

Immunotherapy of Non-Infectious Uveitis using Collagen II-specific regulatory Type 1 (Col-Treg) cells

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Introduction: Non-infectious uveitis (NIU) is a condition characterized by deregulation of the immune system in the eye for which only steroids are currently approved. Col-Treg is a T-cell immunotherapy composed of autologous type-1 regulatory T (Treg) cells specific for collagen-II. We evaluated Col-Treg use for NIU in mice as collagen-II is present naturally in the eye and so triggers the activity of the Col-Treg cells in situ.

Methods: Col-Treg cells were produced from blood of healthy volunteers or from splenocytes of mice transgenic for collagen-II-specific TCR. Cells were characterized for marker expression using FACS and for in-vitro immuno-modulatory function. NIU model was developed by IRPB immunization. In-vivo efficacy was evaluated using ophthalmoscopy and histology. In-vivo tracking was performed using a Col-Treg TCR Vbeta-chain-specific quantitative PCR.

Results: Col-Treg secrete IL-10 and IL-13 and express GITR, CD39 and Granzyme B, molecules known to be involved in the control of inflammation. In vitro assays confirmed the capacity of Col-Treg cells to hydrolyse ATP, kill myeloid cells in a contact-dependent manner and inhibit T effector cell IL-17 and IFN γ secretion using soluble factor dependent pathways. Intravenous administration of Col-Treg inhibited ocular inflammation in NUI mice. Moreover, Col-Treg injection decreased cell infiltration in the ocular tissues, vasculitis and retinal folds. Tracking experiments demonstrated a tropism of Col-Treg for inflammatory eyes. An in vivo GLP toxicity study performed in healthy mice did not reveal Col-Treg related adverse events. Characterization of human Col-Treg GMP batches demonstrated comparability with mouse Col-Treg for marker expression and in vitro function. Human Col-Treg cells did not show evidence of tumorigenicity or uncontrolled proliferation in vitro as witnessed by a limited survival capacity upon chronic stimulation and a strict dependence to exogenous stimulation for their exponential proliferation.

Conclusion: These results demonstrate the safety and efficacy of Col-Treg administration for the treatment of NIU in mice and suggest that Col-Treg could be used as a therapeutic tool for patients with non-infectious uveitis refractory to approved medications. These results will be taken as a basis for a first in Man clinical study with Col-Treg in NUI patients that is expected to start in 1H 2015

Optional abstract:

Non-infectious uveitis (NIU) is an inflammatory condition of the eye and the fourth most common cause of blindness among the working-age population in the developed world, whereas infectious uveitis represent the majority of the cases in the developing countries. Uveitis affects mainly the uvea, or middle layer of the eye but could also affect the lens, retina, optic nerve and vitreous chamber. Currently, all approved treatments remain of uveitis patients remain steroid based. Steroid therapies, even their fast relief of symptoms local are associated with systemic side effects including in particular intra-ocular pressure,

diabetes, hypertension. This highlights the need for these patients of other more targeted therapies as biologics or immunosuppressors, which are used off-label and allow additional management of these auto-immune diseases. However, despite these treatments, a large proportion of patients with uveitis are refractory of treatment and experience reduction of vision.

Therefore, NIU remains a significant unmet medical need. Our approach is to generate from the blood of the patients a well-tolerated alternative based on a cell-based therapy. Where the T lymphocytes from the patients are educated to acquire a specificity and immunological functions which allow the suppression of eye-s inflammation. Such clinical approach has been already addressed for patients with Crohn's diseases and indicated therapeutic potential. For uveitis indication, preclinical data showed the absence of toxicology signs as well as efficacy to reduce both at ophthalmology and histopathology levels the signs of inflammation.

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