

## Somatic cell age and memory in the generation of iPS cells

### Grant Award Details

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Somatic cell age and memory in the generation of iPS cells

**Grant Type:** New Cell Lines

**Grant Number:** RL1-0066g

**Project Objective:** All goals and objectives of this project have been met. Project successfully completed.

**Investigator:**

<b>Name:</b>	Miguel Ramalho-Santos
<b>Institution:</b>	University of California, San Francisco
<b>Type:</b>	PI

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**Human Stem Cell Use:** iPS Cell

**Cell Line Generation:** iPS Cell

**Award Value:** \$1,307,201

**Status:** Closed

### Progress Reports

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**Reporting Period:** Year 1

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**Reporting Period:** Year 2

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**Reporting Period:** Year 3

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**Reporting Period:** Year 4 (NCE)

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## Grant Application Details

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**Application Title:** Somatic cell age and memory in the generation of iPS cells

**Public Abstract:** Pluripotent stem cells can give rise to any cell type of the body and hold enormous promise for regenerative medicine. Pluripotent stem cells, such as embryonic stem (ES) cells, are derived from very young human embryos. It is of great interest to derive pluripotent stem cells from adult cells. In this way, one could potentially model in vitro genetic diseases that afflict patients. In addition, cells derived from patient-specific stem cells would not be rejected upon transplantation back into the patient. A methodology for generating induced pluripotent stem (iPS) cells from adult cells has recently been reported. It involves the forced activation of specific genes in the adult cells. This method is very recent: it was first reported in 2006 and only six groups, including our lab, have to date published work describing it. The published literature documents how remarkably similar to ES cells iPS cells are. However, they are not identical, and a major difference is that ES cells are derived from young embryonic cells, whereas iPS cells are derived from older differentiated cells. Furthermore, the method remains very inefficient, has been used with a limited number of adult cell types and needs to be improved in important ways. It will be essential to address the question of how the age or type of the original cell affects the resulting iPS cells. We propose to generate new iPS cells in order to test two hypotheses: 1) that younger cells may generate better quality iPS cells than older cells. If this hypothesis is true, it will be important to understand what are the critical factors that distinguish young versus old cells in their ability to generate iPS cells. From a practical point of view, it may be important to generate iPS cells at a young age and store them for future use, or to manipulate adult cells in additional ways to assure the quality and safety of the resulting iPS cells. 2) that a "memory" of the original cell may persist in iPS cells. If this hypothesis is true, it will be important to understand how that memory is maintained, and to investigate how it may affect the quality and/or safety of iPS cells. In practice, this may mean that certain cell types may be a better starting point for the generation of iPS cells. Our lab has developed improved methods for generation of iPS cells. We are using cells of different types and ages to generate iPS cells, and will be able to compare them. Our laboratory also has extensive experience with studies of the basic biology of pluripotent stem cells, and we will make use of that expertise in the proposed work. The proposed research is expected to provide the community of stem cell researchers with new pluripotent stem cells from diverse cell types, and to make important contributions towards the development of safe clinical applications of iPS cells.

**Statement of Benefit to California:**

Pluripotent stem cells hold the potential to revolutionize medicine and health care. Research on human pluripotent stem cells may provide new treatments for devastating and presently incurable conditions such as diabetes, Parkinson's disease, muscular dystrophies, spinal cord injuries, and many other diseases. In the case of diabetes alone, tens of billions of dollars per year are spent in California managing the disease. Recently, islet transplantation has provided an alternative path towards a cure for diabetes. However, this approach is severely limited by the short availability of cadaveric islets and the consequences of prolonged immunosuppression to avoid transplant rejection. If cells derived from the patients themselves could be turned into pancreatic beta cells in large numbers, both of these limitations would be overcome. A similar paradigm applies to many other diseases, where the ability to generate patient-matched pluripotent stem cells would provide a major new tool to study the disease in the lab, discover new drugs, or develop cells for transplantation. Recent results indicate that it may be possible to take cells from patients and induce them to become pluripotent stem cells. The method for doing this is very inefficient, and has been used with only a few cell types. Our proposal aims to understand how cells of different types and ages can be induced to become pluripotent stem cells. This research will pave the way for the development of safe clinical applications of human pluripotent stem cells. If we understand how the age and type of the original cells affects the pluripotent stem cells derived from them, we will be able to explore the use of this method to obtain cell types of therapeutic value, while avoiding unintended side-effects. The development of human pluripotent stem cell-based therapies will significantly increase the options available in the California health care system. These new therapies are expected to reduce the long-term health care costs to California by providing cures to diseases, like diabetes, that are currently chronic and require expensive periodic treatment. Our research is also expected to stimulate the development of biotechnology industry focused on drug screening on and clinical applications of human pluripotent stem cells. Such development will be of great benefit to California by attracting high-skill jobs and tax revenues, and by making the State a leader in a field that is poised to be the economic engine of the future. The State of California will also stand to benefit from the intellectual property generated by this research.

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