Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients

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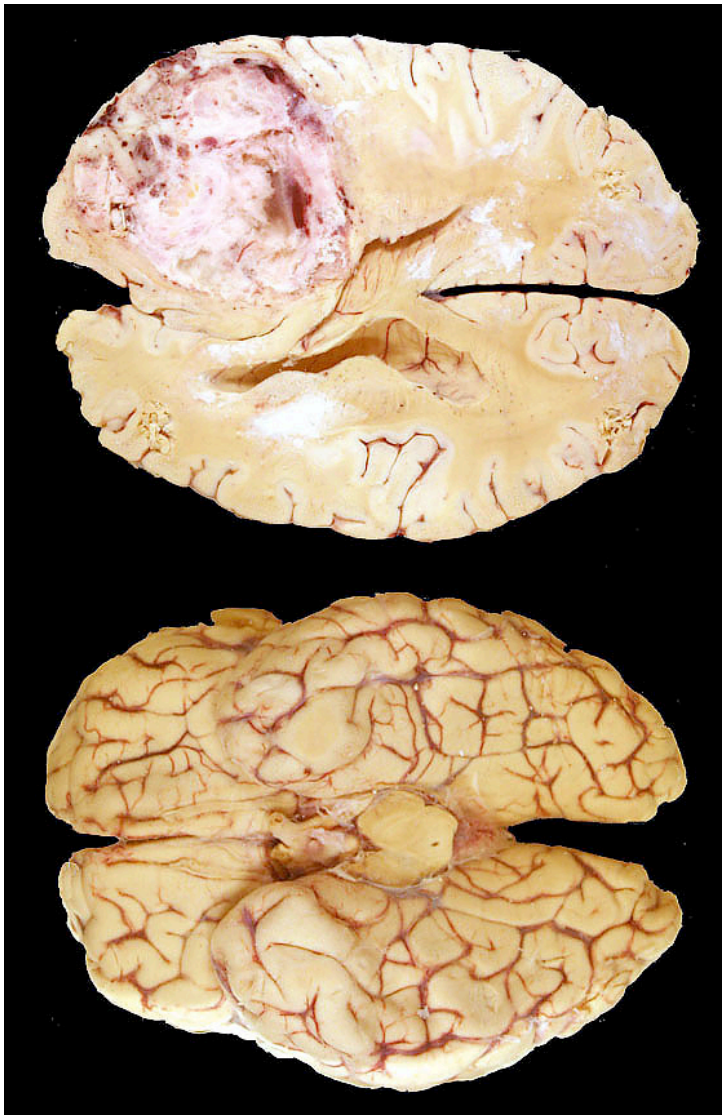
Glioblastomas (GBM)

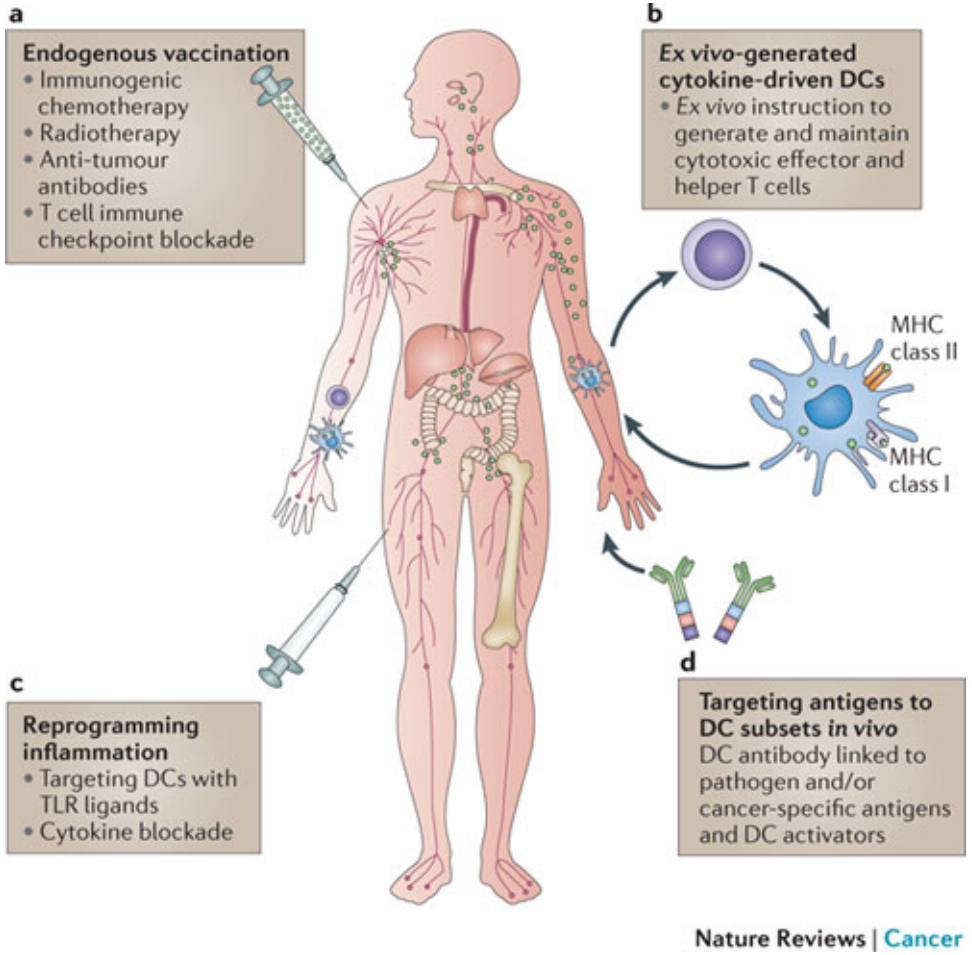
- Tumors that arise from astrocytes (supportive tissue of the brain)
  - Highly malignant -- cells proliferate quickly, supported by a large network of blood vessels
  - Found primarily in the cerebral hemispheres of the brain, but can be found anywhere in the brain or spinal cord
  - Mixed composition -- cystic mineral, calcium deposits, blood vessels, or a mixed grade of cells
  - 17% of all primary brain tumors and about 60-75% of all astrocytomas, increase in frequency with age
  - Surgery, radiation and chemotherapy



American Brain Tumor Association http://www.abta.org/brain-tumor-information/types-of-tumors/glioblastoma.html

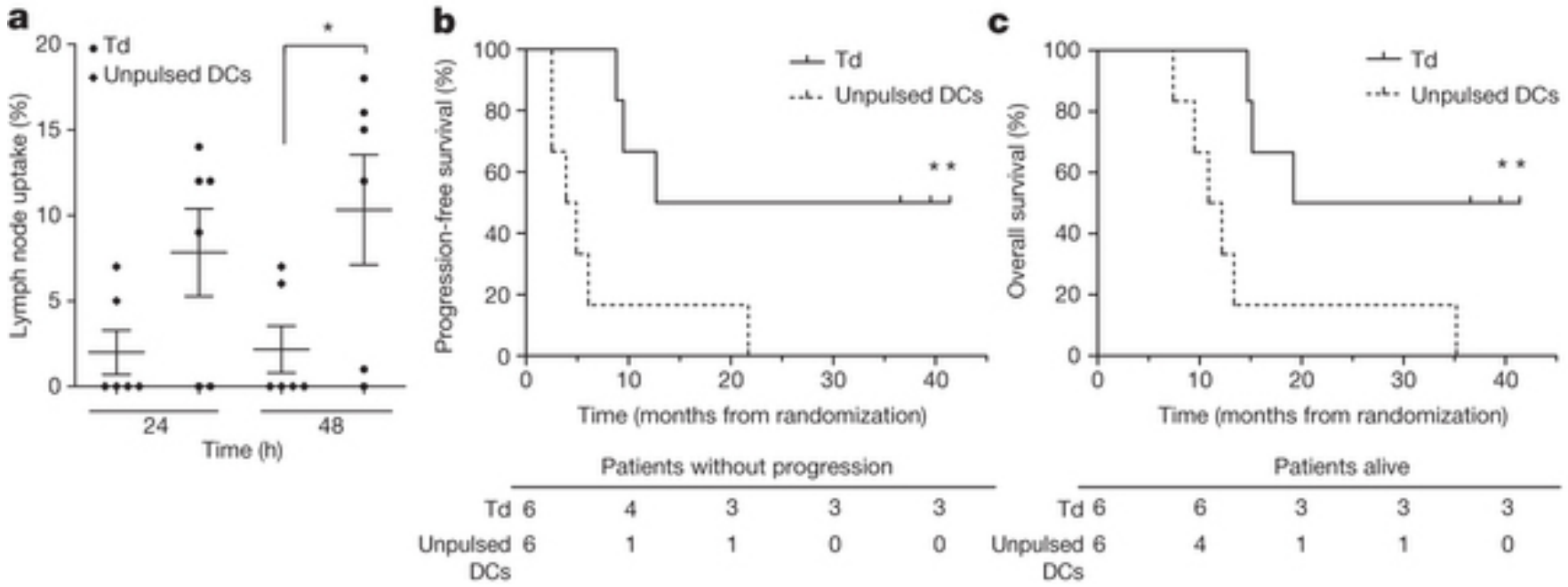
Dendritic cell vaccines

- Generation of protective anti-tumor immunity depends on the presentation of tumor antigens by **dendritic cells (DCs)**
- Provide DCs with tumor-specific antigens (*ex vivo* with adjuvant and reinjecting, inducing antigen uptake *in vivo*) → induce tumor-specific effector T cells → reduce tumor mass → induce immunological memory to control relapse
- Control both immune tolerance and immunity
  - Essential target in efforts to generate therapeutic immunity against cancer
  - "Nature's adjuvants"



Palucka, K. & Banchereau, J. Cancer immunotherapy via dendritic cells. Nature Rev. Cancer 12, 265–277 (2012)

Td pre-conditioning increases DC migration to VDLNs and is associated with improved clinical outcomes



- Patients were adults with newly diagnosed grade IV GBM (most malignant type)
- DCs pulsed with pp65 RNA (highly expressed in glioblastoma) after pre-treatment with either Td or unpulsed
- For migration studies, DCs were labeled with ^{111}In and measured by gamma camera

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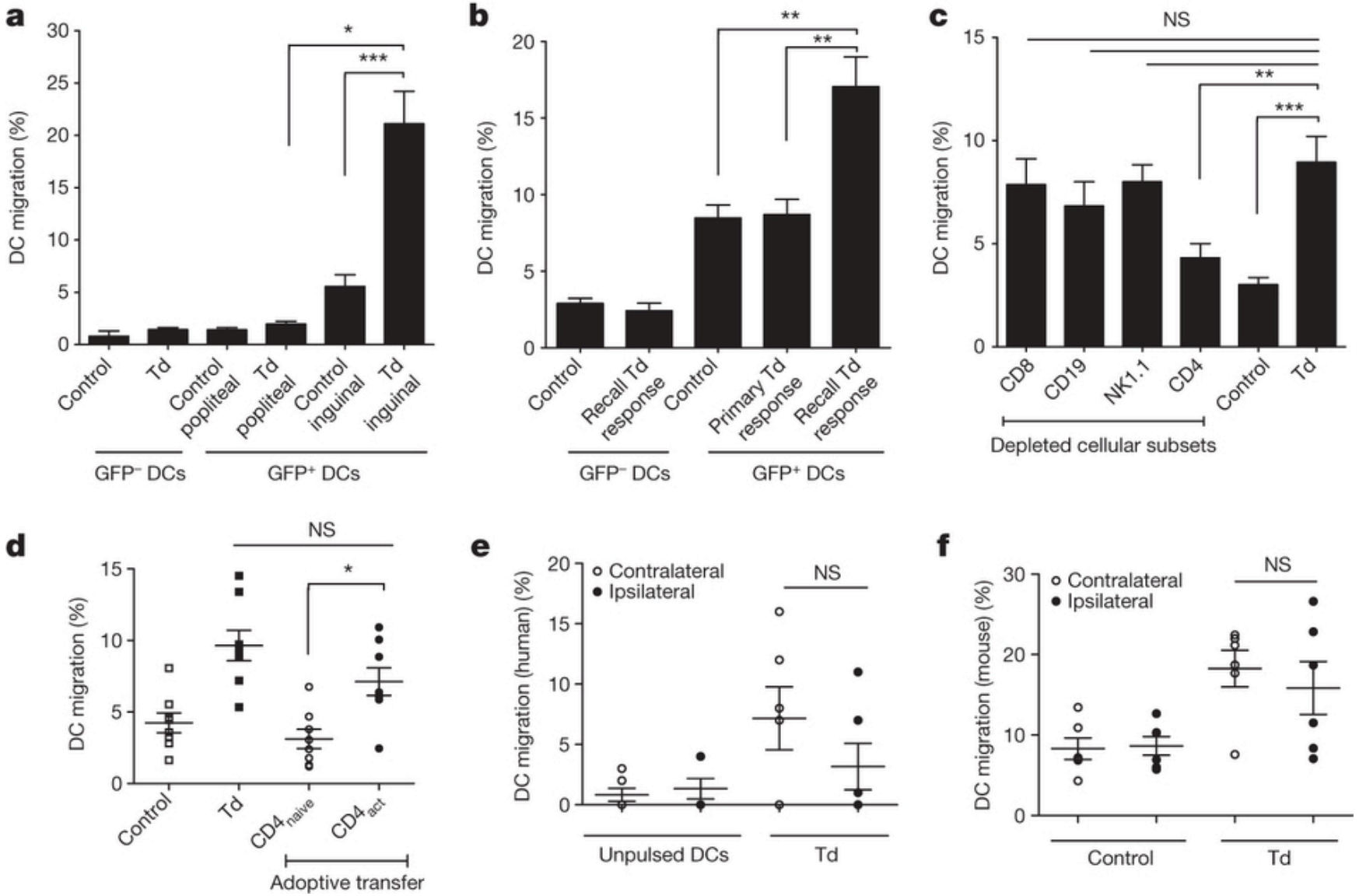
Td recall response activates CD4+ T cells to increase DC migration to VDLNs



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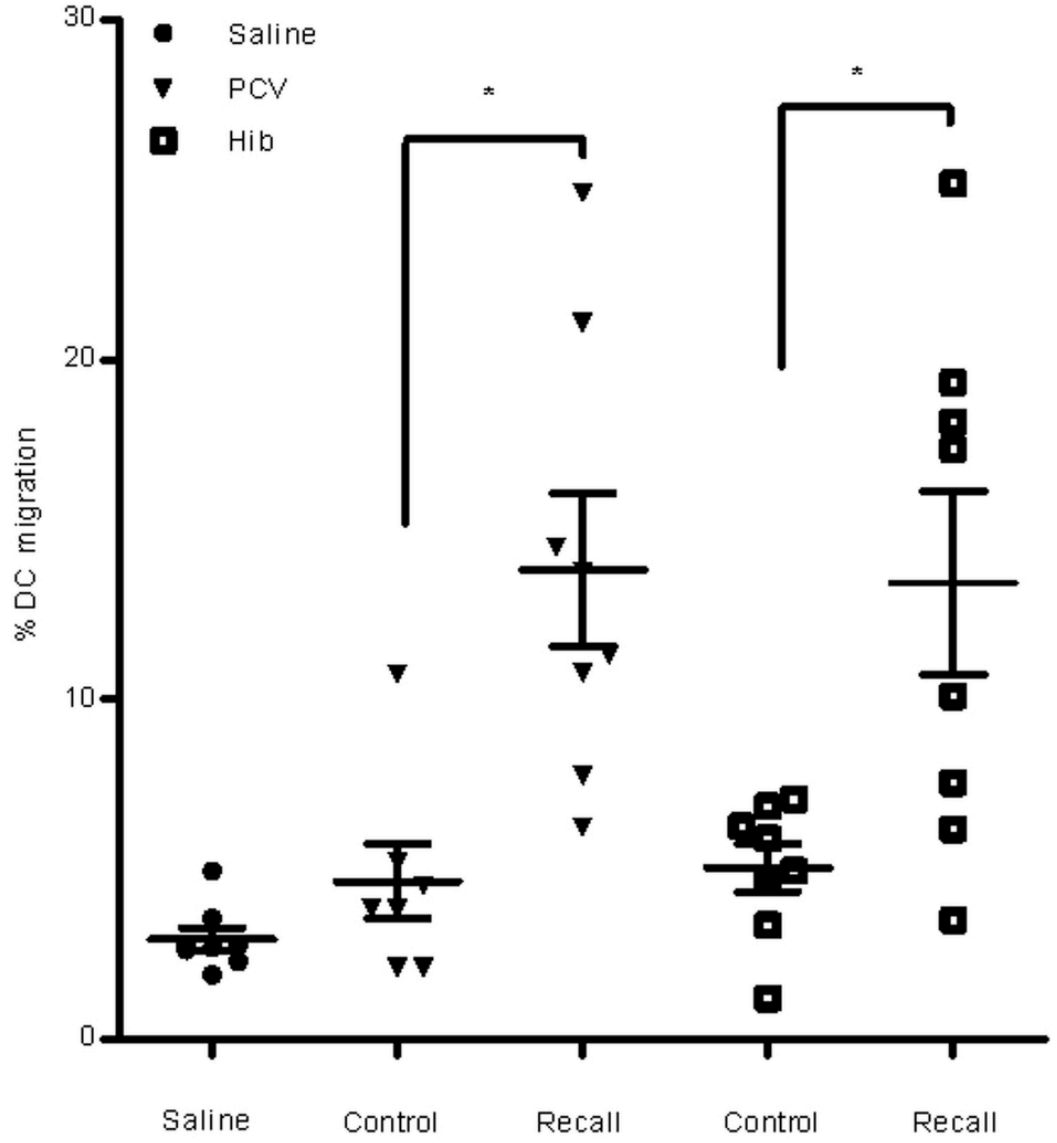
Td recall response is generalizable to other CD4-dependent protein antigens



PCV = pneumococcal 13-valent conjugate
Hib = Haemophilus b conjugate

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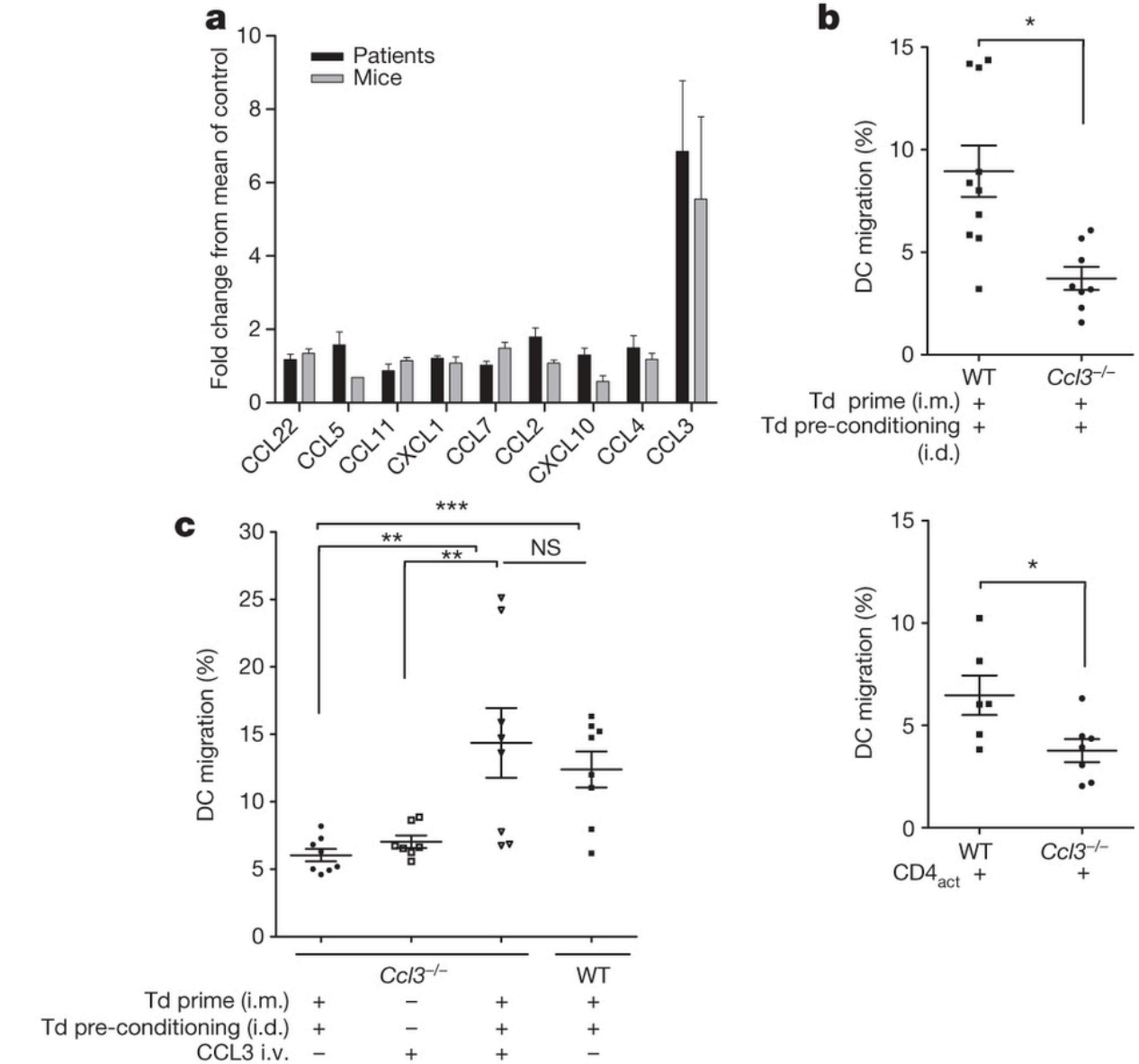
Td recall responses and induced CCL3 cooperate to facilitate DC migration to VDLNs



CCL3

- cytokine belonging to the CC chemokine family that is involved in the acute inflammatory state in the recruitment and activation of PMNs

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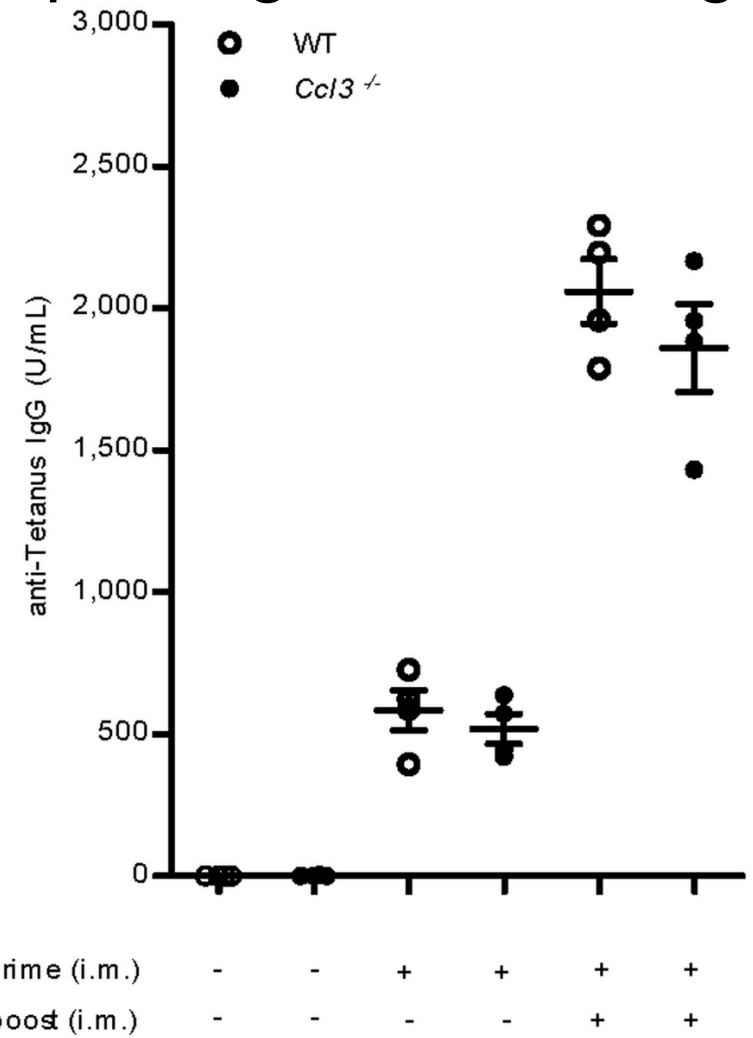
Anti-tetanus toxoid memory responses are induced and maintained in wild-type and *Ccl3*$^{-/-}$ mice throughout Td priming and boosting



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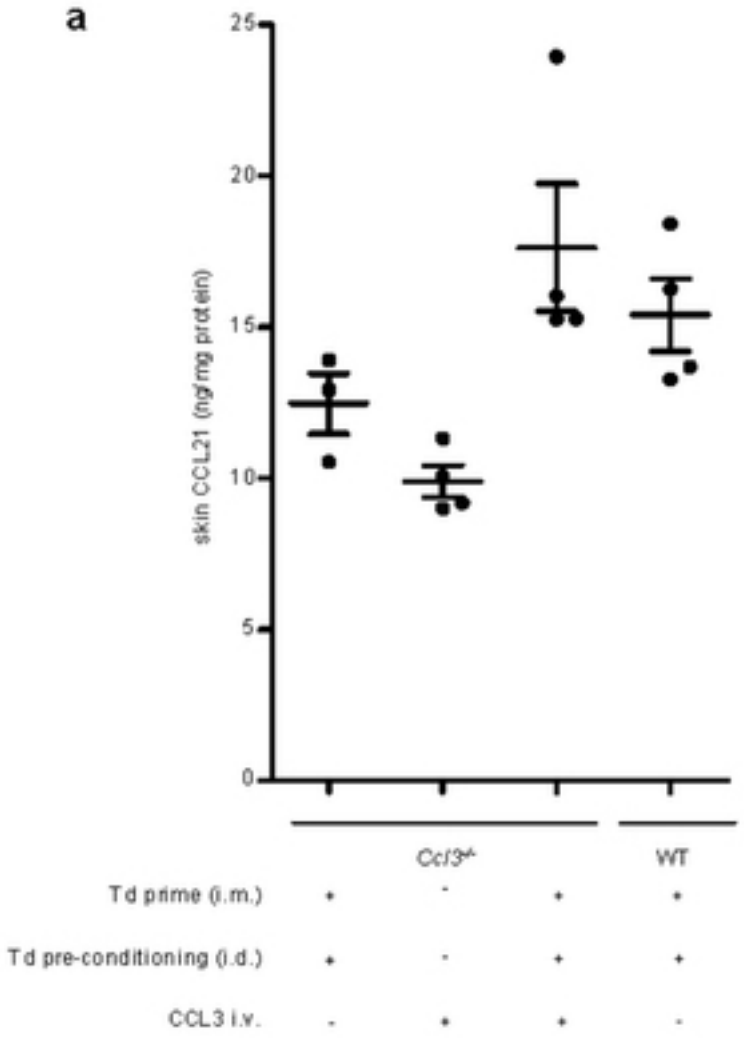
CCL21 levels in Td pre-conditioning skin sites and draining lymph nodes of wild-type and *Ccl3*$^{-/-}$ mice.



CCL21

- biomarker for increased DC migration
- cytokine belonging to the CC chemokine. Inhibits hemopoiesis and stimulates chemotaxis for thymocytes and activated T cells, but not for B cells, macrophages, or neutrophils. May also play a role in mediating homing of lymphocytes to secondary lymphoid organs

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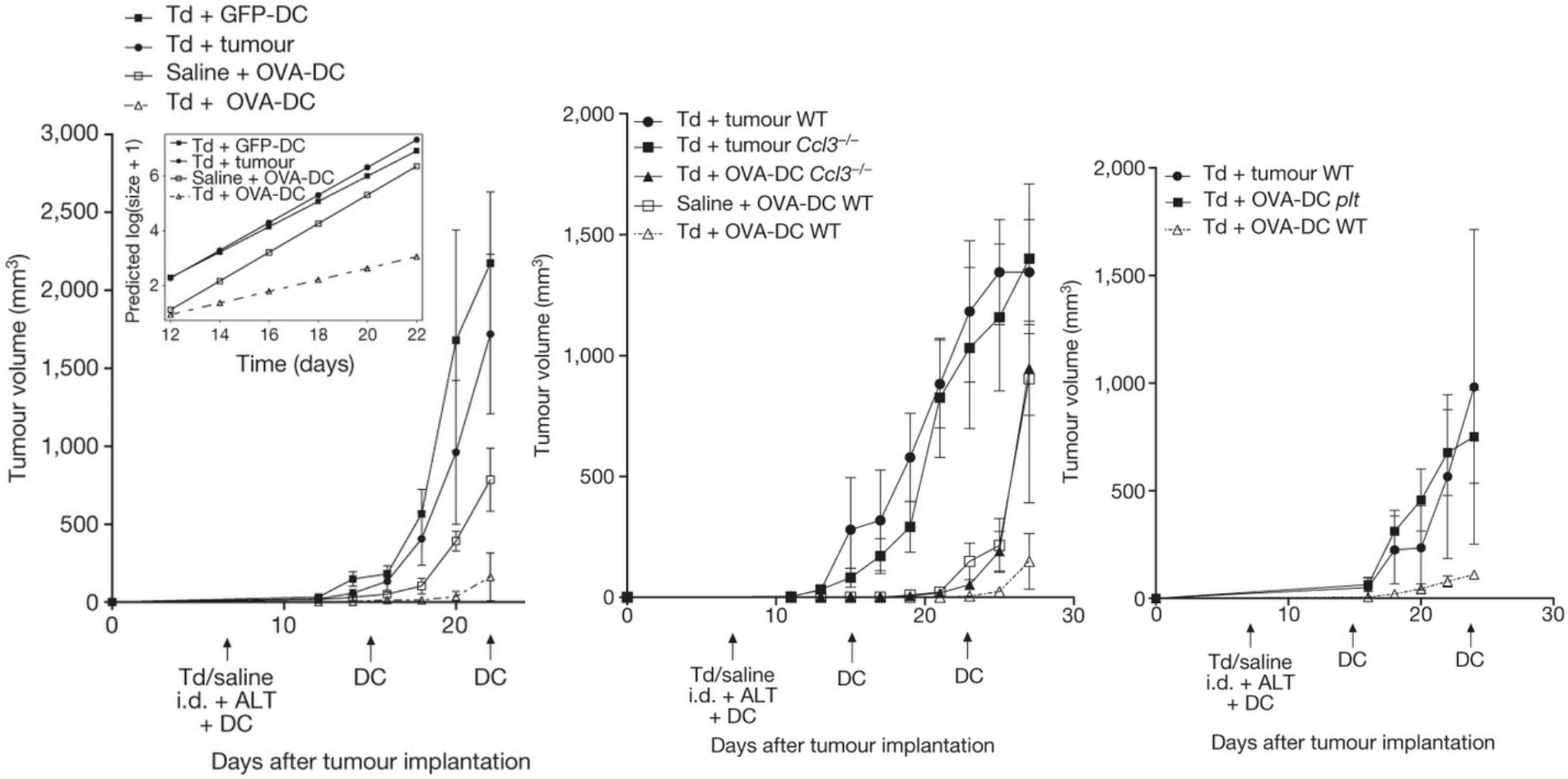
Td pre-conditioning improves responses in tumor-bearing mice



Missing CCL21

- DCs pulsed with ovalbumin RNA (tumor implant antigen) after pre-treatment with either Td or saline

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Conclusions and Future Directions

- Preconditioning a vaccine site with tetanus/diphtheria (Td) recall antigen can significantly improve the lymph node homing and efficacy of tumor-antigen-specific dendritic cells (DC)
- CCL3 is a novel and important mediator of increased DC migration to tumors, CCL21 may have role in DC homing to local lymph nodes
- Td recall antigen represents a viable strategy for improving anti-tumor immunotherapy
- DC migration should be investigated as a predictive biomarker for immunotherapy studies
- Would this work in less specific tumor antigen situations?