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In vivo modeling of neuronal function, axonal impairment and connectivity in neurodegenerative and neuropsychiatric disorders using induced pluripotent stem cells

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ABSTRACT

Modeling neurological diseases using human embryonic or patient-derived induced pluripotent stem cells (iPSCs) improves the understanding of molecular and cellular changes underlying these diseases and can lead to new, potentially personalized therapies. Changes in expression of axon guidance cues and altered cytoskeletal maintenance have been implicated in neurodegenerative and neuropsychiatric disorders. To date, most of the iPSC patient-derived cellular dysfunction and phenotypic studies have been performed in vitro. To study the intrinsic axonal impairments and neuronal connectivity deficits in human disease iPSC-derived neurons we propose to graft these cells into the physiological three-dimensional multi-structural environment of the central nervous system of rodent models to obtain relevant in vivo data. Such human iPSC in vivo chimeric models can allow for neuronal maturation, capture neuropathological phenotypes of axonal and connectivity impairments, and serve as target engagement and drug validation studies using human cells, thus highly relevant for advancement of the drug development process in the late pre-clinical stages.

Contents

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1. Introduction

The increased life expectancy and the size of today's world population contribute to the increased prevalence of neurodegenerative and neuropsychiatric diseases, with a large impact on societal health costs. In

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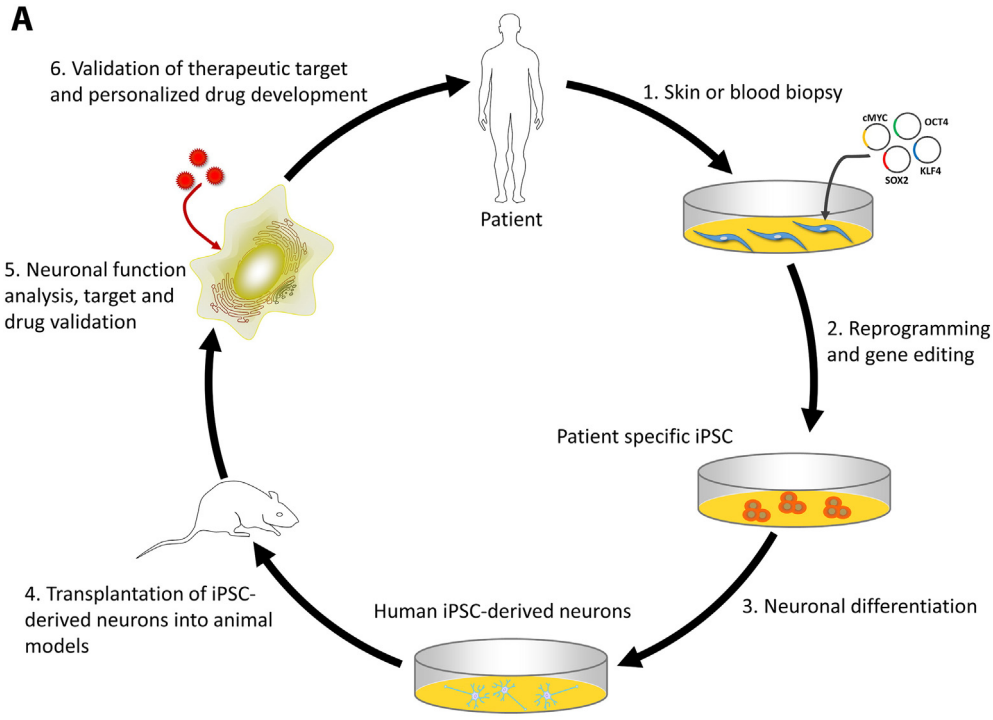
general, the practiced therapies for most of these diseases are referred to as symptomatic treatments and the causes of these diseases are still mostly unknown. One of the main challenges in the field of neuroscience research, in particular in the field of neuropsychiatric disease research, is the lack of adequate in vitro and in vivo models. Recent developments in disease modeling using patient-derived induced pluripotent stem cells (iPSCs) contribute to better understanding of the molecular and cellular changes causal to these diseases and new, potentially personalized therapies.

The adult central nervous system is thought to maintain neuronal circuitry patterns in part through continuous expression of axon guidance cues (Mironova and Giger, 2013). There is a potential dysregulation of axon guidance signaling and cytoskeletal structure in the adult central nervous in Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), schizophrenia and autism, which could have an impact on the etiology of these diseases by inducing alternative axonal plasticity and impairment in neuronal connectivity (further discussed below and reviewed by Van Battum et al., 2015). Transformed synaptic maintenance may trigger early degenerative changes in the years preceding the clinical diagnosis. Altered guidance during brain development may introduce a primary delay in growth or changes in neuronal circuits that can contribute to the development of neurological disease. It is possible that even minor fluctuations in neuronal circuitry can eventually lead to failure in accurate



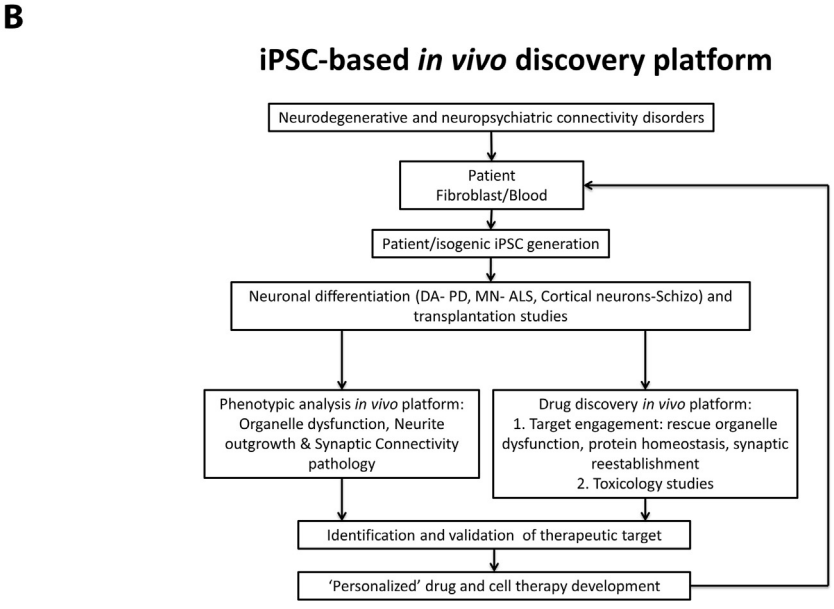


Fig. 1. Generation of iPSC based in vivo discovery platform. A. Flow and **B.** chart diagram showing the use of human iPSCs and iPS-derived young neurons from patients or patients at risk as tools to obtain a relevant in vivo phenotypic bioassay discovery platform used for analyses of neuronal functions altered in neurodegenerative and neuropsychiatric diseases. These models can further allow for drug target validation in pre-clinical research and personalized drug development. Abbreviations: iPSC- induced pluripotent stem cells, PD — Parkinson's disease, DA — dopaminergic neuron, MN — motor neuron, ALS — amyotrophic lateral sclerosis, Schizo — schizophrenia.

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