Treg-based immunotherapy of non-infectious uveitis (NIU)

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Introduction: Col-Treg is a T-cell immunotherapy composed of autologous type-1 regulatory T (Treg) cells specific for collagen-II. Col-Treg are tested in NIU mice as collagen-II is present in the eye, allowing the triggering of their activity in situ. NIU is one of the most common cause of blindness in the developed world.

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

Results: Col-Treg secrete IL10, IL13 and express GITR, CD39 and Granzyme B, molecules involved in the control of inflammation. Col-Treg hydrolyse ATP, kill myeloid cells and inhibit T effector cell IL17 and IFNγ secretion. Intravenous administration of Col-Treg inhibited ocular inflammation in NUI mice with reduction of cellular infiltrates, IL1β, IL6, TNFα. In-vivo-tracking demonstrated a tropism of Col-Treg for inflammatory eyes. In-vivo GLP toxicity study in healthy mice did not revealed 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.

Conclusion: These data demonstrate the safety and efficacy of Col-Treg administration for the treatment of NIU in mice, suggesting that Col-Treg could be used as a therapeutic tool for patients with non-infectious uveitis refractory to approved medications.

Optional abstract:

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.

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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