Rewinding Your Cells to Fast Forward Research: Advances in Alzheimer's Disease Modelling

When you close your eyes, you are thirteen years old again… The room smells faintly of a cloying perfume you begged your mum to buy - notes of vanilla, jasmine, and unwavering teen spirit. You litter eager, uneven footprints down the stairs into the bathroom, and inspect yourself in the mirror, admiring with pride what, in hindsight, is quite possibly the ugliest outfit of all time. Minutes later, when your eyes at last reopen, you are thankfully twenty-one once more, acid-wash jeggings and that terrible metallic crop-top safely exiled to the past. Well, exiled from all but enduring memory…

From regenerating doctors to endlessly repeating days, so many of the stories we read, write, and dream seem to represent an abiding desire to revisit the past. Although a long way from flux capacitors and time-turners, every day we enjoy the remarkable ability to revisit people, places, and moments long departed, stitching the past to the present in the act of remembering. However, it is in disorders of memory such as Alzheimer's Disease (AD), as this portal to the past begins to close, that we truly appreciate just how important these tiny acts of time-travel are. Without them, we lose not only names and stories, but the very sense of who we are.

With Alzheimer's on the rise, scientists are turning to their own, cellular version of time travel: induced pluripotent stem cells (iPSCs). Given the right molecular ingredients, a patient's adult skin cells can be reverted to their earliest, most malleable form, before being reprogrammed into neurons reflecting the donor's specific genetic makeup. This technique may yield new and improved disease models for AD: systems that mimic aspects of the human illness, allowing drug testing and investigation of disease mechanisms. But does this "brain-in-a-dish" approach have what it takes to one day dethrone the trusty lab rat as the face of Alzheimer's disease modelling?

Alzheimer's Disease in a Nutshell:

The leading cause of dementia, Alzheimer's disease affects over 50 million people worldwide, with cases estimated to double within the next 20 years alone.[1] Primarily affecting the elderly, it is a late-onset disorder, characterised by the gradual death of brain cells (**neurodegeneration).**

Although the precise origins of AD remain in debate, two key proteins are consistently found at the scene of the crime: **amyloid-β** (Aβ) and **tau.** A fragment of the much larger **amyloid precursor protein** (APP), Aβ is usually mopped up and broken down by the brain's waste disposal machinery. In Alzheimer's, however, as these clearance systems deteriorate with age, accumulating Aβ fragments join to form plaques around neurons. Tau, normally a scaffolding protein maintaining neuronal structure, similarly aggregates, twisting into intracellular clumps called **neurofibrillary tangles** (NFTs). Researchers propose that Aβ plaques and NFTs trigger the immune system, leading to **inflammation** that damages and ultimately kills neurons.[2] However, as the severity of plaques, tangles, inflammation, and behavioural symptoms is not always correlated, it is difficult to conclusively categorise these hallmarks as either causes or effects of the disease.[3, 4]

The first casualties of AD are the brain's memory and learning hubs: the **hippocampus** and **entorhinal cortex**.[5, 6] Cell death here is largely specific to a population of neurons producing a signalling molecule (**neurotransmitter**) called **acetylcholine**.[7] As neurodegeneration spreads to the parietal and frontal lobes, cognitive impairments progress to mood, awareness, and communication deficits.

With no cure available, current AD treatments target Aβ plaques, acetylcholine levels, and excessive neuronal firing (**hyperexcitation**), achieving variable success in slowing symptom development. [2]

Of Mice and Modelling:

Alzheimer's research has historically employed genetically engineered (**transgenic**) mouse models. While approximately 80% of human AD cases are **sporadic** (sAD), arising unpredictably in later life, there is also an earlier-onset, genetic form of Alzheimer's: **familial AD** (fAD).[8] Over 200 fAD-associated mutations have been identified, with most of the affected genes encoding proteins required to convert APP into Aβ, transport fatty molecules between neurons, or support the brain's immune cells (**glia**).[9] Created using genetic editing techniques such as **CRISPR**, mice carrying these fAD mutations develop hallmark features of human AD, producing tangle-prone forms of tau and Aβ plaques, and exhibiting progressive cognitive decline.[10]

While mouse models have offered vital insights into the disease-causing (**pathogenic**) mechanisms of amyloid-beta and tau, shaping the field's prevailing hypotheses, they are notably limited by interspecies differences in lifespan, neuron structure, and immune function. Similarly, fAD mutations expressed in mouse models drive disease by increasing production of toxic, plaque-forming Aβ variants, whereas human sAD arises mainly from age-related failures in Aβ disposal.[10] Together, these biological and mechanistic differences may explain why transgenic mice don't develop NFTs or the extensive neurodegeneration seen in human AD. [10] What's more, unable to ask about memories of childhood and the hallowed halls of the cages in which they were raised, we resort to potentially reductive spatial tests of memory when assessing treatment outcomes in mice.[11] Consequently, of the hundreds of candidate drugs that prove effective in mouse models, very few successfully translate to human Alzheimer's patients.[2]

Interspecies Differences in Size and Sensibility…

The Dawn of Stem Cell Technology:

Put simply, **stem cells** are a biological "blank slate". Unlike most of your adult cells, which have already committed to a fixed identity and function (**cell fate**), stem cells retain the ability to grow into numerous of cell types. Initially capable of becoming almost any cell type (**pluripotent**), the cells of the human embryo lose access to particular fates during development, eventually becoming **unipotent**. This process, termed differentiation, is directed by networks of **transcription factors**: molecular switches that turn genes on and off to shape a cell's structure and function. Notably, all the cells in your body contain the same genes, but they only switch on those that are relevant to their function; this is why your neurons and red blood cells, for example, look and behave so differently.[12]

A theoretically infinite supply of cells of any type, the therapeutic potential of embryonic stem cells, in replacing damaged or diseased tissue, was unfortunately confounded by ethical concerns associated with harvesting them.[13]

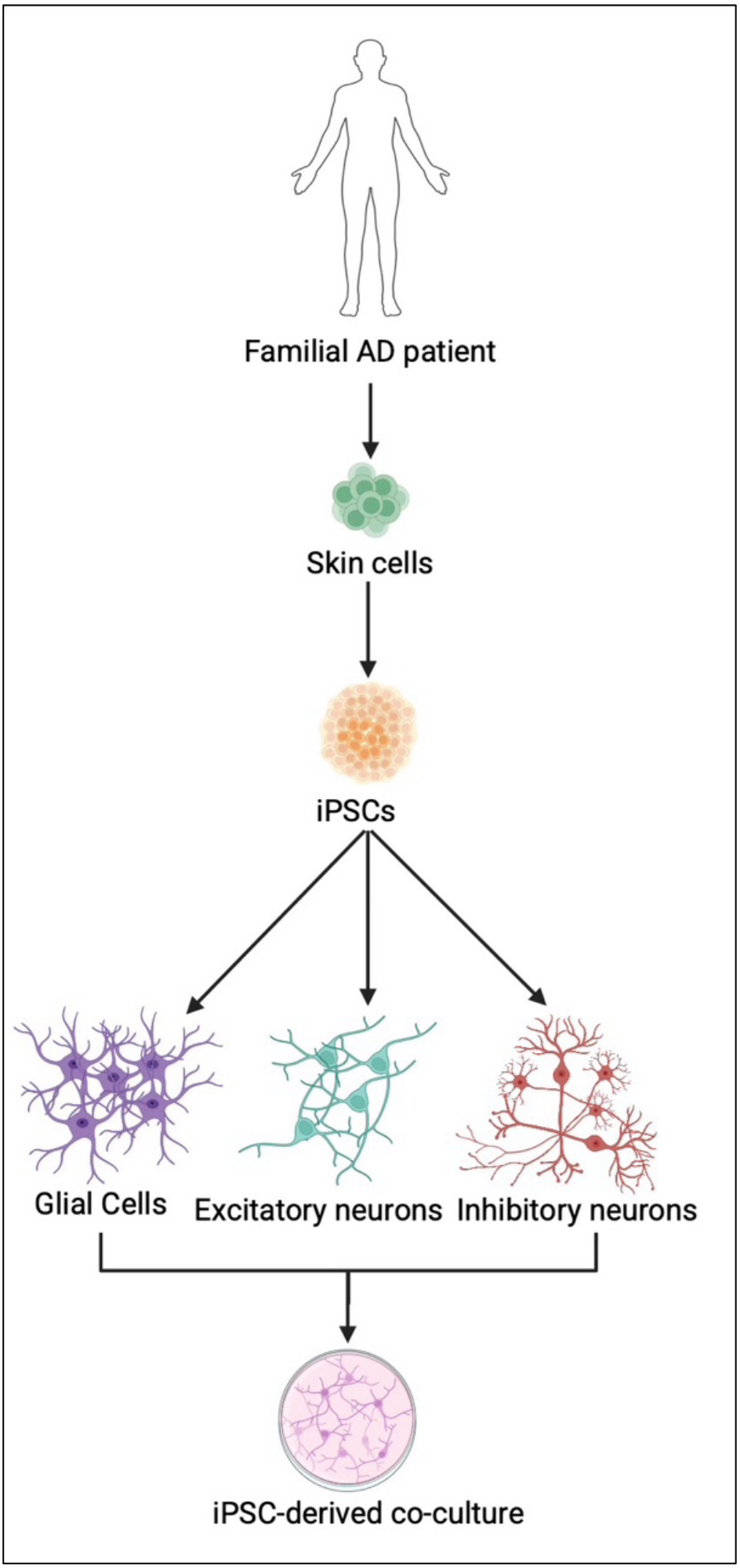
Thus in 2006, when Japanese researcher Shinya Yamanaka successfully reprogrammed adult human skin cells (**fibroblasts**) back into pluripotent stem cells, the field got its second wind. These **induced pluripotent stem cells** (iPSCs) were created by exposing the fibroblasts to transcription factors typically present in the human embryo, switching on the genes that enable pluripotency. A blank slate once again, the iPSCs can then be differentiated into any cell type, simply by choosing the correct combination of transcription factors.[14]

Back to the Glory Days (Pluripotency)…

Stem Cell-Derived Models of Alzheimer's Disease:

Using skin samples from familial AD patients, researchers can produce dishes of iPSC-derived neurons called **cultures**, where each cell carries the donor's set of genes (**genome**), including their predisposition to AD. Simply by adjusting the recipe of transcription factors used, separate cultures are created containing specific neuron or glial cell subtypes. To more faithfully represent the diverse cellular landscape of the human brain, these are often combined in specific ratios to create a **co-culture**.[15]

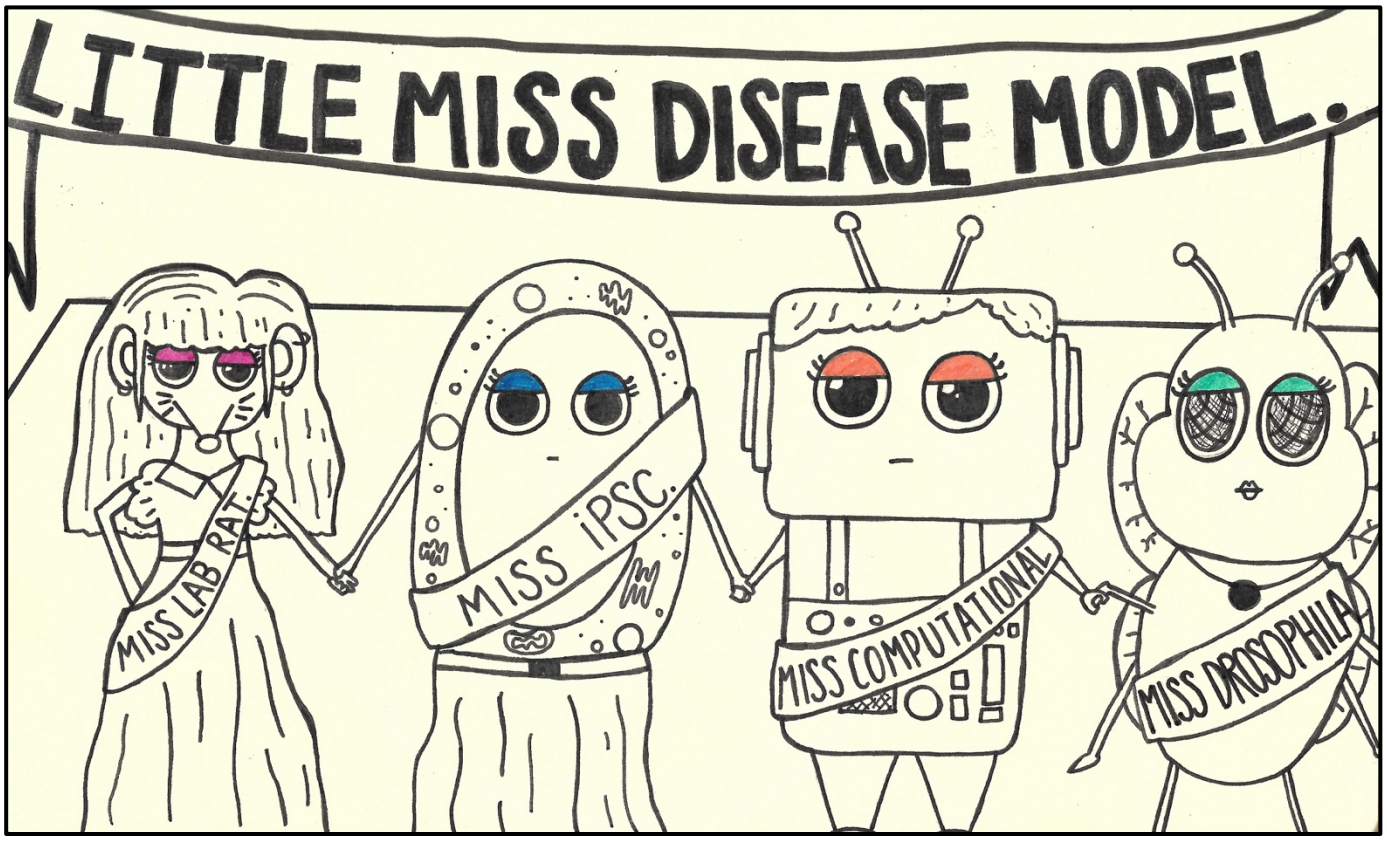
IPSC-derived models offer a rare window into the earliest, most mystifying stages of AD, allowing investigation of the causal and chronological relationships between disease events such as amyloid and tau aggregation, hyperexcitation, and inflammation. As a renewable source of human neurons, perhaps most important is the potential of iPSC-derived AD models in **high-throughput screening** (HTS): using automated systems to test the effects of thousands of potential AD treatments in parallel. [16] Given their identical genetic content, iPSC-derived models can be used to predict the treatment response of the human donor more reliably than transgenic mice, and may also help to explain why existing AD treatments work better for some patients than others.


Familial AD patient
Skin cells
iPSCs
Glial Cells
Excitatory neurons
Inhibitory neurons
iPSC-derived co-culture

However, grown outside of a living organism (**in vitro**), iPSC-derived models are not particularly useful for studying the behavioural aspects of Alzheimer's. In this respect, mouse models remain superior… Since most iPSC cultures are derived from familial, rather than sporadic AD patients,[15] they also share the corresponding limitations seen in mouse models.

One unique pitfall of iPSC-derived models is cellular immaturity. As a disease of aging, it is important that the neurons in AD models are as old and wise as those of human patients. Noticing that iPSC-derived neurons appear smaller than those of adult humans, researchers discovered that the reprogramming process used to induce pluripotency has a de-aging effect, erasing the molecular marks acquired by the fibroblast over time.[17, 18] Even once differentiated, iPSC-derived cells exhibit foetal behaviour, for example producing immature tau rather than the aggregation-prone isoform – as such, iPSC models do not develop neurofibrillary tangles.[19] Emerging solutions aim to bypass pluripotency altogether, converting adult skin cells directly into neurons to preserve their maturity. [20]

In any case, these in vitro models constitute an exciting new arrival in the arena of Alzheimer's Disease modelling, more likely a valuable companion to existing mouse models than a hostile adversary!



Alzheimer's Next Top Disease Model…

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