Reprogramming technology enables differentiated cells of a specific cell type to be converted to another cell type with completely different functions, either through the production of induced pluripotent stem cells (iPSCs) or through direct reprogramming. This technology has enabled scientists to understand the differences in behavior and cell types that are previously inaccessible, such as human neurons. The study of live human neurons in a dish allows human-specific neurodevelopmental properties to be identified and the specific pathways that are defective in cells from patients with neuropsychiatric and neurodegenerative diseases to be dissected. Integrating this technology with the relevant cell types involved in neurodegenerative disease with reproducible and scalable phenotypic assays is a new challenge for the disease-modelling field.

**Human iPSC-derived neural cells**

Understanding basic principles of human brain development

iPSC-derived neurons can be used to determine the neurodevelopmental hallmarks of human neural cells (neurons and glia) and to investigate the cellular mechanisms of the brain during development, the relationships between epigenetic and gene regulation. For example, given that epigenetic changes can influence gene expression and cell fate determination, in vivo, it is highly informative to study the influence of epigenetics during human neurodevelopment, something that is only possible now owing to the use of iPSC technology. These cells can also be used to study the characteristics of human iPSC-derived cells in vitro, which are the closest relatives (such as chimpanzees). Such experiments can provide clues as to how humans evolved such a unique brain.

Understanding and using CNS cell

Cell-reprogramming technology (Fig. 1) has remarkable potential to generate insights into disease mechanisms, particularly in the case of CNS disorders. Researchers can use reprogramming technology to study human disease in living neural cells that carry disease-specific genetic variants (see Table), by comparing derivatives derived from patients and controls or manipulating gene expression in different neuronal subtypes using gene editing, researchers can gain an understanding of basic disease mechanisms.

Studying the development of neural cells derived from patient iPSCs will facilitate our understanding of the early steps of CNS disease processes and could therefore provide new early diagnostic and therapy biomarkers. iPSC-derived cell lines have been used in high-throughput assays for drug screening (Fig. 1b). In this way, reprogramming technology is already informing clinical trials. For example, iPSC-derived human neurons from patients with autism spectrum disorders (ASDs) have been used as a significantly improved phenotype in vivo. Modified versions of iFL2 are now in clinical trials for patients with several types of autistic spectrum disorder. It remains a challenge to predict the materials that will work best in vitro and in vivo, but it is hoped that these new models can help us understand and potentially treat CNS diseases is exciting.

iPSC technology may also allow for the development of patient tailored therapies, where, in the future, reprogramming experiments can be performed on the cells from the patient that will potentially receive the therapy, decreasing the effect of genetic background variability among individuals.

Cellular replacement therapy is also an exciting application of iPSC technology. The first patients are already receiving iPSCs-derivated via transplantation for some neurological diseases; however, caution must be taken on the somatic genetic background variability among individuals.

**Applications of iPSC-derived neural cells**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutated genes</th>
<th>iPSC-derived progeny</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>APP, Aβ42, Aβ40</td>
<td>Neurons, astrocytes</td>
<td>Vulnerability to Aβ toxicity</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>SNCA, DJ-1</td>
<td>Neurons, astrocytes</td>
<td>Vulnerability to α-synuclein toxicity</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>HTT</td>
<td>Neurons, astrocytes</td>
<td>Vulnerability to Huntingtin toxicity</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Disrupted expression of 130 genes</td>
<td>Neurons, astrocytes</td>
<td>Vulnerability to dysregulated gene expression</td>
</tr>
</tbody>
</table>

**Challenges and future directions**

Modelling polygenic and multifactorial CNS disorders using cells derived through reprogramming requires an integrative approach that combines the capacity to detect relevant genetic determinants with the ability to study cellular and phenotypic characteristics in reproducible and scalable biosystems. There remain several technical challenges to the re-organization:

- Generating mature, adult-like neural cell types and refining the methods for detecting the maturation of neuronal activity
- Identifying genomic mutations that result in robust phenotypes in iPSC-derived cells
- Improving reproducibility and scalability of phenotypic assays
- Incorporating gene-editing technologies (such as CRISPR-Cas9 system) to correct relevant changes in iPSCs to better understand disease mechanisms and potentially create cell lines for transplantation strategies

Incorporating other CNS-specific genes (for example, astrocytes, oligodendrocytes and microglia) and/or inflammation factors into the in vitro model to produce more disease-relevant phenotypes

Incorporating the use of 3D culture models (organoid technology) in order to create more-realistic models of development and disease (for example, by stimulating cortical layer formation)

Developing screening platforms for new compounds that can be readily translated to in vivo experiments.

**Cell-reprogramming technology and neuroscience**

Maria C. Marchetto and Fred H. Gage

iPSC-derived cells from patients and control populations

Developing phenotypic assays using iPSC-derived cells

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutated genes</th>
<th>iPSC-derived phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal muscular atrophy</td>
<td>V(D)M</td>
<td>Lower motoneuronal cell survival</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>SNCA</td>
<td>Vulnerability to α-synuclein toxicity</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>APP, Aβ42, Aβ40</td>
<td>Vulnerability to Aβ toxicity</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>ABCD1</td>
<td>Vulnerability to VLCFA toxicity</td>
</tr>
</tbody>
</table>

Acknowledgements

The authors thank the C. Horvitz, L. H. Walls, J. Engman Foundation; the Leona M. and Harry B. Helmsley Charitable Trust; the John S. and James L. Mackenzie Foundation; the John S. and James L. McElroy Foundation; the Robert and Mary Jane Meyer Charitable Trust; and the James S. McDonnell Foundation. Edith Weltman, Kees Engelman, Francisca C. Koch and Kersten K. Bruns provided helpful comments. Funding information: J.M.G. is supported by the Alzheimer’s Association and the National Institute on Aging (R01 AG052819). J.M.G. was funded by the Department of Defense (W81XWH-10-1-0425) and the National Institutes of Health (R01 NS065779 and R01 MH121301). The Robert and Mary Jane Meyer Charitable Trust and the James S. McDonnell Foundation.

Edith Weltman, Kees Engelman, Francisca C. Koch and Kersten K. Bruns provided helpful comments. Funding information: J.M.G. is supported by the Alzheimer’s Association and the National Institute on Aging (R01 AG052819). J.M.G. was funded by the Department of Defense (W81XWH-10-1-0425) and the National Institutes of Health (R01 NS065779 and R01 MH121301). The Robert and Mary Jane Meyer Charitable Trust and the James S. McDonnell Foundation.

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**References**


Supplementary information S1

Abbreviations for the poster ‘Cell-reprogramming technology and neuroscience’ by Maria C. Marchetto and Fred H. Gage

ABCD1, ATP-binding cassette sub-family D member 1; ALDH1L1, aldehyde dehydrogenase family 1 member L1; APP, amyloid precursor protein; AQP4, aquaporin 4; ASC1, achaete-scute homologue 1; ATXN3, ataxin 3; BDNF, brain-derived neurotrophic factor; BRN2, brain-specific homeobox 2; CACNA1C, voltage-dependent L-type calcium channel subunit-α1C; CD11B, CD11 antigen-like family member B; CD31, CD antigen CD31; CDKLS, cyclin-dependent kinase-like 5; CHAT, choline O-acetyltransferase; CNP, 2',3'-cyclic-nucleotide 3'-phosphodiesterase; CRISPR, clustered regularly interspaced short palindromic repeats; CTIP2, COUP-TF-interacting protein 2; CUX1, homeobox protein cut-like 1; CX3CR1, CX3C chemokine receptor 1; DARPP32, protein phosphatase 1 regulatory subunit 1B; DKK1, dickkopf-related protein 1; DISC1, disrupted in schizophrenia 1; ERCC6, excision repair cross-complementation group 6; FGF, fibroblast growth factor; FOXA2, forkhead box protein A2; FMR1, fragile X mental retardation 1; FXN, frataxin; GABA, γ-aminobutyric acid; GALC, galactocerebrosidase; GABA3, cytosolic β-glucosidase; GFAP, glial fibrillary acidic protein; GIRQ2, G-protein-regulated inward-rectifier potassium channel 2; GSK3β, glycogen synthase kinase 3β; HB9, homeobox protein 9; HTT, huntingtin; IBA1, allograft inflammatory factor 1; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor-binding protein 3; IKBKAP, IkB kinase complex-associated protein; ISL1, islet 1; KLF4, krueppel-like factor 4; LHX3, LIM homeobox protein 3; LIN28, protein lin-28 homologue A; LINE1, LMX1A, LIM homeobox transcription factor 1α; LRRK2, leucine-rich repeat kinase 2; MAP2, microtubule associated protein 2; MBP, myelin basic protein; MECP2, methyl-CpG-binding protein 2; MYC, Myc proto-oncogene protein; MYT1L, myelin transcription factor 1-like protein; NANO6, homeobox protein NANO; NEUN, neuronal nuclei; NF, neurofilament; NFIA, nuclear factor 1 A-type; NFIB, nuclear factor 1 B-type; NGN2, neurogenin-2; NKPX6.2, homeobox protein Nkx-6.2; NURR1, orphan nuclear receptor NURR1; O4, forkhead box protein O4; OCT4, octamer-binding protein 4; OLG2, oligodendrocyte transcription factor 2; PARK2, parkin RBR E3 ubiquitin-protein ligase; PINK1, PTEN-induced putative kinase 1; PITX3, pituitary homeobox 3; PLP1, myelin proteolipid protein; PROX1, prospero homeobox protein 1; PSD95, postsynaptic density protein 95; PSEN1, presenilin 1; PSEN2, presenilin 2; PVALB, parvalbumin; RELN, reelin; S100β, protein S100β; SATB2, DNA-binding protein SATB2; SCN1A, sodium channel protein type 1 subunit-α; SHANK3, SH3 and multiple ankyrin repeat domains protein 3; SHH, sonic hedgehog; SMN1, survival motor neuron protein; SNCA, α-synuclein; SOD1, superoxide dismutase 1; SOX2, transcription factor SOX2; SOX9, transcription factor SOX9; SOX10, transcription factor SOX10; SPG14, spastic paraplegia 14; ST18, suppression of tumorigenicity 18 protein; SYN, synapsin; TAU, microtubule-associated protein tau; TARDBP, TAR DNA-binding protein 43 (gene); TDP43, TAR DNA-binding protein 43 (gene product); TH, tyrosine hydroxylase; TRPC6, transient receptor potential cation channel, subfamily C, member 6; TUBB3, neuron-specific class III beta-tubulin; VAPB, vesicle-associated membrane protein-associated protein B/C; WNT3A, protein Wnt3a.