027006 DOI: 10.1089/scd.2013.0511]

135 **Sproul AA**, Jacob S, Pre D, Kim SH, Nestor MW, Navarro-Sobrino M, Santa-Maria I, Zimmer M, Aubry S, Steele JW, Kahler DJ, Dranovsky A, Arancio O, Crary JF, Gandy S, Noggle SA. Characterization and molecular profiling of PSEN1 familial Alzheimer's disease iPSC-derived neural progenitors. *PLoS One* 2014; **9**: e84547 [PMID: 24416243 DOI: 10.1371/journal.pone.0084547]

136 **Yang J**, Zhao H, Ma Y, Shi G, Song J, Tang Y, Li S, Li T, Liu N, Tang F, Gu J, Zhang L, Zhang Z, Zhang X, Jin Y, Le W. Early pathogenic event of Alzheimer's disease documented in iPSCs from patients with PSEN1 mutations. *Oncotarget* 2017; **8**: 7900-7913 [PMID: 27926491]

137 **Armijo E**, Gonzalez C, Shahnawaz M, Flores A, Davis B, Soto C. Increased susceptibility to Aβ toxicity in neuronal cultures derived from familial Alzheimer's disease (PSEN1-A246E) induced pluripotent stem cells. *Neurosci Lett* 2017; **639**: 74-81 [PMID: 28034781 DOI: 10.1016/j.neulet.2016.12.060]

138 **Liu Q**, Waltz S, Woodruff G, Ouyang J, Israel MA, Herrera C, Sarsoza F, Tanzi RE, Koo EH, Ringman JM, Goldstein LS, Wagner SL, Yuan SH. Effect of potent γ-secretase modulator in human neurons derived from multiple presenilin 1-induced pluripotent stem cell mutant carriers. *JAMA Neurol* 2014; **71**: 1481-1489 [PMID: 25285942 DOI: 10.1001/jamaneurol.2014.2482]

139 **Woodruff G**, Young JE, Martinez FJ, Buen F, Gore A, Kinaga J, Li Z, Yuan SH, Zhang K, Goldstein LS. The presenilin-1 ΔE9 mutation results in reduced γ-secretase activity, but not total loss of PS1 function, in isogenic human stem cells. *Cell Rep* 2013; **5**: 974-985 [PMID: 24239350 DOI: 10.1016/j.celrep.2013.10.018]

140 **Li T**, Pires C, Nielsen TT, Waldemar G, Hjermind LE, Nielsen JE, Dinnyes A, Holst B, Hyttel P, Freude KK. Generation of induced pluripotent stem cells (iPSCs) from an Alzheimer's disease patient carrying a M146I mutation in PSEN1. *Stem Cell Res* 2016; **16**: 334-337 [PMID: 27345998 DOI: 10.1016/j.scr.2016.01.001]

141 **Lee HK**, Velazquez Sanchez C, Chen M, Morin PJ, Wells JM, Hanlon EB, Xia W. Three Dimensional Human Neuro-Spheroid Model of Alzheimer's Disease Based on Differentiated Induced Pluripotent Stem Cells. *PLoS One* 2016; **11**: e0163072 [PMID: 27684569 DOI: 10.1371/journal.pone.0163072]

142 **Weick JP**, Held DL, Bonadurer GF, Doers ME, Liu Y, Maguire C, Clark A, Knackert JA, Molinarolo K, Musser M, Yao L, Yin Y, Lu J, Zhang X, Zhang SC, Bhattacharyya A. Deficits in human trisomy 21 iPSCs and neurons. *Proc Natl Acad Sci U S A* 2013; **110**: 9962-9967 [PMID: 23716668 DOI: 10.1073/pnas.1216575110]

143 **Hibaoui Y**, Grad I, Letourneau A, Sailani MR, Dahoun S, Santoni FA, Gimelli S, Guipponi M, Pelte MF, Béna F, Antonarakis SE, Feki A. Modelling and rescuing neurodevelopmental defect of Down syndrome using induced pluripotent stem cells from monozygotic twins discordant for trisomy 21. *EMBO Mol Med* 2014; **6**: 259-277 [PMID: 24375627 DOI: 10.1002/emmm.201302848]

144 **Murray A**, Letourneau A, Canzonetta C, Stathaki E, Gimelli S, Sloan-Bena F, Abrehart R, Goh P, Lim S, Baldo C, Dagna-Bricarelli F, Hannan S, Mortensen M, Ballard D, Syndercombe Court D, Fusaki N, Hasegawa M, Smart TG, Bishop C, Antonarakis SE, Groet J, Nizetic D. Brief report: isogenic induced pluripotent stem cell lines from an adult with mosaic down syndrome model accelerated neuronal ageing and neurodegeneration. *Stem Cells* 2015; **33**: 2077-2084 [PMID: 25694335 DOI: 10.1002/stem.1968]

145 **Dashinimaev EB**, Artyuhov AS, Bolshakov AP, Vorotelyak EA, Vasiliev AV. Neurons Derived from Induced Pluripotent Stem Cells of Patients with Down Syndrome Reproduce Early Stages of Alzheimer's Disease Type Pathology in vitro. *J Alzheimers Dis* 2017; **56**: 835-847 [PMID: 28059787 DOI: 10.3233/JAD-160945]

146 **Maclean GA**, Menne TF, Guo G, Sanchez DJ, Park IH, Daley GQ, Orkin SH. Altered hematopoiesis in trisomy 21 as revealed through in vitro differentiation of isogenic human pluripotent cells. *Proc Natl Acad Sci U S A* 2012; **109**: 17567-17572 [PMID: 23045682 DOI: 10.1073/pnas.1215468109]

147 **Chang CY**, Chen SM, Lu HE, Lai SM, Lai PS, Shen PW, Chen PY, Shen CI, Harn HJ, Lin SZ, Hwang SM, Su HL. N-butylidenephthalide attenuates Alzheimer's disease-like cytopathy in Down syndrome induced pluripotent stem cell-derived neurons. *Sci Rep* 2015; **5**: 8744 [PMID: 25735452 DOI: 10.1038/srep08744]

148 **Brennand K**, Savas JN, Kim Y, Tran N, Simone A, Hashimoto-Torii K, Beaumont KG, Kim HJ, Topol A, Ladran I, Abdelrahim M, Matikainen-Ankney B, Chao SH, Mrksich M, Rakic P, Fang G, Zhang B, Yates JR, Gage FH. Phenotypic differences in hiPSC NPCs derived from patients with schizophrenia. *Mol Psychiatry* 2015; **20**: 361-368 [PMID: 24686136 DOI: 10.1038/mp.2014.22]

149 **Oksanen M**, Petersen AJ, Naumenko N, Puttonen K, Lehtonen Š, Gubert Olivé M, Shakirzyanova A, Leskelä S, Sarajärvi T, Viitanen M, Rinne JO, Hiltunen M, Haapasalo A, Giniatullin R, Tavi P, Zhang SC, Kanninen KM, Hämäläinen RH, Koistinaho J. PSEN1 Mutant iPSC-Derived Model Reveals Severe Astrocyte Pathology in Alzheimer's Disease. *Stem Cell Reports* 2017; **9**: 1885-1897 [PMID: 29153989 DOI: 10.1016/j.stemcr.2017.10.016]

150 **Lancaster MA**, Renner M, Martin CA, Wenzel D, Bicknell LS, Hurles ME, Homfray T, Penninger JM, Jackson AP, Knoblich JA. Cerebral organoids model human brain development and microcephaly. *Nature* 2013; **501**: 373-379 [PMID: 23995685 DOI: 10.1038/nature12517]

151 **Qian X**, Nguyen HN, Song MM, Hadiono C, Ogden SC, Hammack C, Yao B, Hamersky GR, Jacob F, Zhong C, Yoon KJ, Jeang W, Lin L, Li Y, Thakor J, Berg DA, Zhang C, Kang E, Chickering M, Nauen D, Ho CY, Wen Z, Christian KM, Shi PY, Maher BJ, Wu H, Jin P, Tang H, Song H, Ming GL. Brain-Region-Specific Organoids Using Mini-bioreactors for Modeling ZIKV Exposure. *Cell* 2016; **165**: 1238-1254 [PMID: 27118425 DOI: 10.1016/j.cell.2016.04.032]

152 **Bershteyn M**, Kriegstein AR. Cerebral organoids in a dish: progress and prospects. *Cell* 2013; **155**: 19-20 [PMID: 24074857 DOI: 10.1016/j.cell.2013.09.010]

153 **Jorfi M**, D'Avanzo C, Tanzi RE, Kim DY, Irimia D. Human Neurospheroid Arrays for In Vitro Studies of Alzheimer's Disease. *Sci Rep* 2018; **8**: 2450 [PMID: 29402979 DOI: 10.1038/s41598-018-20436-8]

154 **Kondo T**, Imamura K, Funayama M, Tsukita K, Miyake M, Ohta A, Woltjen K, Nakagawa M, Asada T, Arai T, Kawakatsu S, Izumi Y, Kaji R, Iwata N, Inoue H. iPSC-Based Compound Screening and In Vitro Trials Identify a Synergistic Anti-amyloid β Combination for Alzheimer's Disease. *Cell Rep* 2017; **21**: 2304-2312 [PMID: 29166618 DOI: 10.1016/j.celrep.2017.10.109]

155 **Xu X**, Lei Y, Luo J, Wang J, Zhang S, Yang XJ, Sun M, Nuwaysir E, Fan G, Zhao J, Lei L, Zhong Z. Prevention of β-amyloid induced toxicity in human iPS cell-derived neurons by inhibition of Cyclin-dependent kinases and associated cell cycle events. *Stem Cell Res* 2013; **10**: 213-227 [PMID: 23305945 DOI: 10.1016/j.scr.2012.11.005]
156 **Brownjohn PW**, Smith J, Portelius E, Serneels L, Kvartsberg H, De Strooper B, Blennow K, Zetterberg H, Livesey FJ. Phenotypic Screening Identifies Modulators of Amyloid Precursor Protein Processing in Human Stem Cell Models of Alzheimer's Disease. *Stem Cell Reports* 2017; **8**: 870-882 [PMID: 28285880 DOI: 10.1016/j.stemcr.2017.02.006]
157 **Lambert JC**, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thorton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Morón FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fiévet N, Huentelman MW, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuiness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossù P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannefelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltuenen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nöthen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P; European Alzheimer's Disease Initiative (EADI); Genetic and Environmental Risk in Alzheimer's Disease; Alzheimer's Disease Genetic Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* 2013; **45**: 1452-1458 [PMID: 24162737 DOI: 10.1038/ng.2802]
158 **Robbins JP**, Price J. Human induced pluripotent stem cells as a research tool in Alzheimer's disease. *Psychol Med* 2017; **47**: 2587-2592 [PMID: 28805182 DOI: 10.1017/S0033291717002124]
159 **Marion RM**, Strati K, Li H, Tejera A, Schoeftner S, Ortega S, Serrano M, Blasco MA. Telomeres acquire embryonic stem cell characteristics in induced pluripotent stem cells. *Cell Stem Cell* 2009; **4**: 141-154 [PMID: 19200803 DOI: 10.1016/j.stem.2008.12.010]
160 **Suhr ST**, Chang EA, Tjong J, Alcasid N, Perkins GA, Goissis MD, Ellisman MH, Perez GI, Cibelli JB. Mitochondrial rejuvenation after induced pluripotency. *PLoS One* 2010; **5**: e14095 [PMID: 21124794 DOI: 10.1371/journal.pone.0014095]
161 **Miller JD**, Ganat YM, Kishinevsky S, Bowman RL, Liu B, Tu EY, Mandal PK, Vera E, Shim JW, Kriks S, Taldone T, Fusaki N, Tomishima MJ, Krainc D, Milner TA, Rossi DJ, Studer L. Human iPSC-based modeling of late-onset disease via progerin-induced aging. *Cell Stem Cell* 2013; **13**: 691-705 [PMID: 24315443 DOI: 10.1016/j.stem.2013.11.006]
162 **Byers B**, Cord B, Nguyen HN, Schüle B, Fenno L, Lee PC, Deisseroth K, Langston JW, Pera RR, Palmer TD. SNCA triplication Parkinson's patient's iPSC-derived DA neurons accumulate α-synuclein and are susceptible to oxidative stress. *PLoS One* 2011; **6**: e26159 [PMID: 22110584 DOI: 10.1371/journal.pone.0026159]
163 **Cooper O**, Seo H, Andrabi S, Guardia-Laguarta C, Graziotto J, Sundberg M, McLean JR, Carrillo-Reid L, Xie Z, Osborn T, Hargus G, Deleidi M, Lawson T, Bogetofte H, Perez-Torres E, Clark L, Moskowitz C, Mazzulli J, Chen L, Volpicelli-Daley L, Romero N, Jiang H, Uitti RJ, Huang Z, Opala G, Scarffe LA, Dawson VL, Klein C, Feng J, Ross OA, Trojanowski JQ, Lee VM, Marder K, Surmeier DJ, Wszolek ZK, Przedborski S, Krainc D, Dawson TM, Isacson O. Pharmacological rescue of mitochondrial deficits in iPSC-derived neural cells from patients with familial Parkinson's disease. *Sci Transl Med* 2012; **4**: 141ra90 [PMID: 22764206 DOI: 10.1126/scitranslmed.3003985]
164 **Cannon JR**, Tapias V, Na HM, Honick AS, Drolet RE, Greenamyre JT. A highly reproducible rotenone model of Parkinson's disease. *Neurobiol Dis* 2009; **34**: 279-290 [PMID: 19385059]
165 **Hu W**, Qiu B, Guan W, Wang Q, Wang M, Li W, Gao L, Shen L, Huang Y, Xie G, Zhao H, Jin Y, Tang B, Yu Y, Zhao J, Pei G. Direct Conversion of Normal and Alzheimer's Disease Human Fibroblasts into Neuronal Cells by Small Molecules. *Cell Stem Cell* 2015; **17**: 204-212 [PMID: 26253202 DOI: 10.1016/j.stem.2015.07.006]
166 **Zhang Y**, Pak C, Han Y, Ahlenius H, Zhang Z, Chanda S, Marro S, Patzke C, Acuna C, Covy J, Xu W, Yang N, Danko T, Chen L, Wernig M, Südhof TC. Rapid single-step induction of functional neurons from human pluripotent stem cells. *Neuron* 2013; **78**: 785-798 [PMID: 23764284 DOI: 10.1016/j.neuron.2013.05.029]
167 **Mertens J**, Paquola ACM, Ku M, Hatch E, Böhnke L, Ladjevardi S, McGrath S, Campbell B, Lee H, Herdy JR, Gonçalves JT, Toda T, Kim Y, Winkler J, Yao J, Hetzer MW, Gage FH. Directly Reprogrammed Human Neurons Retain Aging-Associated Transcriptomic Signatures and Reveal Age-Related Nucleocytoplasmic Defects. *Cell Stem Cell* 2015; **17**: 705-718 [PMID: 26456686 DOI: 10.1016/j.stem.2015.09.001]
168 **Ra JC**, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, Kim YJ, Jo JY, Yoon EJ, Choi HJ, Kwon E. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. *Stem Cells Dev* 2011; **20**: 1297-1308 [PMID: 21303266 DOI: 10.1089/scd.2010.0466]
169 **Ager RR**, Davis JL, Agazaryan A, Benavente F, Poon WW, LaFerla FM, Blurton-Jones M. Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss. *Hippocampus* 2015; **25**: 813-826 [PMID: 25530343 DOI: 10.1002/hipo.22405]
170 **Yun HM**, Kim HS, Park KR, Shin JM, Kang AR, il Lee K, Song S, Kim YB, Han SB, Chung HM, Hong JT. Placenta-derived mesenchymal stem cells improve memory dysfunction in an Aβ1-42-infused mouse model of Alzheimer's disease. *Cell Death Dis* 2013; **4**: e958 [PMID: 24336078 DOI:

10.1038/cddis.2013.490]
171 **Park D**, Yang G, Bae DK, Lee SH, Yang YH, Kyung J, Kim D, Choi EK, Choi KC, Kim SU, Kang SK, Ra JC, Kim YB. Human adipose tissue-derived mesenchymal stem cells improve cognitive function and physical activity in ageing mice. *J Neurosci Res* 2013; **91**: 660-670 [PMID: 23404260 DOI: 10.1002/jnr.23182]
172 **Yang H**, Xie Z, Wei L, Yang H, Yang S, Zhu Z, Wang P, Zhao C, Bi J. Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an AβPP/PS1 transgenic mouse model. *Stem Cell Res Ther* 2013; **4**: 76 [PMID: 23826983 DOI: 10.1186/scrt227]
173 **Kim KS**, Kim HS, Park JM, Kim HW, Park MK, Lee HS, Lim DS, Lee TH, Chopp M, Moon J. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. *Neurobiol Aging* 2013; **34**: 2408-2420 [PMID: 23623603 DOI: 10.1016/j.neurobiolaging.2013.03.029]
174 **Naaldijk Y**, Jäger C, Fabian C, Leovsky C, Blüher A, Rudolph L, Hinze A, Stolzing A. Effect of systemic transplantation of bone marrow-derived mesenchymal stem cells on neuropathology markers in APP/PS1 Alzheimer mice. *Neuropathol Appl Neurobiol* 2017; **43**: 299-314 [PMID: 26918424 DOI: 10.1111/nan.12319]
175 **Oh SH**, Kim HN, Park HJ, Shin JY, Lee PH. Mesenchymal Stem Cells Increase Hippocampal Neurogenesis and Neuronal Differentiation by Enhancing the Wnt Signaling Pathway in an Alzheimer's Disease Model. *Cell Transplant* 2015; **24**: 1097-1109 [PMID: 24612635 DOI: 10.3727/096368914X679237]
176 **Lee HJ**, Lee JK, Lee H, Carter JE, Chang JW, Oh W, Yang YS, Suh JG, Lee BH, Jin HK, Bae JS. Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. *Neurobiol Aging* 2012; **33**: 588-602 [PMID: 20471717 DOI: 10.1016/j.neurobiolaging.2010.03.024]
177 **Tubsuwan A**, Pires C, Rasmussen MA, Schmid B, Nielsen JE, Hjermind LE, Hall V, Nielsen TT, Waldemar G, Hyttel P, Clausen C, Kitiyanant N, Freude KK, Holst B. Generation of induced pluripotent stem cells (iPSCs) from an Alzheimer's disease patient carrying a L150P mutation in PSEN-1. *Stem Cell Res* 2016; **16**: 110-112 [PMID: 27345792 DOI: 10.1016/j.scr.2015.12.015]
178 **Lee SJ**, Nam E, Lee HJ, Savelieff MG, Lim MH. Towards an understanding of amyloid-β oligomers: characterization, toxicity mechanisms, and inhibitors. *Chem Soc Rev* 2017; **46**: 310-323 [PMID: 27878186 DOI: 10.1039/c6cs00731g]

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