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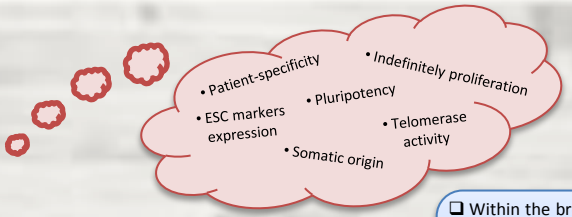
Induced Pluripotent Stem Cells
Medical and Biomedical Potential Applications



Stem cell-based therapies

❑ Within the broad field of regenerative medicine, iPSC are just one more tool for performing stem cell-based therapies, therefore called **iPSC-based therapies**.

This kind of treatment consists of iPSC acquisition from a patient's somatic cells by means of reprogramming. iPSC achievement, combined with their main properties i.e. unlimited proliferation, pluripotency, and *in vitro* state, is the basis for patient-specific treatment as far as iPSC-derived cells may be transplanted back into the patient in an autologous-manner. This application may involve two strategies, both of which harness the possibilities offered by the successful prevention of immune rejection: the first is that iPSC may serve as a stem-cell pool, and the second is that iPSC can provide a means for targeted gene-repair.

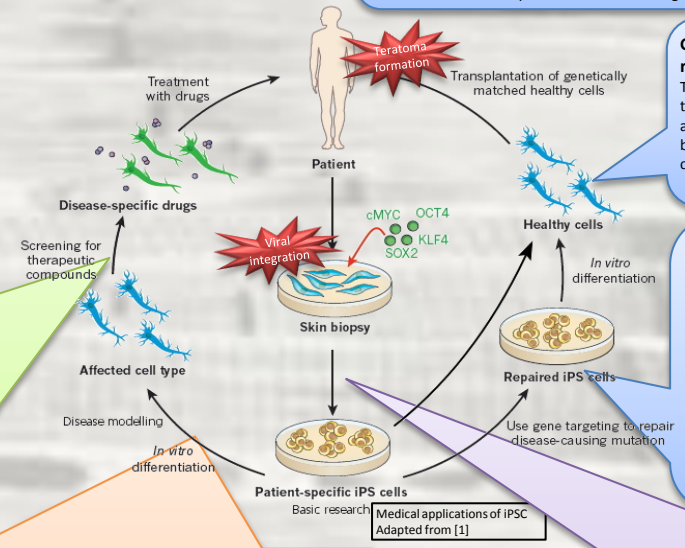
Pharmacological-related applications

❑ **Drug studies or testing** on iPSC lines include activities which range from evaluating the effect of a drug on a particular or many cell types, either healthy or affected by a disease, to analyzing the response of one patient's cells to one or various drugs.

Many combinations are possible: testing may be carried out either on healthy or affected iPSC-derived cell types, which in turn may be patient-specific or not. Simultaneously, pharmacological actions may be evaluated at a disease level or at a personalized level. The variety of possible trials that may be performed include:

- Studying cellular response to a drug, either on healthy or affected cells.
- Studying the properties of a particular drug, such as toxicity, on different cell lines that show the same pathological condition.
- Comparing the effect of different drugs either in one or various disease models, for instance in the event they represent different diseases which affect the same cell type.
- Personalized therapies by testing drugs on patient-specific iPSC-derived cultures: firstly choosing the best drug for the treatment of the obtained cells from a patient's iPSC, and secondly, subsequent analysis of the appropriate levels, dosages, toxicity, adverse effects

iPSC would simplify pharmaceutical procedures because drugs could be tested in high quantities of specialized cells, thus avoiding the use of animals, or at least, reducing their number. Through the development of iPSC lines, metabolic *in vitro* studies could be improved, as could toxicological trials.



Medical applications of iPSC
Adapted from [1]

Gene repair coupled with cell-replacement therapy

This involves genetically manipulation of iPSC to make them either:

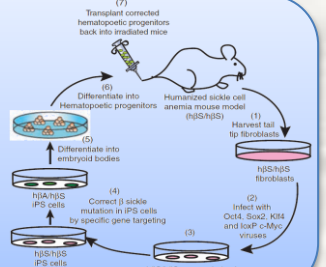
a) Produce a protein
b) Silence the expression of a protein
c) It is possible even to correct specific mutations by means of homologous recombination in iPSC

Establishing a pool of cells

In order to let iPSC proliferate and form a pool that will serve as a source of cells for differentiating and transplanting into patient's cells-lacking tissues. This pool may serve to renew a cell population that has been or is being destroyed by a pathology.

SICKLE-CELL ANAEMIA

Based on mouse model for sickle cell anaemia, skin fibroblasts were first reprogrammed into iPSC. These iPSC were applied targeted genetic therapy, in order to repair the mutation responsible for the disease. Lastly, repaired iPSC were induced to differentiate into blood cell precursors and were subsequently transplanted into the bone marrow in the same anaemic mice. As a result, they were able to produce normal red blood cells, recovered from the anaemia.



Scheme for *in vitro* reprogramming. From [3]

Disease modeling

❑ iPSC represent a new tool for **modeling particular diseases in culture**, i.e. *in vitro*. This enables the study of particular human diseases' pathogenesis, identification of new diagnosis markers or new therapeutic agents, as well as serving as a basis for other iPSC applications.

The generation of disease models based on iPSCS is possible either since these cells retain the same disease genotype as that of the patient from whom they were derived (interesting for genetic diseases modeling); or otherwise, thanks to the possibility of modifying iPSC in order to make them acquire the phenotype of interest, by means of genetic manipulation or not.

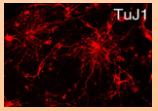
❖ Studying pathogenesis: studying the molecular basis of a disease is an essential to the identification of new diagnosis markers and new therapeutic agents. These models also offer access for determining several aspects of the affected cells in the disease: such as metabolic abilities, drug susceptibilities, resistance or susceptibility to suffer the disease, etc.

❖ Disease treatment: disease models in a dish allow for testing different drugs on the affected cells, which may be patient-specific or not. This represents a very effective way for determining the most effective therapeutic agent.

Since 2008, when first disease model was defined – it showed the phenotype for spinal muscular atrophy (SMA), many iPSC lines have been established, including models for both hereditary and sporadic diseases. However many requirements are needed in order to accept an iPSC line as a disease model, and they are not fulfilled yet. Few from all the large list
of already modeled diseases are:

- SMA
- Parkinson's Disease
- Alzheimer's Disease
- Type 1 Diabetes mellitus
- Fanconi's anaemia
- Sickle-cell anaemia

iPSC colonies derived from fibroblasts of a PD patient with *SNCA* triplication



iPSC differentiation into dopaminergic neurons

Central image: Procedure for generating a disease model would be as depicted in the scheme - iPSC can be achieved from differentiated somatic cells belonging to a patient with the disease of interest (skin biopsy) and subsequent culture and differentiation will provide the in vitro model for the disease.

Basic research

❑ **Basic research** is the study -discovery and understanding- of fundamentals, in this case, related to biology fields. iPSC offer here several possibilities:

❖ Studying iPSC themselves: iPSC still account with limiting features when trying to use them in clinics, so further research is needed to solve them. Furthermore, reprogramming methods must be improved and cheapened; *in vitro* iPSC differentiation programs must be standardized; and importantly, both similarities and differences in comparison with ESC have yet to be unraveled.

❖ Studying cell biology: iPSC prevent the need for living tissues since they can give rise to any tissue's cells.

❖ Studying early embryonic development: iPSC cultures may allow researchers to follow cellular differentiation during initial stages of development, and even to find out how to orchestrate it *in vitro*.

❖ Studying replication and differentiation-associated pathology: it is not know yet what precise mechanisms underlie some illnesses which develop due to replication or differentiation defects, such as tumor formation. In this sense, these mechanisms could be extrapolated from those studied in iPSC. A better knowledge would help us to develop new therapeutic tools.

References

1. ROBINTON, D. A. DALEY, G. Q., 2012. <<The promise of induced pluripotent stem cells in research and therapy>>. *Nature, 481:* 295-305.
2. DREWS, K., et al., 2012. <<Human induced pluripotent stem cells--from mechanisms to clinical applications>>. *Journal of Molecular Medicine (Berlin, Germany), 90:* 735-745.
3. HANNA, J., et al., 2007. <<Treatment of sickle cell anaemia mouse model with iPS cells generated from autologous skin>>. *Science (New York, N.Y.), 318:* 1920-1923.

For more information: Bachelor's degree Final Project – CANALS, B. 2013. << Induced pluripotent stem cells. Medical and biomedical potential applications>>. *UAB - DDD*