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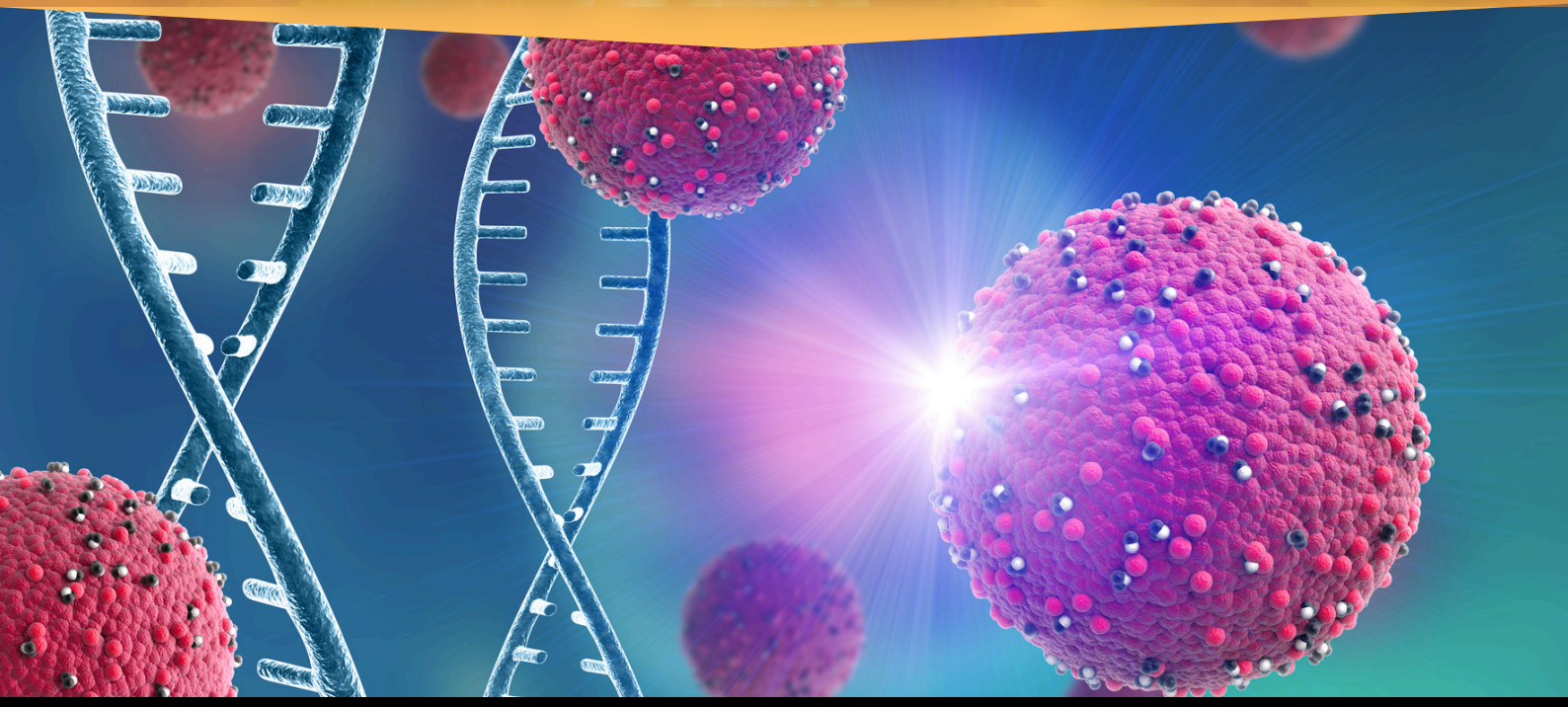
PRESCRIPTION

Latest news and updates from the Faculty of Pharmacy, Universiti Teknologi MARA



FROM BENCH TO BEDSIDE:

iPS Cells at the Frontier of Drug Discovery

By: Dr. Nurfarhana Ferdaos

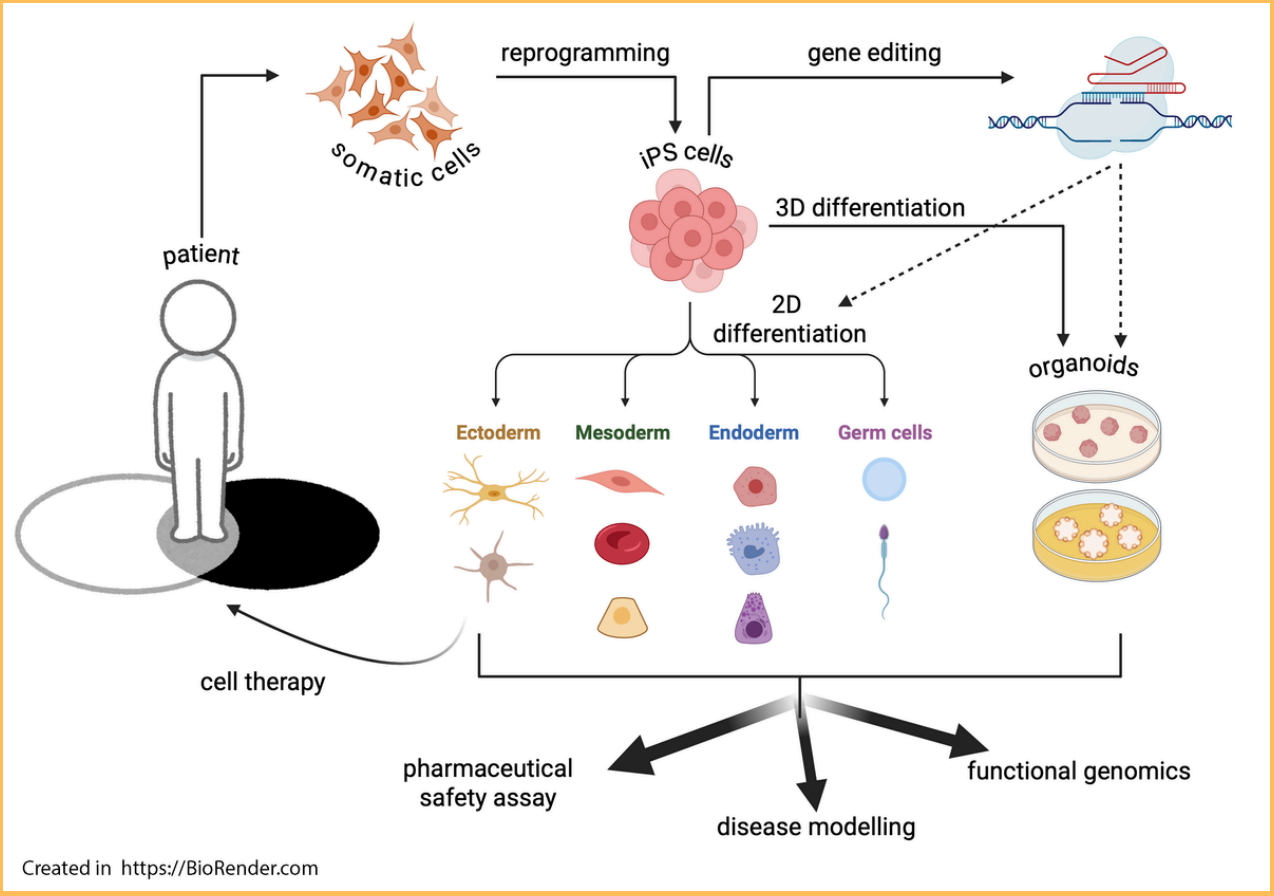
Developing new medicines is often a long and uncertain endeavour. The 'valley of death' in drug discovery is recognised as the disparity between preclinical findings and clinical translation, which results in nearly 96% of failed drug candidates (Akhtar, 2015). This crisis is mainly due to the inaccuracy of animal models in recapitulating human disease biology, which calls for a more relevant preclinical model that can predict clinical outcomes (Van Der Worp et al., 2010; Waring et al., 2015). Developing human-based in vitro assays is therefore crucial for preventing the use of faulty substances in clinical trials, which poses unnecessary risks for patients, as well as avoiding wasting time and resources, given the rising cost of drug development.

IN THIS ISSUE :

The discovery of induced pluripotent stem (iPS) cells by Takahashi and Yamanaka has revolutionised biomedical and pharmaceutical research, allowing the generation of any type of cell in unlimited supplies without ethical controversies (Takahashi et al., 2007). This technology is based on the overexpression of Yamanaka factors in somatic cells, resulting in the reversal of somatic cell fate to the embryonic state, forming human embryonic stem cell-like cells with pluripotent ability – the second highest form of potency in development. In other words, iPS cells can be differentiated into any cell type of the three germ layers. As cardiotoxicity and hepatotoxicity are the main safety issues in drug development, cardiomyocytes and hepatocytes can be derived from iPS cells in large amounts, which is crucial for high-throughput screening. This approach is more advantageous than using primary or immortal cell lines, as the former has limited proliferative capacity and the latter lacks physiological relevance due to genetic alterations. In addition, iPS cells are a great source of cells that are difficult to access, such as human neuronal cells, which transform drug discovery for neurological disorders.

With Nobel Laureate Prof. Shinya Yamanaka, who discovered iPS cells and is the director emeritus of CiRA.

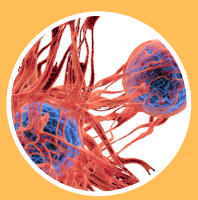
iPS cells are also excellent for modelling human-specific diseases, which are key to testing drug efficacy and precision medicine (Kleiman and Engle, 2021). This advantage is due to the feasibility of establishing iPS cells from both diseased and healthy patients, which also captures their genetic information. Phenotypes of both diseased and healthy iPS cells can be compared upon differentiation. Alternatively, disease modelling using iPS cells can be achieved with gene editing, such as CRISPR-Cas9 or base editing, such as Prime editor. Desired targets may include point mutations, which are known to be the most common human pathogenic variants (Rees and Liu, 2018), or single nucleotide polymorphisms, which are known to be responsible for variable drug responses (Jmel et al., 2024). iPS cells are especially powerful in this respect, as isogenic controls can be established.

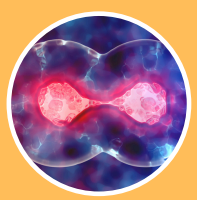


Furthermore, recent advances have reported that disease modeling in iPS cells has entered the third dimension (3D), allowing more accurate recapitulation of human physiology compared to animal models. The combination of iPS cell culture with scaffolds facilitates cell-cell interactions, resulting in the formation of mini organs known as organoids, with higher complexity than monolayer cultures. For example, human iPS-derived cerebral organoids contain outer subventricular zone (oSVZ) cortical neurons, which are important for the elaborate expansion and diversity of the human cortex (Walsh et al., 2024).

These cells are absent in monolayer cultures and in mice, highlighting the value and accuracy of iPS cell-derived organoids. Similarly, iPS-derived hepatocyte organoids are able to produce metabolic enzymes, which are lacking in both monolayer and primary cultures, as well as in mice (Luce, Messina and Duclos-Vallée, 2025).

Therefore, iPS-derived organoids are functionally more relevant than existing preclinical models and may potentially overcome 'the valley of death'.





My research aims to harness the power of iPS cells to create more reliable models for drug discovery. By differentiating iPS cells into key cell types in drug safety screening, such as cardiomyocytes or hepatocytes, as well as into inaccessible cell types such as neurons, the goal is to build a robust triage system for testing various compounds from our diverse medicinal plants. This approach could better predict the safety and effectiveness of therapeutic compounds earlier in the development process; therefore, it is more cost-effective and reduces harm to laboratory animals. As iPS cell applications sit at the intersection of frontier technologies (i.e., organoid, gene editing) and pharmaceutical innovation, I look forward to uncovering how iPS cells can transform the way we discover and develop new medicines.

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About the author

Nurfarhana Ferdaos (PhD) is a senior lecturer in the Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, UiTM. She obtained her PhD from the University of Edinburgh under the supervision of Prof. John Mason, where she pioneered the application of embryonic stem cell-derived cerebral organoids (in Mason's lab) to study neurodevelopment. She recently completed her postdoctoral research at the Centre for Induced Pluripotent Stem Cell Research and Application (CiRA), Kyoto University, working with Assoc. Prof Knut Woltjen. Her postdoctoral project involved establishing and refining a cellular rejuvenation protocol using reprogramming technology, which also involves other key techniques such as mRNA synthesis, flow cytometry, and iPS cell culture. She also analysed omics data from RNA and miRNA sequencing and is therefore equipped with the bioinformatics skills required for big data analysis. She is fascinated by the potential of iPSCs and is therefore highly motivated to apply her knowledge upon returning to Malaysia.

TODAY'S QUIZ

1 WHAT IS THE IMPORTANCE OF DEVELOPING HUMAN-BASED IN VITRO ASSAYS IN DRUG DISCOVERY?

- **A** To improve clinical translation
- **B** To prevent unnecessary risks for patients
- **C** To follow the principles of 3Rs (Replacement, Reduction, Refinement) in animal studies
- **D** All of the above

ANSWER: D

2 WHY ARE IPS CELLS AT THE FRONTIER OF DRUG DISCOVERY?

- **A** Unlimited source of cells for drug screening and toxicity studies
- **B** Accurately model human-specific physiological processes
- **C** Amenable to genetic modification, allowing mechanistic studies
- **D** All of the above

ANSWER: D

3 HOW CAN DISEASES BE MODELED USING IPS CELLS?

- **A** Perform reprogramming directly in somatic cells from diseased patients, followed by cell differentiation
- **B** Induce mutation in healthy iPS cells by gene-editing, followed by cell differentiation
- **C** Make organoids from healthy iPS cells
- **D** A and B

ANSWER: D