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Department of Pharmacy

PHARMA HIGHLIGHTS

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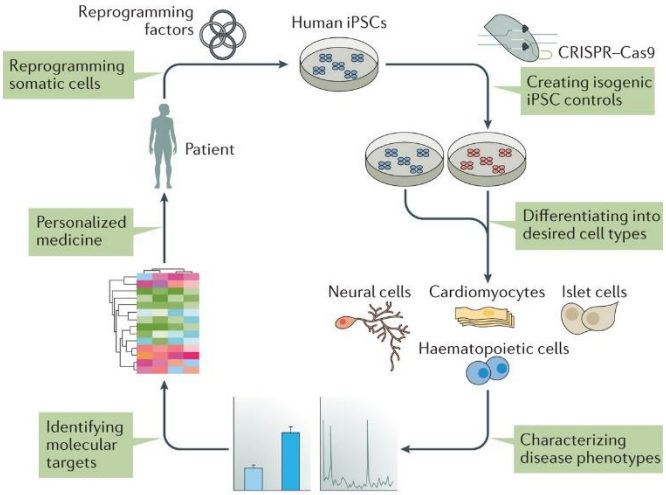
Induced Pluripotent Stem Cells for Disease Modelling and Cell-based Therapies



Since the emergence of induced pluripotent stem cell (iPSC) technology a decade ago, immense progress has been made in stem cell biology and regenerative medicine. iPSCs provide a unique platform to model certain human diseases in vitro and offer the potential to develop cell-transplantation therapies. In 2006, Shinya Yamanaka, a Nobel Prize winning Japanese scientist, made a remarkable scientific and medical breakthrough when he discovered that inducing the activation of a subset of pluripotency transcription factors could reprogram mouse somatic cells back to an embryonic-like state. OCT4, SOX2, KLF4, and c-MYC are the four transcription factors designated as the "Yamanaka factors' ' and the stem cells they produced are termed as induced pluripotent stem cells. These cells have the unique ability to differentiate into any type of cell in the body such as neurons, microglia, hematopoietic cells, macrophages, cardiomyocytes etc.

Human-cell derived iPSCs can be generated in the lab by reprogramming adult cells, such as skin fibroblasts or blood cells by treating them with the Yamanaka factors. Currently, patient-derived primary iPSCs are being widely used to model various diseases in order to obtain a better understanding of underlying pathogenic mechanisms. For example, patient-derived iPSCs from Parkinson's disease (PD) patients are being employed to elucidate disease pathology, uncover and distinguish among disease phenotypes, identify gene-linked PD biomarkers and to aid novel drug discovery. This can potentially lead to the discovery of disease biomarkers for early diagnosis and lead to the development of innovative therapeutic strategies to treat debilitating disorders like PD.

Apart from an excellent research tool, patient-specific iPSCs can also be employed for cell-transplantation therapy, after correction of genetic defects, to treat degenerative diseases by replenishing or replacing damaged or depleted cells in the body. As such, this technology has launched a new avenue in the field of personalized medicine whereby cell-based therapies can be designed using the patient's own cells. In 2014, the first clinical trial using patient-specific iPSC-derived retinal pigment epithelial cells (RPE) was launched for the treatment of macular degeneration, which was found to inhibit further macular degeneration and improved the patient's vision. Subsequently, in 2018, Takahashi and his team in Japan was the first to initiate a human clinical trial of iPSC-derived dopamine neuron transplantation to treat PD.

iPSCs are preferred over human embryonic stem cells because (hESC) because they do not involve destruction of the embryo and thus are devoid of any ethical concerns. Moreover, iPSCs can be developed from easily accessible somatic cells and they can be expanded indefinitely providing a constant supply of cells for research and therapeutic purposes. In addition, the advent of 3D organoid systems and CRISPR-based genome editing tools have made it a much more powerful platform enabling the simulation of the disease microenvironment. The use of iPSC-based disease modeling and cell therapy is still in its infancy. Despite the numerous benefits of iPSCs, there are a number of drawbacks that limit their use in various experimental settings such as, immunogenicity, tumorigenicity, loss of certain cell markers and chromosomal abnormalities. Stringent, well-defined quality control measures are also warranted to ensure their safety and efficacy in patients. Therefore, a lot of improvements and refinements are yet to be made to this excellent technology to enhance its utility further. Currently, research is underway to overcome these shortcomings and the scientific community is optimistic that iPSCs would revolutionize the treatment of various degenerative disorders in the near future.

Reference:
Shi, Y., Inoue, H., Wu, J. C., & Yamanaka, S. (2016). Induced pluripotent stem cell technology: a decade of progress. *Nature Reviews Drug Discovery 2016 16:2*, *16*(2), 115–130. https://doi.org/10.1038/nrd.2016.245

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Medication Errors

There are many different types of medications (medical products), and each one has a specific purpose. A medicine (a medicinal product) is defined as "a product that includes a substance with demonstrated biological effects, as well as excipients or excipients exclusively; it may also contain contaminants." However, the failure of the treatment process that results in, or has the potential to result in, harm to the patient is referred to as a medical error. When selecting which medication and dosage regimen to use (prescribing errors—irrational, inappropriate, and ineffective prescribing, under prescribing, and overprescribing), writing the prescription (prescription errors), manufacturing or dispensing the formulation (wrong strength, contaminants or adulterants, wrong or misleading packaging), administering or taking the medication (wrong dose, wrong label); or administering or taking the medication (wrong dose, wrong label); or administering or taking the medication (failing to alter therapy when required, erroneous alteration). Moreover, some prescription error cause ADRs, on rare occasions, a drug error may cause an unpleasant event that is not an ADR (for example, when a cannula penetrates a blood vessel and a hematoma results). According to a psychological taxonomy of errors, they may be divided into four categories: knowledge-based errors, rule-based errors, action-based errors, and memory-based errors. Despite the fact that pharmacological errors are rare and frequently insignificant, they do occur. Although they are seldom life-threatening, they are also uncommon and often inconsequential. Although they are difficult to detect, it is vital to do so because system failures that result in little errors may quickly escalate into major issues if left unaddressed. It is critical to encourage the reporting of errors by creating an environment that is free of blame and devoid of punitive measures. Prescription errors may be classified into a variety of categories, including illogical, inappropriate, and inefficient prescribing, under prescribing and over prescribing (together referred to as prescribing faults), as well as flaws in the prescription's writing process (including illegibility). Avoiding medication errors is crucial in balanced prescription, which is the use of a medicine that is appropriate for the patient's condition and, within the constraints imposed by the ambiguity that surrounds therapeutic options, in a dosing regimen that optimizes the balance of benefit to harm. A balanced approach to drug prescription means that the mechanism of action of the medication should be matched to the pathophysiology of the illness being treated.

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New FDA-Approved Drugs

When it comes to the development of new drugs and therapeutic biological products, FDA's Center for Drug Evaluation and Research (CDER) provides clarity to drug developers on the necessary study design elements and other data needed in the drug application to support a full and comprehensive assessment. To do so, CDER relies on its understanding of the science used to create new products, testing and manufacturing procedures, and the diseases and conditions that new products are designed to treat.

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1. **Adlarity (donepezil) Transdermal System**
   Company: Corium,Inc.
   Treatment for: Alzheimer's Disease
   Adlarity (donepezil transdermal system) is a once-weekly transdermal formulation of the approved acetylcholinesterase inhibitor donepezil indicated for the treatment of Alzheimer's type dementia.

2. **Nasonex 24HR Allergy (mometasone furoate monohydrate) Nasal Spray**
   Company: Perrigo Company plc
   Treatment for: Allergic Rhinitis
   Nasonex 24HR Allergy is a corticosteroid nasal spray available over-the-counter for the temporary relief of the symptoms of hay fever or other upper respiratory allergies.

3. **Ztalmy (ganaxolone) Oral Suspension**
   Company: Marinus Pharmaceuticals, Inc.
   Treatment for: CDKL5 Deficiency Disorder
   Ztalmy (ganaxolone) is neuroactive GABA-A receptor positive modulator indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD).

4. **Opdualag (nivolumab and relatlimab-rmbw) Injection**
   Company: Bristol Myers Squibb
   Treatment for: Melanoma
   Opdualag (nivolumab and relatlimab-rmbw) is programmed death receptor-1 (PD-1) blocking antibody and lymphocyte activation gene-3 (LAG-3) blocking antibody combination indicated for the treatment of unresectable or metastatic melanoma.

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