Blood natural killer cell deficiency reveals an immunotherapy strategy for atopic dermatitis

Mack MR, Brestoff JR, Berrien-Elliott MM, Trier AM, Yang TB, McCullen M, Collins PL, Niu H, Bodet ND, Wagner JA, Park E, Xu AZ, Wang F, Chibnall R, Council ML, Heffington C, Kreisel F, Margolis DJ, Sheinbein D, Lovato P, Vivier E, Cella M, Colonna M, Yokoyama WM, Oltz EM, Fehniger TA, Kim BS.

Sci Transl Med. 2020 Feb

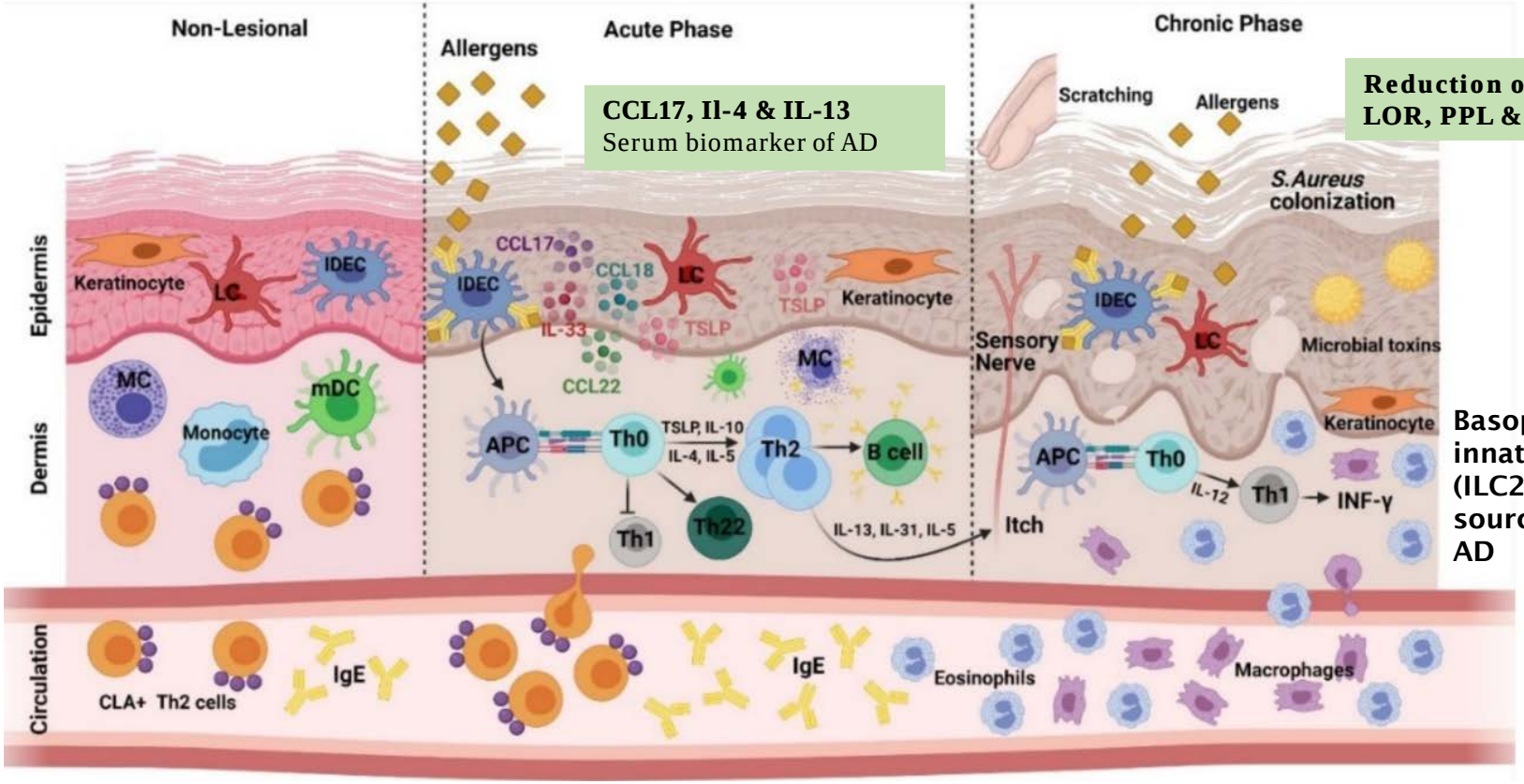
JC: Applied Immunology and Tissue Regeneration

Tamara Wais
23.05.22

Atopic dermatitis (AD)

- Chronic inflammatory skin disease
- 230 million people worldwide are suffering from AD
- Affects almost 15–20% of children in developed countries
- Multifactorial complex disease:
  - Skin barrier abnormalities
  - Itch
  - Skin inflammation
  - Immune dysregulation
  - Genetic and environmental factors

AD and skin inflammation

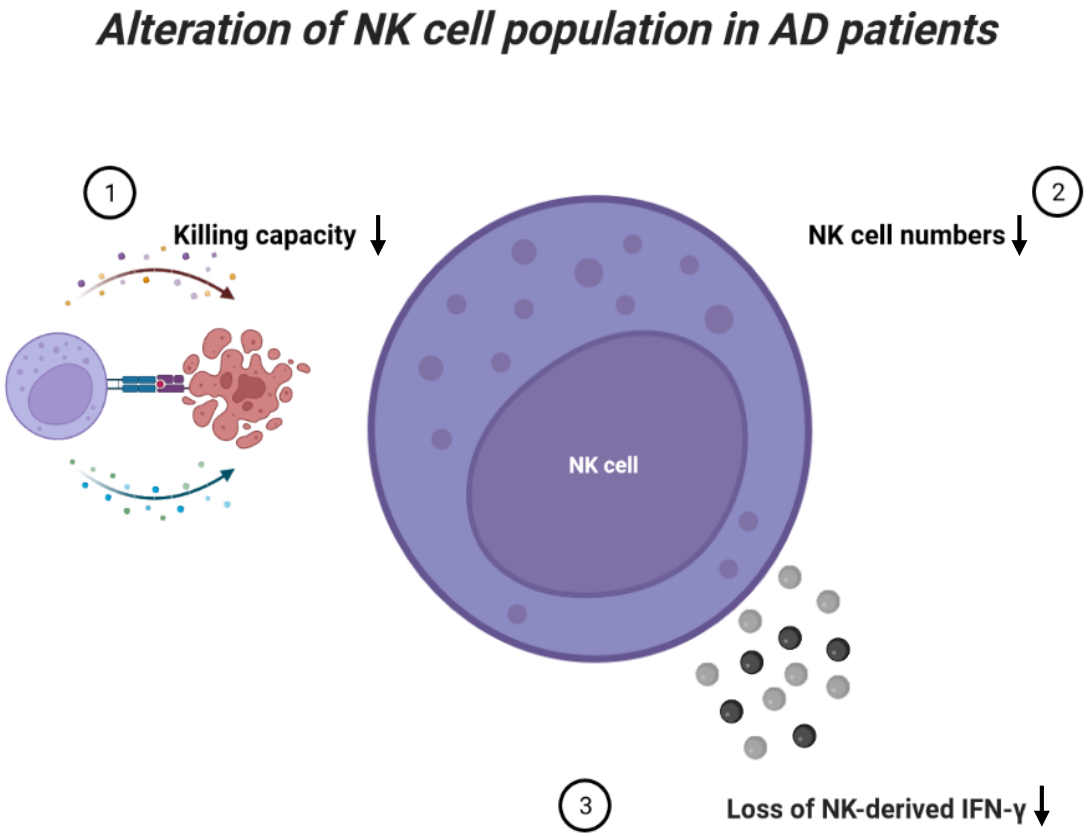


Basophils and group 2 innate lymphoid cells (ILC2s) are major source of cytokines in AD

Type 2 immune cells promote AD pathogenesis

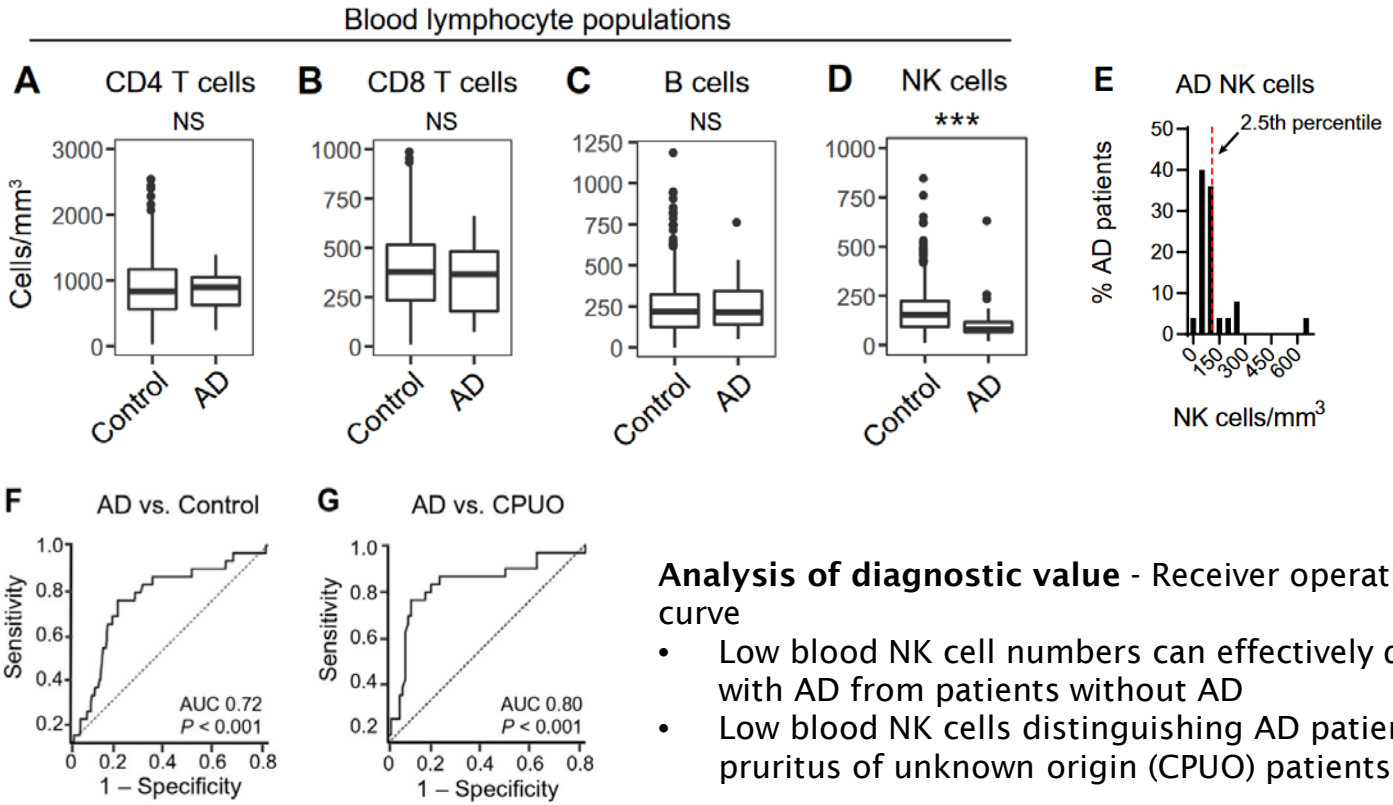
- IFN-γ suppress type 2 inflammation
- NK cells and IFN-γ can restrain ILC2 responses in vitro and during allergic lung inflammation

NK cells are dysfunctional in AD patients and contribute to the disease process



NK cell deficiency is a diagnostic feature of moderate-to-severe AD

- Analysis of blood lymphocyte subpopulations in 25 adult patients with moderate-to-severe AD and compared them to a control cohort

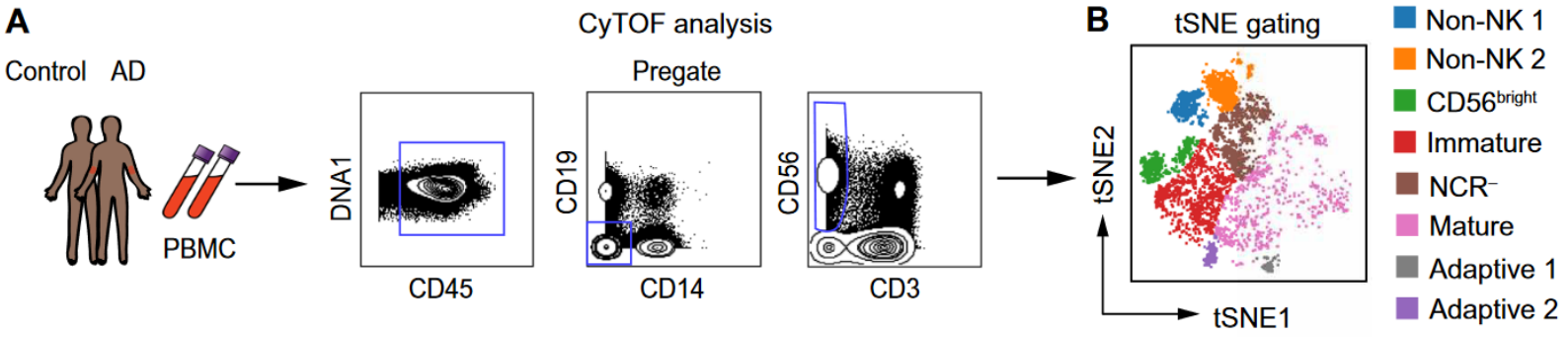


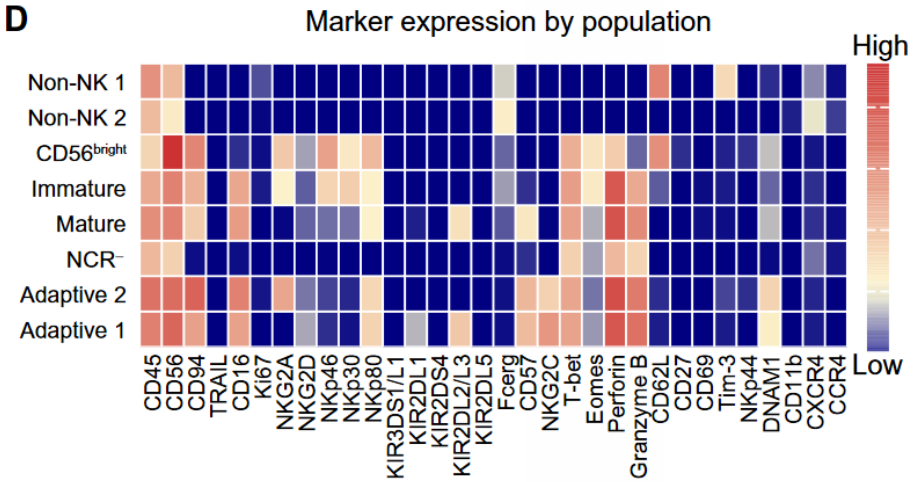
72% of AD cohort had NK cell numbers below the 2.5th percentile of normal (<105 NK cells/mm^3)

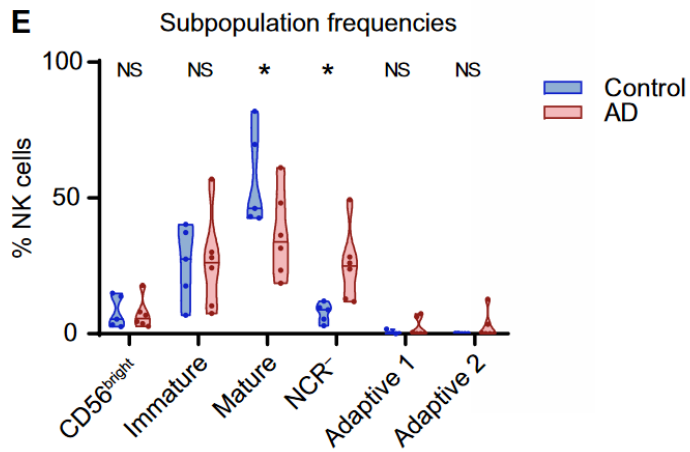
Analysis of diagnostic value - Receiver operating characteristic (ROC) curve

- Low blood NK cell numbers can effectively differentiate patients with AD from patients without AD
- Low blood NK cells distinguishing AD patients from chronic pruritus of unknown origin (CPUO) patients

Patients with AD exhibit alterations in specific subpopulations of NK cells





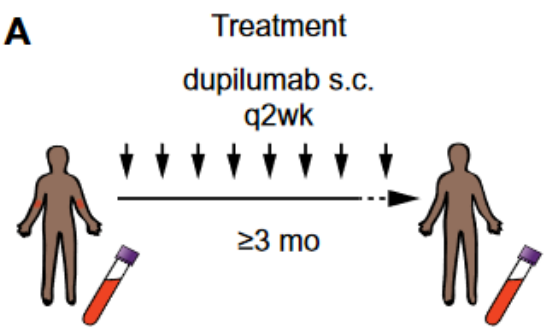


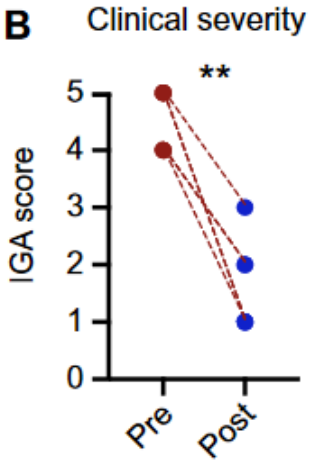
Mature NK cells:
CD56dim, granzyme B, perforin, CD57 and killer Ig-like receptors (KIRs)

- Selective reduction in mature CD56dim NK cells,
- Increased frequencies of nonclassical natural cytotoxicity receptor-negative population(NCR-)

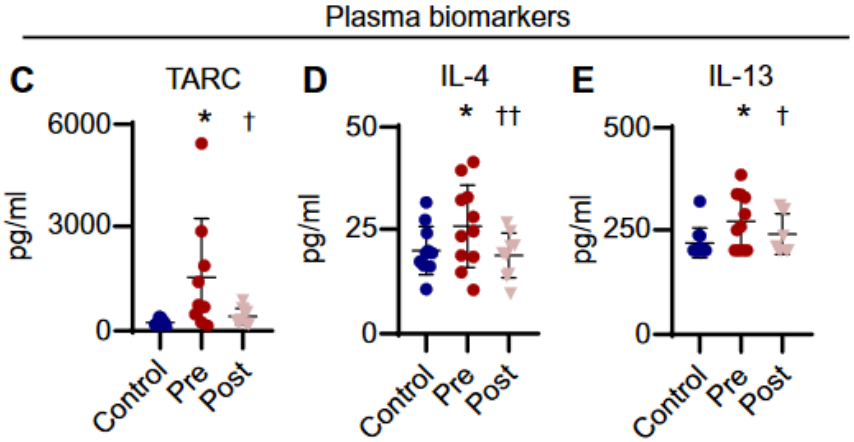
Type 2 cytokine blockade reverses NK cell defects in patients with AD

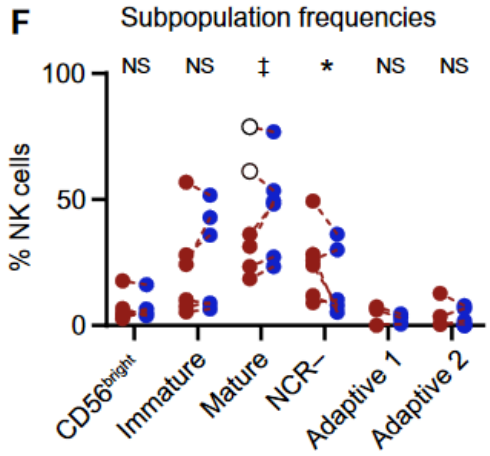
Dupilumab: anti–IL-4 receptor α (IL-4Rα) monoclonal antibody (mAb)
→ Highly effective for the treatment of moderate-to-severe AD

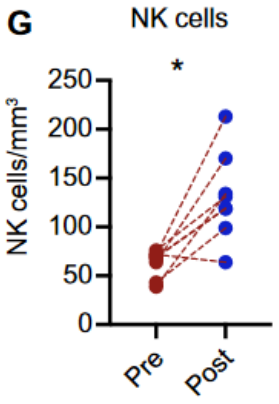




Global clinical assessment of AD severity
0 = no disease
5 = very severe disease



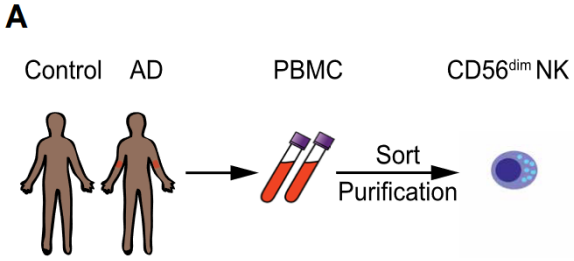


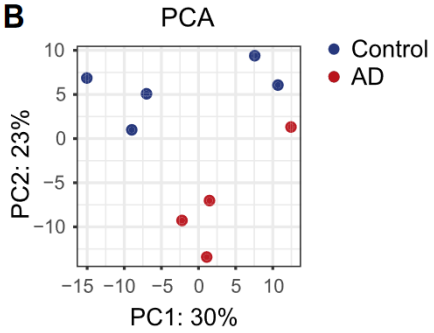


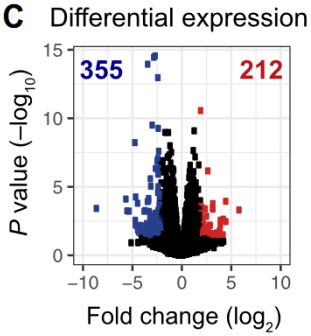
AD serum biomarkers: TARC (CCL17), IL-4, and IL-13

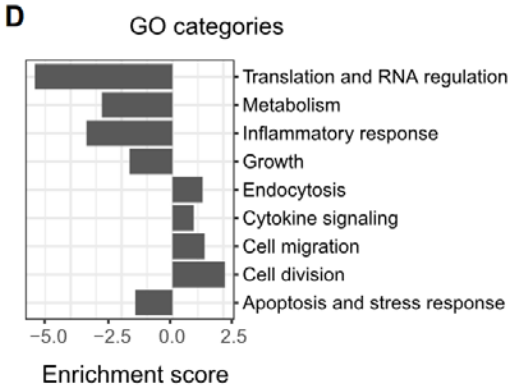
AD NK cells exhibit cellular features of activation-induced cell death

RNA-seq of sort-purified CD56dim NK cells from both patients with AD and control

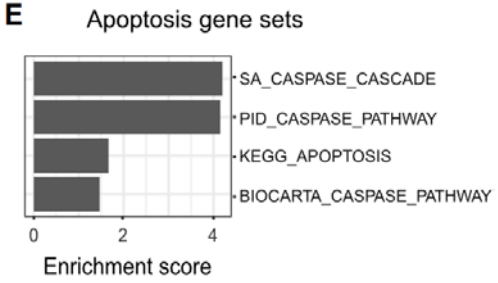


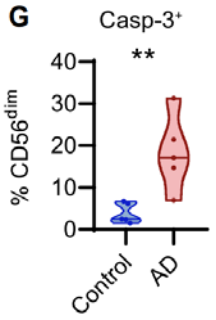






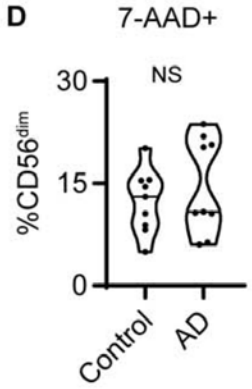
<u>In which cellular mechanisms are these differentially expressed genes involved?</u>
Endocytosis, cytokine signaling, cell migration, cell division, suggest an **enhanced activation state**



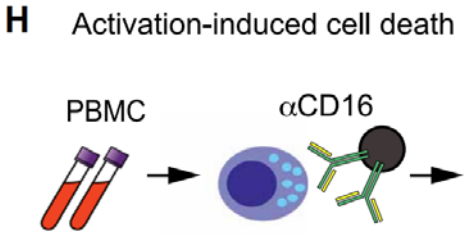


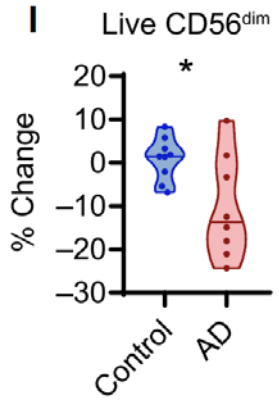
- Caspase-associated and apoptotic gene sets were enriched in AD CD56dim NK cells
- Increased activity of the proapoptotic effector caspase-3 in AD

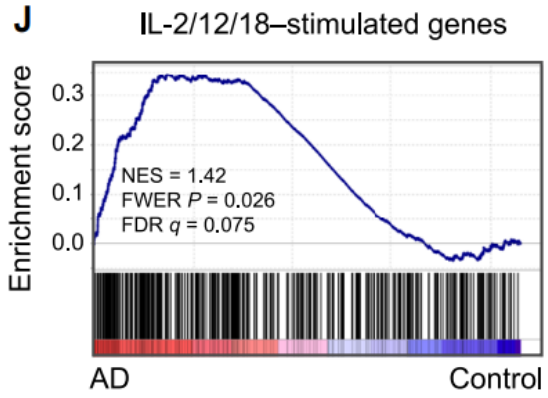
AD NK cells exhibit cellular features of activation-induced cell death

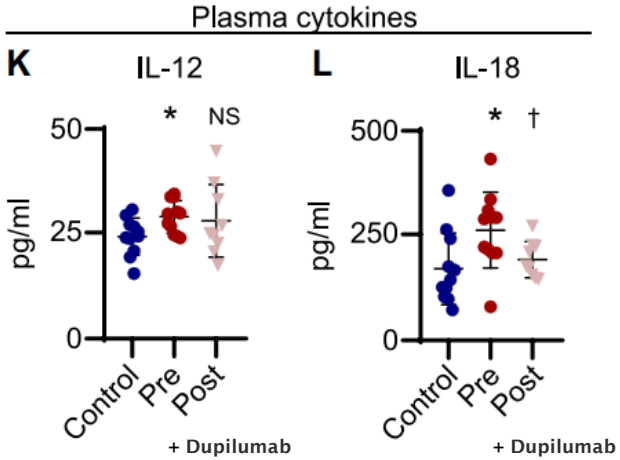


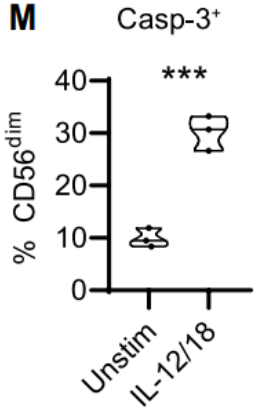
Low-affinity Fc receptor CD16 is a key mediator of antibody-dependent cellular cytotoxicity → **NK undergo AIDC**

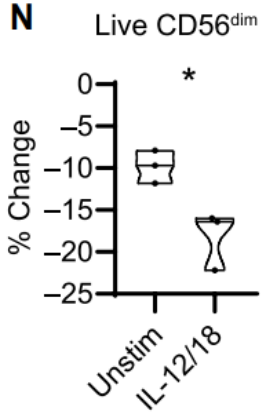








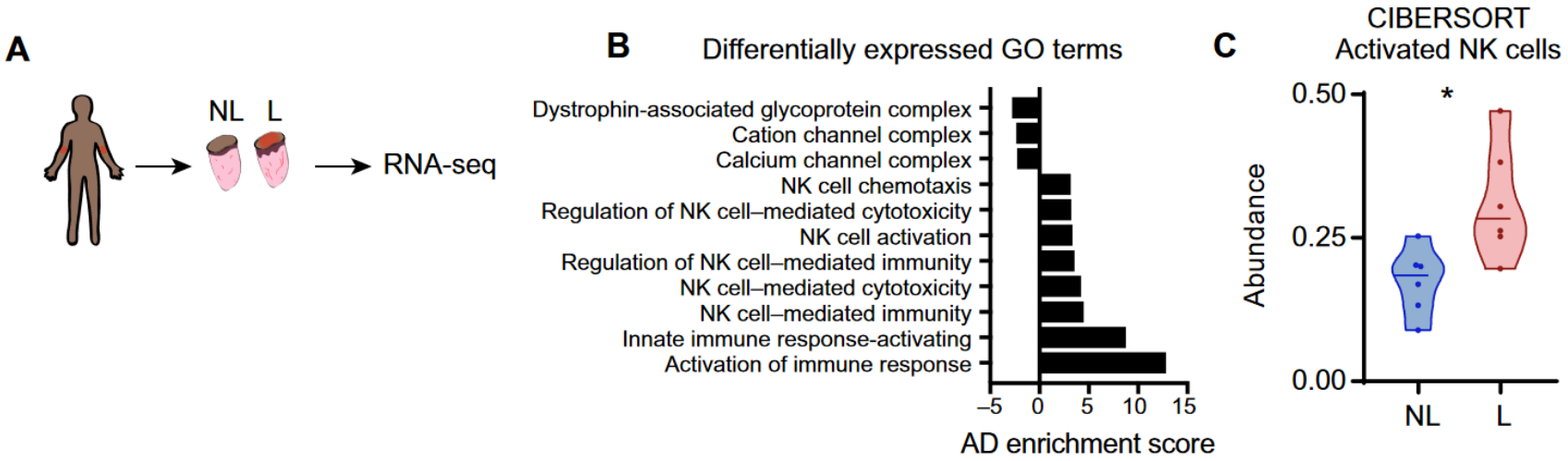




IL-18 may be associated with disease activity

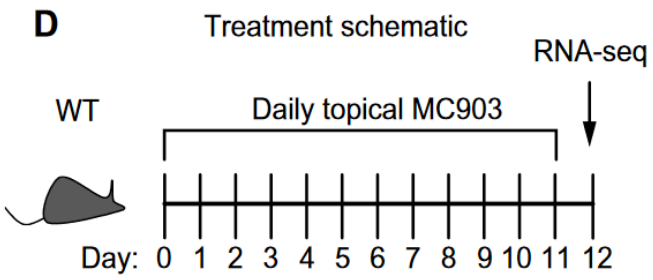
NK cells are enriched in lesional AD skin and limit type 2 inflammation

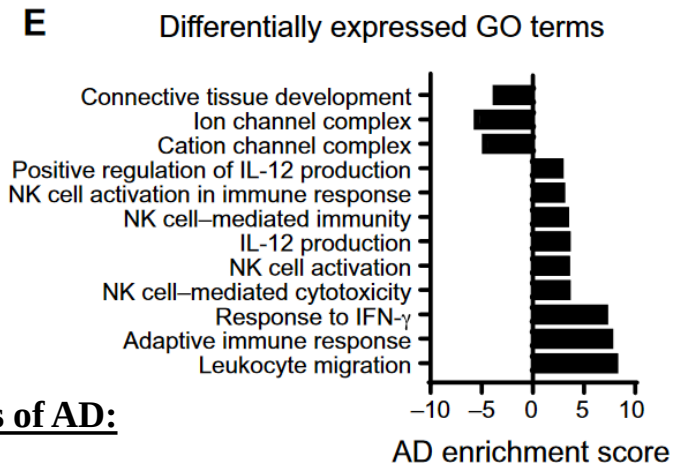
RNA-seq of paired lesional and nonlesional skin biopsies from six patients with AD

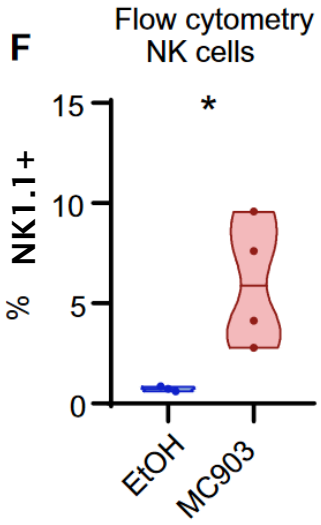


NK cells are enriched in lesional AD skin and limit type 2 inflammation

Standardized protocol of topical MC903 (calcipotriol) application daily for 12 days





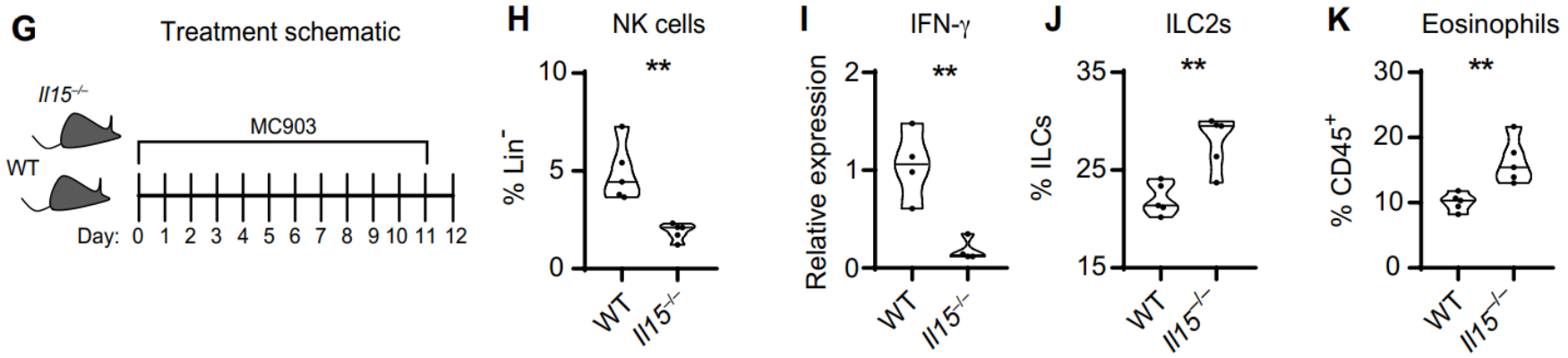


The model capitulates the central features of AD:

- Erythema (redness)
- Scaling
- Blood eosinophilia
- Serum IgE elevation, itch behavior
- inflammatory cellular infiltration

NK cells are enriched in lesional AD skin and limit type 2 inflammation

Does the systemic loss of NK cells in AD patients affect the disease process?



Il15−/− mice are developmentally NK cell deficient

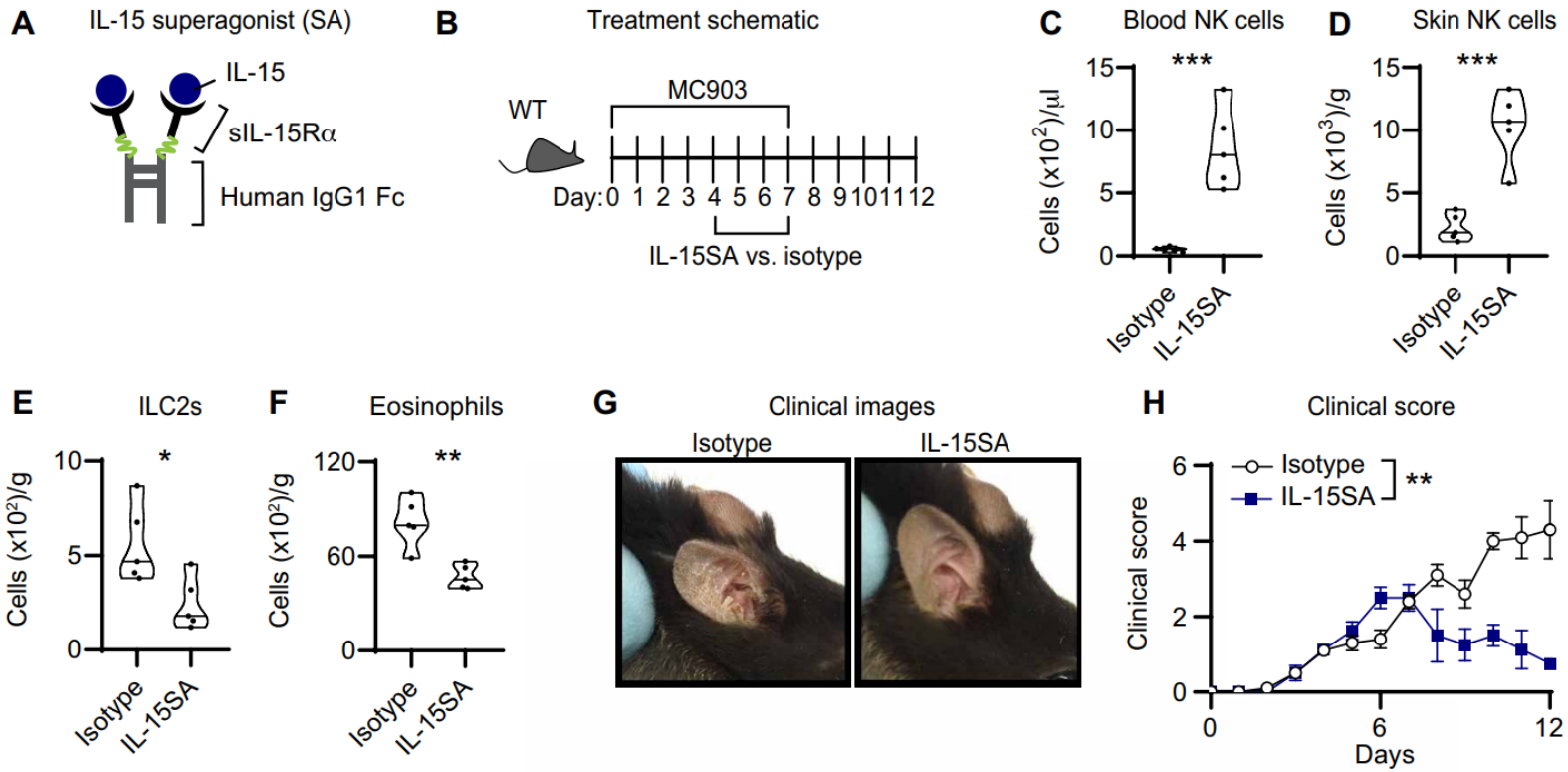
Th2%?

Cytokine levels?

Disease severity?

IL-15 superagonism promotes NK cell–dependent resolution of AD-like inflammation

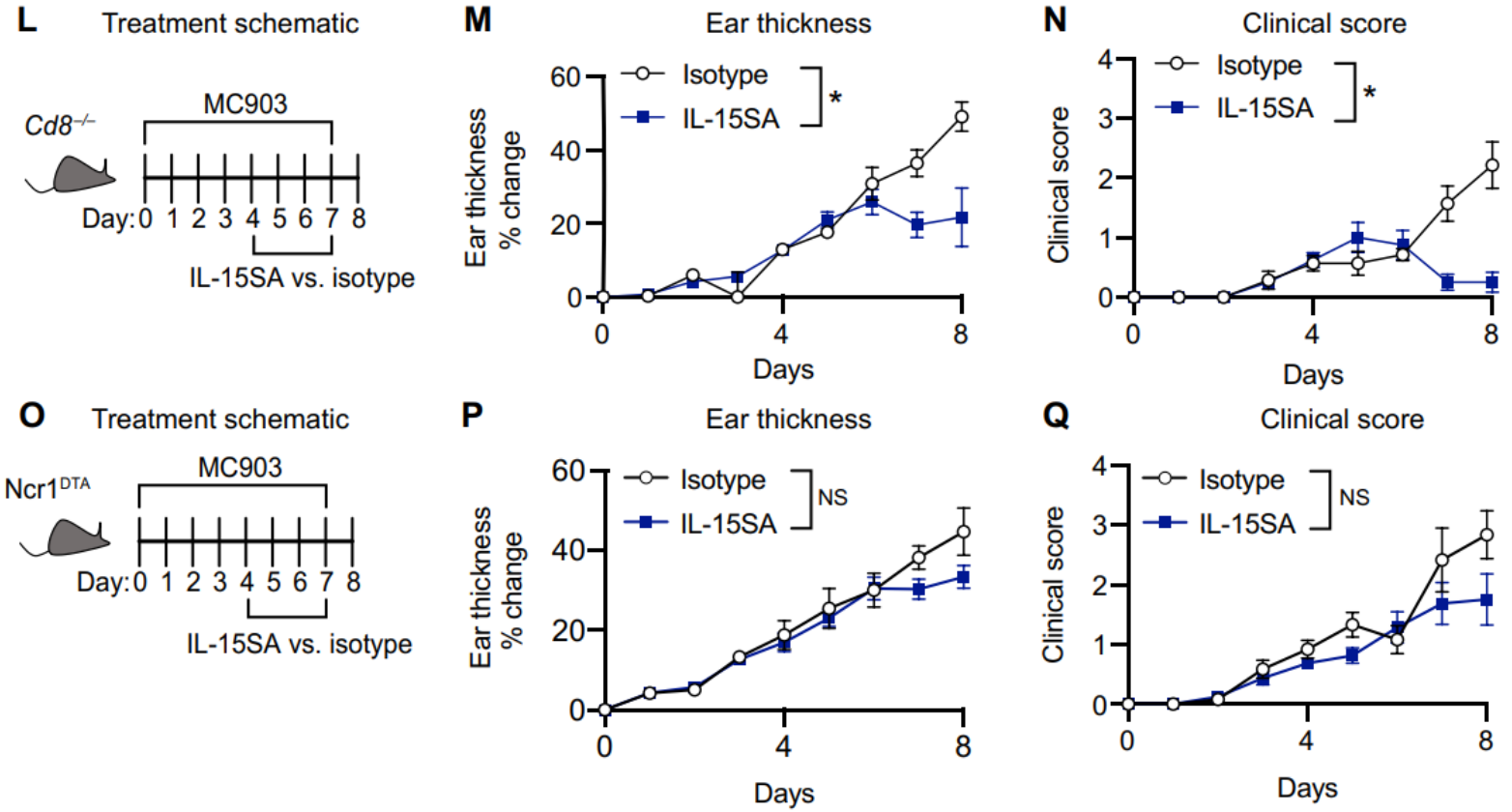
- What happens when NK cells are boosted?



- **These cellular changes were accompanied by a robust reduction in disease severity including clinical scoring, skin thickness and histopathology**

IL-15 superagonism promotes NK cell–dependent resolution of AD-like inflammation

IL-15 is important in generating memory CD8 T cell responses



Summary

- Low peripheral blood NK cells in patients with AD have diagnostic value in distinguishing AD from both our cohort of non-AD patients and specifically patients with CPUO

- CyTOF and RNA-seq analysis of both control and diseased NK cells demonstrated that AD-associated NK cells have a distinct transcriptional program indicative of AICD and a selective loss of a subset of mature CD56dim NK cells

- NK cells are enriched in lesional AD skin and limit type 2 inflammation

- NK cell–boosting by IL-15 superagonist lead to marked improvement in AD-like disease in mice