(Almost) All Immunity is Local—Implications for Vaccines from Tissue Immunodynamics

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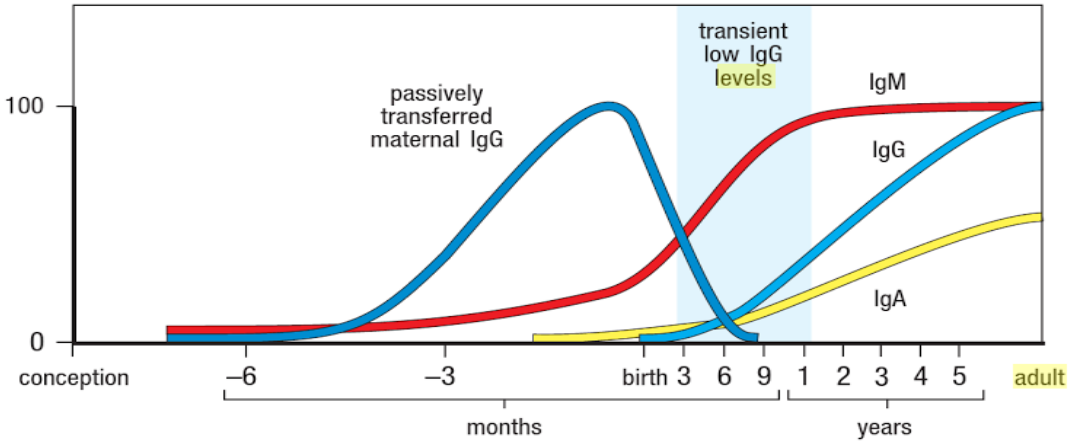
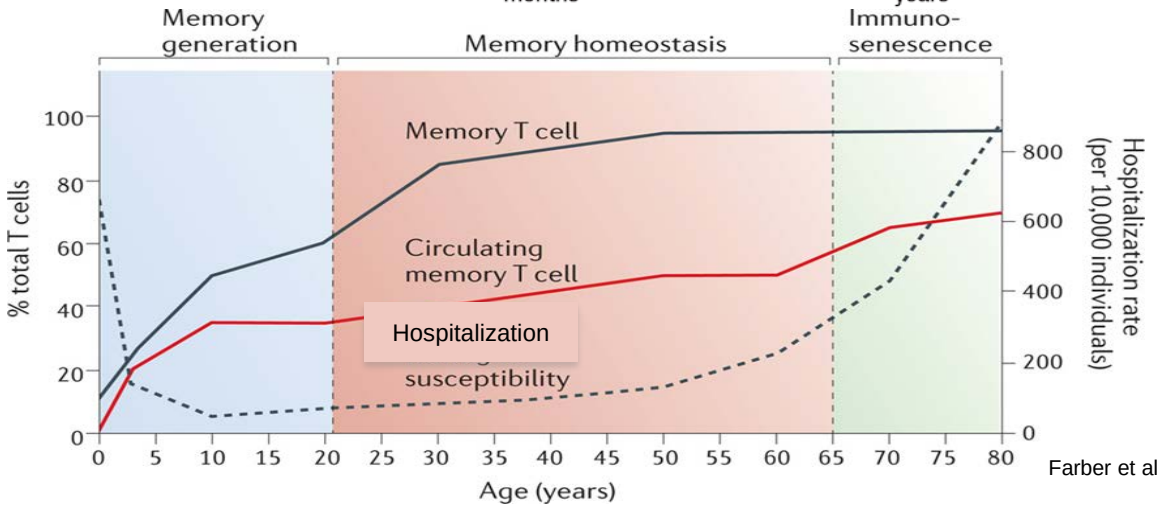
Antibody and T Cell Levels—A Broad Picture of Immunity but Does not Provide Tissue Level Resolution

Antibodies: Percent of adult levels



Janeway's Immunobiology 7th Edition

T cell memory

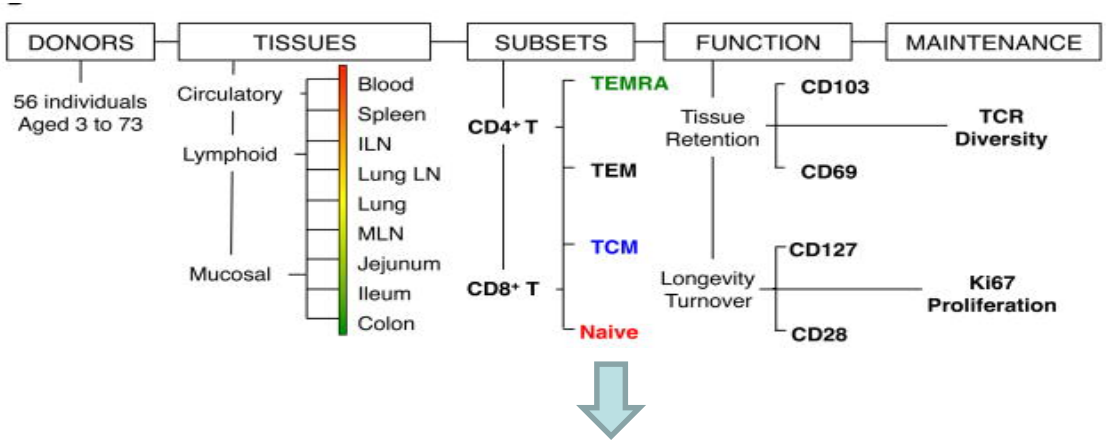


Farber et al Nature Reviews Immunology 2014

Importance of Characterizing Immune Cells in Tissues

- Peripheral blood provides an incomplete picture
  - Blood contains less than 3% of total T cells
  - Lacks significant information about local immunity, such as T-, B-, and antigen presenting cells of mucosal tissues
- Dynamic changes occur in different tissues from infancy through adulthood
- Immune memory is established and maintained in tissues
- Most previous studies were from mice or human tissues removed during surgery; systematic studies of healthy humans now feasible

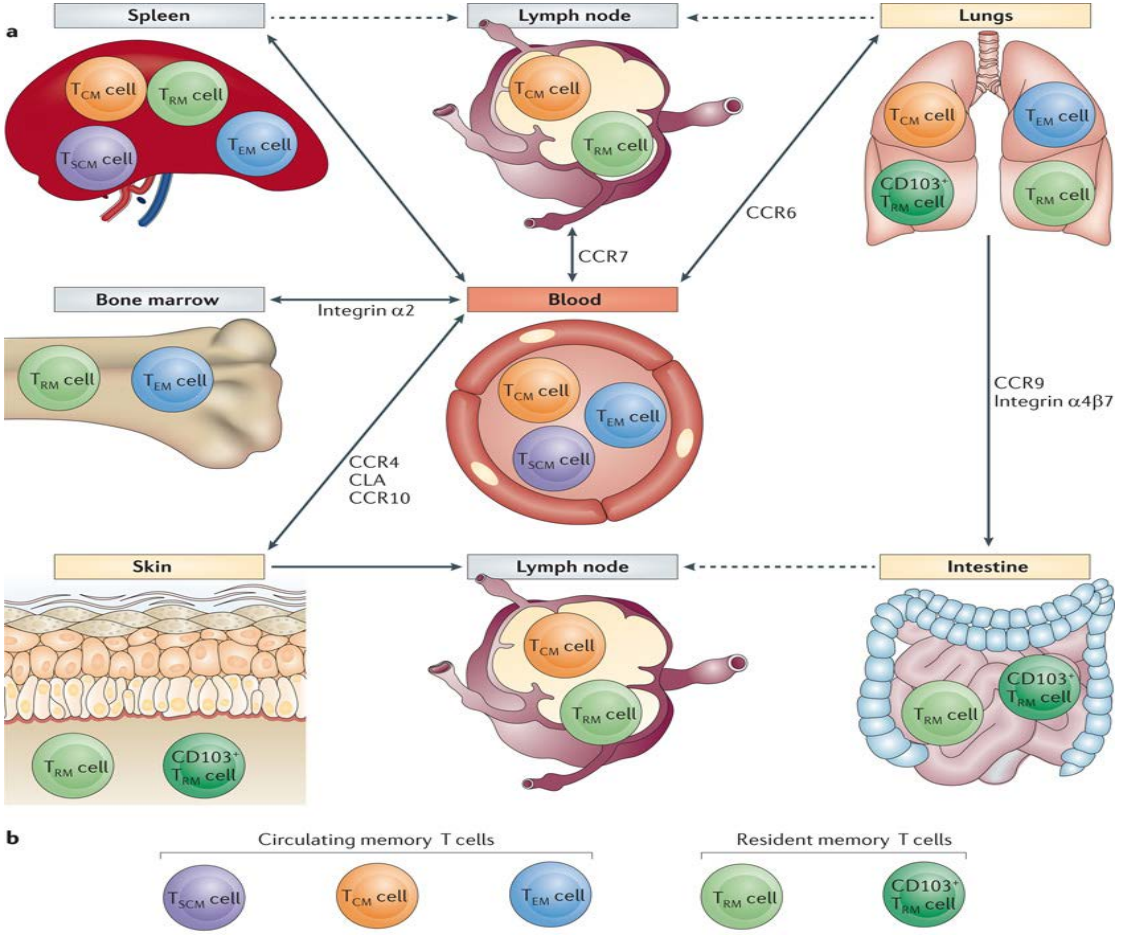
Characterization of T cells in Tissue Compartments of Healthy Human Transplant Donors



- TCM—T central memory
- TEM—T effector memory
- TEMRA—Terminal effector

Adopted from Thome et al… Farber, DL; Cell159:814-828 (2014)

Major Human Memory T Cell Subsets by Tissue



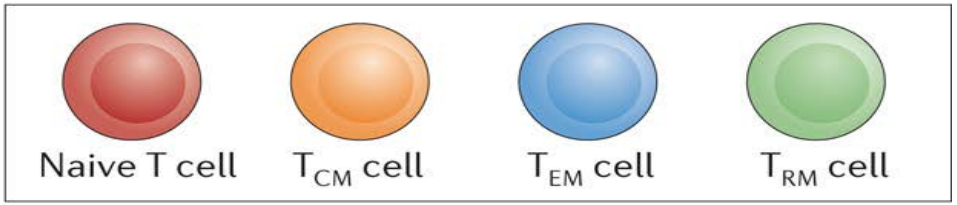
Farber et al Nature Reviews Immunology 2014

Findings from Recent Human Tissue Compartmentalization Studies

- T cells are the major immune cell population in tissues
- T cell subsets are similarly distributed across healthy individuals of a given age group
- Memory T cells predominate in all tissues and accumulate with age; however, aging memory cells exhibit reduced effector function

Emerging Model of Human T Cell Memory Dynamics According to Age and Organ/Tissue

Localization	Frequency				Specificity (Extrapolated from published studies)
	Infant	Youth	Young adult	Adult	
Skin					HSV, VZV, microbiota
Intestine					Rotavirus, microbiota
Lungs					Influenza virus, microbiota
Lymph node					VV
Spleen					EBV
Blood					CMV



Adopted from: Farber et al Nature Reviews Immunology 2014

Implications for Vaccines

- T cell memory establishes early in life—importance of first vaccines
- Antigen specificities differ by organ and account for differences in protection at distinct sites
- Responses to commensal microbiota are important for establishing and maintaining immune defenses and regulatory responses in mucosal tissues and skin
- Regulatory T cells are strongly expressed in most infant tissues except lungs and small intestines—sites to induce immune protection in early life
- Dendritic cells and other antigen presenting cells provide a sentinel function in skin and intestines

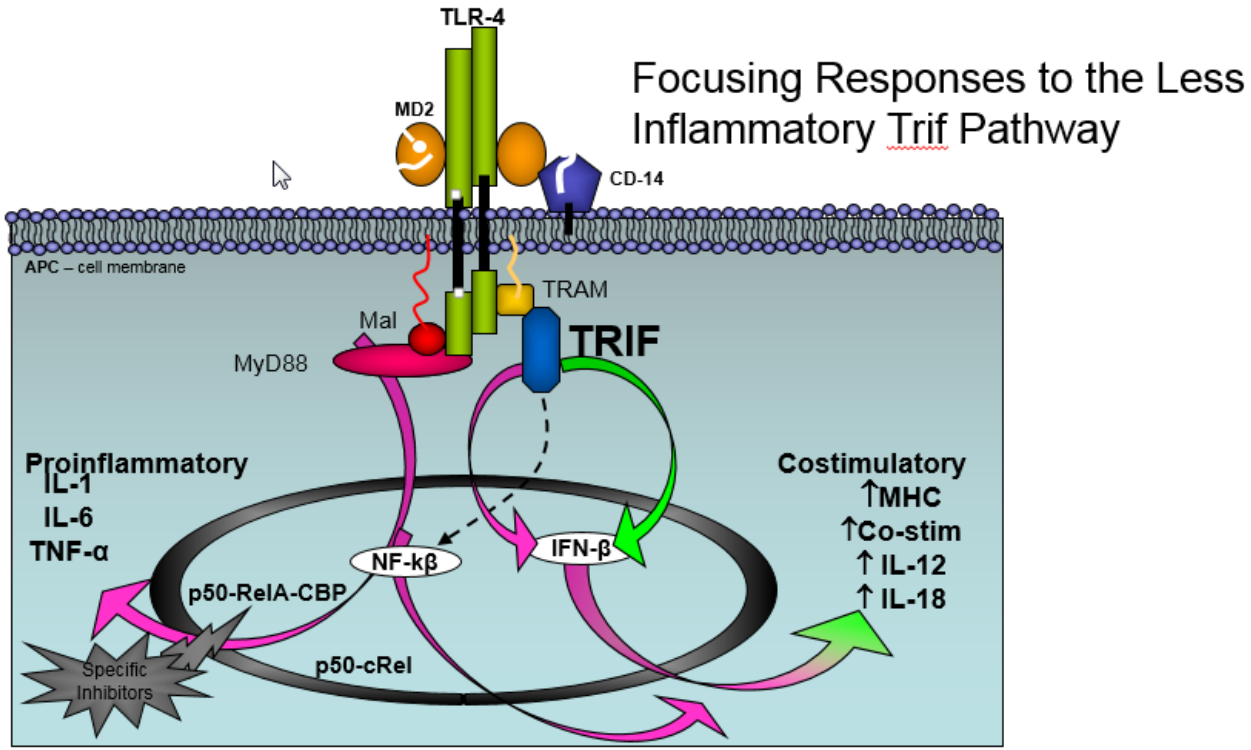
Adjuvants for More Effective Vaccination at Different Ages

- Antigen presenting cells that initiate responses in different tissues and age groups require activation via their innate immune receptors by adjuvants
  - Infants—may need adjuvants to promote long-lived Th1 responses not achieved with alum (e.g. pertussis)
  - Elderly—The GSK trial shingles vaccine contained an adjuvant (AS01) especially effective in older adults
- Adjuvants specifically designed for boosting secondary responses are needed

Pertussis Vaccine Adjuvants Related to Long-Term Protection

- Whole cell pertussis vaccine (discontinued in the US) provided long term immunity
  - Adjuvant activity provided by bacterial cell wall components
  - Reactogenicity varied with vaccine strain
- Acellular pertussis vaccine exhibits waning immunity
  - Adjuvant activity provided by alum (Th2 promoting)
  - Animal model data suggest that an adjuvant eliciting Th1 and Th17 immunity may lead to longer memory
  - Will the acellular vaccine become reactogenic with such an adjuvant?

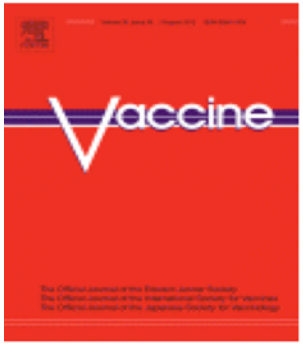
New Developments in Vaccine Adjuvants: Separating Efficacy from Toxicity



“This TRIF-selective signaling response resulted in the production of substantially less of the proinflammatory mediators that are associated with MyD88 signaling, thereby potentially reducing toxicity and improving the therapeutic index of this syntheticTLR4 agonist and vaccine adjuvant.”

A Non-Inflammatory Adjuvant in Development

Vaccine
Volume 30, Issue 36, 3 August 2012, Pages 5373–5381



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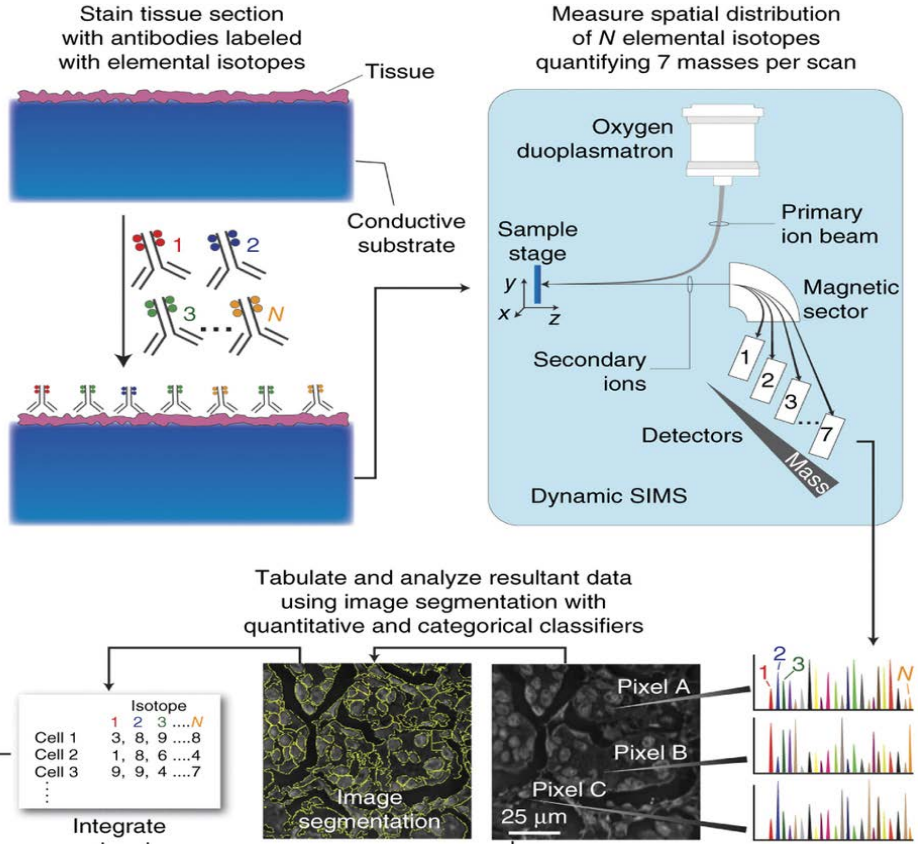
Advax™, a polysaccharide adjuvant derived from delta inulin, provides improved influenza vaccine protection through broad-based enhancement of adaptive immune responses

Yoshikazu Honda-Okubo[a], Fadi Saade[a], Nikolai Petrovsky[a, b, ·]

Multiplexed Ion Beam Imaging: New Technology for Monitoring Immunity in Tissues



From: Multiplexed ion beam imaging of human breast tumors
Michael Angelo, **et al…&** Garry P Nolan *Nature Medicine* **20**,436–442 (2014)

Current NIH Research Programs that Address Human Immune Complexity

- Human Immunology Project Consortium
- Sample-Sparing Assays
- Mucosal Immunology Studies Team
- Infant and Elderly Immunity
- ImmPort Database
- Immune Epitope Database
- NIH Tetramer Facility
- Multiple grants/contracts on
  - Metabolomics
  - Antigen processing and presentation
  - Adjuvants/combination adjuvants