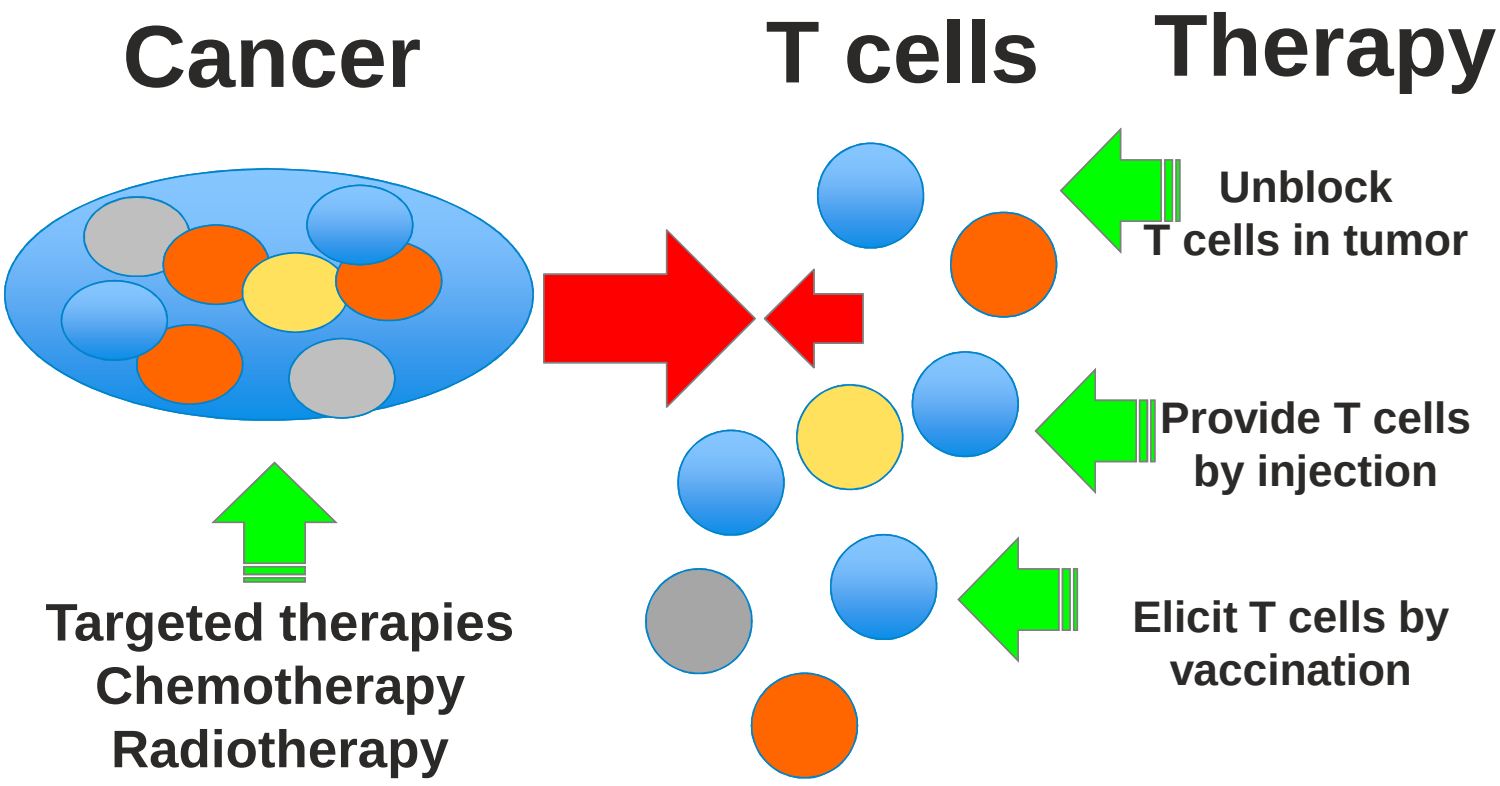
Dendritic cells: basic biology and therapeutic use

Karolina Palucka, MD, PhD

The Jackson Laboratory for Genomics Medicine
Farmington, CT

T cell based immunotherapy

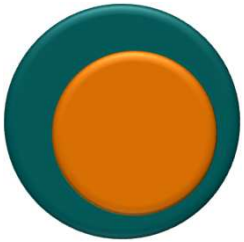


Multifaceted T cells in cancer

Cancer control

Cancer prevention via immune surveillance

Cancer rejection



T cell

Cancer growth

Dysfunctional T cells

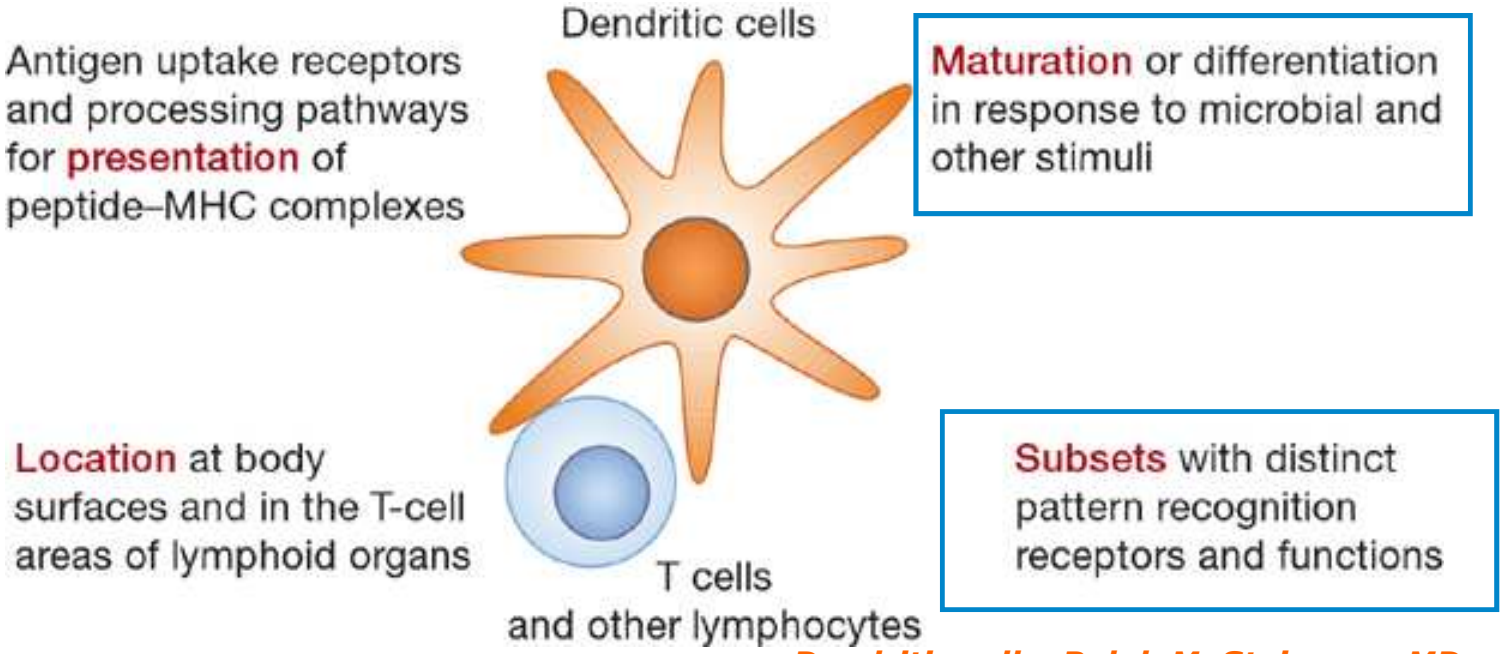
Effector T cell inhibition

T cell corruption:
Pro-tumor inflammation

How to reprogram this system for cancer rejection?

The Jackson Laboratory

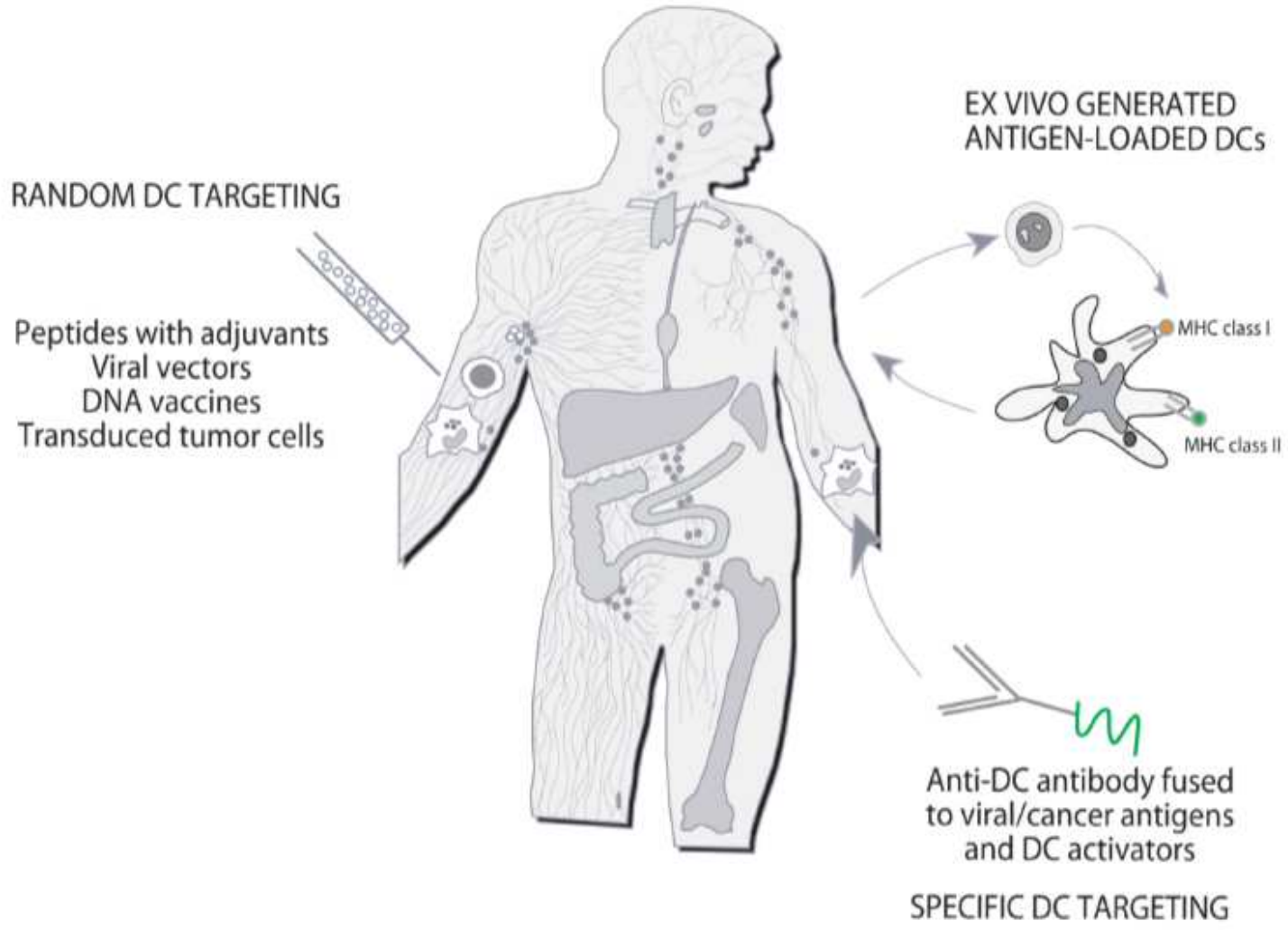
Dendritic cells control T cell differentiation and function

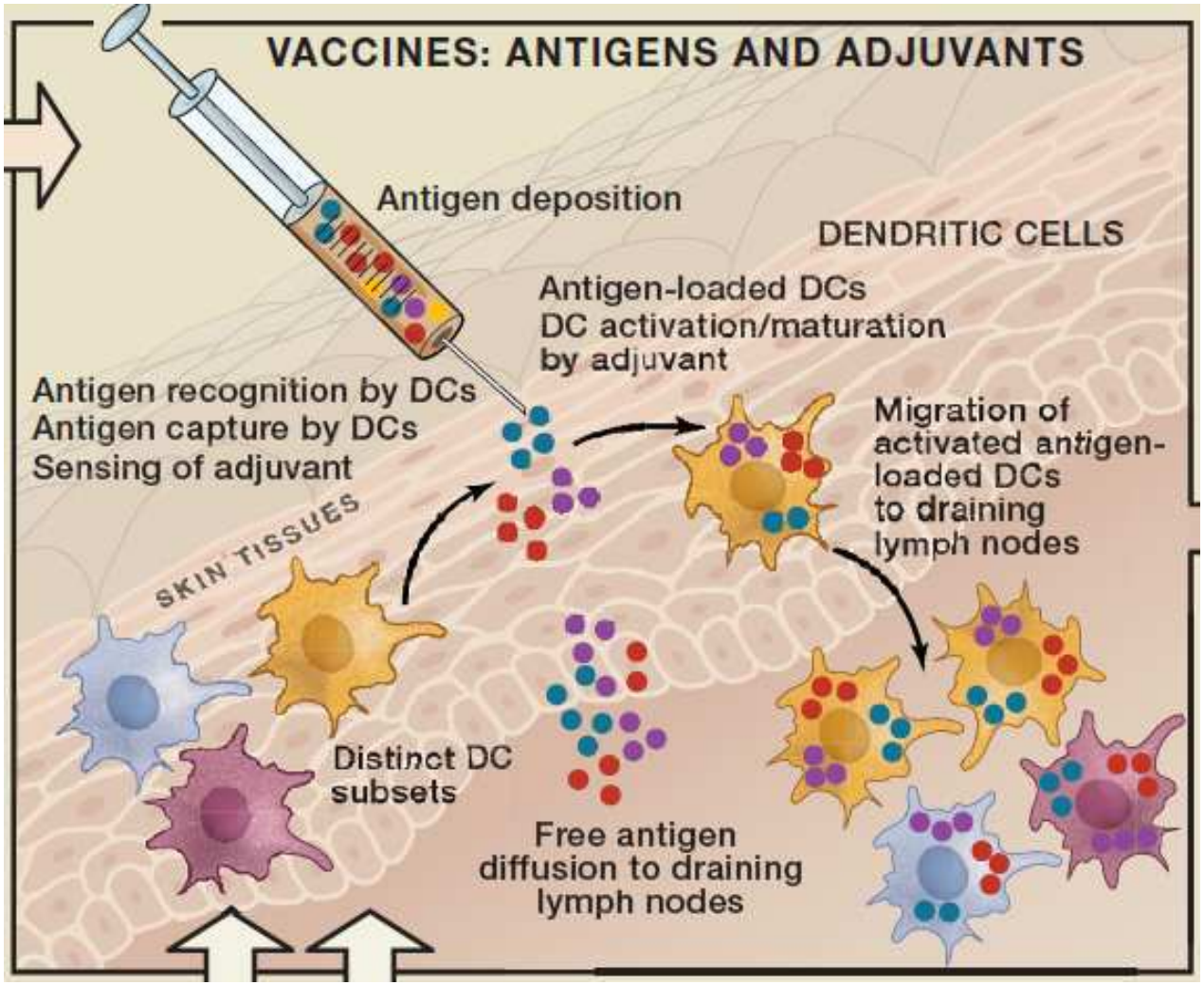


Dendritic cells: Ralph M. Steinman, MD
2011 Nobel Prize in Medicine or Physiology

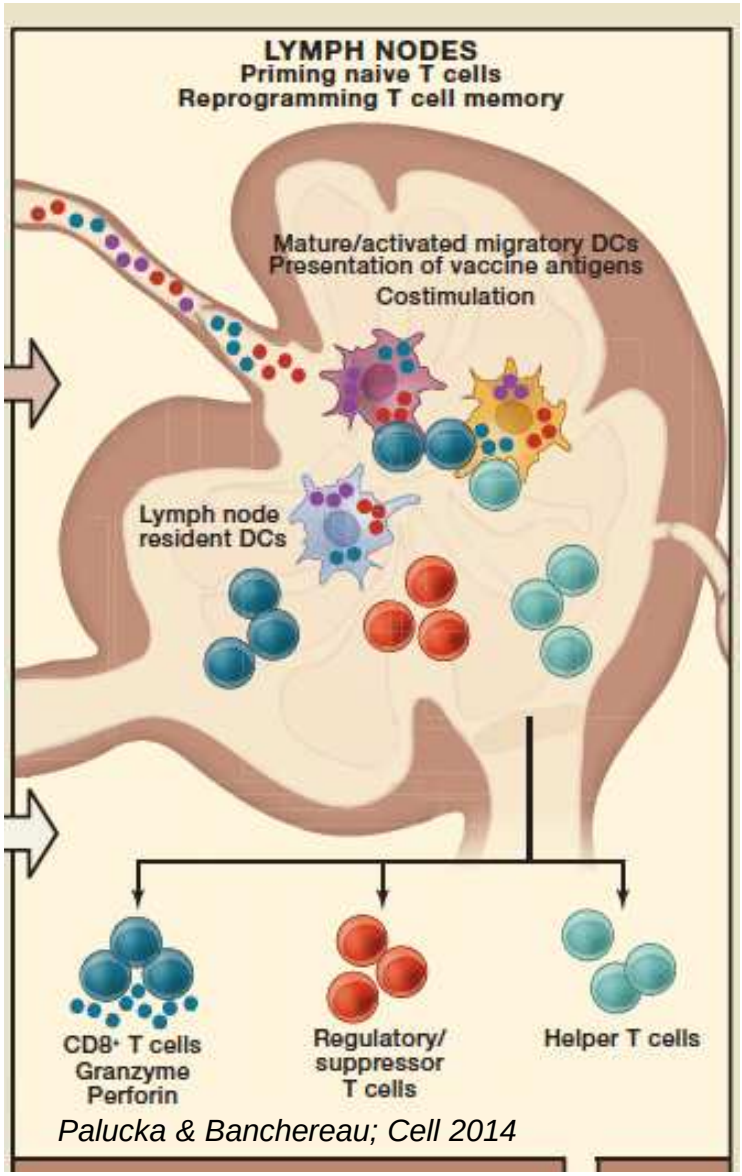
Steinman & Banchereau
Nature 2007

Dendritic cells as cancer vaccines



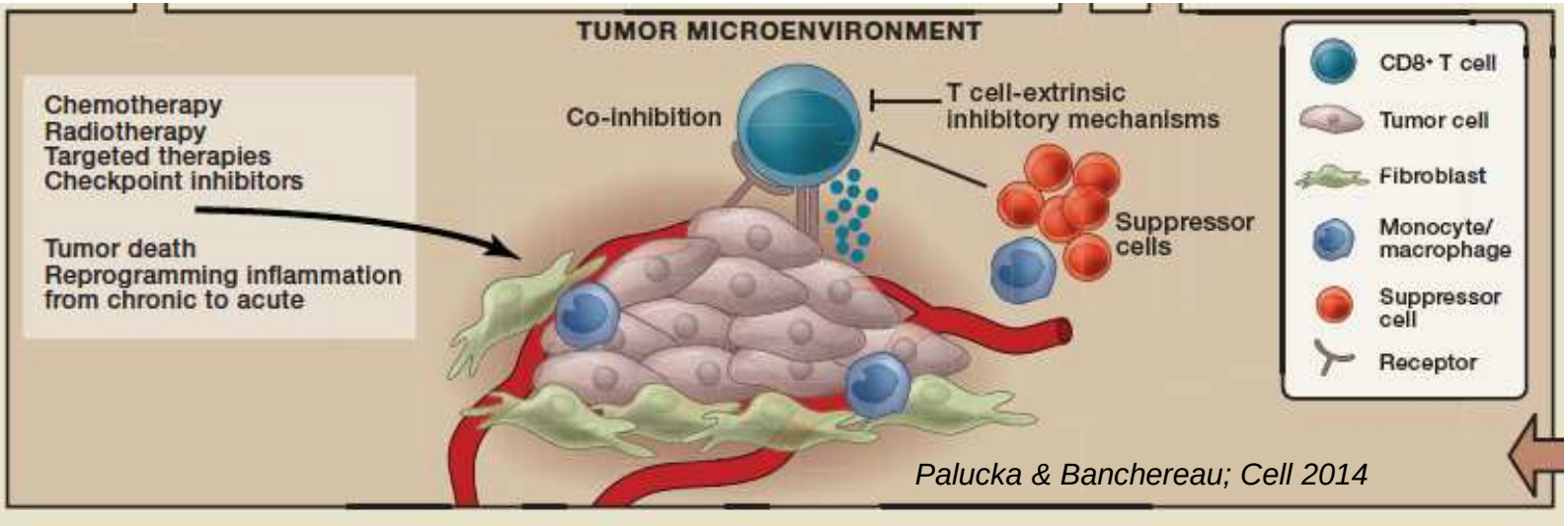


Palucka & Banchereau; Cell 2014

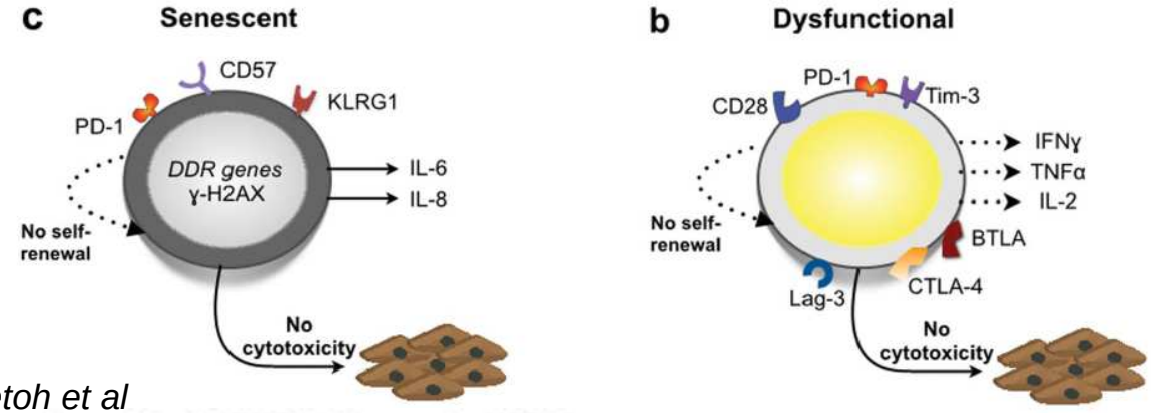


Palucka & Banchereau; Cell 2014

CD8+ T cells in tumor microenvironment



Palucka & Banchereau; Cell 2014



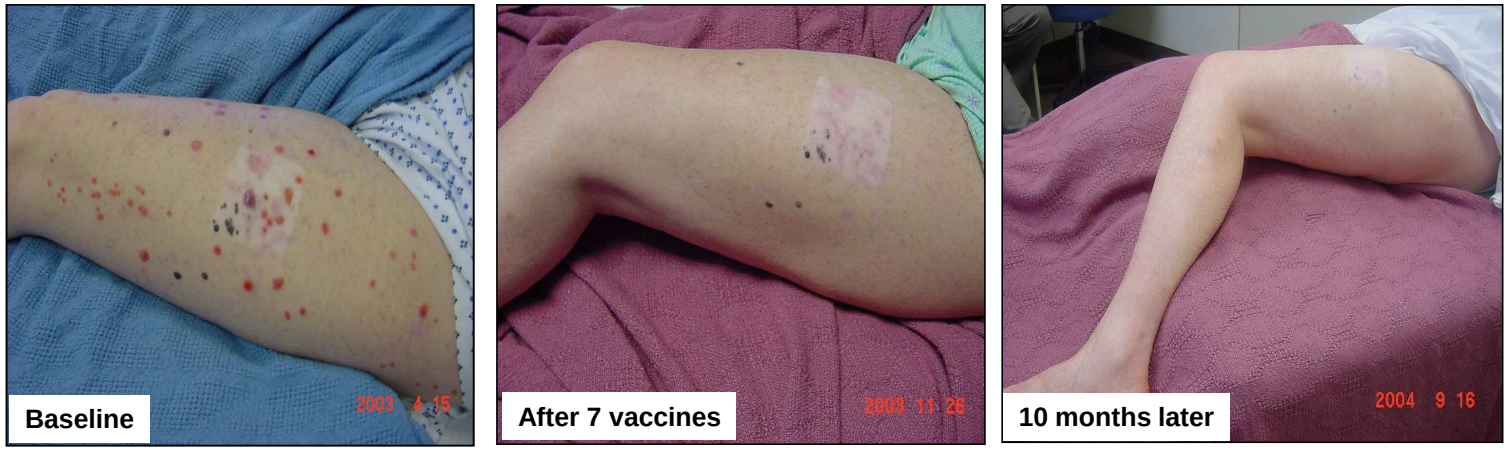
Apetoh et al

OncoImmunology 4:4, e998538; February 1, 2015;

EXAMPLES OF CLINICAL STUDIES WITH EX VIVO GENEREATED DC VACCINES:

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

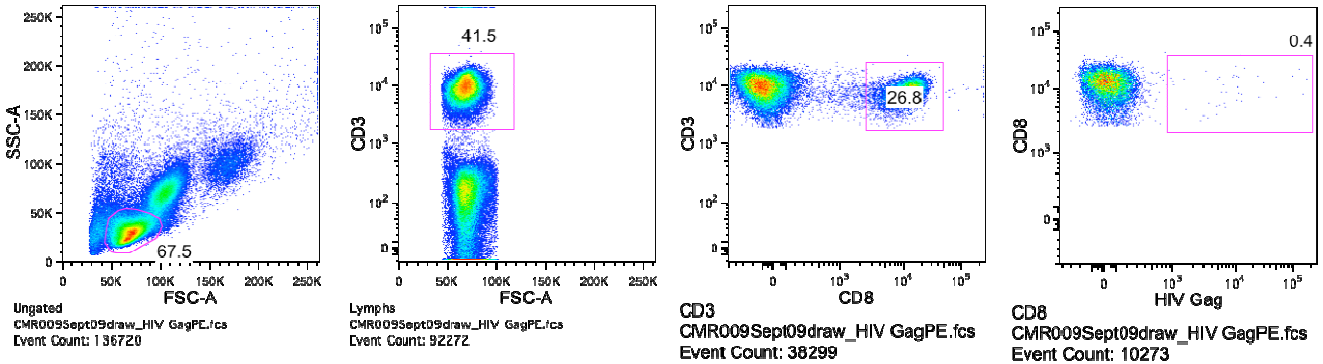
IND #10649, Baylor IRB #002-094



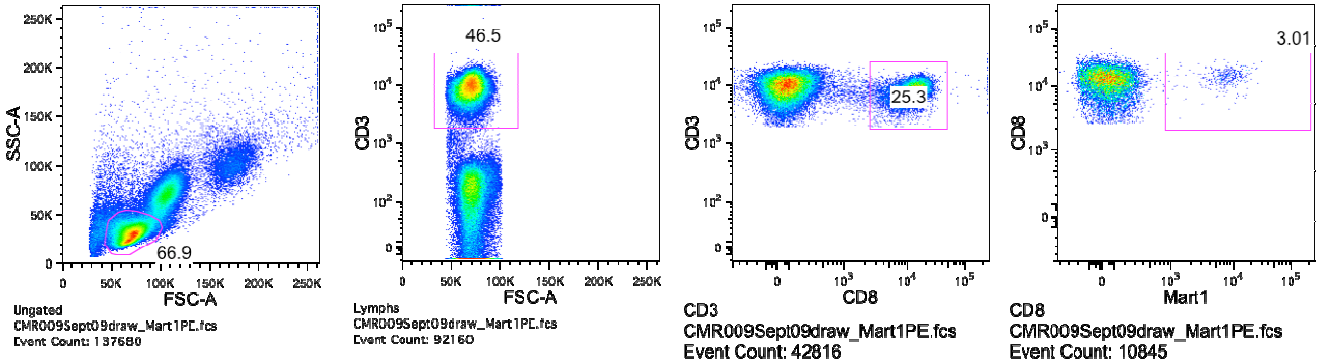
Palucka et al. J Immunotherapy 2006
Schuler et al; Dhodapkar et al; Kalinski et al; Butterfield et al; Coukos et al……

Vaccination via DCs can expand the frequency of circulating shared tumor antigen specific CD8+ T cells in

HIV Gag Tetramer



Mart-1 Tetramer



2009

Palucka et al, 2012

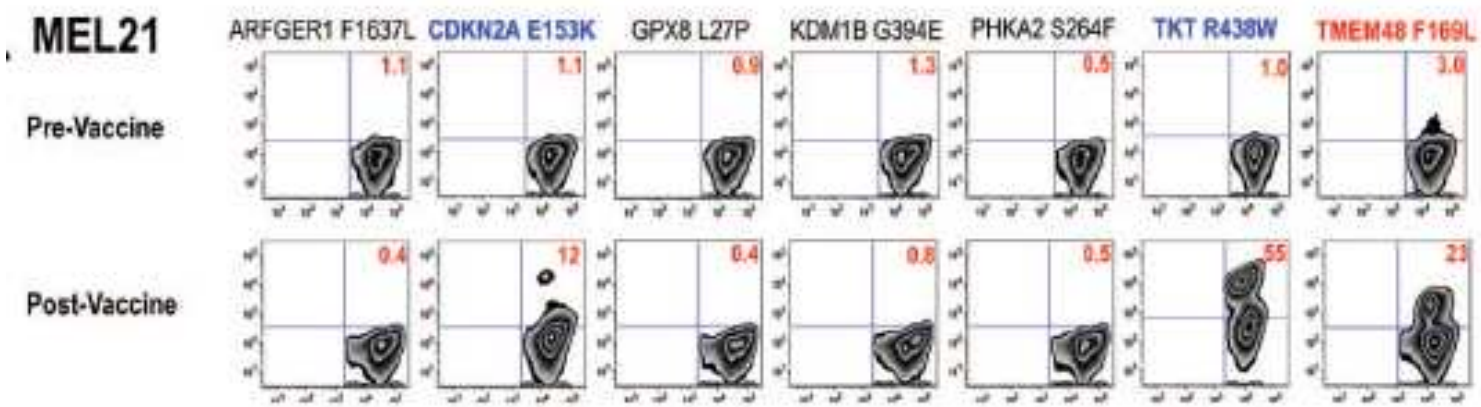
Some approaches to enhance efficacy

NATURE | LETTER
Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients

Duane A. Mitchell et al, Published online 11 March 2015

Pre-conditioning of vaccine site in patients with glioblastoma with either mature DCs or Td before vaccination with DCs pulsed with CMV pp65 RNA significantly improved survival

Loading DC vaccines with neo-antigens

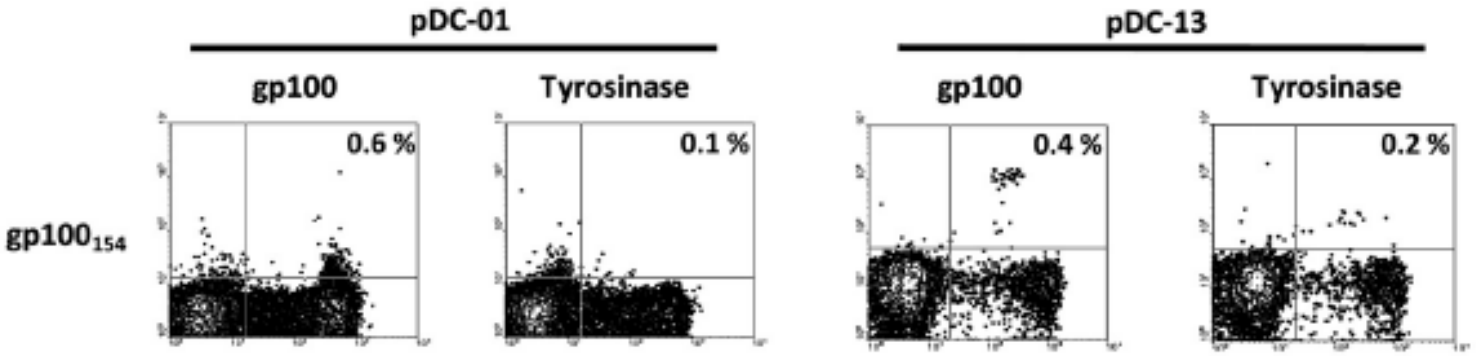


A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells

Beatriz M. Carreno,[1]* Vincent Magrini,[2] Michelle Becker-Hapak,[1] Saghar Kaabinejadian,[3] Jasreet Hundal,[2] Allegra A. Petti,[2] Amy Ly,[2] Wen-Rong Lie,[4] William H. Hildebrand,[3] Elaine R. Mardis,[2] Gerald P. Linette[1]

SCIENCE sciencemag.org 15 MAY 2015 • VOL 348 ISSUE 6236

Intranodal vaccination with blood DCs



Natural Human Plasmacytoid Dendritic Cells Induce Antigen-Specific T-Cell Responses in Melanoma Patients

Jurjen Tel[1], Erik H.J.G. Aarntzen[1,2], Tetsuro Baba[7], Gerty Schreibelt[1], Barbara M. Schulte[1], Daniel Benitez-Ribas[1], Otto C. Boerman[5], Sandra Croockewit[6], Wim J.G. Oyen[5], Michelle van Rossum[4], Gregor Winkels[8], Pierre G. Coulie[7], Cornelis J.A. Punt[2], Carl G. Figdor[1], and I. Jolanda M. de Vries[1,2,3]

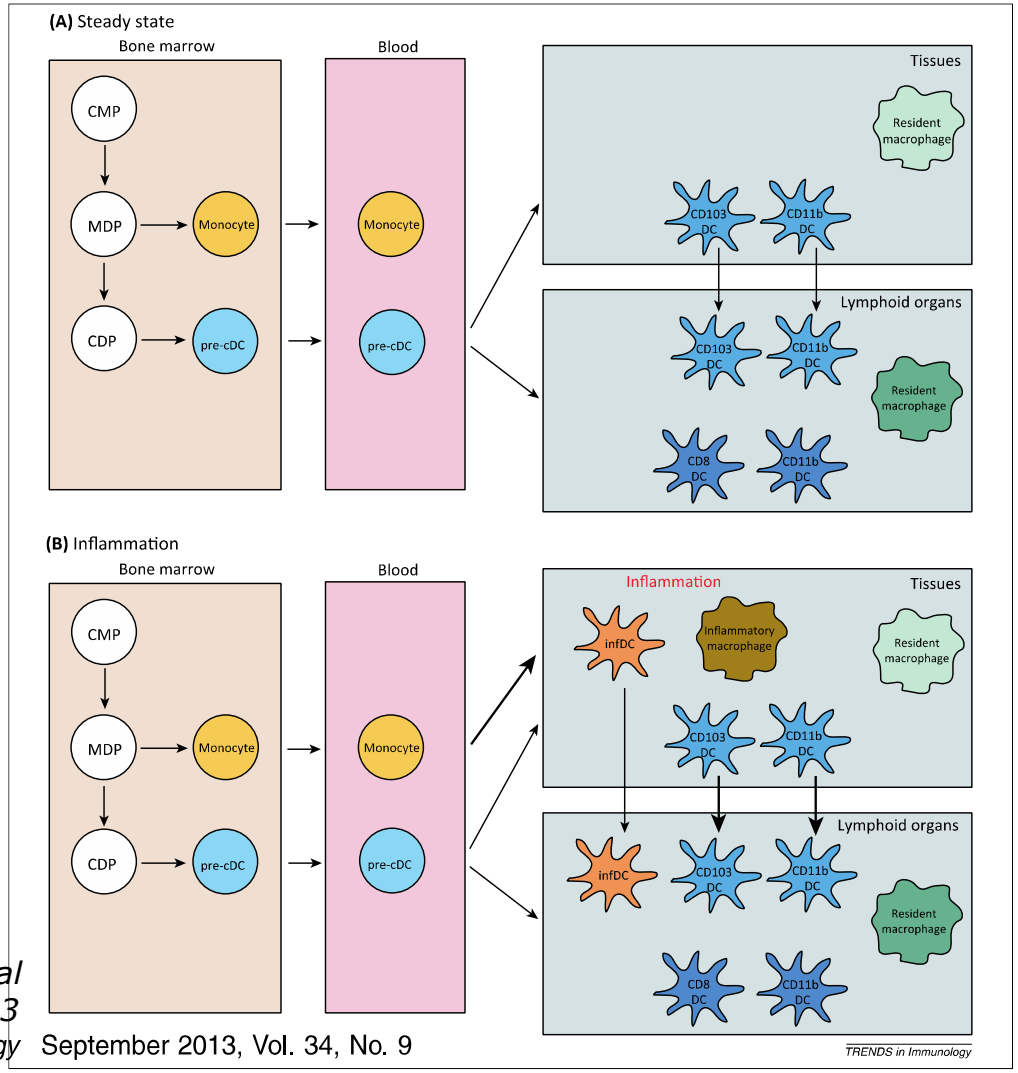
January 23, 2013; DOI: 10.1158/0008-5472.CAN-12-2583

The Human DC Compartment

	pDC	BDCA1$^+$ (CD1c)$^+$	BDCA3$^+$ (CD141)$^+$	LC	CD14$^+$	CD1a$^+$
Phenotype:	Lin$^-$ HLA-DR$^+$ CD11c^{low} CD1a$^-$ CD123^{hi} BDCA2$^+$ BDCA4$^+$	Lin$^-$ HLA-DR$^+$ CD11c$^+$ CD1a$^-$ BDCA1$^+$ BDCA3$^{+/-}$ CD11b^{low}	Lin$^-$ HLA-DR$^+$ CD11c$^+$ CD1a$^-$ BDCA1$^-$ BDCA3$^+$ CD11b^{low} CD141$^+$ Necl2$^+$ Xcr1$^+$ Clec9a$^+$ Dec205^{hi}	Lin$^-$ HLA-DR$^+$ CD11c$^+$ CD1a$^+$ CD14$^-$ BDCA1$^+$ Langerin$^+$ EpCAM$^+$ Sirpα$^+$ CD11b$^{+/-}$ E-cadherin$^+$	Lin$^-$ HLA-DR$^+$ CD11c$^+$ CD1a$^-$ CD14$^+$ BDCA1$^+$ Langerin$^-$ EpCAM$^-$ DC-SIGN$^+$ FXIIIa$^-$ CD163$^-$	Lin$^-$ HLA-DR$^+$ CD11c$^+$ CD1a$^+$ CD14$^-$ BDCA1$^+$ Langerin$^-$ EpCAM$^-$ Sirpα$^+$ CD11b^{hi}
PRRs:	TLR1$^+$, TLR2$^-$, TLR3$^-$, TLR4$^-$, TLR6$^+$, TLR7$^+$, TLR8$^-$, TLR9$^+$	ND	TLR1$^+$, TLR2$^+$, TLR3$^+$, TLR4$^-$, TLR6$^+$, TLR7$^-$, TLR8$^+$, TLR9$^-$	TLR1$^+$, TLR2$^+$, TLR3^{lo}, TLR4$^-$, TLR6$^+$, TLR7$^-$, TLR8$^-$, TLR9$^-$	ND	ND
Murine equivalent:	pDC	cDC	CD8$^+$ cDC	LC	ND	Dermal DC
Location:	Blood and lymphoid tissue			Epidermis	Dermis	
				Cutaneous tissue		

Merad et al. Annual Review of Immunology 2013

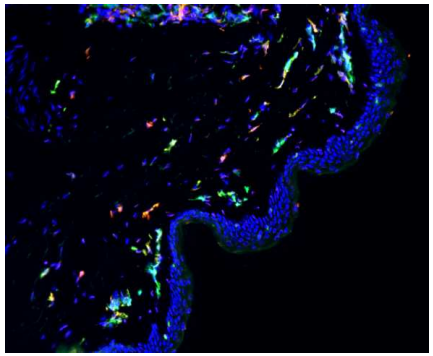
Human monocyte-derived DCs in vivo

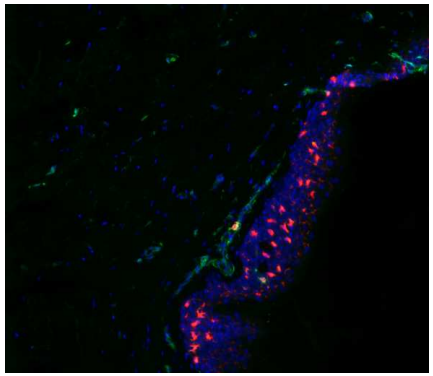


Amigorena et al
Immunity 2013

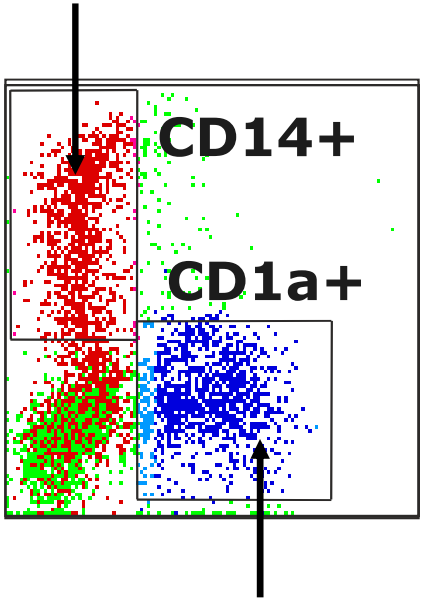
Trends in Immunology September 2013, Vol. 34, No. 9

Distinct Human Dendritic Cell Subsets in the skin





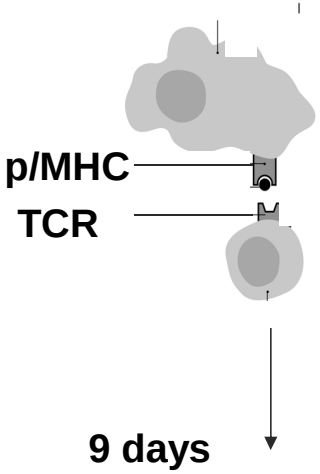
Human Dermal DCs – DC-SIGN positive



Human Langerhans Cells – Langerin positive

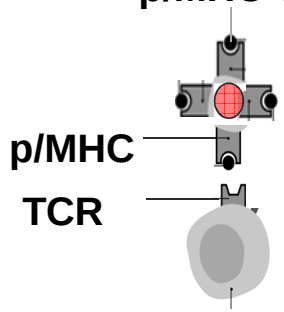
Caux et al, 1996,1997,1998

Langerhans Cells are More Efficient than CD14$^+$ Dermal-DCs in CD8$^+$ T Cell Priming

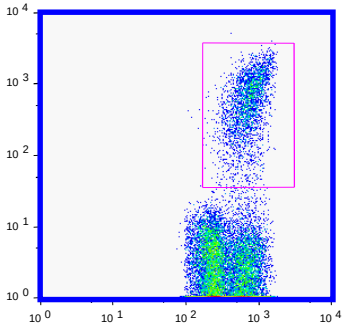


9 days

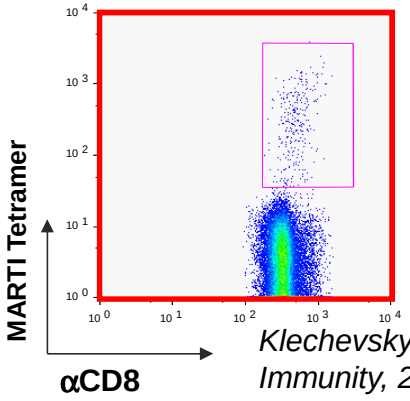
p/MHC Tetramer



LCs

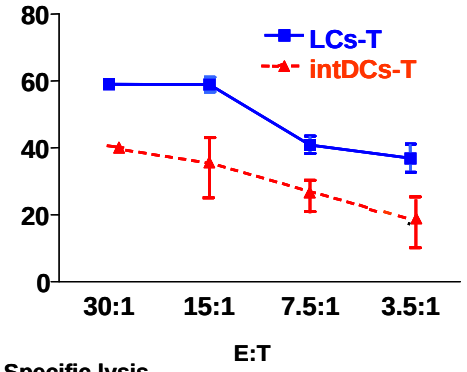


IntDCs



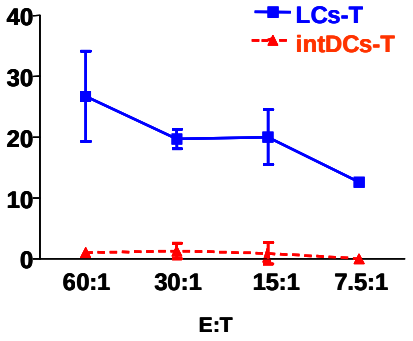
Klechevsky, Ueno, Immunity, 2008

Peptide-pulsed T2 cells

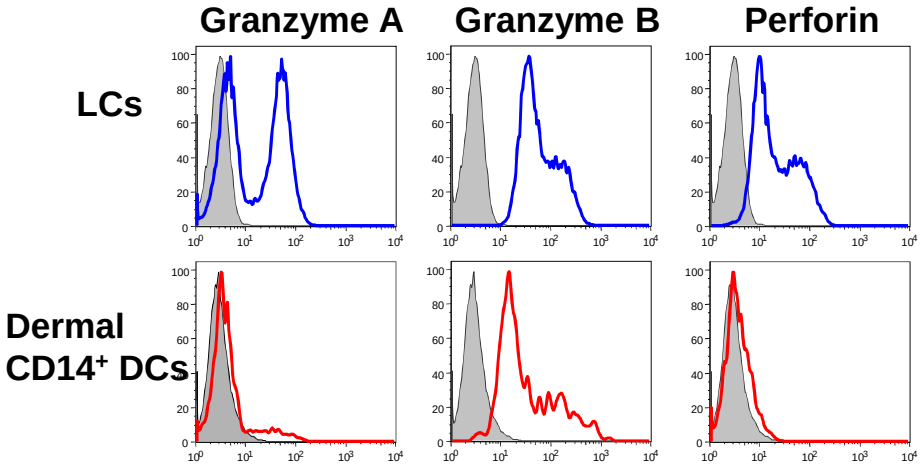


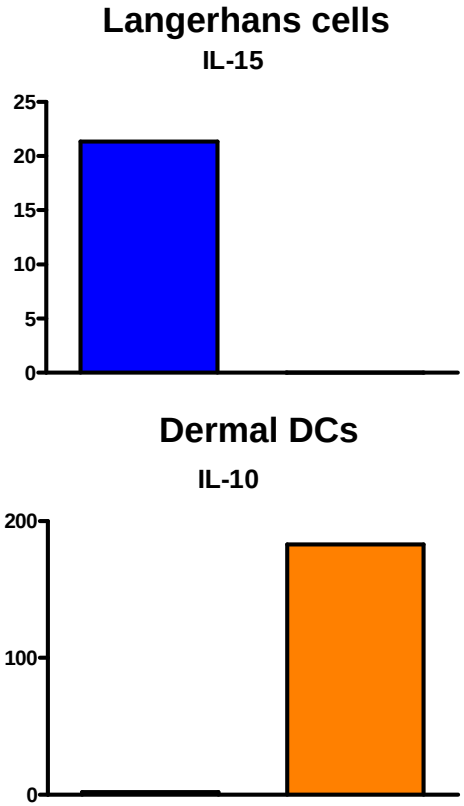
Specific lysis

HLA-A*0201+ melanoma cells



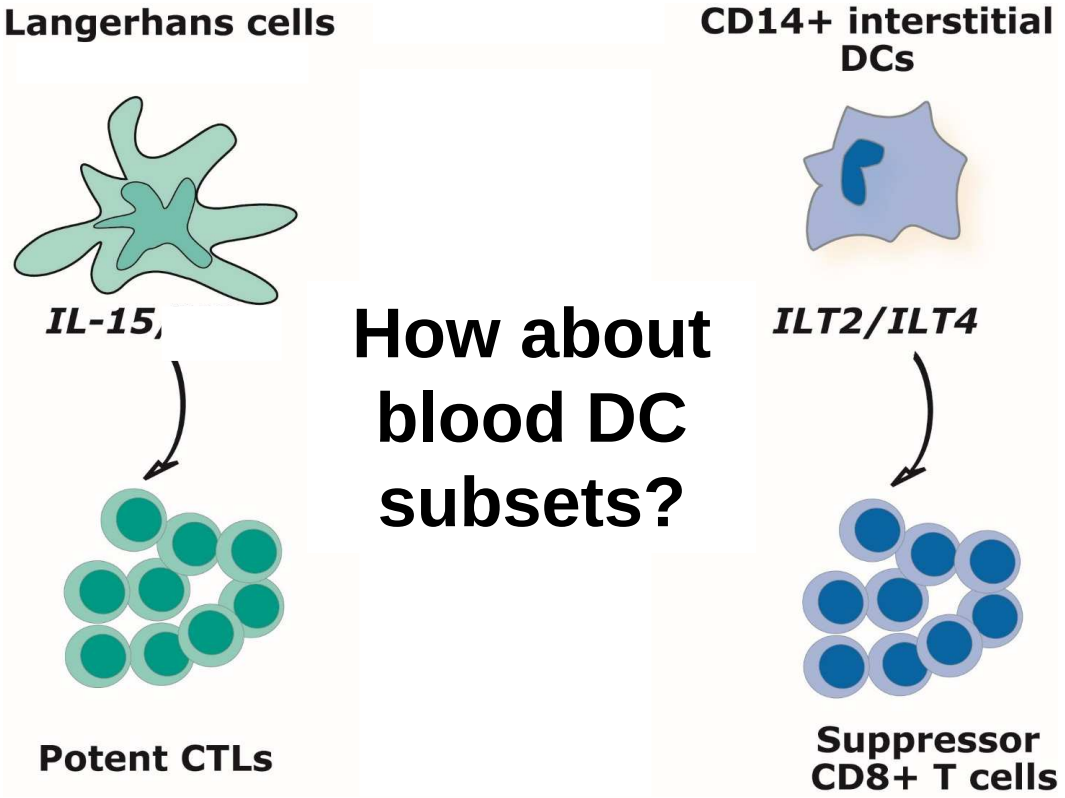
LCs and dermal DCs prime CD8^{+} T cells with distinct phenotypes





Klechevsky et al: Immunity, 2008
Banchereau et al: Blood, 2012
Banchereau, et al: PNAS, 2012

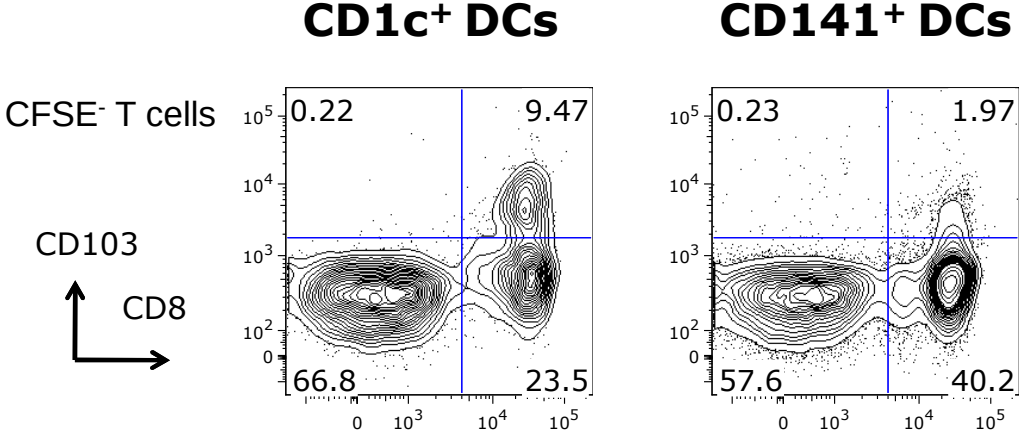
Distinct skin DC subsets elicit CD8^{+} T cells with distinct phenotypes



Palucka & Banchereau Curr Opin Immunol 2013

CD1c$^+$ DCs expand CD8$^+$ T cells expressing CD103 (receptor for E-cadherin), a marker of tissue resident T cells

LAIV 3 days

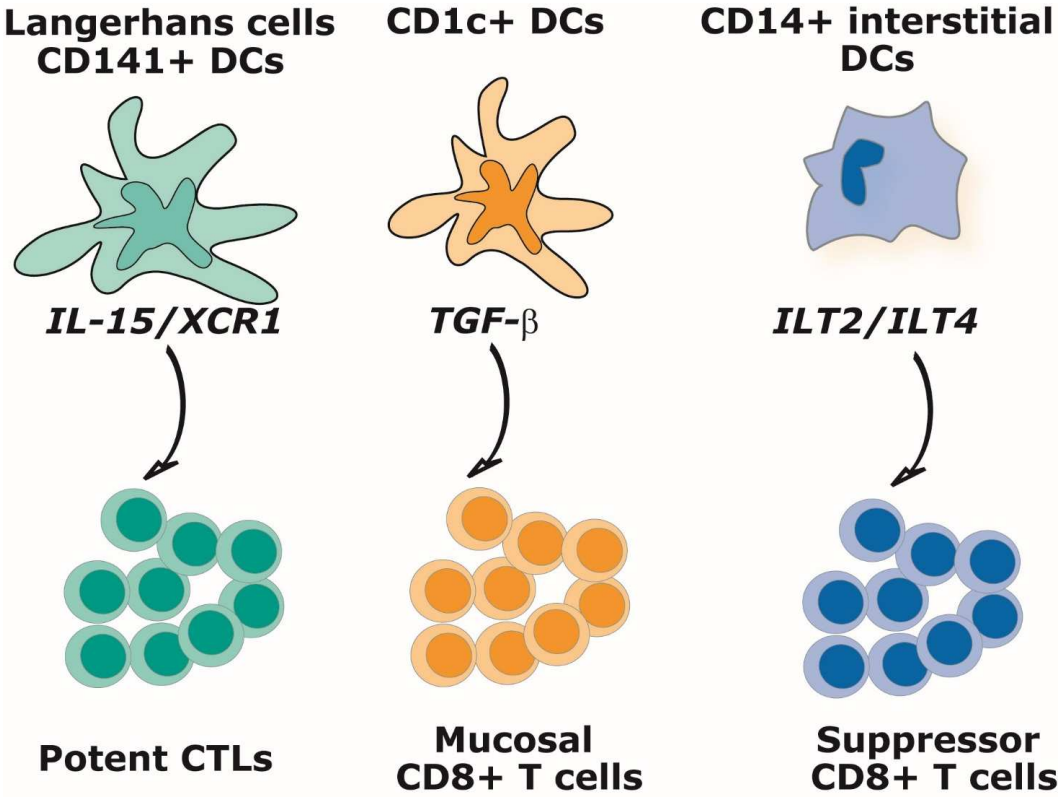


CD103/beta7 integrin enables peripheral CD8$^+$ T cells to reside in epithelial compartments (Sheridan and Lefrancois, 2011).

Human blood/lung DCs
Humanized mice lung/spleen DCs
In vitro & in vivo
Allogeneic and autologous systems

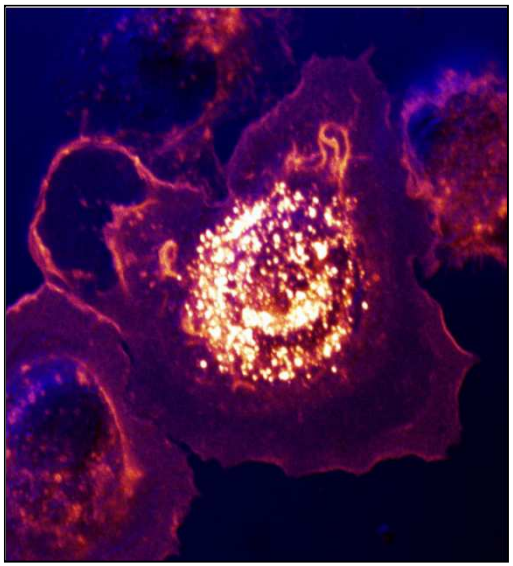
Yu….Palucka, Immunity, 2013

Distinct DC subsets control CD8+ T cell immunity



Palucka & Banchereau Curr Opin Immunol 2013

The type of DC maturation impacts T cell immunity

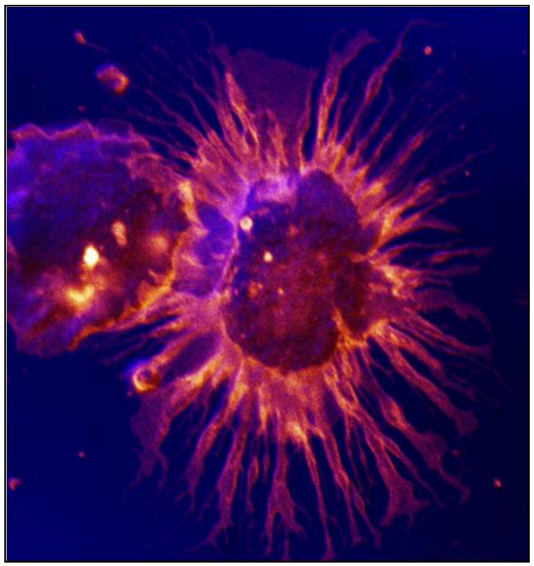


Microbial Products /Adjuvants

Tissue damage

Cells of innate immunity

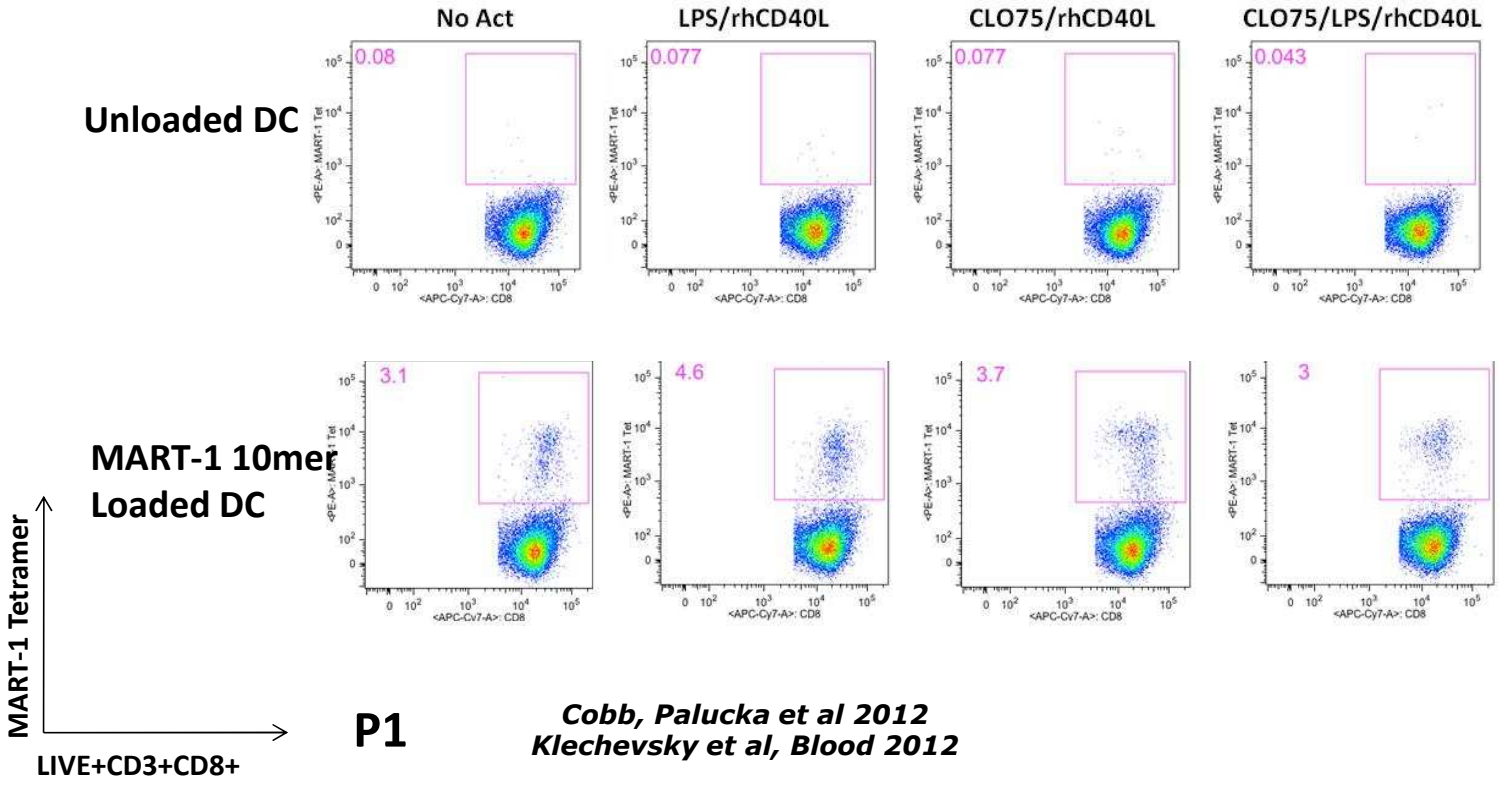
Cells of adaptive Immunity



Immature DC → **Mature DC**

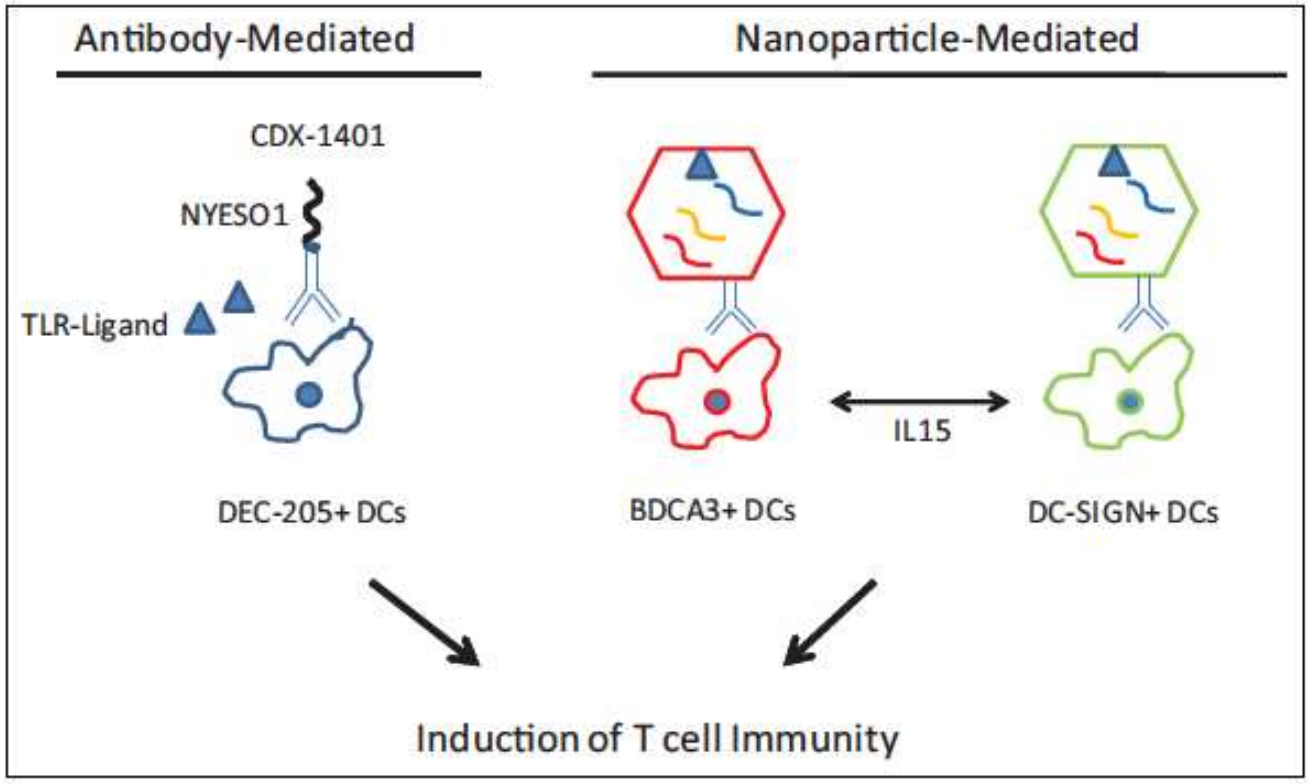
Steinman and Melman
Banchereau et al
Kalinski et al (Th1/Th2)

Optimizing CD8+ T cell immunity: TLR8/TLR4/CD40 activation of DCs allows selection of high avidity melanoma-specific CD8+ T cells in vitro



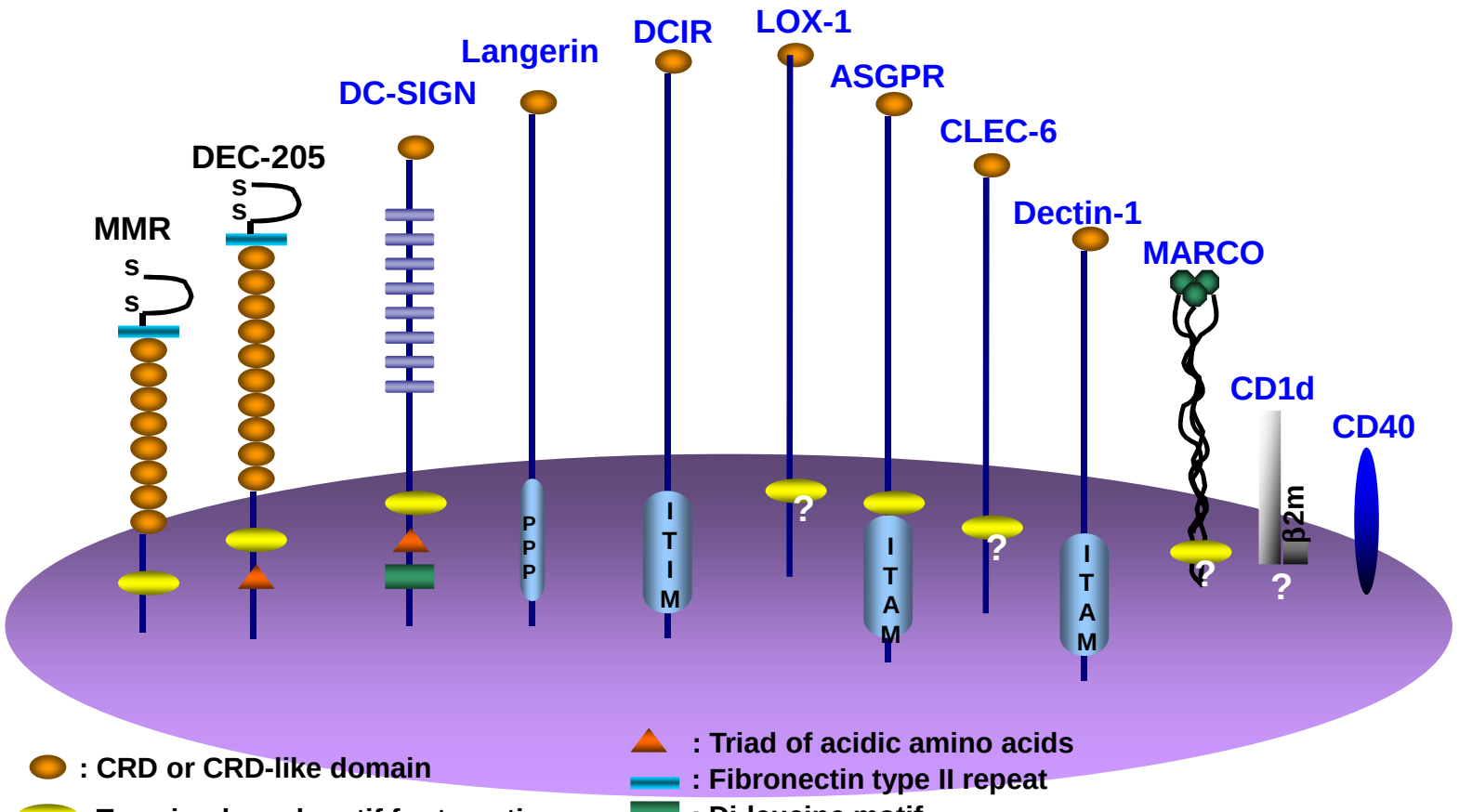
Cobb, Palucka et al 2012
Klechevsky et al, Blood 2012

Emerging strategies for DC targeting in vivo



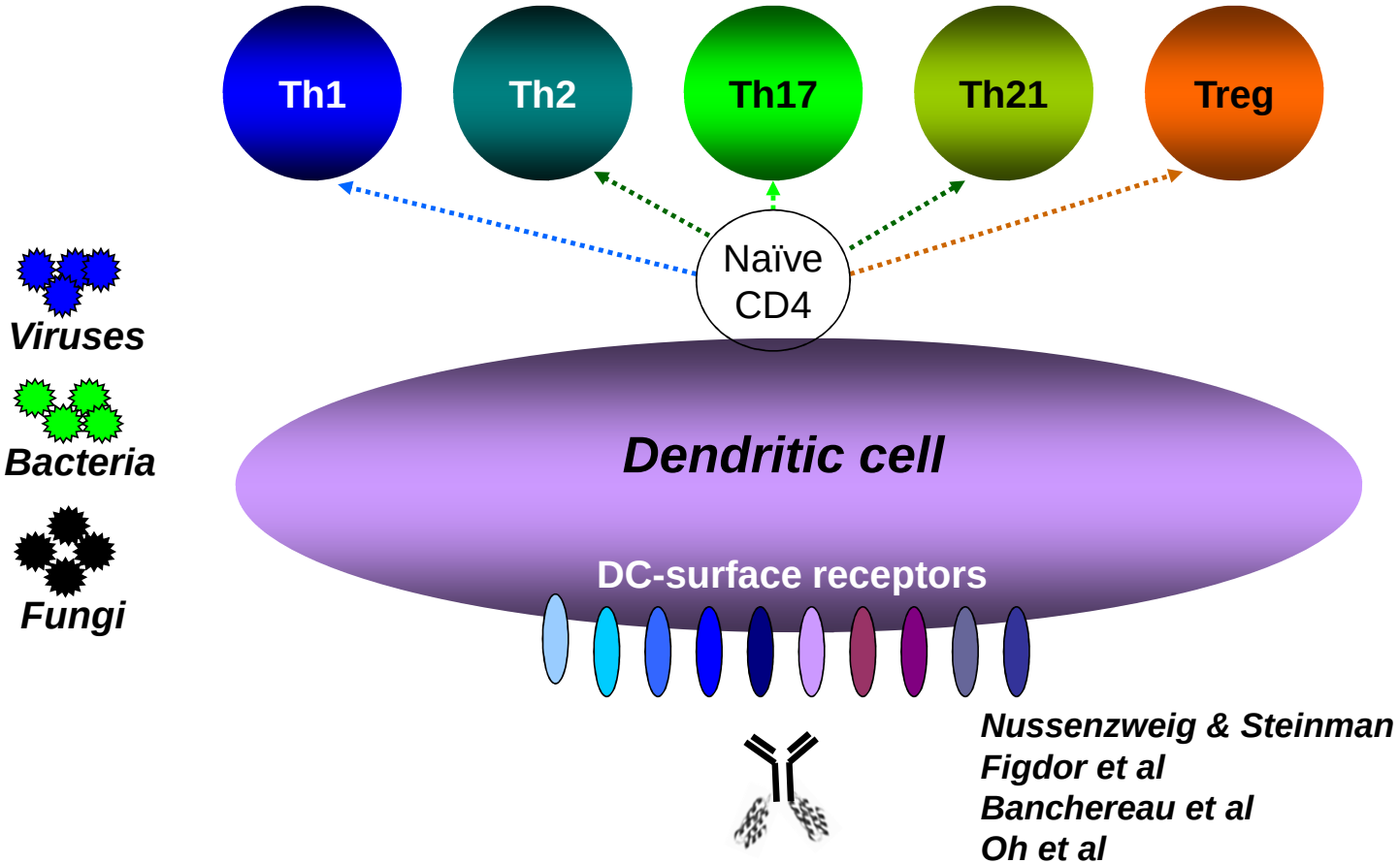
To cite this article: Madhav V Dhodapkar & Kavita M Dhodapkar (2014) Recent advances and new opportunities for targeting human dendritic cells in situ, OncoImmunology, 3:8, e954832, DOI: 10.4161/21624011.2014.954832

Targeting DCs in vivo



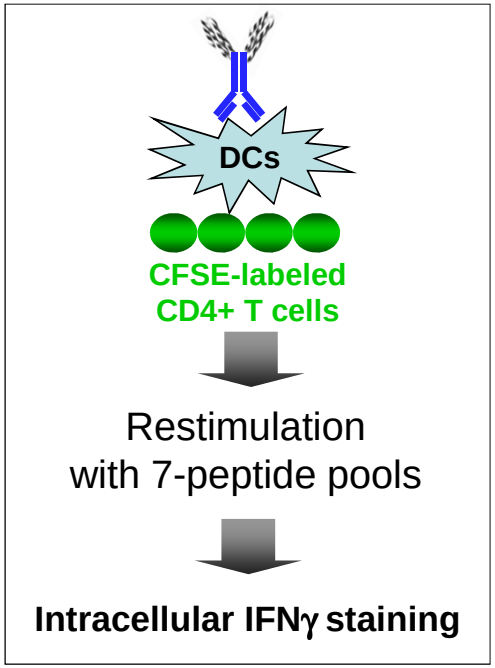
Nussenzweig & Steinman
Figdor et al
Dhodapkar et al

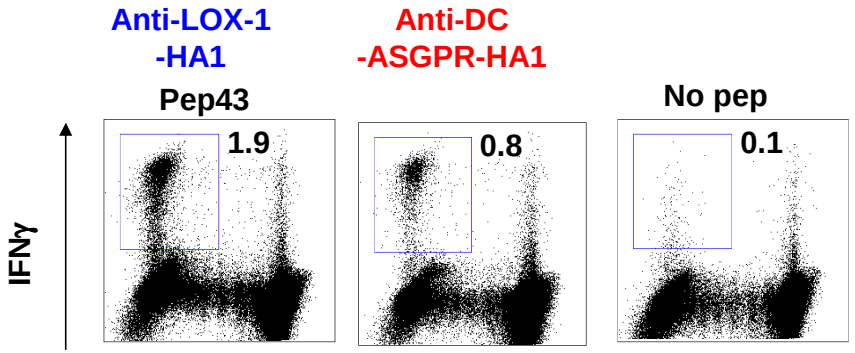
Not All DC Receptors are Equal!



Nussenzweig & Steinman
Figdor et al
Banchereau et al
Oh et al

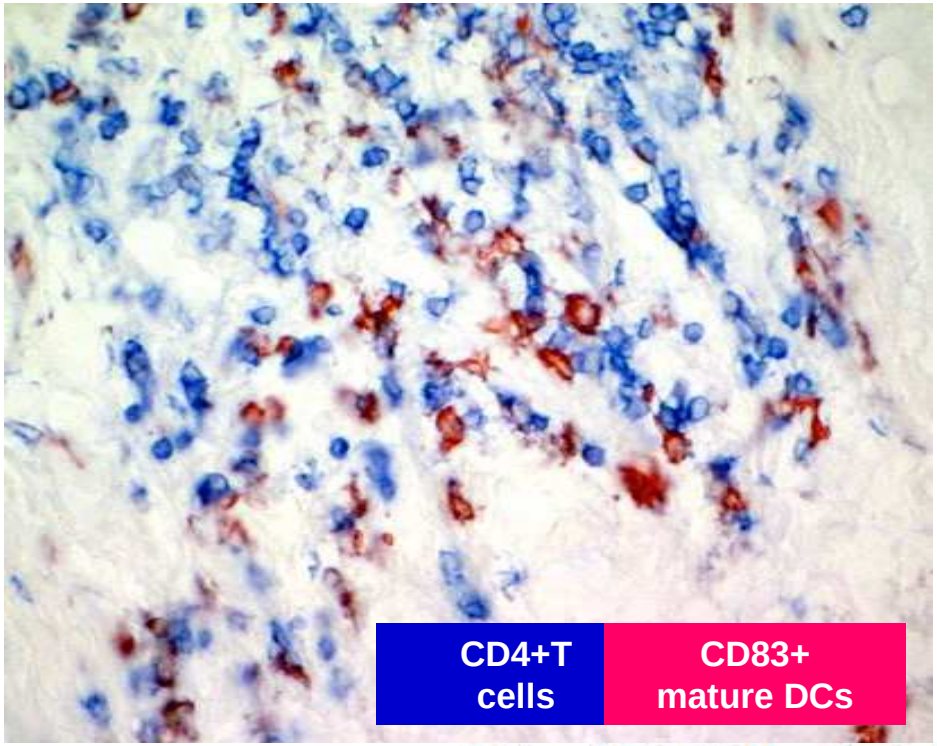
Targeting DCs via distinct lectins leads to distinct types of immune responses





Oh et al, J Exp Med 2012

DCs as organizers of tumor microenvironments



J. Exp. Med. © The Rockefeller University Press
Volume 190, Number 10, November 15, 1999
http://www.jem.org

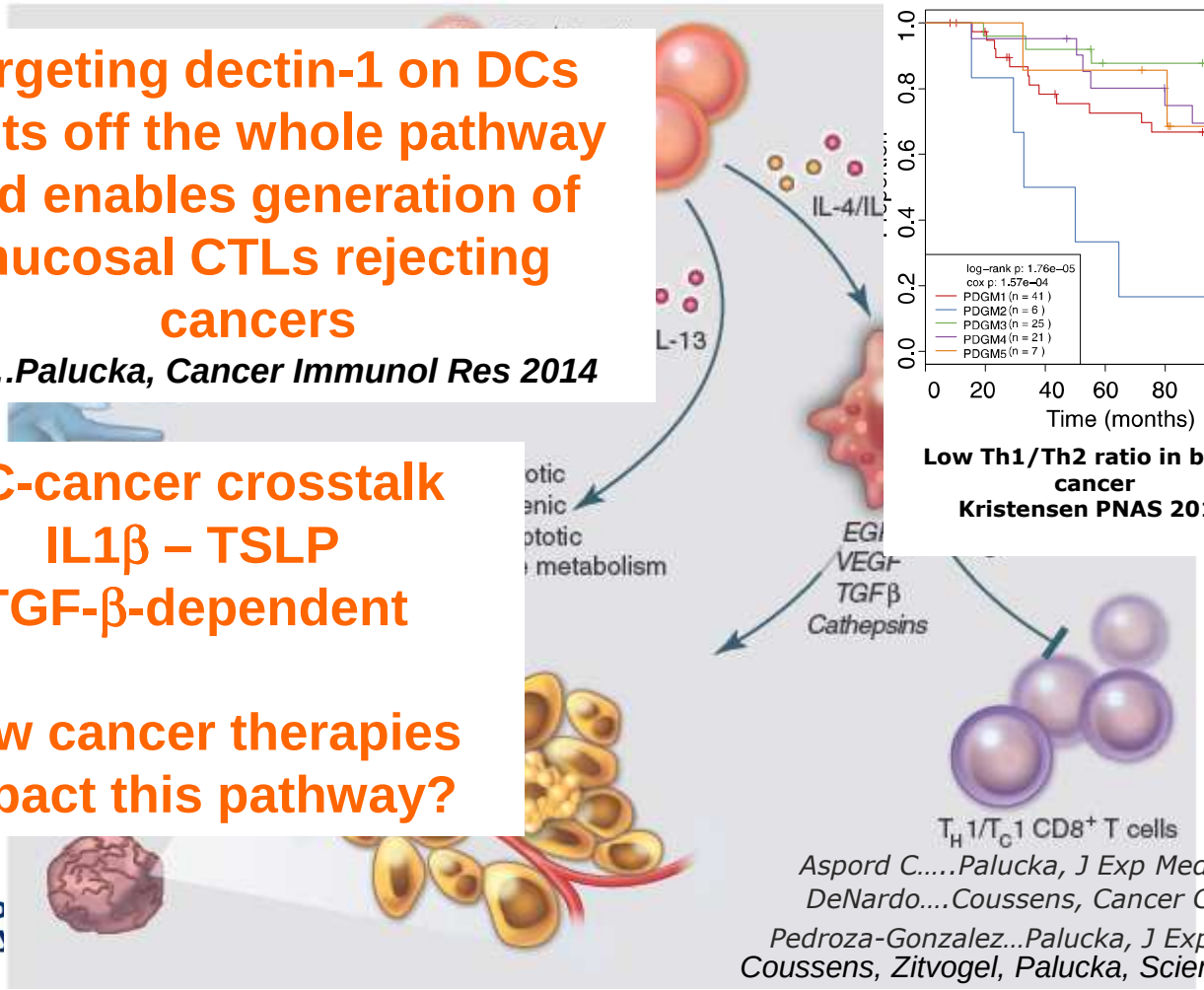
Tumors subvert dendritic cells to orchestrate tumor promoting inflammation

Targeting dectin-1 on DCs shuts off the whole pathway and enables generation of mucosal CTLs rejecting cancers

Wu….Palucka, Cancer Immunol Res 2014

DC-cancer crosstalk
IL1β – TSLP
TGF-β-dependent

How cancer therapies impact this pathway?

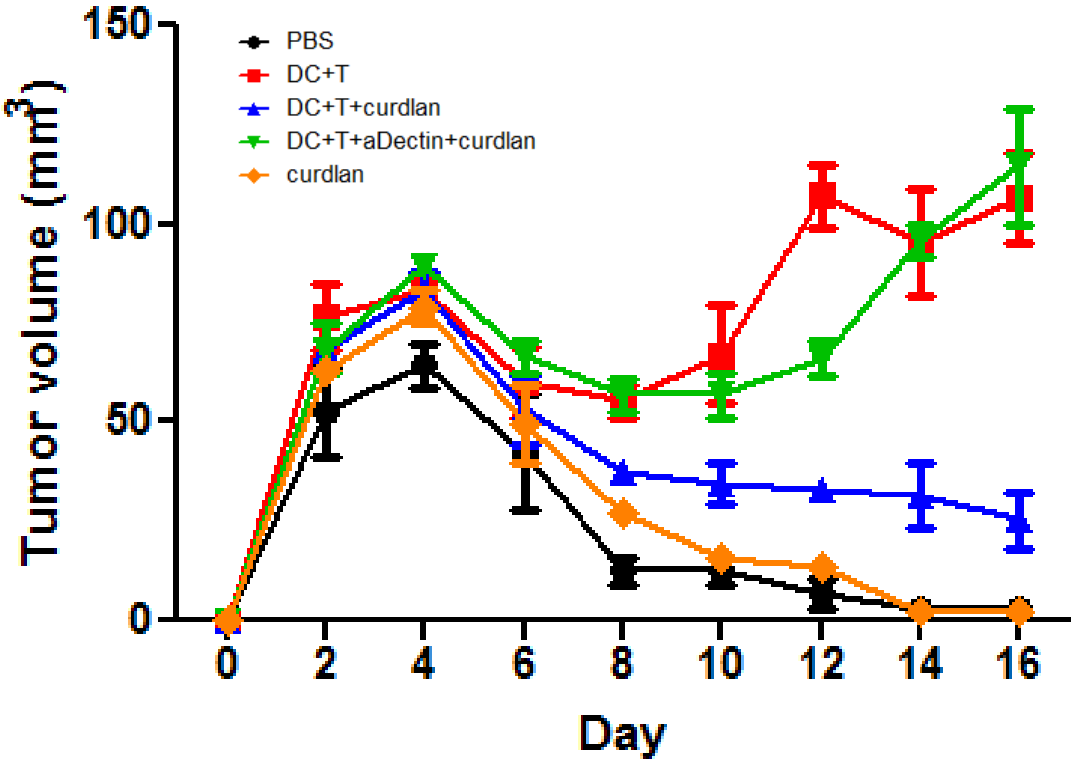


Low Th1/Th2 ratio in breast cancer
Kristensen PNAS 2012

Aspord C…..Palucka, J Exp Med 2007
DeNardo….Coussens, Cancer Cell 2009
Pedroza-Gonzalez…Palucka, J Exp Med 2011
Coussens, Zitvogel, Palucka, Science 2013

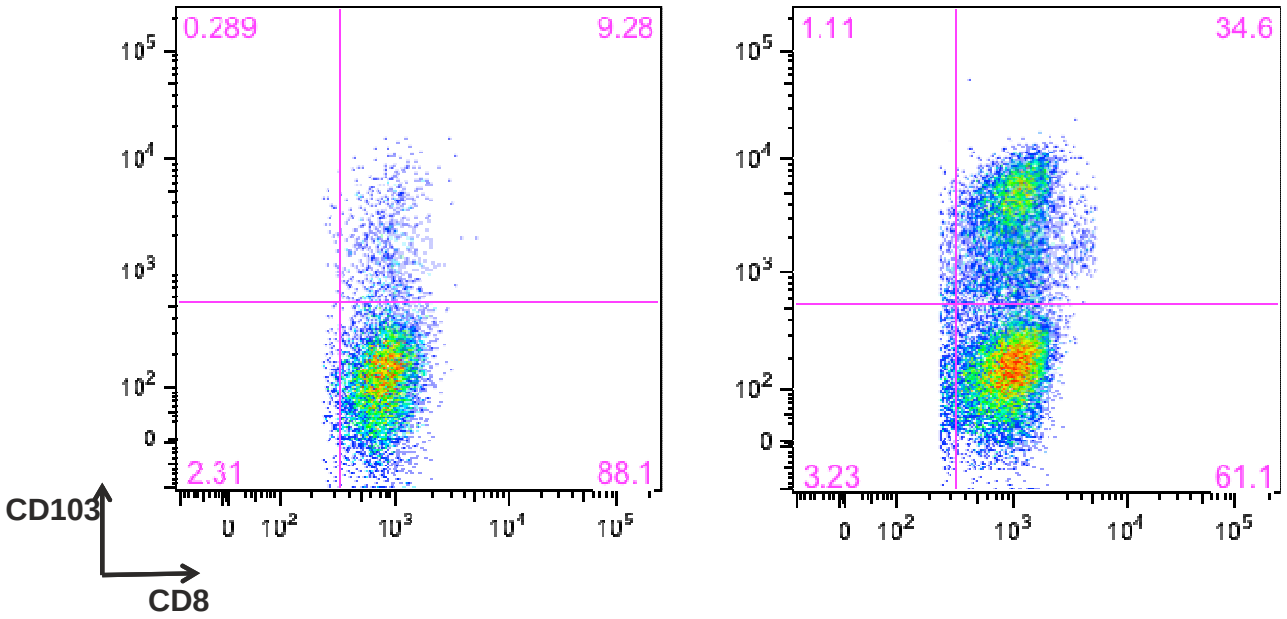
The Jackson Laboratory

β-glucan blocks tumor growth in vivo via Dectin-1, DC surface lectin



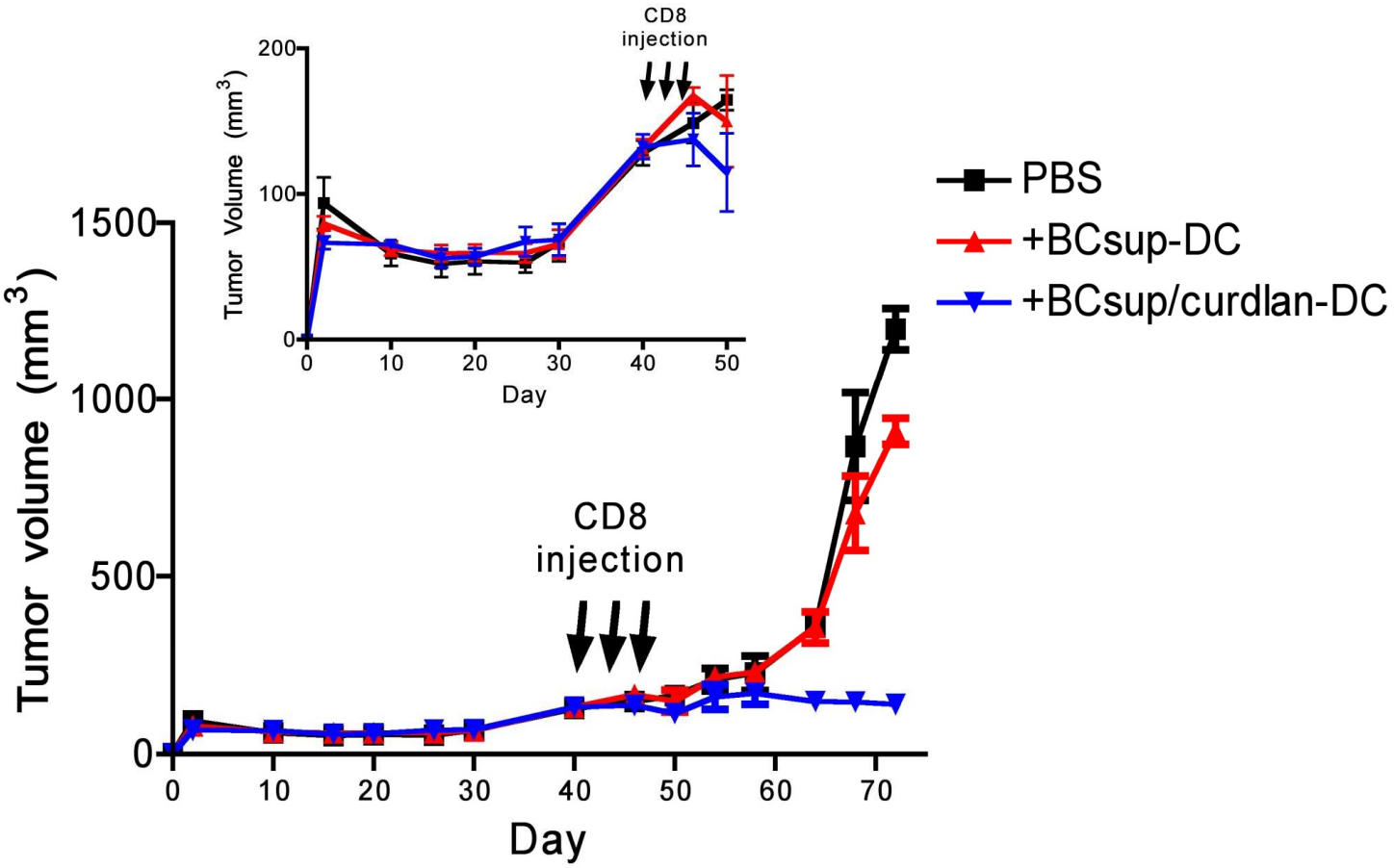
Wu Te-Chia.....Palucka, Cancer Immunol Res 2013

β-glucan-treated tumors show CD8+ T cells expressing CD103, a marker of mucosal T cells



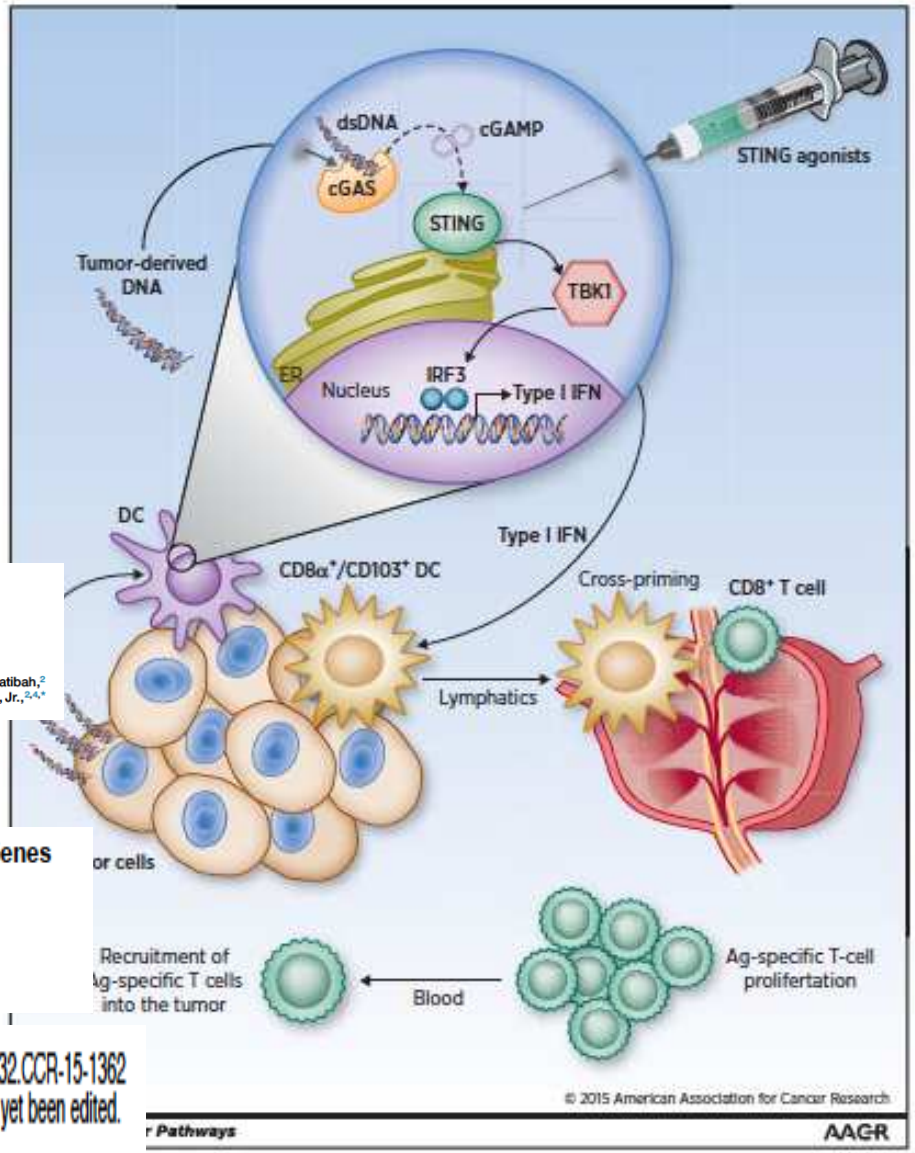
Wu Te-Chia.....Palucka, Cancer Immunol Res 2013

CD8 T cells elicited by β-glucan-treated mDCs reject established tumors



Wu Te-Chia.....Palucka, Cancer Immunol Res 2013

Targeting cytosolic nucleic acid sensors



Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity

Leticia Corrales,[1,2] Laura Hix Glickman,[2,3] Sarah M. McWhirter,[2] David B. Kanne,[2] Kelsey E. Sivick,[2] George E. Katibah,[2] Seng-Ryong Woo,[1] Edward Lemmens,[2] Tamara Banda,[2] Justin J. Leong,[2] Ken Metchette,[2] Thomas W. Dubensky, Jr.,[2,4,*] and Thomas F. Gajewski[1,4,*]

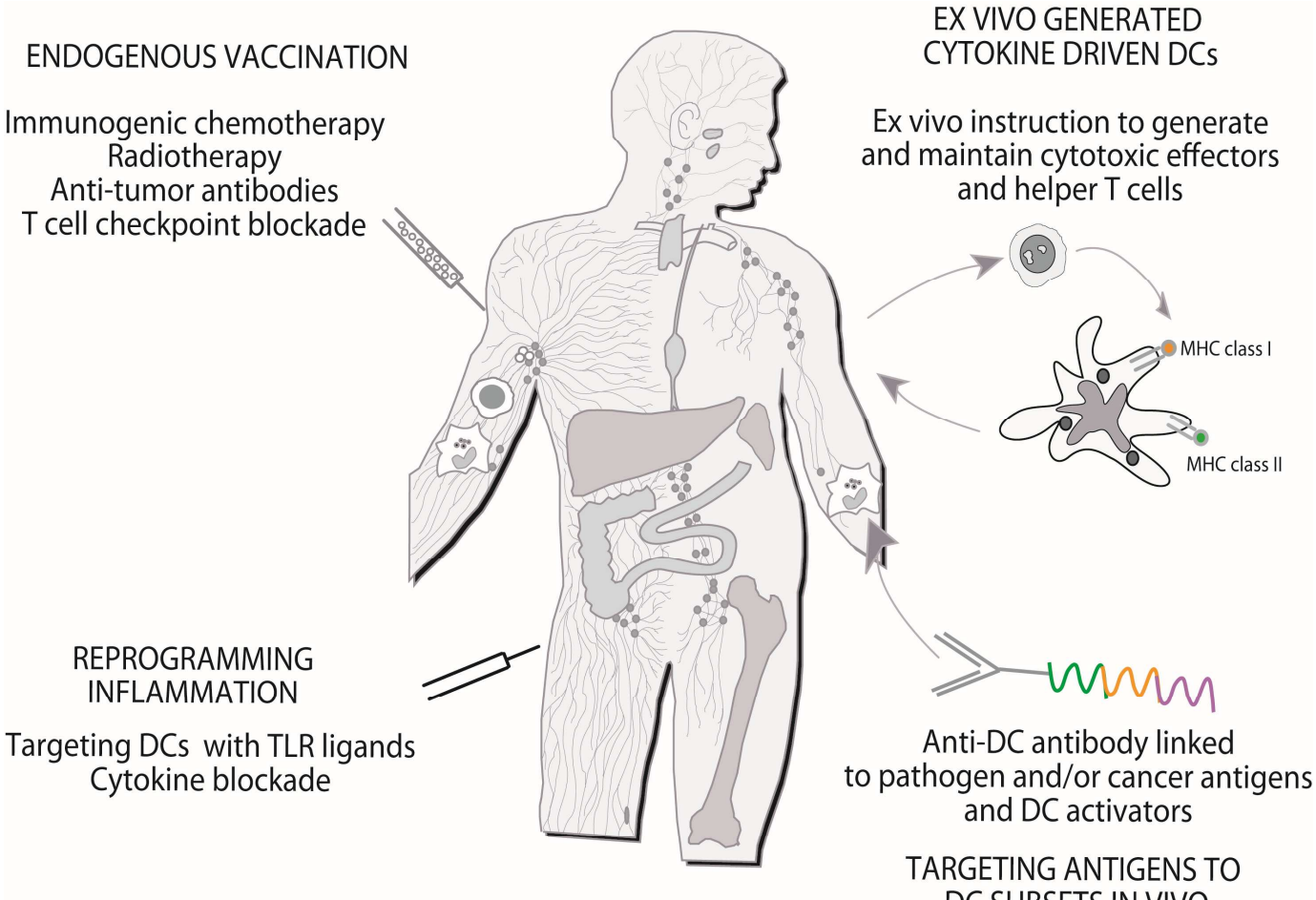
Cell Reports *11*, 1018–1030, May 19, 2015

Molecular Pathways: Targeting the Stimulator of Interferon Genes (STING) in the Immunotherapy of Cancer

Leticia Corrales[1] and Thomas F. Gajewski[1,2]

Author Manuscript Published OnlineFirst on September 15, 2015; DOI: 10.1158/1078-0432.CCR-15-1362
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Cancer immunotherapy via dendritic cells



Palucka & Banchereau, Nat Rev Cancer 2012, Curr Opin Immunol 2013, Immunity 2013, Cell 2015

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Lenny Shultz
Jim Keck
Susie Airhart
Carol Bult
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Scientific Organizers:
A. Karolina Palucka | Hyam I. Levitsky | Laurence Zitvogel
Discounted Abstract Deadline: Nov 5, 2015
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Abstract Deadline: Dec 8, 2015
Discounted Registration Deadline: Jan 7, 2016
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