# Andalusian Laboratory for Cell Reprogramming (LARCEL)

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## Institutions

**LARCEL,** Andalusian Laboratory for Cell Reprogramming
**BIONAND,** Andalusian Centre for Nanomedicine and Biotechnology
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## Keywords

Cell reprogramming, iPSCs, stem cells, neurodegenerative disease, disease modeling

## Research Lines

- ✓ Somatic cell reprogramming analysis. Identification of new factors involved in the process and analysis of pathways involved.
- ✓ Disease in a dish. Use of cell reprogramming for neurodegenerative disease modeling
- ✓ Zebrafish as a model to study cell reprogramming
- ✓ Spinal cord injury : use of iPSC derived Neural stem cells transplantation as a possible therapy.

## Scientific Activity

Our long-term goal is to provide new insights into cellular reprogramming by analyzing molecular pathways, and identifying new factors that could play an important role in cell reprogramming. The results of our work will inform the development of safe and efficient cell reprogramming protocols to be tested in pre-clinical and clinical models of human disease.

Cell reprogramming is also used in our laboratory for neurodegenerative disease modeling. Whether or not a disease can be treated often depends on whether we can gain a good understanding of its basic biology. Disease modelling using iPSC technology allows scientists to explore how a disease works in the laboratory, to search affected pathways and alternative treatment.

### Research lines:

✓ **Somatic cell reprogramming analysis. Identification of new factors involved in the process and analysis of pathways involved**

Cellular reprogramming, briefly defined as the transformation of an specialized cell into another of a different type. When referring to cellular reprogramming in the context of induced pluripotent cells (iPSCs) we can distinguish a first step called dedifferentiation, where cells reach a pluripotent stage and subsequently induced to differentiate into specific cell types. This phenomenon was described for the first time in 2007 by two laboratories simultaneously, Prof. S. Yamanaka and Prof. J.Thomson, showing human fibroblasts transformation to pluripotent cells (iPSCs) through ectopic expression of four transcription factors (OCT4, SOX2, KLF4 and c-Myc or OCT4, SOX2, NANOG and LIN28 respectively).

Although theoretically this is a “simple” protocol, cellular reprogramming is still a very inefficient process and more importantly, the molecular mechanisms governing the transformation of a somatic cell into an iPSC are still not completely understood.

Cell reprogramming is also associated with cellular transdifferentiation, that is a cell from one differentiated lineage is transformed into a different differentiated cell e.g. from fibroblast to sperm without having to be go through the process of dedifferentiation first. While theoretically more simple, this approach is inefficient and is still at stages of development that are even more primitive than iPSC technologies. Nonetheless it has great appealing for future applications in cell therapy due to its safety, and therefore must be pursued in parallel with more established strategies.

✓ **Disease in a dish. Use of cell reprogramming for neurodegenerative disease modeling**

Induced pluripotent stem cells (iPSCs) use is particularly useful for the study of rare diseases, specifically in neurodegenerative diseases. Nervous tissue samples from patients are rarely accessible and animal models, often do not recapitulate all characteristic of the disease.

The discovery that somatic cells from patients affected by neurological disorder can be reprogrammed to a pluripotent state (iPS cells), and once reprogrammed, these cells can expand and differentiate into specific populations of neurons, opened a promising field for research and understanding the molecular and cellular basis of these abnormalities and the development of specific drugs.

Our short term goal is to generate iPSCs and specific cell types affected in different neuropathies such as Ataxias, multiple sclerosis, West syndrome and Huntington disease among others, and to develop in vitro models in which perform functional assays to uncover altered cellular pathways that may explain the origin of the specific pathological states. Through scientific collaborations we anticipate the discovery of new drug targets that may enable the development of pharmacological interventions.

- ✓ **Zebrafish as a model to study cell reprogramming**

We study the role of certain non-canonical histone during zebrafish development to bring light to reprogramming process.

- ✓ **Spinal cord injury**

We are developing a pre-clinic study for iPSC-derived NSC transplantation into a rat model of cervical spinal cord injury.

## Collaborations

- ❖ **Michigan State University** (USA). Jose B. Cibelli, cell reprogramming and cell nuclear transfer.
- ❖ **Houston Methodist Hospital** (USA). Phillip Horner. Spinal Cord Injury cell therapy.
- ❖ **Virgen del Rocío Hospital** (Sevilla, Spain). Javier Marquez. Spinal cord injury cell therapy.
- ❖ **Spanish National Cell Bank** (Barcelona, Spain). Ana Veiga. Spinal cord injury cell therapy.
- ❖ **CABIMER, Andalusian Center for Regenerative Medicine** (Sevilla, Spain). Manuel A. Dolado. Friedreich Ataxia cell transplantation modeling.
- ❖ **Universite Claude Bernard Lyon** (France). Jordane Biarc. Proteomic analysis of secreted factors.

## Research Projects in the last 5 years

- Optimization of cell reprogramming using oocyte specific factors. Fundación Pública Andaluza Progreso Y Salud (Andalusian Health Minsitry own funds) (2015-2016). PIs: Jose Cibelli and Elena Gonzalez muñoz
- Multidisciplinary action for Rare disease and personalized medicine. Huntington disease modeling. AMER (FEDER-INNTERCONECTA R+D statal program) (2013-2016). PIs: Jose Cibelli y Elena González Muñoz
- Generation of cellular models of multiple sclerosis disease using the oligodendrocytic cell types obtained by autologous somatic cell reprogramming. Fundación Genzyme (2015-2017). PI: Elena Gonzalez Muñoz
- Molecular and epigenetic study of adult somatic cell reprogramming, and application in disease modeling for potential therapies. Spanish Economy Ministry. Associated project to “Ramón y Cajal” program (2016-2021). PI: Elena Gonzalez Muñoz
- Adult somatic cell epigenetic reprogramming: New factors involved. SAF2015-66105-R. Spanish Economy Ministry. Project I+D+I, National program for research, development and innovation (2016-2020). PI: Elena González Muñoz
- Preclinical Study using neural stem cells derived from induced pluripotent stem cells for the treatment of spinal cord injury. PI14/00429. Instituto Nacional Carlos III (2015-2017). PI: Jose B. Cibelli
- Developing New Inbred Zebrafish Lines to Enhance Cell Transplantation Models
- The long-term goal of this proposal is to facilitate the implementation of novel human cell therapies. NIH R21OD019915-01(2015-2016). PI: Jose B. Cibelli

## Publications in the last 5 years


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- Goissis MD, Cibelli JB. 2014. Functional characterization of CDX2 during bovine preimplantation development in vitro. Mol Reprod Dev. Sep 22. PMID: 25251051

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- Alicea B, Murthy S, Keaton SA, Cobbett P, Cibelli JB, Suhr ST. 2013. Defining the Diversity of Phenotypic Respecification Using Multiple Cell Lines and Reprogramming Regimens. Stem Cells Dev. 2013 Jun 18. PMID: 23672680.
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## Patents

- Methods for generating induced pluripotent stem cells. Elena Gonzalez Muñoz; Jose Bernardo Cibelli. Holding institution: Michigan State University/Fundacion Publica Andaluza Progreso y Salud. Application number: US/ 62/025,279. Priority country: United States of America. Date: 18/07/2014
- Method of differentiation of morula or inner cell mass cells and method of making lineage-defective embryonic stem cells (2014). Jose B. Cibelli. US 8,753,884 B2. Holding institution: Michigan State University
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- Gynogenetic or androgenetic production of pluripotent cells and cell lines, and use thereof to produce differentiated cells and tissues (2012). Jose B. Cibelli. US 8,273,571. Holding institution: Michigan State University
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- Identification of genes or polypeptides the expression of which correlates to fertility, ovarian function and/or fetal/newborn viability (2010). Jose B. Cibelli. US 7,858,308. Holding institution: Michigan State University
- Embryonic or stem-like cell lines produced by cross species nuclear transplantation and methods for enhancing embryonic development by genetic alteration of donor cells or by tissue culture conditions (2010). Jose B. Cibelli. US 7,696,404. Holding institution: Michigan State University
- Cloning pigs using donor nuclei from non-quiescent differentiated cells (2007). Jose B. Cibelli. US 7,291,764. Holding institution: Michigan State University
- Method for generating immune-compatible cells and tissues using nuclear transfer techniques (2004). Jose B. Cibelli. US 6,808,704. Holding institution: Michigan State University
- CICM cells and non-human mammalian embryos prepared by nuclear transfer of a proliferating differentiated cell or its nucleus (2001). Jose B. Cibelli. US 6,235,970. Holding institution: Michigan State University
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- Cloning using donor nuclei from a non-quiescent somatic cells (2001). Jose B. Cibelli. US 6,215,041. Holding institution: Michigan State University
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