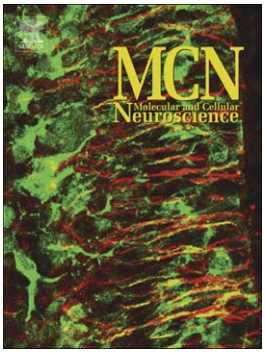


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PII: S1044-7431(15)30037-3
DOI: doi: 10.1016/j.mcn.2015.11.010
Reference: YMCNE 3042

To appear in: *Molecular and Cellular Neuroscience*

Received date: 10 July 2015
Revised date: 5 November 2015
Accepted date: 25 November 2015

Please cite this article as: Mungenast, Alison E., Siegert, Sandra, Tsai, Li-Huei, Modeling Alzheimer's disease with human induced pluripotent stem (iPS) cells, *Molecular and Cellular Neuroscience* (2015), doi: 10.1016/j.mcn.2015.11.010

# Modeling Alzheimer's disease with human induced pluripotent stem (iPS) cells.

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## Abstract

In the last decade, induced pluripotent stem (iPS) cells have revolutionized the utility of human *in vitro* models of neurological disease. The iPS-derived and differentiated cells allow researchers to study the impact of a distinct cell type in health and disease as well as performing therapeutic drug screens on a human genetic background. In particular, clinical trials for Alzheimer's disease (AD) have been often failing. Two of the potential reasons are first, the species gap involved in proceeding from initial discoveries in rodent models to human studies, and second, an unsatisfying patient stratification, meaning subgrouping patients based on the disease severity due to the lack of phenotypic and genetic markers. iPS cells overcome this obstacles and will improve our understanding of disease subtypes in AD. They allow researchers conducting in depth characterization of neural cells from both familial and sporadic AD patients as well as preclinical screens on human cells.

In this review, we briefly outline the *status quo* of iPS cell research in neurological diseases along with the general advantages and pitfalls of these models. We summarize how genome-editing techniques such as CRISPR/Cas will allow researchers to reduce the problem of genomic variability inherent to human studies, followed by recent iPS cell studies relevant to AD. We then focus on current techniques for the differentiation of iPS cells into neural cell types that are relevant to AD research. Finally, we discuss how the generation of three-dimensional cell culture systems will be important for understanding AD phenotypes in a complex cellular milieu, and how both two- and three-dimensional iPS cell models can provide platforms for drug discovery and translational studies into the treatment of AD.

## Introduction

**Alzheimer's disease (AD)** is an age-related neurodegenerative disorder associated with severe memory impairments and has become the 6th leading cause of death in the United States (www.alz.org). The first case of AD was published in 1907 by Dr. Aloysius "Alois" Alzheimer, who described a 51-year-old woman with serious memory loss. Post-mortem analysis of her brain showed severe brain atrophy and neuronal loss, as well as the presence of dense extracellular deposits and intracellular aggregates within neurons (Alzheimer, 1911; Graeber, et al., 1997). These features were eventually identified as amyloid plaques and neurofibrillary tangles, respectively (Glenner and Wong, 1984; Grundke-Iqbal, et al., 1986; Kosik, et al., 1986), and the condition became known as Alzheimer's Disease (Kraepelin, 1910).

Amyloid plaques are extracellular accumulations of β-amyloid (Aβ) peptides that are derived from the proteolytic processing of the β-amyloid precursor protein (APP) (Goldgaber, et al., 1987; Kang, et al., 1987; Robakis, et al., 1987; Tanzi, et al., 1987). The γ-secretase complex cleaves APP at different positions, generating different size amyloidogenic peptides $A\beta_{43}$, $A\beta_{42}$, $A\beta_{40}$, $A\beta_{38}$, and $A\beta_{37}$ (De Strooper, 2010). Of these, $A\beta_{40}$ is the most abundant in both healthy and AD brain tissue, whereas the $A\beta_{42}$ variant has been shown to be likely the most deleterious (Jarrett, et al., 1993; Portelius, et al., 2010). Much of our understanding of the mechanisms underlying AD pathology comes from a small population of individuals with early-onset familial AD (fAD). These cases harbor causal mutations involving primarily the Aβ processing enzymes, presenilin 1 and 2 (*PSEN1, PSEN2*), which are part of the γ-secretase complex (Levy-Lahad, et al., 1995; Levy-Lahad, et al., 1995; Rogaev, et al., 1995; Schellenberg, et al., 1993), or mutations within or duplications of the APP gene itself (Goate, et al., 1991; Goate, 2006; St George-Hyslop, et al., 1987).

The second defining characteristic of AD is the presence of neurofibrillary tangles (NFTs) comprised of intracellular accumulations of the microtubule-associated protein tau in affected neurons (Ballatore, et al., 2007). The extent of tau pathology in human AD has been shown to correlate well to disease severity (Braak and Braak, 1991). Mutations in the gene encoding tau (*MAPT*) have been found to be causal for fronto-temporal dementia, although *MAPT* mutations have not been described in AD (Hutton, et al., 1998; Spillantini, et al., 1998). Overexpression of tau protein in mouse models has been shown to disrupt intracellular trafficking (Zhang, et al., 2006), to induce axonal degeneration (Spittaels, et al., 1999), and the humanized tau overexpression leads to neurofibrillary tangles formation *in vivo* (for review, see (Götz, et al., 2007)). A number of promising drugs have reached late-stage (Phase III) clinical testing, however then failed to prevent cognitive decline (Doody, et al., 2013; Doody, et al., 2014; Salloway, et al., 2014). The reasons are likely two-fold: first, the lack of human data for the successful stratification (separating patient population) according to disease phenotypes and/or genetic risk profiles (Blennow, 2010; Wolozin, 2012), and second, the species gap. Risk factors present in humans may not be adequately modeled in rodents. For example, while variants in the *APOE* gene are the strongest genetic risk factors for sporadic AD identified to date (Bertram, et al., 2008; Corder, et al., 1993; Farrer, et al., 1997), the rodent genome has only one version of this gene.

A number of elegant mouse models have allowed the study of AD phenotypes *in vivo* in the brain, and have resulted in the basis of our current mechanistic understanding of the disease. However, a common drawback to these models is that they typically only capture specific aspects of AD phenotypes such as Aβ or NFTs, but rarely the entire disease spectrum (Webster, et al., 2014). Moreover, most mouse models focus only on the causative mutations in familial AD (fAD), such as those in the genes encoding presenilin 1 and 2 (*PSEN1, PSEN2*) and the amyloid-precursor protein (*APP*). These cases represent an extremely small percentage of the overall human AD burden; though models of fAD are invaluable, the majority of AD cases are sporadic

(sAD). The genetic underpinnings of sAD may result from a combinatorial or additive effect of single nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWAS) (Lambert, et al., 2013), while disease penetrance may depend on a host of non-genetic risk factors, such as age, head trauma, diabetes, lifetime stress, and environmental toxins, amongst others. Studying the distinct impact of AD-associated SNPs in mouse models is challenging, as these variants are often found in non-coding regions of the human genome. Using even the latest and most rapid genome editing techniques to insert multiple SNPs in homologous mouse genome regions would be onerous, expensive, and could be considered a high-risk undertaking. It is often not known whether a single SNP is disease causing, or whether it's a combination of several SNPs particularly as a number of different SNPs are commonly ascribed to a single locus.

**1. Human induced pluripotent stem (iPS) cells**

We will summarize the history, generation, and differentiation of human iPS cells only briefly, as many excellent reviews have covered these topics (Bouwman and de Laat, 2015; Parent and Anderson, 2015; Telias and Ben-Yosef, 2014). One fundamental question in the regeneration field is to find cells that maintain the capability to differentiate into the three germ layers: endoderm, mesoderm, and ectoderm. Embryonic stem (ES) cells have this "pluripotency" capability (Evans and Kaufman, 1981; Martin, 1981; Thomson, et al., 1998). However, ethical issues tempered the initial excitement for human ES cells and therefore alternative strategies were needed (Hotta, 2008; Kamm, 2005). An important step was the discovery that the content of an oocyte's cytoplasm contained factors crucial for reprogramming somatic cells to an embryonic-like stage (Cowan, et al., 2005; Tada, et al., 2001; Wilmut, et al., 1997). Takahashi *et al.* screened 24 of these factors and demonstrated that Oct3/4, Sox2, c-Myc, and Klf4 induced pluripotent stem cells from adult mouse fibroblasts (Takahashi and Yamanaka, 2006). A year later, the same group showed that they could reprogram human fibroblasts with these four "Yamanaka factors" into human pluripotent stem cells (Takahashi, et al., 2007). Other groups have generated similarly pluripotent cells from other peripheral cells, such as blood cells (Okita, et al., 2013) or urine-derived epithelial cells (Zhou, et al., 2012).To distinguish these pluripotent stem cells from ES cells, the cells were named "induced pluripotent stem" (iPS) cells. Currently, much debate exists over the best method for reprogramming somatic cells into iPS cells, as well as how to assess the "stemness" of an iPS cell as compared to an ES cell line (Bock, et al., 2011; Hanna, et al., 2010; Lister, et al., 2011). It is important to keep in mind that exogenous factors, genetic background, and epigenetic of tissue origin of cells influences naïve pluripotency (Hanna, et al., 2010). Therefore certain differences on the epigenetic landscape are expected to exist between ES and iPS cells (Bock, et al., 2011; Lister, et al., 2011). Nevertheless, the advent of iPS cells allows to generate any cell type of interest from a patient's own somatic cells and to develop patient-specific drug treatments. Moreover, these techniques offer a nearly unlimited supply of human cells that can be deposited in repositories and shared between laboratories.

**2. Advantages to modeling neurological disease with iPS cells**

The study of human brain disease is hampered by obtaining live material. The ability to generate neural cultures from post-mortem human brains depends greatly on the quality of the post-mortem brain tissue (Verwer, et al., 2002). Prolonged agonal states such as hypoxia, coma, or ischemic brain damage could add confounding variables to these studies (Monoranu, et al., 2009). This is not to mention the sheer difficulty of gaining access to reliable sources of human brain tissue. The generation of human iPS cells is one way to surmount these limitations. Protocols have been developed to differentiate iPS cells *in vitro* into distinct cell types allowing researchers to examine disease onset and progression directly in a human culture model (Liu, et al., 2012; Sandoe and Eggan, 2013). A number of studies have shown successful reprogramming of iPS cells from fibroblasts derived from individuals with various neurological diseases such as amyotrophic lateral sclerosis (Dimos, et al., 2008), familial dysautonomia (Lee, et al., 2009), Parkinson's disease (Park, et al.,

2008; Soldner, et al., 2009), Rett syndrome (Marchetto, et al., 2010), schizophrenia (Brennand, et al., 2011), spinal muscular atrophy (Ebert, et al., 2009; Yoshida, et al., 2015), ADA-SCID, Gaucher disease type III, Duchenne muscular dystrophy, Becker muscular dystrophy, Down syndrome, Juvenile diabetes mellitus, Huntington disease (Consortium, 2012; Zhang, et al., 2010), and Lesch-Nyhan syndrome (Mattis, et al., 2015; Park, et al., 2008) and AD (Choi, et al., 2014; Hossini, et al., 2015; Iovino, et al., 2015; Israel, et al., 2012; Koch, et al., 2012; Kondo, et al., 2013; Muratore, et al., 2014; Wren, et al., 2015; Yagi, et al., 2011; **Table 1)**.

## 3. Drawbacks of iPS cells in neurological disease modeling

The explosion in human iPS cell use has underscored the need to establish standardized protocols, as cell handling and other factors can influence phenotypes (Boulting, et al., 2011). For example, variable X-inactivation in cells from female donors can have an impact upon both differentiation and phenotype (Boulting, et al., 2011). Also, there is still debate regarding to what extent DNA methylation profiles, and other epigenetic attributes, might be maintained in iPS cells after reprogramming (Kim, et al., 2010; Koche, et al., 2011; Nazor, et al., 2012; Ohi, et al., 2011). To determine the magnitude and nature of variability amongst human iPS cells, (Bock, et al., 2011) performed a human genome-wide reference mapping of the DNA methylation across 20 ES and 12 iPS cell lines. They established two scorecards for evaluating the quality and utility of human pluripotent cell lines; this kind of tool is crucial to the standardization of iPS protocols and is needed to obtain comparable and reproducible results.

Genetic diversity within and between populations, as well as disease onset and progression, can impact the experimental read-out from iPS cells (Rouhani, et al., 2014; Soldner and Jaenisch, 2012). For example, common DNA variants may alter expression levels and pattern of many human genes (Majewski and Pastinen, 2011). Some groups have sought to overcome this diversity by focusing either on few phenotypes in a large collection of lines (Bock, et al., 2011; Rouhani, et al., 2014; Yoshimizu, et al., 2015), or by investigating robust phenotypes in a smaller cohort (Chung, et al., 2013; Israel, et al., 2012). Each iPS cell study is challenged by the question of to what extent the observed phenotypes are related to the disease being modeled. For example, is the phenotype influenced by protective or exacerbating factors in the individual's genotype? Recent advances in genome editing techniques, particularly the use of Cas9 nuclease-based strategies, have made the generation of isogenic iPS cell practicable (Zhang, et al., 2014) and this technology can address the variability inherent in the human genome to some extent.

## 4. Creating isogenic iPS cell lines as a strategy to overcome variability in human genomes

The advent of homology-directed repair techniques for genome editing proved a major advance in our ability to manipulate the human genome. Currently, three systems have been established to perform DNA repair-directed genome editing: Zinc-Finger-Nucleases (ZFN), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced short palindromic repeats (CRISPR) system that uses the Cas9 nuclease. All these nucleases induce guided DNA breaks. The repair of these breaks then either leads to insertion or deletion (indel) mutations, or the break can be repaired by homologous recombination with a donor vector carrying the desired mutation (Byrne, et al., 2014). For a detailed review of the function of each of the nucleases, please refer to the reviews from (Hsu, et al., 2014; Sander and Joung, 2014) as well as to descriptions of experimental strategies and protocols for human pluripotent cells in particular (Byrne, et al., 2014; Chiba and Hockemeyer, 2015; Zhu, et al., 2014).

The first generation of enzyme-directed genome editing used ZFNs. A number of important papers used the first generation ZFNs to generate isogenic iPS cells (Carroll, 2011; Urnov, et al., 2010)) by knocking down genes such as *PITX3* (Hockemeyer, et al., 2009) or *PIG-A* (Zou, et al., 2009), or correcting disease-related

mutations in genes such as α1-anti-trypsin (Yusa, et al., 2011), α-synuclein (*SCNA*;(Ryan, et al., 2013; Soldner, et al., 2011), and tau (*MAPT*(Fong, et al., 2013). However, the success of this technique is limited due to the challenging design of a robust engineered zinc finger nuclease (Hsu, et al., 2014; Ma, et al., 2015; Sander and Joung, 2014). The development of the second generation TALEN technique overcame some of the limitations of the ZFNs by being less context-dependent and easier to design (Joung and Sander, 2013; Miller, et al., 2011; Sander and Joung, 2014), while the efficiency is similar between the two paradigms (Hockemeyer, et al., 2011). Human iPS models established with TALEN technology include manipulations in the *APOB*, *SORT1*, *AKT2*, *PLIN1* (Ding, et al., 2013), *PSEN1* (Woodruff, et al., 2013), and *DISC1* (Wen, et al., 2014). The third generation of genome editing tools is comprised of the CRISPR/Cas9 systems, which are based on the use of the RNA-guided Cas9 nuclease (Jinek, et al., 2012; Mali, et al., 2013; Ran, et al., 2013). One major advantage of the CRISPR system is that the Cas9 component is fixed, and the targeting sequence is supplied via a single-guide RNA (sgRNA); thus, targeting sequences can be easily exchanged or multiplexed by testing multiple sgRNAs (Ding, et al., 2013). Several groups generated iPS cells that stably or inducible express the Cas9 protein. This system allows for rapid cell-based screens to test the consequences of multiple gene knockdowns using sgRNA libraries (Shalem, et al., 2014; Wang, et al., 2014; Zhu, et al., 2014). Algorithms have been developed that predict off target effects of CRISPR-mediated genome editing, which, combined with falling costs for deep sequencing, allow researchers to minimize off-target effects (Hsu, et al., 2013; Tsai, et al., 2015).

The advantage of isogenic lines is that only the disease-associated difference is studied, as the genetic background of the lines should be identical. While this is ideal for the study of disease causative mutations, other genetic variants, such as a haplotype of SNPs, are more difficult to model because they may only be relevant to disease risk in combination. Therefore, it seems advisable to both correct the mutation of interest in a patient-derived cell line, while in parallel introducing it in a control line. Techniques using mutated Cas9 linked to transcriptional activators or repressors also allow us to examine the consequences of enhanced or suppressed expression of specific genes without alterations to the genome itself (Qi, et al., 2013). Therefore, genome editing will be an important strategy to minimize the effect of background variations in human iPS cell-derived lines.

**5. iPS cells as a model for understanding AD onset and disease progression**

In the following chapter, we will focus on studies that use iPS cells to model AD-like phenotypes (summarized in **Table 1**). The two hallmark characteristics of AD in the human brain are first, accumulation of β-amyloid (Aβ) peptides into extracellular aggregates (Aβ plaques), and second, the intracellular accumulation of phosphorylated species of the microtubule-associated protein tau into neurofibrillary tangles (NFTs). Both parameters can be measured *in vitro*: alterations in the presence of Aβ peptides can be measured from culture medium or cell lysates, and the ratios between different species of Aβ peptides, such as the amount of $A\beta_{40}$ versus $A\beta_{42}$, are often reported. To examine tauopathy in AD cellular models, the abundance of different species of phosphorylated tau (pTau) is normalized against total tau levels. Other AD-like phenotypes that can be measured in cultured cells will also be discussed, including endosome cycling and DNA damage.

*5a. Phenotypic characterization of iPS cell AD models*

Several groups have succeeded in creating functional neurons from fAD and sAD iPS cells: In 2011, Yagi et al. used fibroblasts of fAD patients with mutations in either presenilin isoform PSEN1 (A246E) or PSEN2 (N141I; Yagi, et al., 2011). Using retrovirus carrying a five-factor reprogramming mix of OCT4, SOX2, KLF4, LIN28 and NANOG, they created iPS cells that were then differentiated mainly into neuronal cells. After two-week culturing, they observed an elevated ratio of $A\beta_{42}$ to $A\beta_{40}$ for the fAD lines compared to controls. The

authors did not find any level of tauopathy, and speculated that the two-week maturation time may have been too short. Treatment of the cultures with the γ-secretase inhibitors Compound E and Compound W reduced both $A\beta_{40}$ and $A\beta_{42}$ levels, while only the highest dose of Compound W appeared to impact the $A\beta_{42/40}$ ratio. This study was the first to establish a model of fAD phenotypes in iPS cell-derived neural cultures. However the drawbacks of this work might be the relatively short time of neuron maturation as well as the potential high variability between clones of the same genotype.

In 2012, Israel et al. provided a thorough evaluation of AD-like phenotypes in multiple iPS cell-derived neurons from both fAD and sAD individuals (Israel, et al., 2012). They used retrovirus carrying the four Yamanaka factors OCT4, SOX2, KLF4, and c-MYC to create iPS cells lines from healthy, non-demented individuals, two sporadic AD patients, and two familial patients, who carried APP duplications. Neural progenitor cells were purified using fluorescence activated cell sorting and differentiated into heterogeneous neuronal cultures. They observed increased secreted $A\beta_{40}$ in neurons created from one sAD and the two fAD lines. Importantly, the Aβ levels did not differ in fibroblasts from the same individuals, supporting the idea that only distinct iPS-derived cells can model disease-specific phenotypes. No changes were observed in the $A\beta_{42/40}$ or $A\beta_{38/40}$ ratios between cell lines, although the authors noted that detection of the less abundant $A\beta_{42}$ and $A\beta_{38}$ species were often below the detection range of the assay due to the small number of neurons. In a similar pattern, one sAD and both fAD lines showed increased phospho-tau and activation of the tau kinase GSK3β. Treatment of the neuronal cultures with γ- and β-secretase inhibitors reduced $A\beta_{40}$ in one sAD and one fAD line, while only β-secretase inhibitors lowered the levels of active GSK-3β, and phospho-tau. Another AD phenotype that can be characterized in iPS cell-derived cultures is the presence of abnormal endosomes. Large, RAB5-positive early endosomes have been observed in AD mouse models and in the brains of sAD and fAD patients (Cataldo, et al., 2001; Cataldo, et al., 2000). These endosomes may contain aberrantly phosphorylated Aβ (Lee, et al., 2003). Impaired endocytic and mitochondrial trafficking has also been observed in iPS cell models of frontotemporal dementia (FTD) using cells from patients carrying mutations in the MAPT gene (Iovino, et al., 2015; Wren, et al., 2015). Israel *et al*. examined early endosome morphology in iPS-derived neurons seeded onto a layer of commercially-available human astrocytes, and found that the number of medium to large RAB5+ endosomes was increased in neurons derived from one sAD and one fAD compared to the two controls, when they examined early endosome morphology in iPS-derived neurons seeded onto a layer of commercially-available human astrocytes. Finally, they measured synapse formation and function. No differences were apparent in synapse number (synapsin immunoreactivity) or function (voltage clamp recordings) between the AD and control lines.

In 2013, Kondo et al. used episomal vectors to generate iPS cells from dermal fibroblasts from both sAD patients and fAD patients carrying the APP-V717L or the APP-E693Δ fAD mutations (Kondo, et al., 2013). The E693Δ mutation leads to early-onset AD, but without amyloid deposition. Differentiated E693Δ neurons showed decreased $A\beta_{40}$ and $A\beta_{42}$ compared to controls, while neurons from the V717L line have increased extracellular Aβ and an increased $A\beta_{42/40}$ ratio. No significant Aβ secretion was detectable in the medium of the sAD lines. The authors then established astrocyte-rich cultures using protocols modified from Su-Chun Zhang's work (Krencik and Zhang, 2011). Astrocytes from the E693Δ line and one of the sAD lines accumulated Aβ oligomers intracellular. They performed gene expression profiling of the astrocyte/neuronal co-cultures from E693Δ and control cells and observed that oxidative stress-related categories were upregulated in the AD lines, suggesting ER and Golgi perturbation. The levels of these genes were reduced following treatment with DHA, known to alleviate oxidative stress, as well as the production of ROS, in E693Δ cells, without altering the levels of Aβ.

Fong et al (2013) used zinc-finger nucleases (ZFNs) to correct a A152T mutation in the *MAPT* gene (tau), as well as to create an isogenic line homozygous for the mutation, in iPS cells (Fong, et al., 2013). Following

neuronal differentiation, the heterozygous mutant tau neurons showed short, misshapen neurites with punctate tau and significant phospho-tau immunoreactivity. These phenotypes were absent in the corrected lines, and were significantly exacerbated in the homozygous mutant lines, which showed high degrees of phospho-tau (AT8) and blebbing of the neurites. While they found a low percentage of dopaminergic cells (DA) in the mutant lines, the corrected isogenic lines had 4 to 8-fold increased number of DA neurons.

In addition to lines derived from AD patients, several groups have overexpressed fAD mutant versions of PSEN1 or APP in healthy iPS or ES cell lines (Choi, et al., 2014; Koch, et al., 2012). For example, neurons created from a human ES cell line were transduced, as neuroepithelial-like stem cells, with lentivirus carrying cDNAs for $PSEN1_{wt}$, $PSEN1_{D385N}$, or $PSEN1_{L166P}$ under control of the EF1alpha promoter (Koch, et al., 2012). By four weeks of neuronal differentiation, most of the β-III tubulin–positive cells were highly immunoreactive for APP. Interestingly, the inclusion of Exon 15 of APP, a splice variant associated with neurons, was present in neurons after 4 weeks compared to undifferentiated cells. Extracellular Aβ level was reduced in these neuronal cultures following treatment with the γ-secretase inhibitor DAPT. In addition, NSAIDS, such as ibuprofen, slightly lowered Aβ levels only in the PS1wt, but not the PS1D385N, overexpressing neurons. One early screening effort used commercially available iPS cell-derived neurons (iCell Neurons) to screen a library of several hundred compounds for their ability to ameliorate toxicity from exogenously applied Aβ (Xu, et al., 2013).

To date, most studies model AD in patient-derived iPS cells utilize cell lines with defined fAD mutations in PSEN1 and APP. While some studies include cells from sAD patients, the lack of a defined mutation means that isogenic lines cannot be made, and often information is lacking as to the severity or course of disease progression. Two studies in which sAD lines were included observed disease phenotypes similar to fAD cells in only one of two sAD samples (Israel, et al., 2012; Kondo, et al., 2013). Few studies include sAD lines, and this is a concern, as sporadic late-onset AD represents the vast majority of AD cases. And while 60-80% of sAD may in fact have genetic underpinnings (Gatz, et al., 2006), one's *APOE* genotype remains the only robust factor affecting sAD risk. These issues add to the call for development of AD biomarkers that can predict disease risk and age of onset. Much work has begun in this direction, and large-scale human genome-wide association studies (GWAS) combined with mouse and human epigenetic and transcriptome profiling, have derived lists of genes in which variants are consistently associated with an increased risk of AD (Bertram, et al., 2007). These genes tend to be implicated in vesicle trafficking/endocytosis, immune function, and cholesterol metabolism (for review see Olgiati, et al., 2011)). One recent study (Young, et al., 2015) focused upon iPS cells derived from individuals with sAD-associated variants in the *SORL1* gene, which encodes a protein involved in endocytic trafficking, and whose loss of expression has been observed in sAD brains. The authors found that the induction of *SORL1* expression by brain-derived neurotrophic factor (BDNF) treatment, as well as the effect of *SORL1* expression upon Aβ secretion, was affected by *SORL1* genotype in differentiated human neurons. While these studies were hampered by significant variability, which was combated by the inclusion of a relatively large number of cell lines, it was the first to describe a phenotype in human iPS cell-derived neurons resulting from sAD-associated genetic variants. With the increased feasibility of genome editing in iPS cells, particularly to create point mutations, we anticipate that the near future will see many more reports elucidating the roles of sAD risk variants in iPS cell-derived neural cell models.

*5b. AD phenotypes in Down syndrome iPS cells*

Down Syndrome (DS) patients show a high incidence of early-onset AD-like dementia (40-60%). The underlying reasons for this are not clear, but are presumably related to the triplication of the *APP* gene, as well as the tau kinase Dyrk1a gene (Woods, et al., 2001) on chromosome 21 (Beyreuther, et al., 1993; Burger

and Vogel, 1973; Lemere, et al., 1996; Rumble, et al., 1989). Therefore, neural cell models from DS individuals may improve both our understanding of AD-like pathology, as well as providing hope for therapies for DS (2013). To date, no genome editing protocols have been reported that allow for the correction or induction of trisomy in iPS cell models. However, the rare occurrence of monozygotic twins discordant for trisomy 21 (Hibaoui, et al., 2014), as well as creation of iPS cell lines from individuals with mosaic DS (Murray, et al., 2015; Weick, et al., 2013), and the spontaneous reversion to disomy 21 in a DS iPS cell line (Maclean, et al., 2012), provide us with isogenic lines with which to study this disorder. An early paper (2008) demonstrated AD-like deficits in endocytic function in fibroblasts from DS individuals (Cataldo, et al., 2008). In 2012, the Livesey group created iPS cells from one DS patient and one control and examined them for AD-like pathology (Shi, et al., 2012). Interestingly, the DS line secreted far higher levels of both $A\beta_{40}$ and $A\beta_{42}$ as fibroblasts, than did control cells. Following two months in neuronal culture, aggregates of $A\beta_{42}$ were detected in the DS cultures using live staining with the thioflavin T analog, BTA1 and immunocytochemistry against $A\beta_{42}$. A twenty-one day treatment with DAPT nearly abolished both species of Aβ production in the DS neurons. Tau pathology was also evident in neurons differentiated from DS iPS cells, detectable as an abnormal distribution of phospho-tau within the neurons as well as secreted tau in the medium of DS cultures only. Synapse formation did not appear to differ between neurons from DS and control individuals.

Chang *et al* (2015) created neurons from both hES cell and iPS cell lines (Chang, et al., 2015). Similar to Shi *et al*, the authors found increased immunoreactivity for Aβ and phosphorylated tau. Treatment with n-butylidenephthalide (Bdph), an activator of Wnt signaling, delivered via coated nanoparticles, ameliorated AD-like phenotypes in these cultures. Recently, accelerated aging phenotypes were reported in neurons derived from DS iPS cells compared to isogenic controls (Murray, et al., 2015). Unlike previous models, these cells exhibited differences in proliferation and differentiation. Consistent with earlier reports, the DS iPS cell-derived neurons had increased Aβ immunoreactivity in fixed cultures, but did not appear to differ electrophysiologically from controls. The DS neurons also exhibit mitochondrial dysfunction and increased DNA damage compared to the controls. This last phenotype is particularly interesting, and the failure of neurons to maintain their genomic integrity appears to be a hallmark both of normal aging and of neurodegenerative disease (Dobbin, et al., 2013; Goto, 1997; Hasty, et al., 2003; Kim, et al., 2008; Lovell and Markesbery, 2007; Lu, et al., 2004; Sahin and DePinho, 2010; Wang, et al., 2013). In conclusion, iPS cell-derived neurons from DS individuals may be useful for modeling phenotypes that are similar between AD and aging in DS, as these cells appear to exhibit both amyloid and tau pathology as well as phenotypes such as endosome dysfunction and DNA damage.

## 6. Disadvantages in modeling AD with iPS cells

### *6a. Aging in iPS cells*

Work by several groups has suggested that reprogramming of the iPS cells “re-set” the epigenome, and that other phenotypes associated with cellular aging, such as mitochondrial function and telomere length, are returned to a “juvenile-like” state (Mahmoudi and Brunet, 2012; Miller and Studer, 2014). This raises the question: can we model phenotypes associated with aging in human neural cells (Isobe, et al., 2014)? Transplantation studies of human neuronal progenitor cells (NPCs) into the rodent brain have suggested that the human neural cells mature on a human, rather than a rodent, timeline (Espuny-Camacho, et al., 2013). However, simply allowing iPS cells-derived neural cells to age *in vitro* is impracticable and expensive. Therefore, several groups have begun to explore the possibility of accelerated aging in these model systems. One approach is to derive iPS cells from individual with Hutchinson-Gilford Progeria syndrome (HGPS), which maintain a truncated product of the mutated *LMNA* gene, progerin, which triggers fast aging (Blondel, et al., 2014; Liu, et al., 2011). Liu *et al* found that the deleterious progerin protein was absent in HGPS patient-derived cells in the iPS cell stage (Liu, et al., 2011). However, upon differentiation to smooth muscle cells, the

disease phenotype of progerin accumulation, as well as its ageing-associated cellular defects, were recapitulated. In place of using patient cells, progerin can also simply be overexpressed in iPS cells to induce age-related phenotypes such as DNA damage and mitochondrial dysfunction (Miller, et al., 2013). Increases in DNA damage have also been observed in iPS cells derived from individuals with Werner Syndrome, an accelerated aging disorder arising from mutations in the *WRN* gene, which encodes a DNA helicase (Shimamoto, et al., 2015).

Instead of progerin overexpression, other "stimulating" factors might be used, which activate aging pathways. An interesting example has been shown for cardiomyocytes from differentiated iPS cells of patients with arrhythmogenic right ventricular dysplasia. These cells were exposed to a three-factor cocktail, which activates PPAR$\alpha$ and leads to increased fatty acid oxidation instead of glycolysis (Wen, et al., 2015). In this way, the authors recapitulate the adult cardiomyocyte-like metabolism in these cells, which could be pushed to the desired disease pathologies by further treatment with PPAR$\gamma$ activators. Although these techniques appear to induce aging phenotypes in iPS cell derivatives, we first have to understand the underlying association of aging with AD to incorporate systematic approaches to age neurons.

*6b. Neuronal Maturation*

In all iPS cell approaches, it is necessary to confirm the maturity and the functionality of the derived neurons. While some studies in neurodegenerative disorders use nestin and Pax6-positive NPCs as a kind of proxy to neurons (Hossini, et al., 2015), others have gone to lengths to demonstrate the degree to which iPS cell-derived neurons model *in vivo* human neurons (Israel, et al., 2012). The most common methods to confirm neuronal differentiation and matureness are a combination of immunocytochemistry and electrophysiology (Israel, et al., 2012; Nieweg, et al., 2015): Mature neurons should show the ability to fire action potentials when depolarized under current clamp, as well as demonstrating spontaneous excitatory and inhibitory postsynaptic currents under single-cell patch-clamp. Immunocytochemistry for synaptic vesicle proteins, such as VGLUT1, VAMP2, synaptobrevin, and synapsin, are indicative for mature functional synapses (Marchetto, et al., 2010; Nieweg, et al., 2015). One early screening effort emphasized the need to create mature neuronal cultures for reliable drug assays (Yahata, et al., 2011). Thus, one major challenge to researchers is to provide neuronal cultures that are both mature enough to be representative of adult brain neurons, while being abundant enough for multiple types of assays. Occasionally the presence of disease mutations may hamper efforts to create human neural cell models of disease. For example, neurons created from patient-derived iPS cells carrying FTD mutations in *MAPT* have been shown to mature more quickly than control lines, while at the same time displaying disease phenotypes such as hyperphosphorylated Tau (Iovino, et al., 2015). In contrast, another group using iPS cell-derived neurons carrying the same *MAPT* mutation (N279K) reported that these cells had deficits in neuronal maturation compared to control lines (Wren, et al., 2015). The issue of altered proliferation and/or differentiation of neural progenitor cells and neurons seems particularly troublesome in work with Down syndrome lines (Hibaoui, et al., 2014; Murray, et al., 2015).

*6c. Culture Heterogeneity and Disease Phenotypes*

Another important aspect is that in several studies it is not obvious to what extent the reported neuronal cultures contain other cell types, nor whether heterogeneous cultures may encourage neuronal differentiation (Sandoe and Eggan, 2013; Shi, et al., 2012; Shi, et al., 2012). While pure cultures of neurons can form synapses and display connectivity, they may not mature fully in the absence of astrocytes or glial-conditioned medium (Pfrieger, 2009; Pfrieger and Barres, 1997; Ullian, et al., 2004). Along these lines, some groups have found that the addition of astrocytes to iPS cell-derived neuronal cultures enhances the ability to obtain mature neurons (Odawara, et al., 2014; Zhang, et al., 2013); this is an area of active debate and constant methodological improvement. Overall, it is necessary to fully characterize the cell type matureness as well as

the heterogeneity of neural cultures derived from iPS cells. In this regard, the advent of three-dimensional neural cultures derived from human iPS cells may be particularly beneficial as discussed later.

Finally, a major challenge is to generate a distinct cell type to study its involvement in a disease phenotype. It is hypothesized that only a certain subset of cells fails in many neurological diseases, for example, a subpopulation of dopaminergic cells in Parkinson's disease (Sandoe and Eggan, 2013). Moreover, the phenotypes displayed by cells bearing physiological mutations, such as familial AD mutations, may often be less robust than those obtained via the experimental overexpression of mutant proteins. One study compared the effect of compound treatment on neural cells from fAD patients to either heterologous cell lines overexpressing fAD *APP*, or human control ES-derived neural cells overexpressing mutant *APP*. They observed that concentrations of indomethacin that reduced $A\beta_{42/40}$ robustly in the heterologous cells, and more modestly in the APP-overexpressing human cells, had no effect on the human neural cells carrying endogenous fAD mutations (Mertens, et al., 2013). Most researchers who use patient-derived iPS cells carrying familial mutations will be familiar with this issue of comparatively mild disease phenotypes, at least compared to models of gene overexpression or knockdown. Fortunately, the use of isogenic lines with corrected disease alleles may, by reducing variability between lines, allow for the reliable measurement of even modest phenotypes. The increased use of three-dimensional tissue culture systems (see Section 8), may also facilitate disease phenotypes by concentrating protein aggregates and other cellular products in a tissue-like environment that can still be imaged or assayed with ease.

In addition to the issue of variability between iPS cell-derived lines in assays of disease phenotypes, we are faced with the growing awareness that other cell types must be created to model AD in these systems. For example, in the last decade, it has become obvious that glia cells have an important impact in disease onset and progression. Thus, our basic science interests demand that we increase the complexity of our cellular models to adequately represent the disease, while at the same time we are tasked with the production of simplified systems that are amenable to applications such as drug screening.

**7. Differentiation of iPS cells to study cell type-specific impact towards neurological diseases**

Generation of iPS cells typically serves as a starting point to differentiate them into various brain-specific cell types such as neurons or glial cells. Each cell lineage develops, when a combination of exogenous morphogens are applied at distinct time points during development of the iPS cells (Liu and Zhang, 2011). An alternative strategy is the overexpression of cell type-specific transcription factors (Zhang, et al., 2013). In the following, we focus on examples of the successful generation of neuronal and glial cell types from human iPS cells.

*7a. Differentiation to distinct neuronal cell types*

The initial iPS cell study by Takahashi *et al.* demonstrated the successful generation of neuronal cells from iPS cells (Takahashi, et al., 2007). It is now common to perform neuronal differentiation (Denham and Dottori, 2011), and even to differentiate into specific neuronal subtypes, such as forebrain glutamatergic neurons (Zeng, et al., 2010), cortical neurons (Nieweg, et al., 2015; Shi, et al., 2012), GABAergic interneurons (Liu, et al., 2013; Nieweg, et al., 2015), motor neurons (Ebert, et al., 2009), and hypothalamic-like neurons (Wang, et al., 2015). Indeed, there are too many neuronal differentiation techniques in the literature to adequately review here (some recent reviews include (Broccoli, et al., 2015; Broccoli, et al., 2014; Chinchalongporn, et al., 2015; Lai, et al., 2015)). The generation of inhibitory neurons is of particular interest for AD research, since both inhibitory and excitatory neurons are affected (Hazra, et al., 2013; Krantic, et al., 2012), and inhibitory interneurons, such as parvalbuminergic cells, play crucial roles in orchestrating large networks crucial to

memory formation (Bartos, et al., 2007; Mann and Paulsen, 2007). The development of protocols for the differentiation of multiple neural subtypes is a lively area of research.

*7b. Differentiation to glia*

In the brain, glial cells can be divided in three major cell classes: astrocytes, microglia, and oligodendrocytes. Each of them has been proposed to have an important impact in AD's onset and progression; even so it is still debatable, whether they are causative for the disease or just represent a secondary by-standing effect. Overall human AD and mouse gene expression studies show that with AD progression, immune response and inflammatory genes are up- and genes involved in neuronal functions are down-regulated (Blalock, et al., 2011; Blalock, et al., 2004; Gjoneska, et al., 2015). Interestingly, GWAS describe several AD-risk increasing genetic variants, which are linked to genes with identified roles in glial cells, such as *APOE, PICALM, TREM2, CR1, CD33* and *CLU* (Ando, et al., 2013; Antunez, et al., 2011; Bertram, et al., 2008; Bradshaw, et al., 2013; Calero, et al., 2000; Corneveaux, et al., 2010; Crehan, et al., 2013; Deng, et al., 2012; Guerreiro, et al., 2013; Harold, et al., 2009; Hollingworth, et al., 2011; Jonsson, et al., 2013; Lambert, et al., 2009; Lambert, et al., 2010; Wunderlich, et al., 2013; Zhang, et al., 2010). Apolipoprotein *APOE* was originally identified in the liver that mediates the transport and delivery of cholesterol and other lipids through cell surface ApoE receptors (Mahley, 1988; Mahley and Rall, 2000). The human *APOE* gene exists as three alleles. While these three variants have a frequency in the population of 8.4% (ε2), 77.9% (ε3), and 13.7% (ε4), the frequency of the *APOE* ε4 variant (*APOE4*) is increased to at least 40% in sporadic AD patients (Farrer, et al., 1997) making it as one of the greatest risk factors for sAD (Kanekiyo, et al., 2014; Lambert, et al., 2013). Individuals with one *APOE4* allele are three to four times as likely to develop AD than those without *APOE4* alleles, an odds ratio that is by far the highest out of any AD risk gene (Bertram and Tanzi, 2008; Corder, et al., 1993). In both humans and in animal models, the *APOE4* allele is associated with increased levels of amyloid beta (Aβ), as well as amyloid plaque deposition (Castellano, et al., 2011; Fryer, et al., 2005; Kim, et al., 2009; Youmans, et al., 2012). The least common variant, *APOE2*, differs from the *APOE4* variant at just two amino acid positions but appears to be protective against the development of AD (Bu, 2009; Corder, et al., 1993; Liu, et al., 2013). While the contribution of the APOE4 allele to AD risk is well known, the reasons *why* this variant may trigger AD are not at all understood. The study of these *APOE* variants has been particularly difficult in rodent models, which endogenously express only one version of the *Apoe* gene. Thus, the emergence of iPS cell lines with different *APOE* isotypes will greatly advance our understanding of this AD risk factor by either collecting individuals of particular genotypes, or by using genome editing to "switch" between the protective and the disease-causing *APOE* form within one line.

Taken together, two important themes emerge from these observations: 1) neurodegeneration in AD most likely involves an interaction of neuronal and glial pathologies; and 2) understanding the functions of genes implicated in AD, from GWAS or expression studies, will require a thorough characterization of their functions in a cell type-specific manner. Since human and mouse glia are surprisingly divergent (Oberheim, et al., 2006; Oberheim, et al., 2009), which places emphasis on the need for models of human glia for the study of neurodegenerative disease.

*Astrocytes*

Astrocytes are a diverse cell class, which can differ both functionally and morphologically between brain regions (Bribian, et al., 2015; Ma, et al., 1999; Tabata, 2015) as well as displaying significant species divergence (Oberheim, et al., 2006; Oberheim, et al., 2009). Astrocytes are intimately involved in synaptogenesis and synapse maintenance (Haydon and Nedergaard, 2015; Pascual, et al., 2005; Perea, et al., 2009), maintain brain homeostasis, store and distribute energy substrates, and play a major role in the clearance of metabolites and toxins from the brain parenchyma (Jessen, et al., 2015; Xie, et al., 2013). Inflammatory astrogliosis precede or accompany neurodegeneration in many animal models and human

postmortem AD brains, as evidenced by increased immunoreactivity for glial fibrillary acidic protein (GFAP) as well as by the loss of important astrocytic proteins such as glutamine synthase and GLT-1 (Dabir, et al., 2006; Fischer, et al., 2005; Li, et al., 1997; Masliah, et al., 2000; Robinson, 2001; Tilleux and Hermans, 2007). Moreover, astrocytes in the brain are the primary producer of the ApoE protein under physiological conditions, although cell profiling studies have implicated microglia as another prominent ApoE source (Zhang, et al., 2014).

While differentiation from iPS cells focused initially on creating functional human neurons, several groups have now also developed protocols to differentiate astrocytes from iPS cells. In spontaneously differentiating cultures, astrocytes will appear roughly 100 days from the time that neural progenitor cells are placed in differentiation media (Shi, et al., 2012). To obtain faster cultures with a higher purity of astrocytes, techniques have been developed to obtain astrocytes from gliospheres (Krencik, et al., 2011) or by directed differentiation via defined factors (Chen, et al., 2014). Astrocyte-like cells can also be obtained via direct reprogramming of fibroblast cells (Caiazzo, et al., 2015). The admirable plasticity of these glial cells, however, which make them such an important and adaptable cell in the brain, has historically led to issues of how representative primary cultured astrocytes are compared to the *in vivo* situation (Foo, et al., 2011; Hertz, et al., 1998; Sun, et al., 2013). Given the different protocols in development to create iPS cell-derived human astroglia, the issue of variability between different groups and different cell lines is likely to require a concerted effort by the entire neural iPS cell community to address this issue.

*Microglia*

Microglia are complex and dynamic cells responding to their environment by releasing chemical transmitters as well as phagocytize cell debris, synapses, or whole cells. Both pro-inflammatory and neuroprotective roles for microglia have been demonstrated in AD. Local resident microglia become activated and rapidly react to amyloid plaque formation by extending processes, migrating toward plaques, and aggregate around them (Bolmont, et al., 2008; Lue, et al., 2001). Also, microglia are demonstrated to undergo apoptosis in AD brain (Lassmann, et al., 1995; Sugaya, et al., 1997; Yang, et al., 1998) and show dystrophic morphology and fragmentation, which could be the reason of the senescence of these cells (Streit, et al., 2009; Streit and Xue, 2010). The differentiation of microglia from iPS cells appears possible, though perhaps more challenging than other neural cell types, given the unique origin of microglia (Ginhoux, et al., 2010). To date, however, publications only exist for creating mouse microglia (Beutner, et al., 2010; Beutner, et al., 2013; Selvaraj, et al., 2012; Tsuchiya, et al., 2005). We found one patent related to the “Method for obtaining human microglial precursor cells from pluripotent stem cells” (EP 2424976 A1) from the group of Harald Neumann (Neumann, 2012), who also have derived microglial cells from mouse ES cells (Beutner, et al., 2010; Beutner, et al., 2013). Another strategy was introduced by the Filgueira group, who generated microglia from human peripheral blood monocytes using a mixture of recombinant cytokines such as M-CSF, GM-SF, NGFβ, and CCL2 (Etemad, et al., 2012). Some groups have found that, in the process of making embryoid bodies and three-dimensional cultures, that they are able to isolate Cd11b+/CD45+ monocyte-like cells (Schwartz, et al., 2015). However, whether these microglial precursors are representing the same characteristic as the microglia *in vivo* is a matter of debate, and our understanding of microglia and their roles in Alzheimer’s disease remains woefully incomplete. To date, we could not find any work in the literature that focused upon creating microglia from human ES or iPS cells. The production of microglia from human iPS cells is highly desirable, given our increasing awareness of the role of inflammation in neurodegenerative disease, and we look forward to seeing new protocols in the literature soon.

*Oligodendrocytes*

Oligodendrocytes form myelin layers around neuronal axons in order to allow high nerve conductance (Bercury and Macklin, 2015). White matter lesions and myelin abnormalities have been described in human

AD brain and mouse models (Bartzokis, 2011; Desai, et al., 2010; Desai, et al., 2009; Englund, et al., 1988; Kobayashi, et al., 2002; Roth, et al., 2005). The potential that iPS cell-derived oligodendrocyte precursor cells and mature oligodendrocytes have for both the study and treatment of demyelinating disorders has made this an active field, with a number of groups developing protocols. These studies have generated oligodendrocytes and oligodendrocytes precursors from human iPS cells either as a component of heterogeneous cultures (Hu, et al., 2009; Kim, et al., 2012; Swistowski, et al., 2010) or as the result of concerted efforts to generate these particular cell types (Douvaras, et al., 2014; Jang, et al., 2011; Ogawa, et al., 2011; Pouya, et al., 2011; Wang, et al., 2013). Oligodendrocytes derived from human iPS cells have been shown to myelinate neuronal processes *in vitro* (Wang, et al., 2013) and *in vivo* (Douvaras, et al., 2014; Major, et al., 2011; Pouya, et al., 2011; Wang, et al., 2013), and thus hold great promise for studying the impact of myelin abnormalities in AD and other demyelinating disorders.

*7c. Future challenges for cell type differentiation*

For each cell type differentiation, it will be crucial to eliminate remaining pluripotent iPS as well as progenitor cells. There are several options such as fluorescent-activated cell sorting (Sergent-Tanguy, et al., 2003) or magnetic separation, however they are very invasive and could potentially change the epigenetic landscape. It would be from advantage to have a marker of successful differentiation. (Kim, et al., 2011) showed that the microRNA-371-3 cluster could serve as a discrimination factor for neuronal differentiation.

One major challenge will be to define what is a cell type and which cell type is impacted in a disease phenotype. To define a cell type is challenging by itself (DeFelipe, et al., 2013; Fishell and Heintz, 2013; Grange, et al., 2014) but solving this question will be crucial for future studies in iPS cells. This requires that we understand the genetic identity of a cell type, so that we can investigate strategies to specifically promote this cell type to differentiate from iPS cells. Once we know the genetic identity of a natural cell, we can correlate this identity to our engineered cell *in vitro*. Strategies like this are already proposed within the retina (Siegert, et al., 2012) .

**8. Modeling neurological disease in three-dimensional culture systems**

In the previous section, we briefly alluded to the impact of distinct cell types in AD and what are the current efforts in the field to generate these different neural lineages from iPS cells. Although the analysis of a pure cell type population can give valuable insides into the biology of the cell, it is often the interaction between different cell types that are most important to a true model of neural systems: for example neurons exhibit increased synapse formation when they are co-cultured with astrocytes (Pfrieger and Barres, 1997), and astrocytes may look and behave differently in two-dimensional culture than they do in the brain (Cahoy, et al., 2008; Puschmann, et al., 2013). The latter one is a concern for all cell types, since neurons and glia both utilize subcellular specializations, or compartmentalization, to function properly *in vivo* (Khakh and McCarthy, 2015; Tonnesen, et al., 2014). In a monolayer in a culture dish, however, some of this compartmentalization may be lost. One example is the observation of calcium microdomains in astrocytes *in vivo* and in slice preparations, in which specific subregions of the astrocytic arbor exhibit restricted calcium oscillations that may reflect activity to immediately adjacent neurons (Bernardinelli, et al., 2014; Di Castro, et al., 2011; Shigetomi, et al., 2013). Another concern is that phenotypes of aberrant extracellular protein aggregation are lost in two-dimensional cultures simply due to the lack of interstitial compartment, and metabolites of interest may diffuse to the media. To overcome this, recent studies have embedded human ES or iPS cell-derived cells in scaffolding such as hydrogel or Matrigel, to create three dimensional culture systems (Pasca, et al., 2015; Schwartz, et al., 2015; Smith, et al., 2015). These kinds of culture systems, when created with human cells overexpressing fAD proteins or treated with Aβ oligomers, can recapitulate AD-like phenotypes such as extracellular Aβ plaque-like deposits (Choi, et al., 2014; Kim, et al., 2015) and cytoskeletal abnormalities (Zhang, et al., 2014).

To address issues that might arise from overly simplistic culture model systems, a number of groups have taken advantage of tissue engineering approaches that can generate either scaffolded or self-organizing neural cytosystems, such as "organoids". In 2008, the Sasai laboratory demonstrated that mouse and human ES cells could form self-organized apico-basally polarized cortical tissue (Eiraku and Sasai, 2012; Eiraku, et al., 2008). However this technique lacks the later stage of cortical development namely discrete cortical layer formation with the typically inside-out organization, as well as the presence of outer radial glia. (Lancaster, et al., 2013) improved the protocol and could model human brain development in 3D organoid structure. They observed cortical-like neuronal generation and organization and found astrocytes and oligodendrocytes after more than 100 days *in vitro*. To date, AD-like phenotypes have not been reported in self-organizing three-dimensional cultures or organoids from patient-derived cells. However, the three-dimensional cultures reported by Choi *et al.,* which overexpressed mutant APP, also showed an increase in phospho-Tau levels, suggesting that it may be possible to recapitulate many AD phenotypes within one model system, which would be a strong advantage in comparison to AD mouse models (Choi, et al., 2014; Kim, et al., 2015). Three-dimensional neural culture systems have yet to recapitulate complex *in vivo* brain systems that include elements such as the blood-brain-barrier, vascularization, or immune response, which all have an important impact during disease and treatment. Therefore, multiple research groups are focusing on creating vascularization, shown in liver tissue (Masumoto, et al., 2014; Samuel, et al., 2013; Takebe, et al., 2013) or blood-brain-barrier structures from iPS cells (Lippmann, et al., 2014; Lippmann, et al., 2013; Lippmann, et al., 2012; Minami, et al., 2015).

**9. Conclusion**

In this review, we have outlined recent strategies to investigate AD pathology using human iPS cells and to find new therapeutic targets preventing disease onset and progression. The approval rate for AD medications is a scant 4% of all treatments that enter onto Phase I trials (McBride, 2012) with projections of 13.8 million people with AD and $1.2 trillion spent on AD-related care in the year 2050 (Association, 2013; Hebert, et al., 2013). These numbers clearly show that new model systems are needed to better translate observations from rodent models into clinical studies. Human iPS cells will be an important step forward in this direction; they have the potential to recapitulate phenotypes from various neurological diseases in a cell type-specific manner. Creating isogenic iPS cells lines overcomes problems of variability in human genomes and genome-editing technology has become much easier to implement. We have outlined how iPS cells can model disease etiology, progression, and phenotypes in human AD. Several groups have, to date, succeeded in recapitulating multiple AD-like phenotypes in human iPS cells. Thus, the stage appears to be set for the widespread use of iPS cells in preclinical drug trials for AD therapies (reviewed in (Khurana, et al., 2015)). To benefit most from these cellular models, it will be absolutely crucial that all experiments are performed in a controlled and standardized manner that will allow reproducibility between different research groups.

Several areas of iPS cell research remain topics of much debate or even controversy. For example, there is debate over exactly how similar iPS and ES cells are, and how well iPS cells can functionally replace ES cells in translational research (Bock, et al., 2011; Chin, et al., 2009; Doi, et al., 2009; Hu, et al., 2010; Narsinh, et al., 2011; Narsinh, et al., 2011). In addition to the ethical and legal issues that have arisen regarding the creation of ES cells, which hinder the production of new lines, a clear advantage of iPS cells is that the donor is often an adult, sometimes elderly, and thus can provide a health history relevant to the disorder of interest. This is not possible with ES cells. This said, the ability to access patient history in the use of iPS cell research is highly variable between research groups and subject to a great deal of regulation to ensure patient privacy (King and Perrin, 2014; Lomax, et al., 2015; Lomax and Peckman, 2012; Lomax, et al., 2013). As more and more iPS cell lines are characterized and this information added to public databases, we expect that even

researchers without direct access to patient information will benefit from these models. The development of libraries of disease-associated iPS cell lines, of both genders, will allow high-throughput drug discovery and validation, and should make the rocky path from bench to clinic shorter and straighter.

In this review, we also put a strong focus on the impact of different cell types. It will be crucial to investigate the impact of drugs across different cell types. The use of three-dimensional scaffolding combined with differentiated cells (Choi, et al., 2014), or the creation of self-organizing neural tissue structures *in vitro* (Eiraku and Sasai, 2012; Eiraku, et al., 2008; Kadoshima, et al., 2013; Lancaster, et al., 2013; Lancaster and Knoblich, 2014), hold great promise for modeling the intricate micro- and macro-environment of the brain. In the future, it may be possible to screen drugs in these cytosystems, which have the benefit of containing multiple neural cell types in a physiological microenvironment and, with the development of vascularization technique, may include blood-brain barrier penetration in the assay at an early stage of drug discovery.

**Acknowledgements:**
This work was supported by NIH grant R01-AG047661 to LHT.

**Figure 1. Using human patient derived induced pluripotent stem (iPS) cells to model Alzheimer's disease (AD) pathology.** This model figure illustrates the logical path of experiments using iPS cells to study AD phenotypes and screen for novel therapeutics. Somatic cells (etc. blood, skin) are reprogrammed *in vitro* into iPS cell colonies. At this point, or later, genome-editing techniques can be used to create isogenic lines containing specific mutations or transgenes. Techniques exist to differentiate the iPS cells into neural cells that include neurons, microglia, astrocytes and oligodendrocytes, as well as neural progenitor cells (not pictured). From the iPS cell stage, self-organizing tissue cytosystems, or organoids, can also be created in three-dimensional culture. Neural cells differentiated from iPS lines with sporadic or familial AD (sAD or fAD) backgrounds can display a number of AD-like phenotypes that can be assayed *in vitro*. These include amyloid β peptide production and, in the case of three-dimensional culture, amyloid plaques, tau pathology, synaptic dysfunction, immune activation, genomic instability, and aberrant endosome trafficking. High-throughput screens can be designed to examine the impact of small molecule or other treatments upon these and other AD-like phenotypes directly in human neural cells. The development of novel treatments for the AD patient and the success of these treatments in the clinic completes the cycle.

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**Table 1. Literature reviewed.**

| Reference | Lab* | Year | PMID | Cell Source | Disease | Mutation/Gene | Genome Editing/Isogenic lines | Cell Types Examined | Phenotypes Reported | Drug treatment | Profiling |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Yagi et al., 2011** | Suzuki | 2011 | 21900357 | iPSCs from Coriell hFib: AG07768, AG09908; Clone 201B7[1] | fAD, sporadic PD | *PSEN1* A246E, *PSEN2* N141I | | Neurons | Aβ | Compound E, Compound W | Gene expression microarray |
| **Liu et al., 2011** | Izpisua Belmonte | 2011 | 21346760 | H9 ESCs; iPSCs from BJ hFib, Coriell hFib: AG01972, AG11498, AG06297, GM00038, AG05247, AG09602. | HGPS progeria | *LMNA* G608G | | Smooth muscle cells | Premature senescence, nuclear defects | | DNA methylation microarray |
| **Israel et al., 2012** | Goldstein | 2012 | 22278060 | iPSCs from primary patient hFibs | fAD, sAD | *APP* duplication | | NPCs, neurons | Aβ, Tau, GSK3β activity, Endosomes, Vesicle trafficking, Synapse formation/ function | Compound E, DAPT | Gene expression microarray |
| **Koch et al., 2012** | Walter | 2012 | 22510327 | ESCs: I3 (TE03); iPSCs: PKa[2] | fAD, | Overexpression of *PSEN1* L166P and D385N | | lt-NES cells, NPCs, neurons | Aβ, NPC proliferation | DAPT, ibuprofen indomethacin | |
| **Maclean et al., 2012** | Orkin | 2012 | 23045682 | ESCs: CSES2 and CSES13[3]. iPSCs: DS2, DS1 MRC5-IPS7[4] | DS | Trisomy 21 | Spontaneous disomic isogenic lines | Hematopoietic cells | Aβ, hematopoiesis | | |
| **Shi et al., 2012** | Livesey | 2012 | 22344463 | ESCs: DS-ES SC-321, H9; iPSCs: DS1-iPS4[4] | DS | Trisomy 21 | | NPCs, neurons | Aβ, aggregates, Tau | DAPT | |
| **Kondo et al., 2013** | Inoue | 2013 | 23434393 | iPSCs from primary patient hFibs | fAD, sAD | *APP* E693Δ and V717L | | Neurons, astrocytes | Aβ, Cellular/oxidative stress, | DHA, DBM14-26, NSC23766, BACE inhibitor IV (BSI) | Gene expression microarray |
| **Fong et al., 2013** | Huang | 2013 | 24319659 | iPSCs from primary patient hFibs | FTD | *MAPT* A152T | Zinc finger nucleases | NPCs, | Tau, Neural degeneration, Dopaminergic phenotypes | | |
| **Xu et al., 2013** | Zhong | 2013 | 23305945 | ESCs: H9, iPSCs: hiPS-C4 line. iCell Neurons. | AD | Exogenous Aβ | | NPCs, neurons | Neuronal viability, Cell cycle, Neurogenesis, Differentiation | Cdk inhibitors | Compound screen |
| **Weick et al., 2013** | Bhattacharyya | 2013 | 23716668 | iPSCs from Coriell hFib: AG05397, GM02504. | DS | Trisomy 21 | Disomic isogenic cells via mosaicism | NPCs, neurons | Cellular/oxidative stress, Synapse formation/ function | | Gene expression microarray |
| **Miller et al., 2013** | Studer | 2013 | 24315443 | iPSCs from Coriell hFib: AG06917, AG06297, AG11498 | HGPS Progeria, PD | *LMNA* C1824T; *PINK1* Q456X; *Parkin* V324A. | | Neurons | Cellular/oxidative stress, Cellular aging, Lewy-body-precursor-like inclusions, DNA damage, Mitochondrial dysfunction | | RNA-Seq |
| **Choi et al., 2014** | Kim | 2014 | 25307057 | ReN cell VM human neural stem (ReN) cells (Millipore) | fAD | Overexpression of *APP* K670N/ M671L/V717I; *PSEN1*(ΔE9 | | 3D neural culture in Matrigel | Aβ, Tau, Neural degeneration | Compound E, BACE inhibitor IV (BSI), DAPT, SGSM41 | |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hibaoui et al., 2014** | Feki | 2014 | 24375627 | iPSCs from primary patient hFibs | DS | Trisomy 21 | Isogenic cells from discordant monozygotic twins | NPCs, neurons, neurospheres | Synapse number, NPC Viability, DYRK1A activity, Neurogenesis, Differentiation | epigallocatechine gallate (EGCG) | RNA-Seq |
| **Muratore et al., 2014** | Young-Pearse | 2014 | 24524897 | iPSCs: hFibs from HSCI | fAD | *APP* V717I | | iPSCs, NPCs, Neurons | Aβ, Tau, APP cleavage, Endosomes | DAPT, Compound E, BACE inhibitor C3, Anti-Aβ antibodies | Nanostring gene expression array |
| **Sproul et al., 2014** | Noggle | 2014 | 24416243 | iPSCs: hFibs from Coriell AG07671, AG07768, AG08446 | fAD | *PSEN1* A246E, M146L | | iPSCs, NPCs, neurons | Aβ, differentiation | *Recombinant Norrin* | Gene expression microarray |
| **Wren et al., 2015** | Bu | 2015 | 26373282 | iPSCs from primary patient hFibs | FTD | *MAPT* N279K | | NPCs | Tau, Endosomes, Vesicle trafficking, Cellular/oxidative stress | | |
| **Iovino et al., 2015** | Spillantini | 2015 | 26220942 | iPSCs from primary patient hFibs, Coriell hFib: ND32854, ND40076 | FTD | *MAPT* N279K, P301L | | Neurons | Tau, Mitochondrial dysfunction, α synuclein, Neurogenesis, Differentiation | | RNA-Seq |
| **Young et al., 2015** | Goldstein | 2015 | 25772071 | hFibs from UCSD ADRC, J.C.V. | sAD | *SORL1* SNPs | | NPCs, neurons | Aβ, SORL1 induction | | |
| **Murray et al., 2015** | Nizetic | 2015 | 25694335 | Young adult hFibs from Galliera Genetic Bank | DS | | Disomic isogenic cells via mosaicism | Neurons, hematopoietic cells | Aβ, Mitochondrial dysfunction, DNA damage, proliferation | | |
| **Chang et al., 2015** | Su | 2015 | 25735452 | ESCs: TWI iPSCs: allantoic fluid-derived | DS | Trisomy 21 | | NPCs, neurons | Aβ, aggregates, Tau, Wnt signaling | F127-Bdph | |
| **Hossini et al., 2015** | Adjaye | 2015 | 25765079 | ESCs: H1, H9 iPSCs: NFH-46 hFibs | sAD | | | NPCs/neurons | Tau, gene expression | Compound E | Gene expression microarray |

*Corresponding Author. PMID: PubMed ID. hFib: Human fibroblast. iPSCs: Induced pluripotent stem cell. ESCs: Embryonic stem cell. sAD/fAD = sporadic/familial Alzheimer's disease. PD = Parkinsons' disease. HGPS = Hutchinson–Gilford Progeria syndrome. FTD= Frontotemporal Dementia. DS = Down syndrome. NPCs = neural progenitor cells. HSCI = Harvard Stem Cell Institute.


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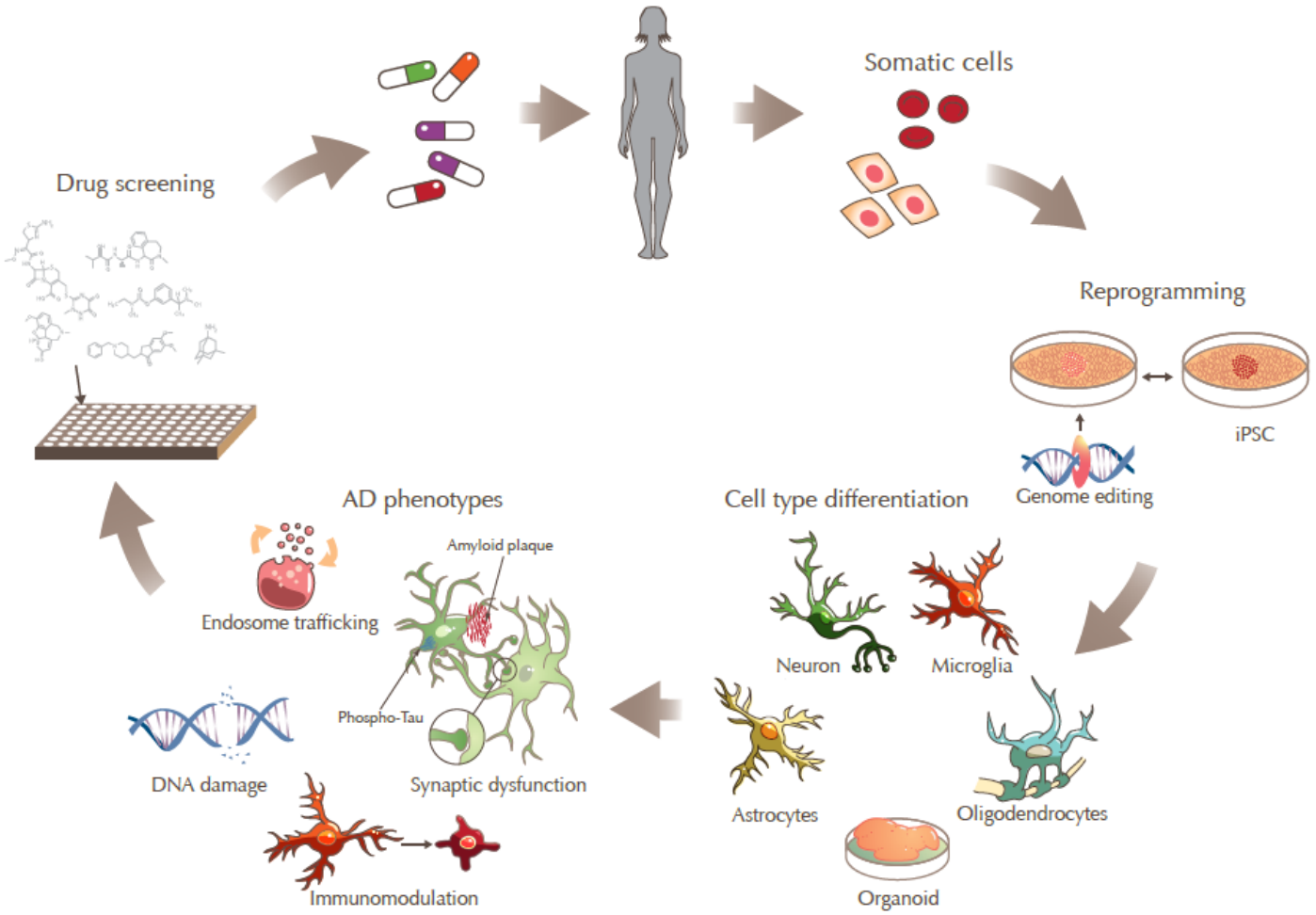
**Figure 1**



**Graphical abstract**