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Thymic tissue regeneration using natural scaffolds

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Thymus transplantation has great clinical potential, but the shortage of transplant donors limits the progress of this therapy. Creation of a bioengineered thymus, where the cellular component is autologous, will overcome two major obstacles in transplantation: the lack of organs and the toxicity arising from lifelong immunosuppression. Here, we show how the induction of ectopic Oct4 in adult TEC could allow the expansion of thymic epithelial progenitor-like cells (pTECs) in 2D and 3D culture systems, retaining their capability to differentiate into mature TECs and potentially form a functional thymus *in vivo*. In order to obtain bipotent TECs precursors that could differentiate into both cortical and medullary TECs we transduced freshly isolated TECs with a lentiviral vector (LV) that allows for ectopic expression of Oct4. Through LV transduction we were able to achieve high levels of Oct4 expression in adult TECs. Moreover, we demonstrated that ectopic expression of Oct4 is sufficient to promote the de-differentiation of primary mature TECs into pTECs, inducing the expression of the progenitor markers, such as Thy1.2, Sca1 and CD44, and decreasing the expression of maturation markers, such as MHCII. To improve thymic organogenesis and restore its functions both *in vitro* and *in vivo*, we exploited a 3D collagen type I scaffolds, mimicking the thymus structure, for the culture of TECs. Our results showed that collagen type I scaffolds allow the efficient expansion of pTECs. pTECs grown on scaffolds displayed a high proliferation rate without losing their developmental potential. To induce pTECs maturation and thymic regeneration, we are now evaluating a LV-based strategy for Oct4 inducible expression that allows us to switch off Oct4 expression and control pTECs differentiation. We will then perform a morphological and phenotypical characterization of TECs cultured on scaffolds and evaluate their ability in restoring thymic function both *in vitro* and in vivo.

Biography

Ileana Bortolomai has completed her PhD with the Open University of London at the IRCCS Istituto dei Tumori di Milano in 2011. At Yale University School of Medicine she completed her first postdoctoral studies at Dr.Santin lab where she was involved in evaluating the targeting potential of CPE functionalized PLGA-NPs for gene therapy against cervical cancer cells. In 2014 she has joined the group of Dr. Anna Villa at Istituto San Raffaele Telethon (TIGET) where she is involved in the project of thymus regeneration, as innovative research on gene transfer and cell transplantation for successful clinical application for genetic diseases.

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