Human iPSC-derived neurons and lymphoblastoid cells for personalized medicine research in neuropsychiatric disorders

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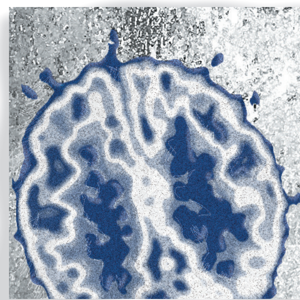

The development and clinical implementation of personalized medicine crucially depends on the availability of high-quality human biosamples; animal models, although capable of modeling complex human diseases, cannot reflect the large variation in the human genome, epigenome, transcriptome, proteome, and metabolome. Although the biosamples available from public biobanks that store human tissues and cells may represent the large human diversity for most diseases, these samples are not always sufficient for developing biomarkers for patient-tailored therapies for neuropsychiatric disorders. Postmortem human tissues are available from many biobanks; nevertheless, collections of neuronal human cells from large patient cohorts representing the human diversity remain scarce. Two tools are gaining popularity for personalized medicine research on neuropsychiatric disorders: human induced pluripotent stem cell-derived neurons and human lymphoblastoid cell lines. This review examines and contrasts the advantages and limitations of each tool for personalized medicine research.

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Introduction

Over recent decades, there has been persistent movement toward individualized medicine—medical treatments tailored for the individual patient based on genetic and genomic information derived from a patient's own biological samples (blood and biopsied tissues). Individualized medicine has also been termed "personalized" medicine and more recently, "precision" medicine.[1,2] Its major aims are prescribing the right drug at the right dosage and time for each patient, thereby improving drug efficacy, minimizing drug-induced adverse events, and improving the overall cost-effectiveness of health care. Precision medicine also aims for earlier diagnosis so that patients can receive preventive therapeutics before a disease causes irreparable damage. Great strides have been made toward personalized medicine in oncology, where biomarkers identified in biopsied tumor tissues or blood—such as tumor-specific mutations, as well as gene expression and/or protein signatures—allow tumor-tailored therapy choice.[3,4] Yet, personalized medicine research outside oncology is of-

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ten hampered by lack of high-quality biological samples. This remains a key barrier, in particular for personalized medicine research on neuropsychiatric disorders. Indeed, brain tissues are typically scarce and their postmortem nature adds undesired background noise[5]; furthermore, peripheral tissues or cultured cells do not always reliably represent brain-specific biological pathways. One of the greatest challenges in molecular psychiatry remains the inaccessibility of living human brain tissue. Better neuroimaging technologies that allow the identification of disease and treatment biomarkers in brains of live patients are definitely needed.[6] Until this challenging goal is reached and such technologies incorporated into routine clinical practice, which may take decades—keeping in mind the inadequacy of animal disease models for studying the genomics of complex human diseases (animal models cannot reflect the unique human DNA sequence variation and its epigenome diversity[7-9])—in vitro human cell systems seem to be the most credible resource available for research on personalized medicine in treatment of neuropsychiatric disorders.

Two different in vitro research tools are increasingly being employed for research on personalized medicine in neuropsychiatric disorders; they are described below, discussing their advantages and limitations. One is human induced pluripotent stem cell (iPSC)-derived neurons (*Table I*), a relatively new tool gaining in popularity because these cells present neuronal phenotypes of the specifically desired human brain area while carrying the genome sequence of carefully selected diseased or healthy control individuals.[10-12] This tool was first described in the scientific literature in 2008.[13] The desired neuronal subtype, such as midbrain dopaminergic neurons, hippocampal dentate gyrus neurons, or cerebellar neurons, are derived from iPSCs by use of specific gene transfection protocols.[14]

Another useful tool is human lymphoblastoid cell lines (LCLs), used in biomedical research for decades and first described in 1963.[15] Although they are derived from peripheral blood B lymphocytes and present a typical B-lymphocyte phenotype, these cells have certain advantages for personalized medicine research, including for neuropsychiatric disorders, as discussed below and summarized in *Table I*.

Human iPSC-derived neurons

iPSC-derived neurons have been instrumental for studying many neuropsychiatric disorders. Studies employing iPSC-derived neurons have been published about schizophrenia,[16-18] autism spectrum disorder (ASD),[19-21] bipolar disorder (BD),[22-24] Parkinson disease (PD),[25-27] and Alzheimer disease (AD).[28-30]

Item	Human iPSC-derived neurons	Human LCLs
Neuronal phenotype	**Yes, of desired neuronal subtype**	No (lymphoid phenotype)
DNA sequence stability	**High**	**High**
Clonality	Monoclonal	**Polyclonal**
Somatic mutations	Common	**Rare**
Original donor epigenome	Not entirely	Not entirely
3D structure of DNA maintained	Not entirely	Unknown
Ease of preparation	Requires high costs and expertise	**Simple and inexpensive**
Ease of use	High preparation and maintenance costs	**Low cost and ease of handling**
Ease of shipping	Requires freezing	**May be shipped as live cultures**
Biobank availability	Limited	**Large disease cohorts available**
Suitability for PGx studies	**Yes**	**Yes**
No. PubMed articles*	227 (since 2009)	**10 398 (since 1963)**
Avg No. PubMed articles/year	32	196

Table I. Key advantages and limitations of human iPSC-derived neurons and human LCLs for personalized medicine research in central nervous system disorders. Advantages are indicated in bold font. This list is not meant to be comprehensive, and readers are advised to refer to citations in the main text. 3D, three-dimensional; Avg, average; iPSC, induced pluripotent stem cell; LCL, lymphoblastoid cell line; miRNA, microRNA; No., number; PGx, pharmacogenomics. *Based on a PubMed search performed on June 14, 2016 (including all manuscript types).

Most current research employing human iPSC-derived neurons starts with biopsied skin fibroblasts engineered into iPSCs. An alternative notable source is urine-harvested renal proximal tubule epithelial cells, recently used as starting cells for generating iPSC-derived neurons from multiple sclerosis patients.[31] Such noninvasive patient-specific primary neurons displayed distinctive neuronal morphology and functionality; devoid of permanent genetic manipulation during the course of differentiation, such urine-derived cells seem a notable resource for personalized medicine studies of central nervous system (CNS) disorders.

Several recent studies using iPSC-derived neurons have taken a step toward novel disease-specific neuronal features that may in future facilitate personalized treatments for CNS disorders. Among them, some are particularly notable as examples for the potential of iPSC-derived neurons for personalized medicine research. Cooper et al[26] analyzed iPSC-derived dopaminergic neurons from healthy controls, PD patients, and presymptomatic individuals carrying mutations in the PTEN-induced putative kinase 1 (*PINK1*) and leucine-rich repeat kinase 2 (*LRRK2*) genes, common PD risk genes. They demonstrated mitochondrial dysfunction in iPSC-derived neuronal cells from familial PD patients and at-risk individuals; moreover, the mitochondrial dysfunction phenotype could be rescued with coenzyme Q_{10}, rapamycin, or the LRRK2 kinase inhibitor GW5074. As mitochondrial dysfunction is thought to underlie PD dopaminergic neuronal pathology, the iPSC-derived neurons may thus reflect PD risk even before the individuals from whom they were derived become symptomatic for PD. Schöndorf et al[27] showed that iPSC-derived midbrain dopaminergic neurons from PD patients carrying mutated acid β-glucocerebrosidase (*GBA1*)—responsible for Gaucher disease and also implicated in PD—exhibited elevated glucosylceramide, α-synuclein, and neuronal calcium-binding protein 2 levels, along with deficient autophagy and lysosomal capacities. These patient-specific midbrain dopaminergic neurons displayed dysregulation of calcium homeostasis and increased stress vulnerability involving elevated cytosolic calcium; furthermore, correction of the *GBA1* mutations rescued the pathological disease phenotypes. Mertens et al[24] differentiated the iPSCs prepared from BD patients and control fibroblasts into hippocampal dentate gyrus granule cell–like neurons. They showed that the BD iPSC-derived hippocampal neurons presented mitochondrial abnormalities. In addition, RNA sequencing of these cultured neuron-like cells indicated differential gene expression profiles between cells derived from healthy and BD individuals, as well as between BD patients who were clinically responsive or nonresponsive to lithium, the first-line BD therapy. Moreover, patch-clamp recording showed that iPSC-derived hippocampal neurons from BD patients were hyperactive compared with control neurons (exhibiting more rapid action-potential firing), and this hyperexcitability phenotype was reversed by in vitro lithium treatment in neurons derived only from BD patients who responded to lithium treatment in the clinic. This study demonstrates the novel utility of iPSC-derived neurons for personalized medicine research in psychiatric disorders: the cellular pathways leading to the hyperexcitability phenotype in BD neurons, albeit not entirely delineated, responded to lithium in iPSC-derived neurons from lithium-responsive BD patients only. This suggests that the epigenomic signatures associated with lithium responsiveness in BD patients are maintained (in addition to DNA sequence) when their fibroblasts are converted to iPSCs and then differentiated to hippocampal dentate gyrus neurons. Differences in DNA sequence between lithium responsive or nonresponsive BD patients also account for such observations, although polymorphic alleles in only two related genes—both being long noncoding RNAs (AL157359.3 and AL157359.4)—were recently identified as predictive for lithium response in a genome-wide association study (GWAS) comparing lithium responsive and nonresponsive BD patients.[32] Whatever the reason underlying lithium nonresponse in a subset of BD patients, it also affects the in vitro lithium response of their iPSC-derived neurons, attesting to the potential of this tool for personalized medicine research of neuropsychiatric disorders.

Human iPSC-derived neurons of specified subtype are also gaining increased interest as potential personalized therapies for CNS disorders. Human iPSC-derived dopaminergic neuron grafts were shown to restore normal behavior in a rat PD model.[33] Human iPSC-derived neurons have also been used for generating humanized animal models of other CNS disorders. For example, human iPSC-derived cerebellar neurons were beneficial for modeling Niemann-Pick type C1.[34] Additionally, iPSC-derived γ-aminobutyric acid (GABA) neurons from Huntington disease (HD) patients carrying

the CAG repeat in exon 1 of the huntingtin gene were developed as a first step for generating an animal model for HD.[35] Also, iPSC-derived motor neurons from familial amyotrophic lateral sclerosis (ALS) patients were shown to have the relevant in vitro phenotype for generating ALS animal models.[36]

Unsolved issues and pitfalls of using iPSC-derived neurons

Although iPSC-derived neurons are becoming an increasingly popular tool for exploring the cellular mechanisms underlying neuropsychiatric disorders, their widespread use is presently limited because of limited availability from public biobanks, coupled with the high level of expertise and high costs required for preparing individual lines of iPSC-derived neurons from large cohorts of selected patients and matched controls. Most published original research articles have employed very few (typically up to six) iPSC-derived neuronal lines. Each such neuronal cell line represents a single individual; thus, the limited utility of this tool for large cohort population studies stands out as a key limitation (*Table I*). Cheaper and simpler technologies for generating iPSC-derived neurons (or stem cell–derived neurons) from large patient cohorts (and matched controls) are definitely needed for harnessing this tool for personalized medicine research. Further unresolved issues also limit the utility of iPSC-derived neurons for personalized medicine research. Notably, such cells are by definition monoclonal, arising from a single nonpluripotent cell, meaning that two lines generated from the same patient (or a healthy control) may present different phenotypes.[37] This aspect can be overcome by generating several clones for each patient-derived iPSC line; however, this further increases research costs. In addition, reprogramming iPSCs to neurons increases cell variability due to the introduction of mutations in the genomic DNA along with the insertion of exogenous reprogramming genes.[38] Nevertheless, as more recently demonstrated, several separate batches of commercially available neurons originating from the same iPSC clone from a single patient presented similar neuronal phenotypes, as well as similar transcriptomic signatures and drug sensitivity profiles, meaning that the step of generating neurons from iPSCs is highly reproducible and does not add noise.[39]

Another unresolved problem is that reprogrammed cells maintain residual DNA-methylation signatures of the somatic tissue of origin, which may affect their transcriptomic profiles,[40] as well as hotspots of aberrant epigenomic reprogramming.[41] Long periods of continued culture may also affect the transcriptomes and phenotypes of iPSCs.[42] In addition, as somatic cells (typically fibroblasts), used by the majority of published studies as the starting cells for preparing iPSCs, accumulate somatic mutations during a patient's lifetime, separate iPSC clones prepared from the same individual may harbor different somatic mutations, as recently demonstrated for mitochondrial DNA (mtDNA) somatic mutations in iPSC-derived neurons.[43] In that study, the authors showed that whereas pooled mtDNA from skin and blood contained few point mutations, a panel of 10 individual iPSC lines from each tissue or clonally expanded fibroblasts carried an elevated load of such mutations, suggesting that somatic mutations randomly arise within individual cells although not detected in whole tissues, an aspect apparently most relevant for mtDNA. The latter study also showed that frequencies of mtDNA mutations found in iPSCs increased with higher donor age, with many mtDNA mutations being nonsynonymous (leading to changed amino acid).[43] Keeping in mind the importance of mtDNA mutations for neurodegenerative disorders, such observations highlight a major limitation of iPSC-derived neurons for personalized medicine research and a need to monitor mtDNA mutations in iPSCs, as well as in iPSC-derived neurons, especially when generated from older patients. Such considerations are particularly crucial when employing iPSC-derived neurons in the study of neurodegenerative disorders, where patients and their matched controls are typically of old age.

An additional unresolved issue concerning iPSCs and their derived neuronal cell lines that has only recently been raised is the fidelity of three-dimensional (3D) DNA structures compared with the donor's original cell, and potential effects on some cellular phenotypes. The genomes of pluripotent cells are folded in a topological hierarchy that undergoes reorganization during cell differentiation, and the extent to which chromatin architecture is reconfigured during somatic cell reprogramming is poorly understood.[44] Fine-resolution architecture mapping with epigenetic marks and gene expression profiles in iPSCs showed that the majority of pluripotency genes reconnect to target enhancers during reprogramming and that iPSC genomes exhibit imperfectly rewired 3D folding resulting in inaccurate-

ly reprogrammed gene expression.[44] Similar concerns have been demonstrated by further recent studies.[43,45] Guanine nucleotide quadruplex structures (G4) also play a role in 3D DNA folding and affect many biological processes.[46] That said, it is noteworthy that pluripotent stem cells, as well as germ-line stem cells, showed less G4 staining compared with most other cells.[47] At this time, to my knowledge, no published studies have examined G4 staining in iPSC-derived neurons compared with somatic neurons. This important aspect needs to be resolved.

Some, but not all, of the above limitations can be overcome by converting somatic cells directly to neurons rather than using iPSCs as an interim step. Such a method was recently described by Meyer et al[48] who demonstrated a technique for the direct conversion of adult human biopsied primary skin fibroblasts into induced neural progenitor cells (iNPCs) by timely restricted expression of four genes.

The unresolved issues above reflect some of the current concerns for employing iPSC-derived neurons for personalized medicine research. However, these should be viewed as features that need to be clarified rather than as shortcomings of this innovative research tool.

Human lymphoblastoid cell lines (LCLs)

Large cohorts of human LCLs from diseased and control individuals represent another novel tool for personalized medicine research. This tool was originally developed over 50 years ago,[15,49] firstly for research on leukemia[50,51] and viral diseases,[52-54] and used for human antibody production[55,56] and later for studying human DNA sequence, transcriptome, and proteome diversity,[57,58] also in the context of human migration and ethnic ancestry.[59,60] Recently, large panels of human LCLs have been used to study interindividual drug response phenotypes and their DNA sequence and transcriptome correlates,[61-64] including for neuropsychiatric disorders, as discussed below.

Human LCLs are considered the most reliable, inexpensive, and convenient representation of cells from unrelated individuals for in vitro research. These human cell lines arise from peripheral B lymphocytes infected in vitro with the Epstein-Barr virus (EBV), a process that immortalizes them. This is made possible by EBV genes that when expressed in human cells inhibit apoptosis, a process that would otherwise affect human peripheral blood lymphocytes grown in vitro, limiting the time period that they can be used for study to only a few days. By contrast, LCLs can be maintained in continuous in vitro growth over many months, even over a year, until they cease dividing.[64] The genomes of LCLs remain stable during subsequent cell divisions; this is in contrast to human cancer cell lines, which undergo frequent genetic rearrangements (shuffling of DNA within and between chromosomes) such that the DNA sequence in these cell lines, as well as the transcriptomes, proteomes, and phenotypes, keeps changing as they are grown, thus reducing the value of these cell lines for research and sometimes causing inconsistent observations. The stable genome and transcriptome properties of cultured LCLs in part reflects the fact that the EBV genome is not incorporated into the germ-line genome but rather remains in the cell cytosol; moreover, unlike cancer cells, the entire machinery taking care of faithful DNA replication and repair during cell division in LCLs remains intact. Of note, the EBV strain used for LCL generation is produced by culturing a macaque cell line known as B95-8.[65] Human LCLs are prepared from a large number of peripheral blood lymphocytes, and the resulting cell lines are therefore of polyclonal nature, unlike iPSCs.

Owing to these properties, human LCLs remain to this date, over half a century since first reported, among the best research tools for representing an individual; thus, they are sometimes referred to as "personal cell lines." This representation also includes, to some extent, the individual epigenome, reflecting epigenomic modifications due to disease, chronic toxin or drug exposures, diet, smoking, and other lifestyle effects. Although some of the epigenomic signatures are lost during the EBV immortalization process and subsequent in vitro propagation, many of them persist in vitro and may aid discovery of disease-related epigenomic modifications. For example, a study by Brennan et al[66] compared the DNA methylation profiles in peripheral blood leukocytes with those of LCLs generated from the same leukocytes and observed differential 5' region methylation profiles in only 8% of 318 tested genes. However, other groups reported higher levels of methylation discordance between LCLs and their matched blood leukocytes and noted that *hyper*methylation was more predominant than *hypo*methylation in LCLs.[67]

Numerous examples illustrate the utility of LCLs as a research tool: a PubMed search (June 2016) identified

over 10 000 manuscripts mentioning the word "lymphoblastoid" compared with only 227 mentioning iPSC-derived neurons (*Table I*). Adding the words "drug response" yielded 959 PubMed manuscripts for LCLs but only 11 for iPSC-derived neurons. LCLs in particular remain the best resource for representing large cohorts of unrelated individuals, including their individual genomes, transcriptomes, proteomes, metabolomes, and in vitro phenotypes, such as cell growth rates, DNA repair efficiency, mitochondrial respiration, glycolysis rates, cytosolic pH, calcium concentrations, and additional phenotypes. Studies comparing LCL cohorts from diseased vs healthy individuals allowed insights into disease pathophysiology that would have otherwise required far more time and costs. In recent years, and in spite of their lymphocyte-like phenotypes, LCLs have emerged as a valuable personalized medicine research tool for neuropsychiatric disorders, including schizophrenia,[68,69] autism,[70-72] BD,[73-75] and additional CNS disorders.

In our lab, we used LCLs from unrelated healthy individuals for a genome-wide search of transcriptomic drug response biomarkers for personalized treatment of major depressive disorder (MDD).[76-78] As a consequence, low peripheral blood mononuclear cell (PBMC) expression levels of integrin β3 (*ITGB3*), coding for a cell adhesion protein that also functions as a cofactor for the serotonin transporter, were recently suggested to be implicated in MDD, as *ITGB3* expression in LCLs from four unrelated healthy individuals was found to be the top upregulated gene after long-term in vitro treatment with the antidepressant drug paroxetine.[78] We proposed that the augmented expression of *ITGB3* in turn supports neurogenesis and synaptogenesis and thereby assists the remission of depression symptoms. *ITGB3* expression was recently corroborated as a tentative MDD biomarker in a clinical cohort of MDD patients.[79] These findings may help clarify why around one third of MDD patients do not respond to selective serotonin reuptake inhibitor (SSRI) antidepressants, currently the first-line MDD therapeutics. Furthermore, they may allow the introduction of blood-based diagnostics, such as PBMC *ITGB3* messenger RNA (mRNA) or protein levels, for potentially identifying MDD patients who are unlikely to be helped by SSRI antidepressants so that they may be treated with other antidepressant therapeutics and prioritized for more frequent clinic visits.

Studying transcriptomic signatures in patient LCLs has advantages compared with studying whole blood, leukocytes, or plasma: RNA signatures of blood cells or plasma exosomes may be affected by time of blood sampling, diet, gut microbiome, hormones, infectious diseases, therapeutics, and environmental influences, such as extreme temperatures or poor air quality. By contrast, LCLs are immortalized in many labs via an essentially similar protocol; moreover, LCLs from diseased and healthy individuals are typically grown in parallel for experimentation. Thus, modifiers that may affect phenotypes and transcriptomic signatures of peripheral blood lymphocytes are far less likely to impact the phenotypes, transcriptomes, proteomes, and metabolomes of cultured LCLs. Thus, research with LCLs typically provides accurate and consistent data and at lower research costs. This allows reproducible findings even with smaller cohorts, further facilitating personalized medicine research when funds are limited.

Limitations and pitfalls of LCLs

The key limitation of using LCLs for personalized medicine research on CNS disorders is that these cells have a B-lymphocyte phenotype, quite different from that of in vitro cultured neuronal cell lines or iPSC-derived neuronal-like cells. Moreover, the immortalized nature of LCLs means that some epigenomic signatures in the original blood lymphocytes may have been changed as a result of the presence of EBV. Yet, these cell lines maintain some of the original donors' epigenomic signatures.[66,67] Researchers may nonetheless use human LCL panels for studying tentative genomic, proteomic, or metabolomic drug response biomarkers, while keeping these limitations in mind.

Biobanks: an essential resource for personalized medicine research

Human biobanks, biorepositories for storing human biological samples, are essential for personalized medicine research: they are the most accessible and often the best quality resource for human tissues, blood, primary or immortalized cell lines, and DNA samples from large cohorts of individual donors, either healthy controls (population cohorts) or individuals afflicted by certain diseases. Some of them include longitudinal blood samples from the same donors, a valuable asset. Large population biobanks, such as the UK Biobank have recently published genomic studies with large co-

horts (>100 000 individuals) investigating Alzheimer disease and the apolipoprotein E (ApoE) genotype,[80] and pleiotropy between neuroticism and physical and mental health.[81]

Many biobanks store human cell lines for research projects. Yet, presently, few biobanks offer iPSC collections, creating a barrier for use of iPSC-derived neurons for personalized medicine research.[82] Among public biobanks currently distributing iPSCs is the Coriell Institute. However, as of June 2016, their online catalog included just 16 healthy and 26 diseased iPSC lines. By contrast, the same catalog currently lists >30 000 LCLs. Small collections of iPSCs are also available from several commercial providers. A novel collection of iPSCs and iPSC-derived neurons from Alzheimer disease patients is available at the University of California Irvine Alzheimer's Disease Research Center (UCI-ADRC).

The current scarcity of biobanked iPSC collections highlights the key current advantage of LCLs: large cohort availability (*Table I*). Hopefully, this will change within the next few years, facilitating the use of iPSCs for personalized medicine research for complex diseases, including neuropsychiatric disorders. Notably, techniques have been reported for converting LCLs into iPSCs.[83,84] Hence, an untapped potential exists for transforming existing biobanked human LCL collections into large iPSC collections.

Large patient cohorts vs "N-of-1" studies: implications for use of in vitro research tools

Traditionally, epidemiological studies, which form the basis for personalized medicine research, have applied strategies of large patient cohorts for the obvious reason that larger patient cohorts afford better statistical power, and hence better research insight. Yet, we should keep in mind that "N-of-1" studies have the novel virtue of being capable of capturing extremely rare disease or drug response phenotypes, a quality that is nearly unattainable (or obscured) using large patient cohorts.[85,86] For example, a recent meta-analysis of published "N-of-1" trials showed that amphetamine and methylphenidate are effective treatments for pediatric attention deficit/hyperactivity disorder (ADHD).[87] The unique advantages of "N-of-1" studies in epidemiology are reflected by emerging in vitro technologies for genotyping or phenotyping single cells, such as single-cell sequencing, of utmost importance for designing personalized cancer therapy,[88] or single-cell laser tagging for subsequent genomic, flow cytometry, or ultramicroscopy studies.[89]

That said, one can readdress the above comparison of the advantages and limitations of the new tool, iPSC-derived neurons, vs the older tool, large LCL collections. LCLs can be viewed as the in vitro equivalent of the traditional epidemiological study tool, where the emphasis is on large patient cohorts; whereas iPSC-derived neurons, at least for the time being, represent the research laboratory equivalent of "N-of-1" studies (or, for that matter, "N-of-small number" of iPSC-derived neuronal-like cell lines). This comparison, albeit imperfect, captures some of the essential differences between the two in vitro laboratory research tools discussed here.

Future directions

One of the top challenges currently faced in molecular psychiatry is the inaccessibility of living human brain tissue. This review has briefly explored and compared the key advantages and limitations of two key in vitro cellular tools, human iPSC-derived neurons and human LCLs, as used in personalized medicine research on neuropsychiatric disorders. Both tools have their benefits and pitfalls; some are obvious and some are unresolved aspects that may be clarified by further studies (*Table I*). This author's opinion is that at this time, both tools should be used in personalized medicine. For addressing basic biological questions on the pathophysiology and the transcriptomic and epigenomic events affected in CNS disorders, iPSC-derived neurons offer the utmost advantage of having neuronal phenotypes—and moreover, of specific neuronal subtype—so that disease and drug response pathways can be studied in the correct context and compared with findings from postmortem brain tissues.[90] For large-scale studies comparing diseased and matched control cohorts, human LCLs offer the clear advantages, at least for the time being, of having better availability (including from public biobanks), ease of handling (and sample sharing among research groups), and lower costs even when large cohorts are required. In future, improved availability of biobanked human iPSC-derived neuronal cells will probably tip the scale in favor of using them more frequently (and hopefully at lower costs) for personalized medicine research on CNS disorders. Today, some features of

human iPSC-derived neurons remain unresolved and need clarification. Such improvement should go hand in hand with the development of improved brain imaging and other noninvasive CNS research tools, along with the creation of large phenotypic databases for patient data from large disease and control cohorts. ❑

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Neuronas derivadas de las iPSC (células madre pluripotenciales inducidas) y células linfoblastoides humanas (LCLs) para la investigación de los trastornos neuropsiquiátricos en medicina personalizada

El desarrollo e implantación clínica de la medicina personalizada depende, de forma crucial, de la disponibilidad de muestras biológicas humanas de alta calidad; aunque los modelos animales sean capaces de modelizar enfermedades humanas complejas, no permiten reflejar las amplias variaciones del genoma, epigenoma, transcriptoma, proteoma y metaboloma humanos. Además, y a pesar de que las muestras biológicas disponibles en los biobancos públicos de tejidos y células humanas pueden representar la amplia diversidad humana en muchas enfermedades, no siempre son suficientes para desarrollar biomarcadores a medida de los pacientes en las terapias de los trastornos neuropsiquiátricos. Si bien existen tejidos humanos postmortem disponibles en muchos biobancos, siguen siendo escasas las colecciones de células neuronales de grandes cohortes de pacientes que representen la diversidad humana. Hay dos herramientas que están ganando popularidad para la investigación de los trastornos neuropsiquiátricos en medicina personalizada: las neuronas derivadas de células madres pluripotenciales inducidas y las líneas celulares linfoblastoides humanas. Esta revisión examina y contrasta las ventajas y limitaciones de cada una de estas herramientas para la investigación en medicina personalizada.

Neurones humains dérivés des cellules souches pluripotentes induites (iPSC) et cellules lymphoblastoïdes pour la recherche médicale personnalisée dans les troubles neuropsychiatriques

Le développement et l'implantation clinique de la médecine personnalisée dépendent essentiellement de la disponibilité d'échantillons biologiques humains de haute qualité ; les modèles animaux, même s'ils peuvent reproduire des maladies humaines complexes, ne peuvent pas refléter la grande variabilité des génome, épigénome, transcriptome, protéome et métabolome humains. Les échantillons biologiques des biobanques publiques, qui conservent les cellules et les tissus humains, sont représentatifs de la grande diversité de la plupart des maladies humaines mais ne sont pas toujours suffisants pour développer des biomarqueurs de traitements personnalisés pour les troubles neuropsychiatriques. De nombreuses biobanques disposent de tissus humains post mortem, néanmoins les collections de cellules neuronales humaines établies à partir de grandes cohortes de patients représentatives de la diversité humaine restent rares. La recherche en médecine personnalisée sur les troubles neuropsychiatriques dispose de deux outils de plus en plus utilisés : les neurones dérivés des cellules souches pluripotentes humaines et les lignées cellulaires lymphoblastoïdes humaines. Cette revue analyse et compare les avantages et les limites de chacun de ces outils pour la recherche en médecine personnalisée.

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