SELECTED OPPORTUNITIES IN IMMUNOLOGY - INFLAMMATION

Ltα Negatively Regulates the Immunosuppressive Functions of T Regulatory Cells (BIO17326|BIO19134)

LTA NEGATIVELY REGULATES THE IMMUNOSUPPRESSIVE FUNCTIONS OF T REGULATORY CELLS (BIO17326|BIO19134)

Product factsheet

Preclinical

- **Target:**
  - Lymphotoxin alpha
- **Product:**
  - Tested: Foxp3+CD4+ Tregs from LTα-/- mice (LTα-/- Tregs)
  - Could be generated: CAR-Treg LTα-/- or lymphotoxin α blocking agent (e.g., antibodies)
- **Application:**
  - Transplantation, autoimmune inflammatory diseases
- **Rational:**
  - By their immunosuppressive and anti-inflammatory activities, Foxp3+CD4+ regulatory T cells (Tregs) play a central role in peripheral tolerance and thus critically prevent the development of autoimmune and inflammatory disorders
  - The inventors showed that thymic and splenic Foxp3+CD4+ Tregs express higher levels of lymphotoxin α (LTα) than conventional CD4+ T cells
  - Thymic and splenic Foxp3+CD4+ Tregs from LTα-/- mice (LTα-/- Tregs) exhibit a signature of highly suppressive cells, indicating that LTα negatively regulates the immunosuppressive functions of this cell type
- **POC:**
  - **In vivo:** The adoptive transfer (AT) of LTα-/- Tregs protects from dextran sodium sulfate (DSS)-induced colitis, cures inflammatory bowel disease (IBD) and attenuates the development of colitis-associated cancer (CAC). The AT of LTα-/- Tregs also attenuates the severity of multi-organ autoimmunity
  - **In human:** The expression of LTα in Foxp3+CD4+ Tregs is conserved in human
- **Patent and publication:**
  - WO 2019/081078

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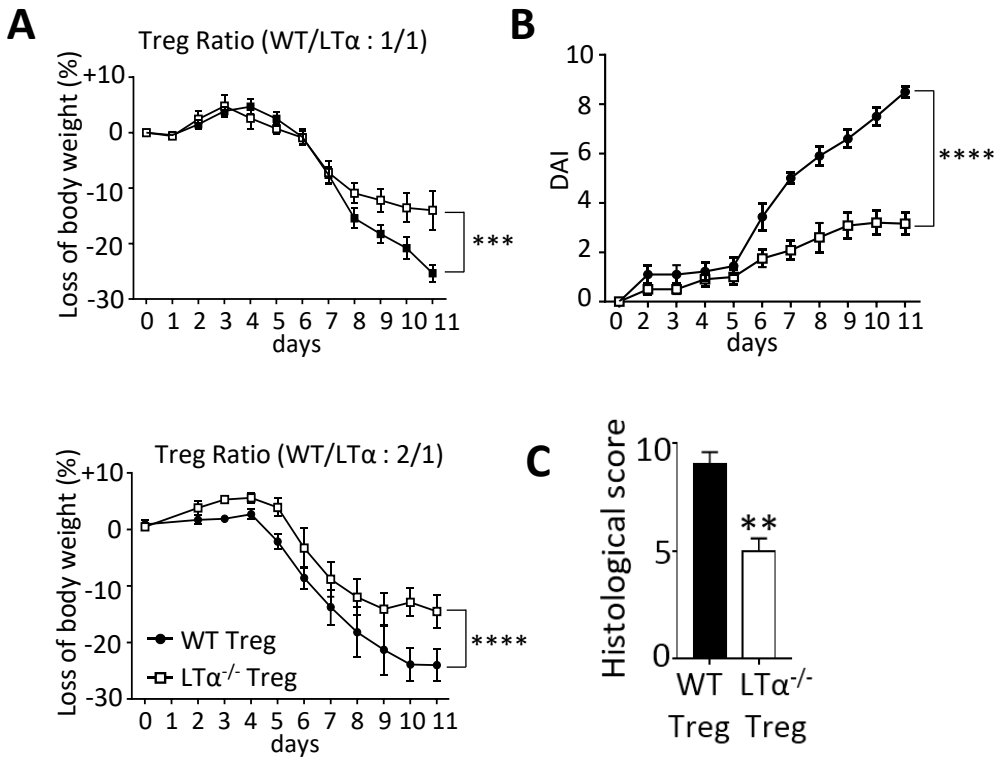
Proof of concept

The adoptive transfer of LTα-/- Tregs protects from ulcerative colitis



A. Body weight loss relative to the initial weight on day 0 of WT mice injected with $2x10^5$ WT or LTα−/− Tregs. Data are derived from 3 independent experiment with 4 mice per group.

B. Disease activity index (DAI) was monitored during the course of DSS-induced colitis.

C. The histogram shows the histological score of the colon in both groups of mice.

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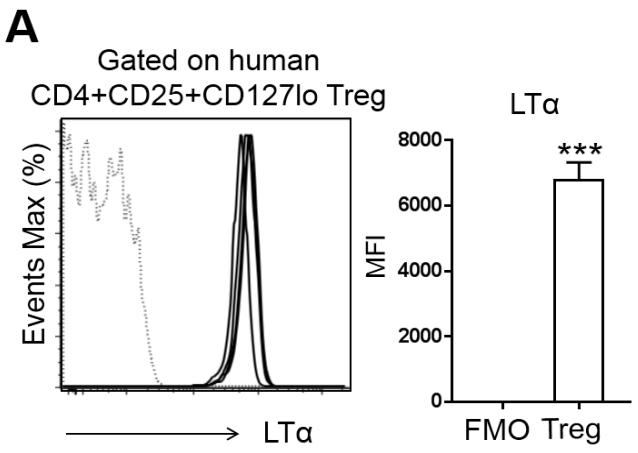
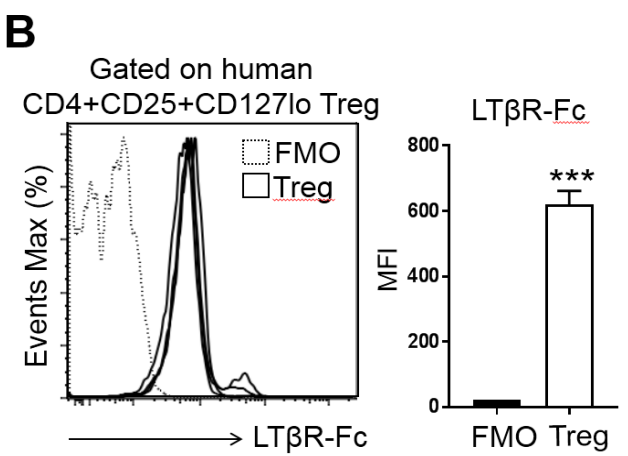
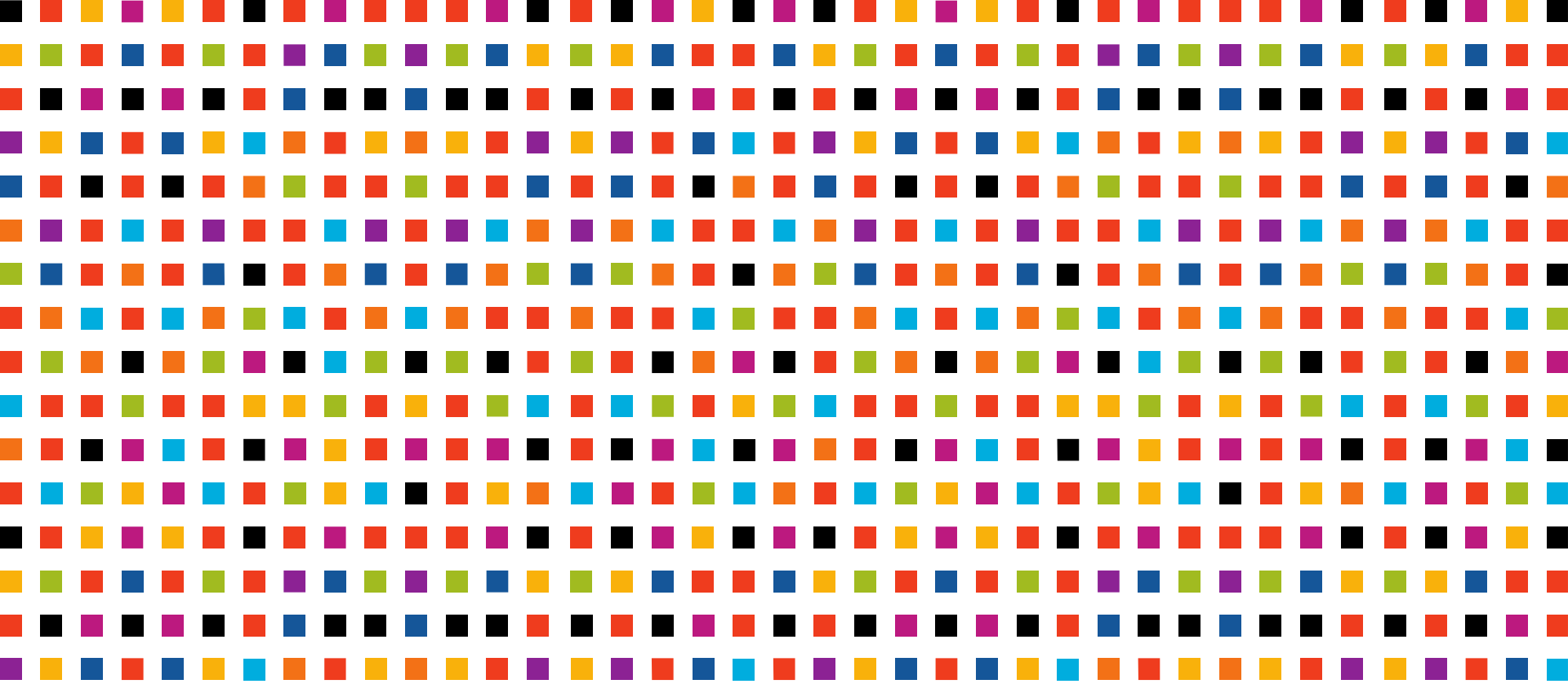
Proof of concept

LTα expression is conserved in human Tregs derived from peripheral blood

Expression of **(A)** intracellular LTα protein and **(B)** cell-surface LTα1β2 heterotrimer detected by staining with the soluble LTβR-Fc receptor was analyzed by flow cytometry in $CD4^{+}CD25^{-}CD127^{lo}$ Tregs derived from peripheral blood of male and female patients.







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