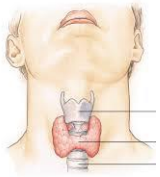
USZ Universitäts Spital Zürich

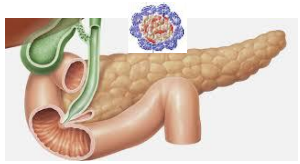
Autoimmunität

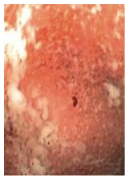
Dr. med. Urs Steiner

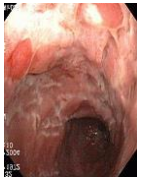
Autoimmune diseases

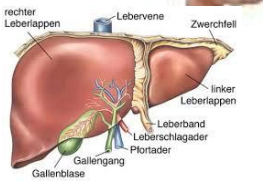
organ specific

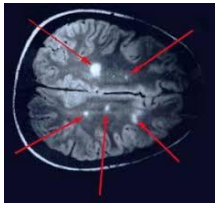




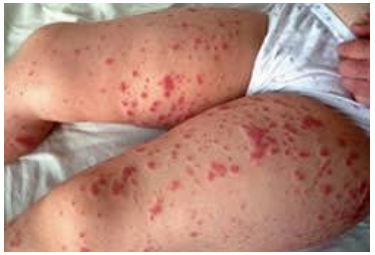


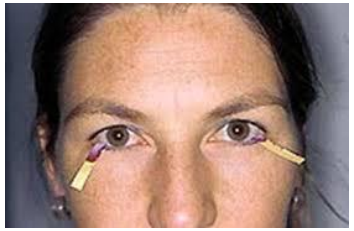


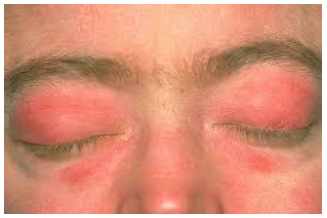




systemic



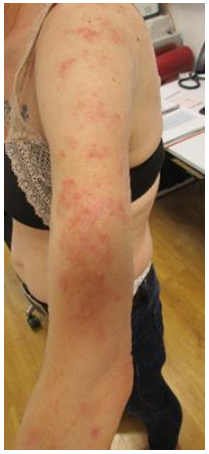


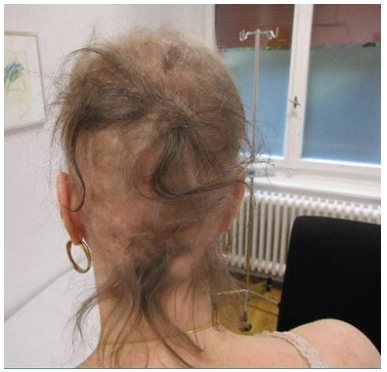


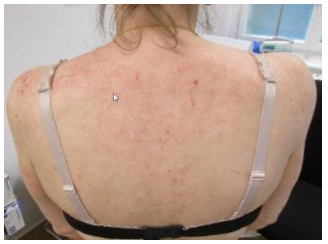
J.S. 1971

Medical history

- eczematous skin lesions since 2005
- scaring alopecia since 2006
- arthritis of the joints of fingers and toes since 2011
- Fatigue
- anxiety disorder/depression

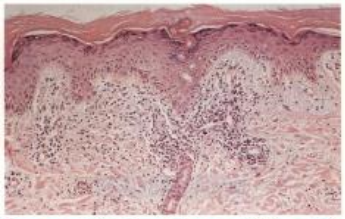


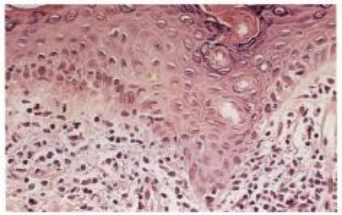




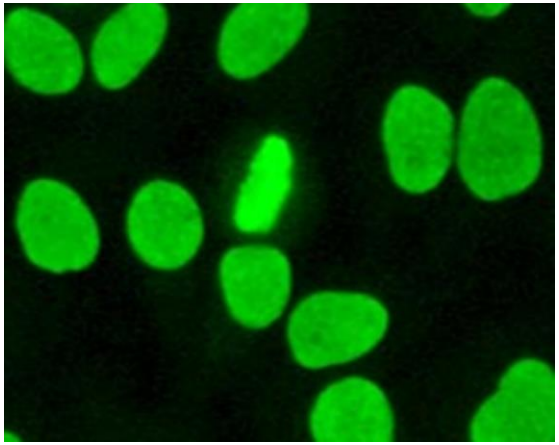
Histology

- Skin biopsy: Interface-Dermatitis with vacuoles





J.S. 1971



Laboratory results

- Immune serology
  - ANA increased with increased anti SSA-, anti SS-B-, anti ds-DNA-, anti SmD-, anti-C1q-, anti Cardiolipid IgM- antibodies
  - complement factors C3 und C4 decreased

- Hematology
  - lymphopenia; hemoglobin and platelets normal

- Kidney- and liver parameter normal, urine sediment normal

Systemic Lupus erythematodes (SLE)

Systemic Lupus International Collaborating Clinics (SLICC) criteria

Clinical Criteria

- Acute cutaneous LE
- **Chronic cutaneous LE**
- Oral or nasal ulcers
- **Non-scarring alopecia**
- **Arthritis**
- Serositis
- Renal (Protein / Crea Ratio or Protein 24h urine >0.5g)
- **Neurologic** (seizures, psychosis, Myelitis)
- Hemolytic anemia
- Leukopenie (<4000/μL) or **Lymphopenie (<1000/μL)**
- Thrombozytopenia (<100.000/μL)

Immunologic Criteria

- **ANA-Titer**
- **Anti-dsDNA**
- **Anti-Sm**
- **Anti-Phospholipid Ab**
- **Low complement (C3, C4, CH50)**
- Direct Coombs -Test (not with hemolytic anemia)

Classification as SLE:

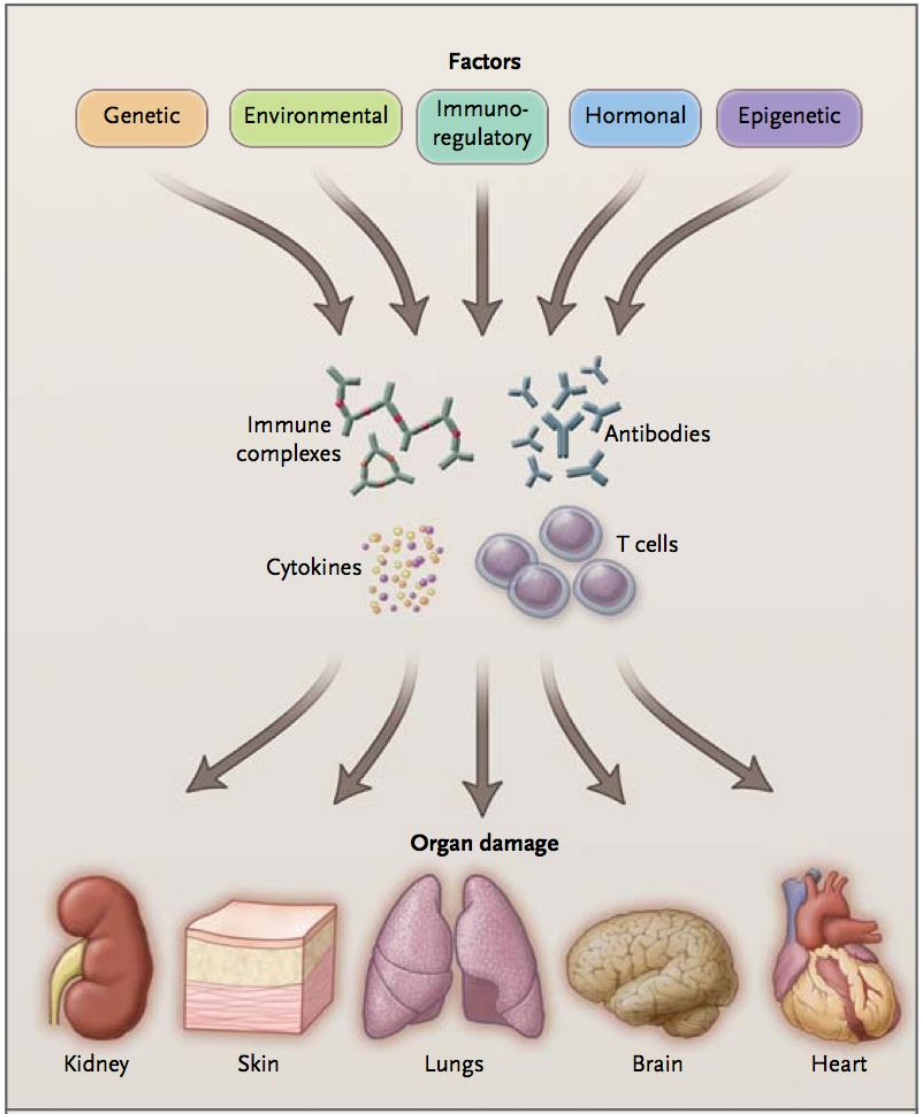
- **≥ 4 criteria positiv** (at least 1 clinical and 1 laboratory criteria)

OR

- **Positive ANA** or **anti-dsDNA** with biopsy proven **Lupus-Nephritis**

Petri M et al. Arthritis Rheum. 2012 Aug;64(8):2677-86.

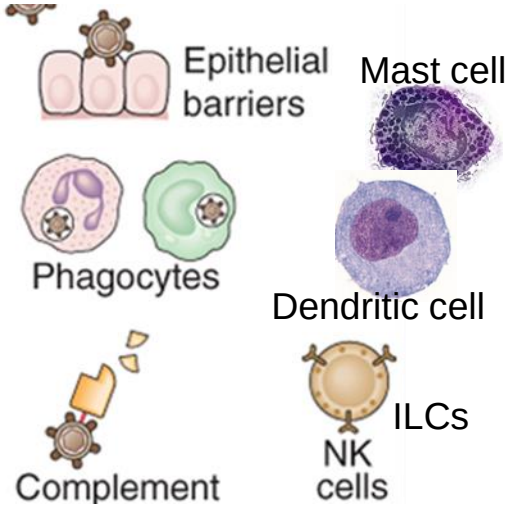
Systemic Lupus erythematodes (SLE)



Tsokos. *NEJM.* 2011

Immune System

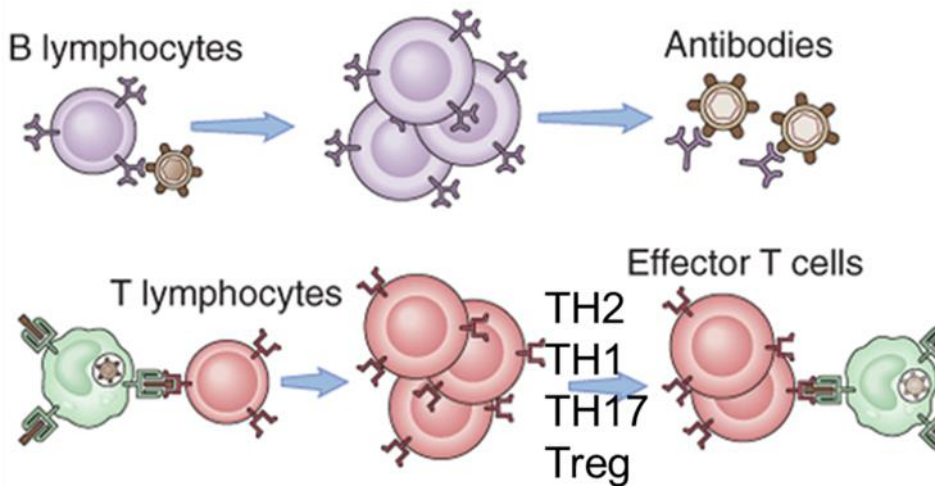
Innate Immunity



cytokines

rezeptors

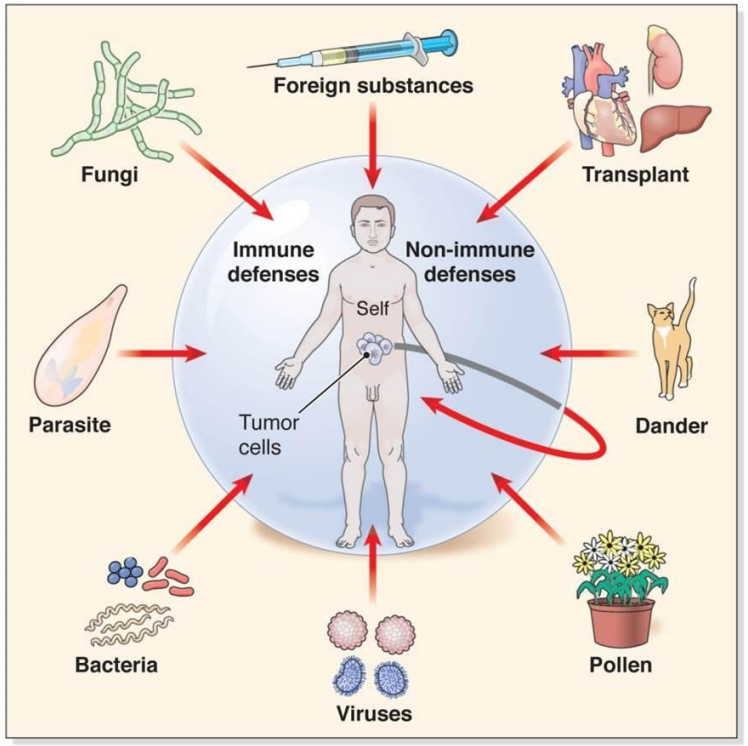
Adaptive Immunity

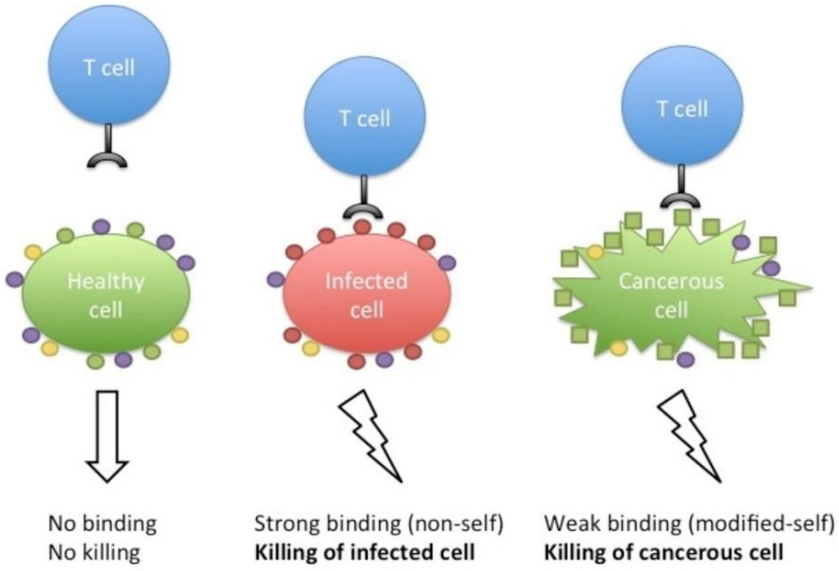


Abbas. Basic Immunology

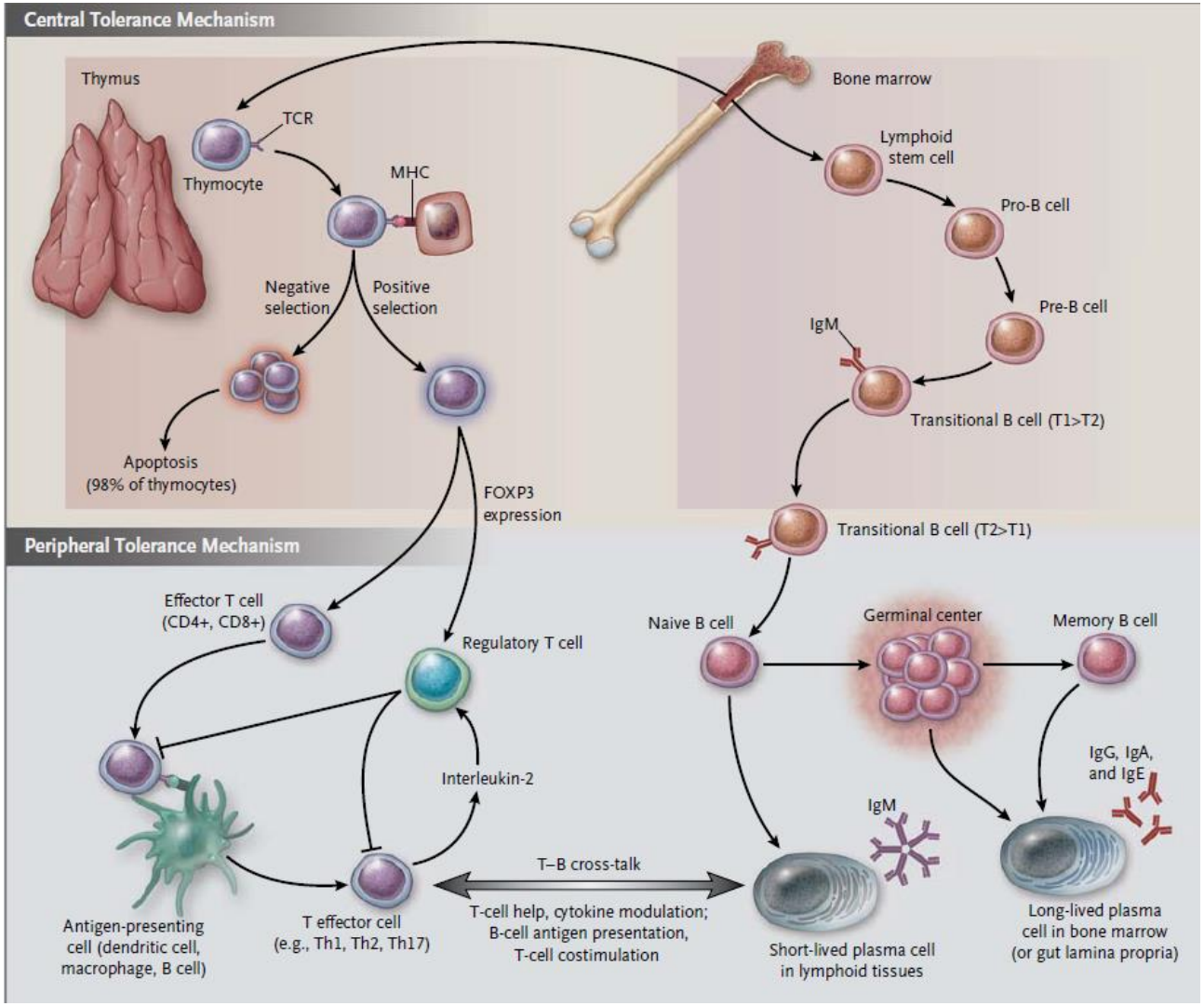
Immunotolerance

Differentiaton of self and non-self





Immunotolerance

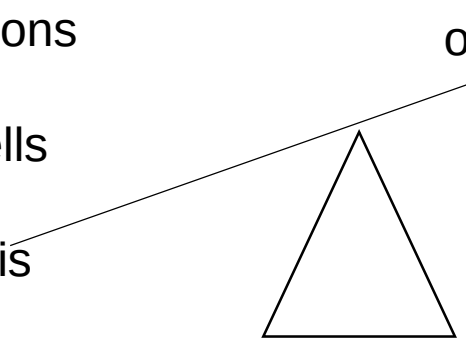


Gregory Feero W et al. *NEJM* 2011

Autoimmunity

Dysregulation of the immune system

- Excessive/uncontrolled immune mediated inflammation with damage of own cells/tissues



- Defence against infections
- Elimination of tumor cells
- Elimination of cell debris
- Defence of foreign cells (transplant)
- Elimination/supression of autoreactive immune cells → immunotolerance

Autoimmunity

Dysregulation of the immune system

- Genetic mutations

  → in the MHC-Region on chromosome 6
  → of the innate immune function (eg NOD2-Protein→ M. Crohn)
  → of cell-receptors
  → of cytokines and cytokine-receptors (IL-23)
  → of transcription factors

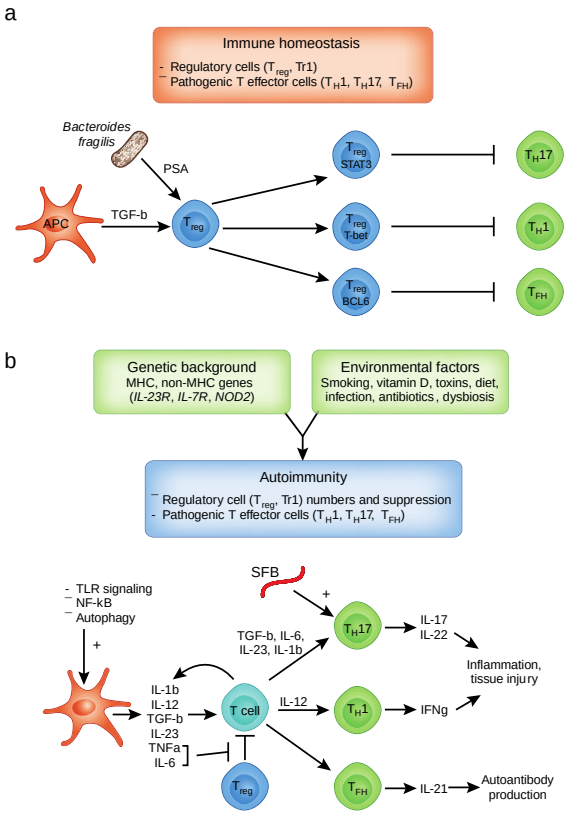
Selective survival advantage
In a highly infectious environment?

- Environmental factors

  → Infections
  → smoking
  → Microbiotica-nutrition
  → Toxins (dioxin)

on a defined genetic background
a specific environmental trigger becomes a risk factor for developing autoimmune disease

Autoimmunity

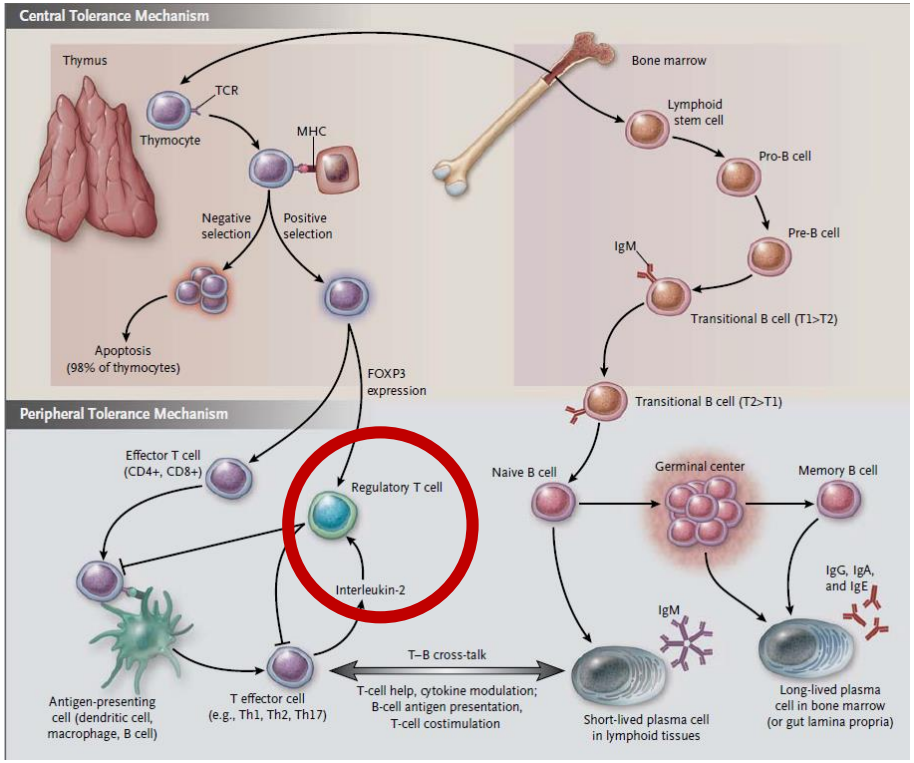


- Reduced Treg number and/or failure in their function

Kuchroo VK et al. *Nature Medicine* 2012

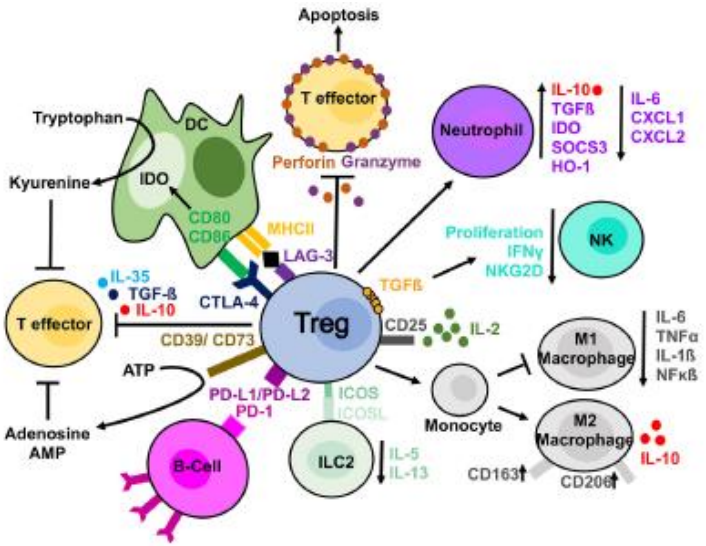
Regulatory Tcells in autoimmunity

Thymus is the crucial organ for the generation of Tregs



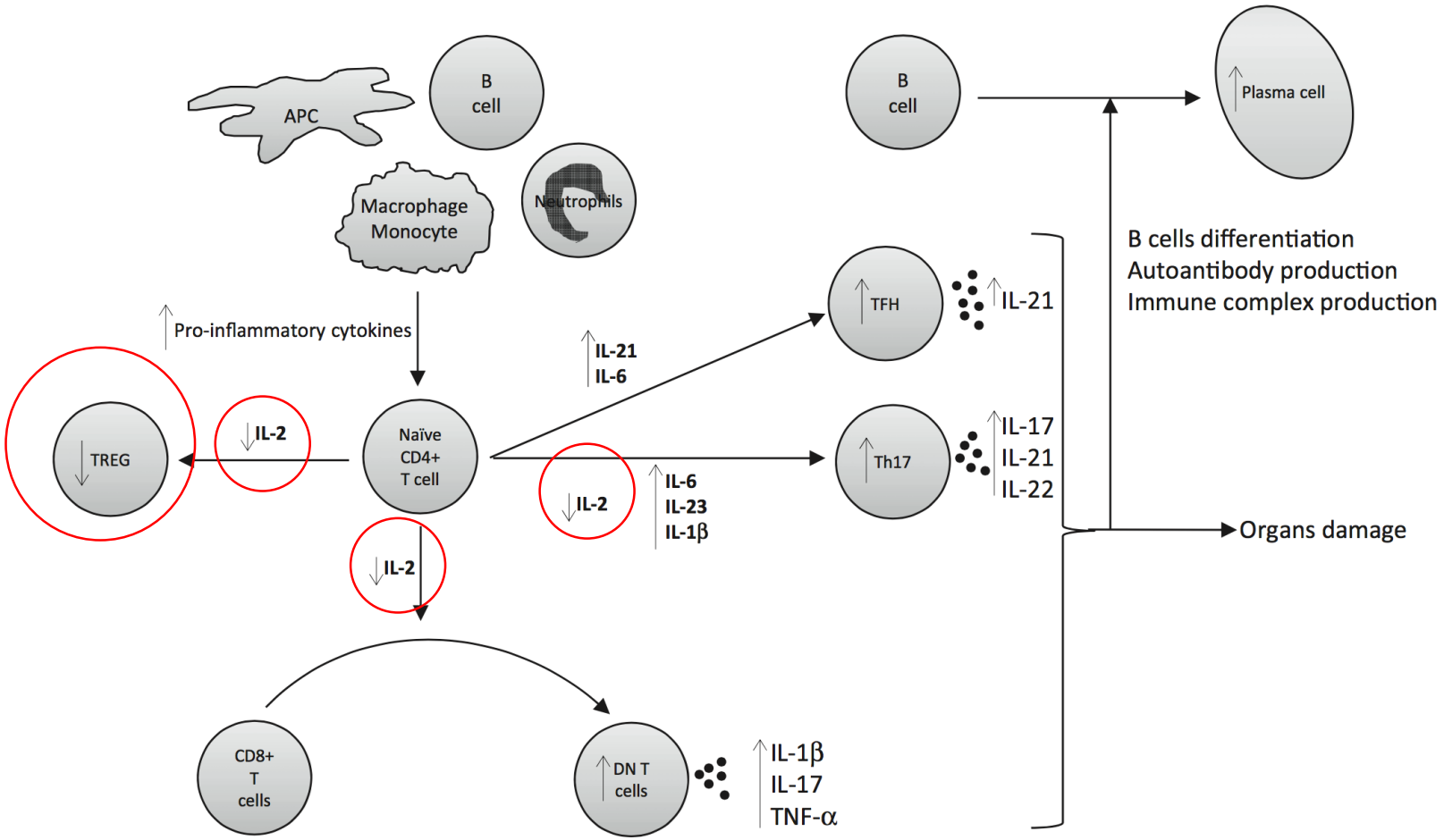
Gregory Feero W et al. *NEJM* 2011

Treg suppression of different cells by direct and indirect mechanisms



Romano et al. *Front.Immunol.* 2019

Role of IL-2 and regulatory T cells in SLE



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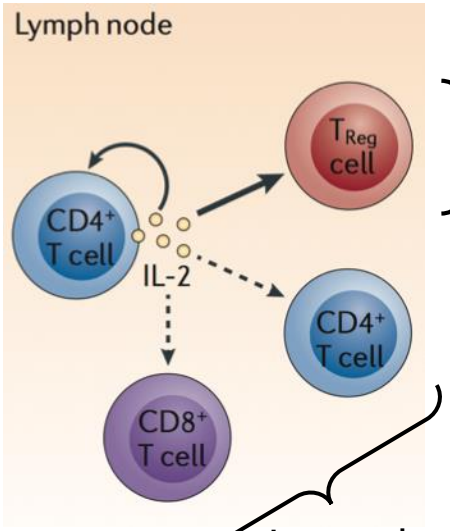
Comte et al. *Lupus* 2015

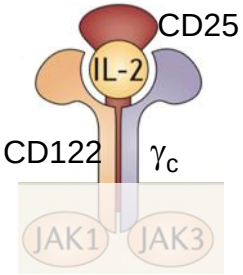
Biology of interleukin-2 (IL-2)



Immune regulation

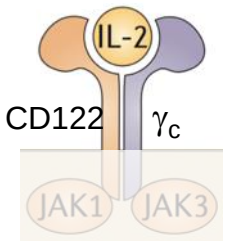
Immunity
- cancer
- infection

Trimeric receptor



Stimulation via
IL-2 receptor α (CD25)

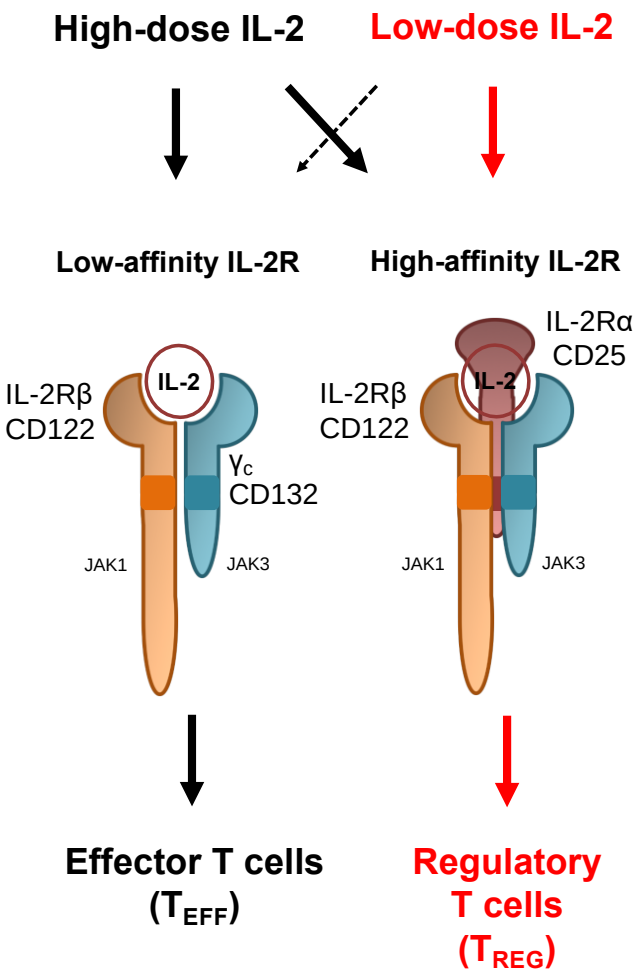
Dimeric receptor



Stimulation via
IL-2 receptor β (CD122)

Adapted from Boyman & Sprent. *Nat Rev Immunol* 2012

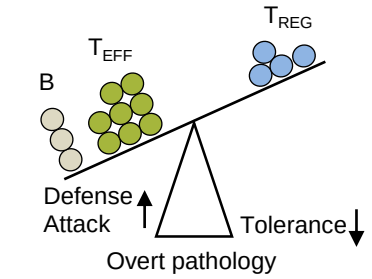
Biased IL-2 immunotherapy



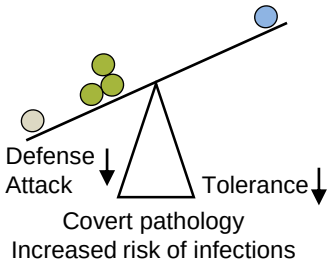
Adapted from *Raeber et al., Immunol Rev 2018*

Interleukin-2 and regulatory T cells (T_{REG})

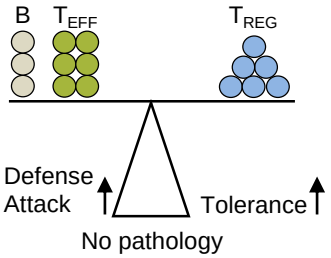
Systemic Lupus Erythematosus (SLE)



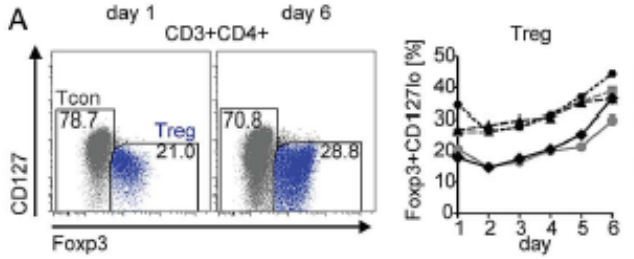
Immunosuppressive drugs

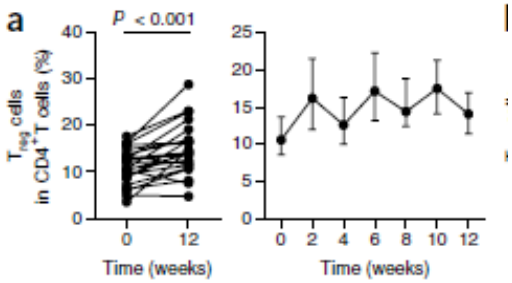


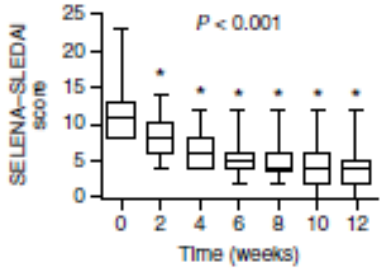
Interleukin-2



Low dose IL-2 in SLE

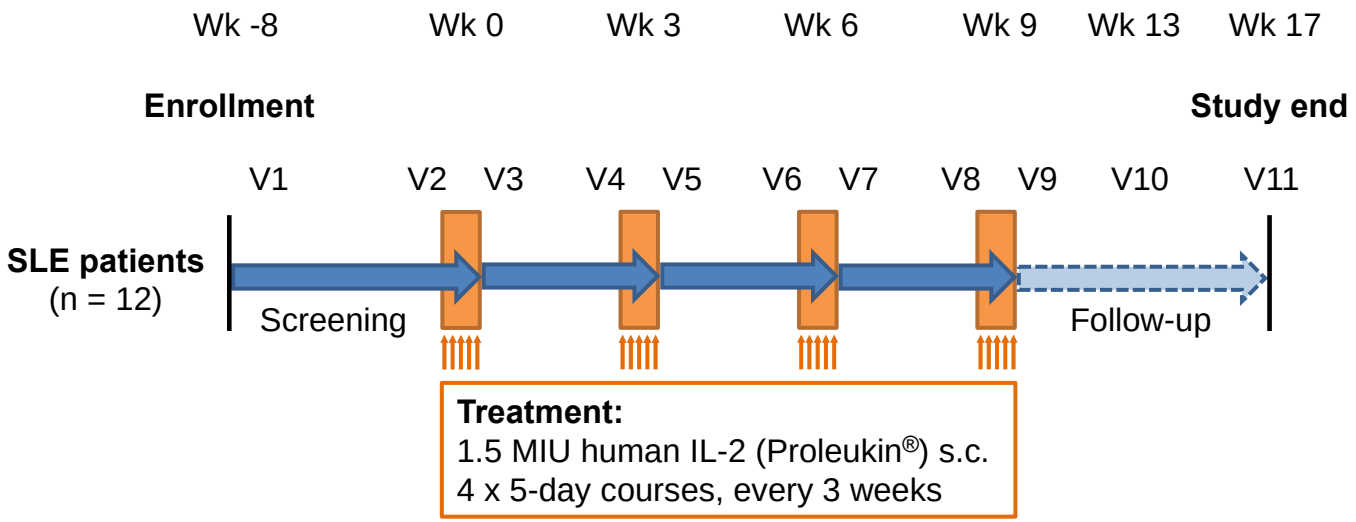






Humrich et al. Ann Rheum Dis. 2015
von Spee-Mayer et al. Ann Rheum Dis. 2016
He et al. Nat Med. 2016
Rosenzwajg et al. Ann Rheum Dis. 2018

Low-dose IL-2 trial in SLE patients
The Charact-IL-2 Trial (NCT03312335)

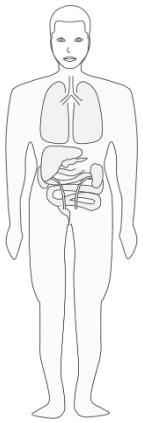


1° Endpoint: - Expansion of T_{REG} cells (V2 & V9)

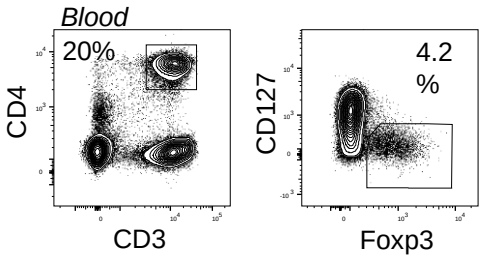
2° Endpoints:
- Immunophenotyping in blood and skin (V2-V9)
- Clinical response (V2, V5, V9)
- Reduction in concomitant medication (V2-V9)
- Safety (V2-V11)

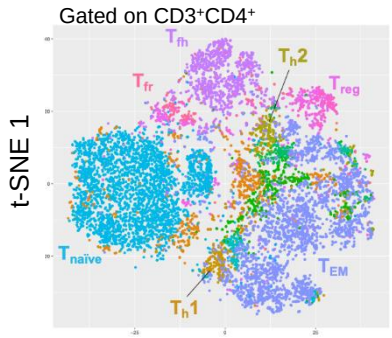
Raeber and Boyman. *https://clinicaltrials.gov/ct2/show/NCT03312335*

Charact-IL-2 Trial – Experimental analyses



Immunophenotyping of blood and skin



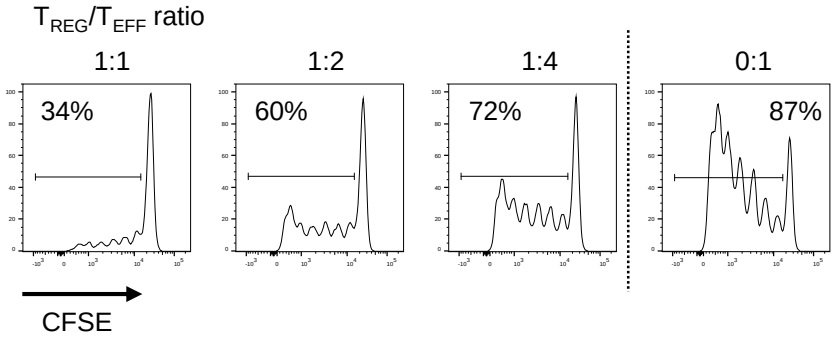


Analysis of soluble blood components

- Antibodies
- Cytokines
- Routine laboratory values

Functional assays

- T_{REG} suppression assay



Biobanking

- Peripheral blood mononuclear cells
- Serum
- RNA from sorted cells for sequencing (T_{REG}, $CD4^+$ T_{EFF}, $CD8^+$, $CD19^+$)

Charact-IL-2 Trial – Experimental analyses

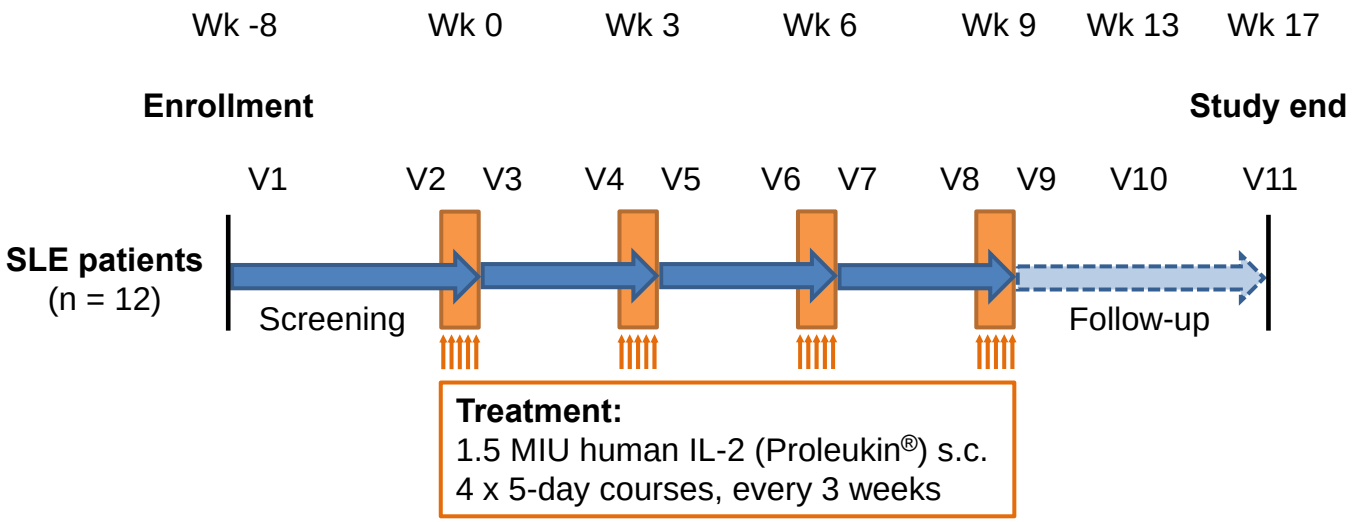
BD FACS Symphony: Acquisition of two times 24-30 parameters

Table 1: Flow cytometry panels for the Charact-IL-2 trial.

Panel	Colors	Cellular subsets
A	13	*Lineage discrimination:* $CD4^+$ and $CD8^+$ T cells; $Foxp3^+$ $CD127^{lo}$ $CD25^{hi}$ Treg; T resident memory cells. *Expression:* CD39, Ki67.
B	9	*Lineage discrimination:* Neutrophils (CD16, CD66b). *Expression:* CD124, CD132, CD123a1, CXCR1, CXCR2, MPO.
C	28	*Lineage discrimination:* B cells (memory, naïve, plasmablasts, regulatory B cells); NK cells ($CD56^{brigth/dim}$); NKT cells; ILCs (ILC1, ILC2, ILC3); DCs (BDCA1, BDCA3, CD16 monocyte derived DC, plasmacytoid DC); monocytes (classical, intermediate, non-classical); $CD4^+$ T_{fh}, $CD127^{lo}$ $CD25^{hi}$ Treg; $CD4^+$ and $CD8^+$ $T_{naïve}$, T_{CM}, T_{EM}, T_{EMRA}; $CD4^+$ and $CD8^+$ γδ T cells. *Expression:* CD25, CD122, PD-1.
D	22	*Lineage discrimination:* $CD4^+$ T_h1, T_h1*, T_h2, T_h17, T_h22, T_{fh}; $CD4^+$ and $CD8^+$ $T_{naïve}$, T_{CM}, T_{EM}, T_{EMRA}, T_{SCM}; $CD4^+$ and $CD8^+$ γδ T cells; $CD127^{lo}$ $CD25^{hi}$ Treg. *Expression:* CD25, CD122, PD-1, TIM-3, CCR8.

Abbreviations: Tfh, follicular helper T; Treg, regulatory T; Tfr, follicular regulatory T; MPO, myeloperoxidase; NK, natural killer; ILC, innate lymphoid cell; DC, dendritic cell; Tnaïve, naïve T; TCM, central memory T; TEM, effector memory T; TEMRA, effector memory RA T; TSCM, stem cell memory T; PD-1, programmed cell death 1; TIM-3, T cell immunoglobulin and mucin-domain containing protein-3.

Charact-IL-2 Trial



- **11 patients included**
- **9 have completet the study**
- ***1 additional patient needed***
- **Therapy is well tolerated and effective**
- **2 patients decided to continue the therapy in off label use**

Raeber and Boyman. *https://clinicaltrials.gov/ct2/show/NCT03312335*

Conclusion and future perspectives

- Regulatory T cells (Tregs) can prevent autoimmunity and control inflammation
- Low-dose IL-2 treatment:
    - is well tolerated and expands and activates Tregs
    - restores Treg homeostasis in a physiological way
    - directly addresses the pathophysilogy in SLE and has the potential to become a novel targeted treatment strategy in SLE
- The potential use of CD25-biased IL-2 complexes (Boymanlab, USZ) will further increase the in vivo half life of IL-2 and the selectivity for Tregs

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Vielen Dank für Ihre Aufmerksamkeit!

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