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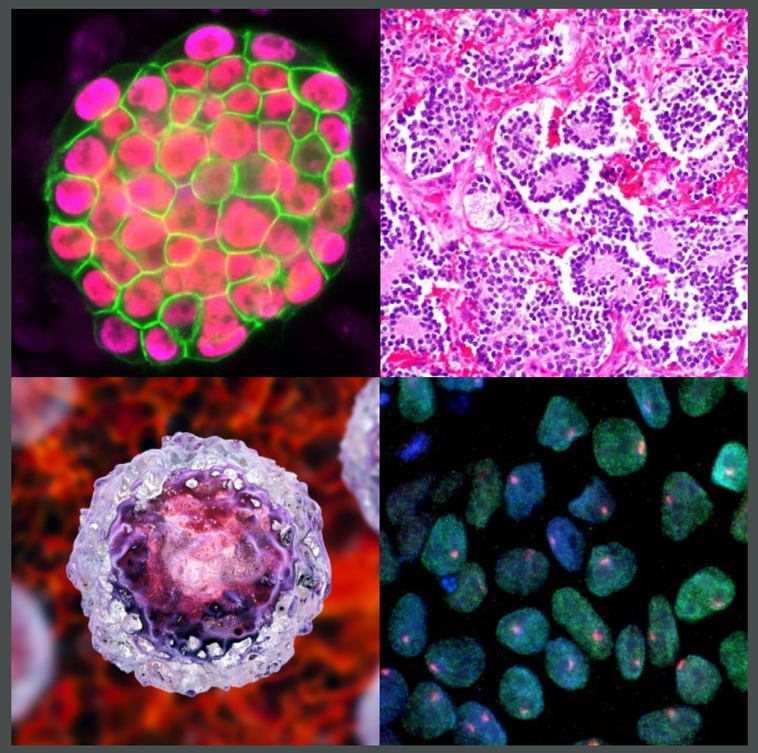

A Brief Guide to Induced Pluripotent Stem Cells

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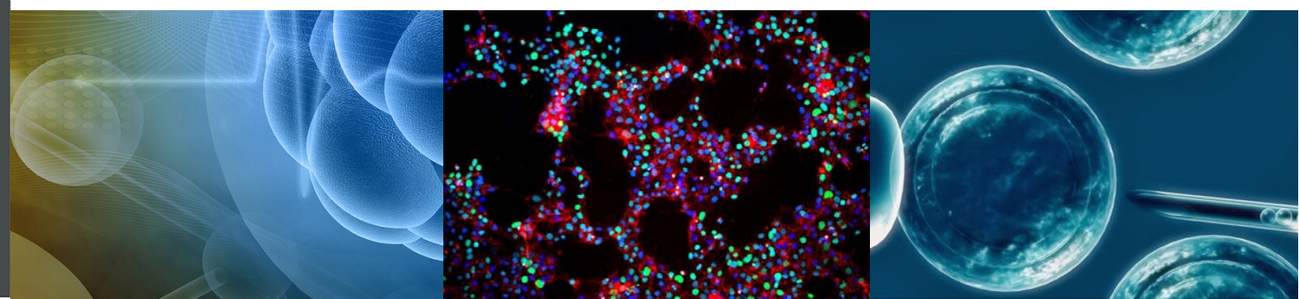

Induced Pluripotent Stem Cells research overview

Pluripotent stem cells are progenitors which stand at the top of stem cell hierarchies and can give rise to any cell type in the body. In mammals, pluripotent stem cells arise after fertilization within the inner cell mass of the early developed embryo and disappear quickly during development. Because of their origin, these are known as embryonic stem cells (ESCs). These cells represent the originating cells of human life and carry all of the biological codes that are required for tissue development and maintenance throughout a lifetime. Because of these critical roles the study of pluripotent stem cells has always been of fundamental interest, and has enhanced our understanding of both developmental biology and human diseases. Furthermore, research in pluripotent stem cells has also inspired innovation and rapid growth in regenerative medicine.

In 2006, the field of stem cell biology witnessed a major milestone which fundamentally changed the field by overcoming obstacles of resource shortage and ethical concerns relating to human ESCs. Shinya Yamanaka discovered that mature cells can be reprogrammed and become pluripotent by reactivating their internal pluripotent network. He named the cells induced pluripotent stem cells (iPSCs).

The outstanding potential of iPSCs is exhibited by their similarity to ESCs but much easier accessibility. Like ESCs, iPSCs can self-renew and grow indefinitely under suitable laboratory conditions. The cells have the potential to differentiate into every cell type. iPSCs can be efficiently produced from many types of different mature somatic cells, such as skin fibroblasts. Because they contain the genetic information of the donor, iPSCs have provided a new way to create patient- or donor-specific cell banks for a wide range of research and clinical applications.

Importance of Induced Pluripotent Stem Cells?

iPSC technology provides researchers with greater ability to obtain sufficient donor-specific cellular samples, creating the possibility to study disease mechanism(s) in a patient-dependent manner and significantly facilitates a personalized therapeutic development.

In more traditional approaches the study of human disease involved the use of animal models and pathological tissue specimens and cells harvested from patients. However, the former can lead to inaccurate results because of biological differences between human and other species. This explains why many drug candidates succeed in preclinical studies and fail in clinical assessment. Secondly, although patient specimens are valuable in revealing disease phenotypes, these may not always be available, because of rareness, mortality or risk induced by tissue harvesting.

The iPSC-based modelling approach comprehensively addresses these issues where minor and minimally invasive procedure is required for harvesting patient tissue from, for example, skin, blood or urine. Reprogramming helps to turn these somatic cells into iPSCs to re-gain the capacity of unlimited growth and pluripotent differentiation. iPSCs are generally used as a sustainable resource for producing mature cell types. The use of patient-derived iPSCs facilitates the fidelity of disease phenotypes, enhancing the probability of success in drug discovery.

In addition, the field of tissue regeneration also strongly benefits from iPSC technology. Tissue repair is often hampered due to limited self-regenerative capacity. Tissue engineering applications, utilising cells to rebuild organs, may be hindered by the limited cell supply. iPSC technology supports the feasibility of large-scaled autologous cell therapy and tissue regeneration.

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Current research in Induced Pluripotent Stem Cells at National University of Ireland Galway (NUIG) and how this could impact industry?

Our research focuses on applying stem cells for investigation and therapeutic innovation of osteoarthritis, which is the most common form of joint disease and a leading cause of disability worldwide. Unfortunately, the global burden of osteoarthritis is still rapidly increasing as a result of age, lifestyle and obesity and there is yet no approach to prevent, cure and reverse disease progression.

The slow pace of therapeutic development is partially due to limited understanding of disease mechanisms. In our study, we applied iPSC-derived disease models and successfully uncovered the principle of hereditary osteoarthritis. iPSC technology allowed us to turn patients' skin fibroblasts into cartilage chondrocytes. This revealed the novel association between the gene mutation, chronic cell stress to defective cartilage formation. In the future, these iPSC models will help on drug screening to discover new treatment for familial osteoarthritis.

Apart from disease modelling, we also research the feasibility of using iPSCs as a source of mesenchymal stem cells (MSCs) for treating osteoarthritis. The difficulties in obtaining MSCs from adult tissues is an obstacle but, given their remarkable growth and differentiation capacities, iPSCs may become an alternative source for producing unlimited MSCs to meet the needs of large-scale clinical application. The overall aims of our ongoing projects are (1) to develop an optimal process for differentiating iPSCs into MSCs; (2) to evaluate the quality and function of iPSC-derived MSCs in treating osteoarthritis and (3) to upgrade this system into an automated platform.

Taken together, achieving these research ambitions requires active cooperation between academia and industry. Under the CALIN programme, our research topics can generate new collaboration opportunities and attract companies with matching research interests to enhance their competitive strength in the cell therapy market.

Application of research into Induced Pluripotent Stem Cells?

Since its beginning in 2006, iPSC technology has been gradually introduced into multidisciplinary areas and has made remarkable contributions in different aspects. A rapidly accumulated knowledge of cell reprogramming and differentiation supports the innovation in iPSC-related fields.

Consistently optimized reprogramming methods allow researchers to created iPSC from a wide array of different cell types, facilitating sample collection from patients with specific conditions. According to the global human pluripotent stem cell registry (hiPSCreg), the number of registered iPSC lines has doubled annually since 2014 and, as of July 2020, there are 2385 iPSC lines recorded.

These iPSC lines containing diverse and unique genetic information, making them tremendously valuable in disease studies and drug screening. Between 2006 and 2016, there are 3323 iPSC-related articles published. Based on the research focuses, iPSCs have been extensively used in understanding neurodegenerative diseases. The findings from these work have successfully driven the pharmaceutical innovation, such as treating Parkinson's disease with RTB101 (ongoing Phase 1b/2a trial). Notably, the application of iPSC-based models is also steadily increased for other pathological conditions, including cardiac, musculoskeletal, immunological and respiratory diseases.

Furthermore, with the concerted efforts of the academic community, more and more approaches are developed to differentiate iPSCs into different cell types. Effective cell lineage manipulation facilitates the development of iPSCs-based novel autologous cell therapy. The first wave of clinical trials predominantly focuses on treating retinal degeneration in the eye. To date, this number has risen to 53 and the disease category has expanded from tissue degeneration to steroid-resistant acute graft-versus-host disease and acute myeloid leukaemia.

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Summary

Pluripotent stem cells hold great promise for unravelling mechanisms of human development, modelling diseases and tissue regeneration. However, the destruction of human embryos is an essential step for harvesting the cells, which raises ethically and politically controversial. iPSC technology creatively offers a new strategy to generate pluripotent stem cells from mature body cells. Attractively, iPSCs not only remain the critical features similar to embryonic stem cells but also can be produced from patients or healthy individuals in a manner not possible before. Own to the same genetic background as their donor counterpart, iPSCs have propelled the fields of personalized pharmacological treatment and autologous cell therapy. Importantly, iPSCs provide sufficient donor-specific cell sources, which supports the development of large-scale applications.

Furthermore, the iPSC approach is also working closely with other modern technologies to enhance their capacity in various medical application. For instance, CRISPR-Cas9, a tool of gene editing, has been used to correct the mutation in iPSCs. After treatment, patient iPSCs can produce healthy cells to replace the disease ones in the body. Besides, the development in the fields of biomaterial and bioprinting supports the creation of iPSC-derived 3D tissue organoids. Although the research is still in its early phase, encouraging results have shown the possibility of producing skin tissue, cartilage, bone and blood vessel from iPSCs.

The discovery of iPSC technology has driven revolutionary in many biological-related fields, the potential of which is given hope to develop new treatments for currently incurable diseases. However, undoubtedly, before reaching the full potential of iPSCs, there are many technical hurdles and knowledge gaps needed to be overpassed. It will request worldwide collaborations with scientists from different areas to solve the current and future challenges.

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