NIAID: CCHI,HIPC;CHAVI
NCI
NIAMS
DANA

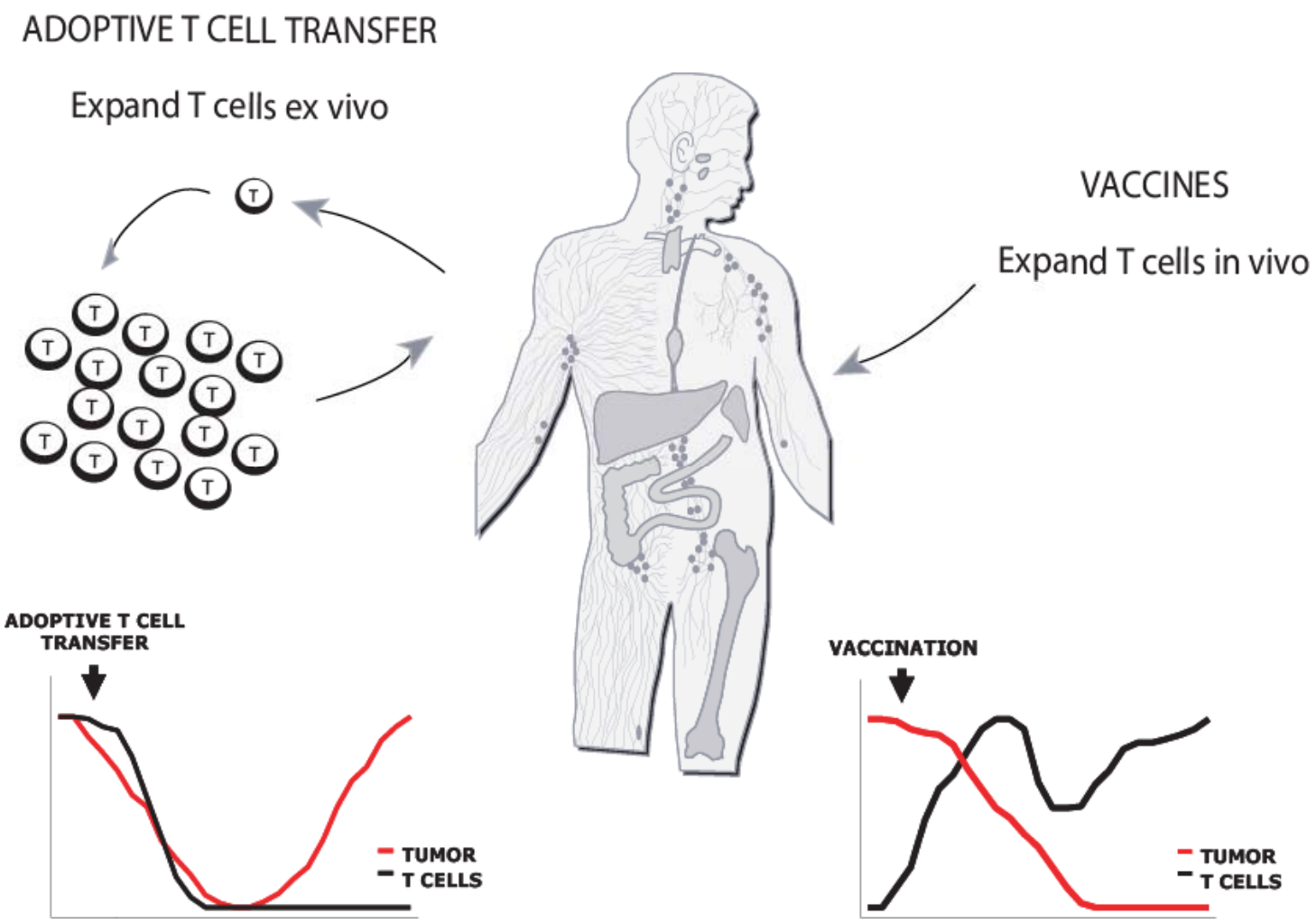
Will Dendritic Cells Help Us Address the Challenge of Cancer Vaccines?

Jacques Banchereau; Damien Chaussabel; Helene Dutartre; Joe Fay; Patrick Lecine; Yves Levy; Sangkon Oh; Karolina Palucka; Virginia Pascual; Louis Sloan; Hideki Ueno; Gerard Zurawski

BAYLOR INSTITUTE FOR IMMUNOLOGY RESEARCH
(Est.1996)

INSERM RESEARCH LABORATORY - U 899
CENTER FOR HUMAN VACCINES
CENTER FOR PERSONALIZED MEDICINE
Mount Sinai School of Medicine, New York: Dept of Cell and Gene Therapy; Dept of Medicine; Immunology Institute

How to exploit the immune system for cancer therapy



After many disappointments…..

CancerVax Canvaxin, CellGenesys GVAX, Corixa Melacine

Cancer vaccines are on the move

• Provenge: FDA approval for metastatic prostate cancer
Improved overall survival in phase III
(4.1 months), Dendreon (PBMCs plus GM-CSF-Antigen)

• BiovaxID in follicular lymphoma:
Improved median time to relapse in phase III
(13.6 months), Kwok et al

• Peptide plus Montanide and IL-2 in melanoma:
Improved progression free-survival in phase III
(2.9 months), Hwu et al

Next Generation of Therapeutic (Cancer) Vaccines:

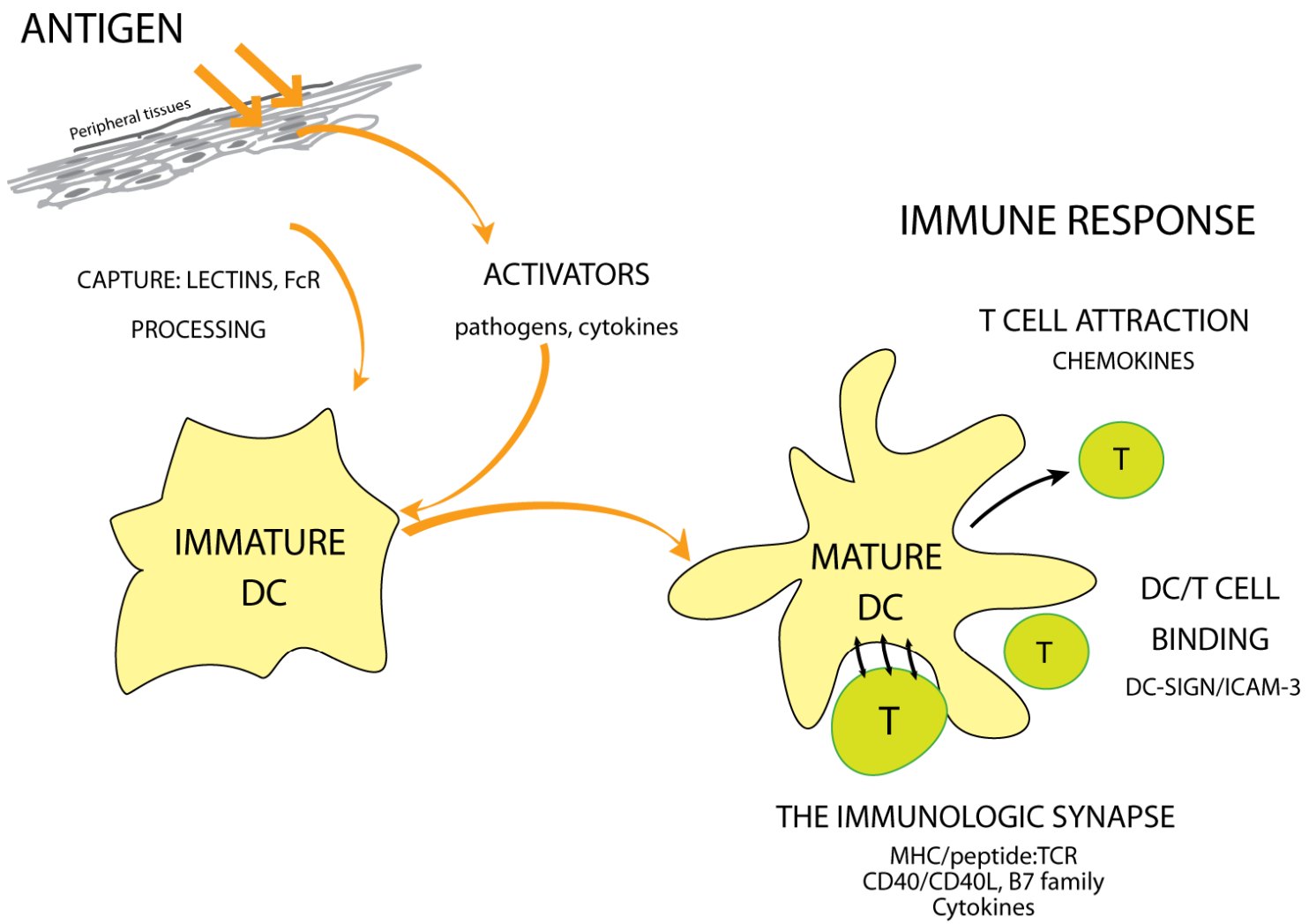
Designing Vaccines Based On Immunology

Immunology has the potential to
identify vaccines, i.e.,
antigen-specific, durable, non-noxious
preventions and therapies
for infections, cancer, allergy,
autoimmunity, transplantation

Quoted from Ralph Steinman

REPROGRAMMING THE IMMUNE SYSTEM

Dendritic Cells are central to vaccination

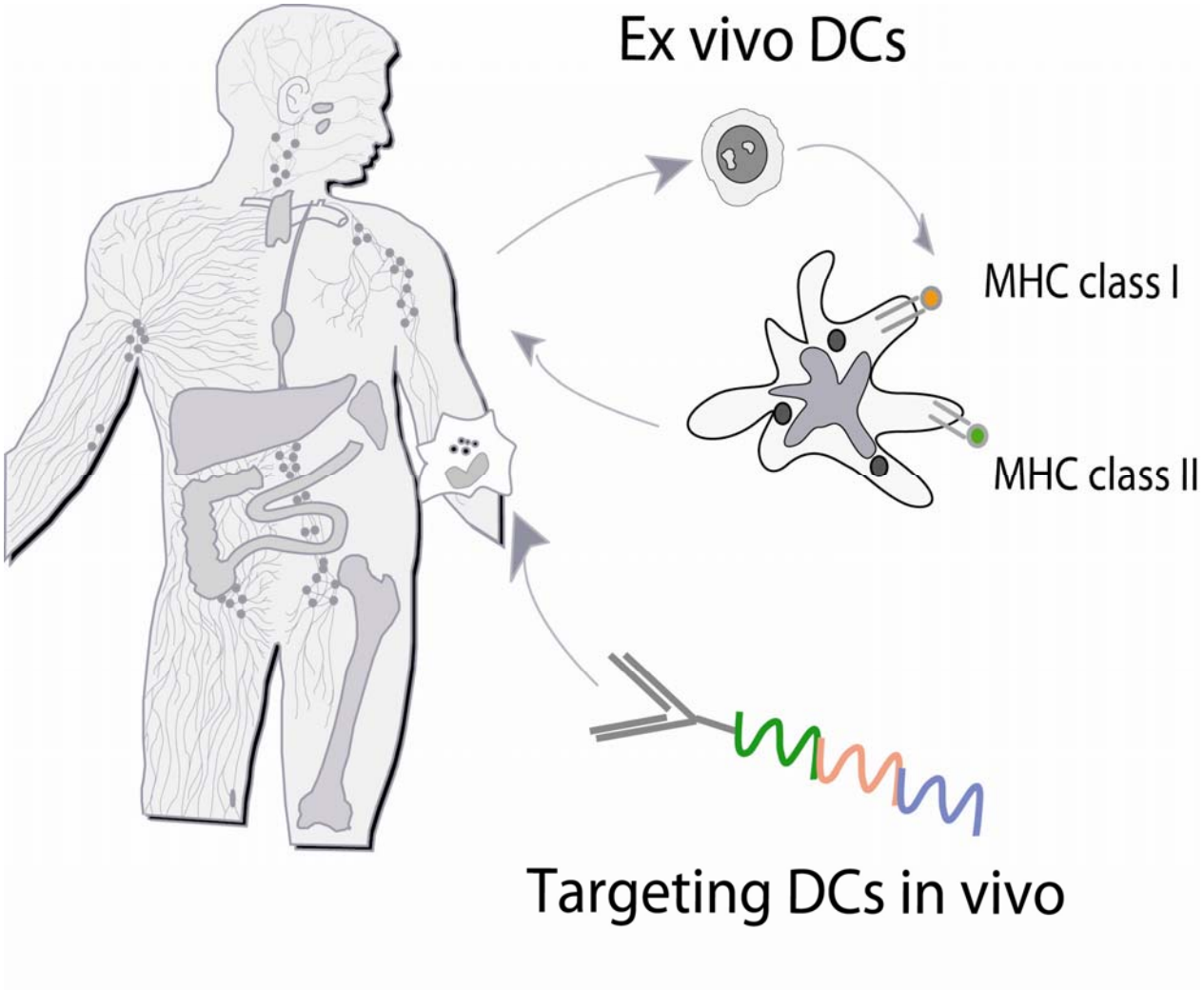


Desired features of DC vaccines

- Induce high avidity CTLs
- Induce long term memory $CD4^+/CD8^+$T cells
- Do not induce regulatory T cells
- Induce CD4+ T cells that help CD8+ T cells

Palucka, Banchereau et al Nat Rev Immunol 2005, Immunol Rev 2007, 2010

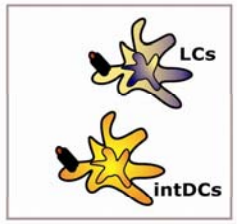
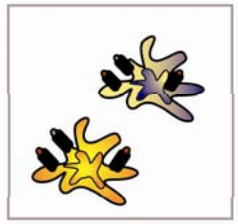
Our two paths to therapeutic DC-based HIV and cancer vaccine



First generation DC vaccines

Antigen: Short 9-10aa peptides KLH | Killed allogeneic tumor cells

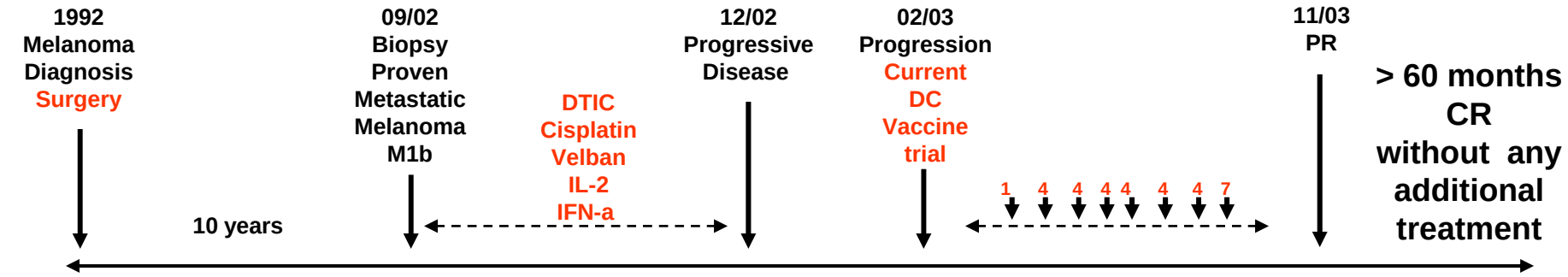
DC vaccine:

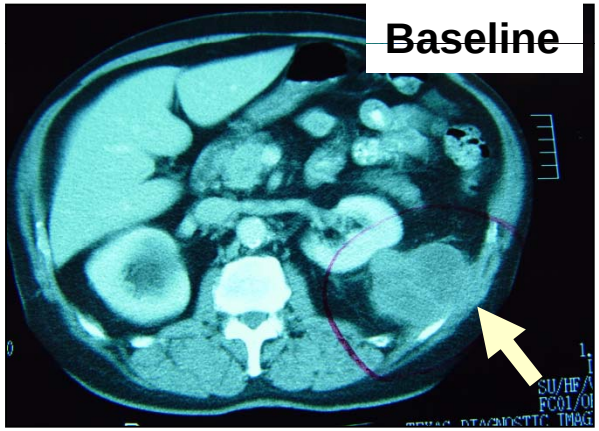
CD34-DCs	activated CD34-DCs	GM/TNF MoDCs	activated GM/IL4 MoDCs	GM/IFNa MoDCs
				

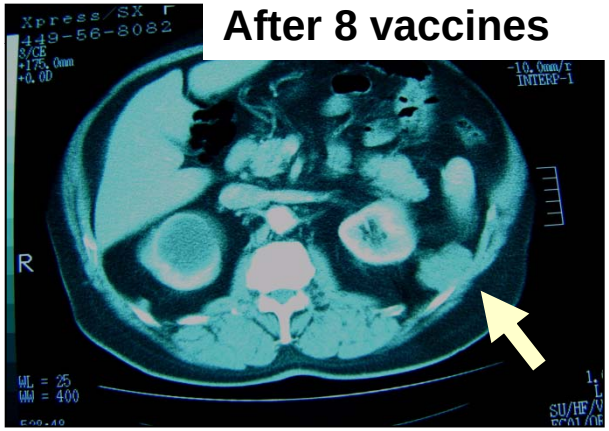
Conclusions:

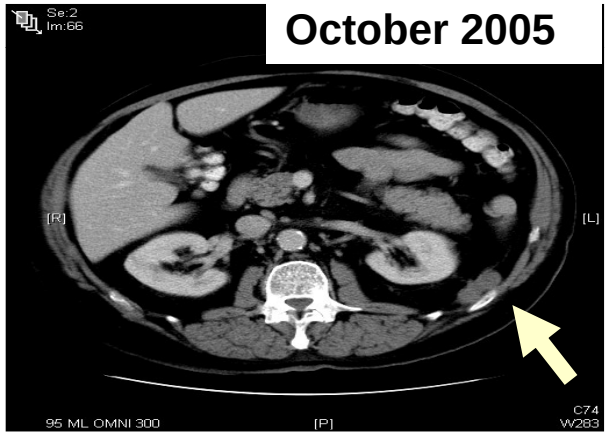
- Immunogenicity
  Clinical responses
- The quality of activation signal
- Immunogenicity
  Clinical responses
- Improved DCs
  Closed system
  Frozen vaccine

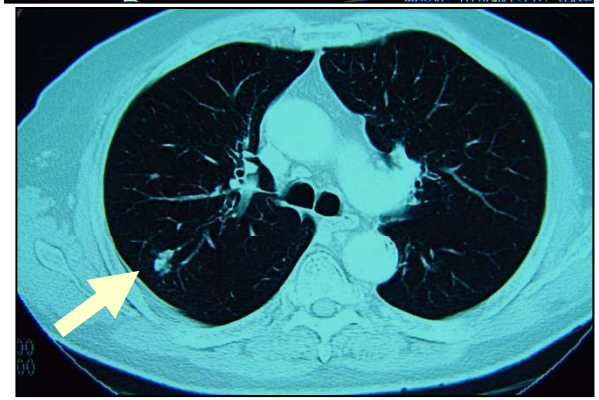
DC vaccine loaded with killed allogeneic melanoma cells can induce durable clinical responses (2+1/20 patients)

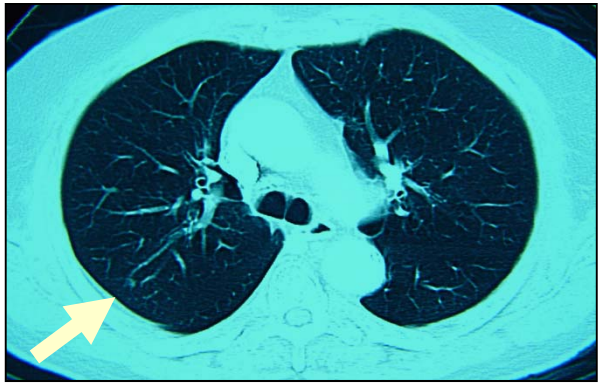


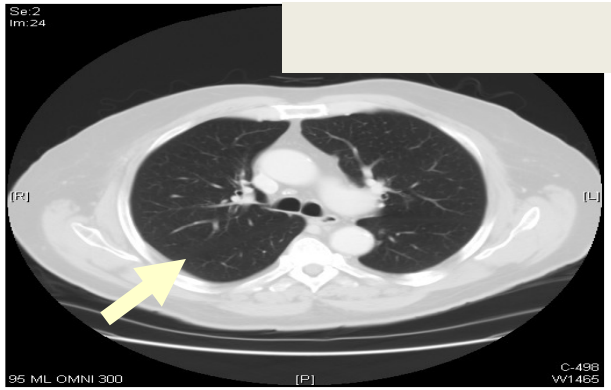








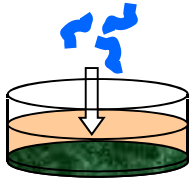




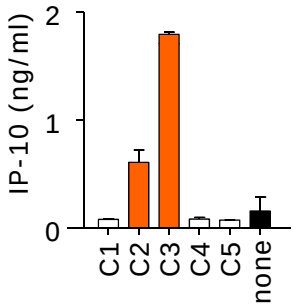
Palucka et al. J Immunotherapy 2006

EPIMAX: Comprehensive high throughput assessment of antigen-specific T cell repertoire

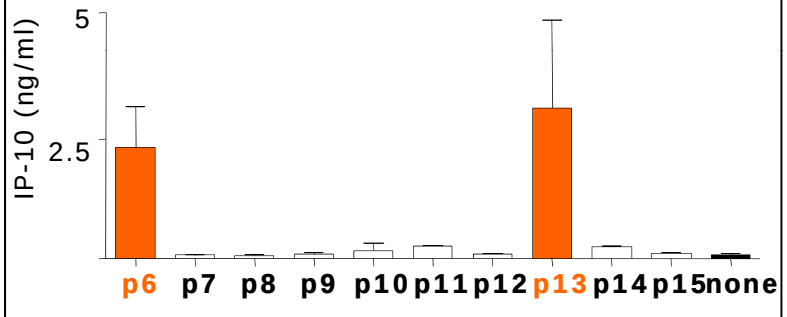
PBMCs + Peptides



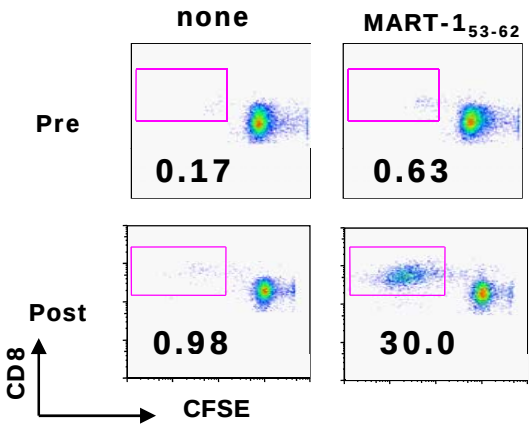
Cluster analysis 48hrs cytokines



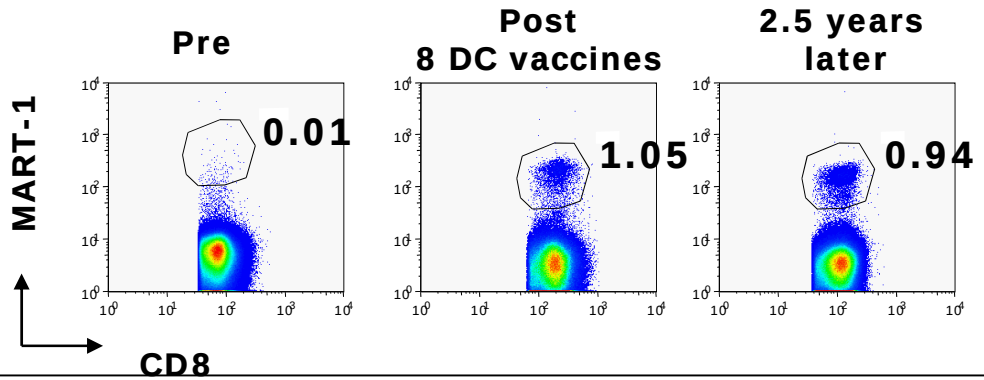
Peptide analysis 48hrs cytokines



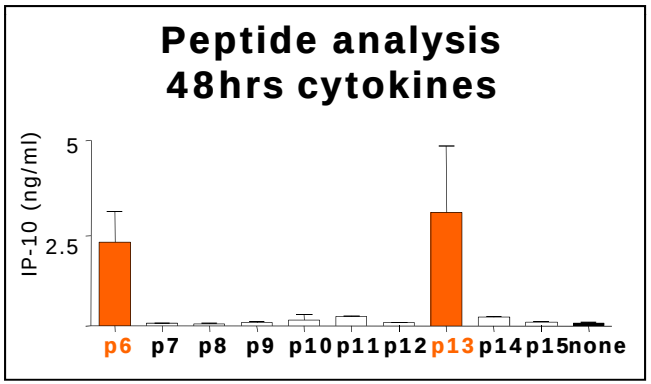
7d Proliferation

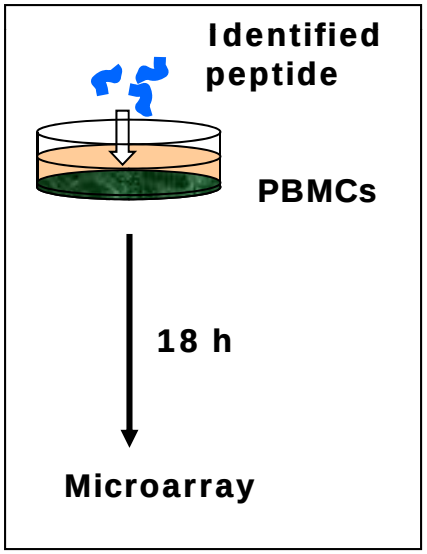


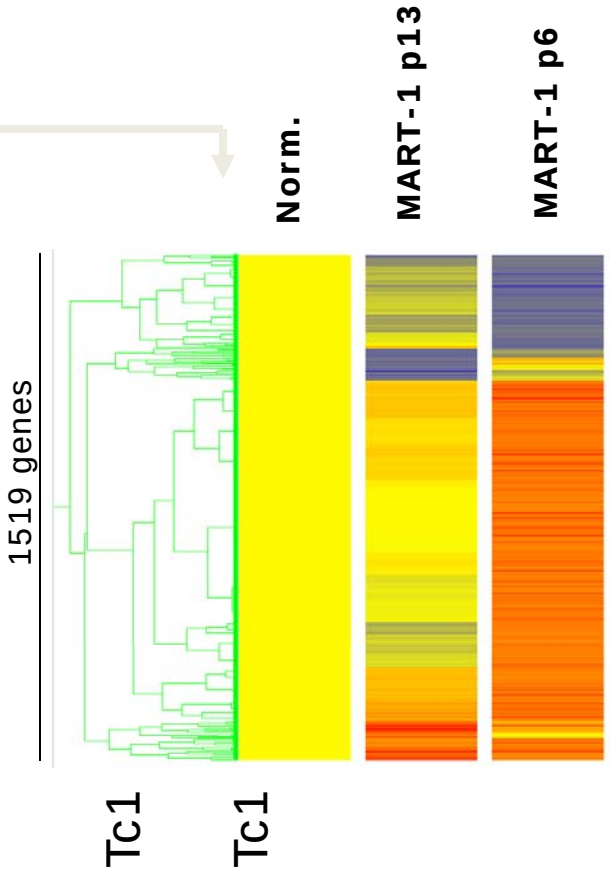
Tetramer



Distinct MART-1 CD8+ T cell epitopes elicit distinct transcriptional responses (and Immune Responses?)







Ueno & Chaussabel

DC vaccines can expand high avidity polyfunctional MART-1 melanoma-antigen specific CD8+ T cells

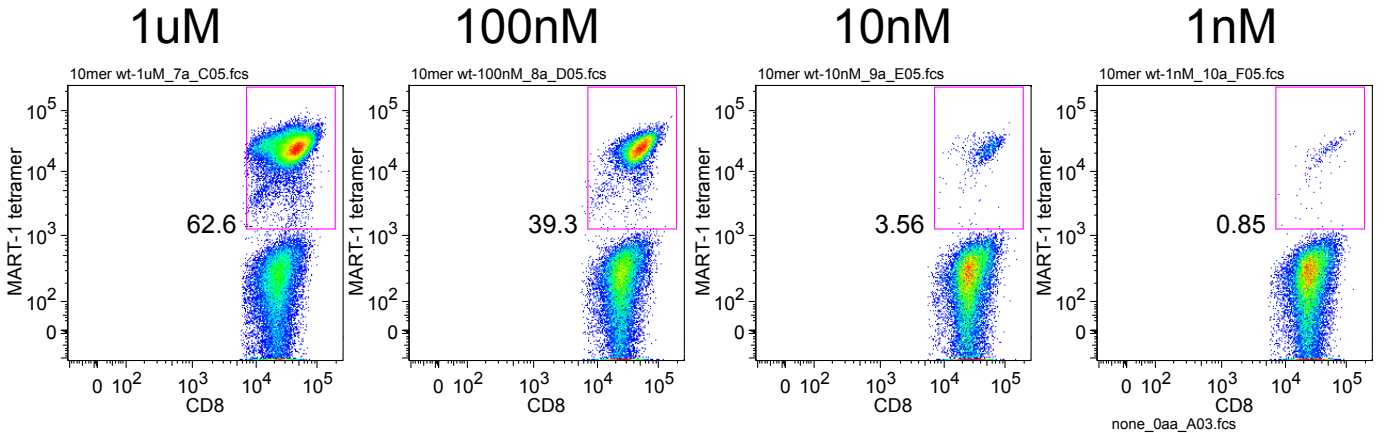
PBMCs
+
Peptides

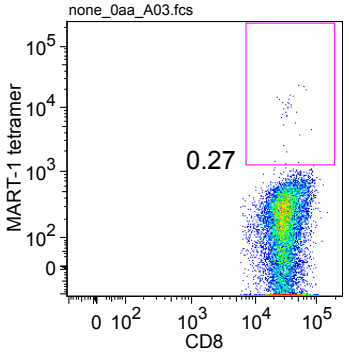
⬇

D7 4hrs
Restimulation

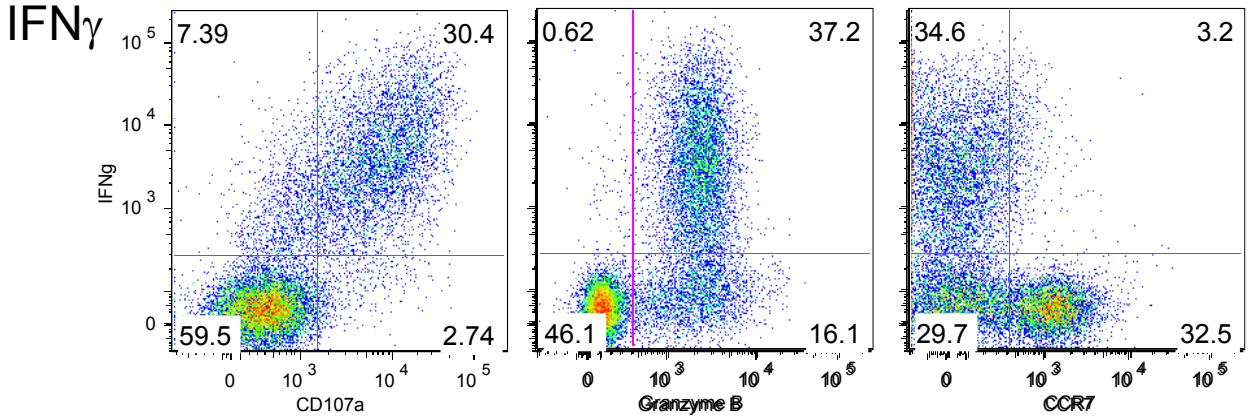
⬇

Tetramer
Assay
ICS
CTL assay





No peptide

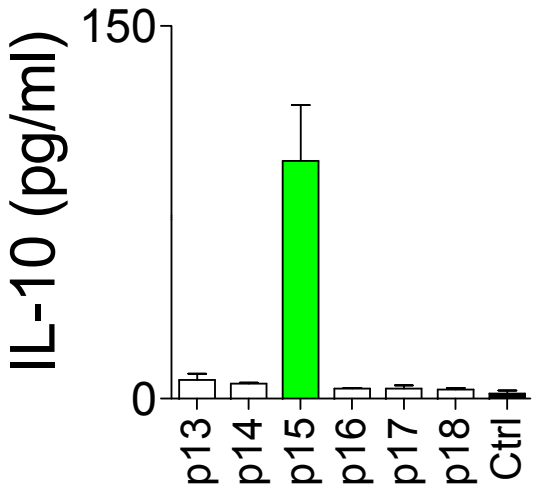


CD107 Gr B CCR7

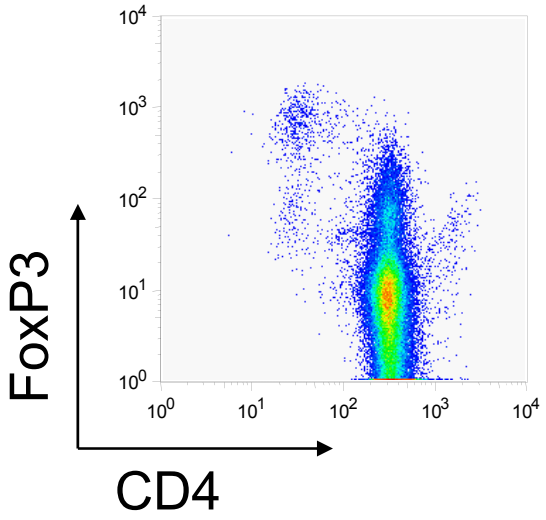
Chun, Israyleyan, Goldberg

Patients with Metastatic Melanoma Display Circulating Tumor Antigen-specific T regs

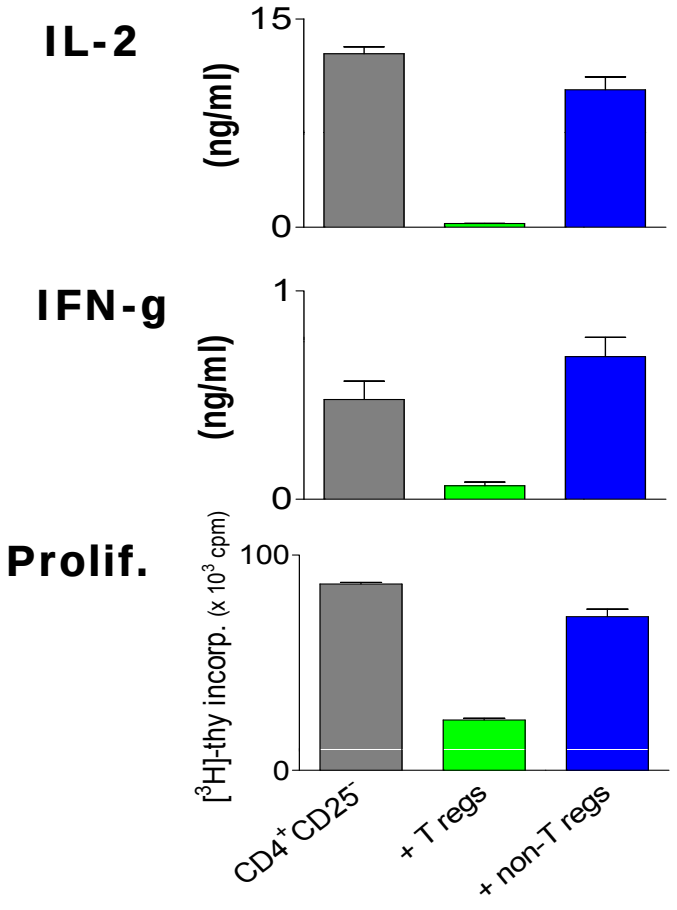
Determination of IL-10-inducing peptide



Proliferation of peptide-specific T regs

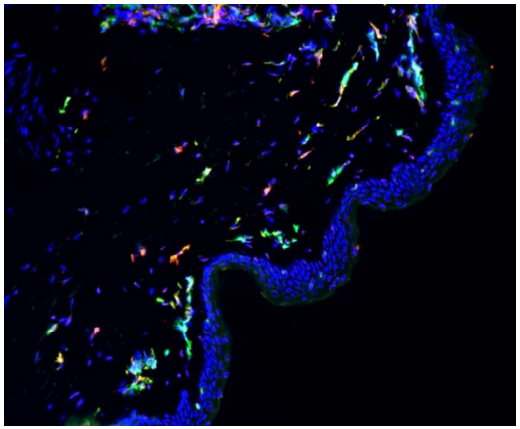


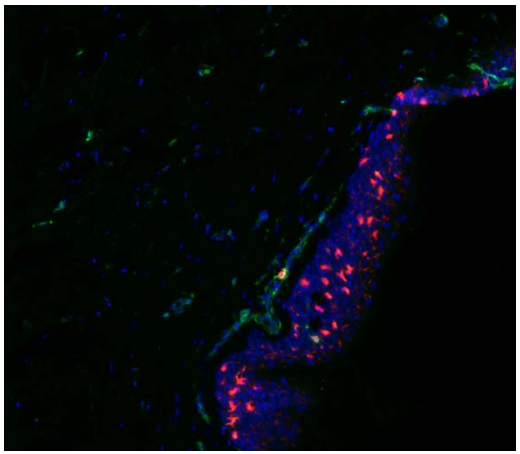
Suppressive function of specific T regs



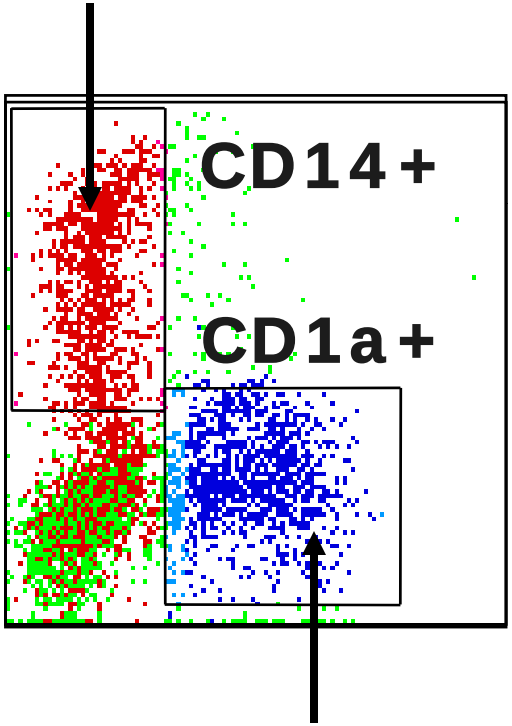
Vence et al. PNAS, 2007

Human Dendritic Cell Subsets In Vivo and In Vitro

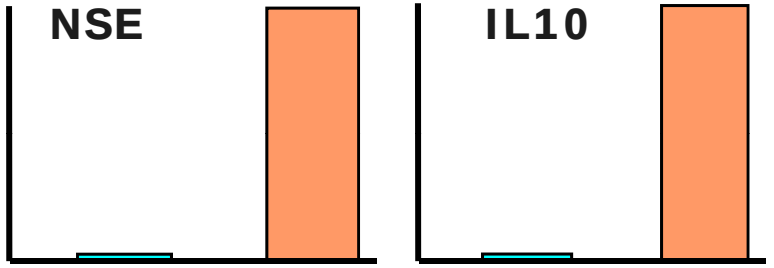


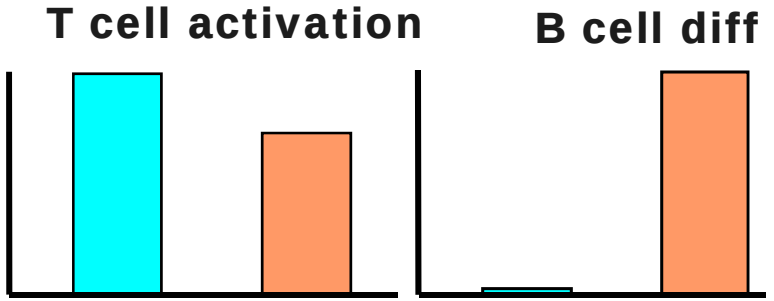


Human Dermal DCs – DC-SIGN positive



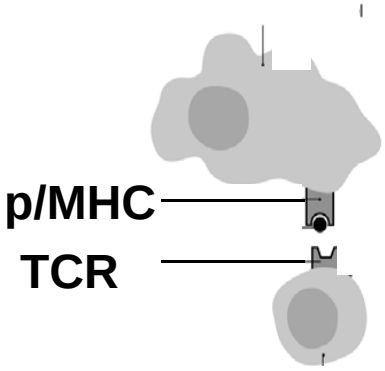
Human Langerhans Cells – Langerin positive





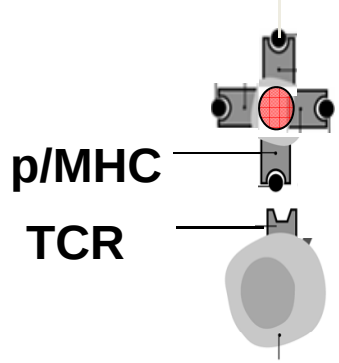
Caux et al, 1996,1997,1998

Langerhans Cells are More Efficient than Interstitial-DCs in CD8+T Cell Priming



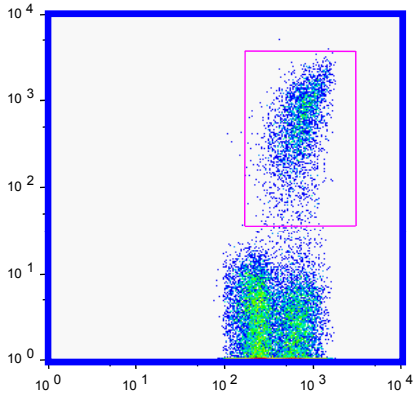
9 days

p/MHC Tetramer

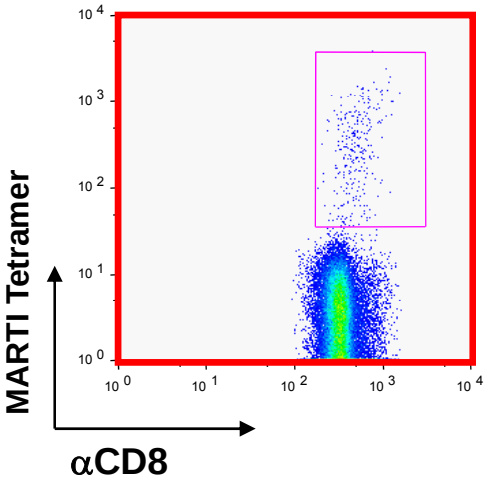


Klechevsky, Ueno

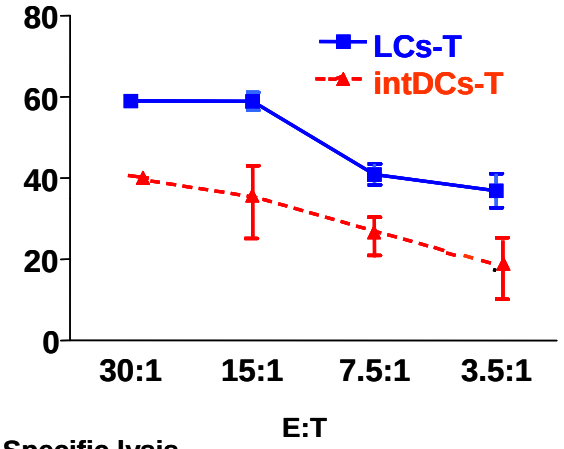
LCs



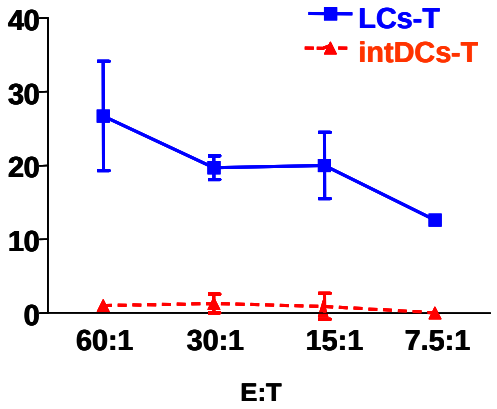
IntDCs



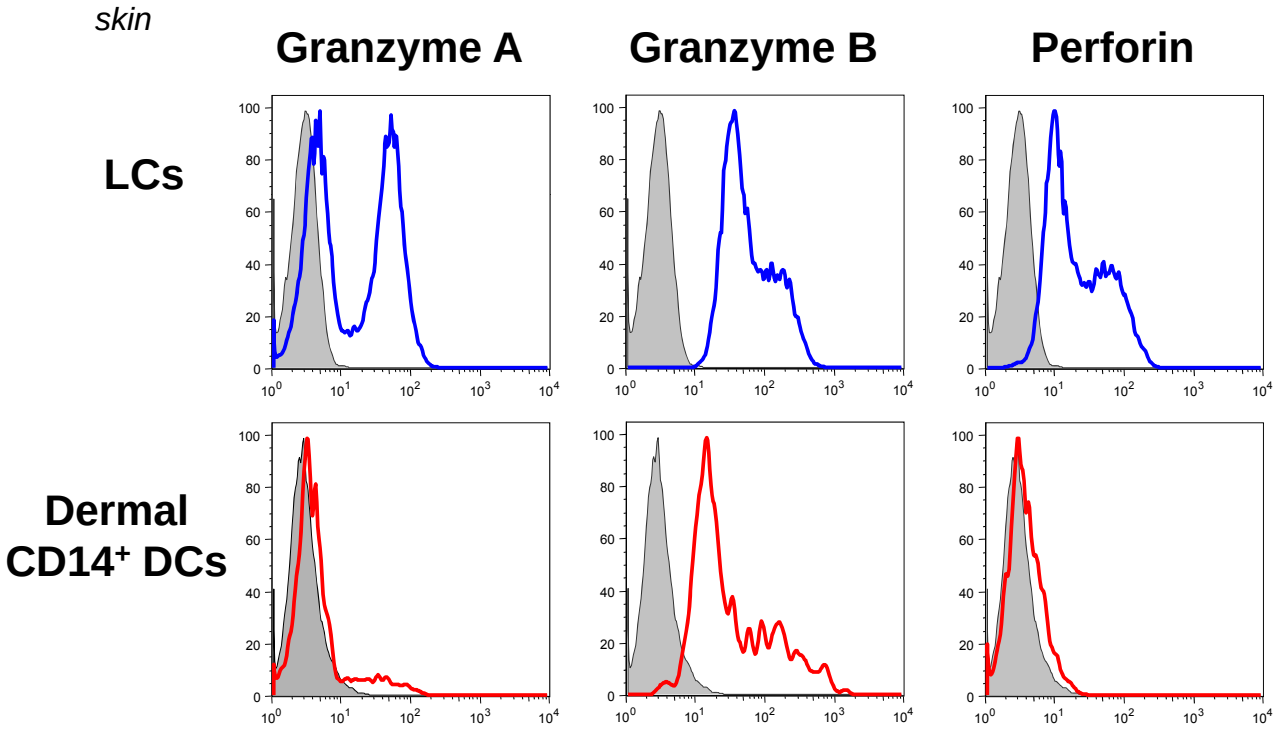
Peptide-pulsed T2 cells



HLA-A*0201+ melanoma cells



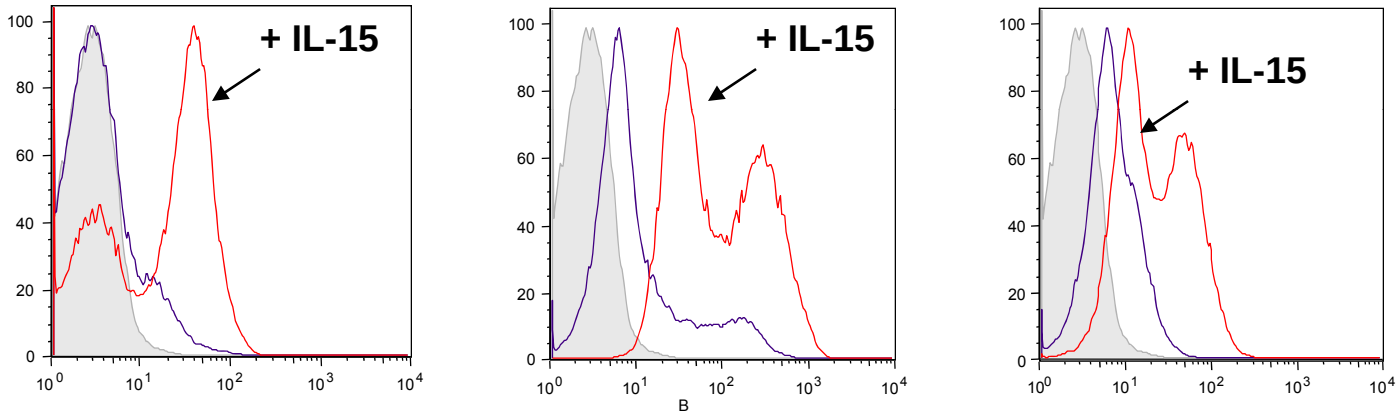
LCs efficiently prime effector CD8⁺ T cells



Klechevsky, Ueno et al, Immunity, 2008

IL-15 might explain the biological functions of LCs on CD8+T cells

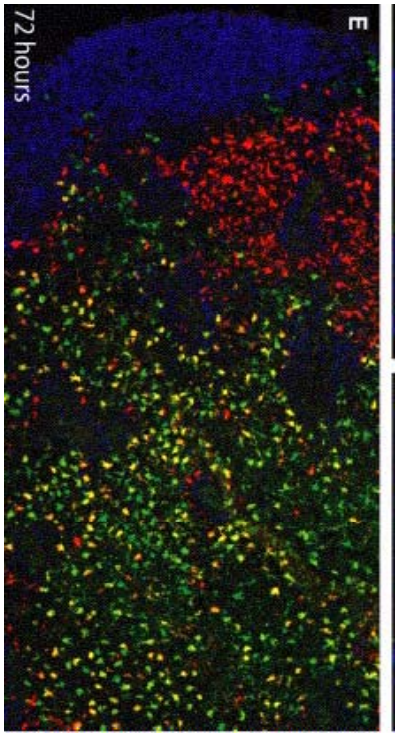
Granzyme A **Granzyme B** **Perforin**



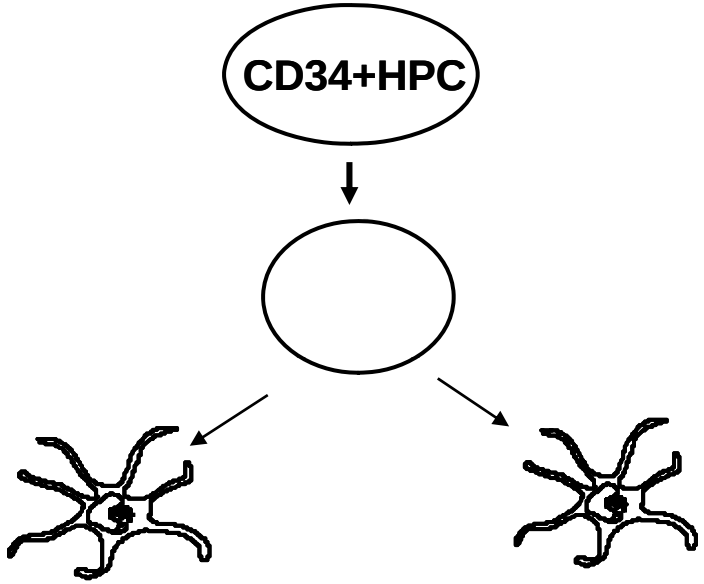
CD8+ T cells primed by dermal DCs in the presence of IL-15

Eynav Klechevsky

LCs Preferentially Control Cellular Immunity While intDCs Preferentially Control Humoral Immunity



Kissenpfennig et al
Immunity 2005; 22, 643



Interstitial DC
B cell priming
Tfh priming

Langerhans DC
CD4+CD8+T cell priming

HUMORAL IMMUNITY

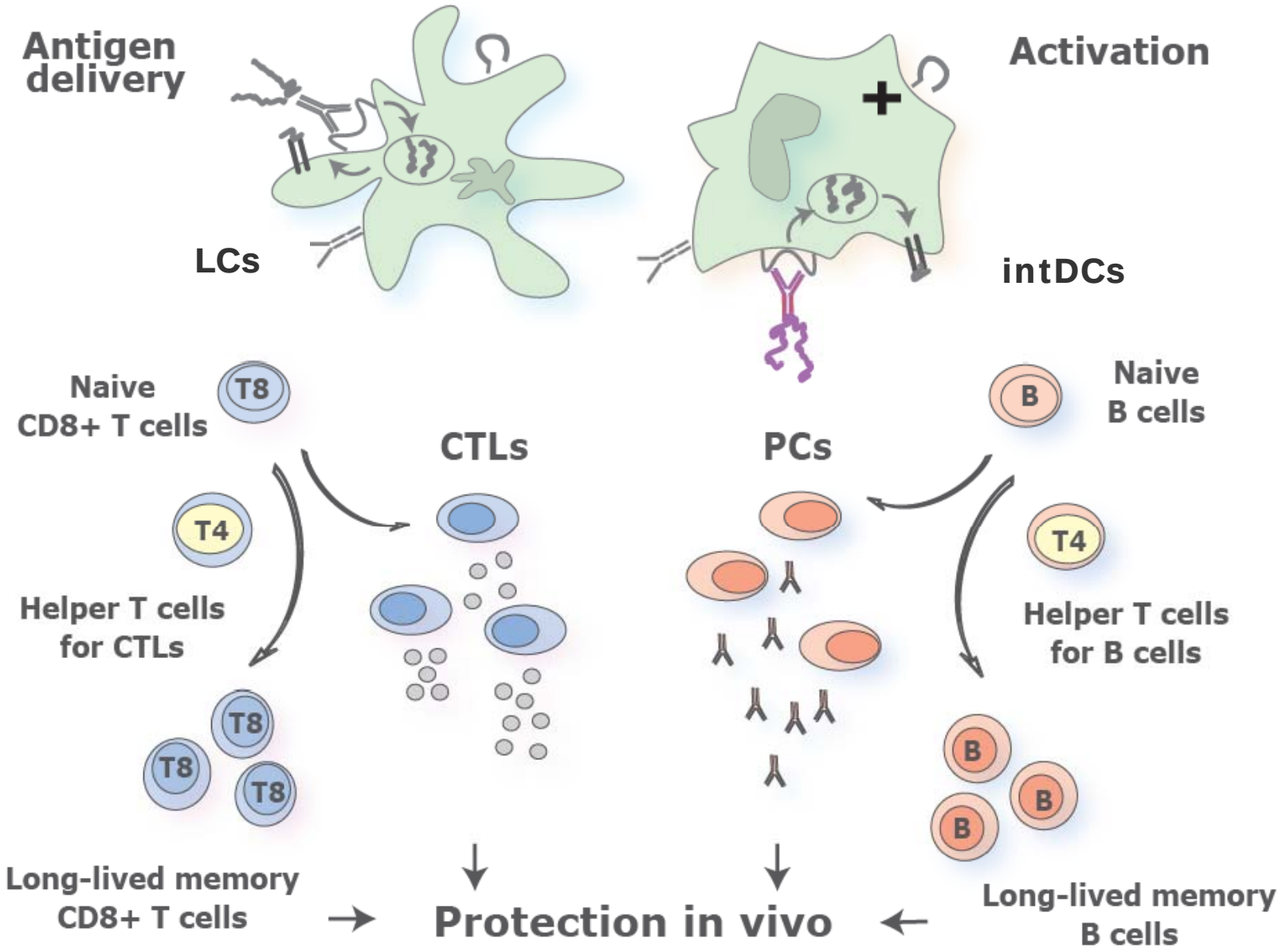
CELLULAR IMMUNITY

IL12

IL15

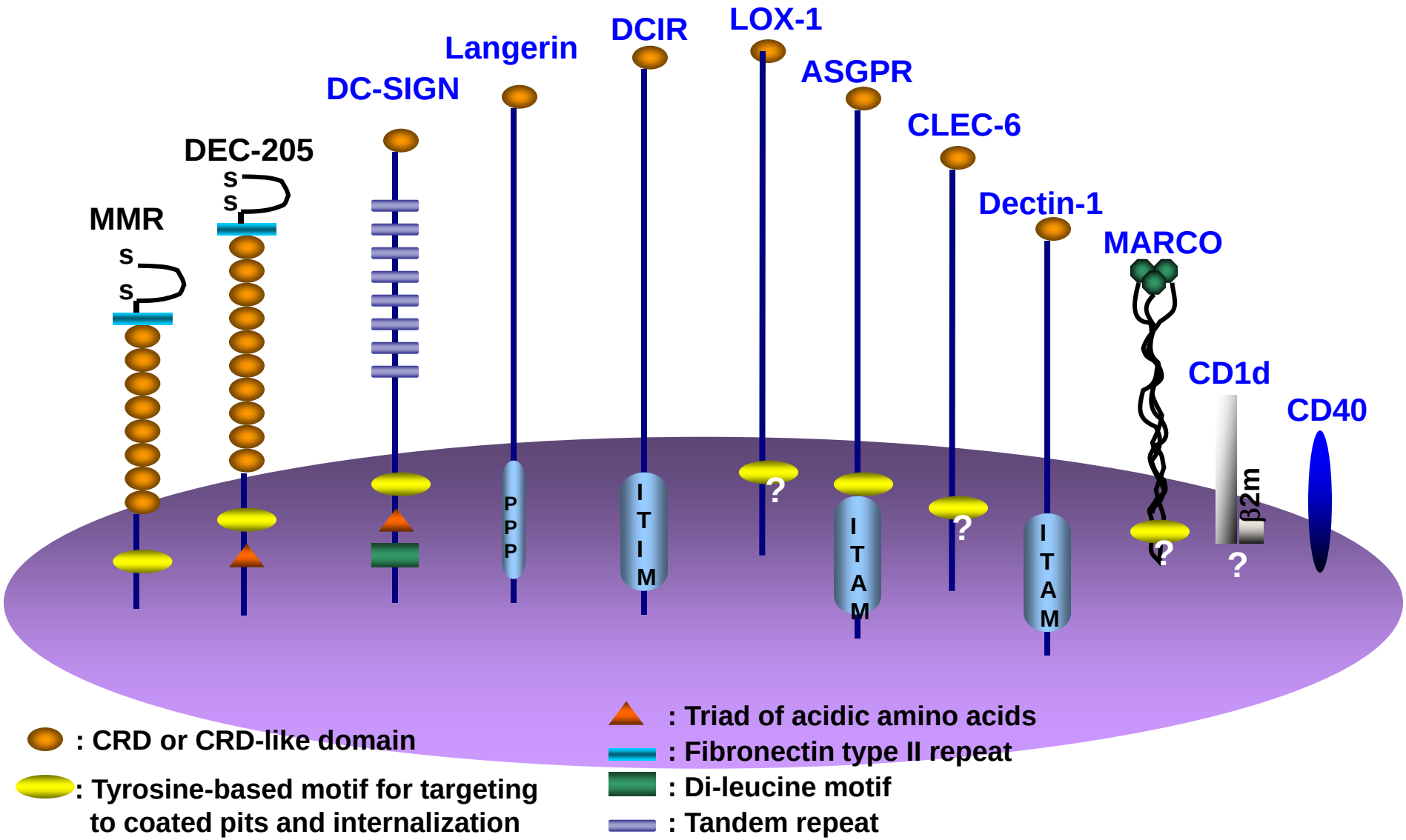
Activation of memory T and B cells

LANGERHANS CELLS PREFERENTIALLY CONTROL CELLULAR IMMUNITY WHILE DERMAL DC PREFERENTIALLY CONTROL HUMORAL IMMUNITY



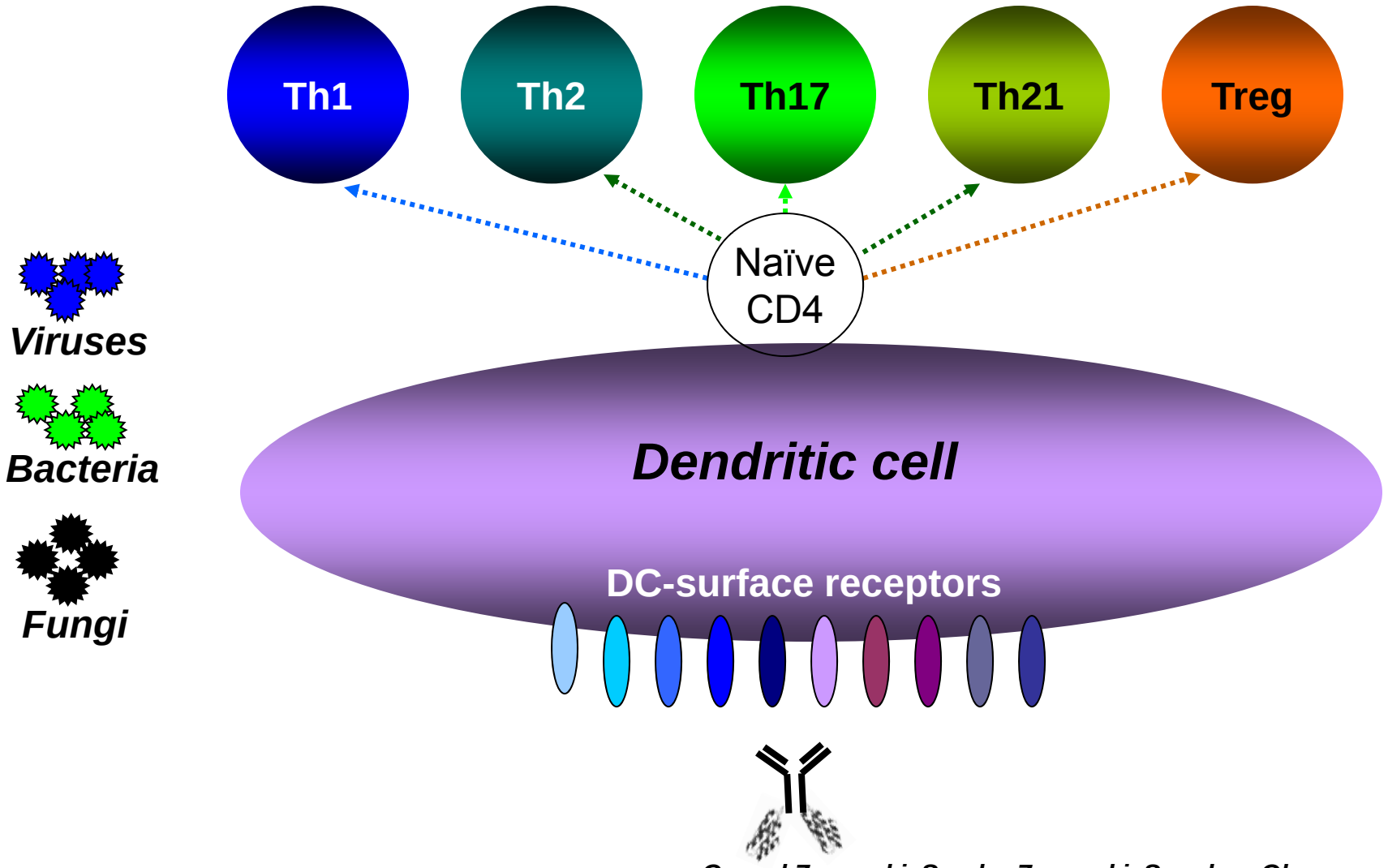
Klechevsky, Ueno et al Immunity 2008

Which DC Receptors can target Antigens?



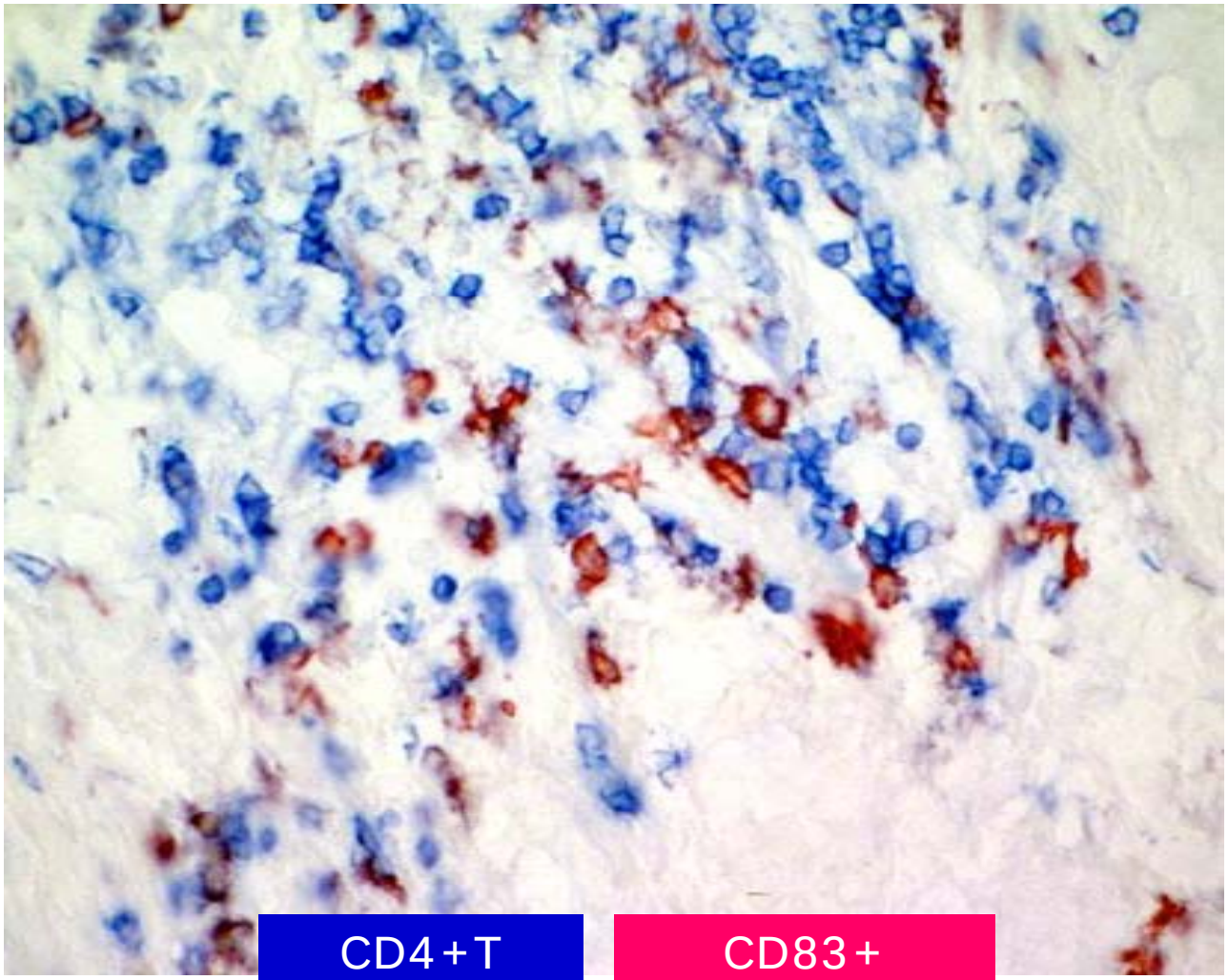
Gerard Zurawski, Sandra Zurawski, Sangkon Oh

Are All DC Receptors Equal?



Gerard Zurawski, Sandra Zurawski, Sangkon Oh

Mature dendritic cells in breast cancer co-localize with T cells



CD4+T cells

CD83+ mature DCs

Bell et al JEM 1998

Breast tumor tissue can be induced to produce a wide range of T cell cytokines

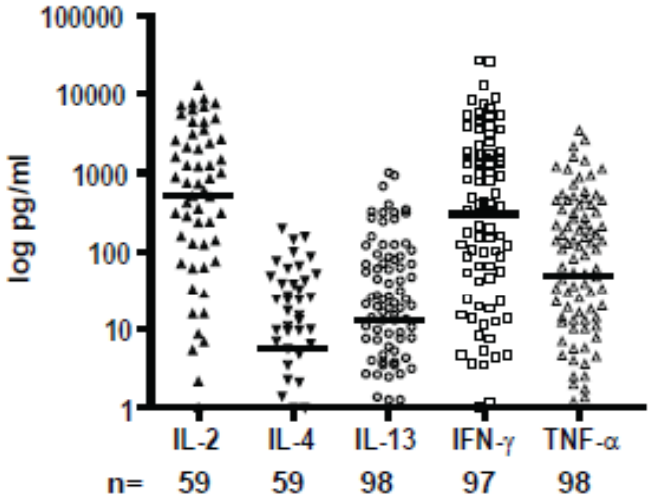
Tumor (T)

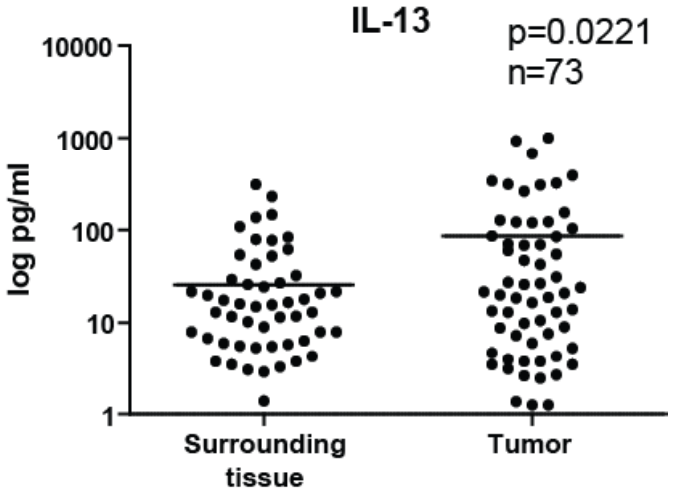
Surrounding tissue (ST)

Activate in PMA/inomycin for 18 hrs

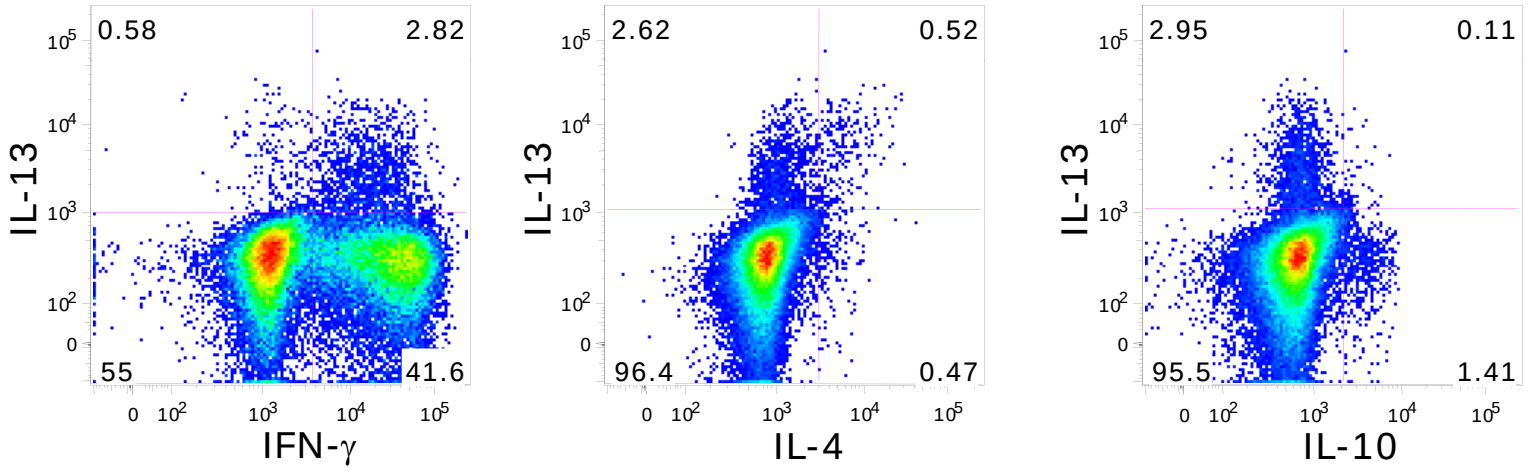
Collect supernatant

Luminex assay





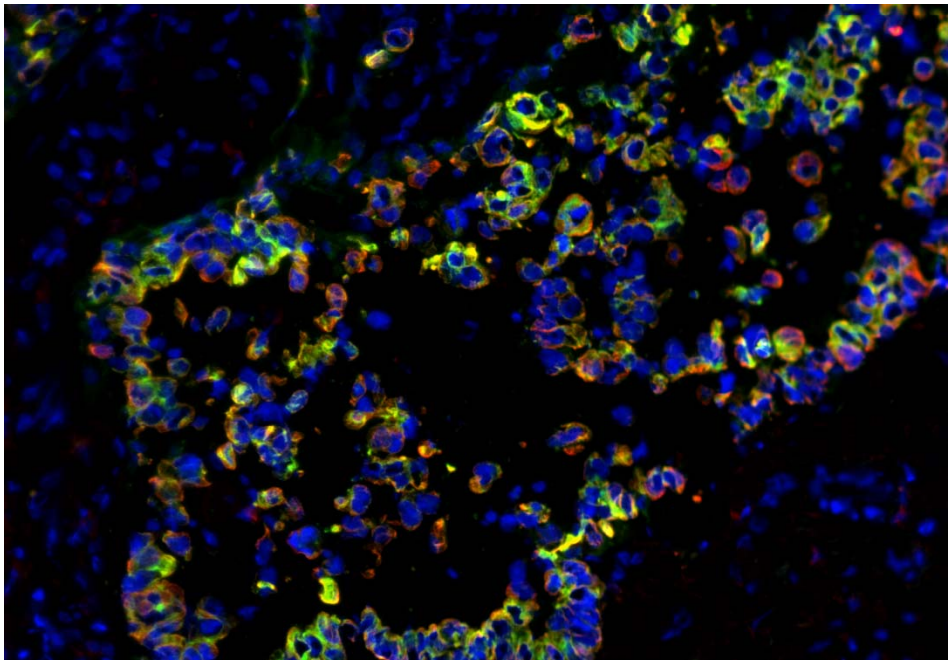
Tumor infiltrating T cells produce type 2 cytokines, particularly IL-13



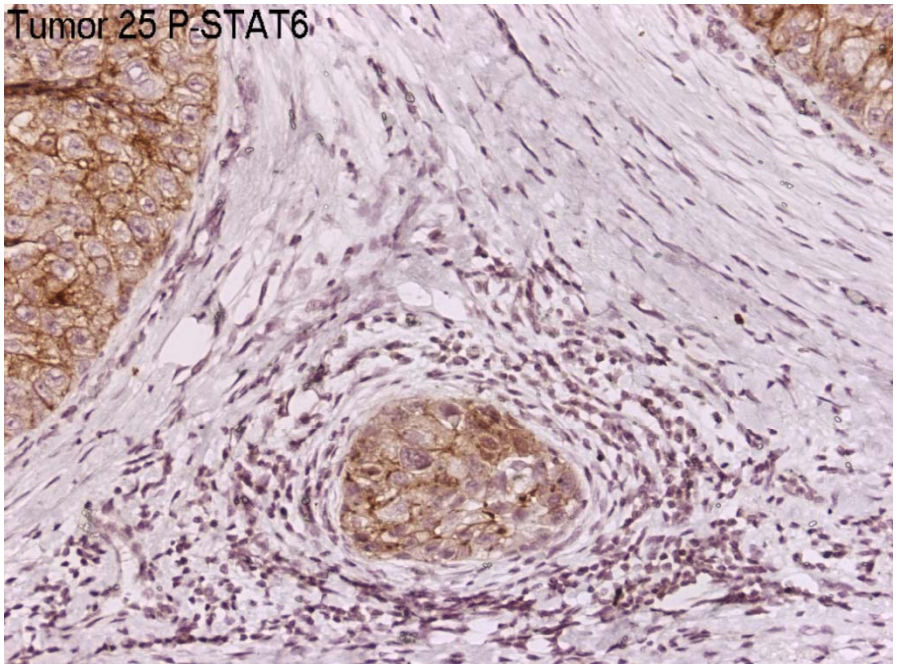
Cell gating: Live/CD45+/CD3+/CD4+

Breast cancer cells show IL-13 staining and display an IL-13 signature (pSTAT6)

IL-13/Cytokeratin



pSTAT6

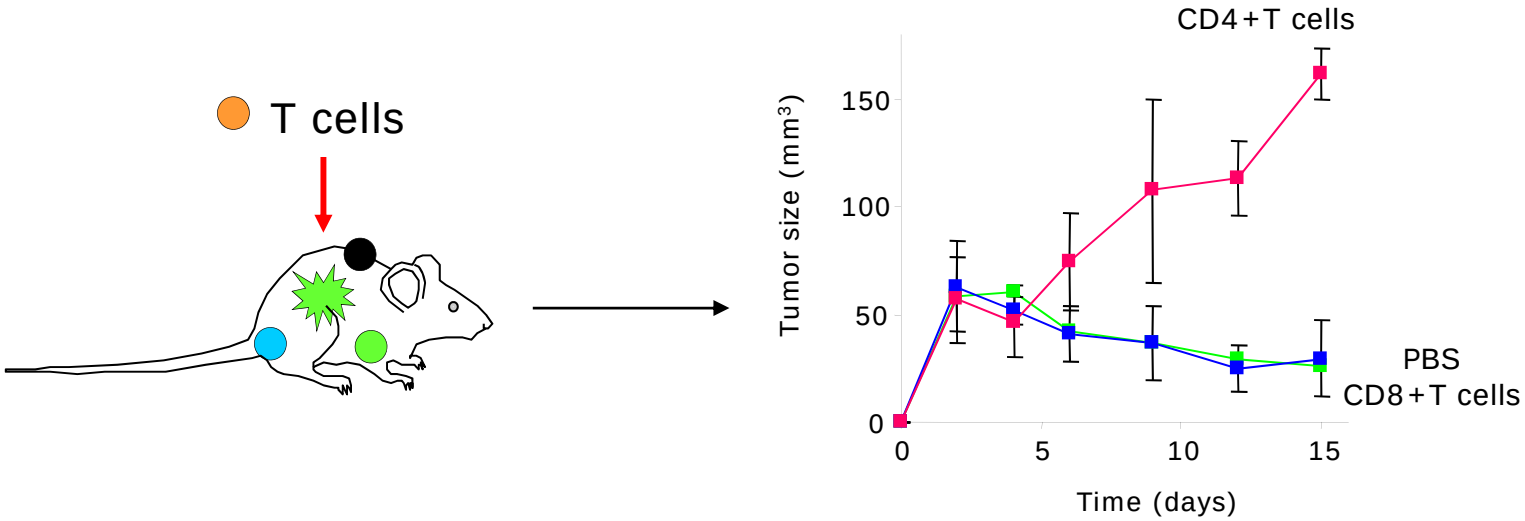


Aspord, Pedroza et al JEM 2007

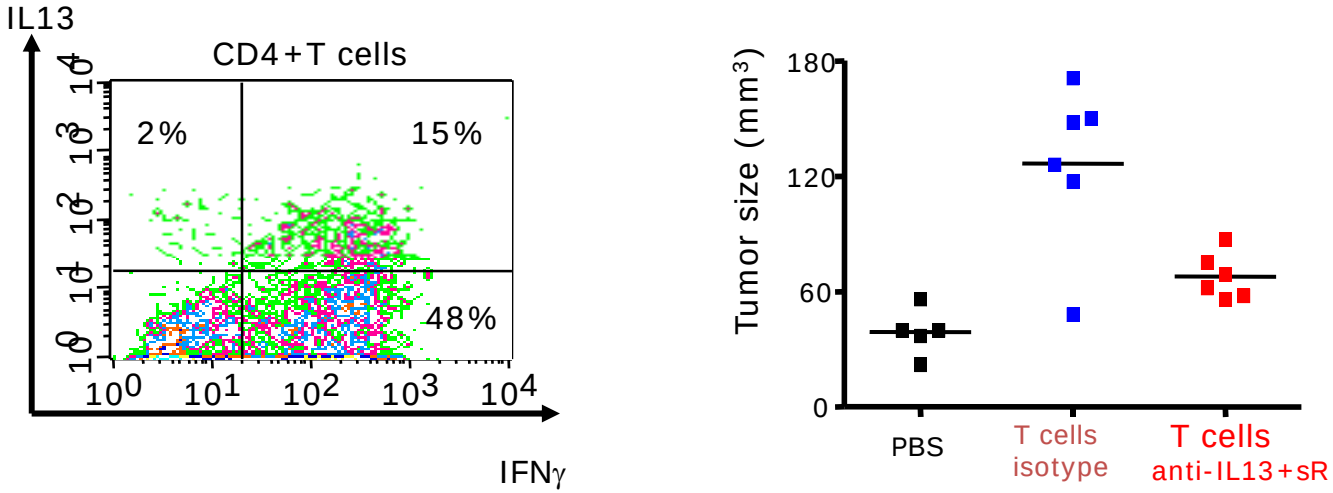
The IL-4/IL-13/Stat6 signalling pathway promotes luminal mammary epithelial cell development

Khaled W. et al. Development 134, 2739-2750 (2007)

CD4⁺ T cells promote early tumor development

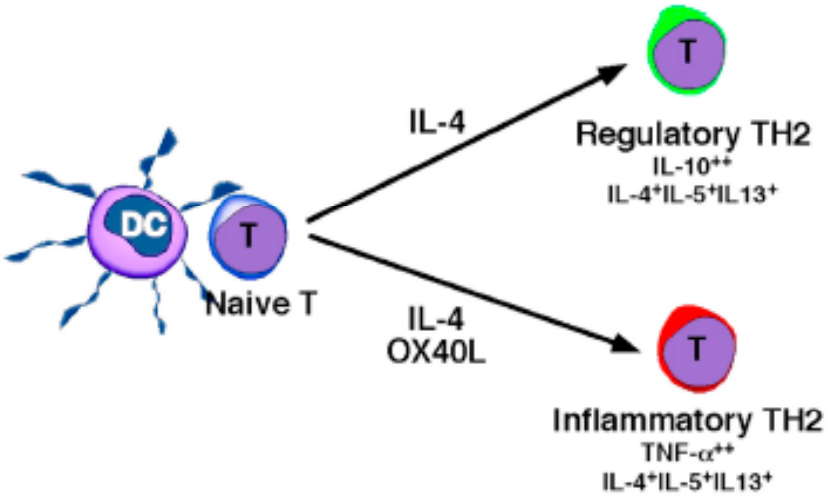


… which can be prevented by IL-13 antagonists

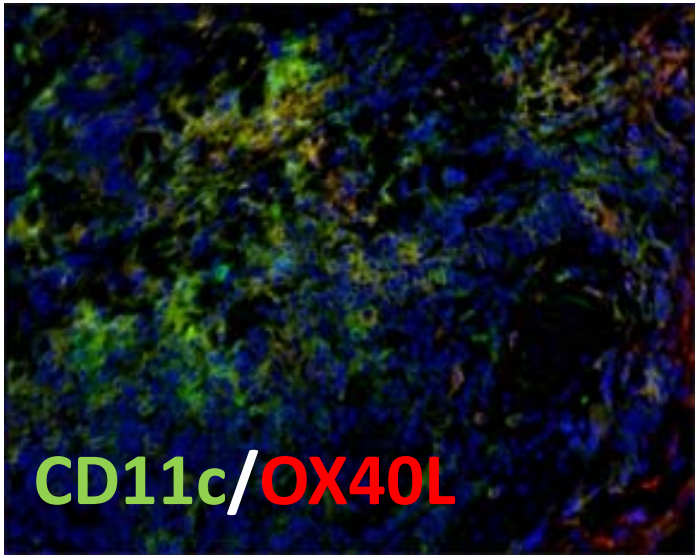


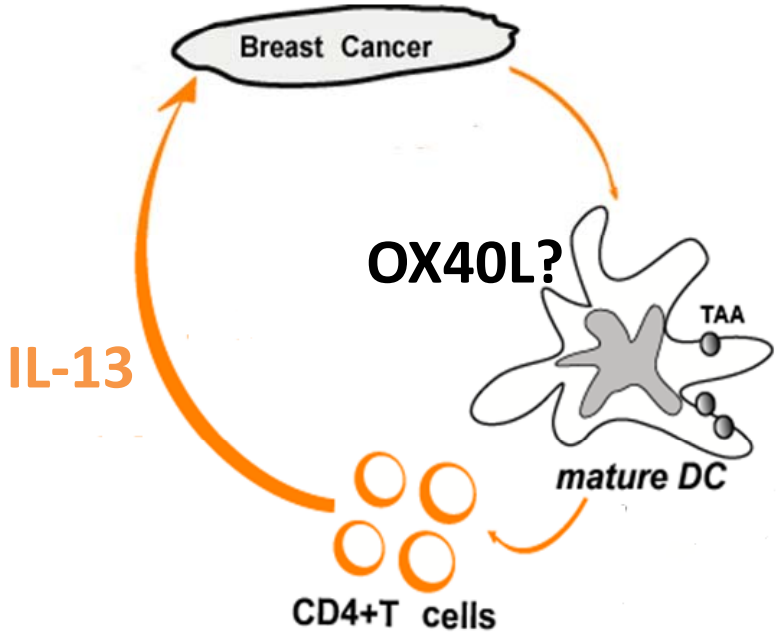
Aspord, Palucka et al. J.Exp.Med. 2007 Vol.204: 1037

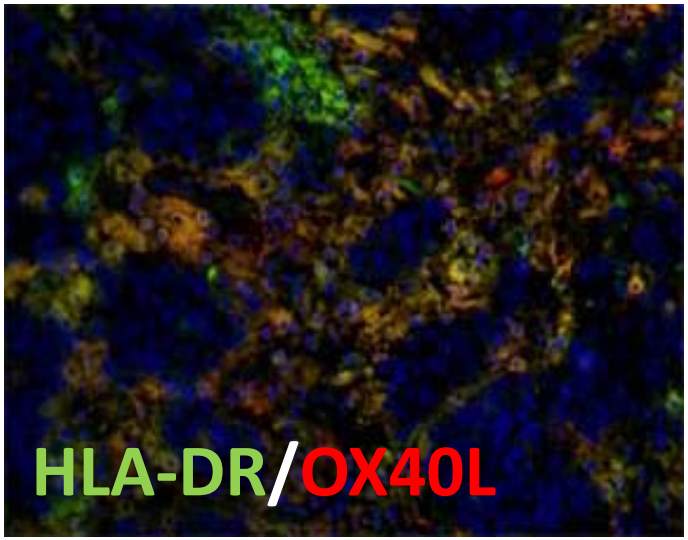
Breast tumors are infiltrated with OX40L+ HLA-DR+ CD11c+ DCs



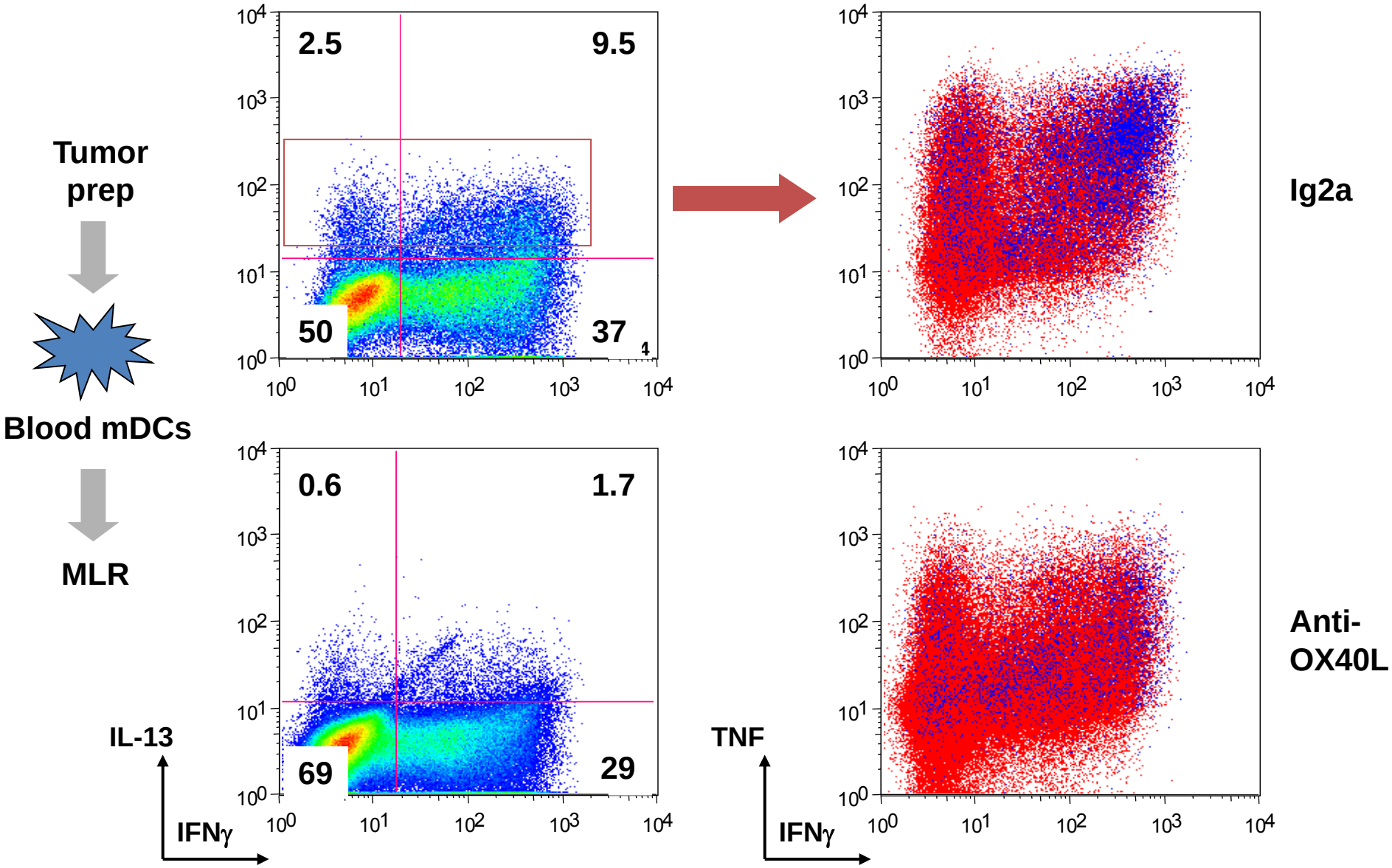
Ito *et al*. *JEM* 2005



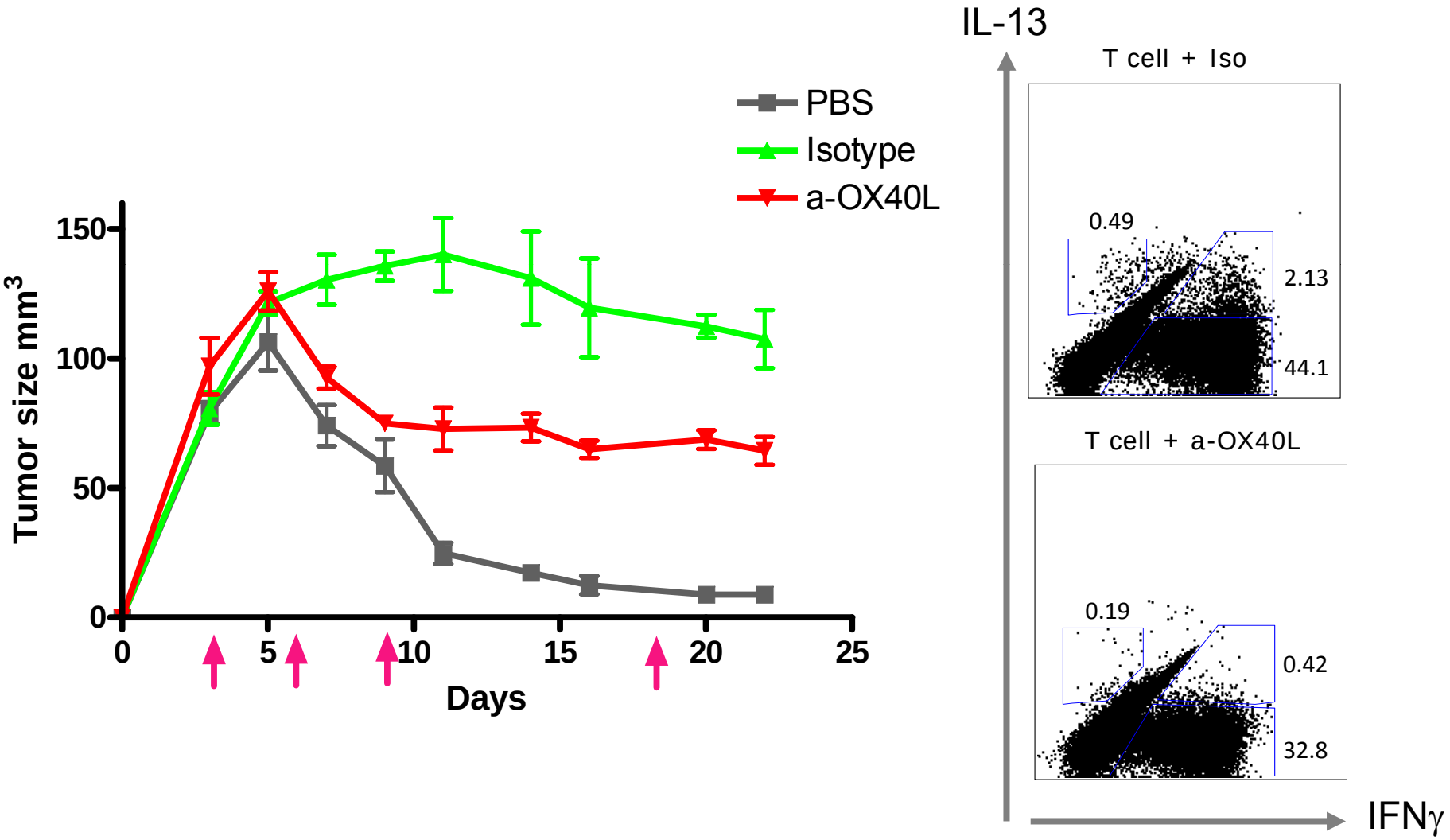


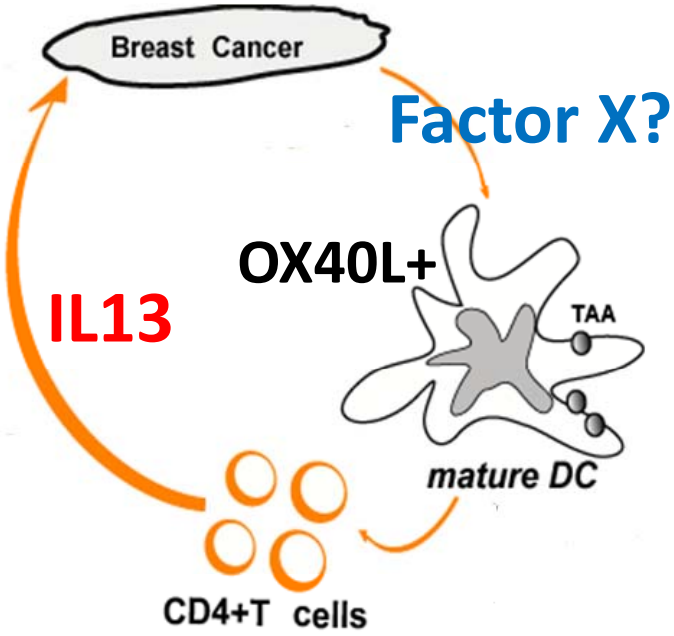


OX40L+ mDCs drive pro-inflammatory type 2 CD4+T cell response in breast cancer in vitro



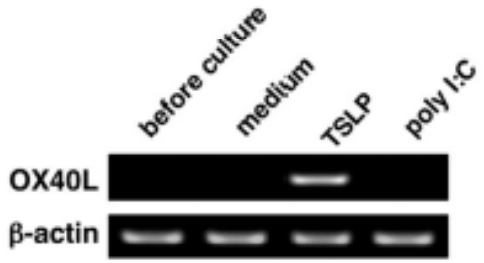
OX40L drives pro-inflammatory type 2 CD4$^+$ T cell response in breast cancer in vivo

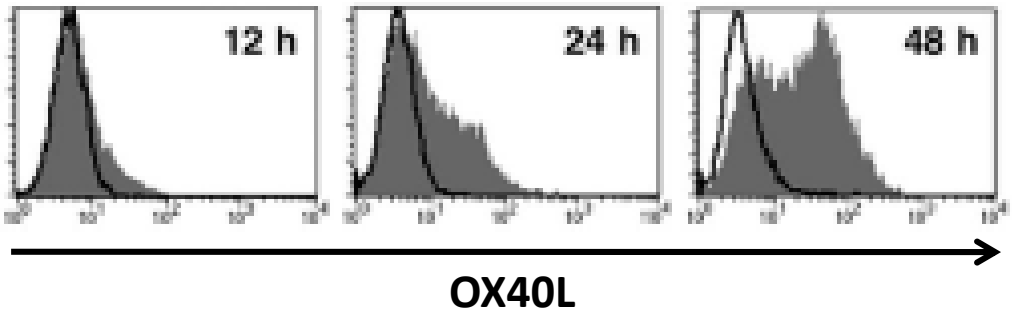




Factors that can up-regulate OX40L on DCs

- Thymic stromal lymphopoietin (TSLP)

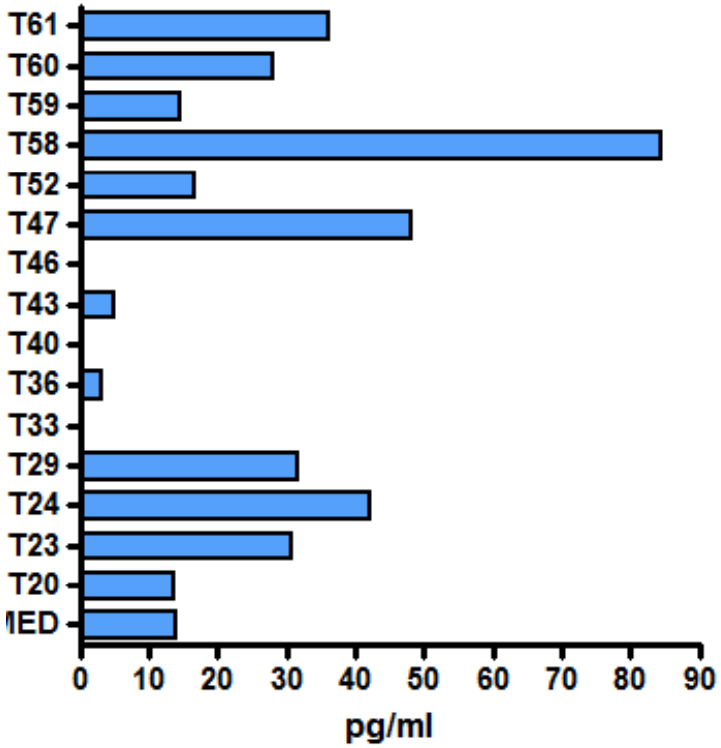




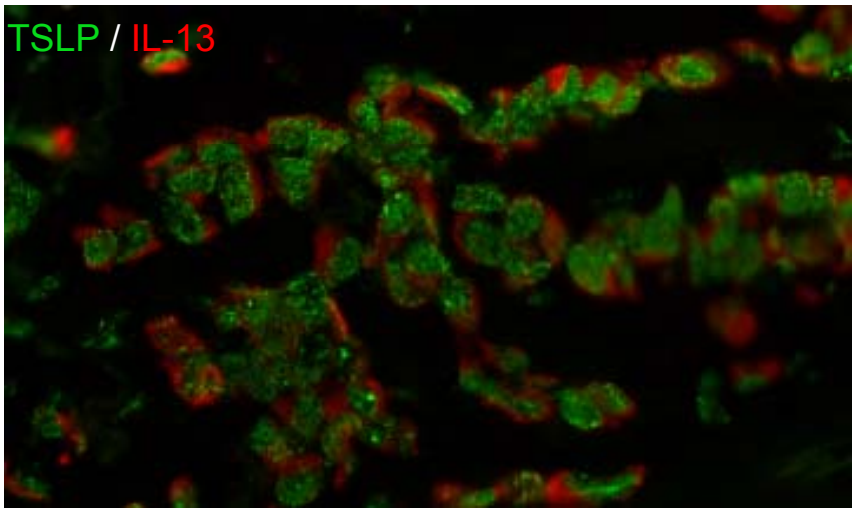
Ito *et al. J Exp Med* 2005

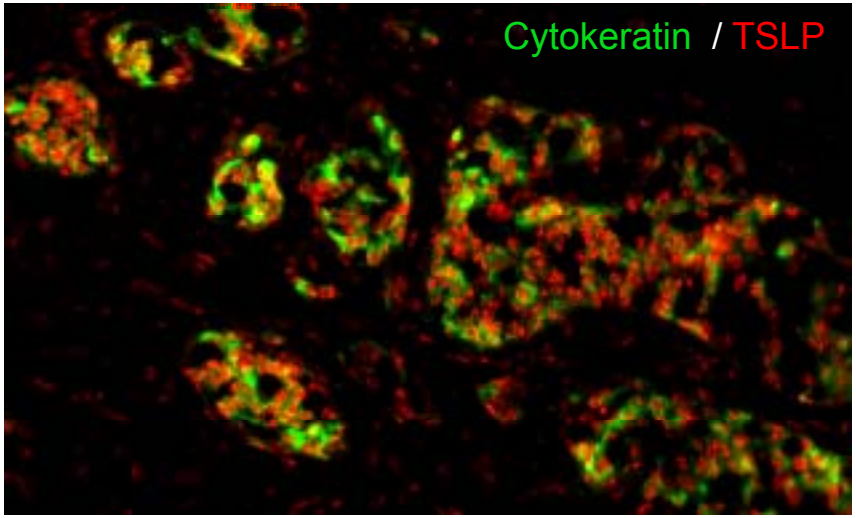
TSLP is present in breast cancer microenvironment

Fresh sonicated human breast tumors



TSLP



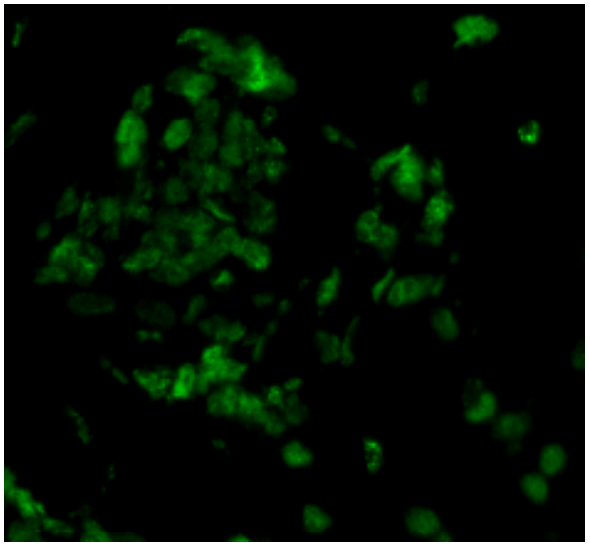


Primary tumors

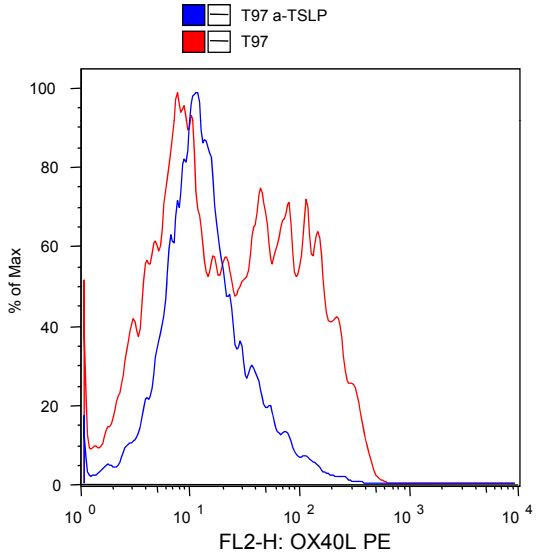
OX40L induction on mDCs can be abolished by TSLP blockade

Sonicated
Breast Cancer
+ anti-TSLP Ab

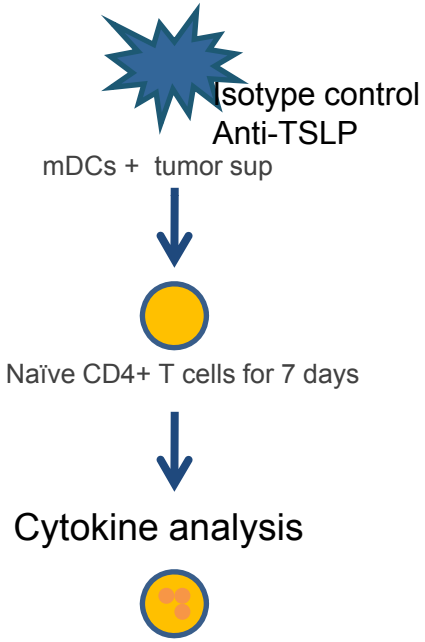
OX40L
staining

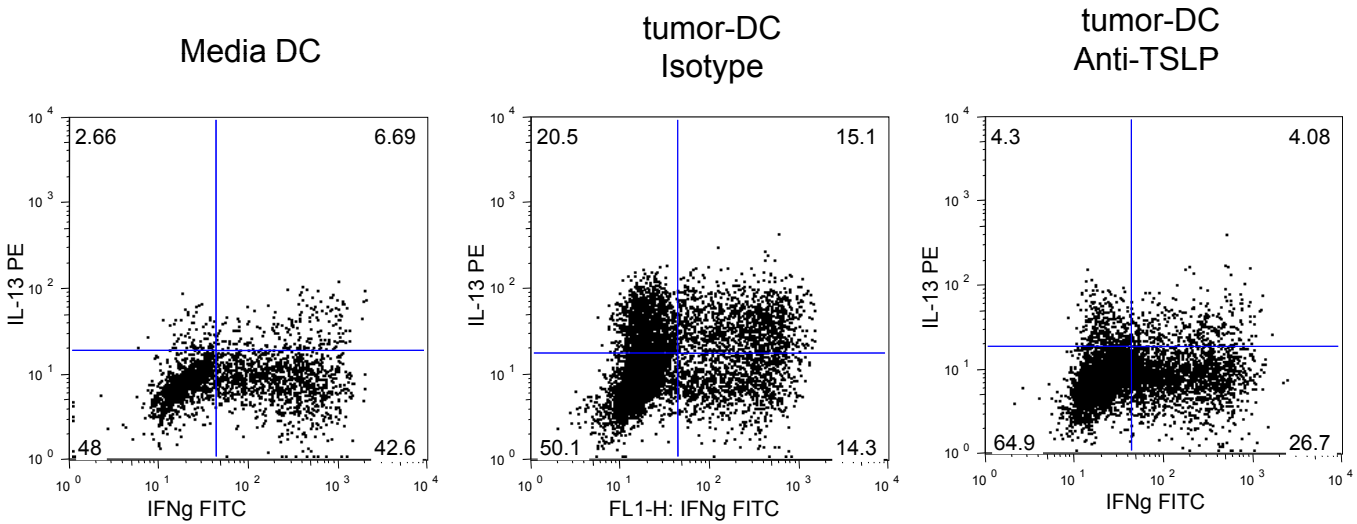


TSLP

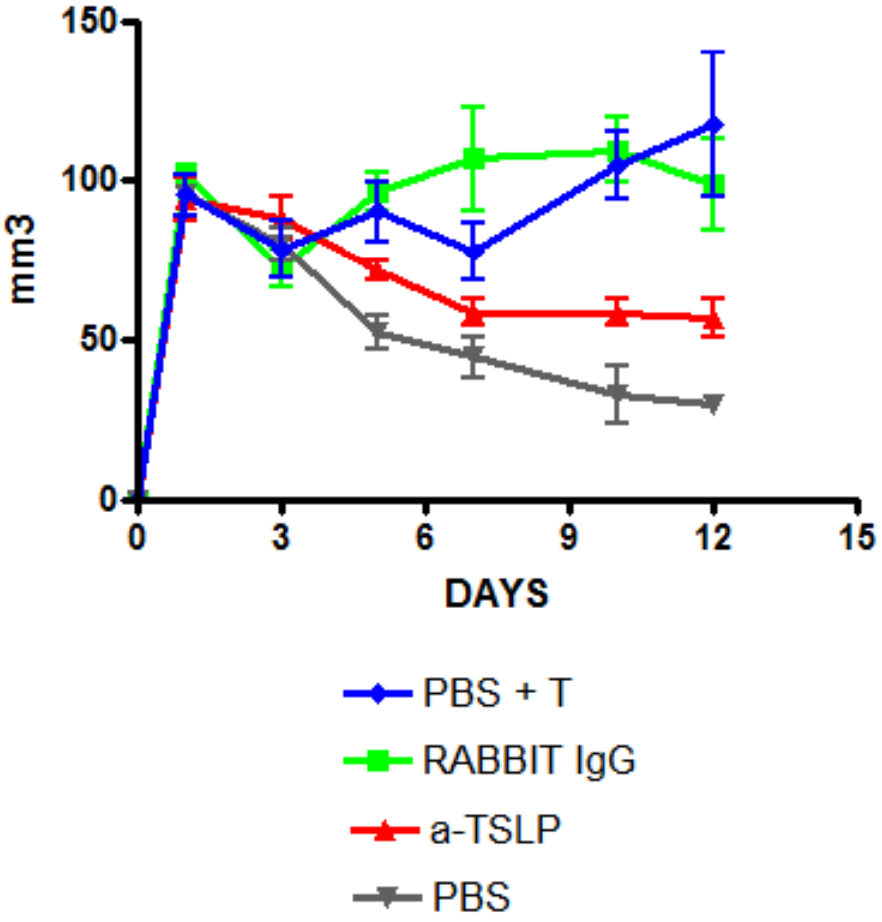


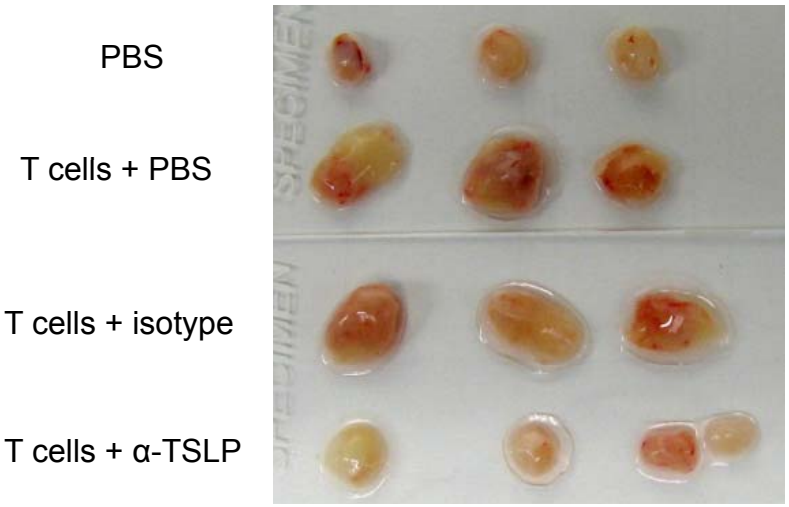
TSLP is critical for induction of OX40L on DCs and their capacity to generate IL-13 secreting CD4+ T cells

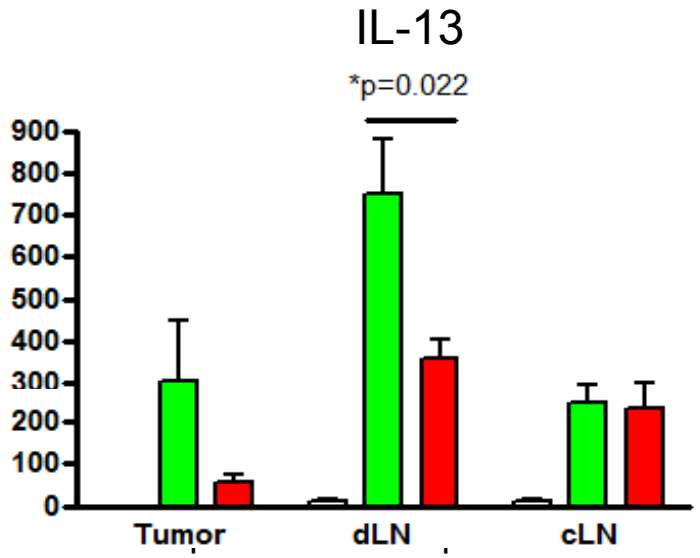




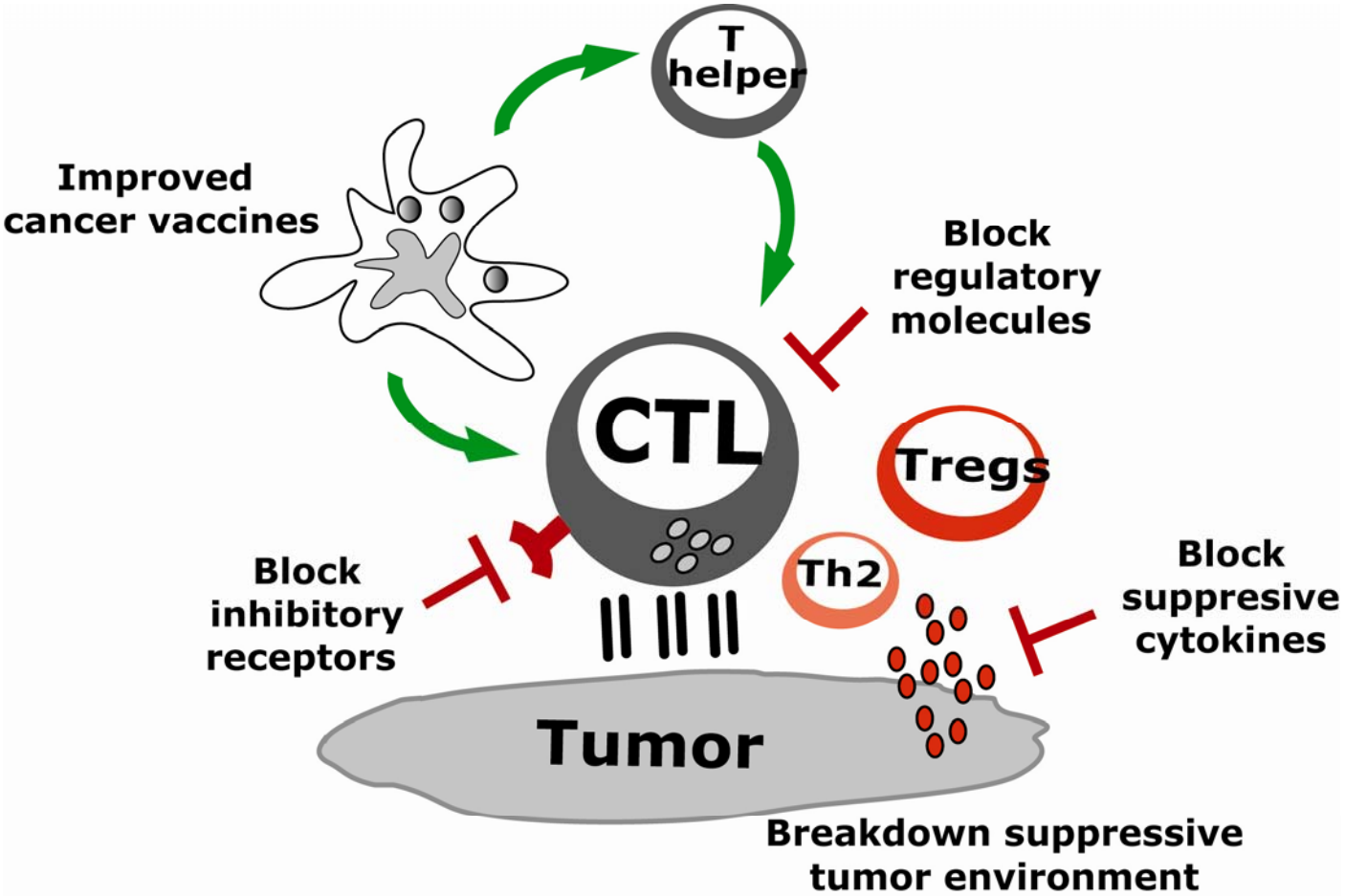
TSLP is involved in tumor development







Next generation DC vaccination trials:
Patient selection
Combined therapies



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JACQUES BANCHEREAU

AND MANY BIIR MEMBERS.....