

EDITORIAL

DISEASE MODELLING AND DRUG DEVELOPMENT WITH IPSC-DERIVED CELLS: A BRAVE NEW WORLD?

DESENVOLVIMENTO DE MODELOS DE DOENÇAS E DE MEDICAMENTOS A PARTIR DE CÉLULAS ESTAMINAIS PLURIPOTENTES INDUZIDAS (iPSC): UM ADMIRÁVEL MUNDO NOVO?

Natália Oliva-Teles^I

According to the National Institutes of Health (NIH, USA), induced pluripotent stem cells (iPSC) are “adult cells that have been genetically reprogrammed to an embryonic stem cell-like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells”.¹ In 2006, the remarkable studies of induced pluripotency of somatic cells led to the attribution of a Nobel Prize to Shinya Yamanaka who, with his colleagues, demonstrated the ectopic expression of Oct3/4, Sox2, Klf4 and c-Myc as the four fundamental transcription factors in mouse fibroblasts, reprogramming these cells to mouse iPSC.² Human iPSC were first reported a year later, in late 2007, and from the first establishment of these cells the expectation was that they would “work” as pluripotent stem cells and might be considered “clinically similar” in any number of ways; in other words, the *rationale* behind iPSC research in humans was to create cells *in vitro* by using reprogramming mechanisms that would be used as models for diseases for which there still is no cure, thus becoming invaluable in translational medicine. The ethical issues behind the use of human embryos for producing pluripotent cells for human use and clinical treatment were over!

Initially derived from human skin fibroblasts and blood cells, iPSC have also been successfully obtained from, among other cell types, keratinocytes (hair follicles) and bone marrow cells. Several methods for reprogramming have been perfected using different factors; during the last decade scientific enthusiasm has continually increased leading to the development of more and more advanced techniques in culturing and reprogramming of iPSC that may have diverse medical applications such as cell therapies (ex: diabetes, cardiac infarctions), drug discovery (ex: ezogabine for epilepsy) and toxicology screening to detect unanticipated adverse effects of experimental drugs in humans.³ Although a great advantage of these cells is their extraordinary capacity of division making them invaluable resources for cost-effective drug development and much less time consuming disease developmental studies their efficiency constantly needs to be improved. Cell reprogramming has become a reality and completely novel opportunities have been opened to disease developmental studies and 3D organoid-based approaches, as demonstrated by recent clinical trials.⁴

Apart from the generation and reprogramming of cell cultures both from patients and controls, several steps must occur before safe application in humans is achieved namely mutation analysis, mycoplasma detection and karyotype analysis – in order to confirm a normal chromosomal constitution without polyploidy, gain or loss of chromosomes and large chromosomal aberrations.^{5,6} The main objective of validating iPSC cell lines successfully is to search and establish molecular phenotypes and mechanisms that will mimic human conditions, such as genetic disorders and degenerative diseases and, ultimately, enable disease modelling and new therapeutic approaches.⁷ Although iPSC technology still needs refining, it certainly is one of the most innovative breakthroughs and promises to deliver hope for scientists, clinicians and patients.

I. Centro de Genética Médica Jacinto de Magalhães; Centro Hospitalar Universitário do Porto. 4099-001 Porto, Portugal.

II. Unit for Multidisciplinary Research in Biomedicine, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto (UMIB/ICBAS, UP). 4050-313 Porto, Portugal. natalia.teles@chporto.min-saude.pt

REFERENCES

1. NIH Stem Cell Information Home Page. In Stem Cell Information [World Wide Web site]. Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2016 [cited March 23, 2020] Available at <https://stemcells.nih.gov/info/basics/6.htm>.
2. Elliott MS, Barbar L, Tesar PJ. Drug screening for human genetic diseases using iPSC models. *Human Molecular Genetics*. 2018; 27:R89–R98.
3. Karagiannis P, Takahashi K, Saito M, Yoshida Y, Okita K, Watanabe A, *et al.* Induced pluripotent stem cells and their use in human models of disease and development. *Physiol Rev*. 2019; 99:79-114.
4. Ilic D, Devito L, Miere C, Codognotto S. Human embryonic and induced pluripotent stem cells in clinical trials. *British Medical Bulletin*, 2015, 116:19–27.
5. Yamanaka S. Induced Pluripotent Stem Cells: Past, Present, and Future. *Cell Stem Cell*. 2012; 10:678-84.
6. Ustyantseva EI, Medvedev SP, Vetchinova AS, Illarioshkin SN, Leonov SV, Zakian SM. Generation of an induced pluripotent stem cell line, ICGi014-A, by reprogramming peripheral blood mononuclear cells from a patient with homozygous D90A mutation in SOD1 causing Amyotrophic lateral sclerosis. *Stem Cell Res*. 2020; 42:101675.
7. Rodríguez-Traver E, Díaz-Guerra E, Rodríguez C, Arenas F, Orera M, Kulisevsky J, A collection of three integration-free iPSCs derived from old male and female. *Stem Cell Research*. 2020; 42: 101663.