

Scientific Challenges for the Development of an HIV Vaccine

AIDS 2006

Toronto

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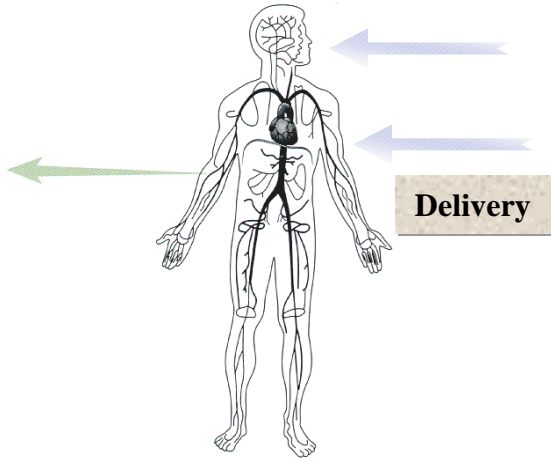
Theme 2

Theme 1

Theme 3

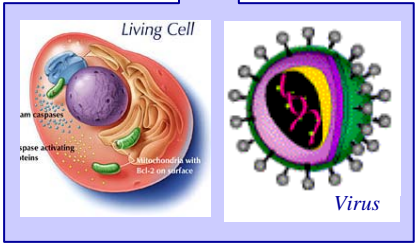
Host response

- ◆ Immune response
- ◆ Side effects
- ◆ Efficiency



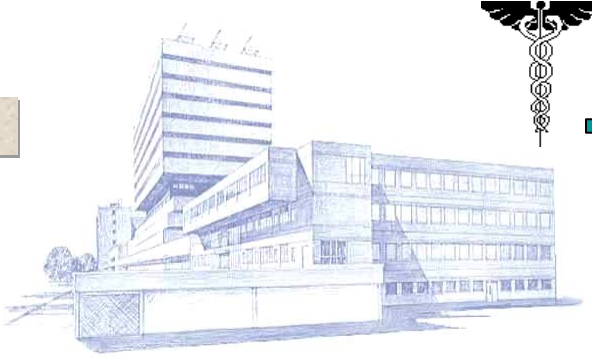
Antigens

Adjuvants

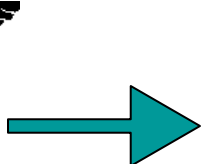
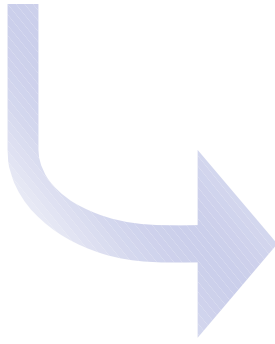


Theme 4

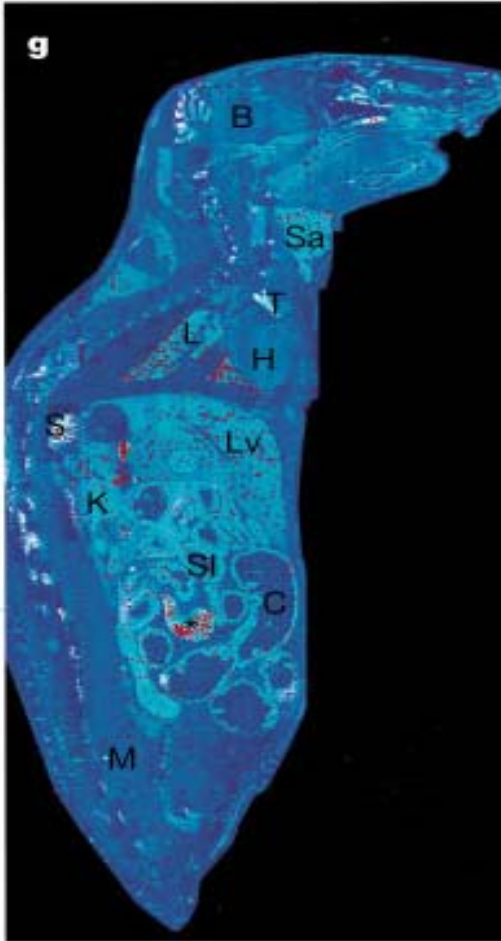
Clinical trial



Vaccine

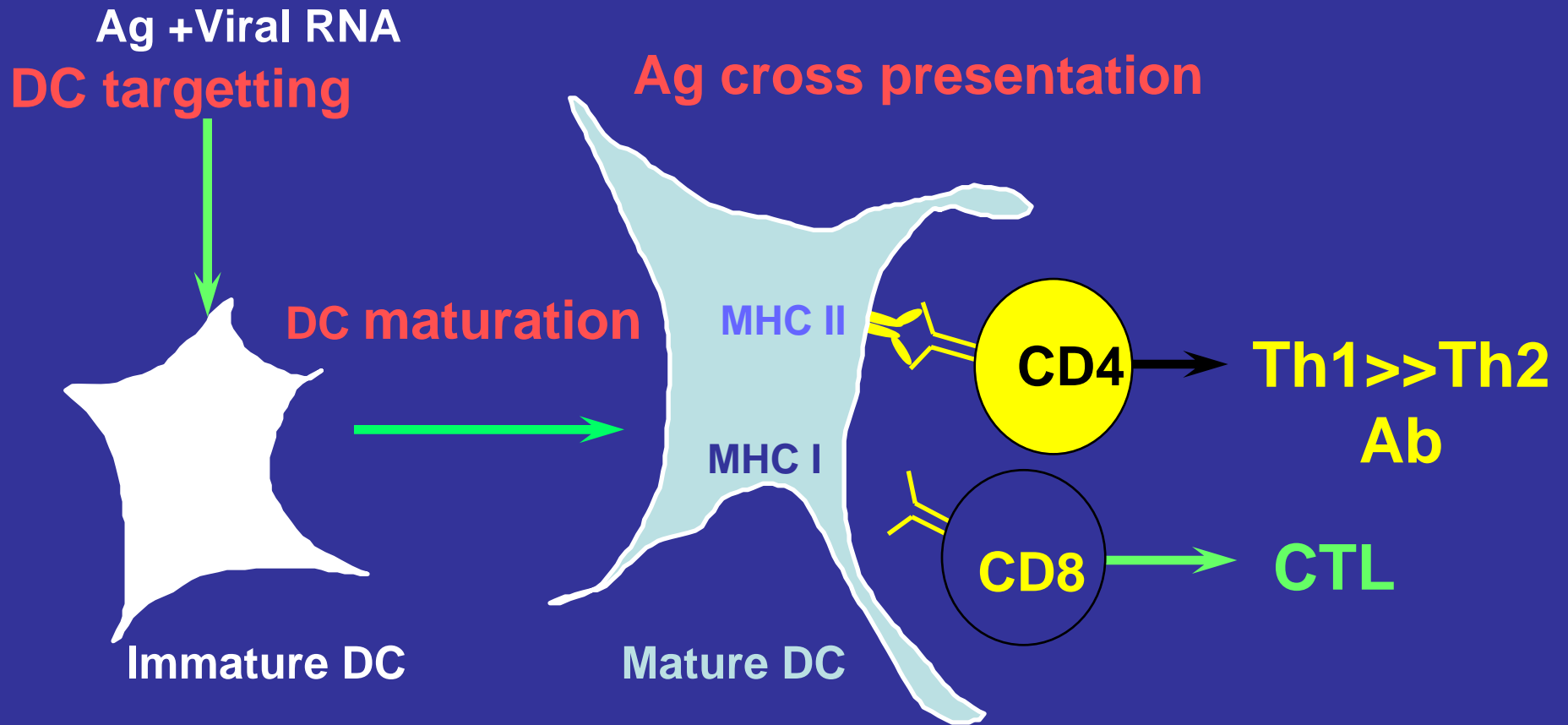


Complexity of the immune system



- The immune system is a complex multicellular system (T cells, B cells and APCs) that relies on the delicate balance between a set of positive and negative regulators of cell function for optimal function
- These cells encounter Ags at mucosal interfaces and in lymph nodes
- Ensuring the proper recruitment of these cells at mucosal interfaces has been a challenge

The Immune response: a complex set of cellular and molecular interactions



Challenges facing the scientific community for HIV vaccine development

- Lack of knowledge of effector cells and molecules involved in vaccine induced protection
- Lack of knowledge of mechanisms enabling the establishment and persistence of long term memory T and B cells
- Lack of knowledge of effector cell and molecules of mucosal immunity
- Lack of understanding of mechanisms leading to the generation of neutralizing antibodies

Challenges facing the scientific community for HIV vaccine development

- Optimal immunogen design for HIV vaccines still to be determined although it is established that polyvalent immune responses are associated with protection
- Strong adjuvants which can trigger all arms of immune responses still the quest of many although TLR ligands are most promising in inducing multifunctional immune responses

Progress made in addressing these challenges

- Enhanced knowledge of mechanisms of immune responses
- Novel appreciation of the central role of Dendritic cells and in particular the function of TLR ligands
- Novel understanding of cross presentation which allows the design of new generation vaccines
- Novel understanding of cells and molecules which can attenuate immune response : Tregs and concept of breaking tolerance

Progress made in addressing these challenges

- Development of novel standardized assays to obtain quantitative and qualitative assessment of immune responses
- Development of animal models that can allow the in vivo deciphering of protective immune responses
- Structure of HIV envelope protein complexed with neutralizing antibodies
- Map of the HIV external surface showing the organization of envelope subunits on the surface of virions

**Correlates of Immune protection : an
important clue for the design of
efficacious vaccines**

Establishment of Standardized Preclinical and Clinical Laboratory Assessment

- *"A more transparent and standardized preclinical evaluation system for candidate immunogens is essential for defining and developing successful vaccine regimens."*
- *"Standardized protocols and immunogenicity measurements need to be widely implemented at the preclinical and clinical stages of vaccine development to measure humoral and cell-mediated immunity and to provide a test bed for reproducibly assessing the immune response to HIV antigens and adjuvants."*

Novel Multiparametric assays to decipher protective immune responses

- Rationale :
 - The Immune response is complex and correlates of immune mediated protection cannot be equated to a single or two parameters
 - The use of technologies which allow the analysis of multiple parameters is better suited for that purpose
 - Such technologies allow the dissection of the different effector arms of the cellular , humoral and innate immune responses

Decoding the Immune Response

- Memory and effector CD4⁺ and CD8⁺ responses
- Innate immunity
- Potency assays for dendritic cells
- Mucosal immune responses
- Neutralising antibodies

Novel assays

- Polychromatic flow cytometry
 - Allows a definition at the single cell level of up to 17 parameters
 - These parameters include :
 - Cell surface markers which define distinct subsets of different maturation stages
 - Functions such as cytokine production, cytotoxic T cell function , degranulation
 - Cell cycle stages

Novel assays

– Genomics

- Can be performed on isolated subsets of cells
 - Sensitivity allows the analysis on single cells
- Can be also performed on whole blood which provides a very simple assay
- Generates enormous amount of data and the caveat resides in the analysis and bioinformatics

Lessons learned from other Viral vaccines

- A role for cellular immunity and in particular memory T cells and effector CD8 cells
- A role for a broad immune response directed against multiple T cell epitopes
- A role for multifunctional cells including IL-2 producing T cells
- A role for IL-12 produced by dendritic cells

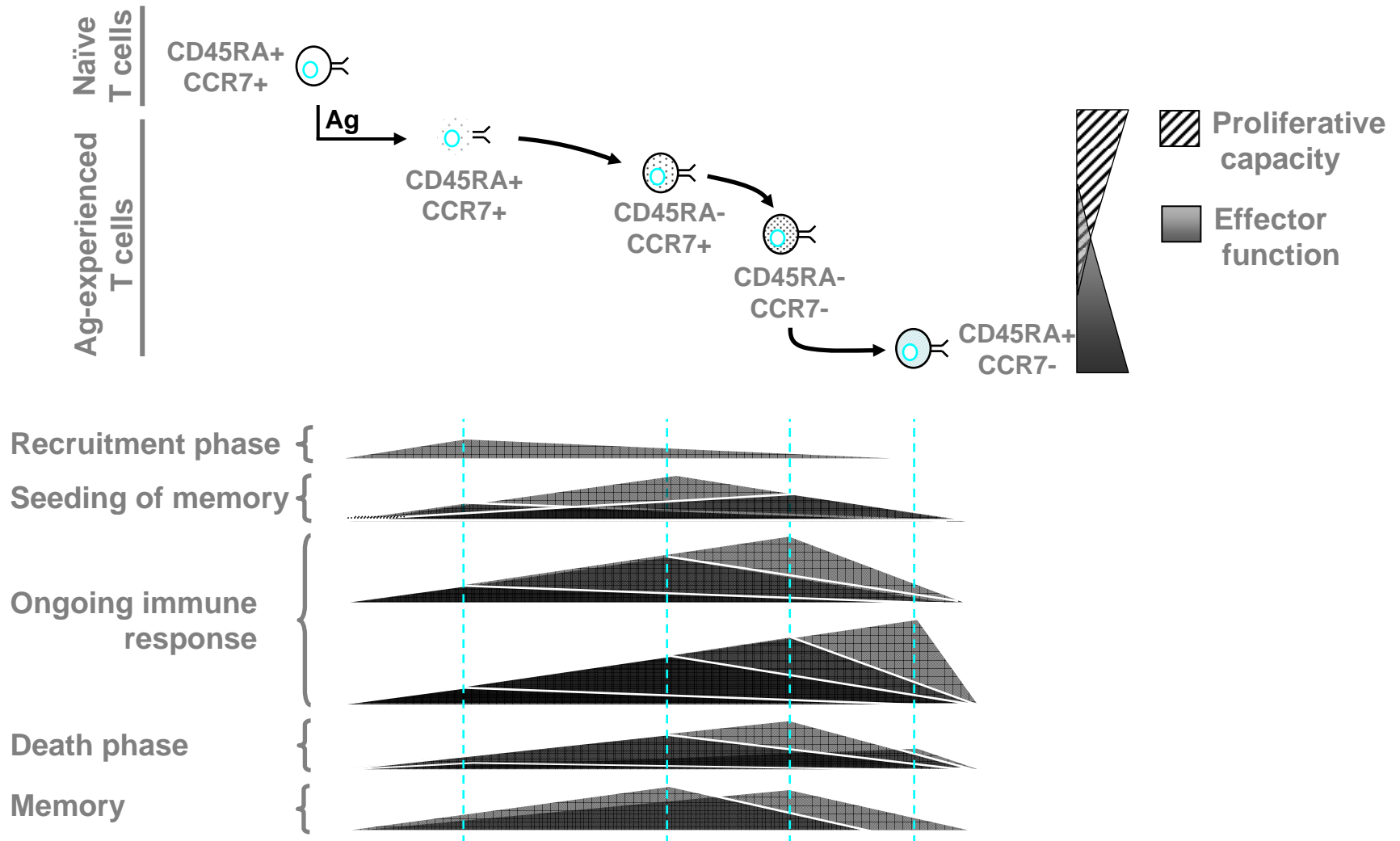
Memory T cells : the ultimate correlate of protection

- Memory T cells are the stem cells of the immune response
- They provide the long term immunity which is the hallmark of vaccine induced protection
- Several vaccines tested to date induce long term memory T cells which can transfer the protection from one individual to another

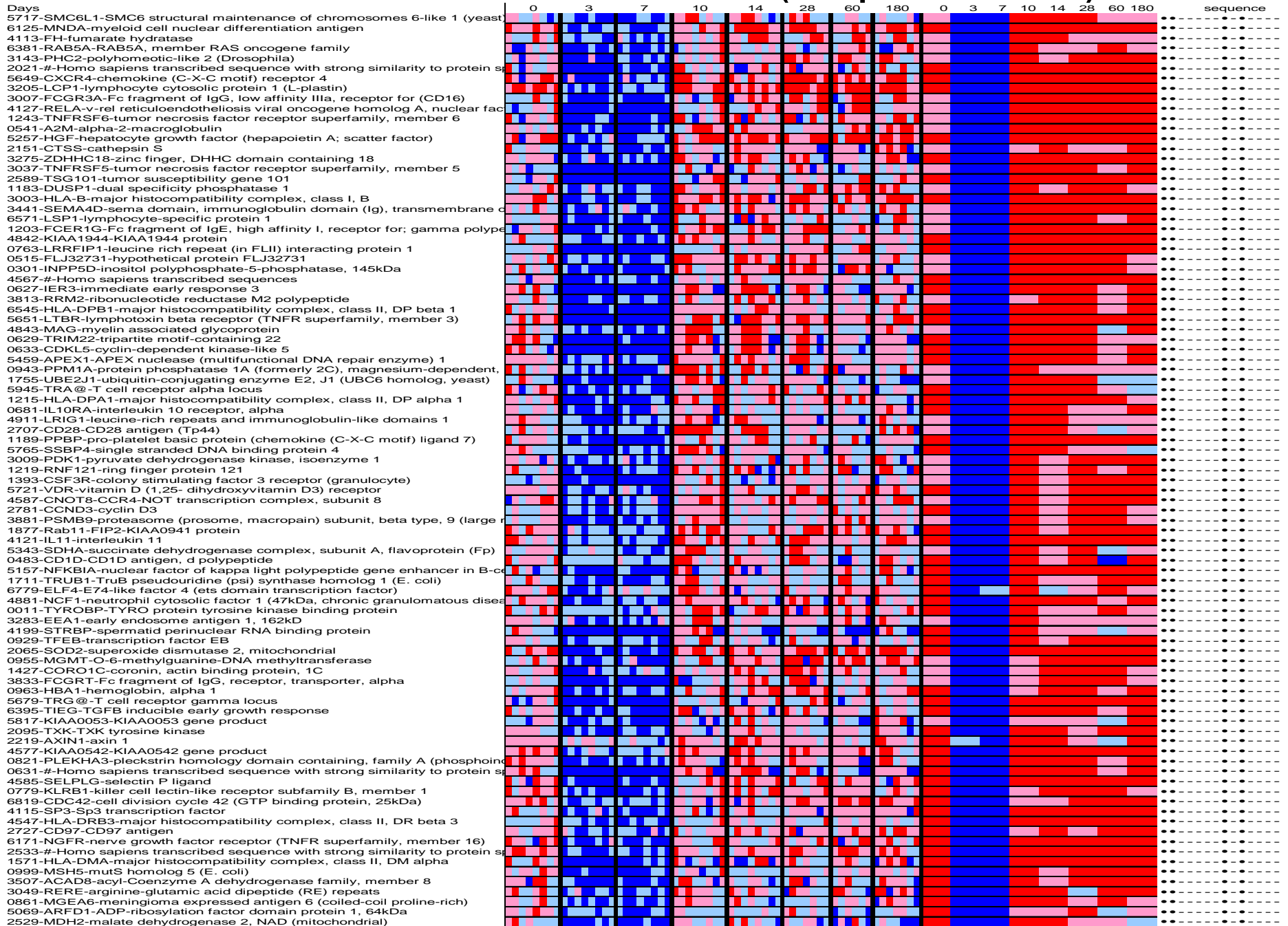
Memory T cells : the ultimate correlate of protection

- Memory CD4 T cells are associated to protection in Long term non progressors
- Memory CD4 T cells are induced by most efficient vaccines including vaccines to acute viral infections (Flu ; yellow fever;small pox)
- Recent work by Letvin and Nabel has shown in the SIV model the critical role of central memory T cells in vaccine induced protection

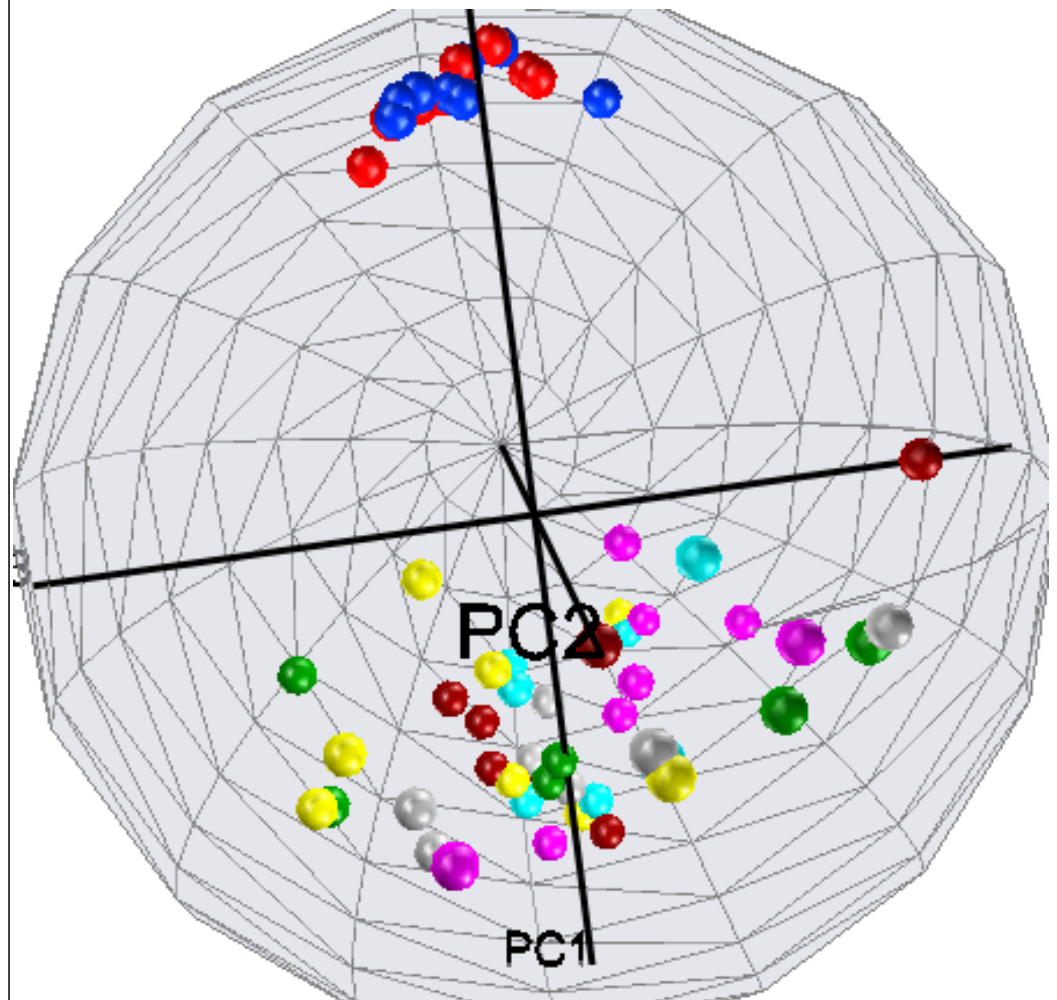
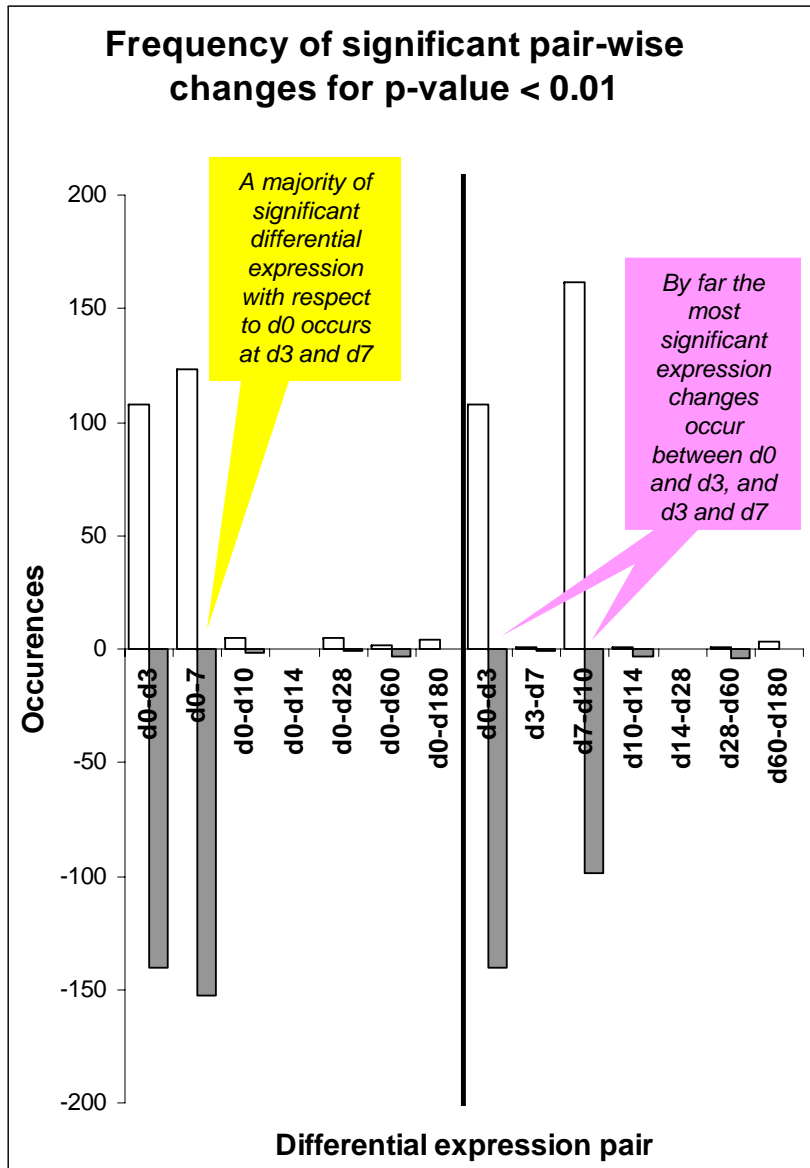
T cell differentiation and the seeding of T cell memory



Characteristic Profile R1 (Repressed 1)

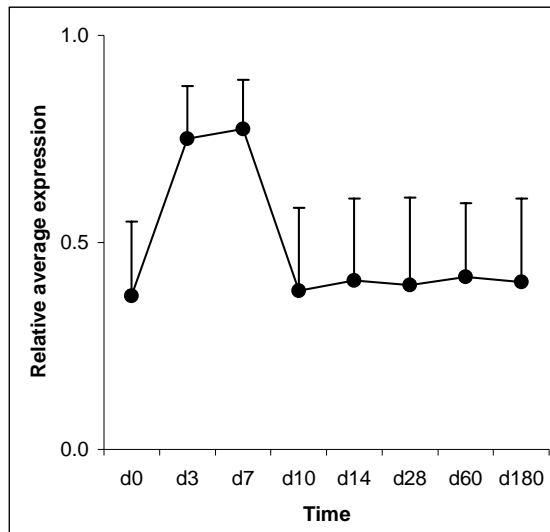


At differential expression T-test p-values ≤ 0.01 an overwhelming majority of the changes occur between d0 and d10



Characteristic Profile S1 (Stimulated 1)

characteristic profile								
S1	56	••-----	•-•-----					
time	d0	d3	d7	d10	d14	d28	d60	d180
average	0.37	0.75	0.77	0.38	0.41	0.40	0.42	0.40
stdev	0.18	0.13	0.12	0.20	0.20	0.21	0.18	0.20

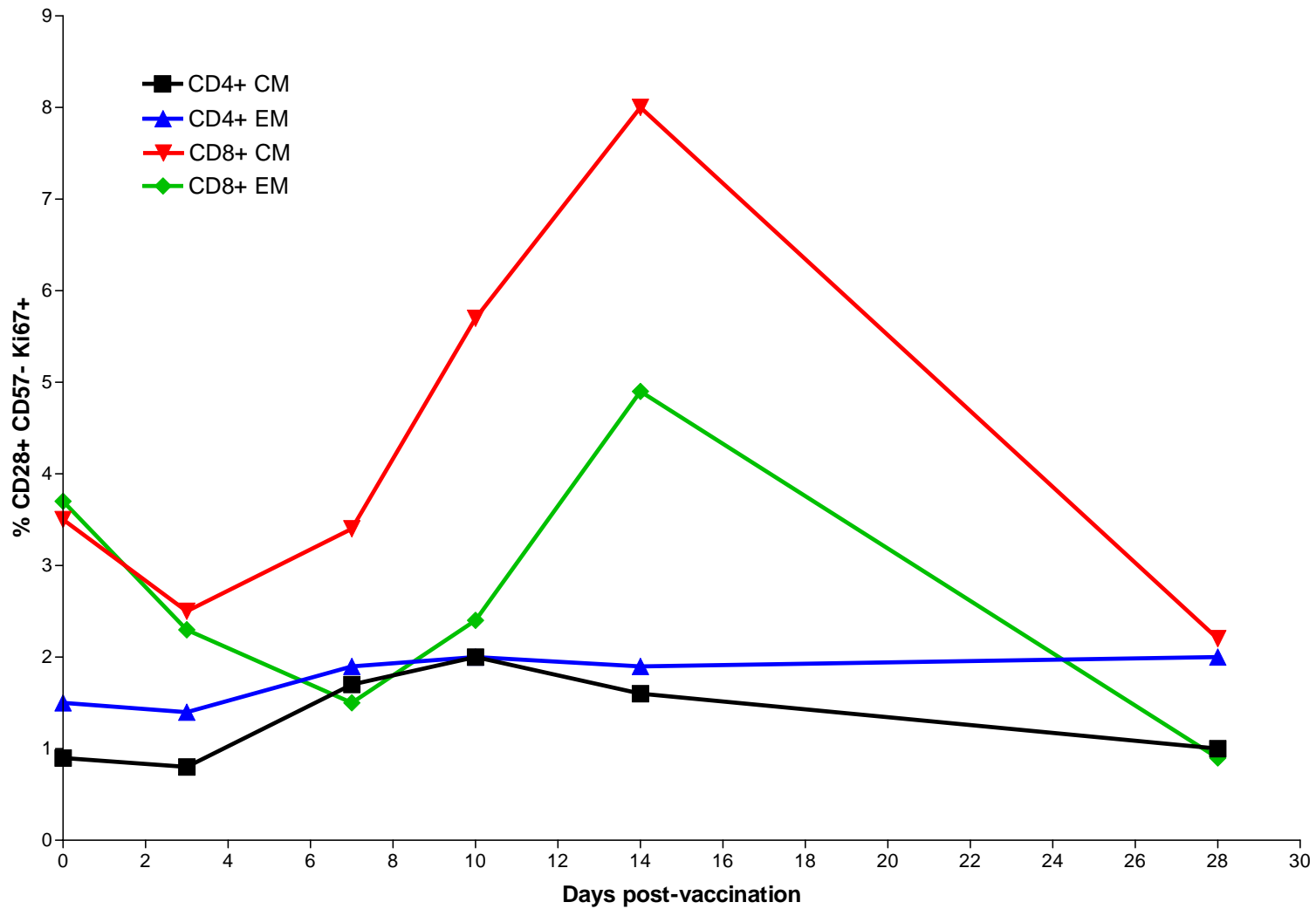


Genes associated with this profile 55 Genes

Pro-survival Genes

- ERK3
- IL-7R
- TRAK (activate NF κ B pathway)
- TNFR11 (co-stimulation, inhibit apoptosis
By recruiting c-IAP1)

Early induction of Central memory CD4 and CD8 T cells \ following yellow fever vaccination



Correlates of protection in Yellow fever vaccination

- YF vaccination induces very potent innate and adaptive immune responses
- These responses occur as early as day 3 and may be earlier
- The YF-specific immune response has an equilibrated TH-1/ TH2 profile
- Several pro-survival genes are induced very early
- The establishment of memory occurred as early as day 5
- The immune response to YF varies quantitatively amongst patients.

Conclusions

- Several assays are now in place to identify correlates of protection
- Identification of such correlates should be a priority
- Identification of these correlates will provide a benchmark for a successful HIV vaccine
- The quest for adjuvants that can trigger long term memory should be a priority

Thank you