nature medicine

Ankersmit Laboratory
for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

Common clonal origin of central and resident memory T cells following skin immunization

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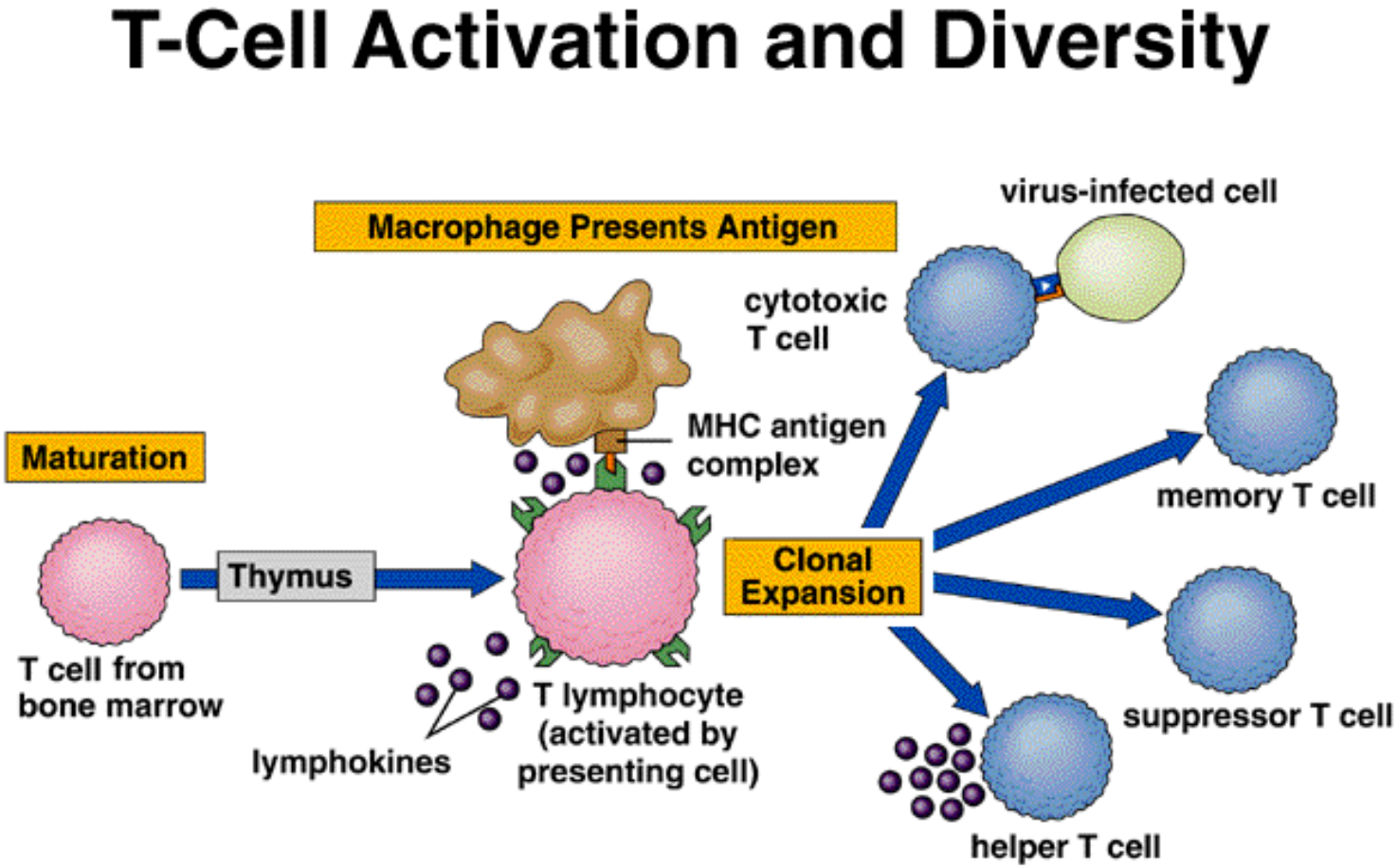
Presented by Lucas Nemec

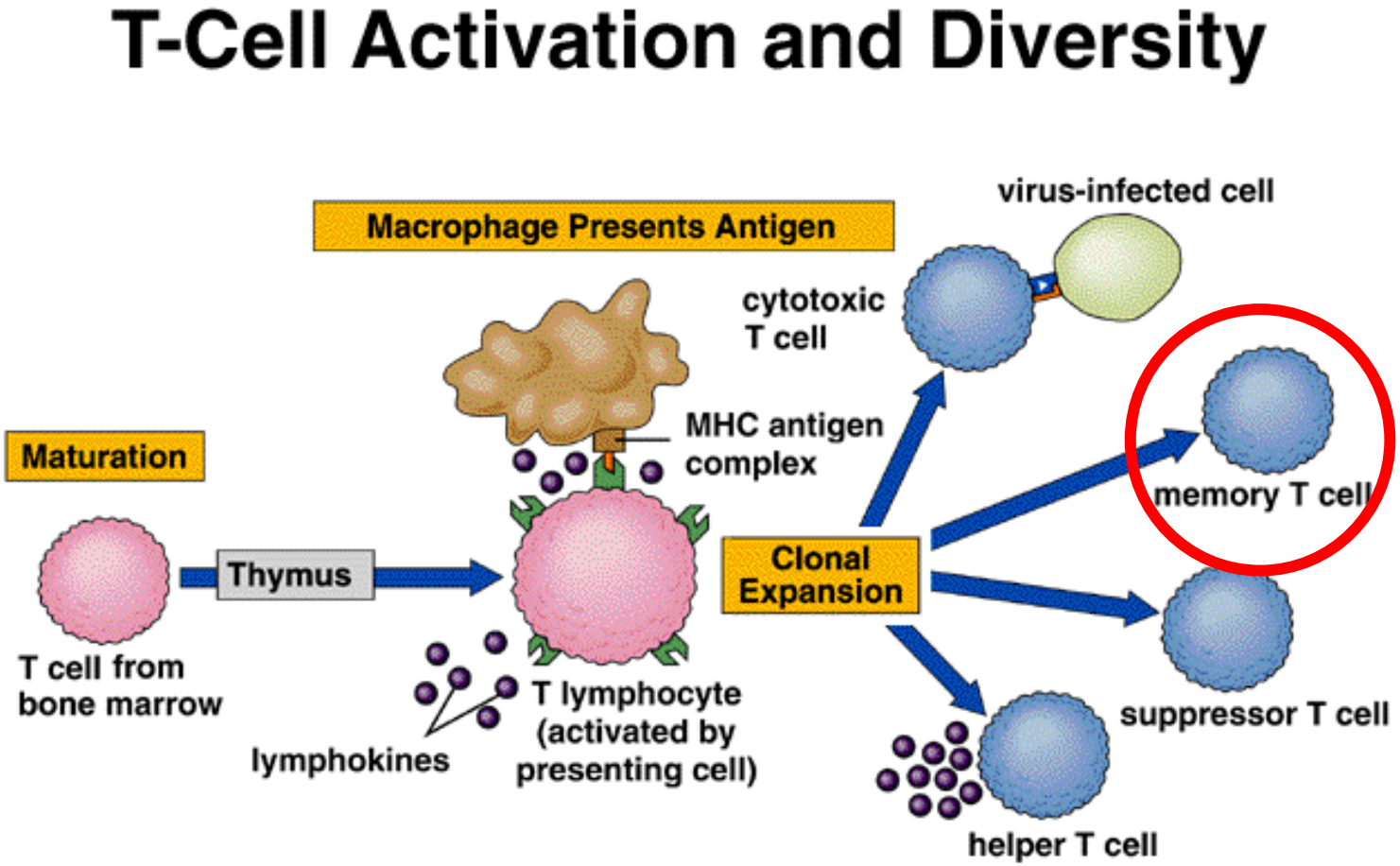
Nat. Med. 21, 647–53 (2015)

Introduction



Sylvia S. Mader, Inquiry into Life, 8th Edition, 1997

Introduction



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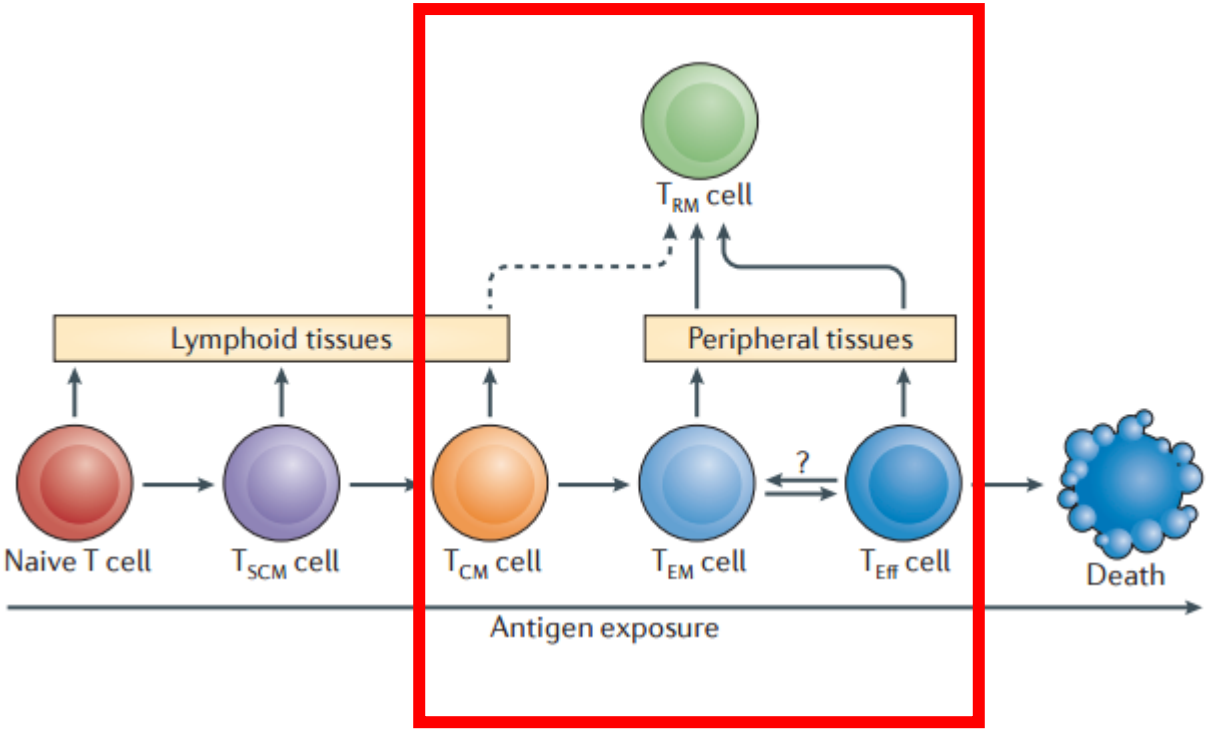
Introduction

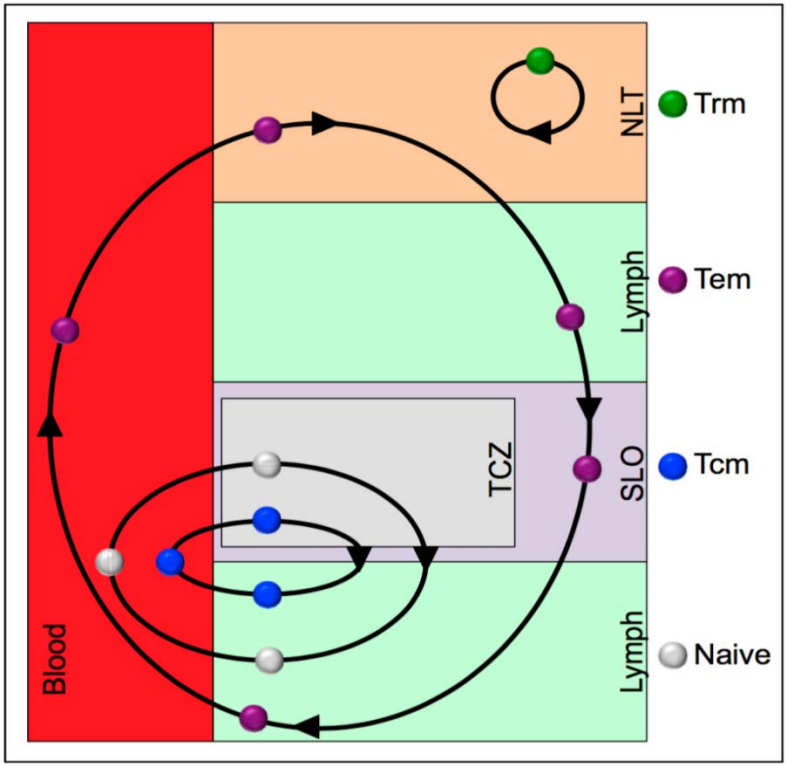
Memory T cell subsets



Nat. Rev. Immunol. 14, 24–35 (2014)

Introduction

Circulation of Memory T cell subsets



Remain at tissue only

Scan for Antigen everywhere

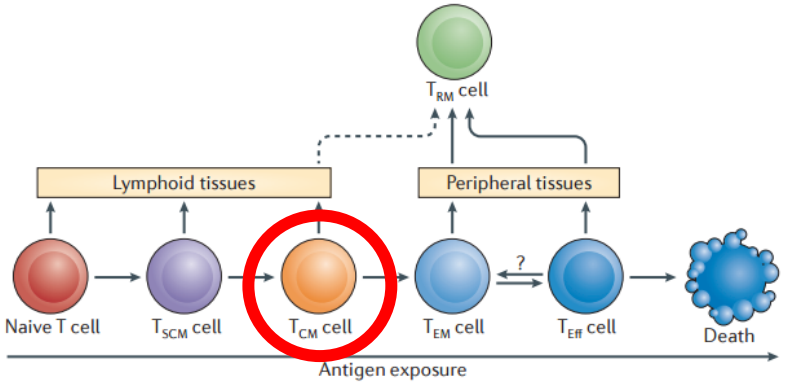
Remain in lymph and blood

Scan for new antigen

Immunity 41, 886–897 (2014))

Introduction

Central memory T cell (T_{CM})

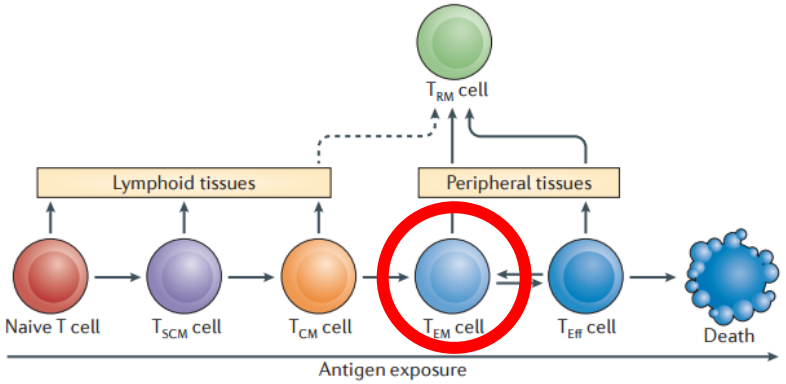


- **CCR7**
- **CD62L** (L-selectin, vascular addressin)
- Limited effector function or protective capacity
- Ability to replenish T_{RM} compartment upon activation

Nat. Rev. Immunol. 14, 24–35 (2014)
Nat. Med. **21,** 688–697 (2015)

Introduction

Effector memory T cell (T_{EM})



- **Low** expression of **CCR7** and **CD62L**
- **CLA** (E-selectin ligand)**, CCR4**, **CCR8**, **CCR10** → skin homing
- **α4β7**, **CCR9** → gut homing

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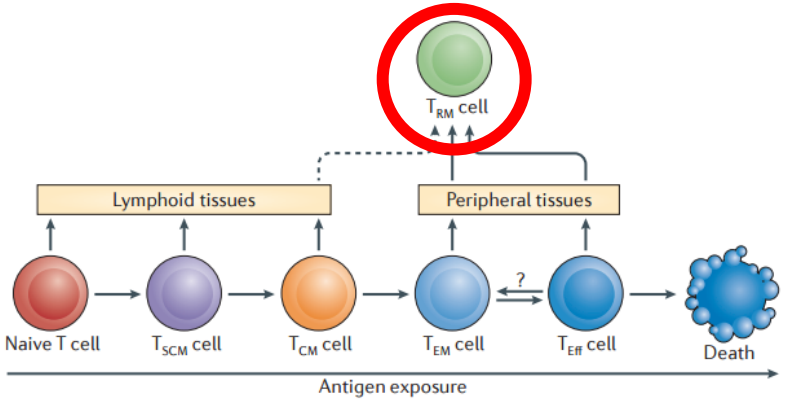
Introduction

Tissue-resident memory T cells (T_{RM})



- Reside in epithelial barrier tissue
  - gastrointestinal tract (GI)
  - respiratory tract
  - reproductive tract
  - skin

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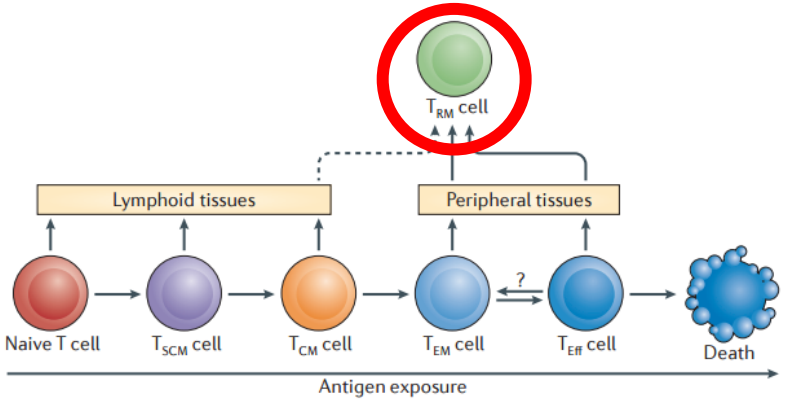
Introduction

Tissue-resident memory T cells (T_{RM})



- **CD69**$^{+}$ (involved in tissue retention)
- Mostly **CD103**$^{+}$
- Sphingosine 1 phosphate receptor (**S1P1**)↓
- Kruppel-like factor 2 (**KLF-2**)↓

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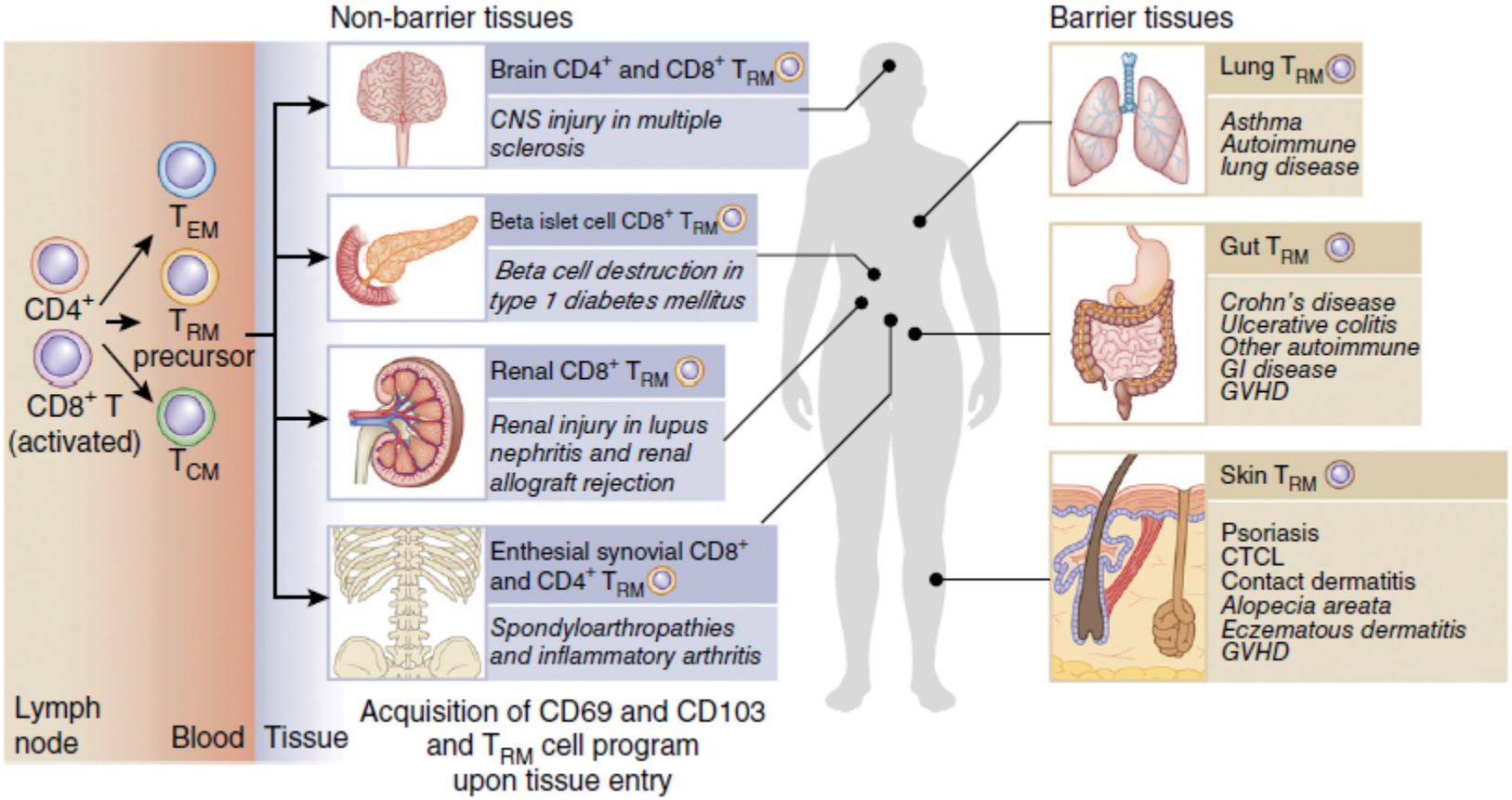
Introduction

Tissue-resident memory T cells (T_{RM}) in tissue-specific autoimmune and inflammatory diseases



Nat. Rev. Immunol. 14, 24–35 (2014)

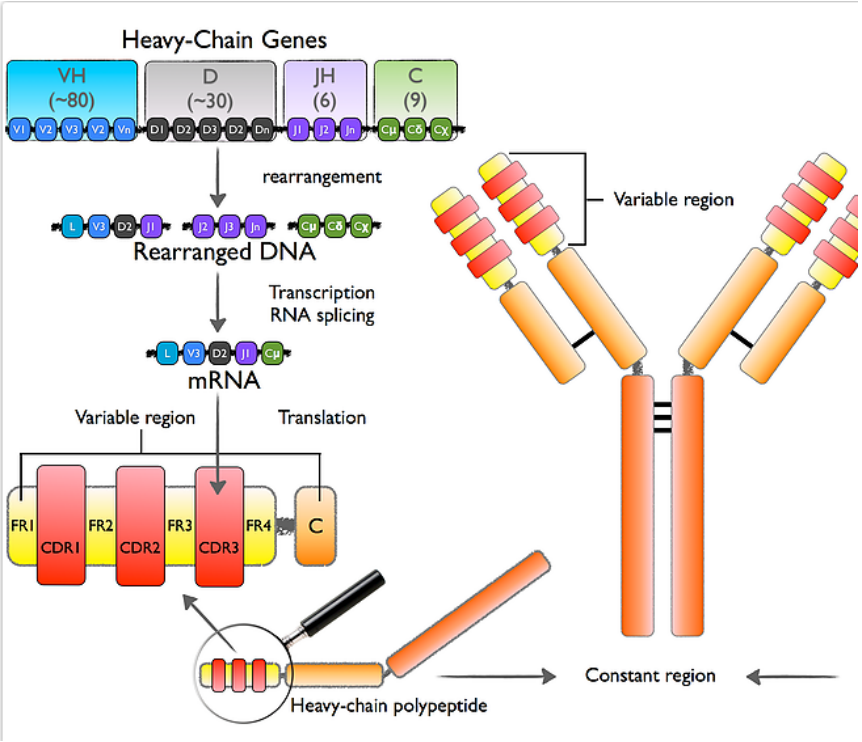
Aim/Questions addressed

- The investigation of the clonal origin of T_{CM} and T_{RM}
- Effect on abundance of T_{RM} after repetitive sensitization
- Differences in kinetics between allergen-specific T_{CM} and T_{RM}
- Generation of T_{RM} due to DPCP induced ACD

Methods

High-throughput sequencing (HTS) of T cell receptor (TCR) β-chain (TRB)

- **CDR3** sequence (part of variable region, highly specific)
- Possibility to track thousands of unique T cells



Nat. Med. **21,** 688–697 (2015)
http://www.irepertoire.com/the-immune-repertoire

Methods

Antigen challenge to skin

- Ovalbumin (OVA) + adjuvant cholera toxin (CT)
- Dinitrofluorobenzene (DNFB)
- Modified Vaccinia Ankara (MVA)

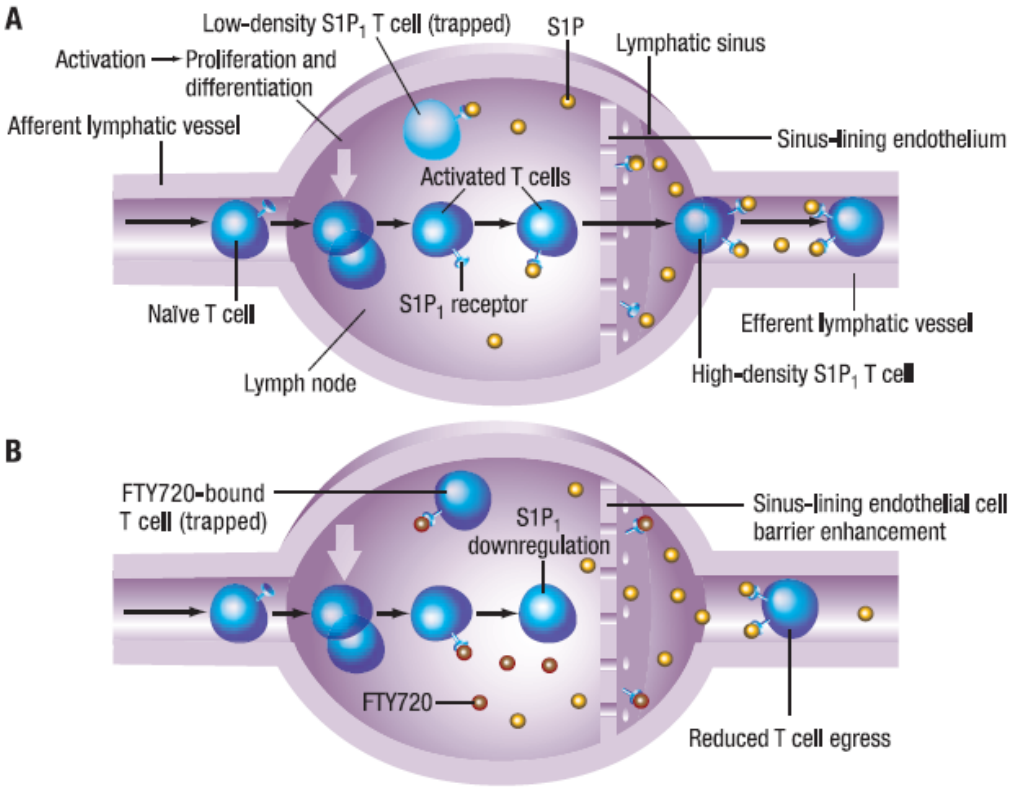
Nat. Med. **21,** 688–697 (2015)

Methods

Antigen challenge to skin

- Fingolimod (FTY720) T cell retention

Figure 1 Mechanism of action of FTY720

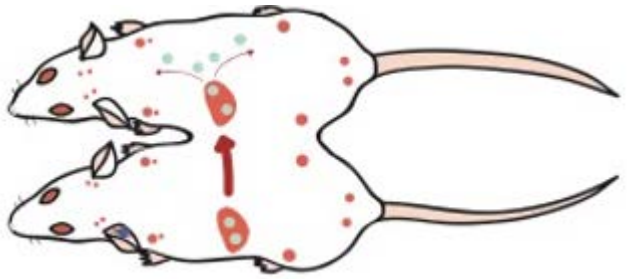


Nat. Med. **21,** 688–697 (2015)
Off. J. Am. Acad. Neurol. **74,** 47–53 (2010)

Methods

Parabiotic surgery

- Sex- and age-matched mice
- Connection of a sensitized mouse to a naive mouse
- Common blood circulation
- Separation after 4 weeks



Nat. Med. **21,** 688–697 (2015)

Methods

Study subjects and skin samples

- 11healthy volunteers
- Diphenylcyclopropenone (DPCP) immunization and challenging → allergic contact dermatitis (ADC)
- Skin biobsies (day 4, 13 and month 4)

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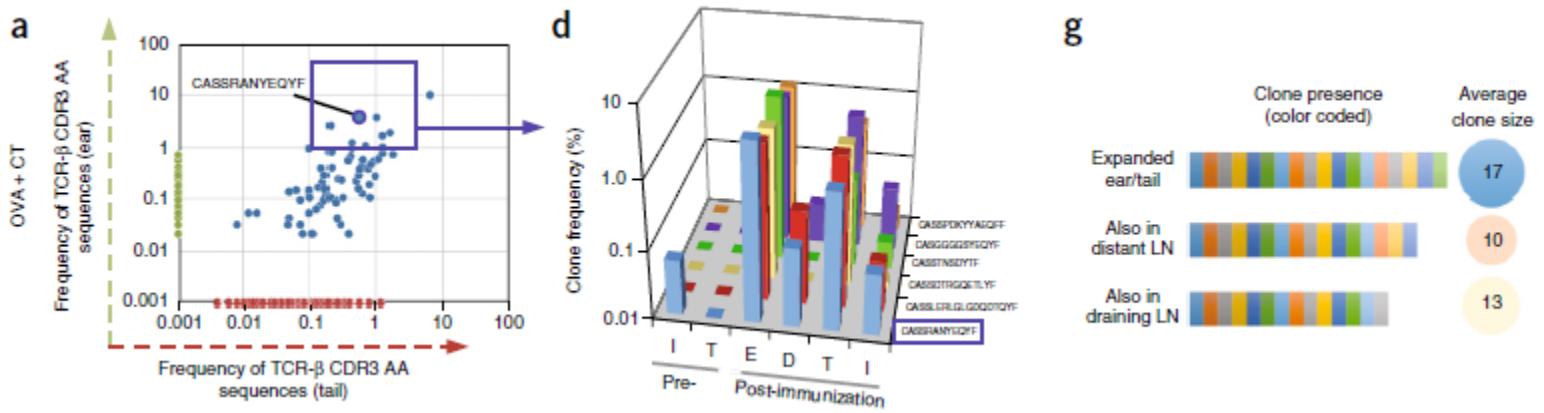
Results

Skin immunization with **OVA+CT** generates skin T_{RM} cells and TCR-identical T_{CM} cells in LNs



I = inguinal LN
T = tail skin

E = ear skin
D = draining LN (ear draining)

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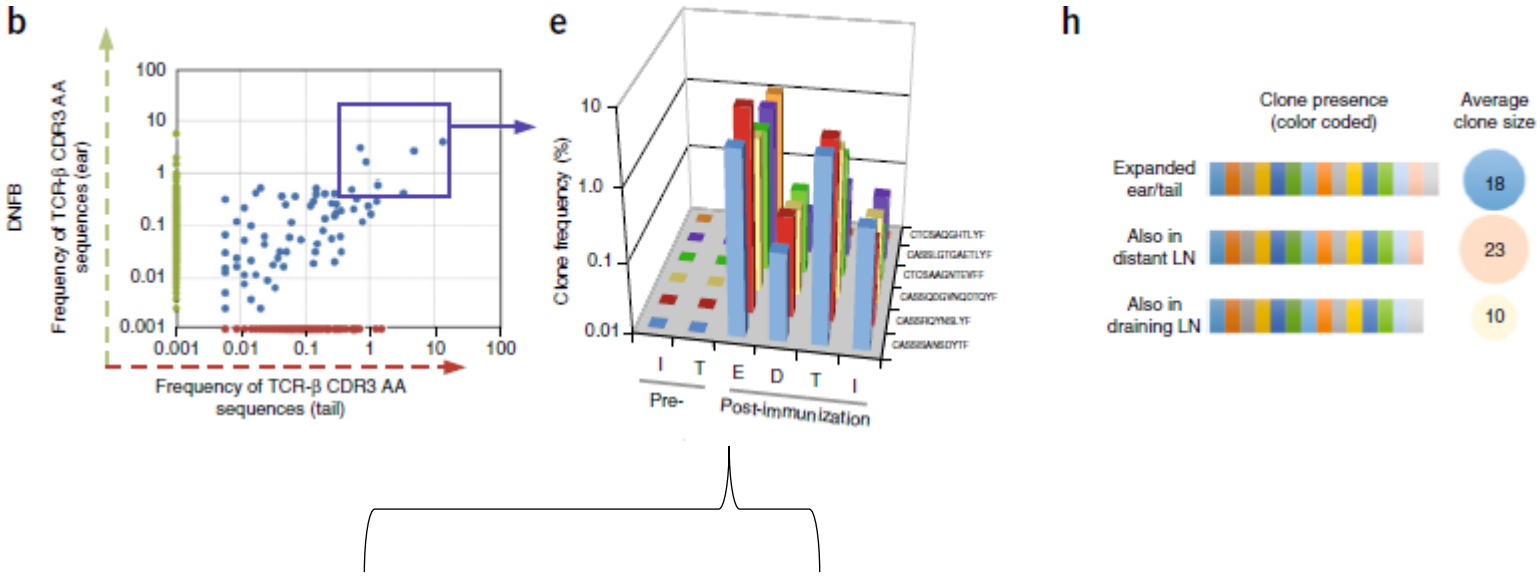
Results

Skin immunization with **DNFB** generates skin T_{RM} cells and TCR-identical T_{CM} cells in LNs



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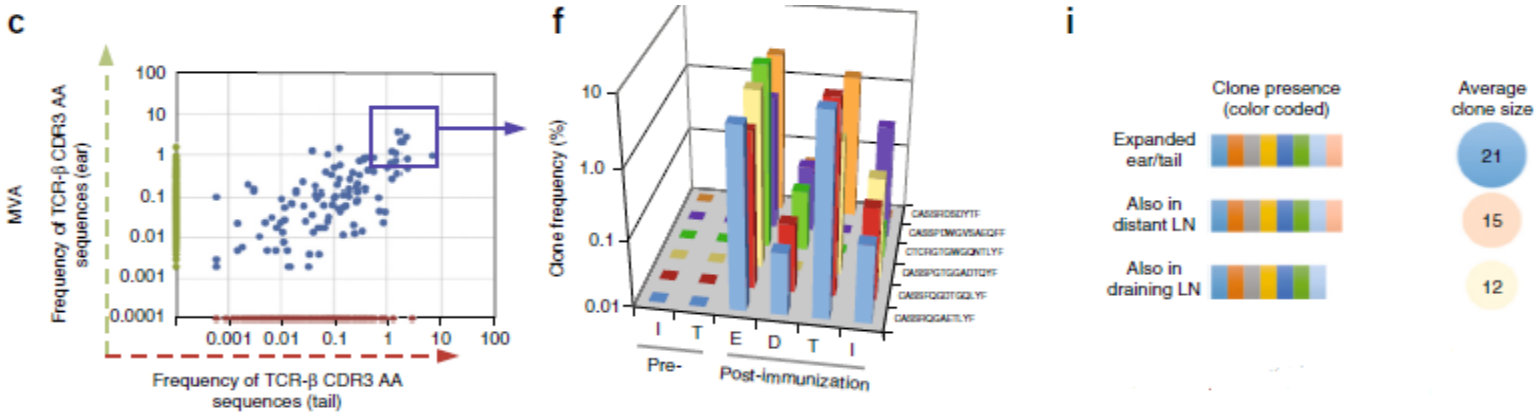
Results

Skin immunization with **MVA** generates skin T_{RM} cells and TCR-identical T_{CM} cells in LNs



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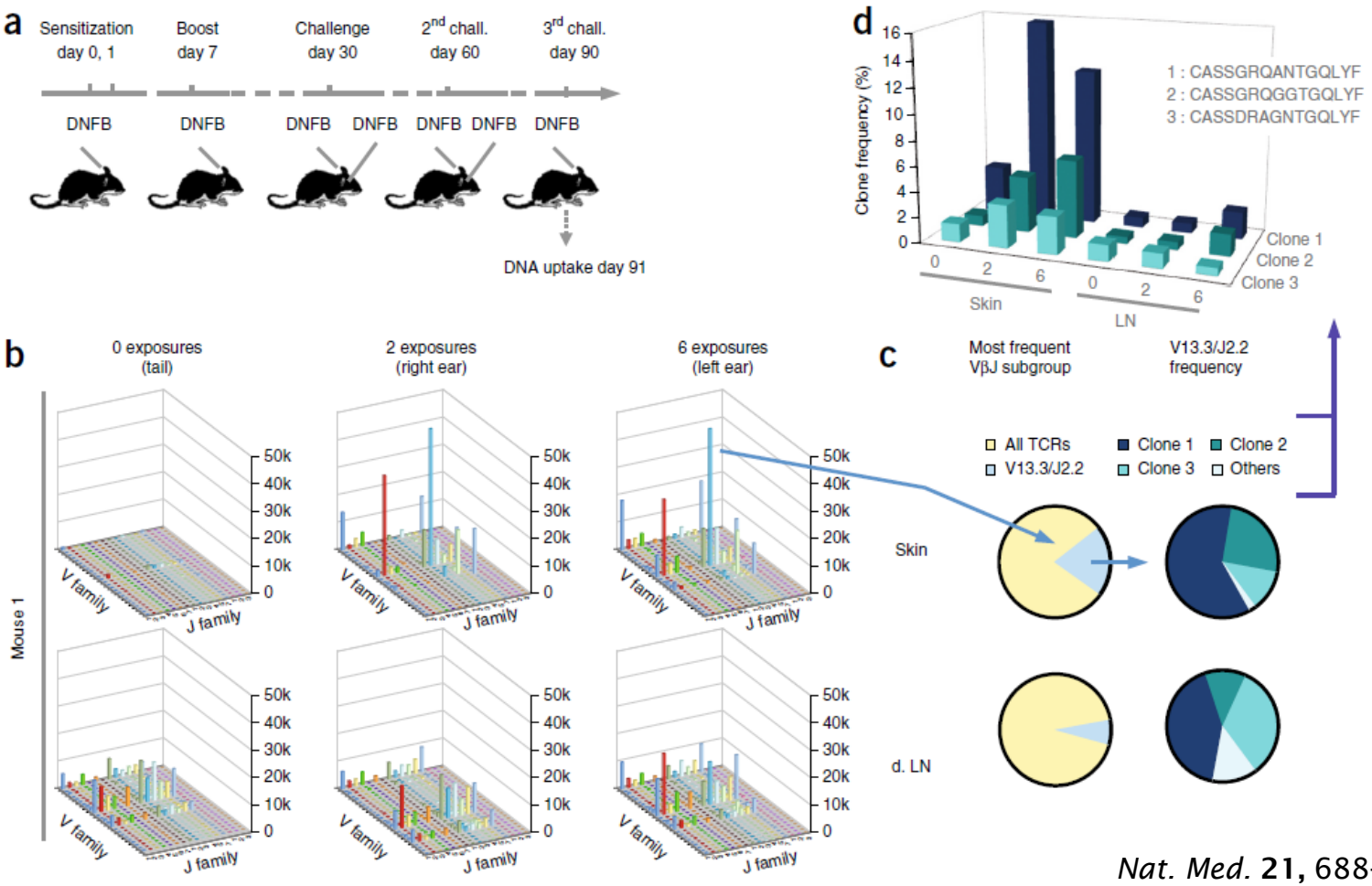
Results

Repetitive sensitization increases the abundance of T_{RM} cells in skin



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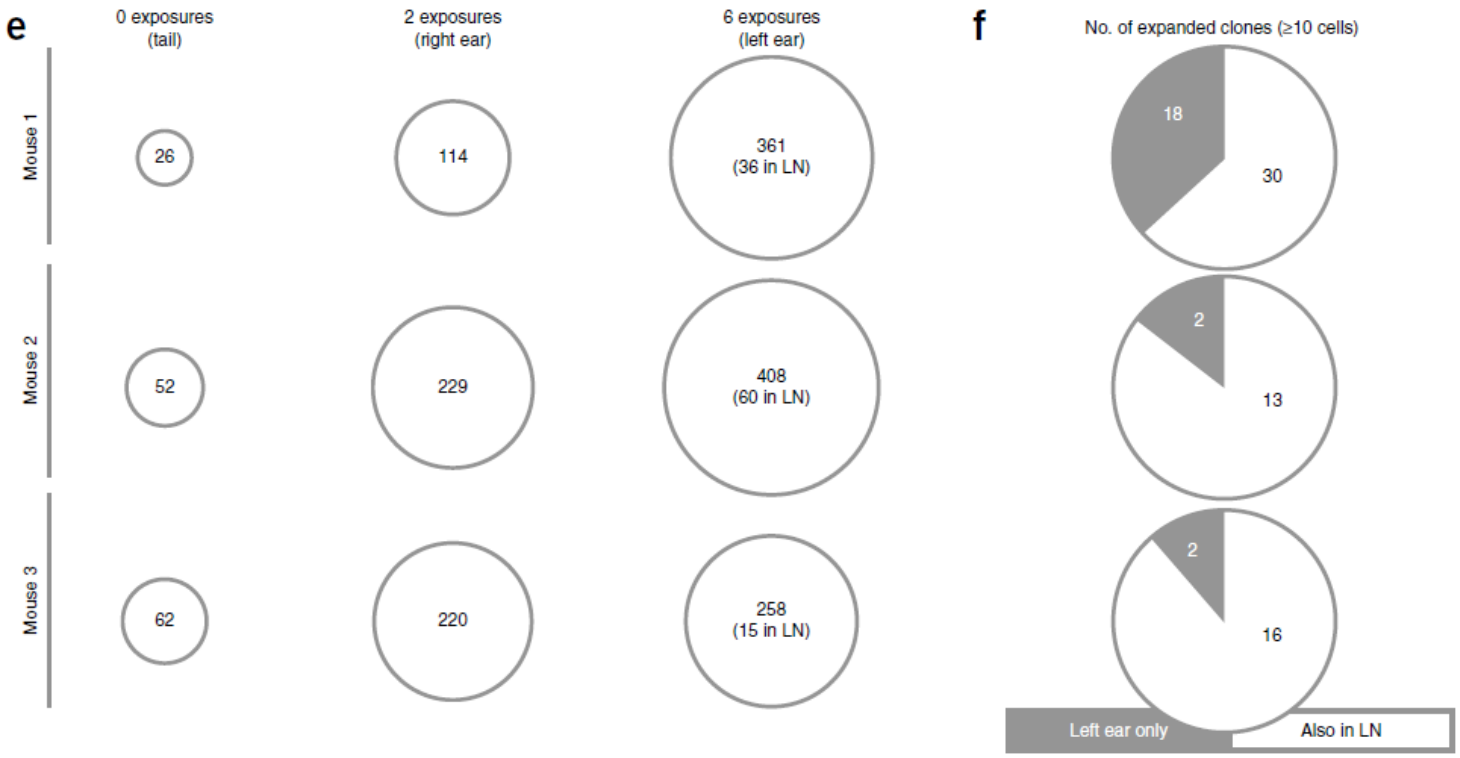

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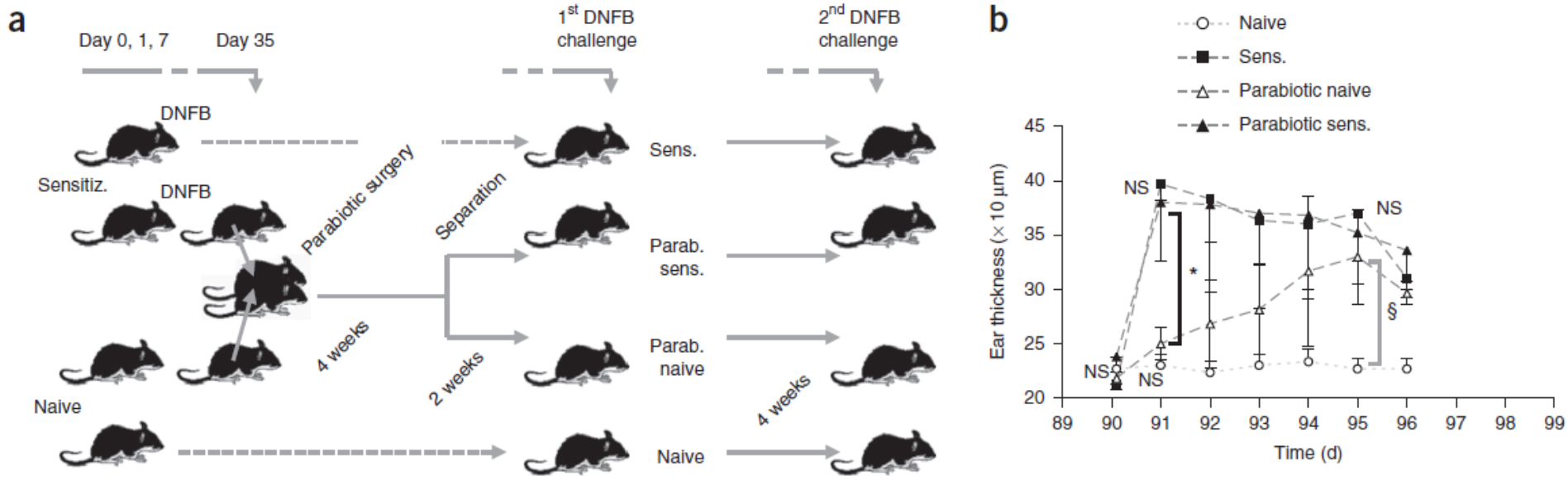
Results

T_{RM} cells mediate rapid skin contact hypersensitivity (CHS) responses, whereas T_{CM} cells mediate delayed attenuated CHS responses.



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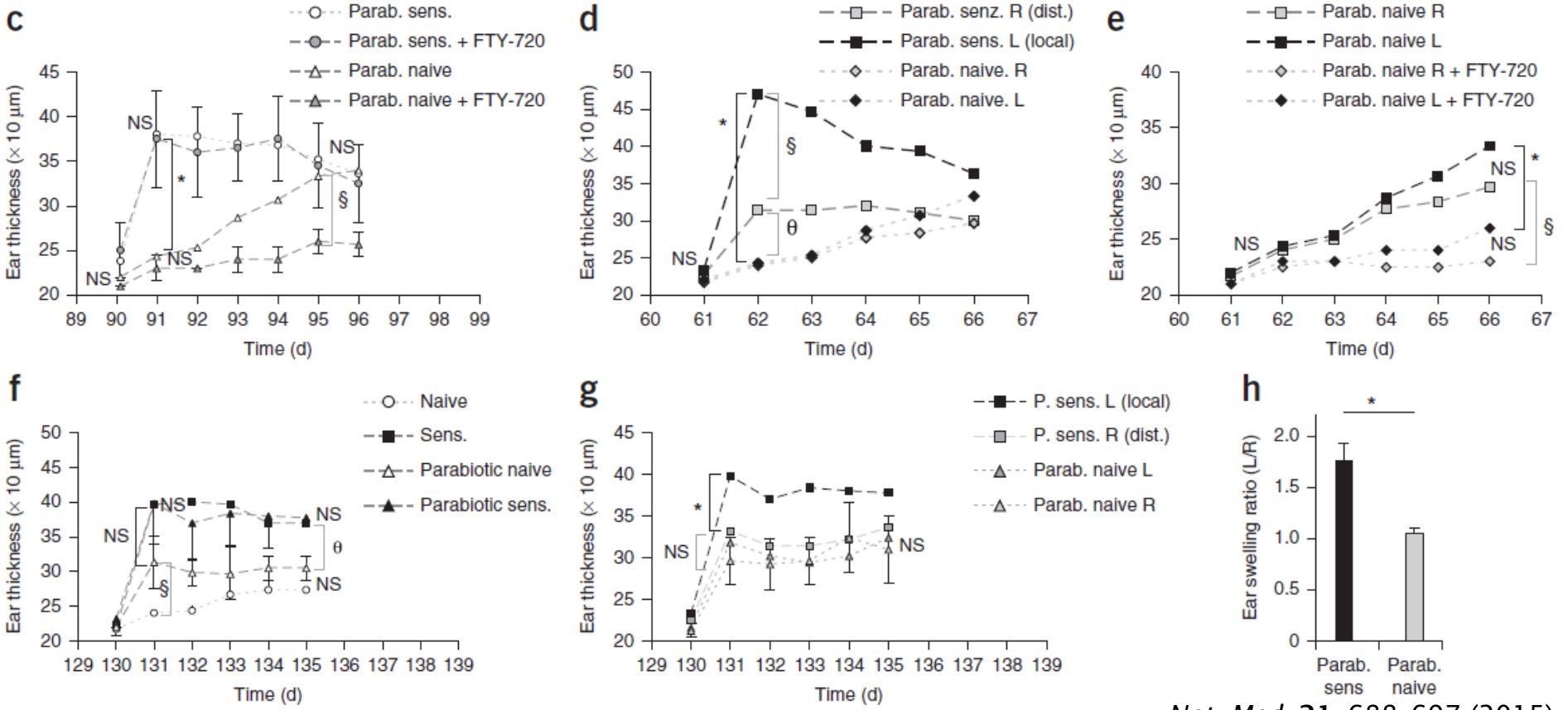

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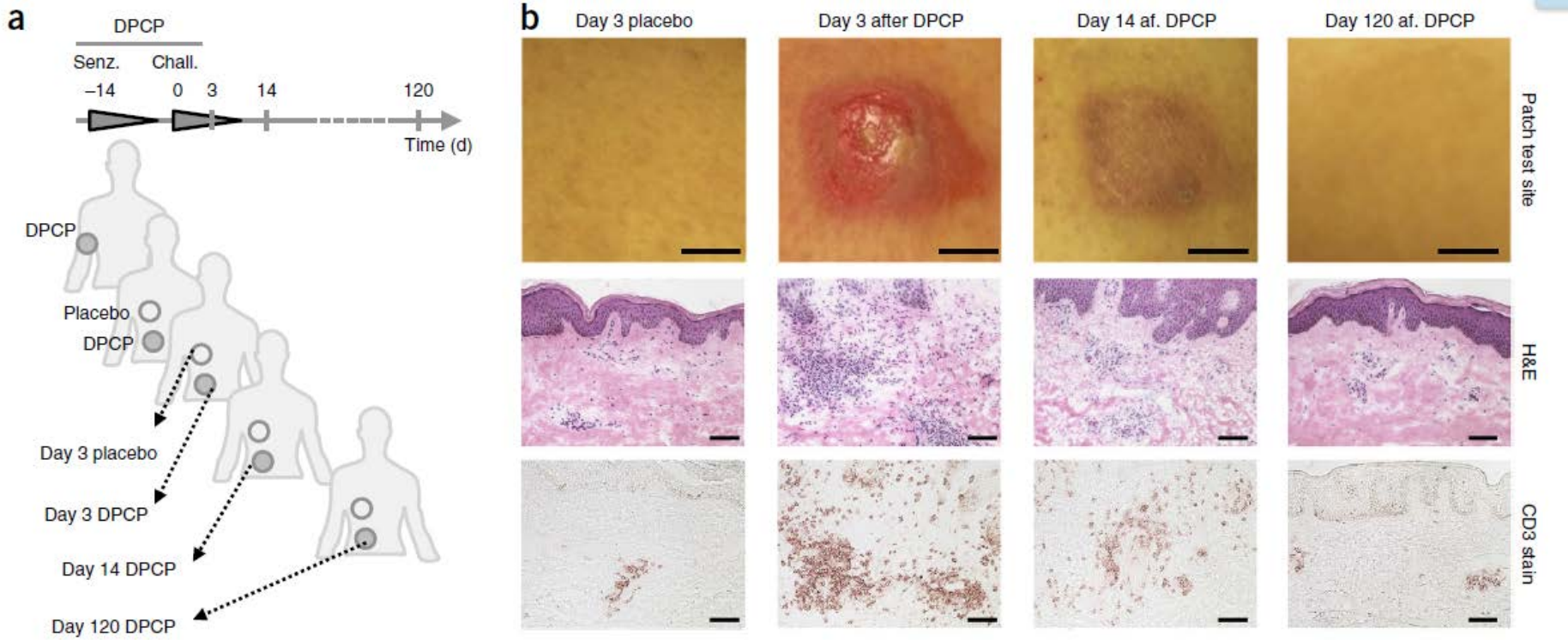
Results

Contact dermatitis to DPCP induces T_{RM} cells in human skin.



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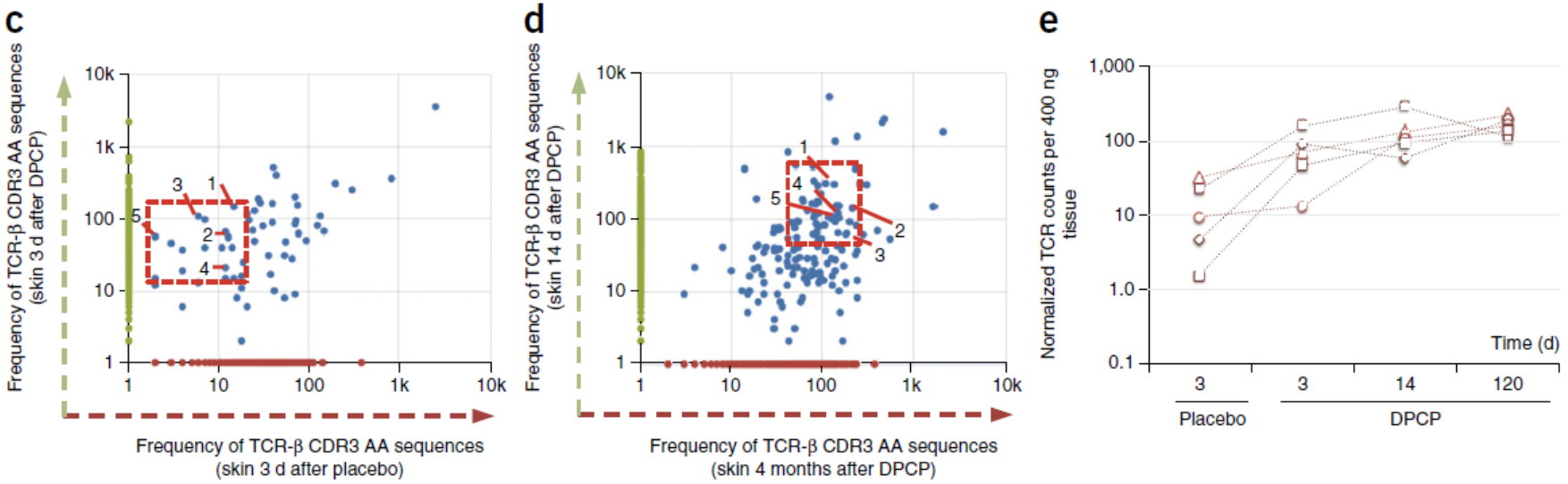

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Summary

- Skin immunization with different antigens generates skin T_{RM} cells and TCR-identical T_{CM} cells in LNs.
- Repetitive sensitization increases the abundance of T_{RM} cells in skin.
- T_{RM} cells mediate rapid skin contact hypersensitivity (CHS) responses, whereas T_{CM} cells mediate delayed attenuated CHS responses.
- Contact dermatitis to DPCP induces T_{RM} cells in human skin.

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Conclusion

- Allergic contact dermatitis (ACD) mediation by $\mathbf{T_{RM}}$ explains recurrent and site-specific nature of disease.
- TCR-identical $\mathbf{T_{RM}}$ (peripheral tissue) and $\mathbf{T_{CM}}$ (LN) → two compartments of memory T cells with identical TCR but different effector properties.
- Human diseases that recur episodically in barrier tissue may be mediated by $\mathbf{T_{RM}}$.

Thank you for your attention