REWINDING THE CLOCK IN INDUCED STEM CELLS (IPS)

Madrid, 6 February 2009. Today, the on-line edition of *Cell Stem Cell* publishes a paper from the Telomeres and Telomerase Group led by Maria A. Blasco at the Spanish National Cancer Centre (CNIO) reporting the results of their research on the analysis of telomeres of stem cells generated following the protocol established by Shinya Yamanaka in 2006, which are known as iPSs (induced Pluripotent Stem cells). In this paper, the researchers Rosa M. Marión and Katerina Strati are joint first authors.

Research on stem cells took a huge step forward a couple of years ago when it became available a simple method for obtaining stem cells from adult tissues. As Rosa M. Marión remarks, "the deal is to set back adult cells to their pluripotent embryonic status by the addition of three genes". iPSs cells have the capability to generate all kind of tissues, a feature that it is expected to be of great usefulness for regenerative medicine.

The team of Maria A. Blasco has discovered that for the effective generation of iPSs cells the starting cells must be telomerase-proficient. Katerina Strati points out "when the cells are deficient in telomerase, they do not become pluripotent stem cells". To overcome the former limitation, the researchers of the Telomeres and Telomerase Group have resorted to the re-introduction of the enzyme telomerase during the process leading to the generation of iPSs cells that are fully functional and able to generate any kind of tissue in the organism.

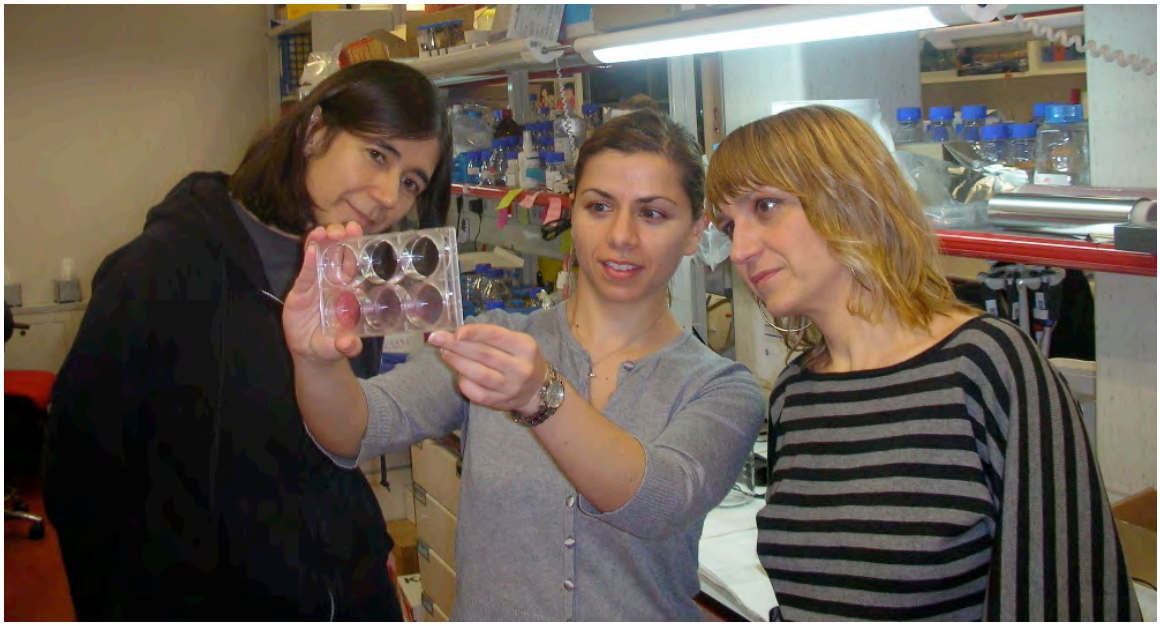
So far, it had remained unknown the putative effect of reprogramming on telomeres, the molecular clocks measuring cellular age. The group at CNIO has now observed that after reprogramming the telomeres rejuvenate to levels identical to those of an embryonic cell and that for this to happen the enzyme telomerase is required.

Maria A. Blasco indicates "to be reprogrammable a cell has to have a functional telomerase gene". This is the first identified Achilles Heel of the Yamanaka protocol for the generation of iPSs cells since it was first published.

The authors have used genetically modified mice to accomplish their reprogramming study. The success of this Spanish research may hopefully facilitate in the future the development of a cell therapy to be administered to patients with a deficit in telomerase who exhibit premature ageing stemming from the presence of very short telomeres. This type of pathologies includes diseases such as *diskeratosis congenita* and certain variants of aplasic anaemia and of pulmonary fibrosis, which are characterised by premature loss of tissue regeneration.

The prestigious journal *Science* credited in 2008 the so called "Cellular Reprogramming", term used when referring to research focused on iPSs cells, as being the most important discovery o the year. The proven feasibility to generate iPSs cells allows to elicit the sensitive ethical issues linked to the traditional techniques for obtaining stem cells, known as "nuclear transference" or "therapeutic cloning" which implies the use of human eggs and the artificial generation of human embryos.

The study published today in *Cell Stem Cell* is the second one on iPSs cells carried out in Spain, after that from a research group at *Centro de Medicina Regenerativa,* in Barcelona, published in 2008. It places Spain among of the reduced group of countries leading the research on stem cells generated from adult cells.



CNIO Researchers Maria A. Blasco, Katerina Strati and Rosa M. Marión (left to right).

re-programming “à la Dolly” (1997)

donor

enucleated oocyte

pre-implantation embryo

nucleus healthy cell

patient

healthy cell

lengthening of telomeres

iPS

pluripotent cells

healthy cells for transplant

Oct3/4

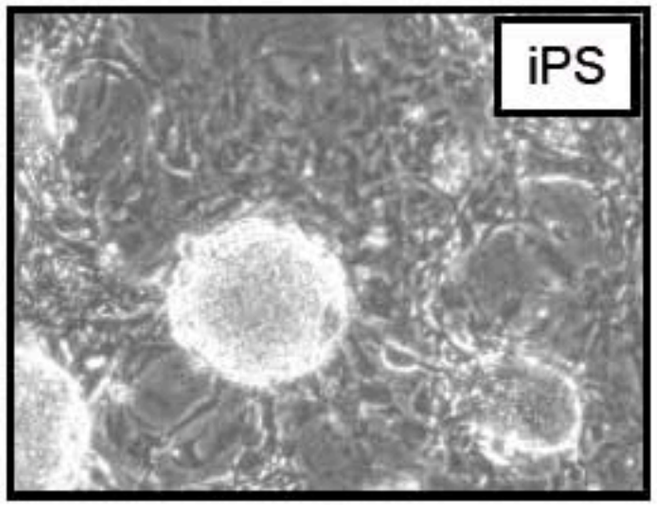
cMyc

Klf4

Sox2

re-programming “à la Yamanaka” (2006)

pluripotent stem cells obtained at the CNIO



iPS cells can produce chimeric mice and contribute to the germ line