Background and Description of Invention. Rapamycin is an immunosuppressive compound currently used to prevent acute graft rejection in humans. It is known that rapamycin allows operational tolerance in murine models. However, a direct effect of rapamycin on the T regulatory (Tr) cells, which play a key role in the induction and maintenance of peripheral tolerance, has not been demonstrated so far. The naturally occurring Tr cells (CD4+CD25+FoxP3+) contribute to tolerance induction after solid organ transplantation and protect from graft versus host disease (GvHD) lethality in bone marrow transplantation models. Moreover, it has been recently observed that patients with autoimmune diseases such as type 1 diabetes, multiple sclerosis, and rheumatoid arthritis are deficient in CD4+CD25+ Tr cells. Scientist at OSR have established a method that selectively expands the naturally occurring CD4+CD25+FoxP3+ Tr cells in vitro. In vitro long-term exposure of murine CD4+ T cells to rapamycin induces expansion of the naturally occurring CD4+CD25+FoxP3+ Tr cells, which retain their suppressive functions.

The rapamycin-expanded Tr cells suppress T cell proliferation in vitro and prevent allograft rejection in vivo. (Battaglia M, Stabilini A, Roncarolo MG. Rapamycin selectively expands CD4+CD25+FoxP3+ regulatory T cells. Blood. 2005). Furthermore, rapamycin allows the selective expansion and survival of human CD4+CD25+FOXP3+ Tr cells from peripheral blood of both healthy subjects and patients with type 1 diabetes (Battaglia M et al J.Immunology 2006). Recent data demonstrate that a “pre-GMP” protocol for the expansion of human FOXP3+ Tr cells with rapamycin is feasible and that rapamycin-expanded human Tr cells are not contaminated by potential pathogenic T cells (such as Th17 cells).


Stage of Development.
• In vitro long-term exposure of murine CD4+ T cells to rapamycin induces expansion of the naturally occurring CD4+CD25+FoxP3+ Tr cells, which retain their suppressive functions in vitro and in vivo.
• The ability of CD4+CD25+FoxP3+ Tr cells expanded in vitro by rapamycin to suppress an immune response in vivo has been successfully tested in a murine model of allogeneic pancreatic islet transplantation.
• Treatment of human CD4+ T cells, which includes both T effector cells and CD4+CD25+ Tr cells (5-10% of the total CD4+ T cells), increases by 20 fold the number of CD4+CD25+FOXP3+ Tr cells. The ability of rapamycin to selectively expand CD4+CD25+FOX3+ Tr cells to such levels may be limited to the in vitro approach.
• A pre-GMP protocol for the expansion of human CD4+CD25+FOXP3+ Tr cells in the presence of rapamycin has been defined.
• Human rapamycin-expanded Tr cells are not contaminated by Th17 cells and retain their suppressive activity even upon in vivo transfer in immunodeficient mice.
Potential Applications and Competitive Advantages. Rapamycin can be used to expand in vitro the CD4+CD25+FOXP3+ Tr cells for cellular therapy in T-cell–mediated diseases, in association with organ transplantation or bone marrow transplantation, and in the treatment or prevention of GvHD.

Potential advantages are summarized:

- Rapamycin expands both murine and human CD4+CD25+FOXP3+ Tr cells with suppressive ability in vitro obtained from peripheral blood or secondary lymphoid organs.
- Murine CD4+CD25+FoxP3+ Tr cells expanded in vitro by rapamycin prevent allograft rejection in vivo.
- The major disadvantage of cellular therapy with in vitro expanded Tr cells is the risk to concomitantly expand the T effector cells that could be deleterious once transferred in vivo. Indeed, the present invention also relates to methods of eliminating/reducing CD4+CD25+ T effector cells (namely Th17 cells).
- CD4+CD25+ Tr cells may also be able to modulate GVHD whilst preserving the graft versus tumor (GVT) or graft versus leukemia (GVL) effect.

Relevant Publications.

- Battaglia M. Potential T regulatory cell therapy in transplantation: how far have we come and how far can we go? Transplantation 2010; 23(8):761-70. Review

We seek a commercial partner with a strong pipeline in cellular immunotherapy protocols to further explore the clinical use of rapamycin-expanded Tr cells for the treatment of T-cell mediated diseases.

For further information on this project please contact:

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