Vitamin D: Should a regular dose be part in immunomodulation of regulatory T cells in immunomediated diseases?

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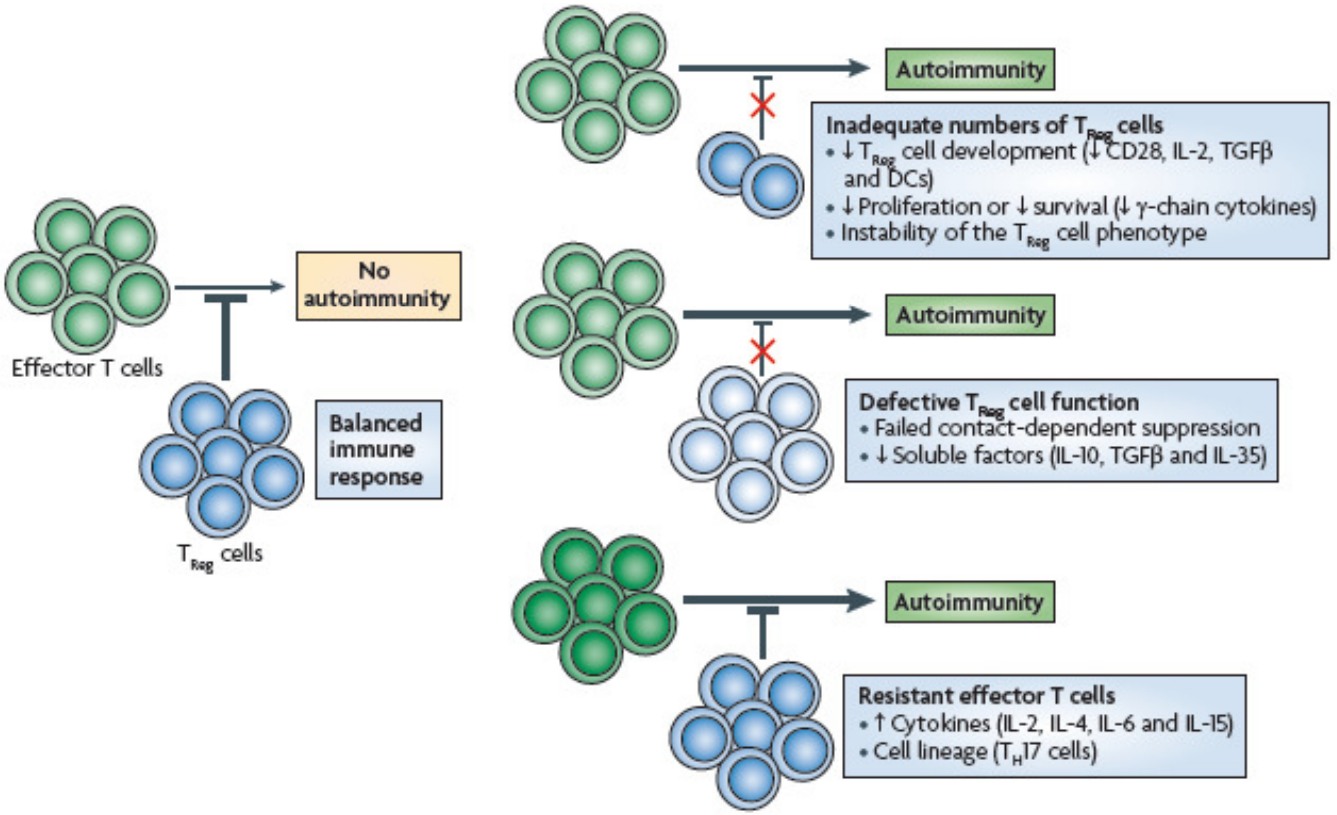
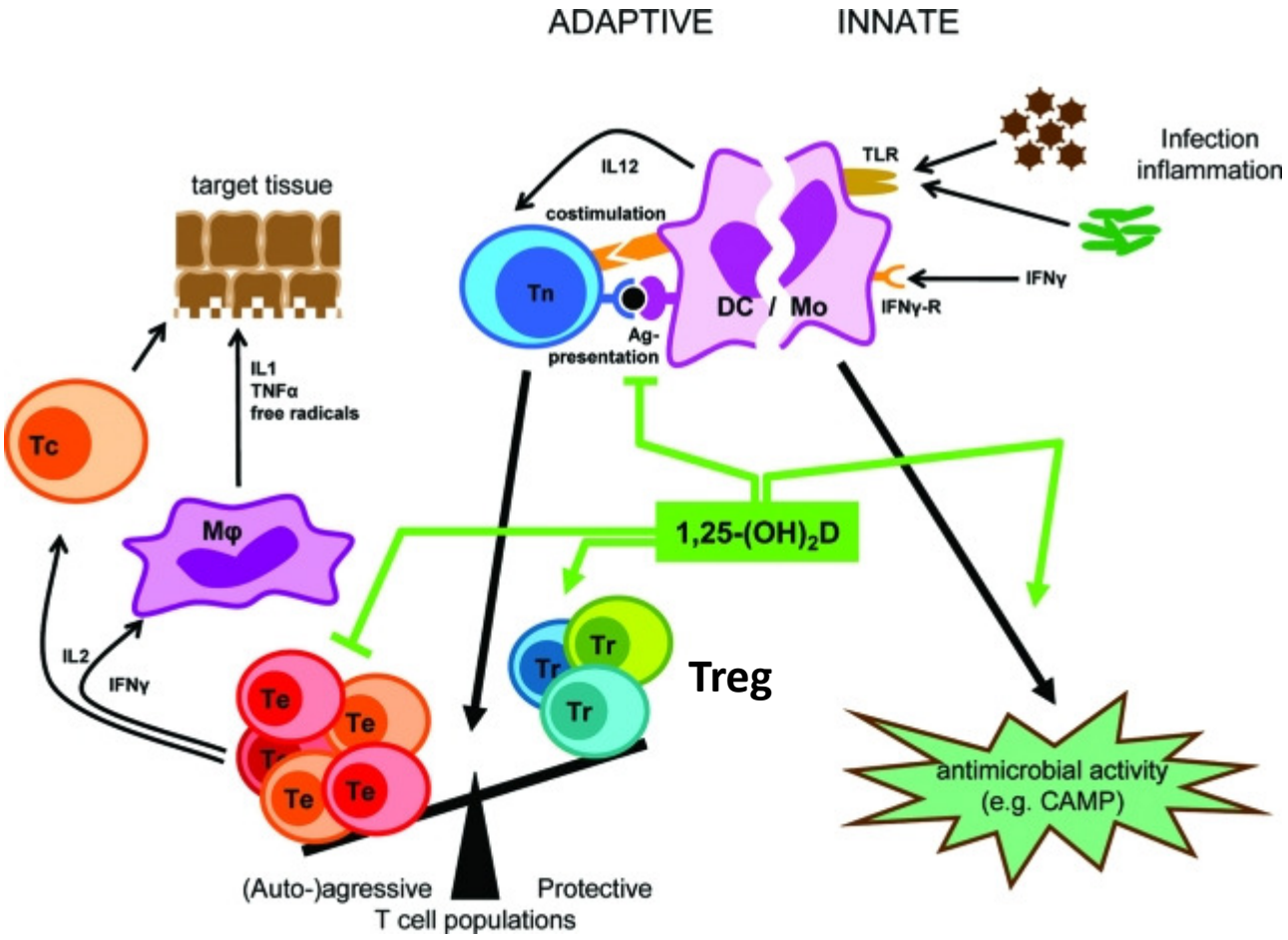
3rd Immunology Summit, Baltimore, 30. September 2014

The role of regulatory T-cells in autoimmunity



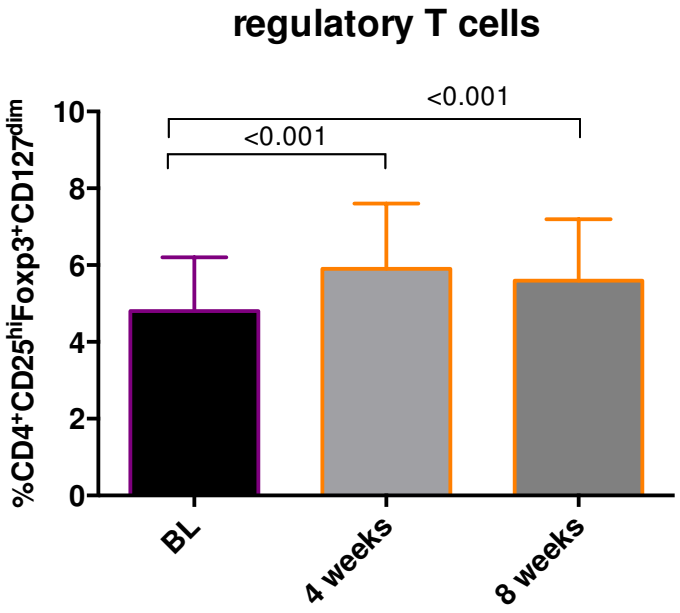
Buckner, Nat Rev Immunol, 2010

Effects of Vitamin D in the immune system



Bouillon, Endocrine Reviews, 2008

Vitamin D supplementation and regulatory T cells in healthy humans

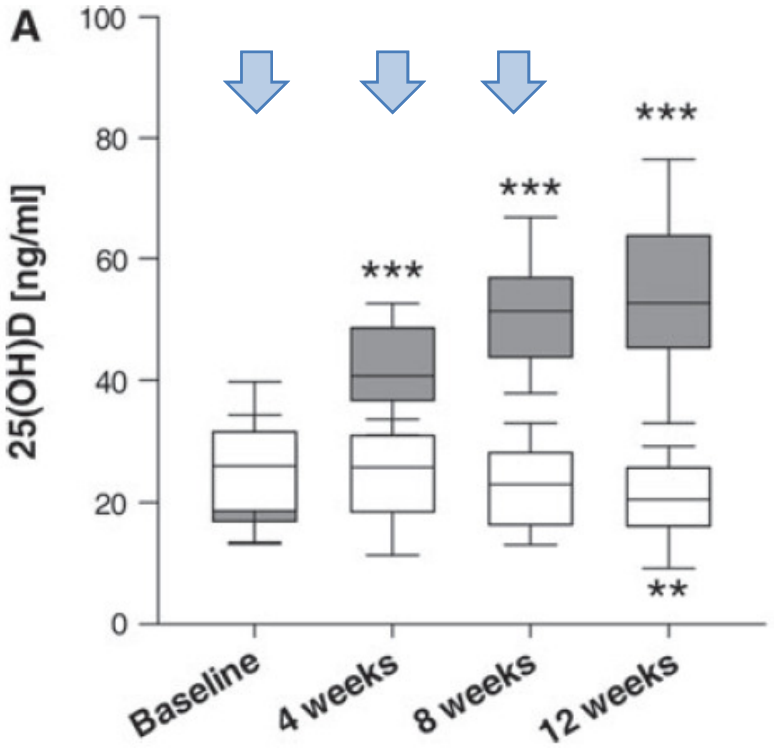


Pilot study	1x 140.000 IU Cholecalciferol
n	50
Age (yrs)	31±8
Females (%)	64
BMI (kg/m²)	23.3±4.3

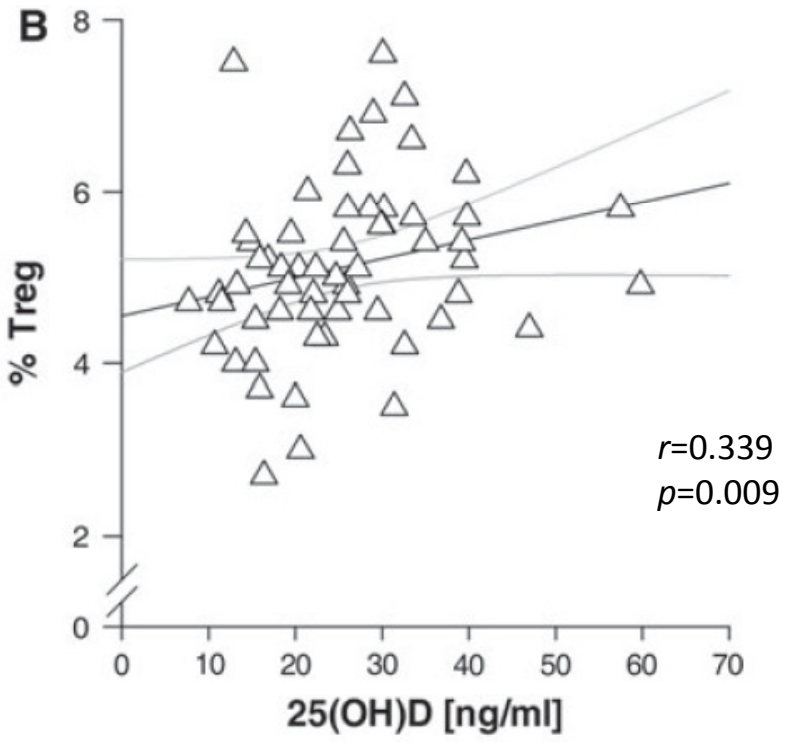
Prietl B, Pilz S et al IMAJ 2010

High-dose cholecalciferol supplementation significantly increases peripheral CD4$^+$ Tregs in healthy adults without negatively affecting the frequency of other immune cells

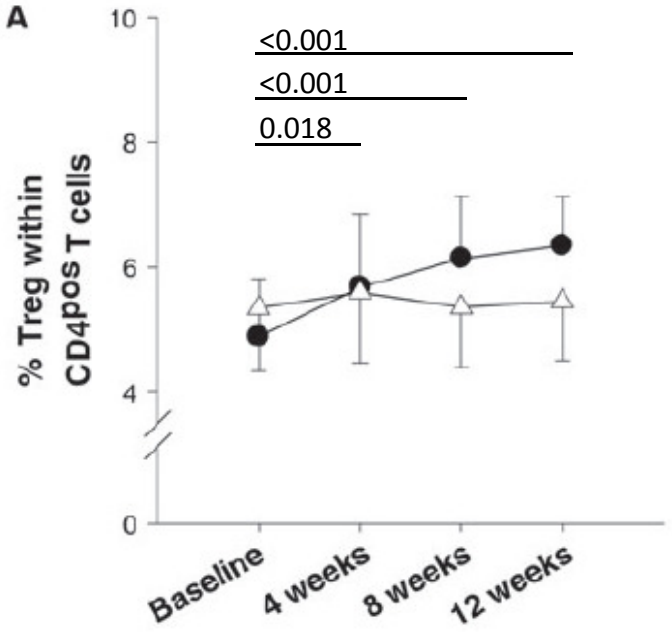
140.000 IU Vit D3

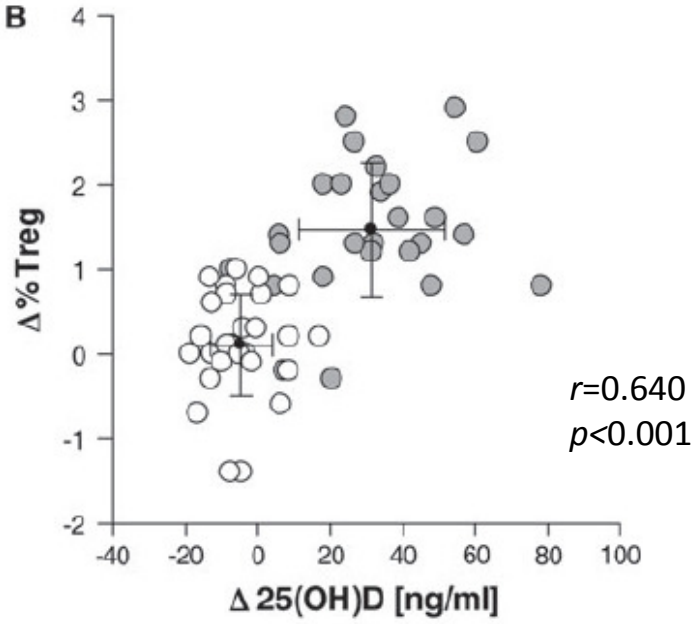


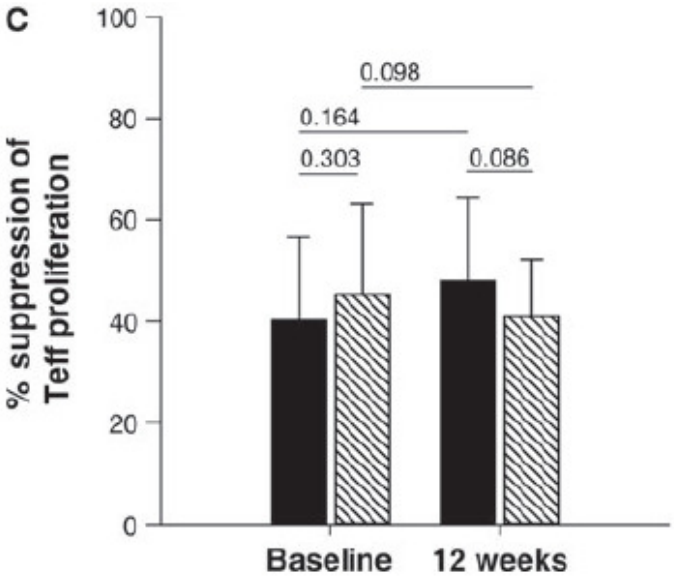
Baseline



Prietl B, Treiber G et al Eur J Nutr 2014







- Significant increase in % Treg in $CD4^{pos}$ T cells
- Unchanged Treg suppression function in healthy humans
- Other immune cells not effected
- No treatment related side effects

Prietl B, Treiber G et al Eur J Nutr 2014

Regulatory T cells in Typ 1 Diabetes

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- T1D: no global deficiency in Treg cell numbers , but functional capacity like suppression of Treg cells is impaired. *(reviewed in Bruckner Nat Immun 2010)*
  - **Targeting the Treg population directly in vivo to increase frequency and/or function of Treg**
- Analog of active form of vitamin D ($1,25(OH)_2D_3$) **increased** $CD4^+CD25^+$Treg in pancreatic lymph nodes in NOD mice. *(Gregori 2002)*
- VitD3 **increased** $CD4^+CD25^+FoxP3^+$ T cells in pancreatic lymph nodes and reduced diabetes development in NOD mice. *(Takiishi Diabetes 2014)*
- 2000 IU VitD3 **increased** regulatory $CD4^+CD25^+FoxP3^+$ T cells and slower decline of residual ß-cell function in new onset T1D. *(Gabbay APDM 2012)*

RCT: Vit D3 in patients with T1D

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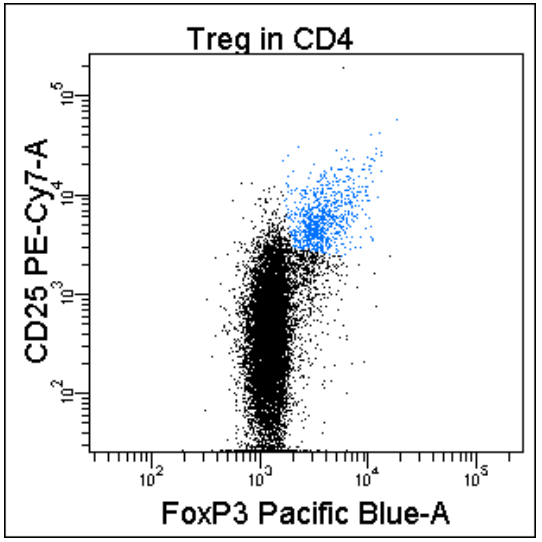
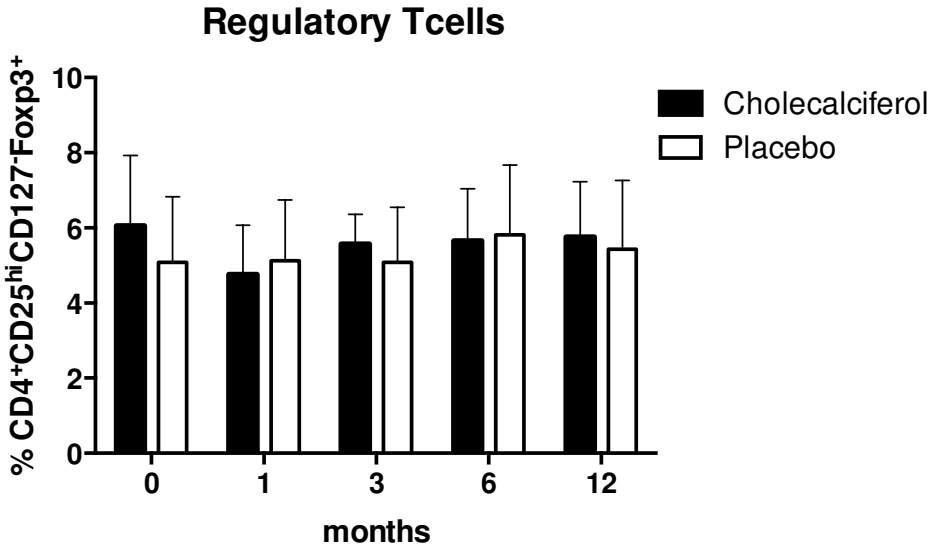
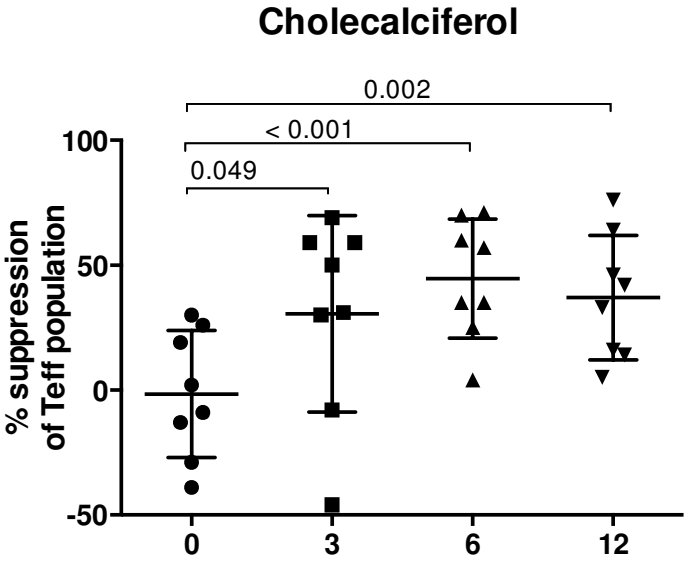
- 30 Patients with **new-onset T1D** (<12 weeks)
- Intervention 12 month:
  - oral therapy of cholecalciferol (70IU/kg bodyweight/day)
  - or placebo

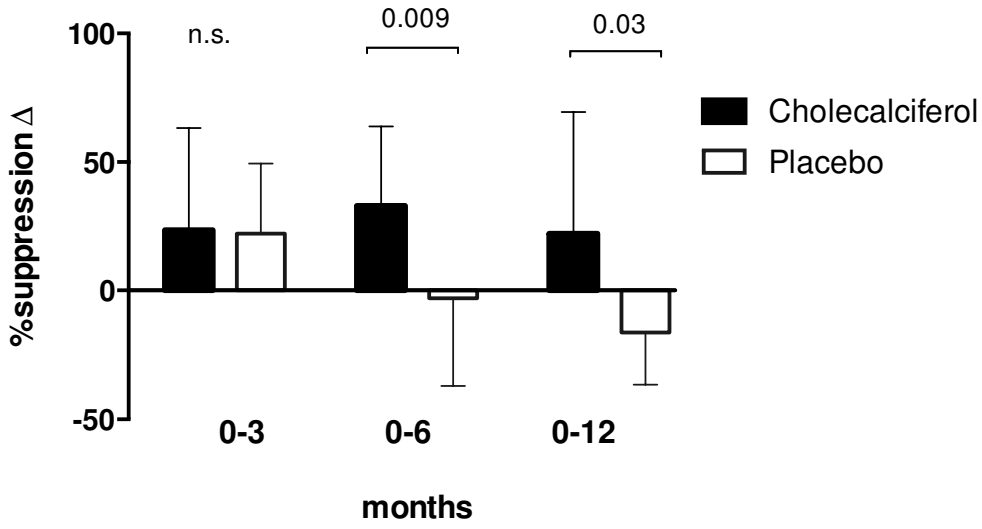
- Immunologic Assessment at month 0, 3, 6 and 12:
  - **Immune phenotyping**: FACS-analysis
    - **$CD4^{pos}CD25^{hi}Foxp3^{pos}$ $CD127^{dim}$ Treg**
    - Th-Subtypes (Th1, Th2, Th17)
    - DC , B-cells, NK, NKT-cells
  - **functional tests**: FACS sorted Treg and Teff
    - **ex vivo suppression co-cultures** ($[^3H]$-thymidine incorporation)
    - Apoptosis (AnnexinV/7-AAD)

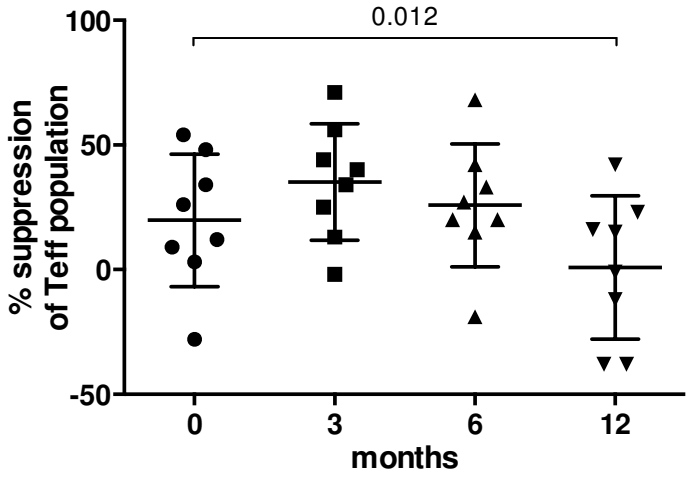


RCT: Vit D3 in T1D



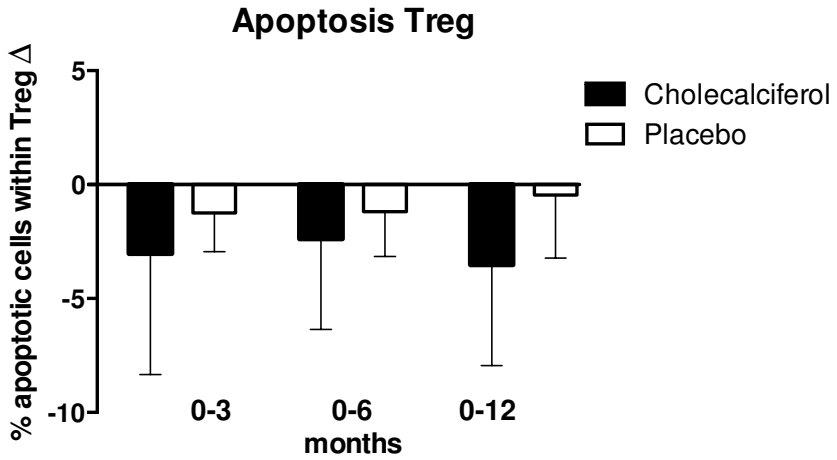


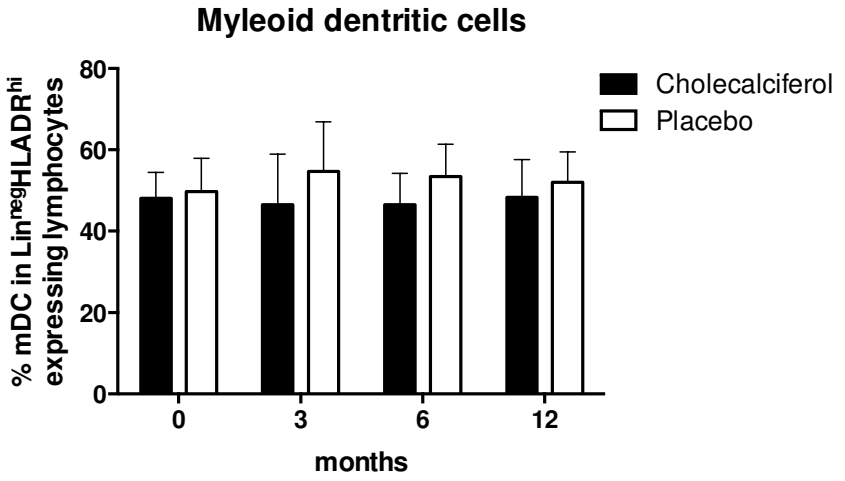




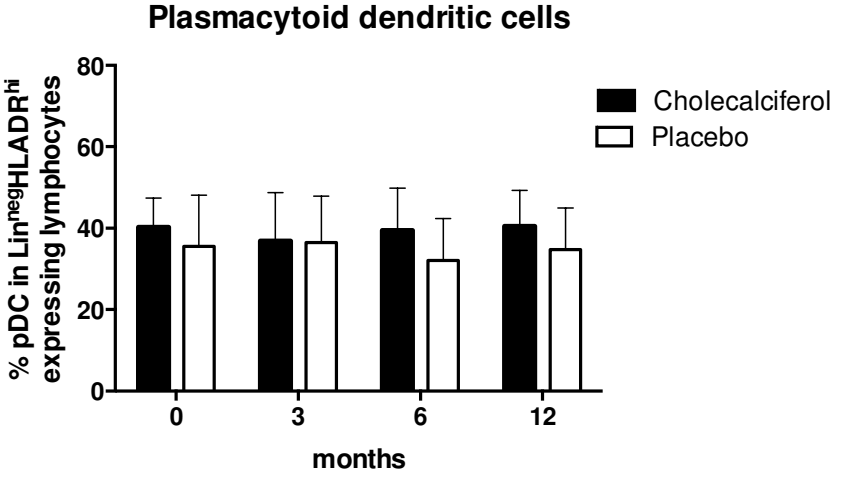
Treiber G et al in preperation

RCT: Vit D3 in T1D





- No significant effect on the frequency of other peripheral immune cells
  - Th1 /Th2 / Th17 cells
  - B cells
  - Cells from the innate immune system



RCT: Vit D3 in T1D

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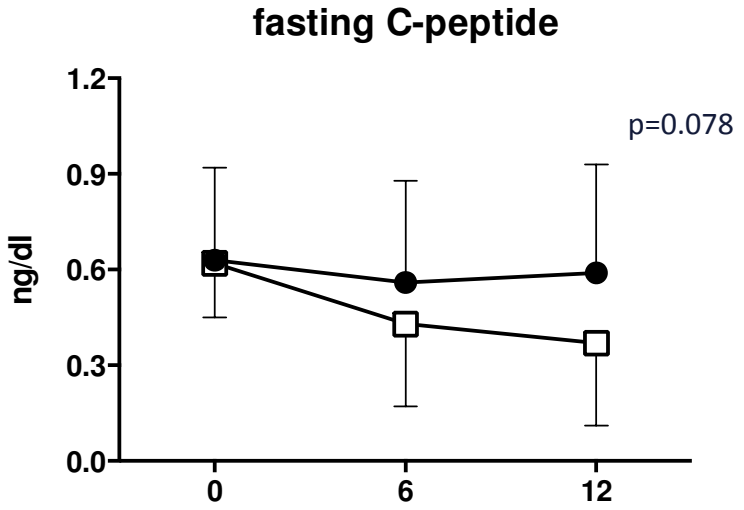
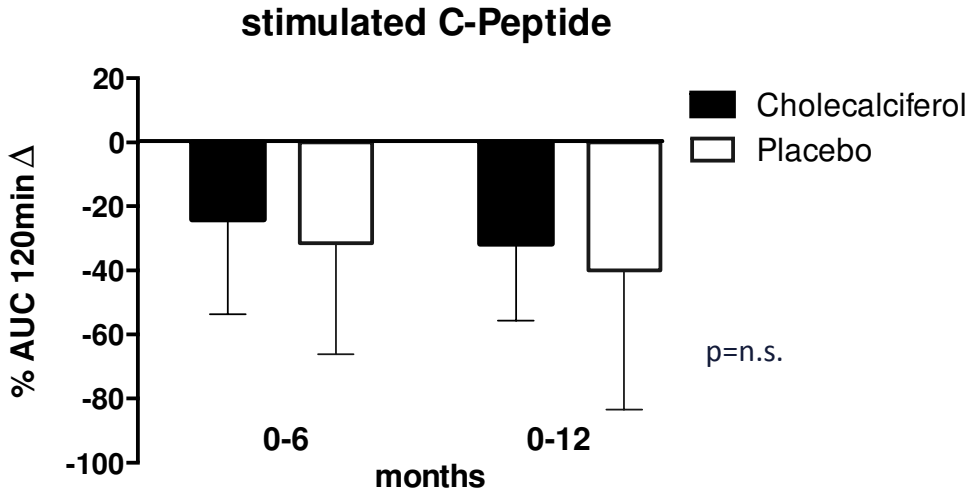
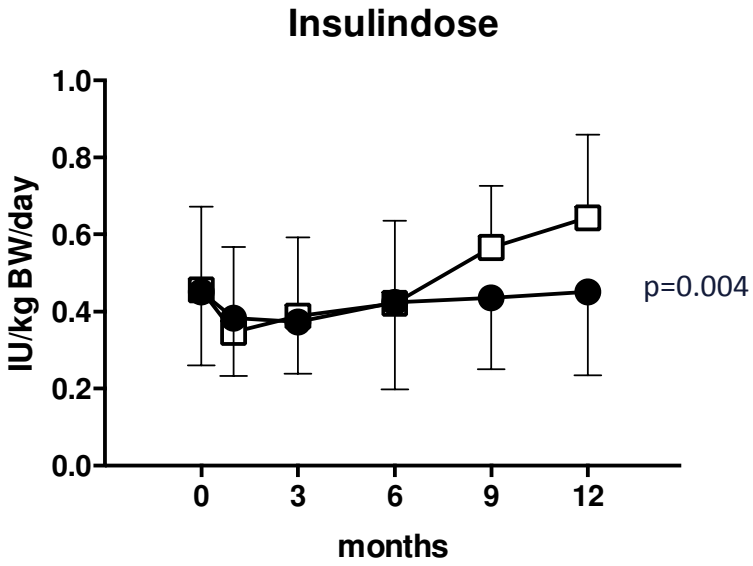
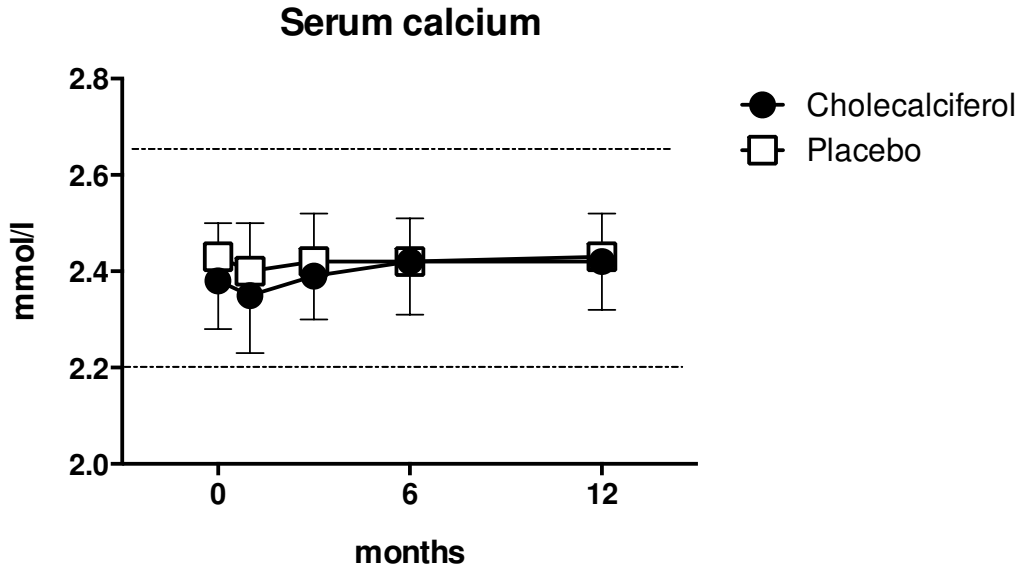
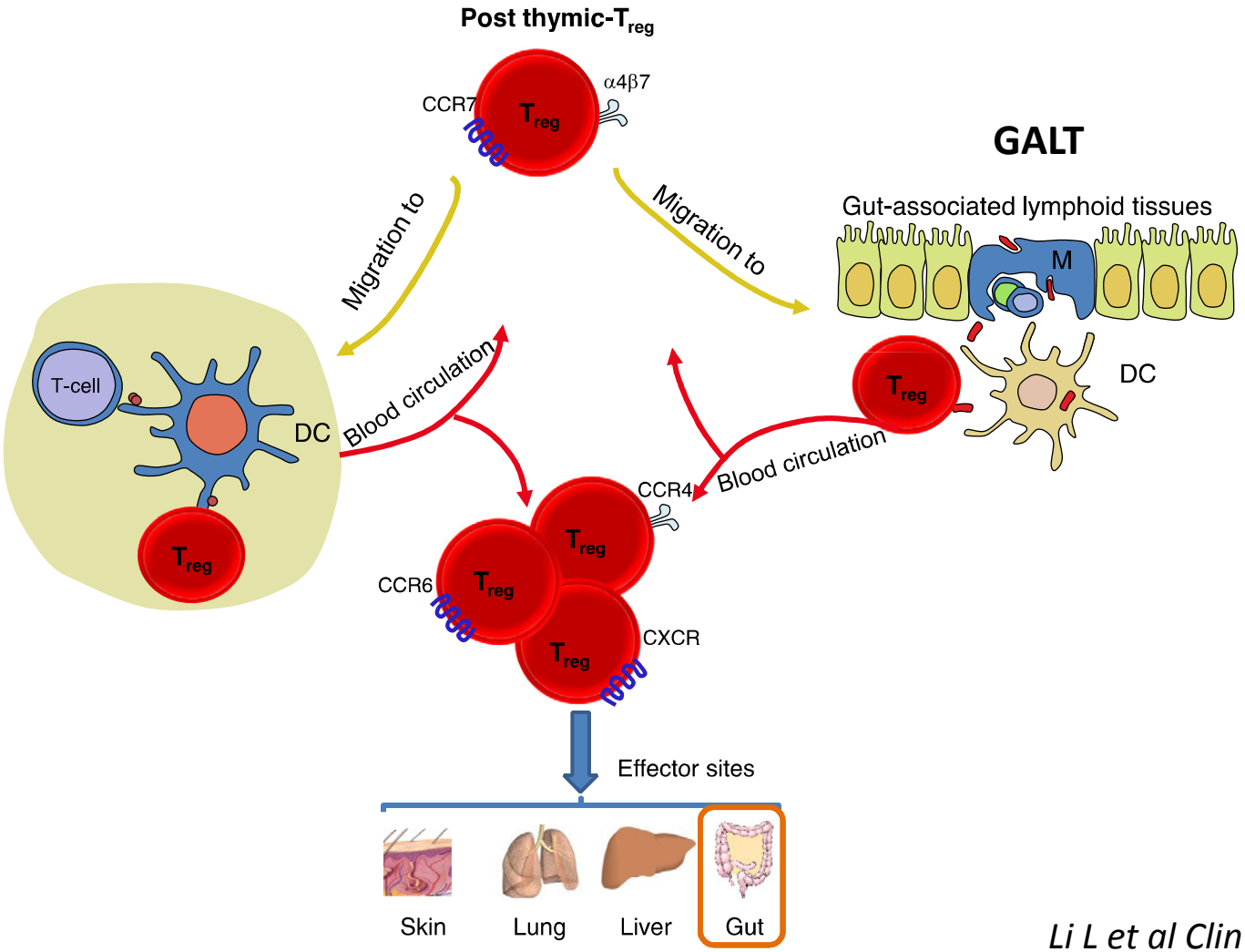








Treg origin: Thymus and Gut associated lymphoid tissue



Li L et al Clin Immun 2011

GALT: interface for maintenace of immune homostasis

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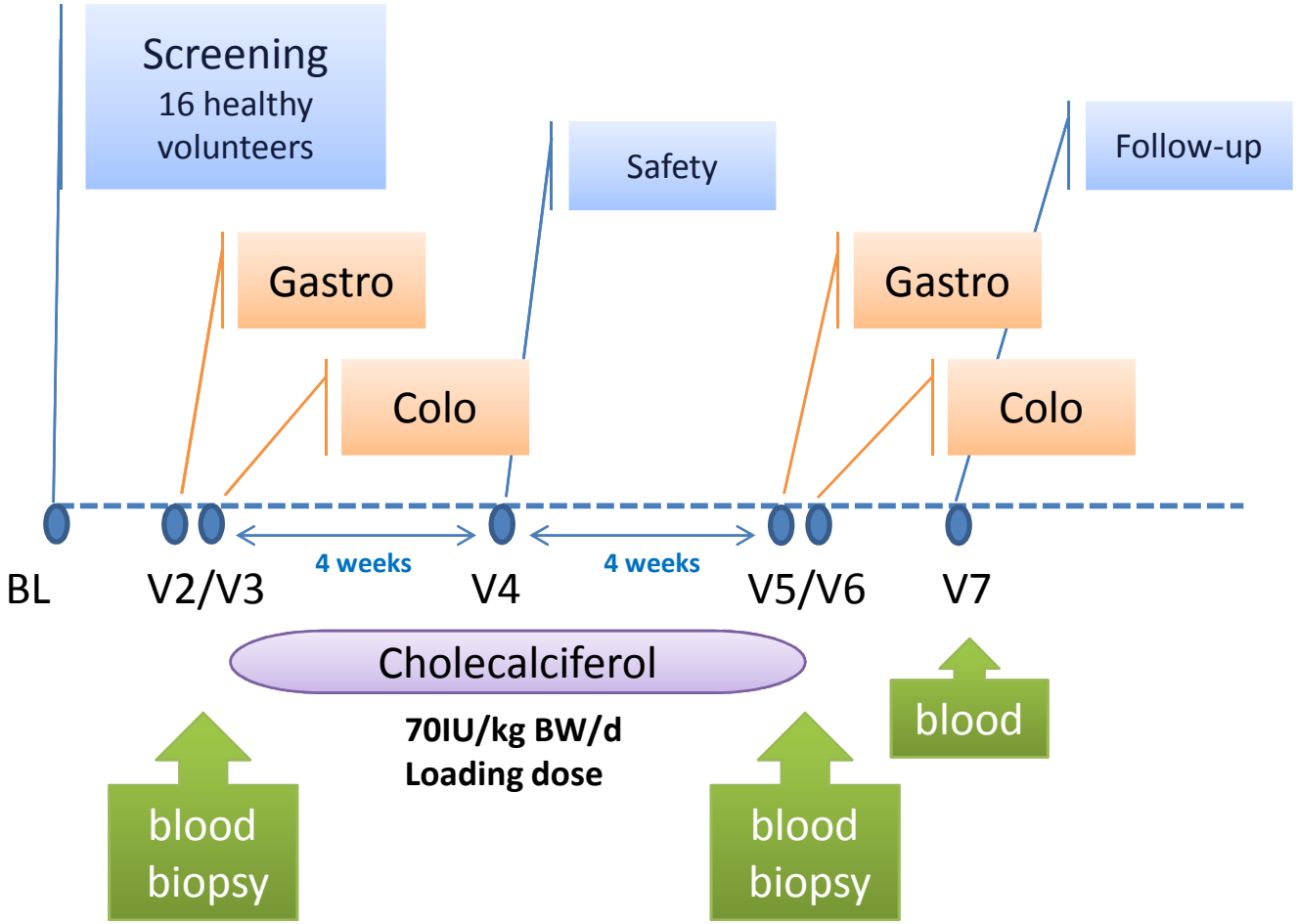
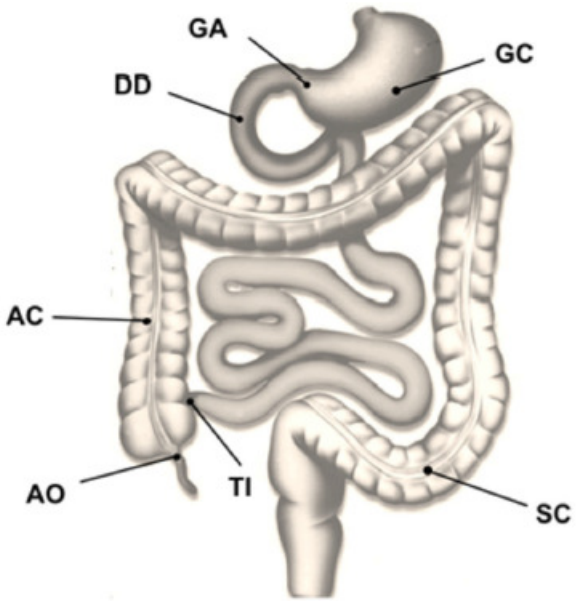
- T1D: I**ncreased** intestinal permeability precedes clinical onset of type 1 diabetes. *(Bosi Diabetologia 2006)*
- Cow milk, early cereal exposure and enterovirus infection riskfactors for **islet autoimmunity**. *(Lempainen DMRR 2012)*
- T1D: **reduced** regulatory $Foxp3^+$T cells in duodenal biopsies *(Badami Diabetes 2011)*
- IBD: **Decreased** frequency of $CD4^+Foxp3^+$ Treg in PBMC and increased $Foxp3^+$ cells in inflamed mucosa *(Wang JDD 2011).* Increased apoptosis of regulatory T lymphocytes in peripheral blood and in mucosa. *(Veltkamp C Gut 2011)*

  - **Vit D3 effect on Treg in gastrointestinal mucosa in humans unknown**

Vit D3 effect on Treg in gastrointestinal mucosa in humans

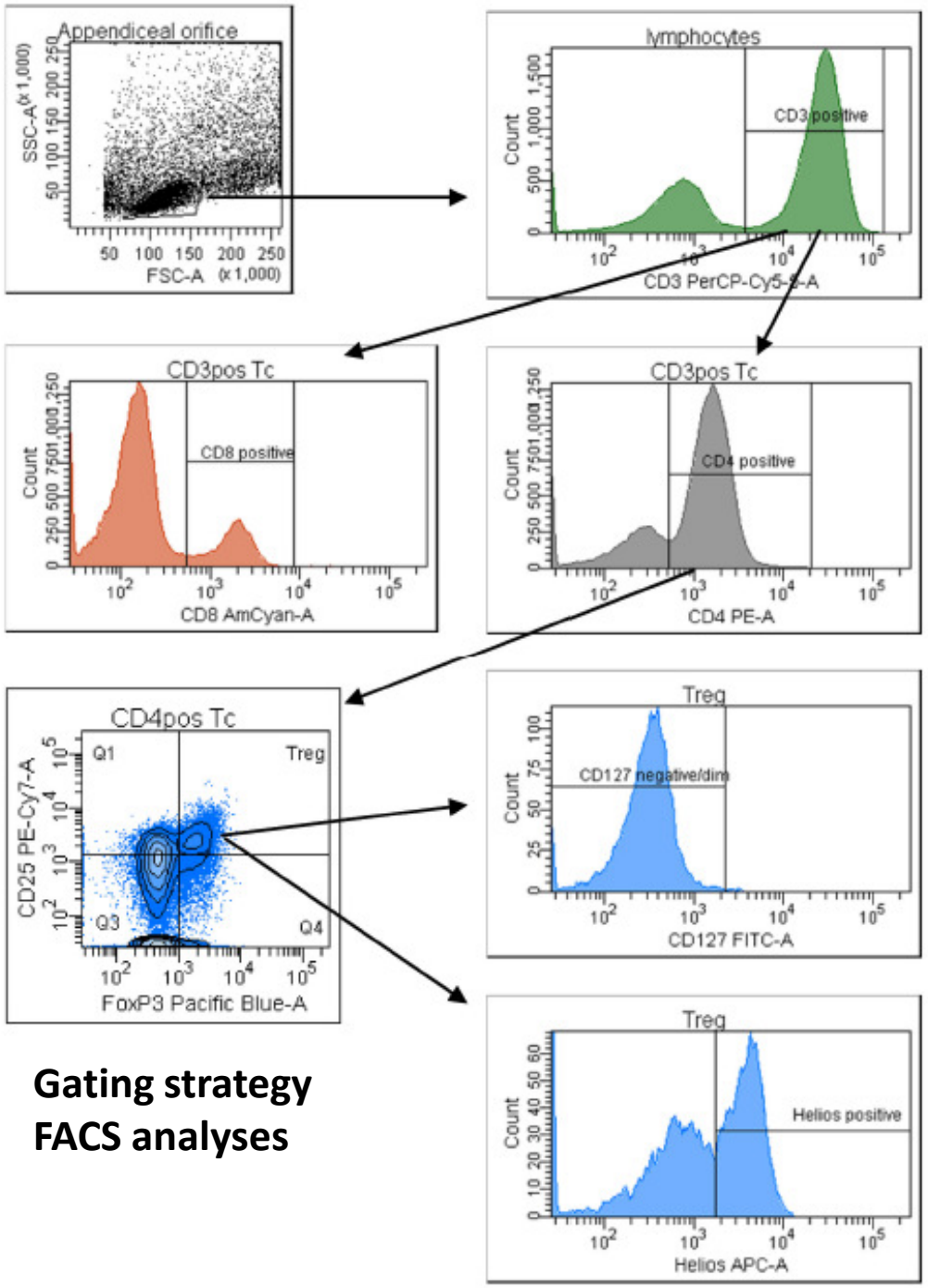


Biopsy regions



systematic assessment of upper and lower GI tract

healthy humans	16
Age (yrs)	25±4
Females (%)	44
BMI (kg/m²)	23±3



Gating strategy
FACS analyses

OPEN ACCESS Freely available online

PLOS ONE

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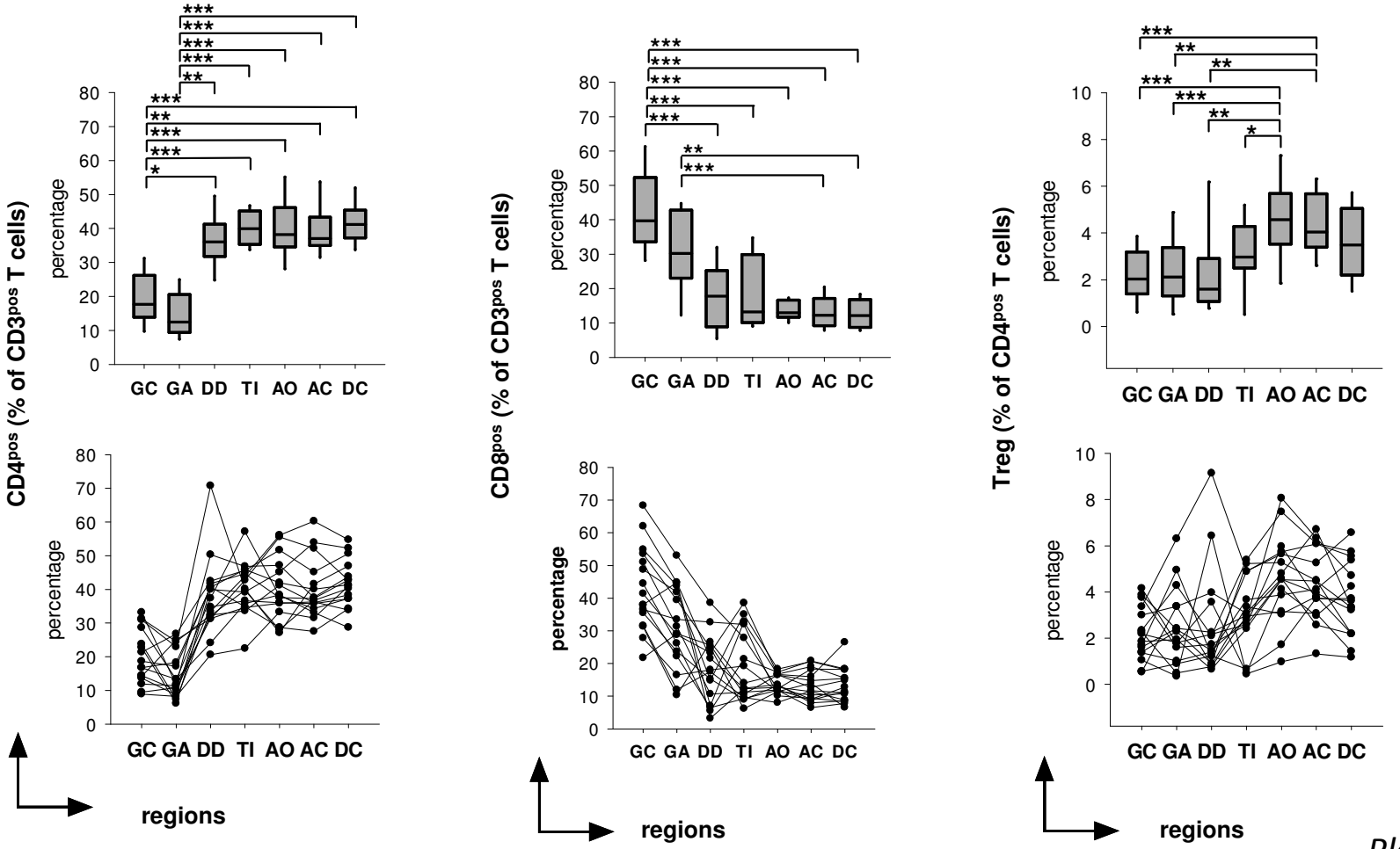
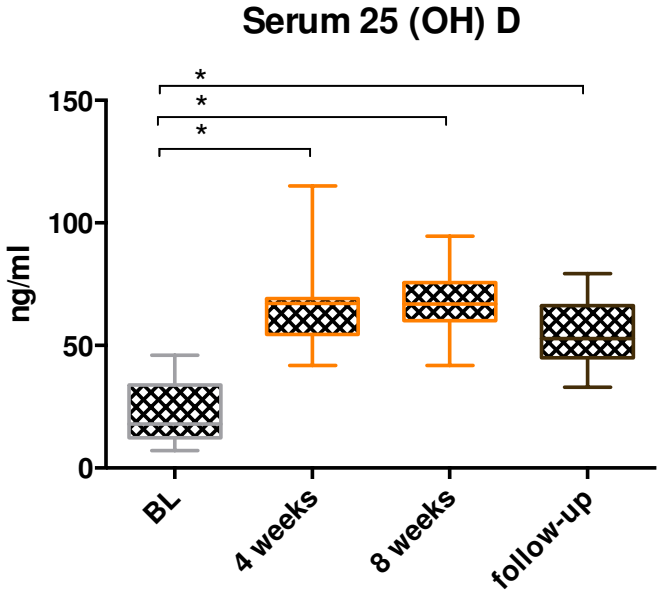
Distribution of CD4^{pos} -, CD8^{pos} – and Regulatory T Cells in the Upper and Lower Gastrointestinal Tract in Healthy Young Subjects

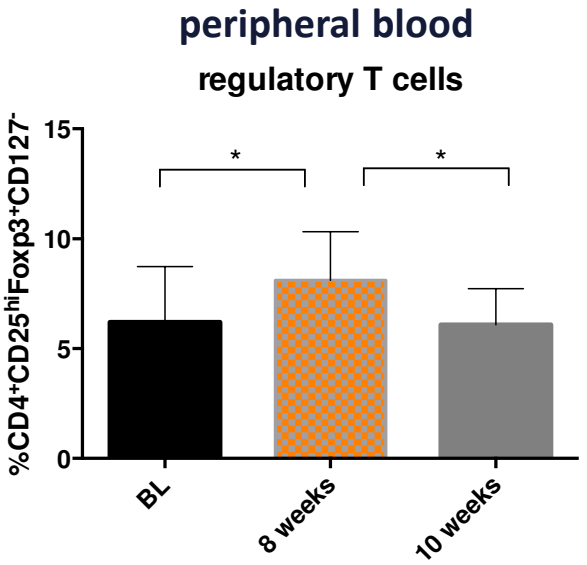
Martin Tauschmann[1], Barbara Prietl[1], Gerlies Treiber[1], Gregor Gorkiewicz[2], Patrizia Kump[3], Christoph Högenauer[3], Thomas R. Pieber[1*]

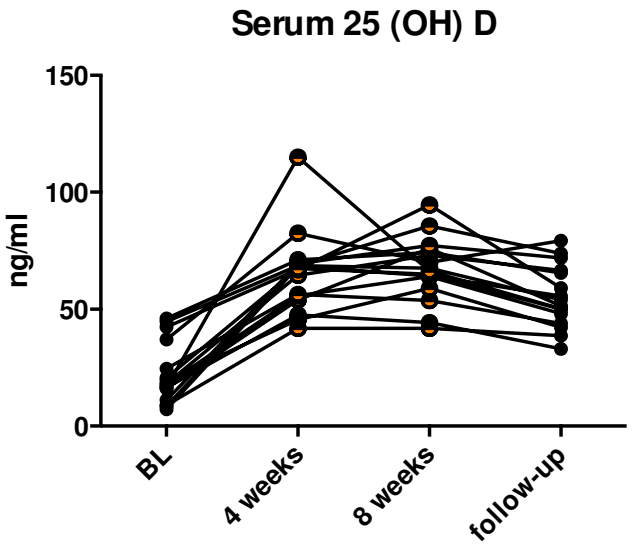


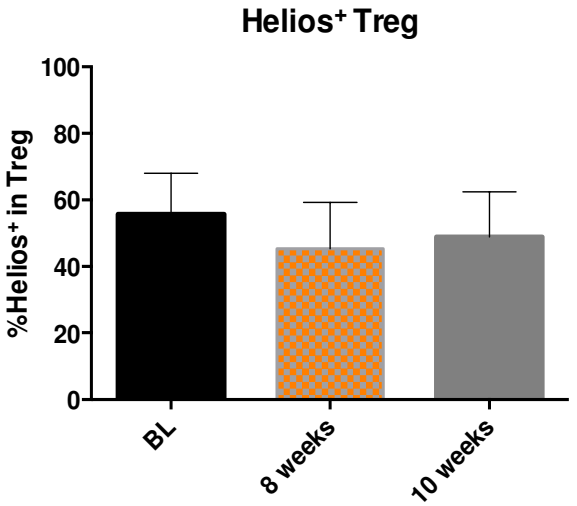
Plos one 2013

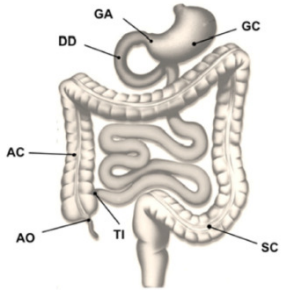
Vit D3: on blood Treg











Vit D3 on GI CD4⁺ and CD8⁺

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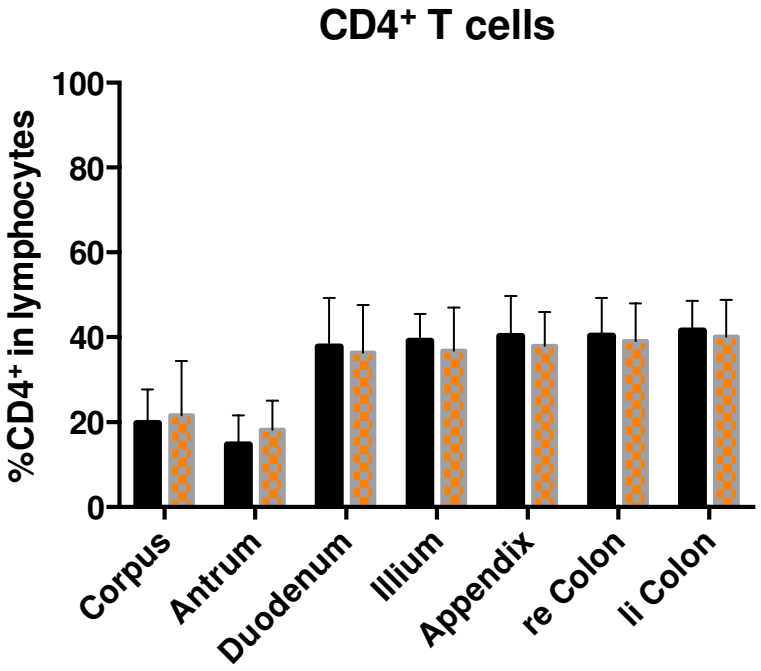

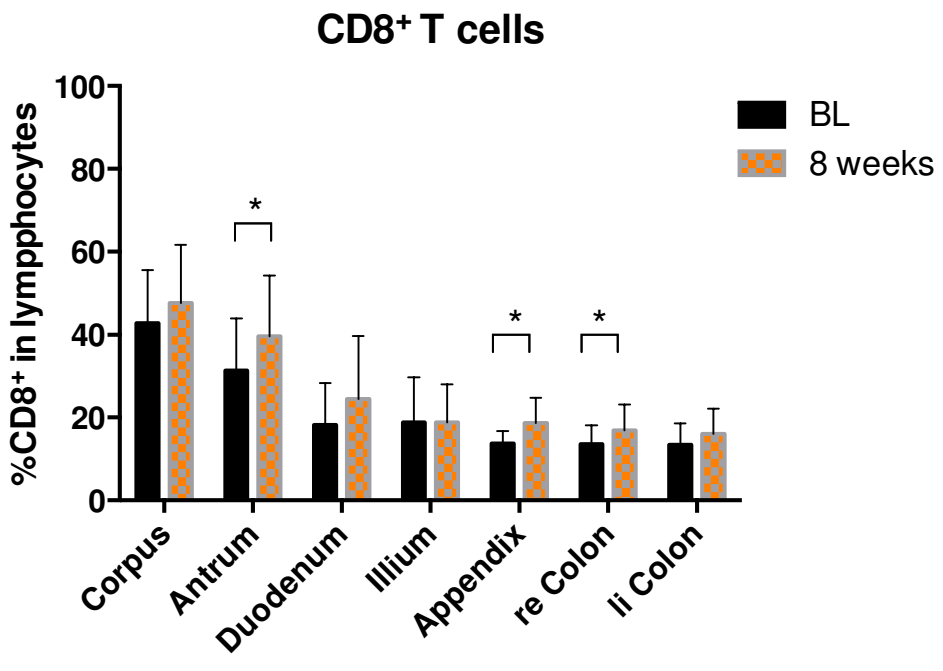

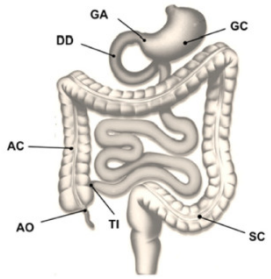

Vit D3 on GI Treg

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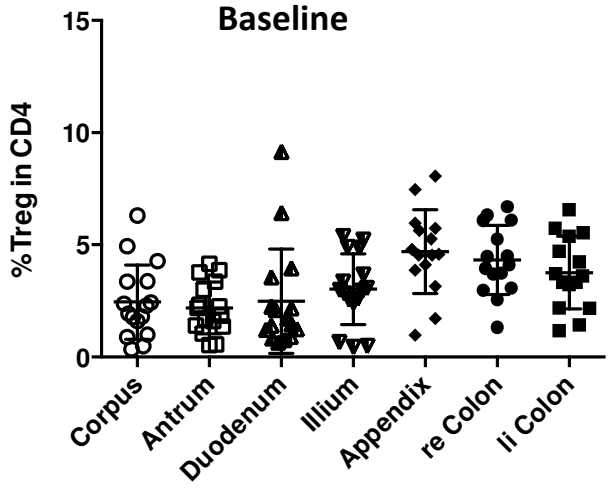
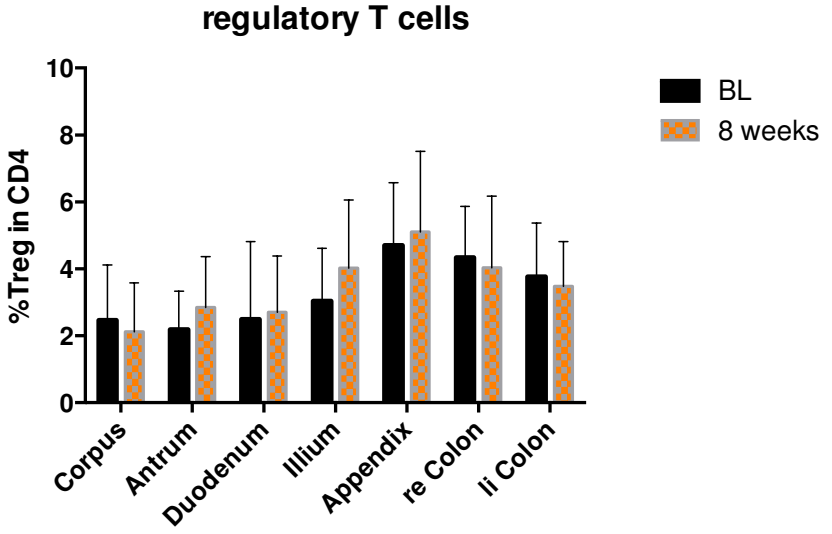
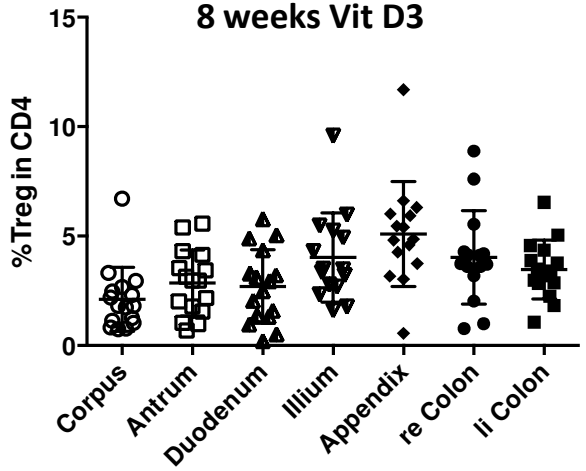
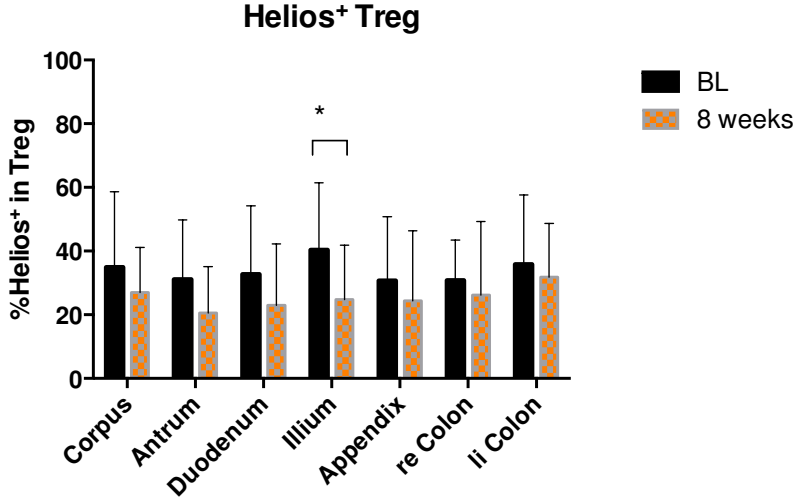
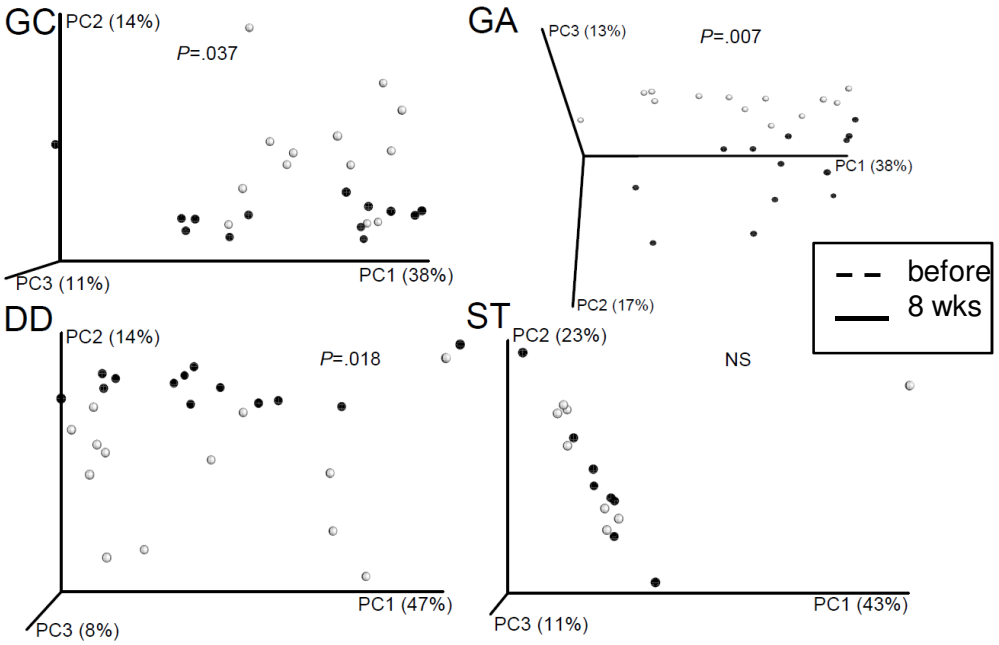


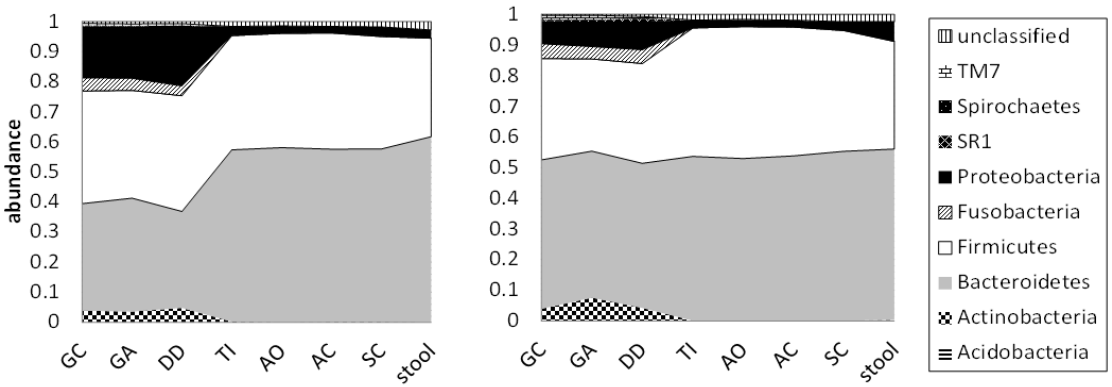






Vit D3 and Mikrobiom





- Vit D alters upper GI community structure
- Reduction of Proteobacteria
- Increase of richness in upper GI

Summary and Conclusion

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- Vitamin D3 – Cholecalciferol - **increases** peripheral regulatory T cells in healthy humans
- Impaired suppressive capacity in type 1 diabetes **improved** with Cholecalciferol supplementation along with preservation of fasting C-peptide
- 8 weeks of VitD3 did not alter total number of Treg in gastrointestinal mucosa in healthy humans but showed an distinct pattern in **Helios^{+} Treg** compartment
- Vitamin D3 **elevates** CD8^{pos} cytotoxic T cell numbers, accompanied by modulation of the gut microbiome with marked **reduction** of Gammaproteobacteria

  - Potential as **adjunctive immunomodulatory therapy** of immunomediated diseases like T1D in combination with other future immune therapies

Acknowledgements

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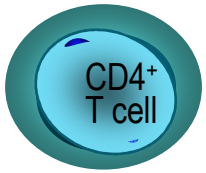
- Verena Pfeifer



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- Gregor Gorkiewicz
- Stefan Pilz

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- **ADPP Network**

ADPP
AUSTRIAN DIABETES PREVENTION PROGRAMME

- **Research support**
  - EASD and EFSD

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Biomarker for Personalised Medicine in Common Metabolic Disorders

Thank you!