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**BAYLOR INSTITUTE FOR IMMUNOLOGY RESEARCH  
INSERM RESEARCH LABORATORY - U 899**

**CENTER FOR HUMAN VACCINES  
CENTER FOR PERSONALIZED MEDICINE**

**Mount Sinai School of Medicine, New York: Dpt of Cell and  
Gene Therapy; Dpt of Medicine; Immunology Institute**

***Autoimmunity***

**CYTOKINE BLOCKADE**

**VACCINES**

***Cancer***

***Dendritic Cells***

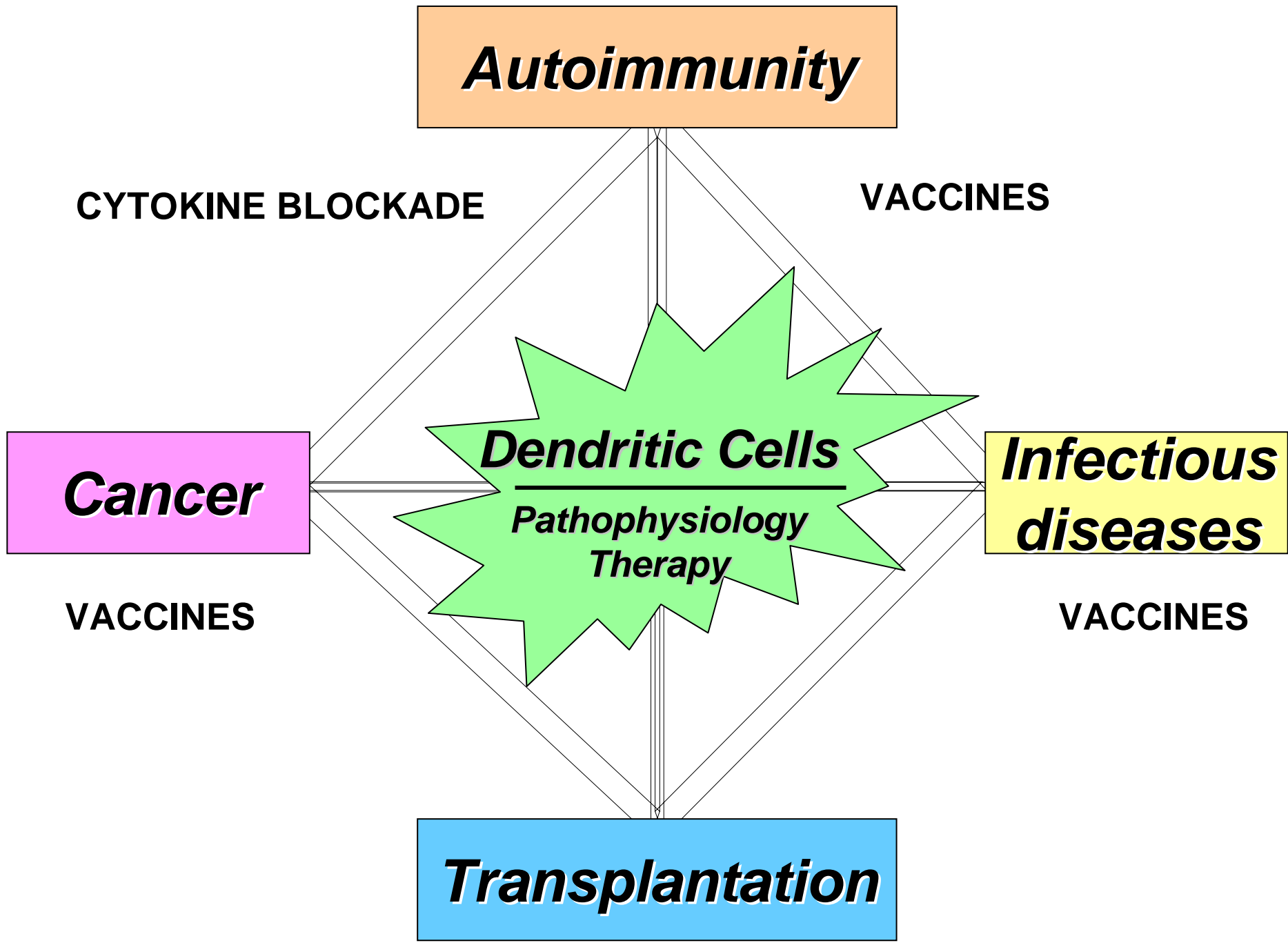
***Pathophysiology  
Therapy***

***Infectious  
diseases***

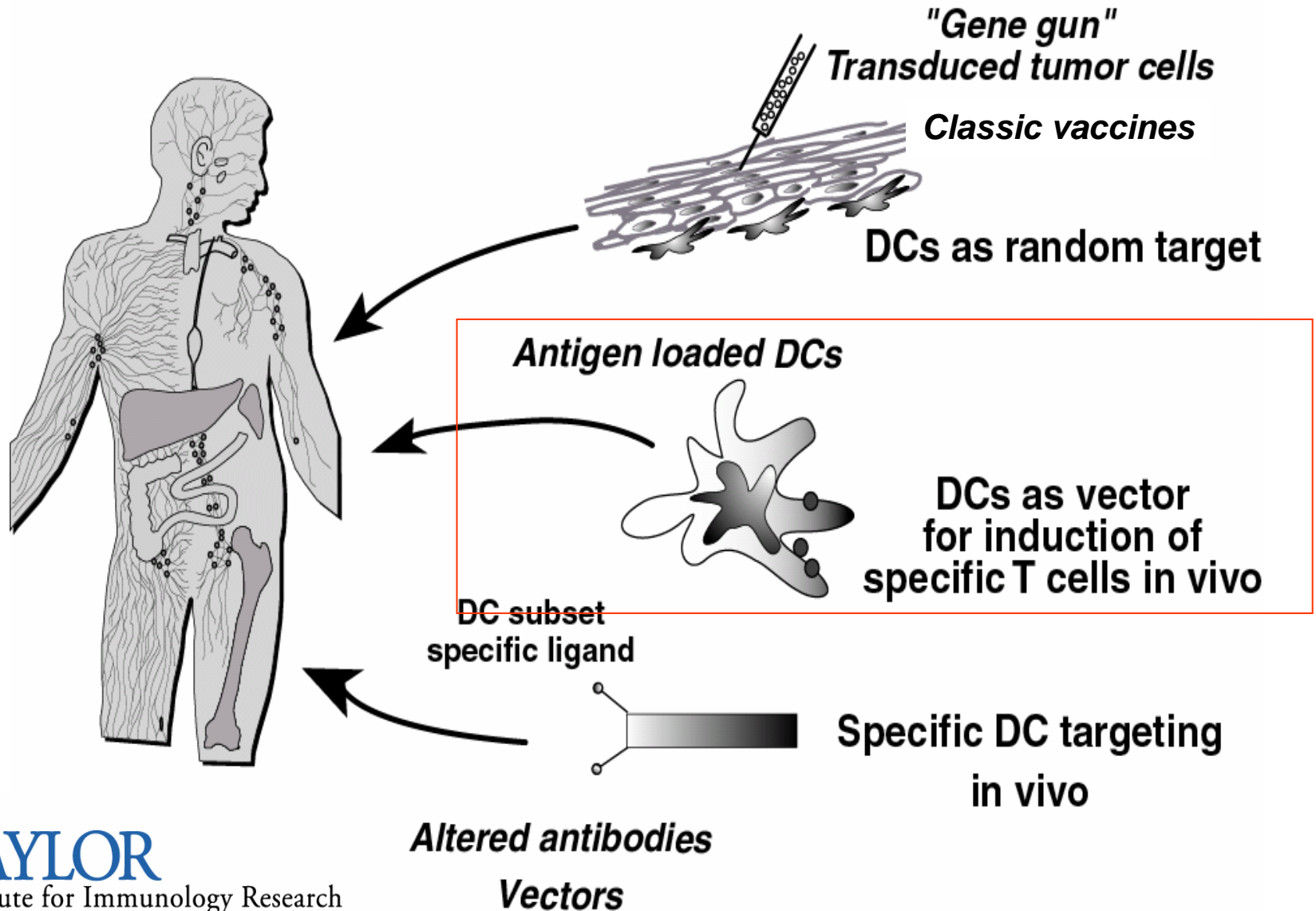
**VACCINES**

**VACCINES**

***Transplantation***



# HARNESSING DENDRITIC CELLS TO BUILD CANCER VACCINES



# DEVELOPMENT OF NOVEL VACCINES

*Vaccine development teams*

*DC targeting teams*

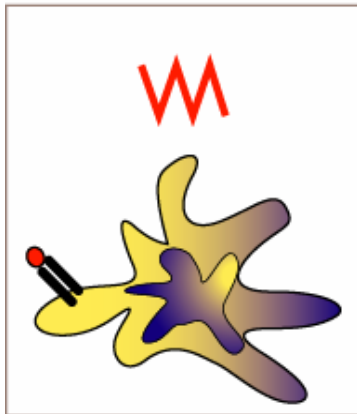


**SangKon Oh, Karolina Palucka, Lee Roberts, Hideki Ueno, Gerard Zurawski**

# Vaccine Development Strategy

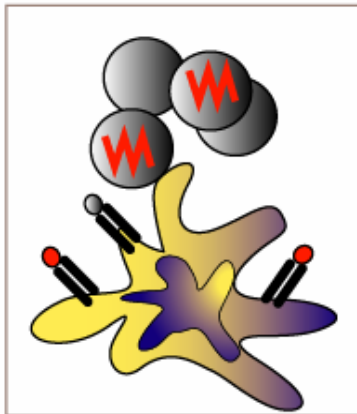
## LOADING DENDRITIC CELLS WITH ANTIGENS

short synthetic peptides



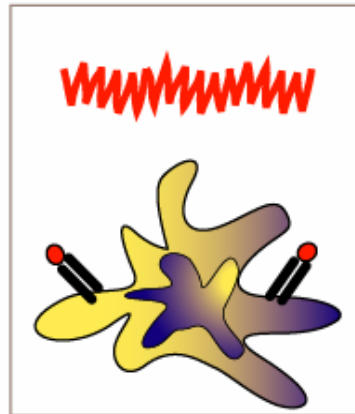
MHC restriction  
no CD4+ T cells

killed tumor cells



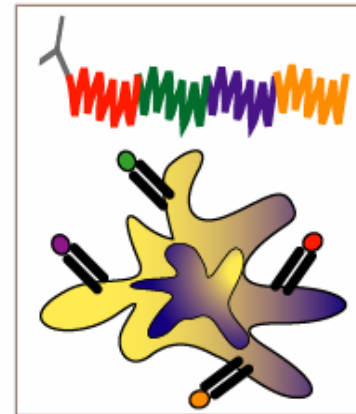
no MHC restriction  
CD8+ and CD4+ T cells  
broad antigen repertoire  
potential Treg expansion

long synthetic peptides



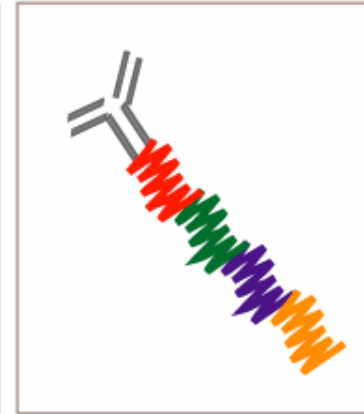
work in progress

ex vivo targeting



antigen delivery  
together with activation  
signal

in vivo targeting



no need  
for ex vivo DC  
generation

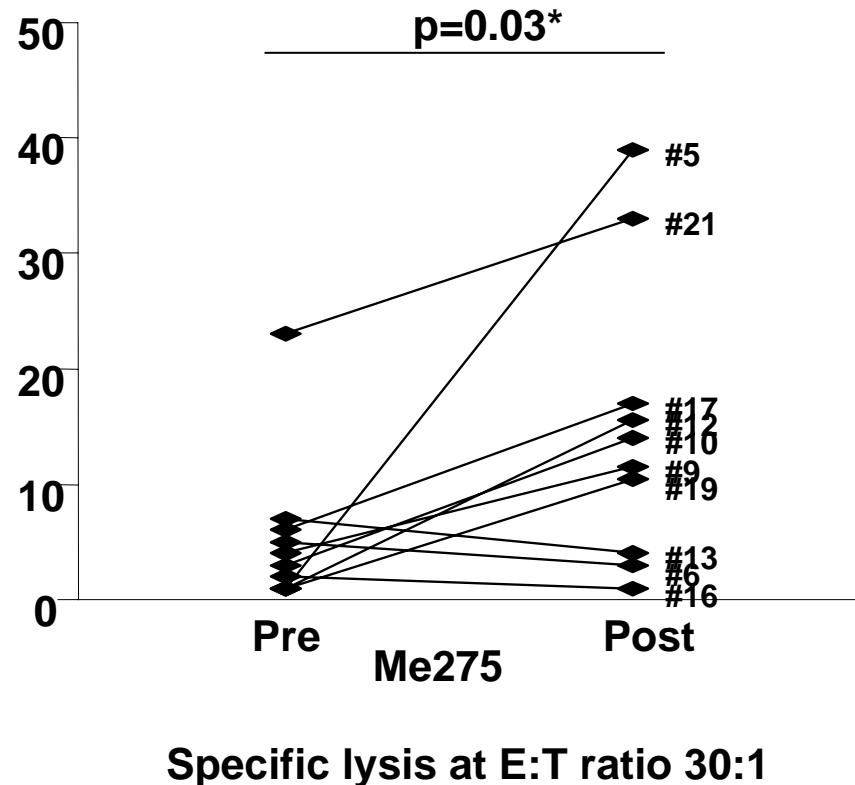
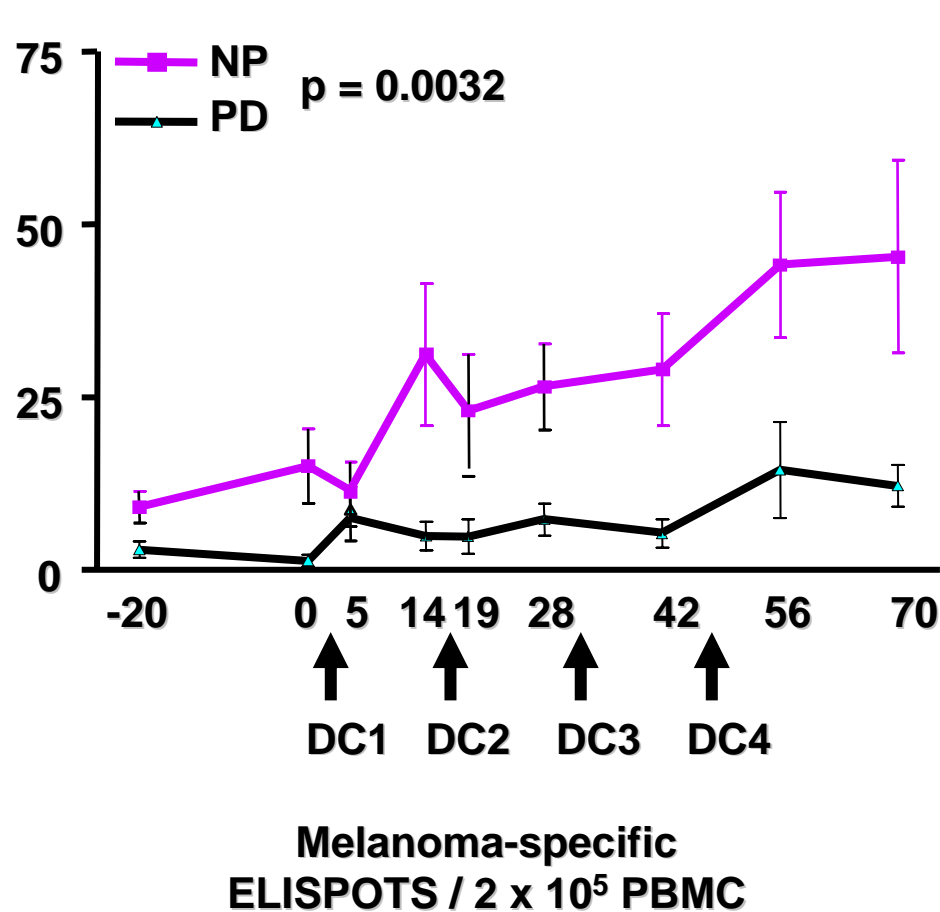
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metastatic disease

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adjuvant

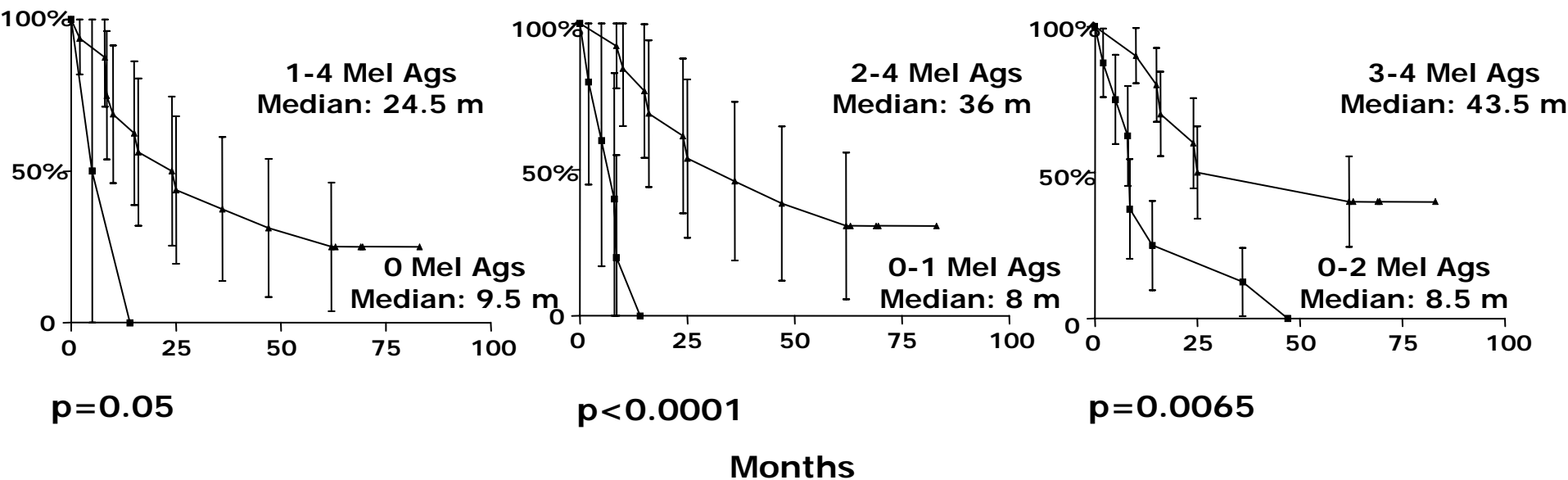
# Progressive patients do not mount TAA-specific responses



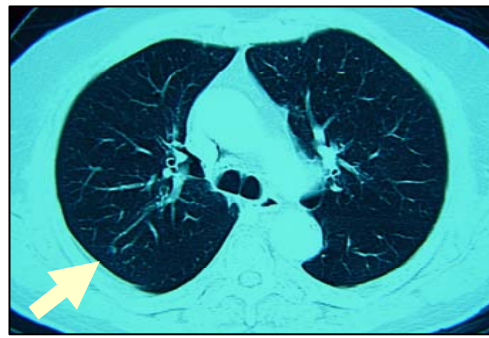
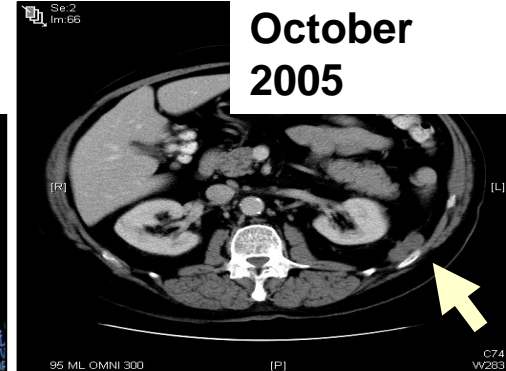
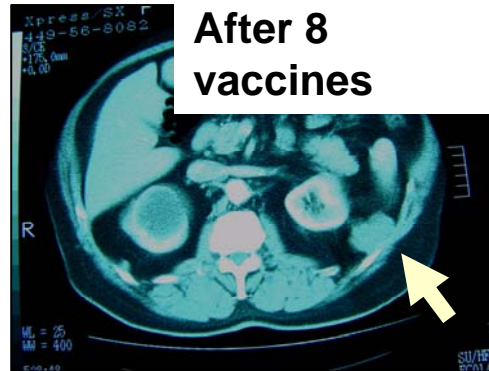
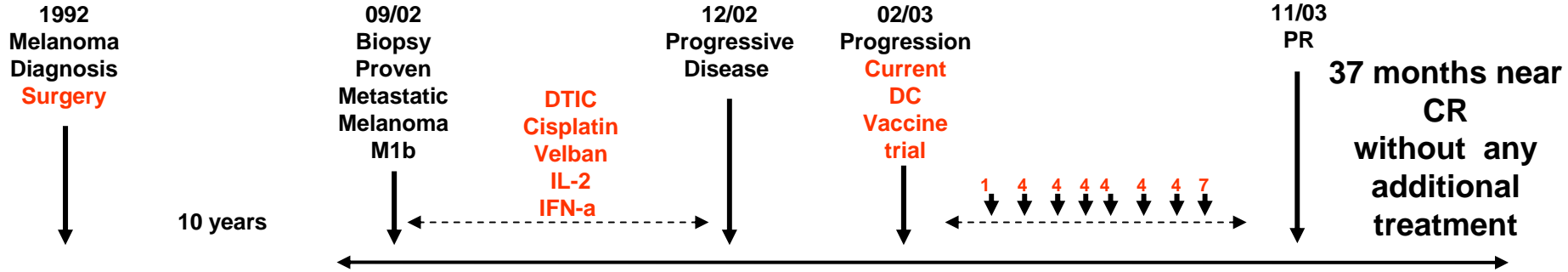
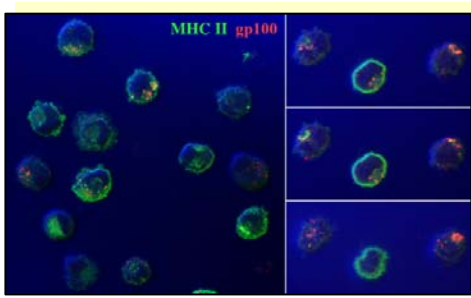
# Patients who mount immunity to several melanoma antigens survive longer

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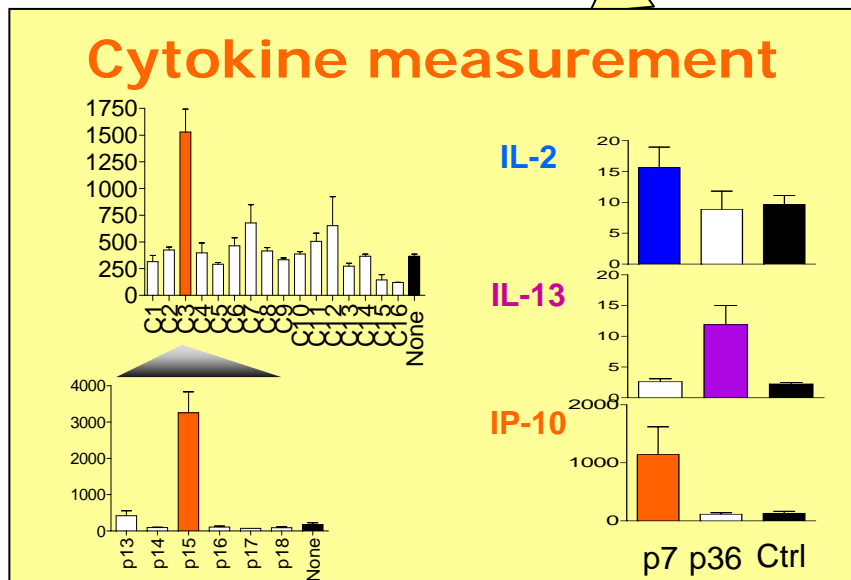
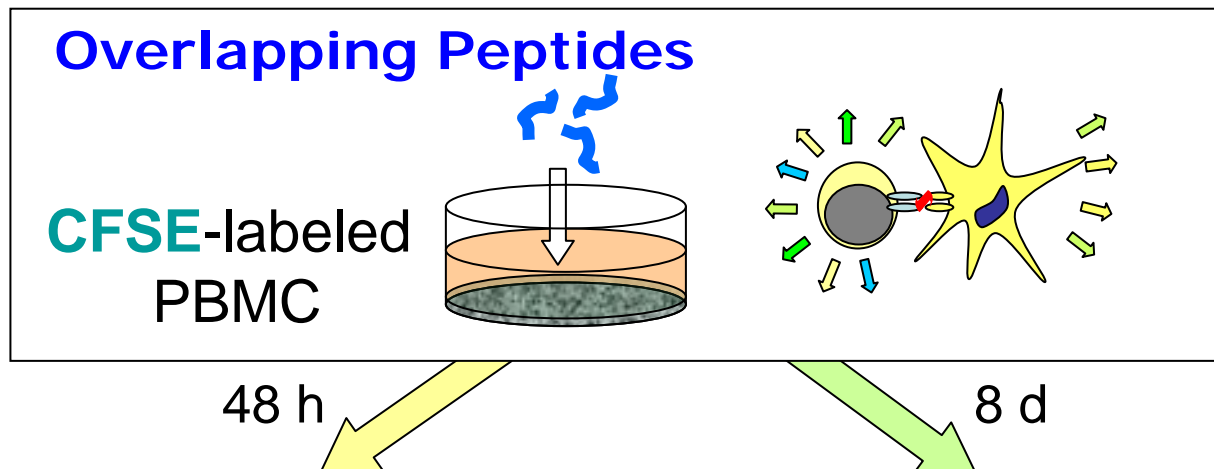
## Overall survival



# DC vaccine loaded with killed allogeneic melanoma cells can induce durable clinical responses

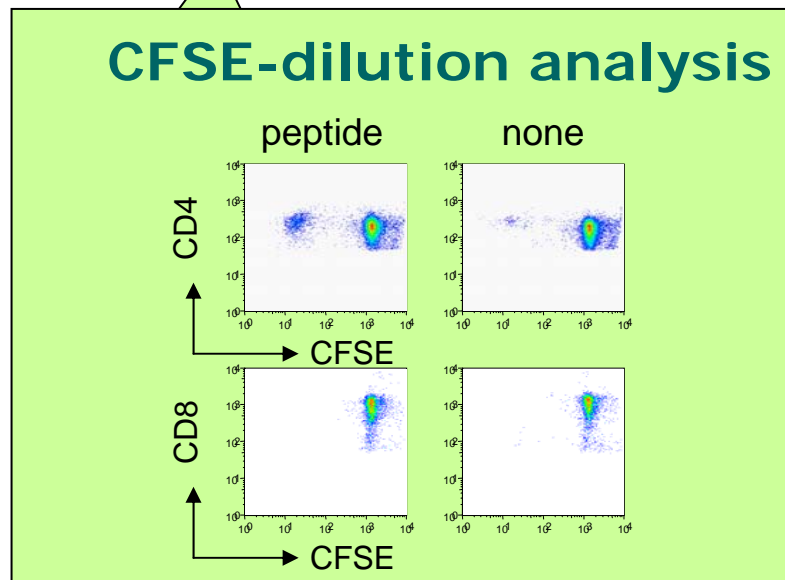


# Detection of Antigen-specific T cell responses with EPIMAX



## Determination

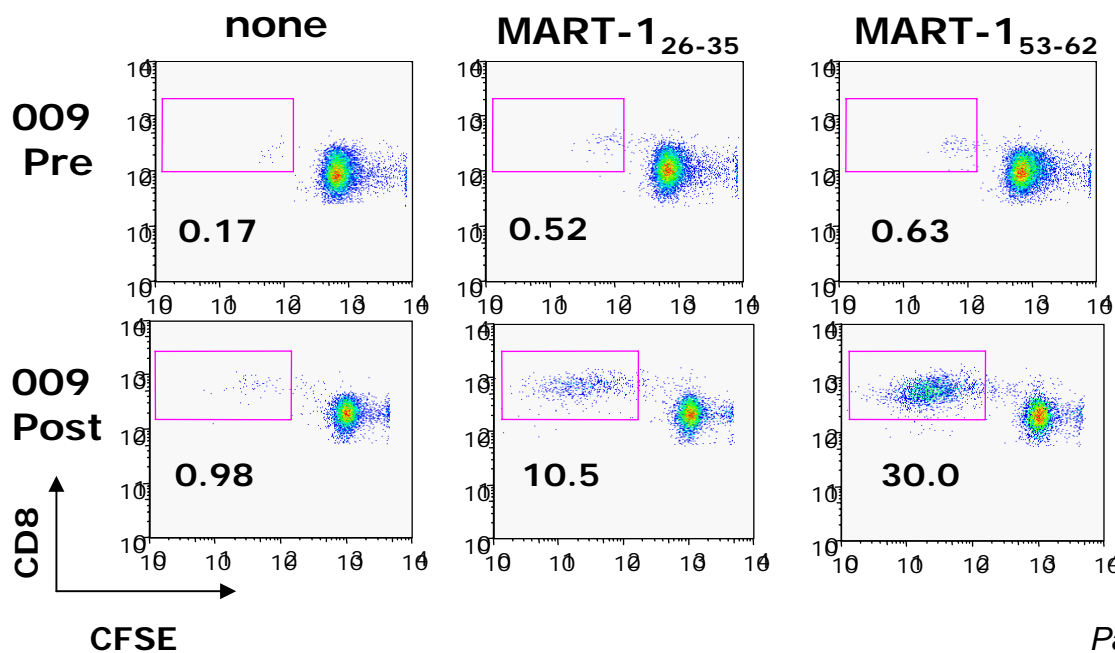
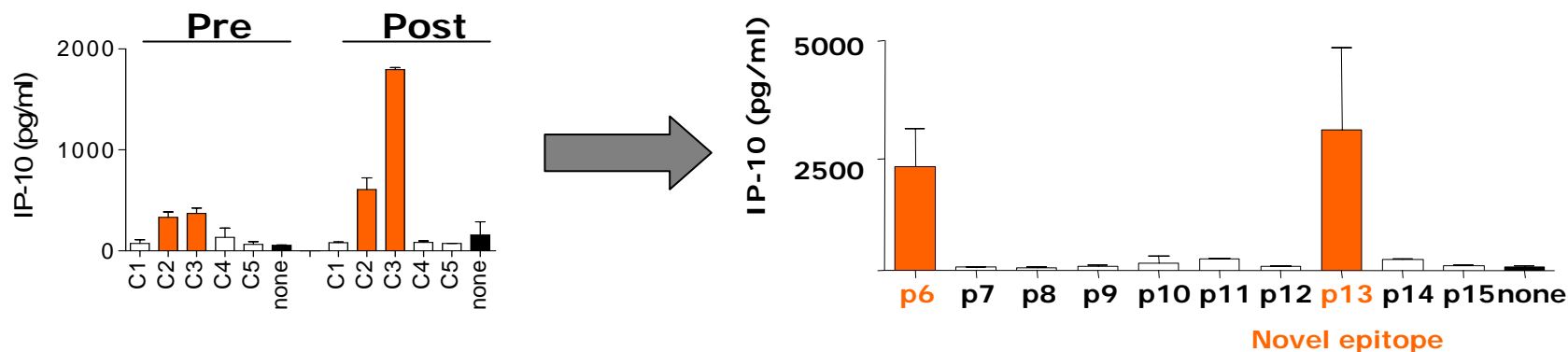
- T cell epitopes
- Type of responses



## Determination

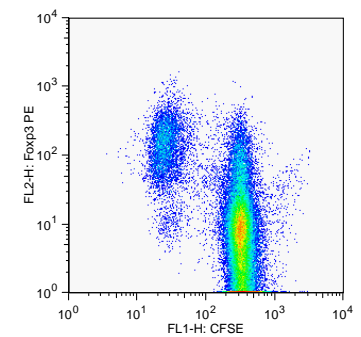
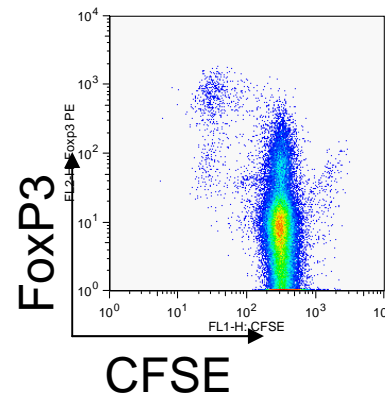
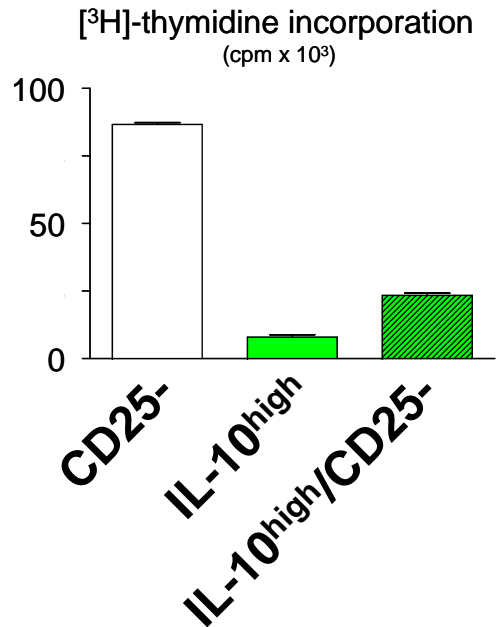
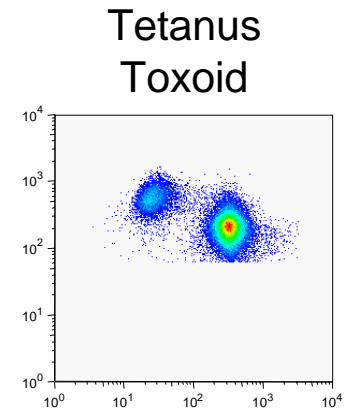
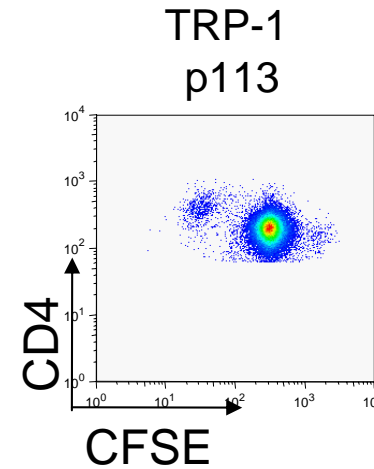
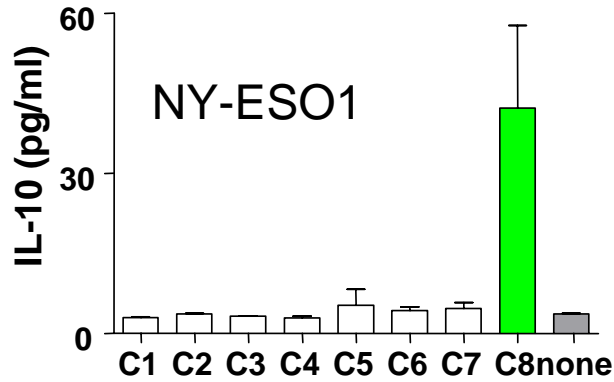
- CD4/CD8

# DC vaccination expands antigen-specific T cells and improves their function



Eight days PBMC + peptide

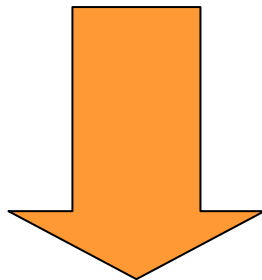
# IL-10-secreting CD4<sup>+</sup> T cells express high levels of FoxP3 and act as suppressor cells



# Conclusions from early clinical trials

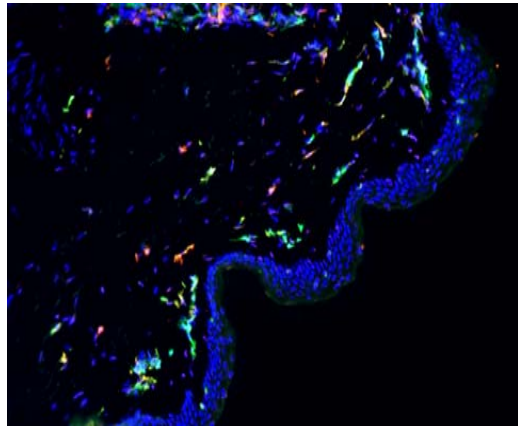
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- **DC vaccines are safe**
- **DC vaccines elicit immune responses**
  - **Low rate of clinical responses**

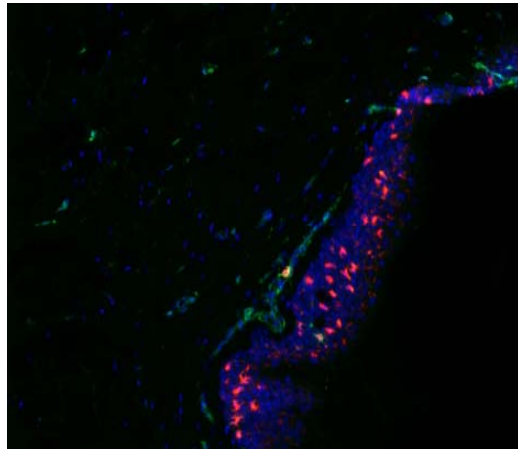
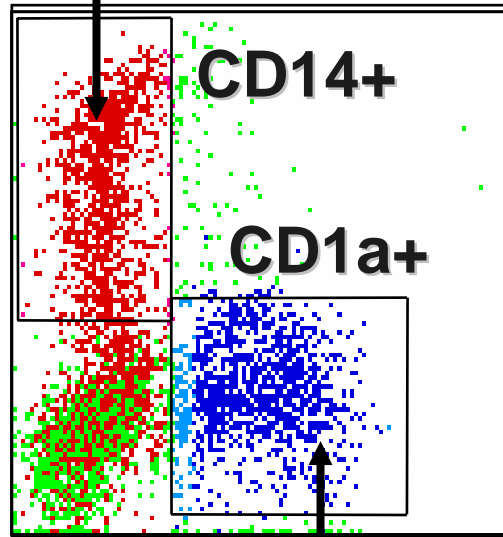


**How to improve the efficacy  
of DC vaccination in cancer?**

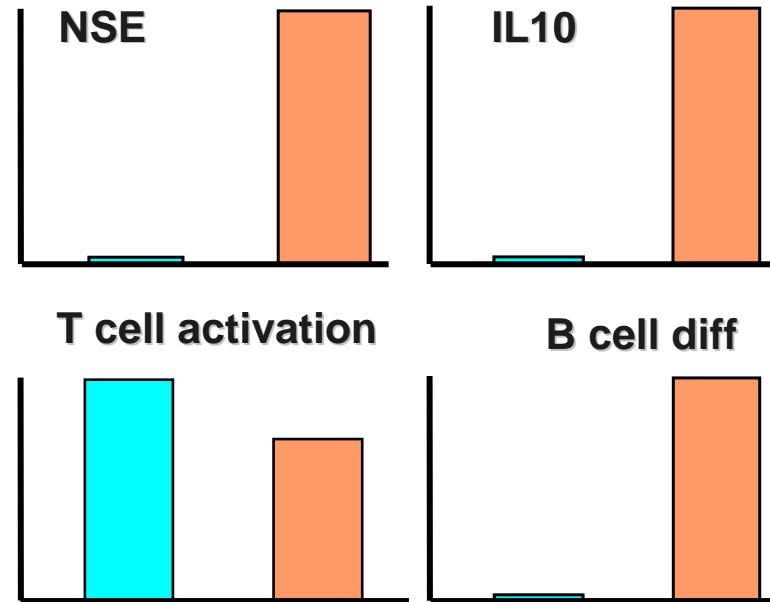
# Human Dendritic Cell Subsets In Vivo and In Vitro



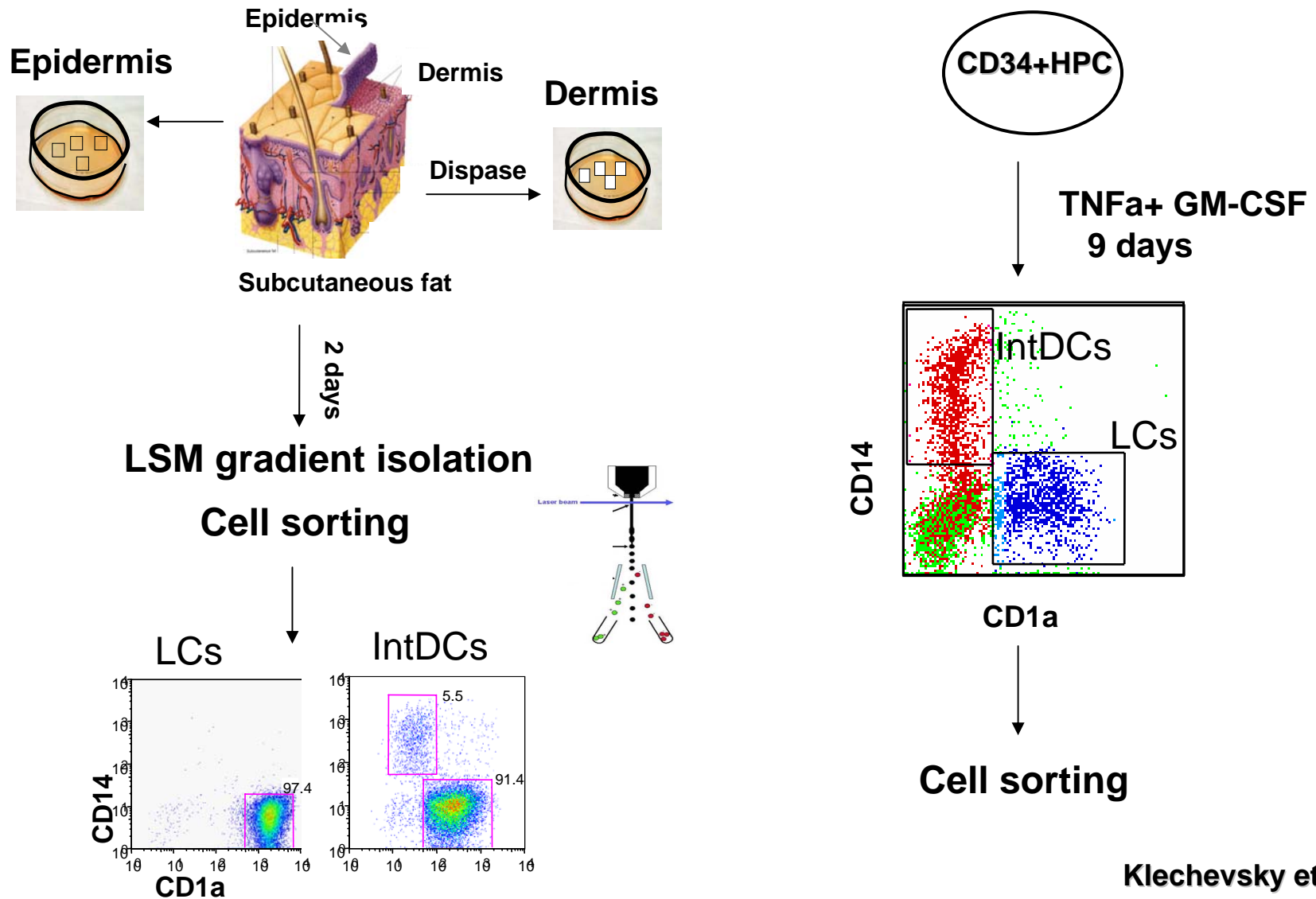
Human Dermal DCs –  
DC-SIGN positive



Human Langerhans Cells  
– Langerin positive

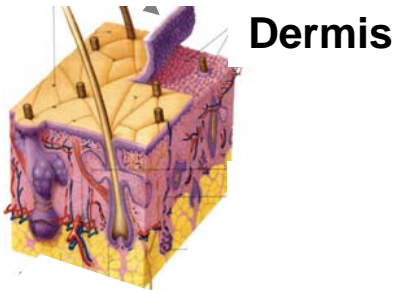


# Human Langerhans Cells and Interstitial-DCs Purified from the Skin or Differentiated from CD34+ HPCs

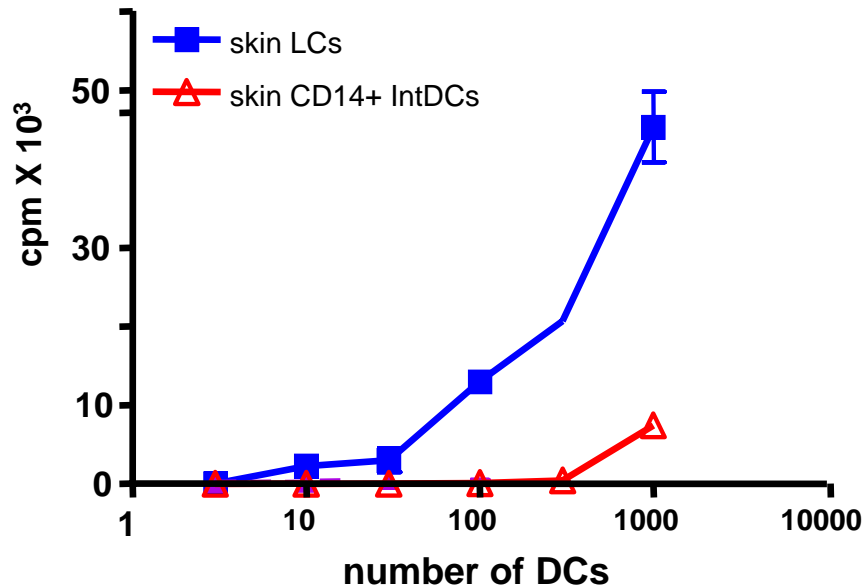


# LCs are More Efficient than CD14+IntDCs at Inducing the Proliferation of Naïve Allogenic CD4+ and CD8+T Cells

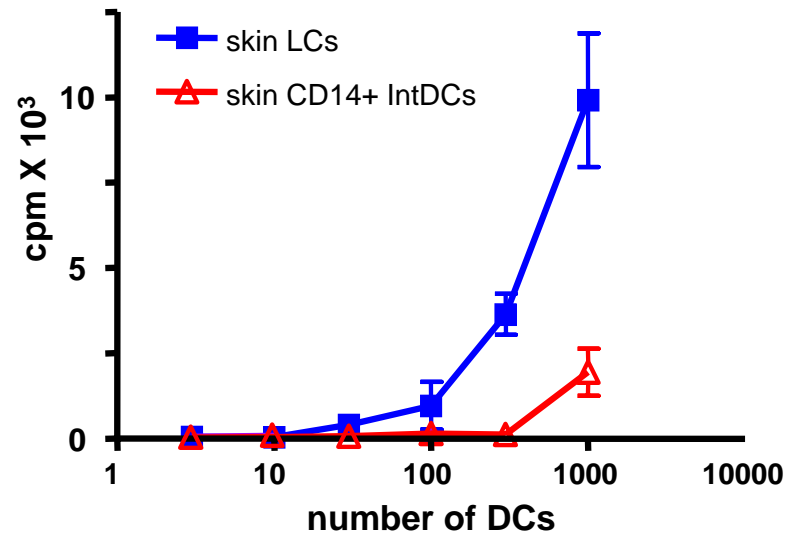
Epidermis



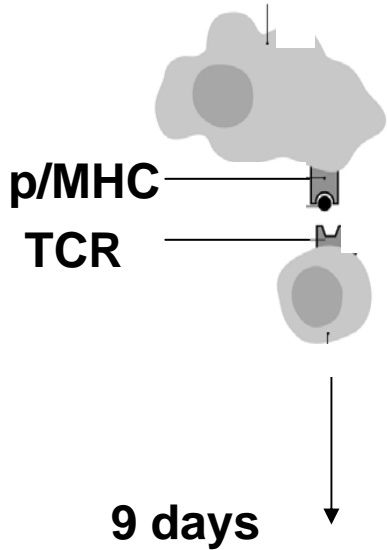
## CD4



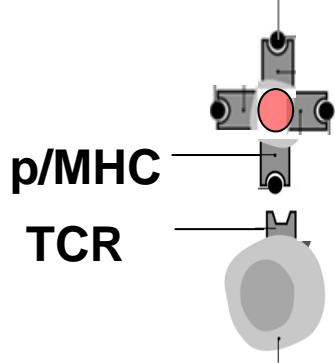
## CD8



# Langerhans Cells are More Efficient than Interstitial-DCs in CD8+T cell priming

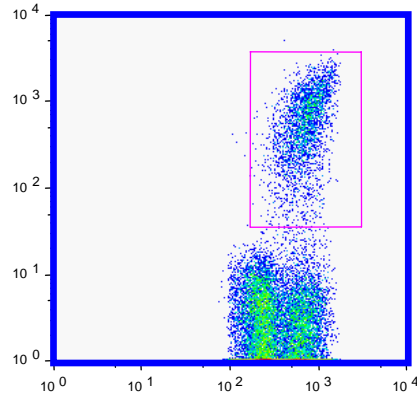


p/MHC Tetramer

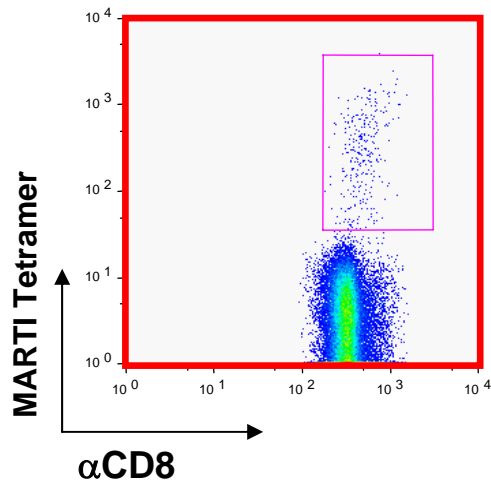


Klechevsky

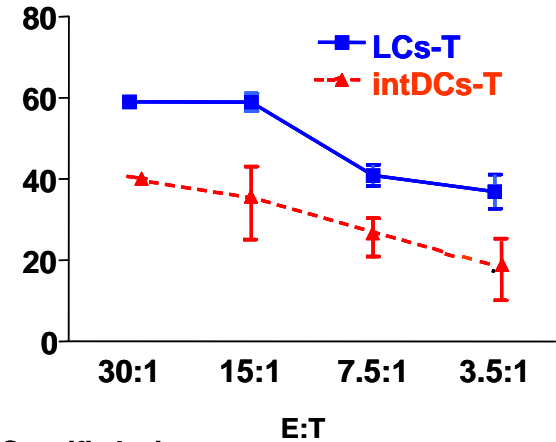
LCs



IntDCs

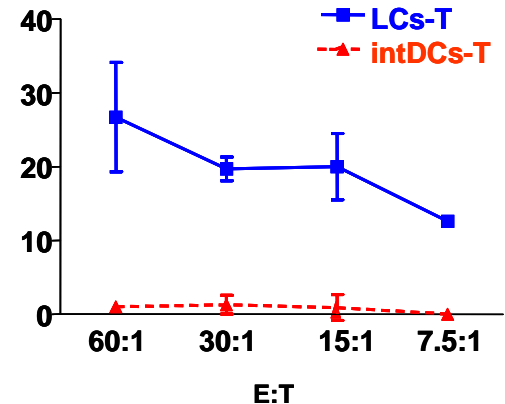


Peptide-pulsed T2 cells

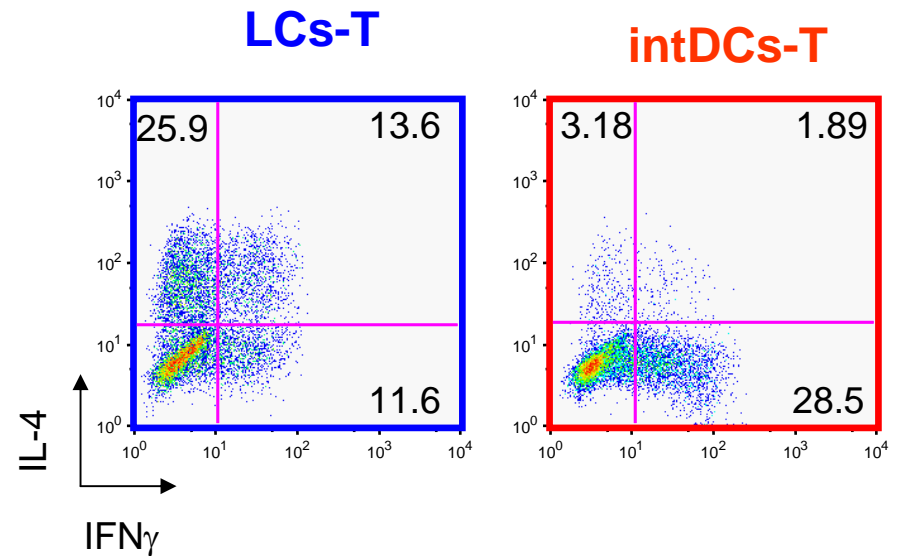
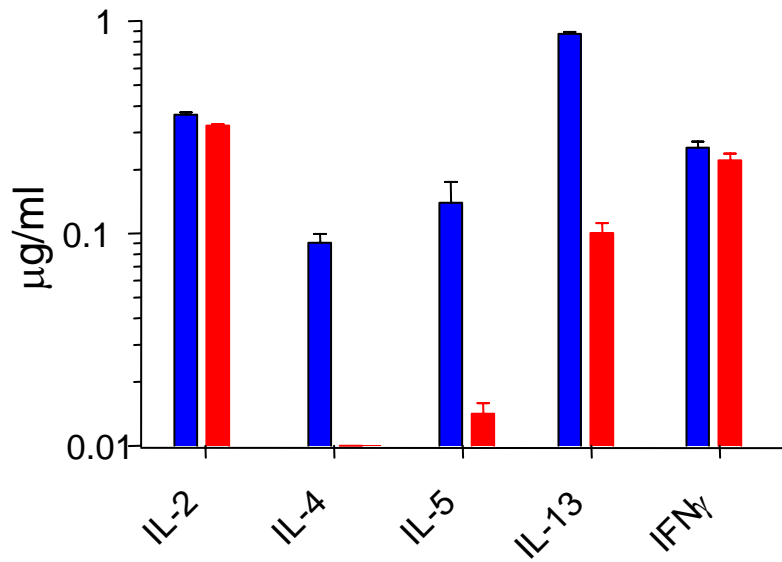
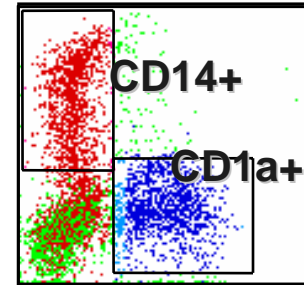
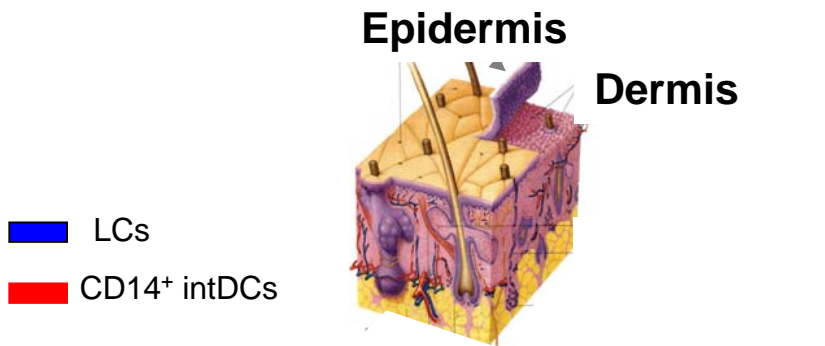


Specific lysis

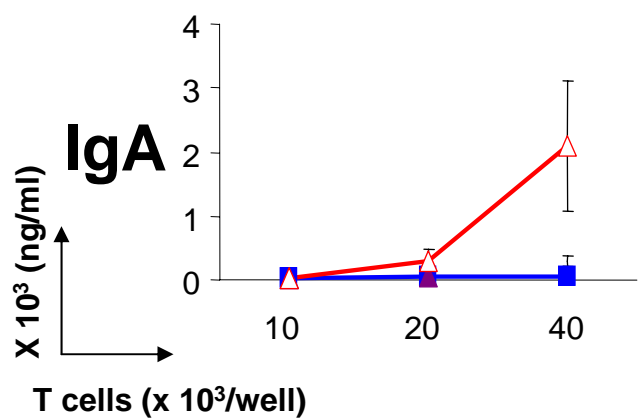
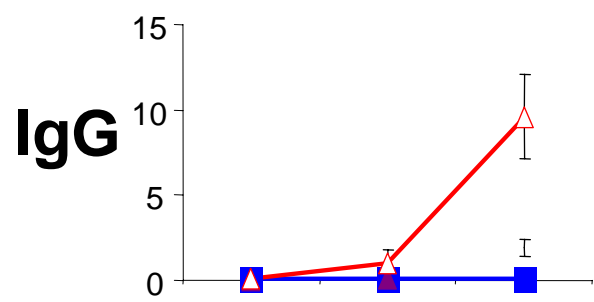
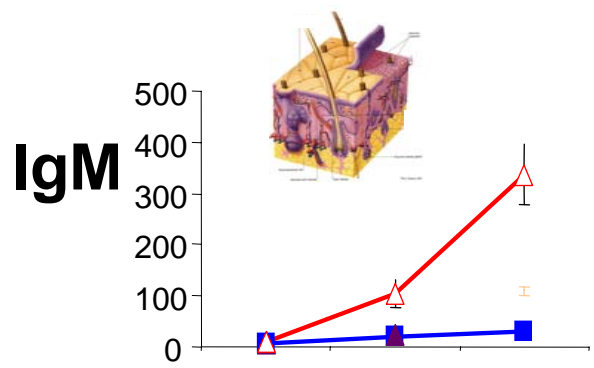
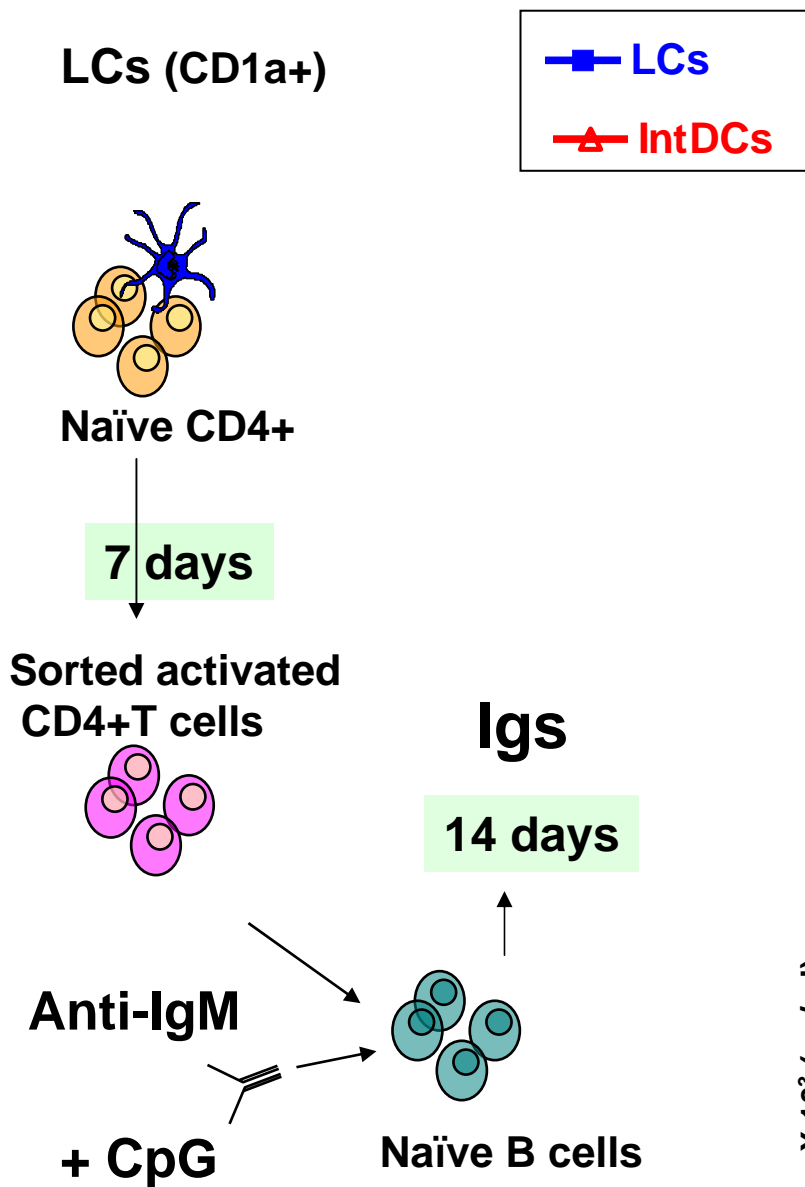
HLA-A\*0201+ melanoma cells



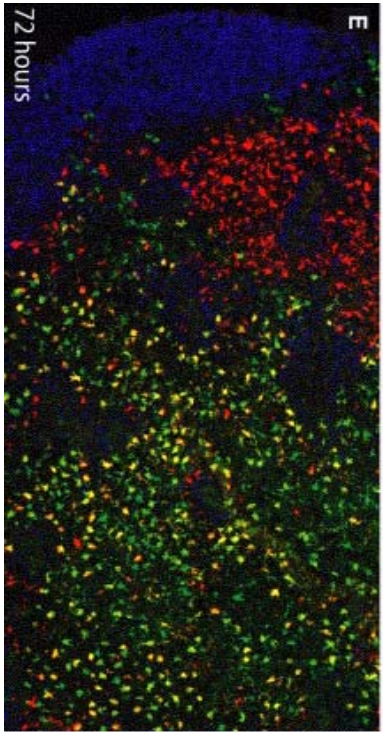
# LCs Efficiently Polarize Naïve CD4+ T Cells toward the Th2 Phenotype



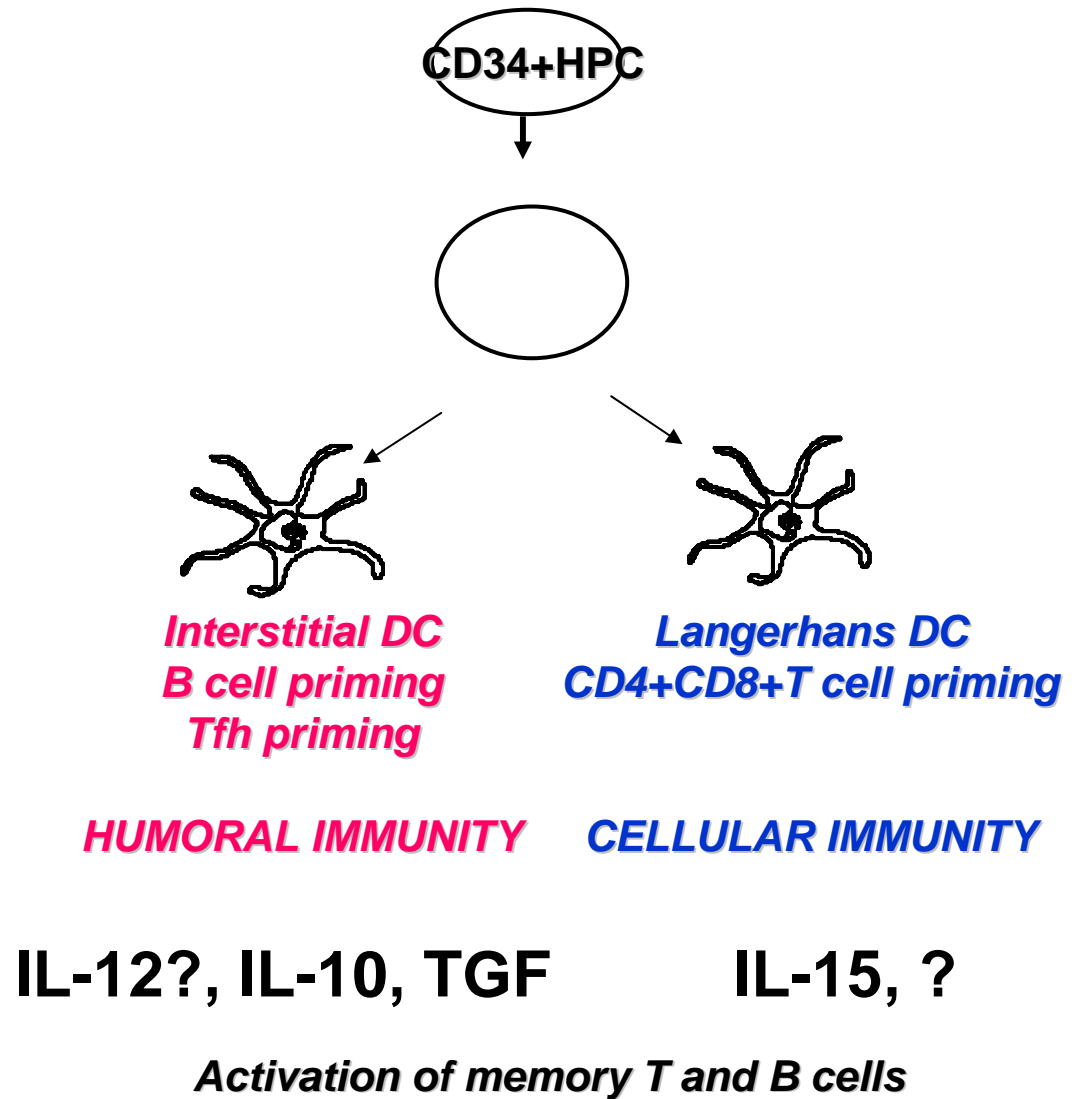
# Interstitial DCs but not Langerhans Cells Prime Follicular Helper CD4+ T cells



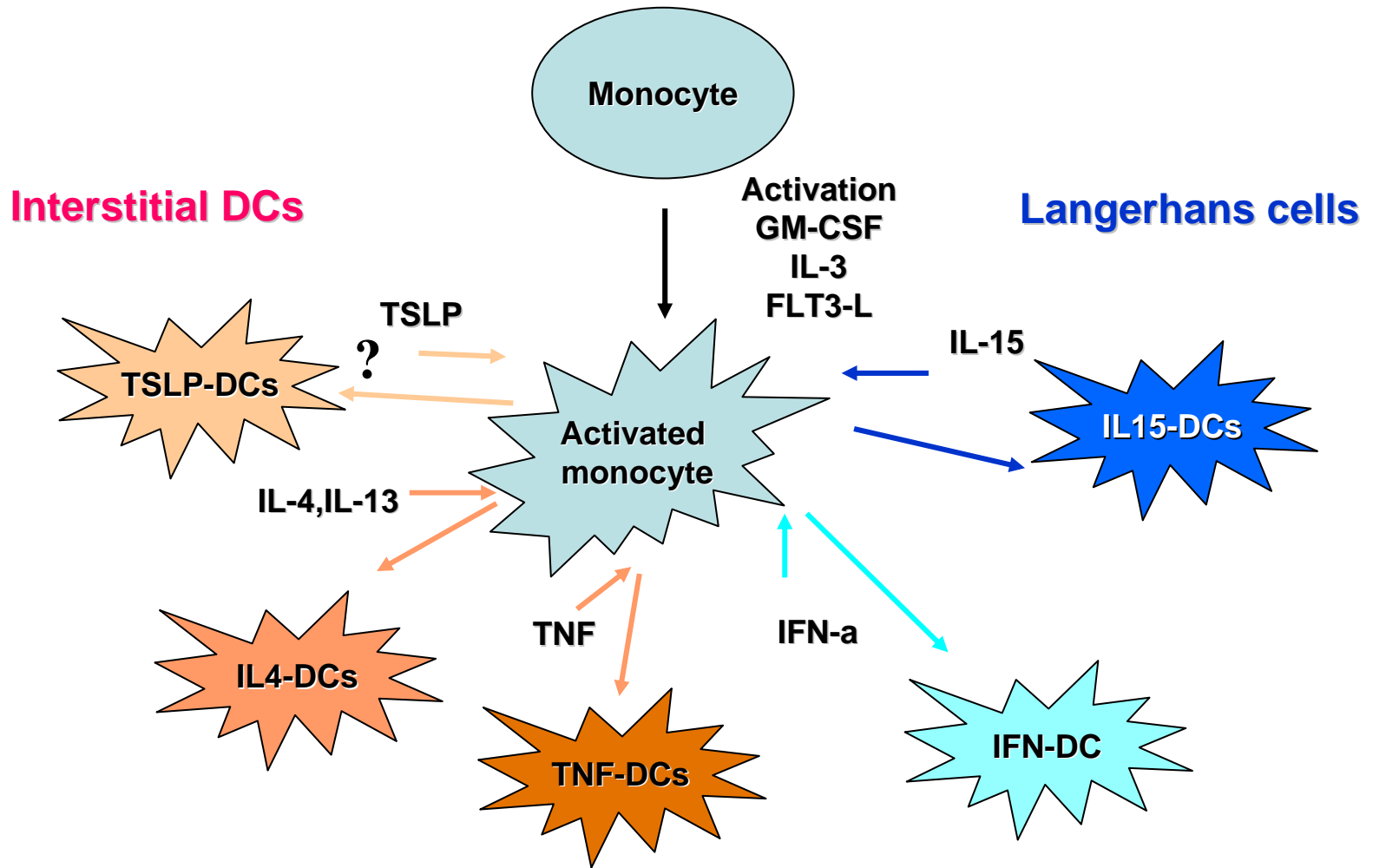
# LCs control cellular immunity while intDCs control humoral immunity



Kissenpfennig et al  
*Immunity* 2005; 22, 643



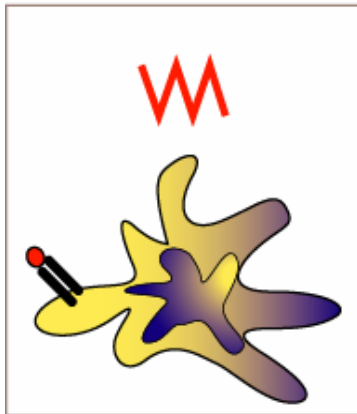
# PLASTICITY OF MONOCYTE-DERIVED DCs



# Vaccine Development Strategy

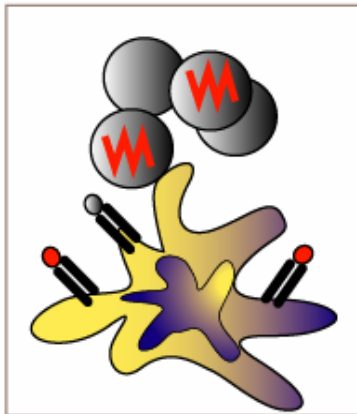
## LOADING DENDRITIC CELLS WITH ANTIGENS

short synthetic peptides



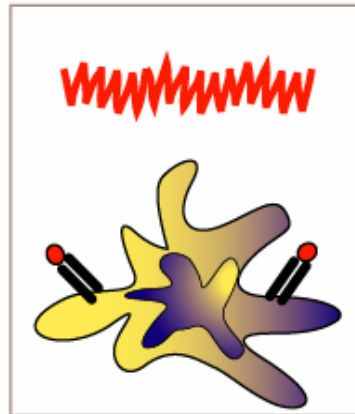
MHC restriction  
no CD4+ T cells

killed tumor cells



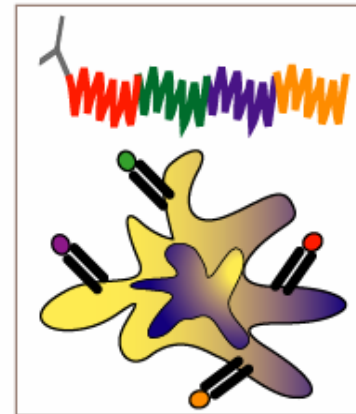
no MHC restriction  
CD8+ and CD4+ T cells  
broad antigen repertoire  
potential Treg expansion

long synthetic peptides



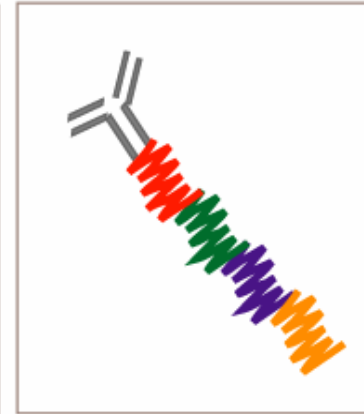
work in progress

ex vivo targeting



antigen delivery  
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in vivo targeting



no need  
for ex vivo DC  
generation

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metastatic disease

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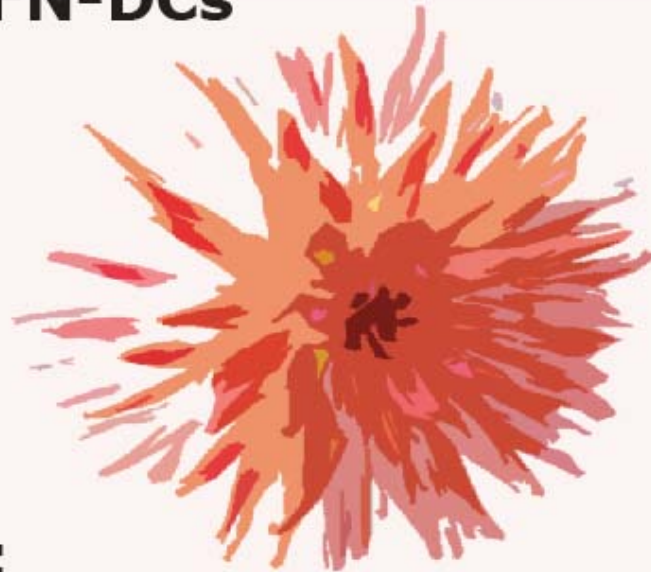
adjuvant

# Dendritic cells And Lipopeptides induced Immunity against Aids

## DALIA trial

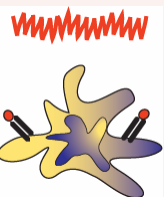
**Antigen Presenting Cells:  
LPS-activated IFN-DCs**

**Therapeutic Immunity  
in chronic HIV  
infection**

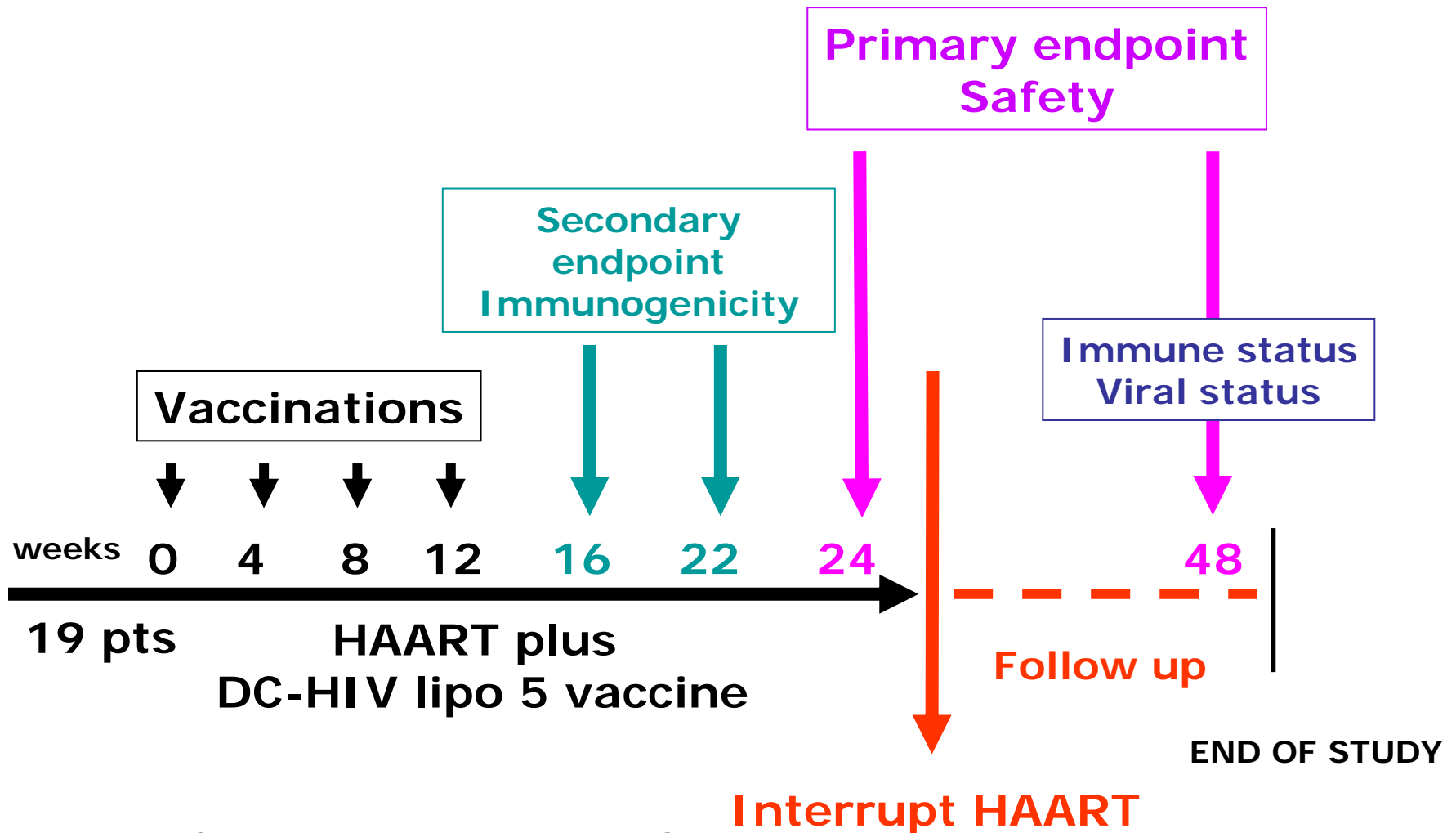


**Antigen:  
HIV Lipopeptides  
conserved regions**

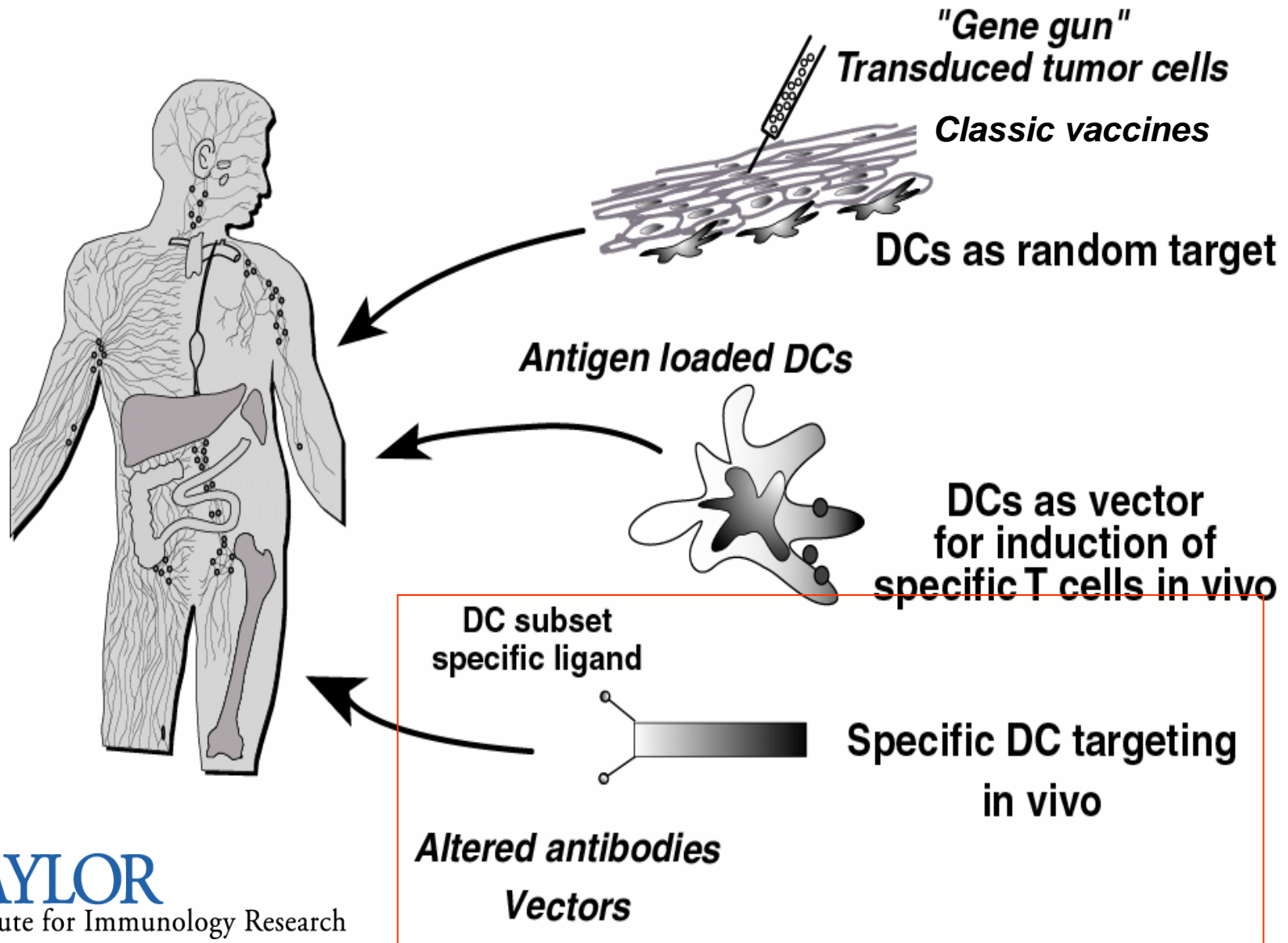
**Resistance to HAART  
withdrawal**



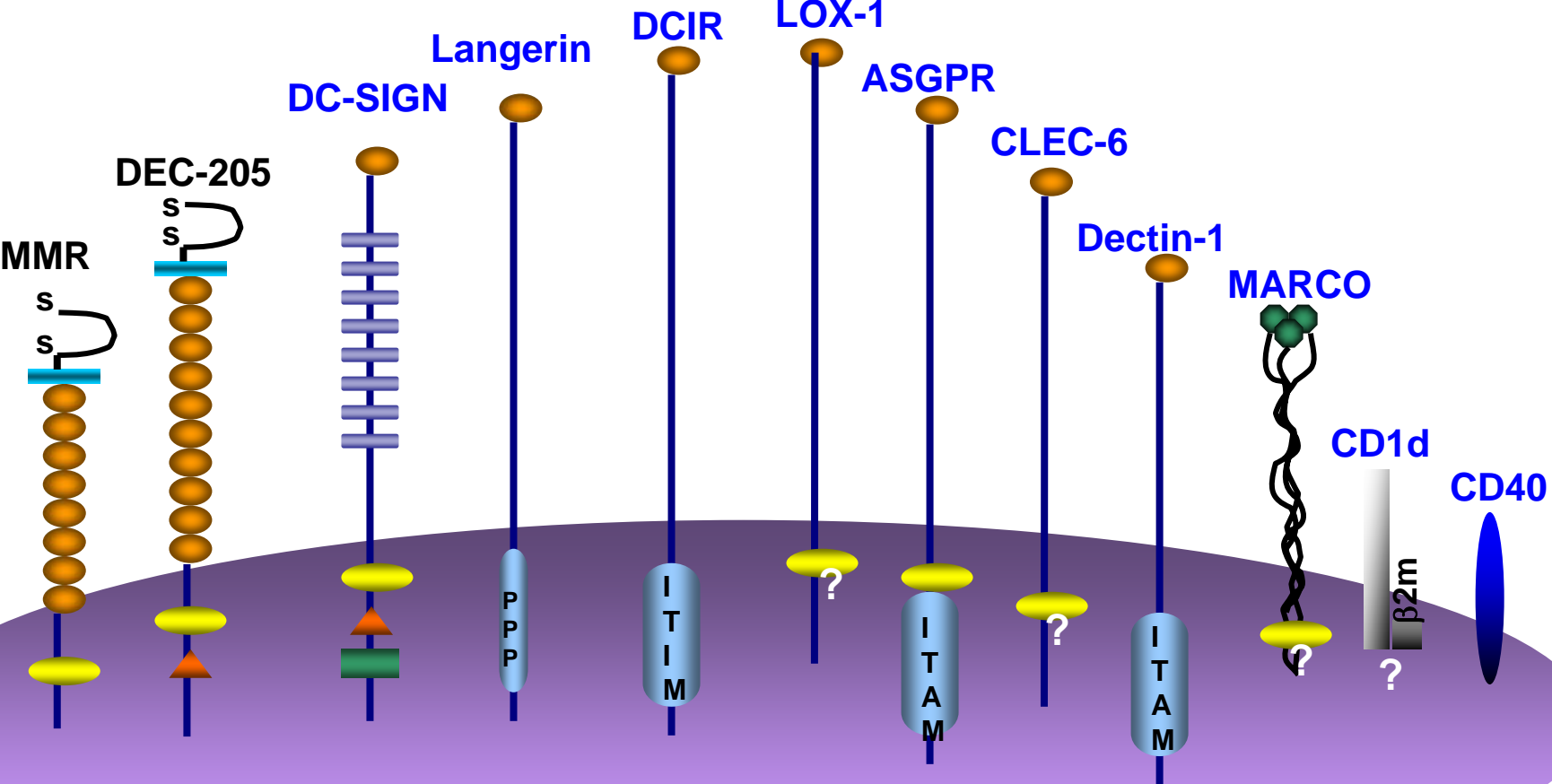
# Assessing the value of a potential HIV vaccine inducing HIV-specific T cells (IND#13748) The DALIA trial



# The central role of dendritic cells in vaccination

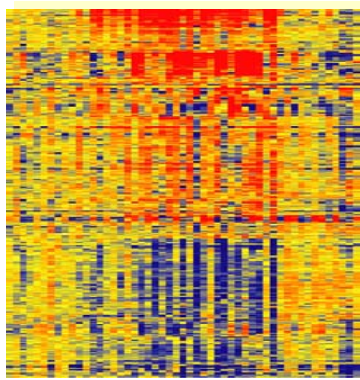


# Candidate Molecules for DC-targeting



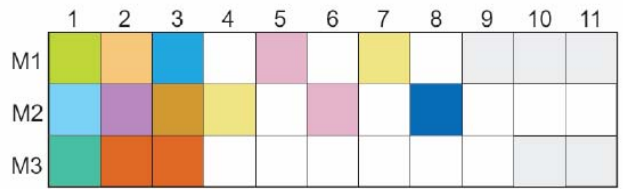
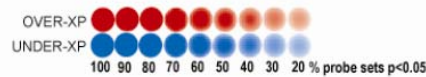
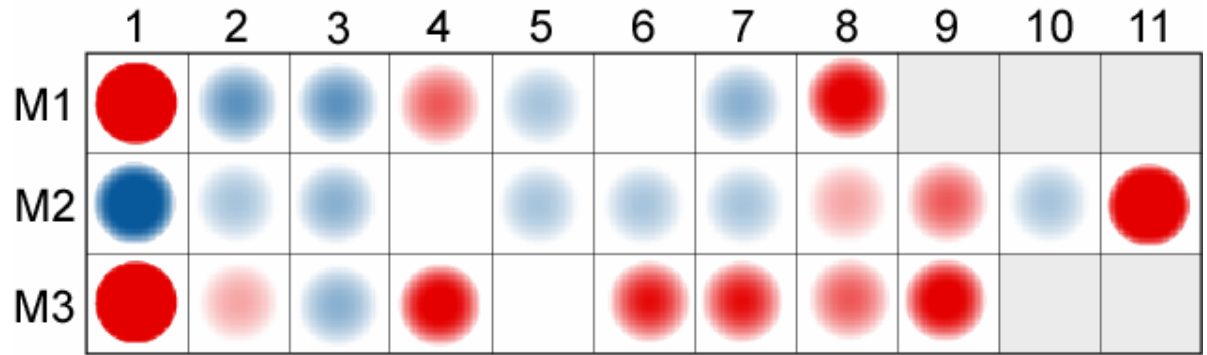
● : CRD or CRD-like domain  
● : Tyrosine-based motif for targeting to coated pits and internalization

▲ : Triad of acidic amino acids  
▬ : Fibronectin type II repeat  
▬ : Di-leucine motif  
▬ : Tandem repeat

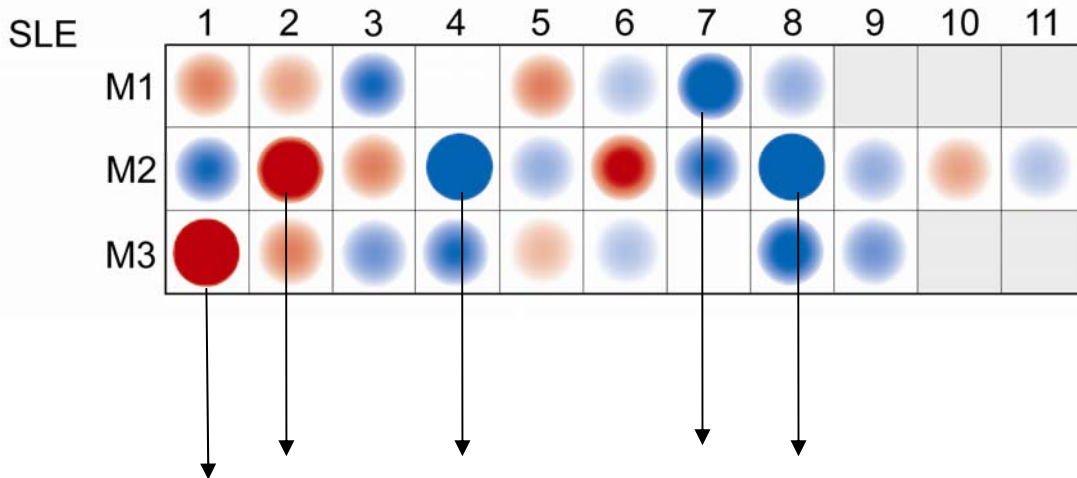


# Blood Gene Expression Profiling

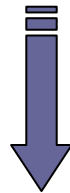
## From Microarrays to Fingerprints



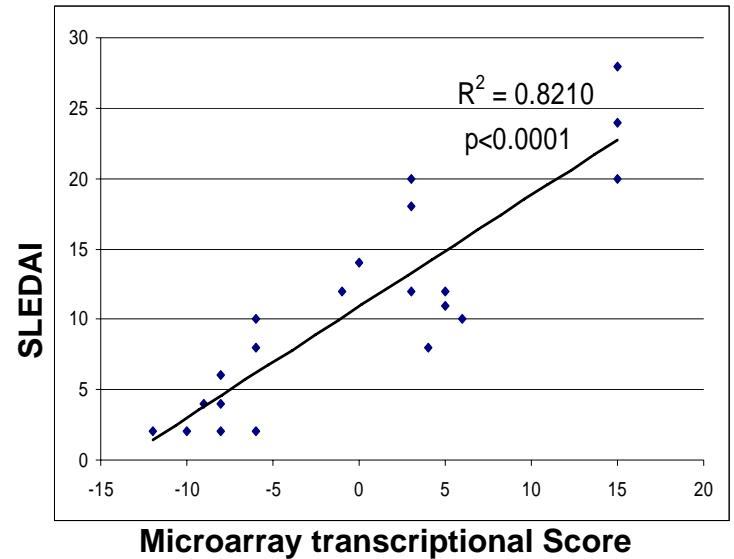
# Genetic Score to Assess Disease Severity



Correlate with SLE Disease Activity Index



Compute multivariate scores based on module-level Leukocyte transcriptional data

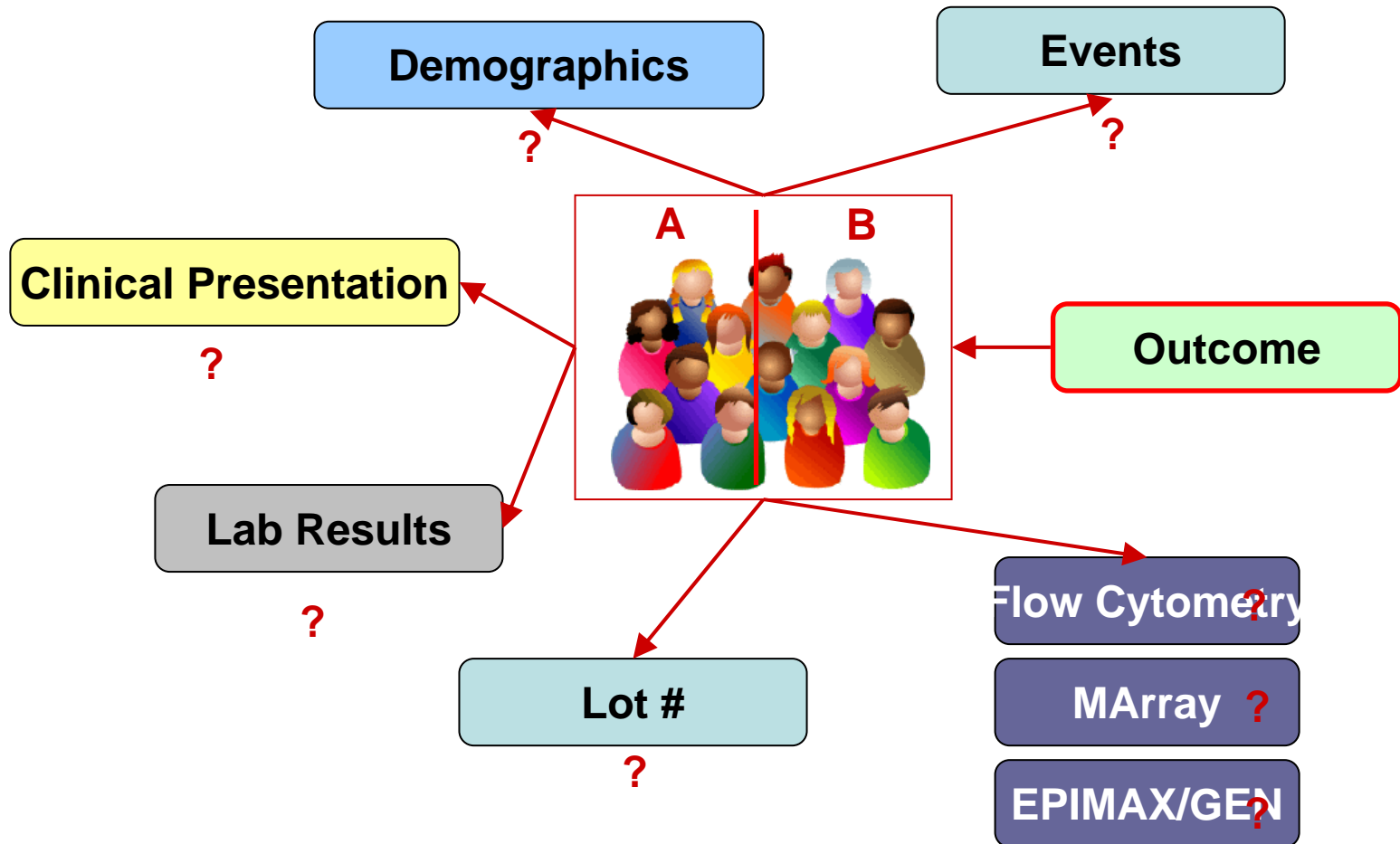


M3.1 IFN  
M2.2 Neutrophil

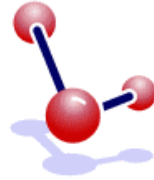
M2.4 Ribosomal  
M2.7 Lymphopenia

M1.7 Ribosomal

# REACHING ECSTASY: WHAT DISTINGUISHES CLINICAL RESPONDERS FROM NON-RESPONDERS?



## **ACKNOWLEDGEMENTS**



### **Bioinformatics**

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**Jason Skinner**

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**Katherine Madson**  
**Rolando Cimaz**  
**CARRA**  
**Octavio Ramilo**  
**Michelle Gill**  
**Pierre Quartier**

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**Minning Wu**  
**Vicky Cantrell**  
**Gabriela Garcia-Reyes**  
**Patrick Blanco**  
**Raj Raganathan**  
**Rimpei Morita**  
**Eynav Klechevsky**  
**Nathalie Schmitt**  
**Dapeng Li**  
**Anne Laure Flamar**

**VIRGINIA PASCUAL**  
**HIDEKI UENO**  
**DAMIEN CHAUSSABEL**  
**KAROLINA PALUCKA**  
**GERARD ZURAWSKI**  
**SANDRA ZURAWSKI**  
**JOHN CONNOLLY**  
**SANGKON OH**