UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

Fondazione Don Carlo Gnocchi Onlus

Long-term persistence of T cell memory in Italian vaccinees

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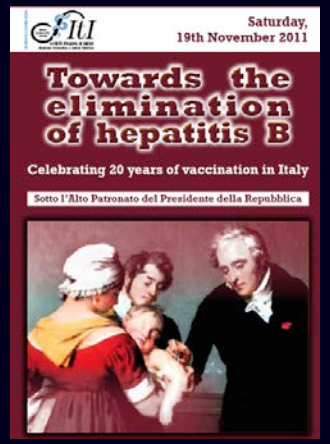


Milano, VHPB Meeting, Novembre 2011

What is immunological memory?

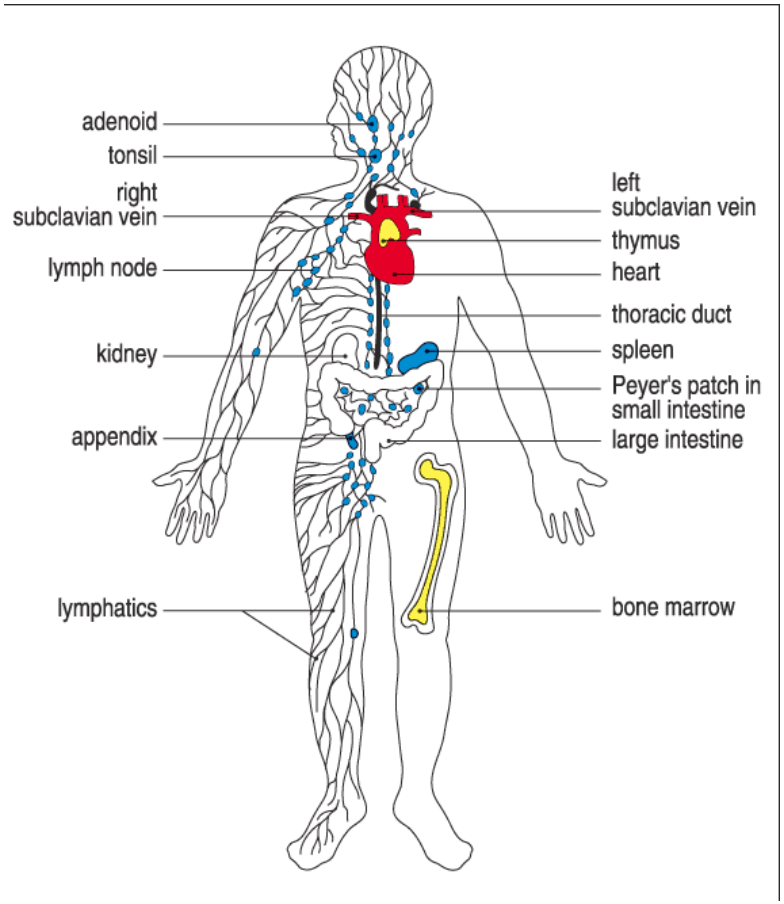
Memory is a modification of the frequency and the properties of antigen-specific lymphocytes that persists after antigen is eliminated.

Memory has two properties carried out by different cells:

- Immediate protection → **Plasma cells and antibodies**; **Effector memory and Terminally differentiated T**
- Secondary responses → **Memory B cells**; **Central memory T**

1. *How are memory cells generated ?*
2. *How are they maintained for our lifetime ?*

Lymphoid Tissue



- Central
  - Bone marrow
  - Thymus
- Secondary
  - Spleen
  - Lymph nodes
  - GALT (gut associated lymphatic tissue)
    - Tonsils
    - Peyer's patches
    - Appendix

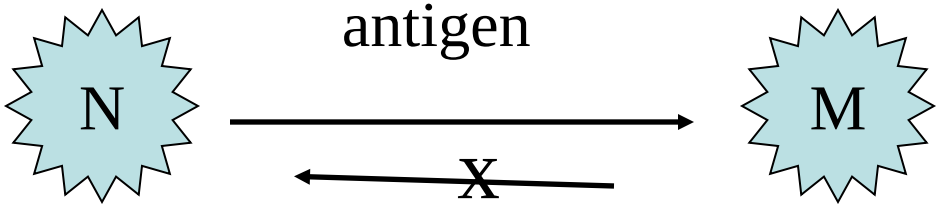
Production
Maturation

Interaction with Ag

LYMPHOCYTES: MEMORY/NAIVE

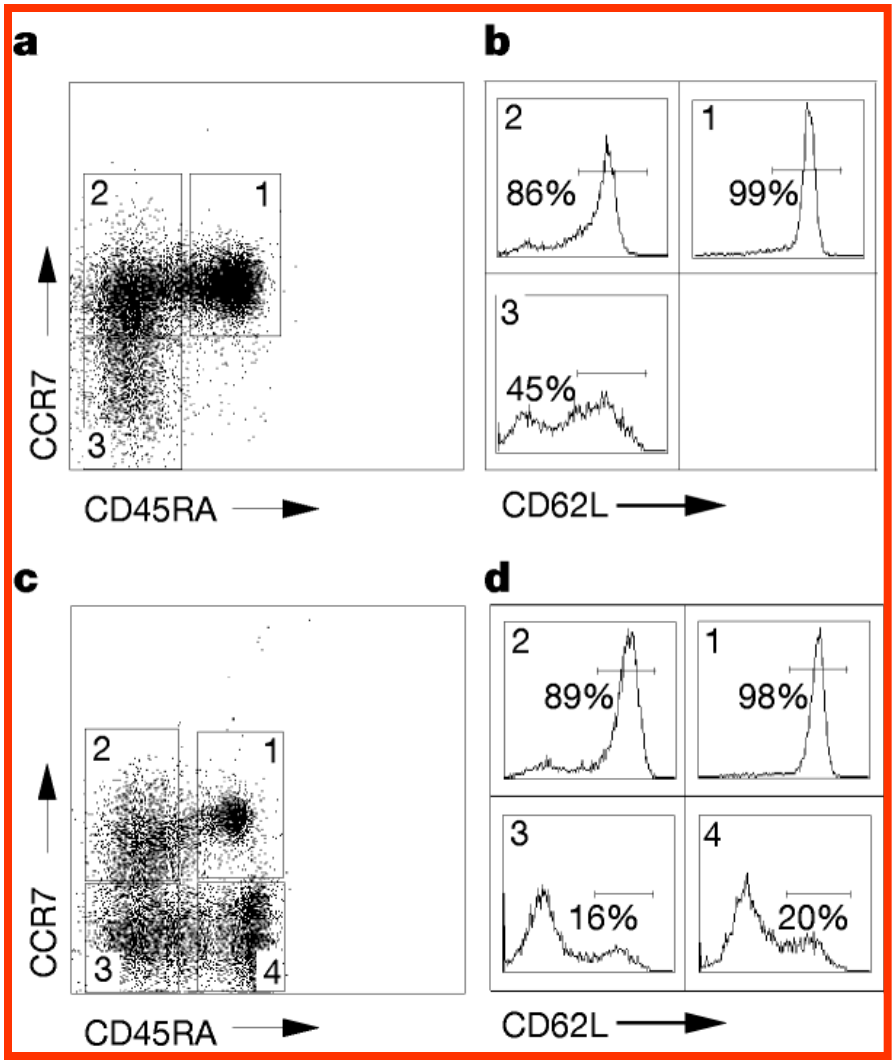
B LYMPHOCYTES: Naive: IgM and IgD
Memory IgG

T LYMPHOCYTES: Naive: CD45RA/CD62L-
Memory: CD45RO



T LYMPHOCYTES: MEMORY/NAIVE

Different patterns of co-expression of CCR7 and the isoforms of CD45 allow the differentiation of different subsets of memory and naive cells



CD4⁺ and CD8+ T cells.

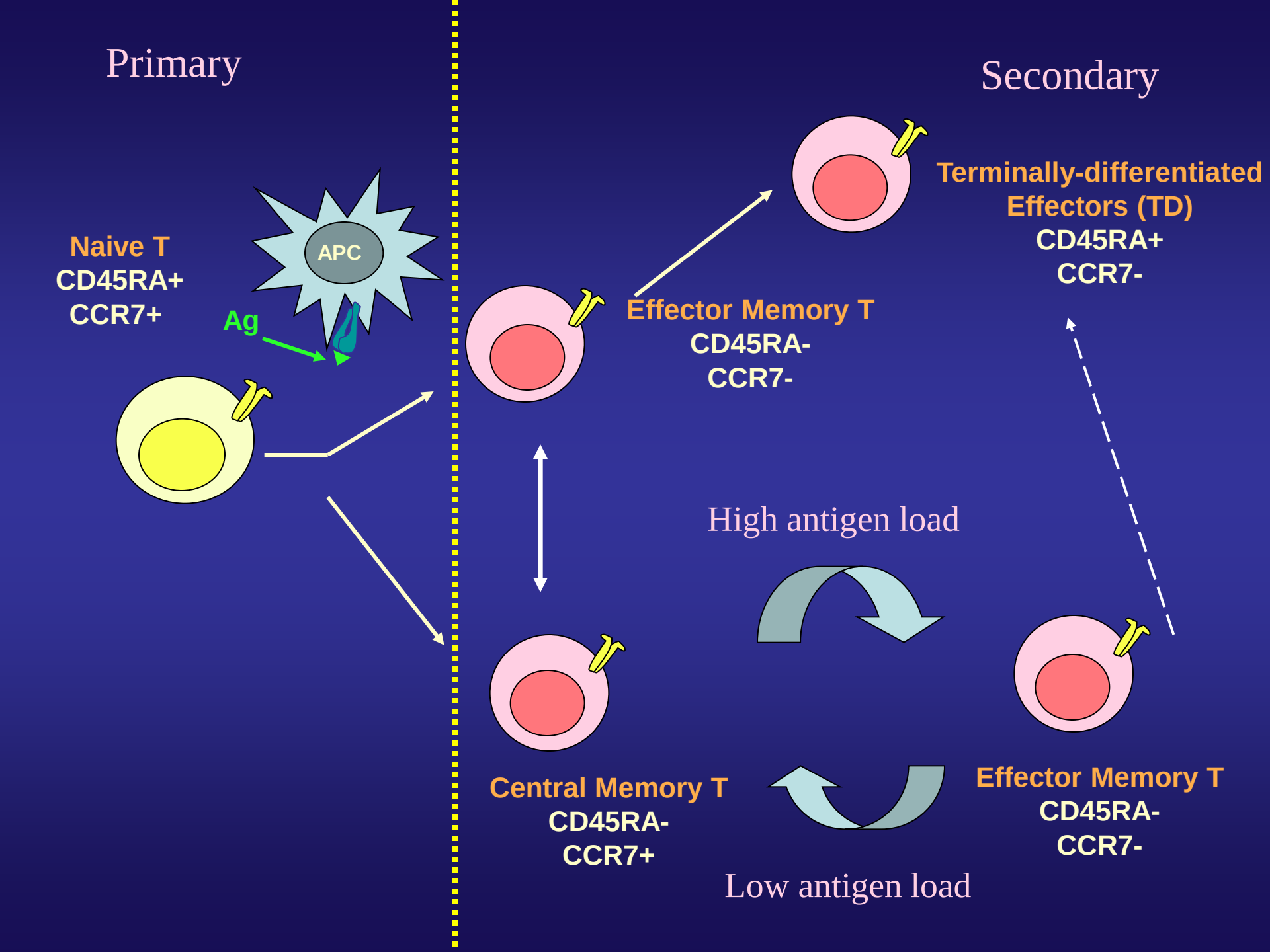
CCR7⁺ CD45RA⁺ **T naive**

CCR7⁺ CD45RA⁻ **T_{CM} central memory**

CCR7⁻ CD45RA⁻ **T_{EM} effector memory**

CCR7⁻ CD45RA⁺ **T_{TD} terminally differentiated**

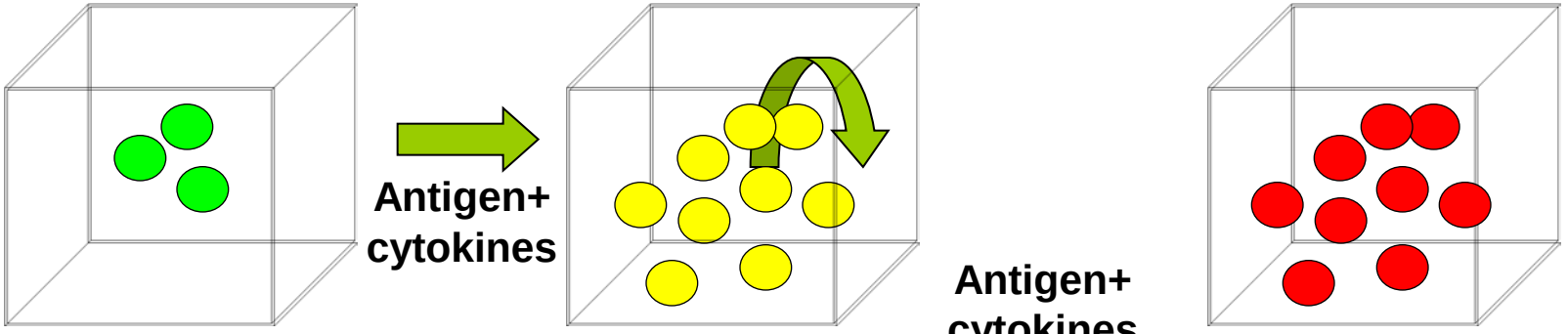
TWO SUBSETS OF MEMORY T LYMPHOCYTES WITH DISTINCT HOMING POTENTIAL AND EFFECTOR FUNCTIONS. F.Sallusto et al., Nature, 1999.


Primary
Secondary
Naive T
CD45RA+
CCR7+
APC
Ag
Effector Memory T
CD45RA-
CCR7-
Terminally-differentiated
Effectors (TD)
CD45RA+
CCR7-
High antigen load
Central Memory T
CD45RA-
CCR7+
Effector Memory T
CD45RA-
CCR7-
Low antigen load

Homeostasis of memory T cells

secondary lymphoid organs

peripheral tissues



Naïve T

Central memory T

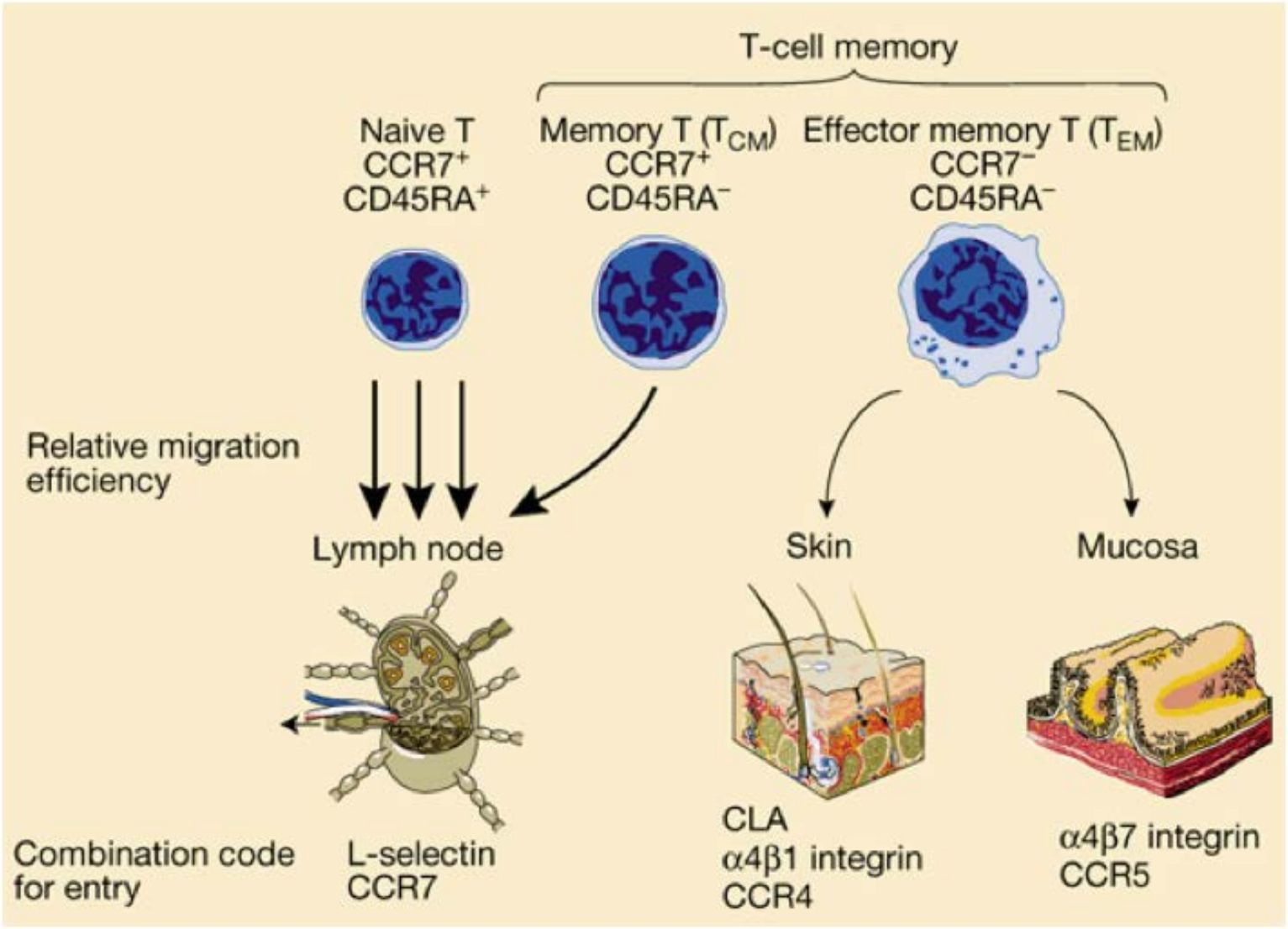
Effector memory T

and Terminally differentiated

persisting antigen

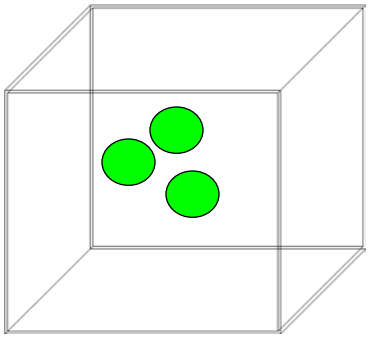
The localization of CCR7+ and CCR7- cells is different

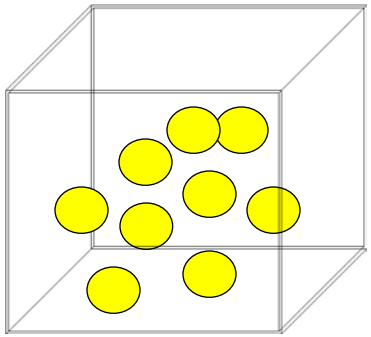
- CCR7+ cells (Naive and CM) are prevalent in lymph nodes
- CCR7- cells (EM and TD) are dominant in tissues and peripheral blood.

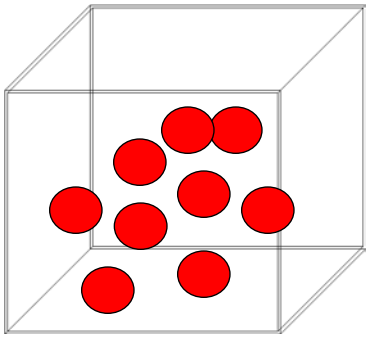

T-cell memory
Naive T
CCR7+
CD45RA+
Memory T (TCM)
CCR7+
CD45RA−
Effector memory T (TEM)
CCR7−
CD45RA−
Relative migration efficiency
Lymph node
Skin
Mucosa
Combination code for entry
L-selectin
CCR7
CLA
α4β1 integrin
CCR4
α4β7 integrin
CCR5

Division of labour among memory T cells

secondary lymphoid organs | **peripheral tissues**







Naive T → (**Ag-cyto**) → **Central memory T** → (**Ag-cyto**) → **Effector memory T and Terminally differentiated**

Home to lymph nodes
DC and B cell help
Precursors of effectors

Secondary responses
"Protective memory"

Home to non-lymphoid tissues
Immediate effector function
(cytokines, cytotoxicity)

Immediate protection
"Reactive memory"

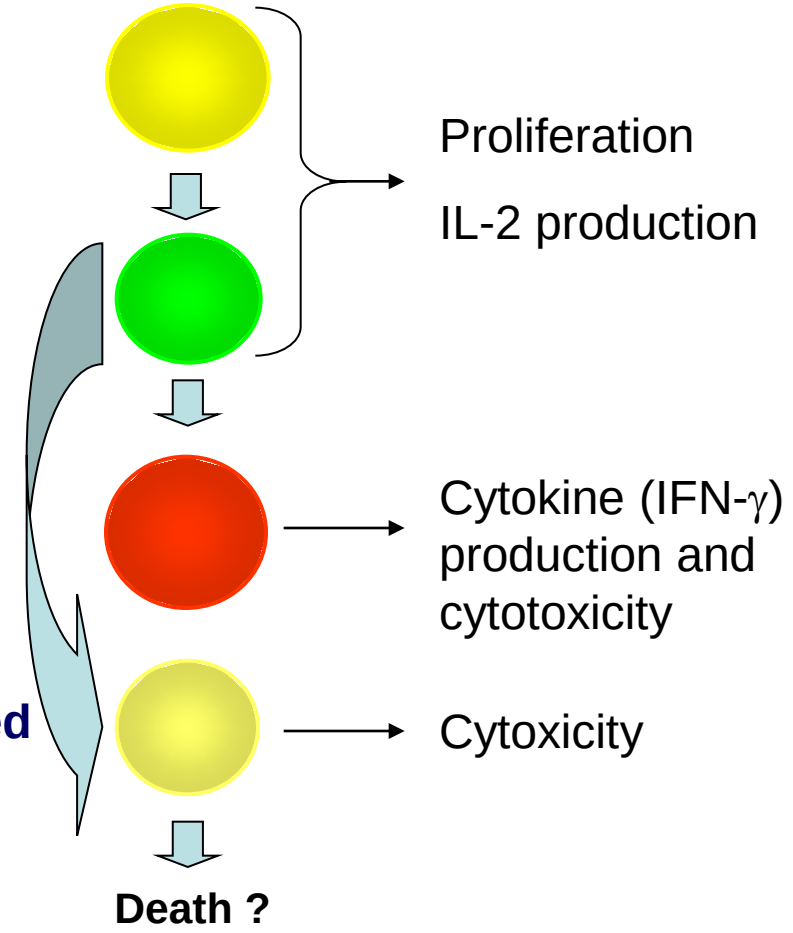
Human CD8 T cell subsets

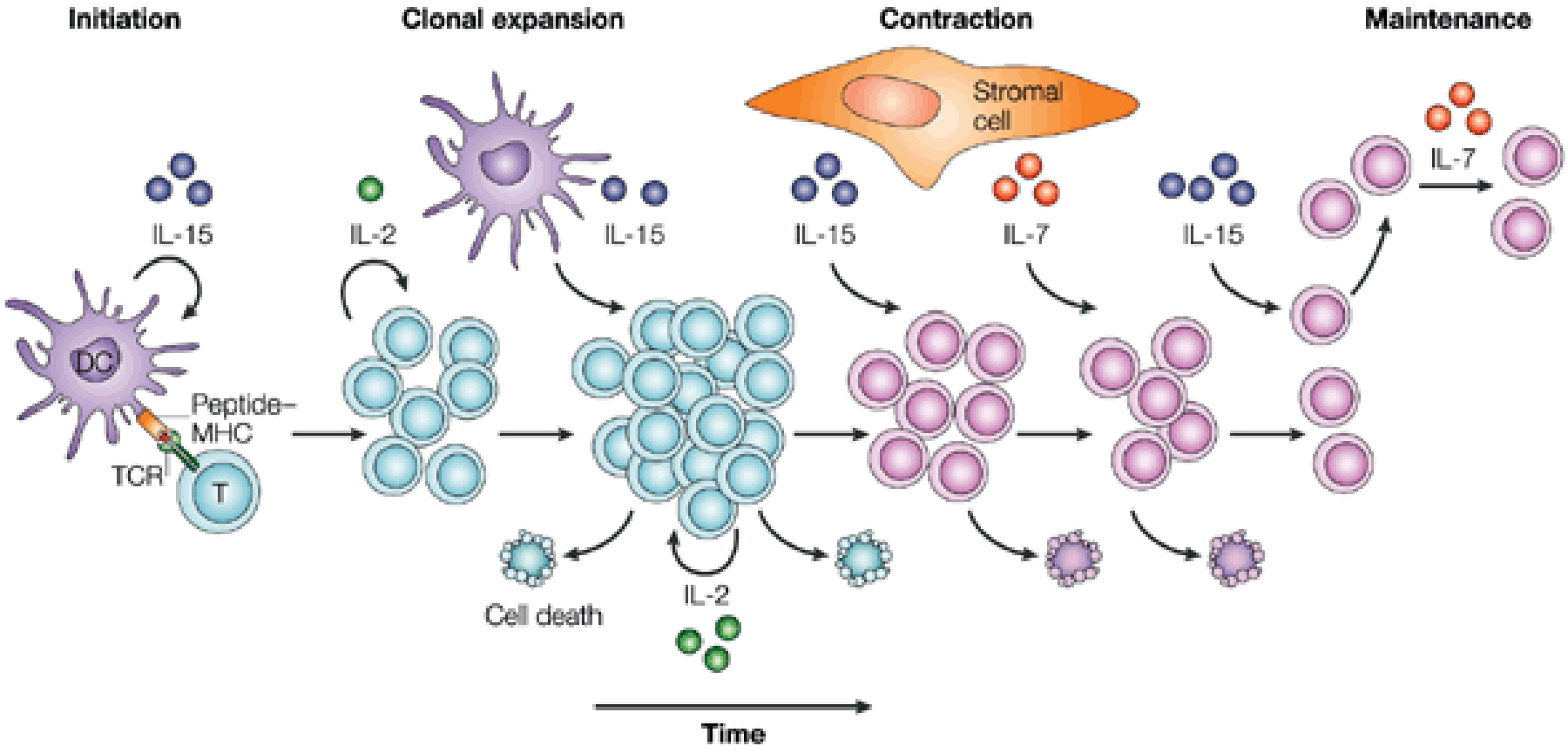
Naive
CD45RA$^+$ CD27$^+$
CCR7$^+$ CD62L$^+$

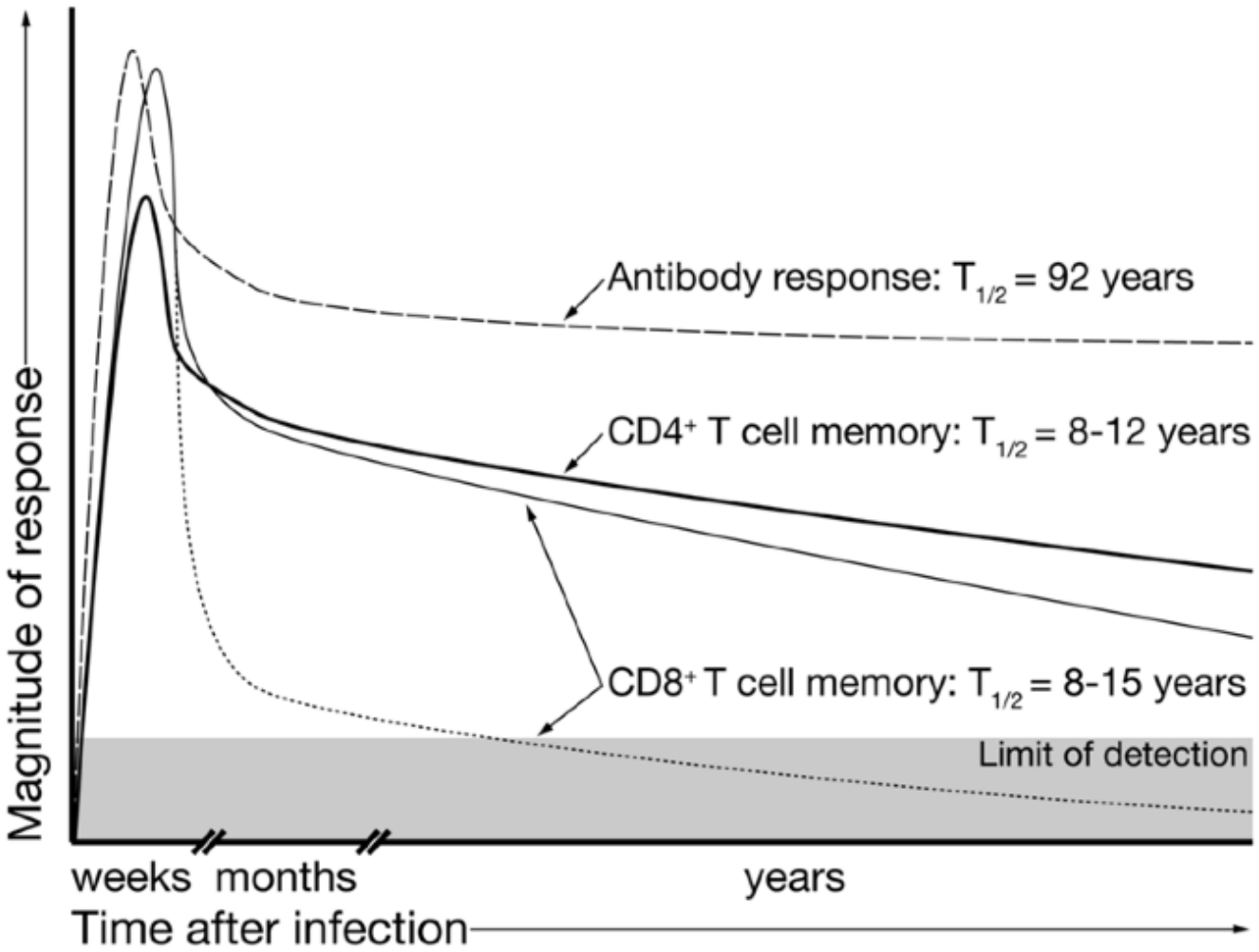
Central memory
CD45RA$^-$ CD27$^+$
CCR7$^+$ CD62L$^+$

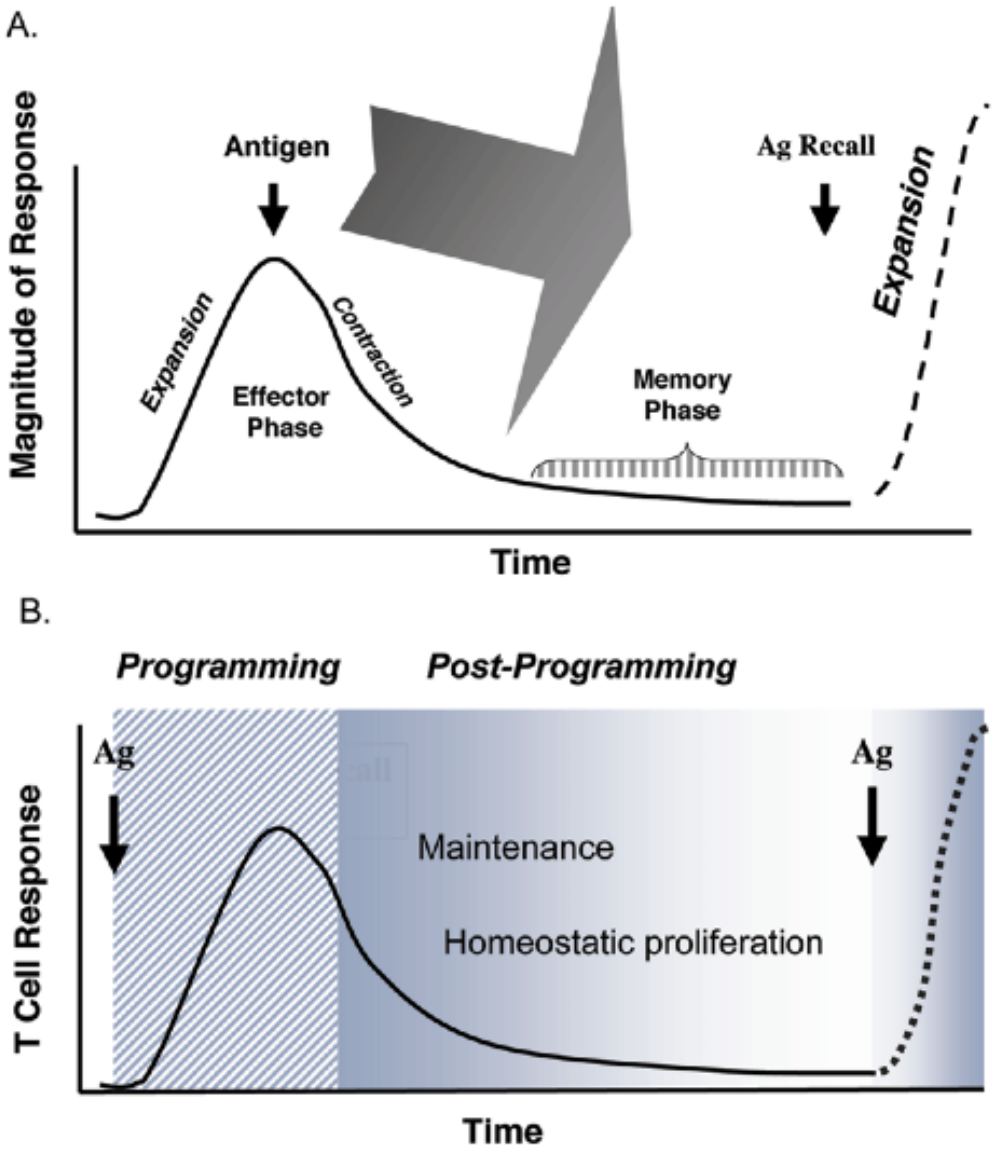
Effector memory
CD45RA$^-$ CD27$^-$
CCR7$^-$ CD62L$^-$

Effector memory RA$^+$
and **Terminally differentiated**
CD45RA$^+$ CD27$^-$
CCR7$^-$ CD62L$^-$




Initiation
Clonal expansion
Contraction
Maintenance
Stromal cell
IL-15
IL-2
IL-15
IL-15
IL-7
IL-15
IL-7
DC
Peptide–MHC
TCR
T
Cell death
IL-2
Time


Magnitude of response
Antibody response: $T_{1/2}$ = 92 years
CD4+ T cell memory: $T_{1/2}$ = 8-12 years
CD8+ T cell memory: $T_{1/2}$ = 8-15 years
Limit of detection
weeks
months
years
Time after infection


A.
Magnitude of Response
Antigen
Ag Recall
Expansion
Contraction
Effector Phase
Memory Phase
Expansion
Time
B.
Programming
Post-Programming
T Cell Response
Ag
Ag
Maintenance
Homeostatic proliferation
Time

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Persistence of Anti-HBs Antibody and Immunologic Memory for Hepatitis B Surface Antigen in Two Cohorts of Children Immunised with Hexavalent Vaccines: Implication for Policy and Booster Vaccination – Immunologic study

D. Trabattoni, L. Romanò, M. Pacei, A. Zanetti, M. Clerici

Background

- In Europe two vaccines, Hexavac® (Sanofi Pasteur, MSD) and Infanrix®-hexa (GlaxoSmithKline) were licenced for use in October 2000.

- Both vaccines protect against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type b and hepatitis B.

- In Sept 2005, following the observation of a reduced immunogenicity of the hepatitis B component in the Hexavac® EMA recommended the withdrawal of Hexavac® from the market.

Aim

A multicenter study was carried out to investigate whether vaccinated children could respond to a booster dose of hepatitis B vaccine 5 years after primary immunization.

- To evaluate if the decline in antibody titers under protective threshold (10 mIU/ml), observed in children receiving Hexavac®, reflects a loss of immune memory.

- To demonstrate whether T cell memory persist even when serum antibodies decline.

Materials and Methods

- 105 subjects, 65 Hexavac® and 40 Infanrix® were enrolled.

- Antigen specific T cell responses and T memory subsets were evaluated 5 years after HBV vaccination.

Data were analysed comparing:

- Infanrix- *vs* Hexavac-vaccinated subjects

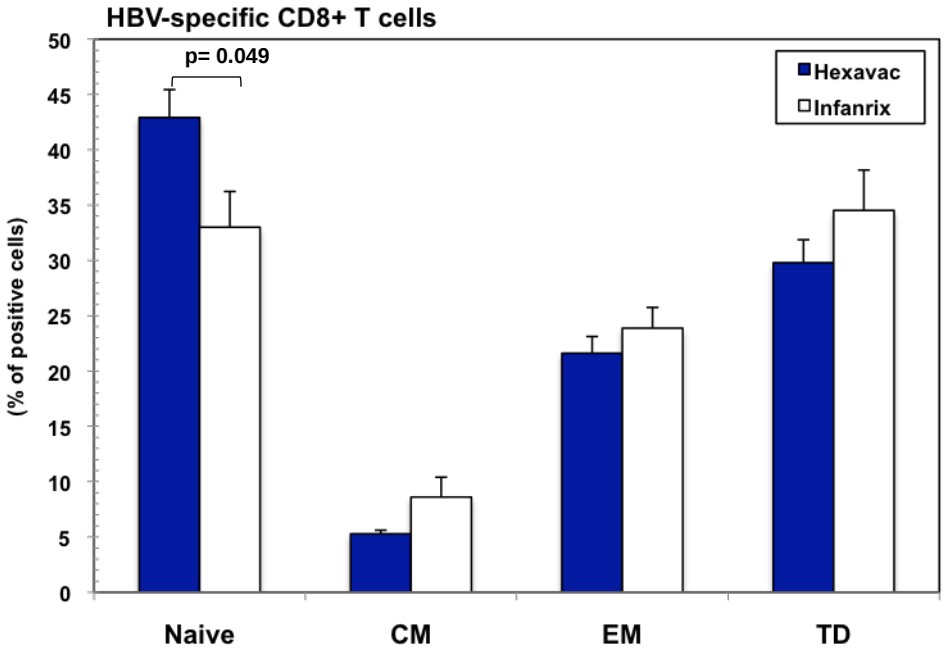
and

- Subdividing children on the base of humoral responses to the vaccines: Responder (anti-HBV Ab titles >10mIU/ml); Non Responder (anti-HBV Ab titles <10mIU/ml).

Results: Naive, Central Memory, Effector Memory and Terminally Differentiated CD4+ T cells

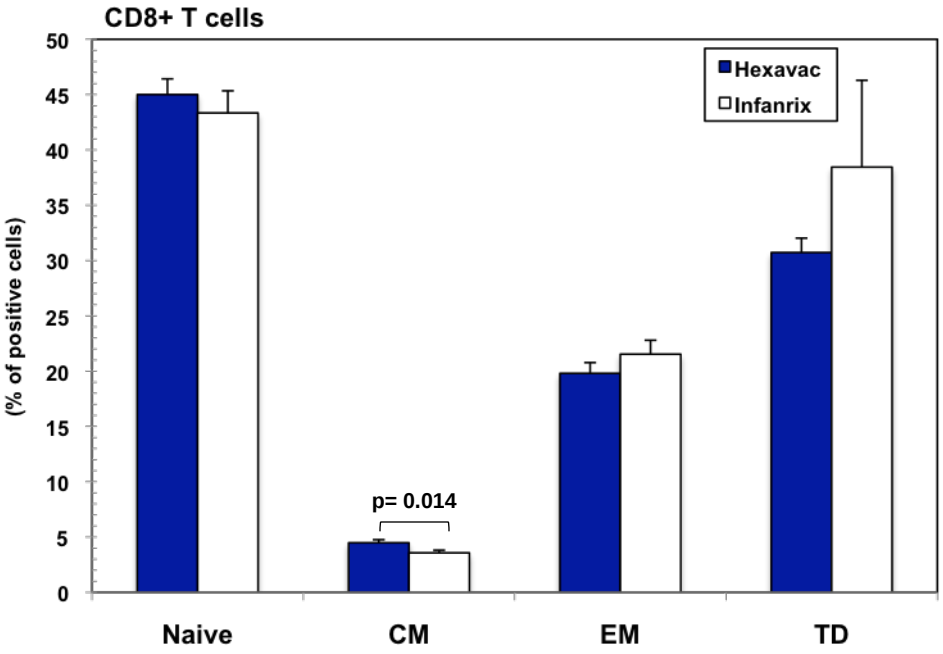
Naive, CM, EM and TD CD4+ T cells were similar in Hexavac- and Infanrix-vaccinated children

Results: Naive, Central Memory, Effector Memory and Terminally Differentiated CD8+ T cells



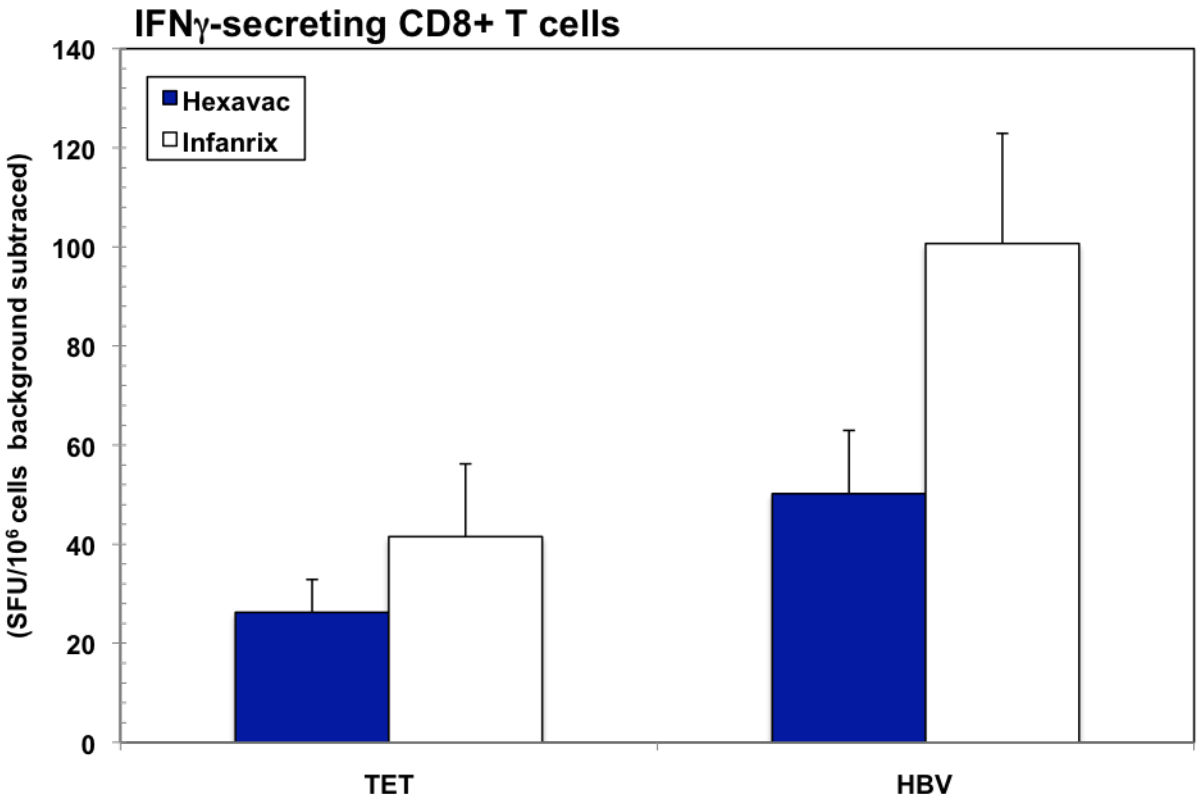
Naive CD8+ T cells were higher, CM, EM and TD cells were lower in Hexavac- compared to Infanrix-vaccinated children

Results: HBV-specific Naive, Central Memory, Effector Memory and Terminally Differentiated CD8+ T cells



HBV-specific Naive and CM CD8+ T cells were higher, EM and TD were lower in Hexavac- compared to Infanrix-vaccinated children

Results: HBV-specific IFNγ-secreting CD8+ T cells



HBV-specific IFNγ-secreting CD8+ T cells were lower in Hexavac-compared to Infanrix-vaccinated children

Results: Naive, Central Memory, Effector Memory and Terminally Differentiated CD4+ T cells

Naive, CM, EM and TD CD4+ T cells were similar in Responders and Non Responders

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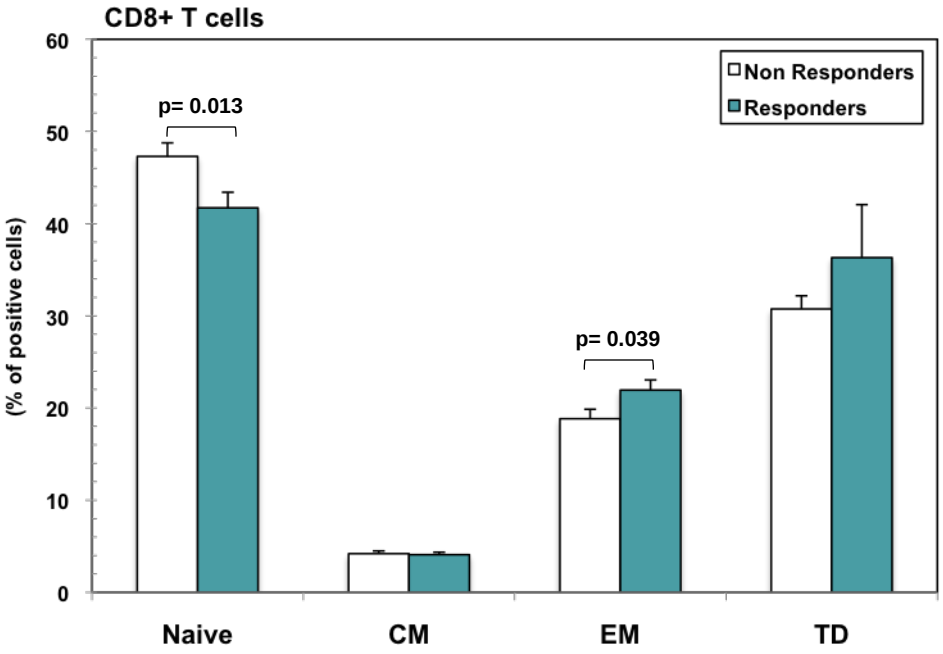

Naive CD8+ T cells were lower, EM and TD were higher in Responders

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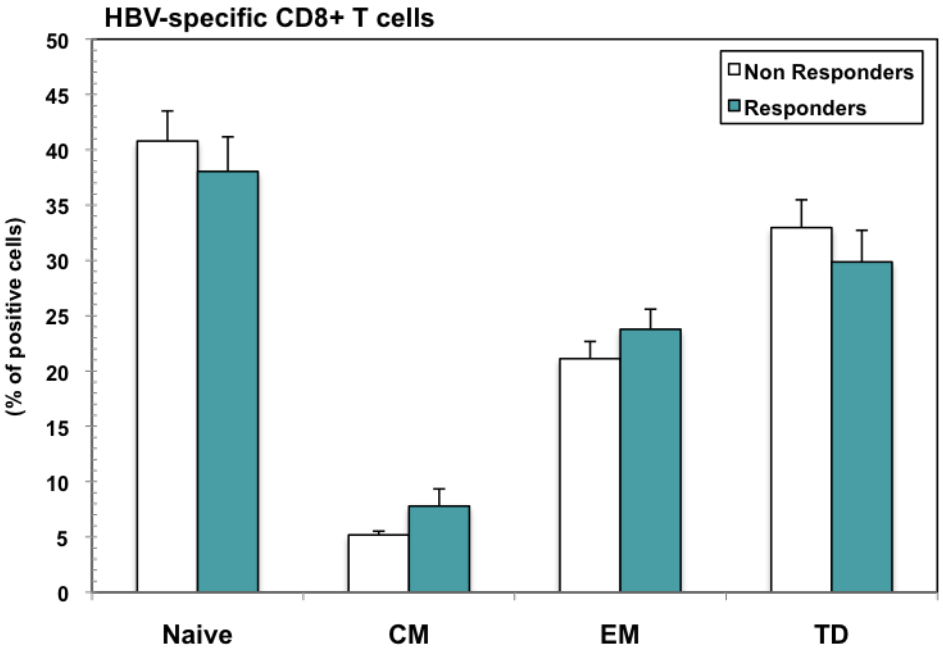
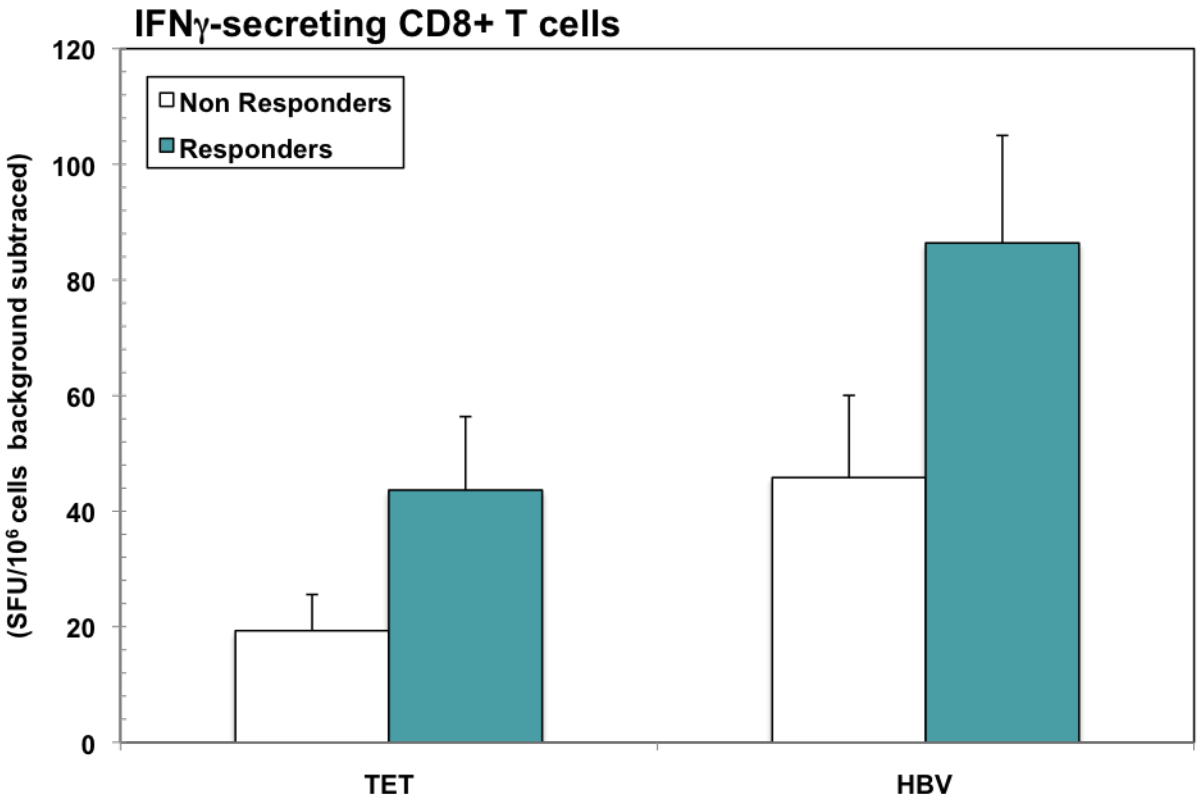
Results: HBV-specific Naive, Central Memory, Effector Memory and Terminally Differentiated CD8+ T cells



Naive cells were lower, CM and EM were higher in Responders

Results: HBV-specific IFNγ-secreting CD8+ T cells



HBV-specific IFNγ-secreting CD8+ T cells were augmented in Responders

Conclusions

- T cell memory is extremely complex and still very unclear
- HBV specific memory T cells are detected in peripheral blood >5 years after vaccination
- The reduced efficacy, as well as the lack of Ab-measured immunogenicity of a vaccine are reflected in alterations of the different circulating subsets of memory T cells.