SELECTED OPPORTUNITIES IN IMMUNOLOGY - INFLAMMATION

RANKL to boost thymic regeneration (BIO16458)

RANKL TO BOOST THYMIC REGENERATION (BIO16458)

Product factsheet

preclinical

- **Target:**
  - RANKL
- **Product:**
  - Tested: RANKL polypeptide
  - Could be generated: stabilized RANKL polypeptides
- **Application:**
  - Treatment of thymic injury that occurs after myeloablative conditioning and aging.
- **Rational:**
  - Thymic injury is related to severe damages on thymic epithelial cells (TECs), which result in delayed de novo thymopoïesis and a prolonged period of T-cell immunodeficiency.
  - RANK ligand (RANKL) is strongly upregulated in lymphoid tissue inducer (LTi cells) and to a lesser extent in CD4+ SP cells during the early phase of thymic regeneration.
  - Importantly, whereas the administration of a neutralizing RANKL antibody severely alters TEC regeneration, the administration of RANKL protein after total body irradiation and BMT boosts the regeneration of cortical and medullary TEC subsets and thymic epithelial progenitor-enriched cells (TEPCs).
  - The results indicate that RANKL would be clinically useful to improve T-cell function recovery after BMT not only in young but also in aged individuals by controlling multiple facets of thymic regeneration.
- **POC:**
  - **In vivo:** in animal models, RANKL administration increases specifically in LTi cells, lymphotoxin α (LTα), which is critical for both TEC regeneration and T-cell reconstitution after BMT. RANKL treatment has also beneficial effects on thymic recovery upon BMT in aged individuals
  - **In human:** the expression of RANKL receptor, RANK, is conserved in the thymic medulla in Human
- **Patent and publication:**
  - WO2018/154122
  - Lopes N, Vachon H, Marie J, Irla M. Administration of RANKL boosts thymic regeneration upon bone marrow transplantation. EMBO Mol Med. 2017;9(6):835-851.

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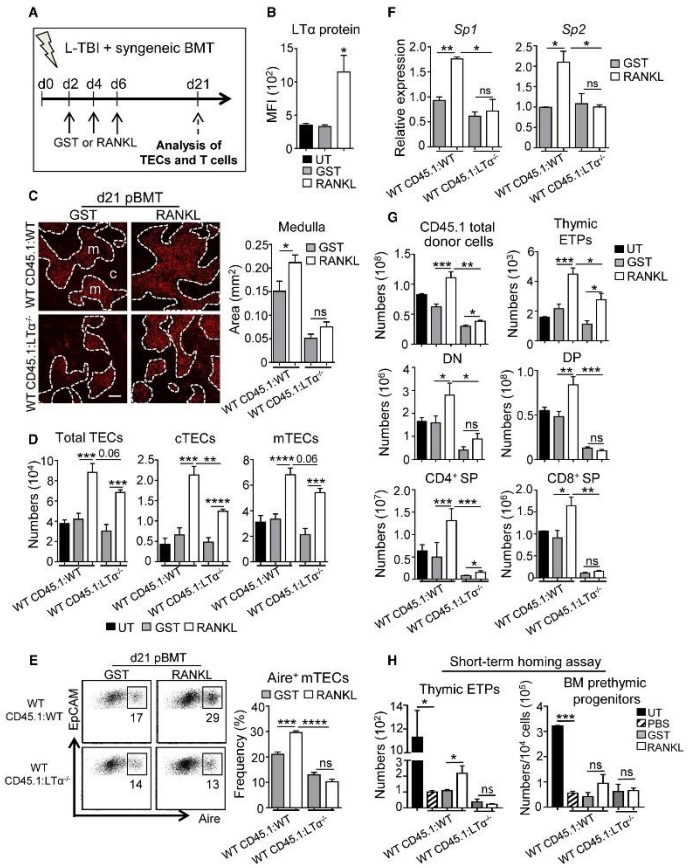
RANKL TO BOOST THYMIC REGENERATION (BIO16458)

Proof of concept

- RANKL administration enhances thymic regeneration upon BMT in an LTα-dependent manner



A. Experimental setup: WT CD45.1:WT and WT CD45.1:LTα−/− chimeras were treated with GST or RANKL-GST proteins at d2, d4, and d6 after BMT and TEC regeneration and T-cell reconstitution were analyzed at d21 after BMT.
B. Expression level of LTα protein in thymic LTi cells in UT mice or treated with GST or RANKL-GST.
C. Thymic sections from WT CD45.1:WT and WT CD45.1:LTα−/− mice treated with GST and RANKL at d2, d4, and d6 after BMT were stained for the expression of K14 at d21 pBMT. The histogram shows quantifications of medullary areas. m and c denote the medulla and the cortex, respectively. Twenty sections were quantified for each condition; scale bar: 100 µm.
D, E. Numbers of total TECs, cTECs, and mTECs (D) and flow cytometry profiles of Aire+ mTECs in total EpCAM+ TECs (E).
F. Expression of mRNAs coding for TRAs (Sp1 and Sp2) in CD45?thymic stromal cells analyzed by qPCR.
G. Numbers of total cells and thymocyte subsets of CD45.1 donor origin analyzed in the thymus.
H. Numbers of ETPs of CD45.1 donor origin in the thymus and prethymic progenitors in the BM from CD45.2 WT or LTα−/− recipients 48 h after i.v. injection of CD45.1 BM cells.

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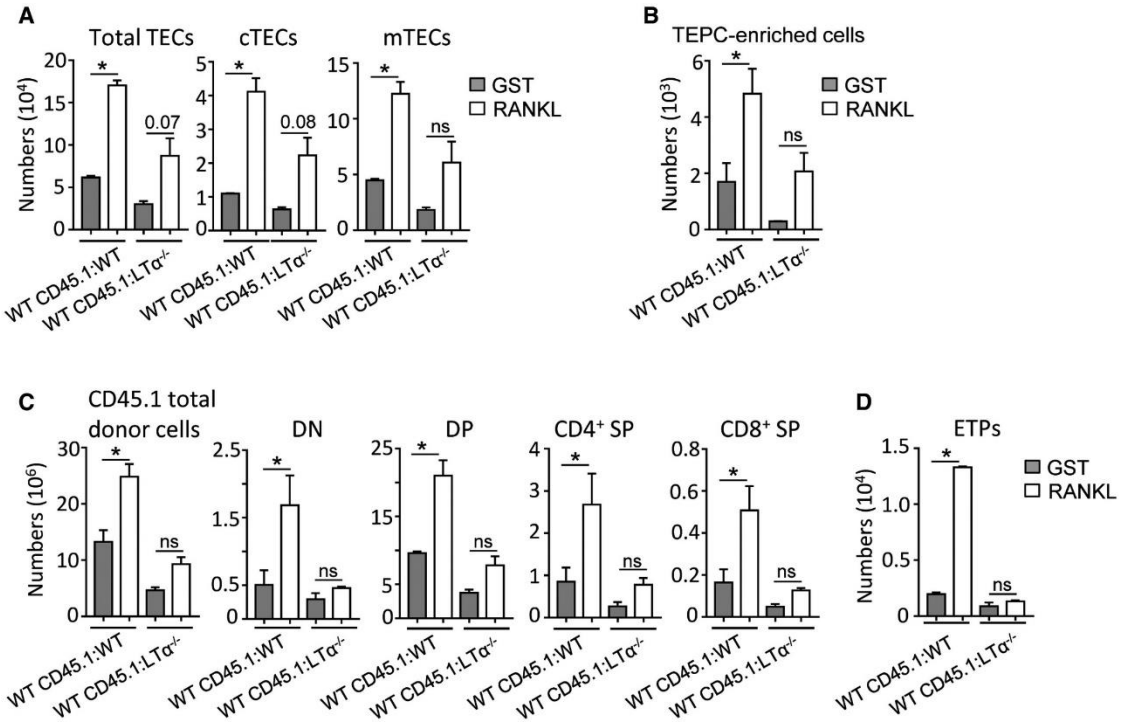
Proof of concept

- RANKL treatment also ameliorates thymic recovery upon BMT in aged individuals



Beneficial effects mediated by RANKL treatment on thymic regeneration after BMT require LTα expression in aged mice
A, B.Numbers of total TECs, cTECs, mTECs (A), and TEPC-enriched cells (B) were analyzed at d21 upon BMT in the thymus from WT CD45.1:WT and WT CD45.1:LTα−/− chimeras of 6–8 months of age treated with GST or RANKL proteins.
C, D. Numbers of total thymic cells, thymocyte subsets (C), and ETPs (D) of CD45.1 origin.

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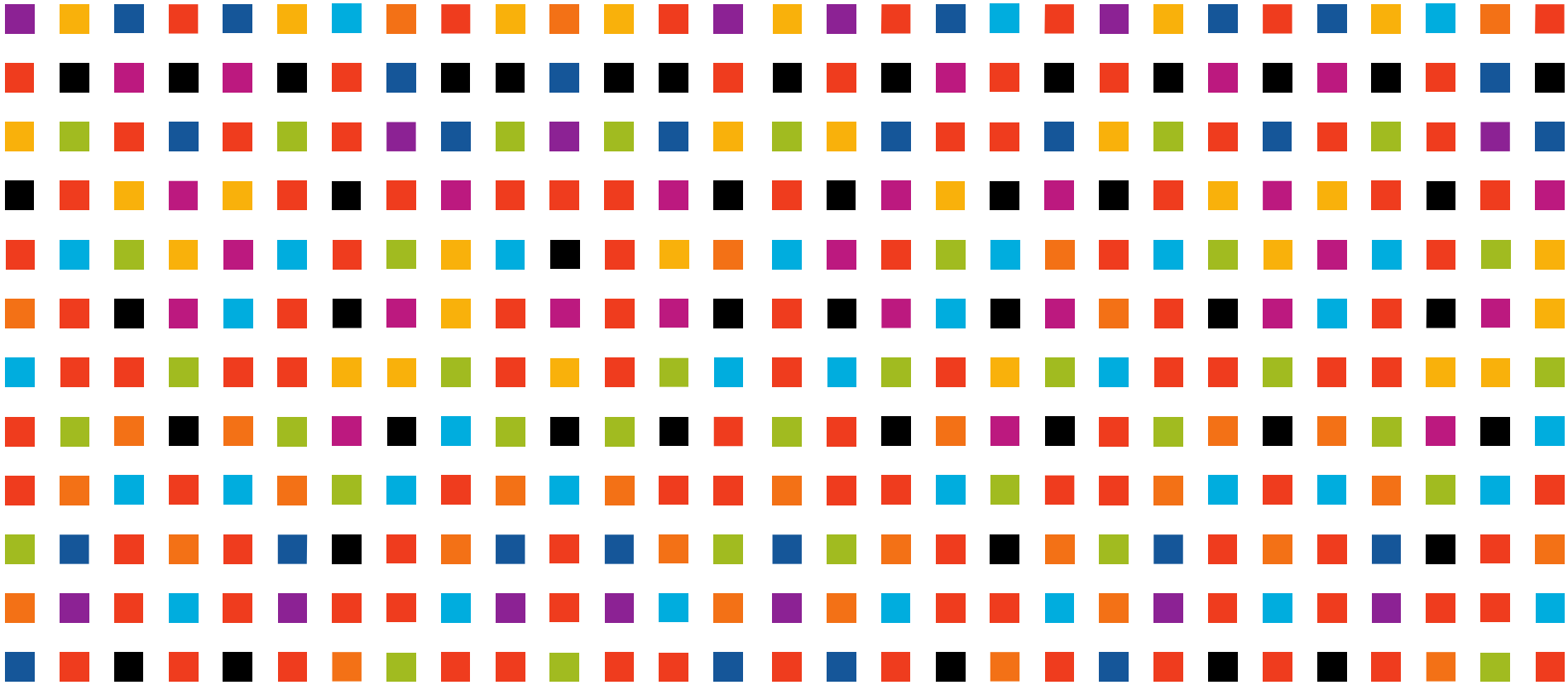

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