

CONTROLLED RELEASE FORMULATIONS FOR IMMUNO-REGULATION: *TOWARDS A
SYNTHETIC TOLEROGENIC DENDRITIC CELL*

Abstract

Transplant rejection and autoimmunity are characterized by adverse inflammatory reactions and the absence of immuno-regulatory mechanisms. One of the most common treatments for these conditions is the use of immunosuppressive agents that non-specifically suppress immune cell function. However, these agents are associated with many drawbacks that include renal and hepatic toxicities as well as increased risk of infections and malignancies. A promising alternative to immunosuppressants is the utilization of the immune system's natural regulatory mechanisms. Cellular therapies, comprising of tolerogenic dendritic cells (tDC) and regulatory T cells (Treg), which exploit these regulatory mechanisms are currently under development. Unfortunately, therapies that use tDC and Treg are associated with many challenges such as; difficulty in isolating these cells, problems in maintaining their regulatory phenotype under *ex vivo* culture conditions, and the prohibitive infrastructure requirements in culturing these cells under 'GMP' conditions. A potential solution to these problems is the development of prospective therapeutics that would alter regulatory cell numbers and function *in vivo*. To this end, we developed three new degradable and biocompatible formulations to modulate regulatory immune responses. The first formulation involves the encapsulation of an immunosuppressant, rapamycin, into appropriately-sized microparticles (rapaMP) that can specifically be targeted to phagocytic cells *in vivo*. RapaMP-treated DC show lowered expression of co-stimulatory markers and decreased ability to stimulate T cell proliferation, both of which are suggestive of their capacity to suppress immune responses *in vivo*. The second formulation involves the encapsulation of a chemokine capable of Treg recruitment (CCL22) into sustained release vehicles (CCL22MP). Our data demonstrates that CCL22MP are able to recruit Treg *in vivo*, and show promise in delaying cell and composite tissue graft rejection. The third formulation involves the encapsulation of factors (IL-2, TGF- β and rapa; FactorMP) that we have identified as agents capable of Treg induction. We show that FactorMP are capable of inducing functional Treg populations from both mouse and human cells, and could possibly create a local immunosuppressive environment *in vivo* that favors Treg proliferation. Controlled release formulations such as these, could potentially be developed as "off-the-shelf" therapeutics for the treatment of transplant rejection and autoimmunity.