

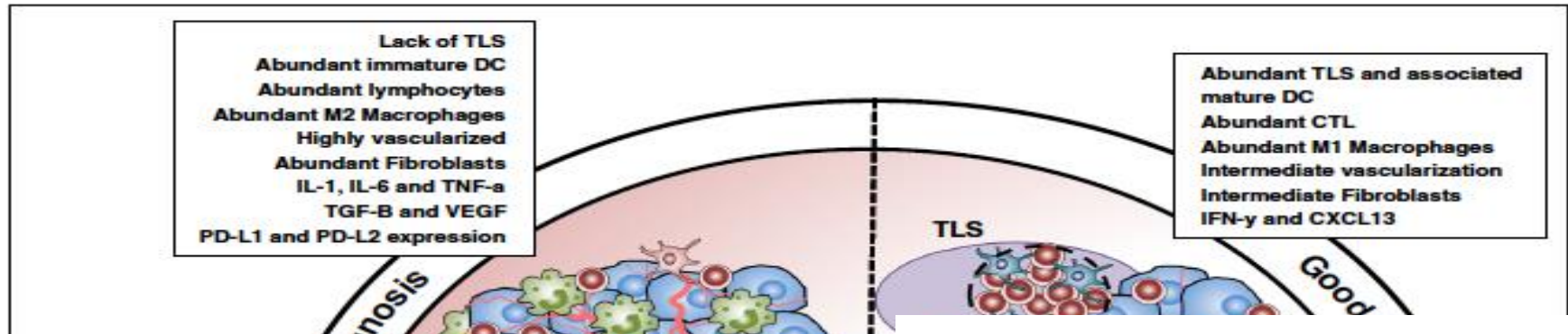
Dendritic cells and antigen presentation

Karolina Palucka, MD, PhD

**The Jackson Laboratory for Genomics Medicine
Farmington, CT**

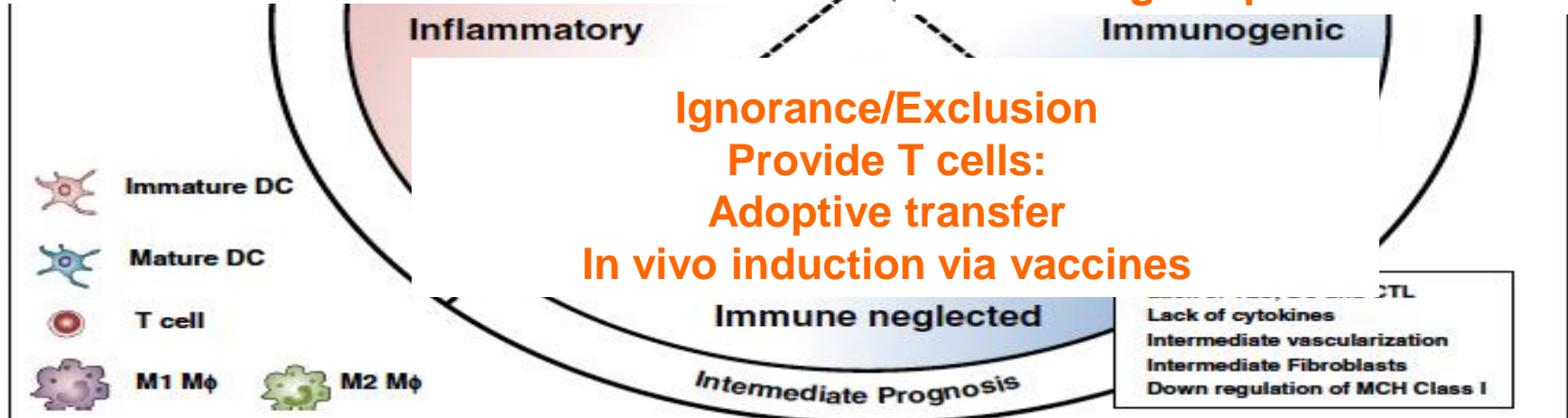
**SITC Primer
November 2017**

No relevant disclosures

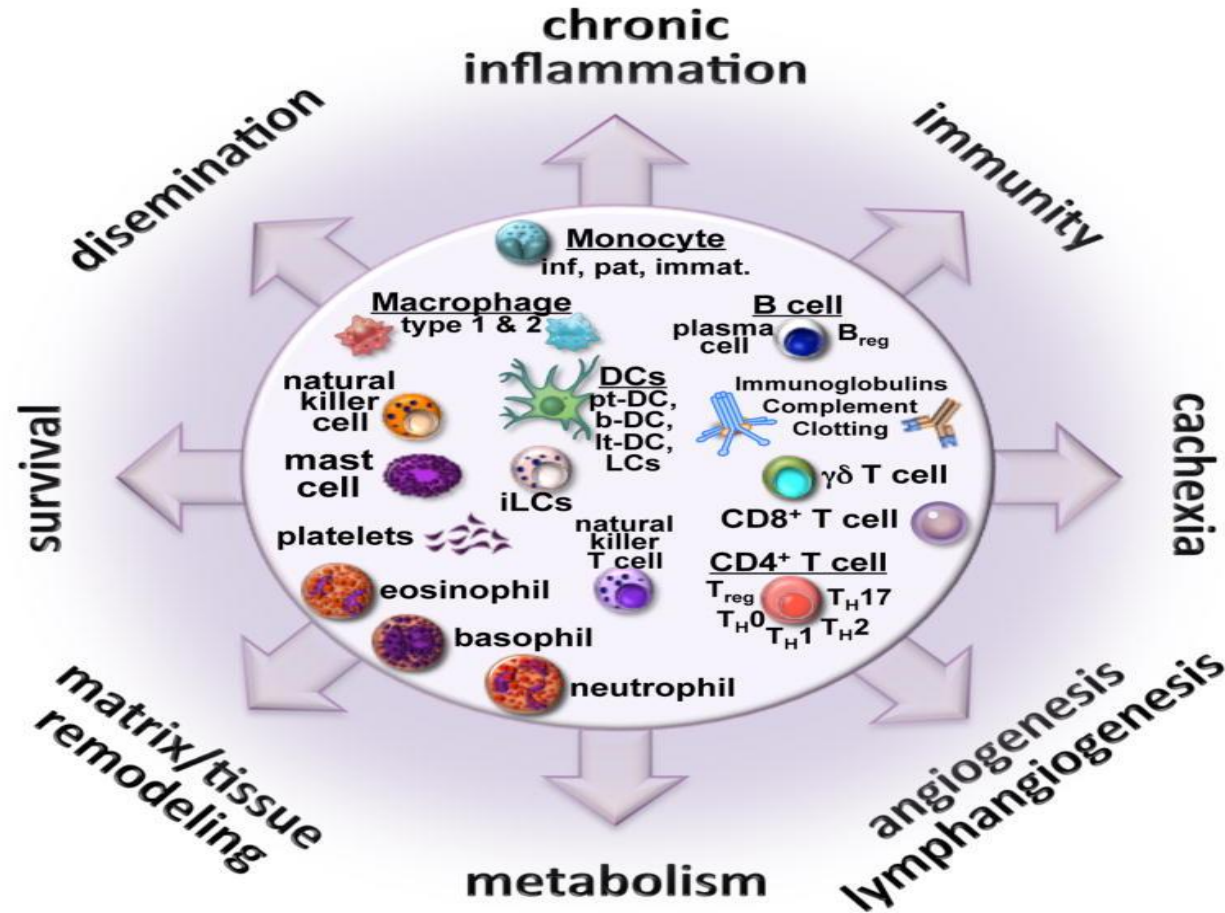


Reprogramming of immune cells in TEM
Endogenous vaccination

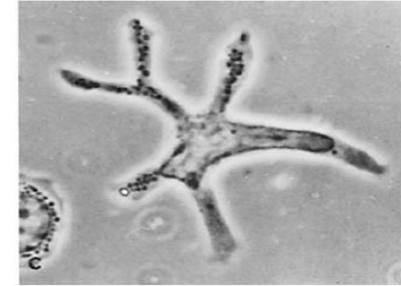
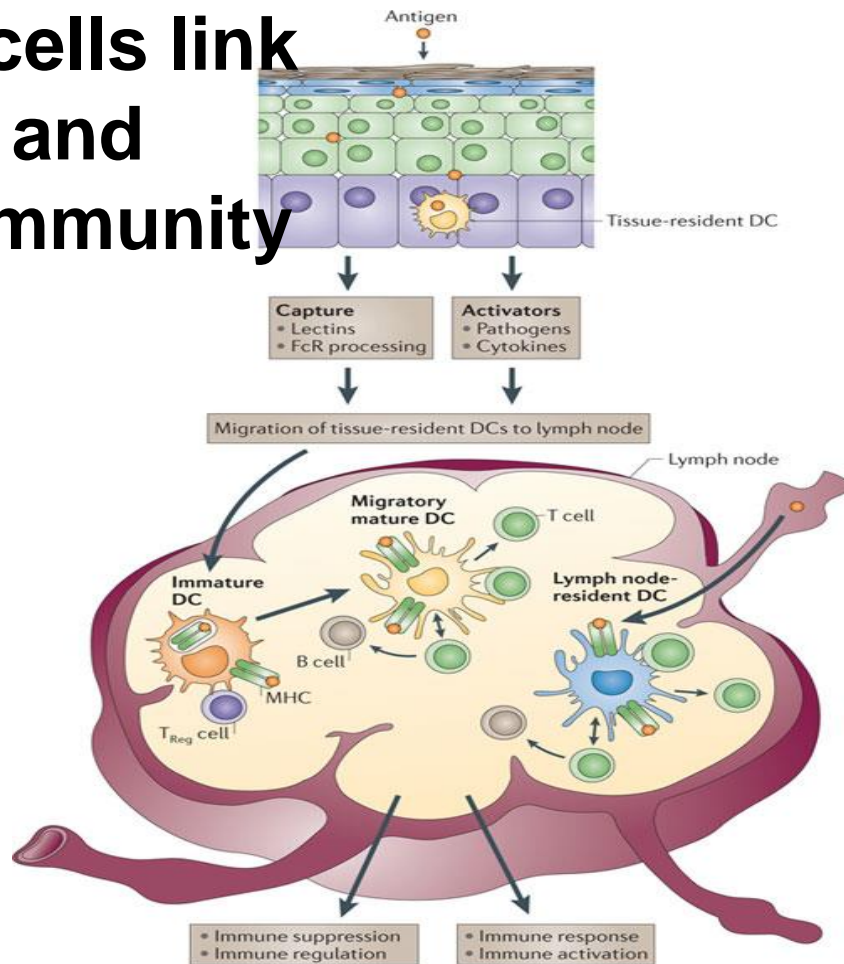
Checkpoint inhibitors
Boost T cell function
Overcoming adaptive resistance



Myeloid cells organize tumor microenvironments

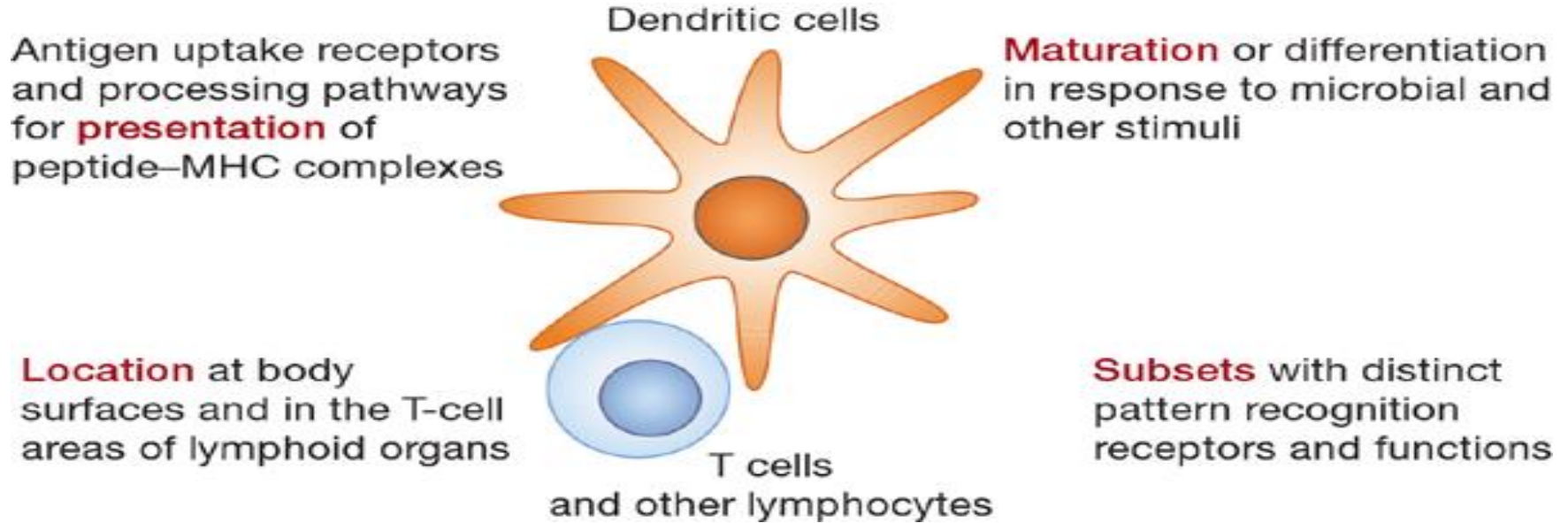


Dendritic cells link the innate and adaptive immunity



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

Features of dendritic cells critical for priming of immune responses



***Steinman & Banchereau
Nature 2007***

Dendritic cells are professional antigen presenting cells that launch CD4 T cell immunity

Internalization
of antigen
into APC

Antigen
processing

Processing generates
multiple peptides,
one of which can bind
to class II allele

T cells
respond to
immunodominant
peptide epitope

Multiple possible
epitopes

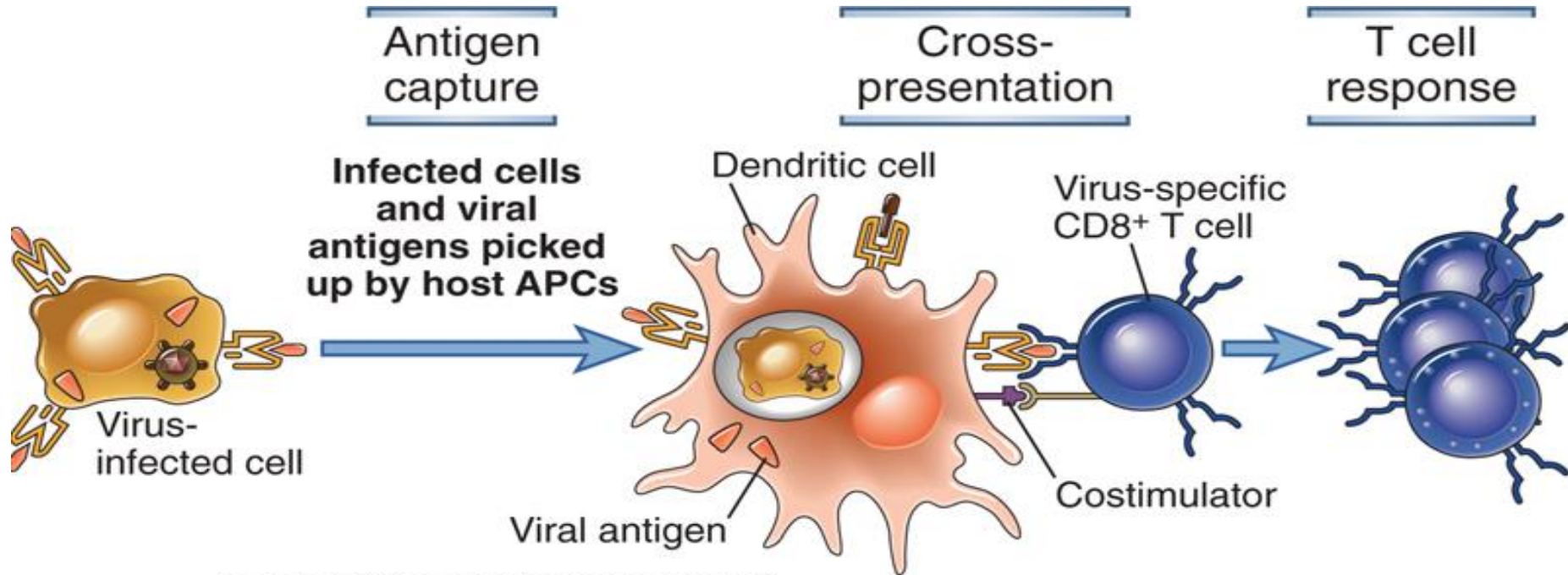
Immunodominant
epitope

CD4⁺
T cell

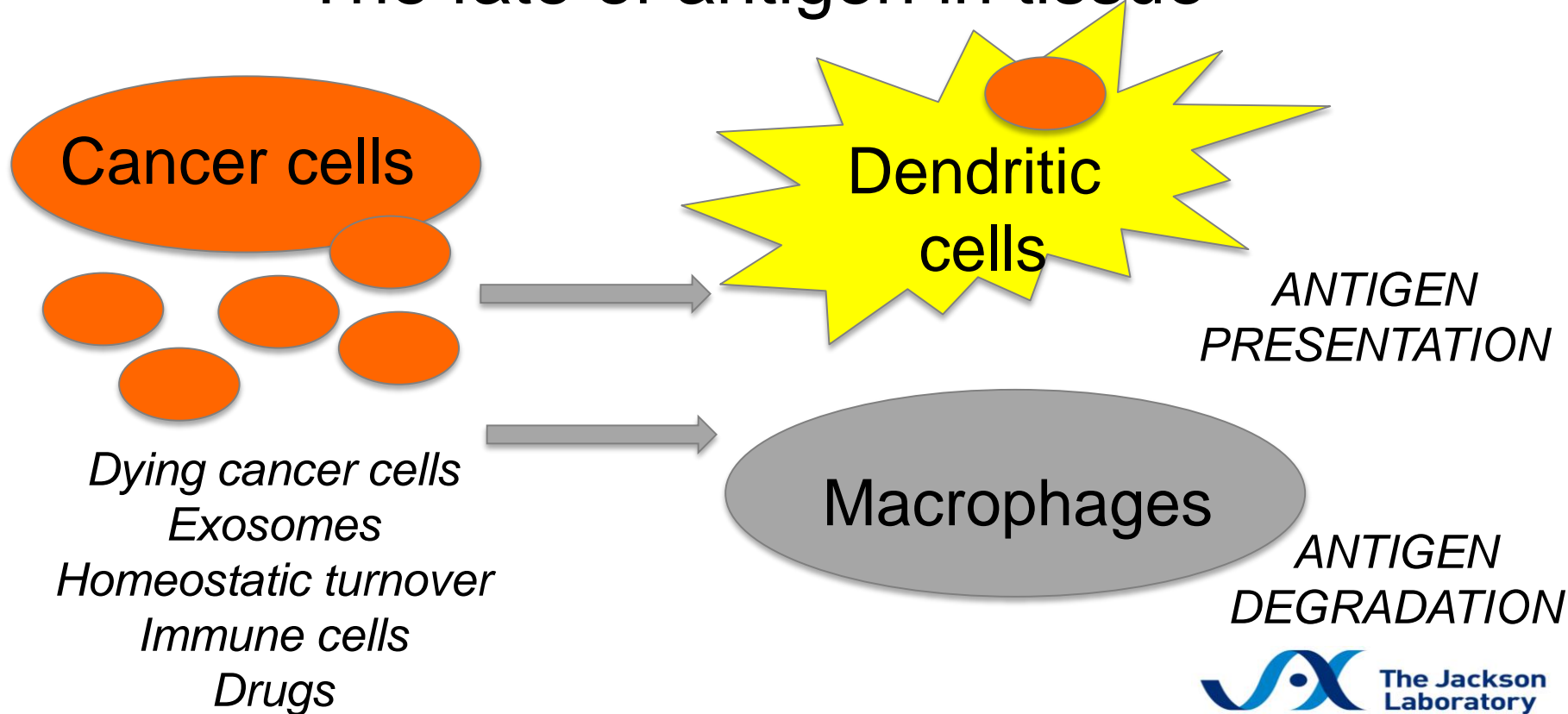
Abbas et al: Cellular and Molecular Immunology, 7e.

Copyright © 2012, 2007, 2005, 2003, 2000, 1997, 1994, 1991 by Saunders, an imprint of Elsevier Inc.

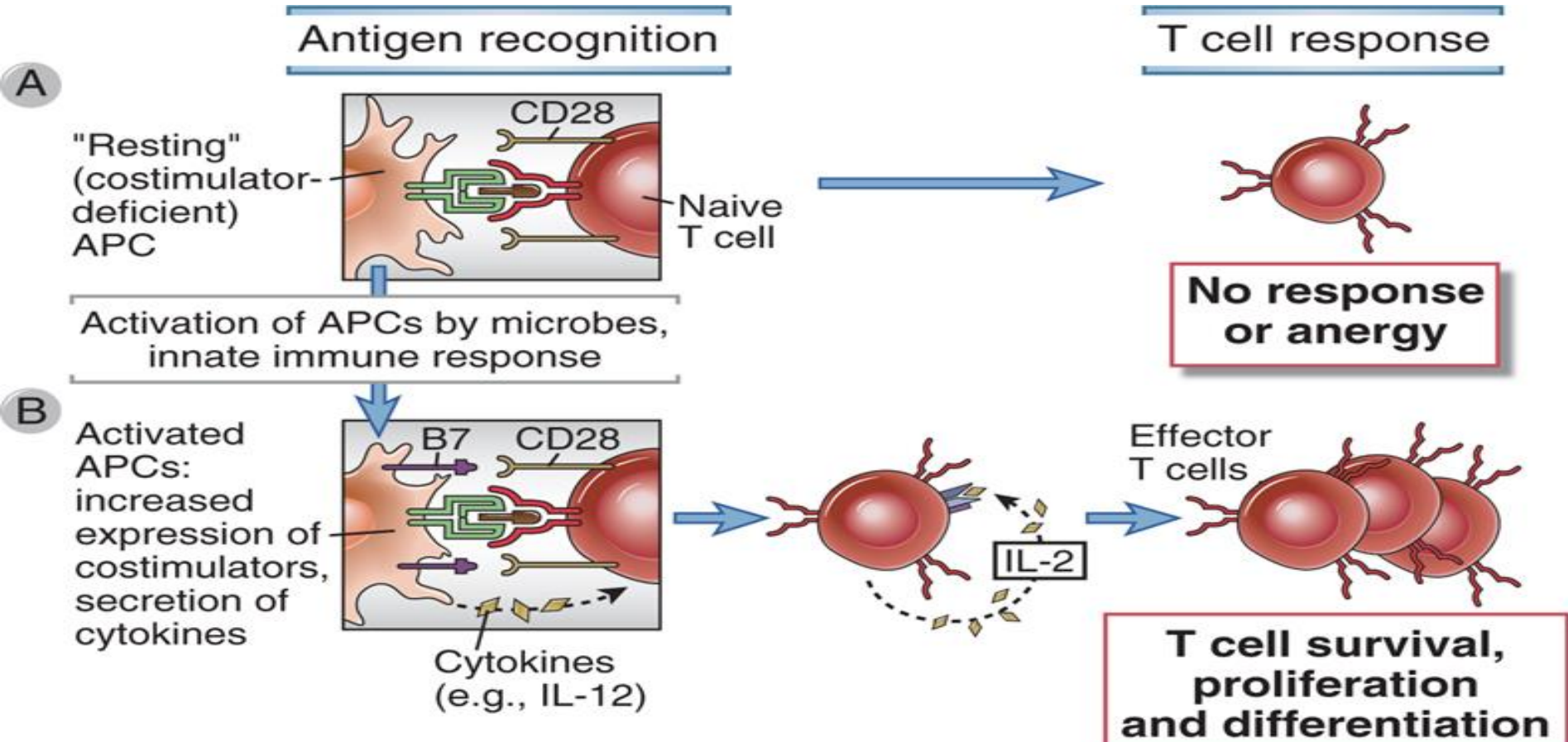
Dendritic cells are professional antigen presenting cells that launch CD8 T cell immunity to antigens from other cells: cross-presentation



Why it is important to be professional: The fate of antigen in tissue



Why it is important to be professional?



DC maturation as checkpoint of cellular immunity

Microbial Products/Adjuvants:

TLR, NOD and lectin ligands

LPS, DNA, RNA

Tissue damage:

Uric acid, HSPs

Cells of innate immunity

pDC, NK, NK T,

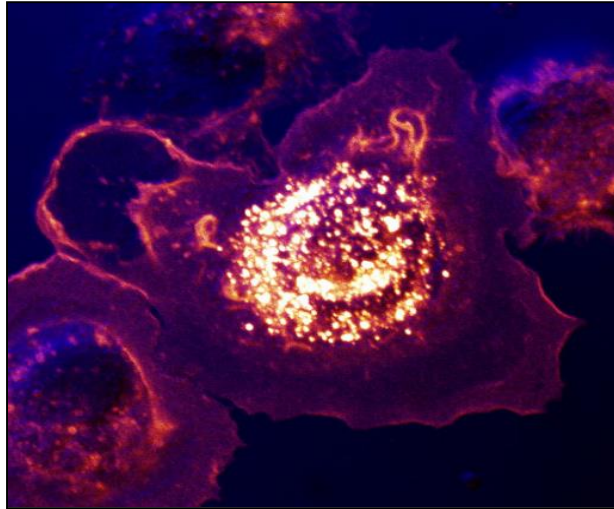
Neutrophils

IFN, TNF, GM-CSF

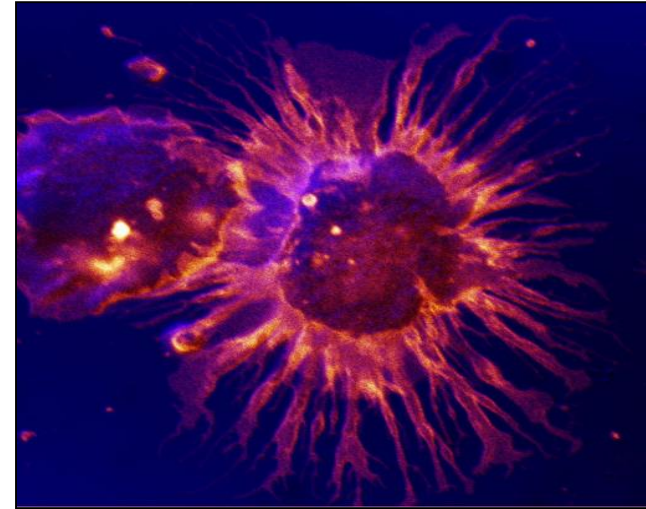
Cells of adaptive immunity

T and B cells

CD40 L, RANK



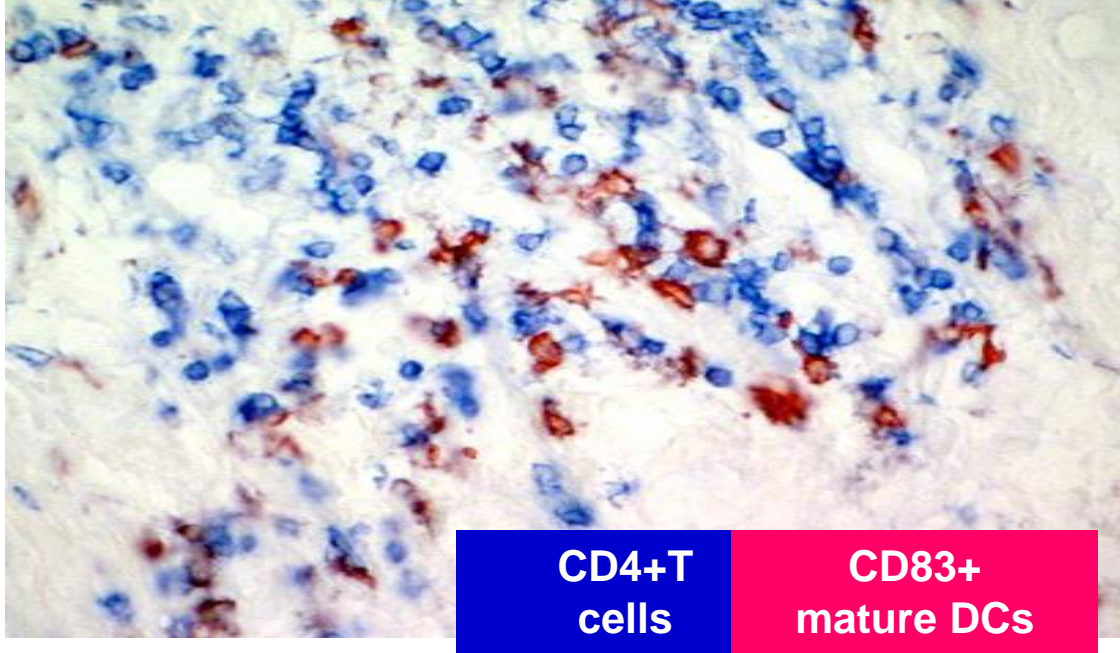
Immature DC



Mature DC

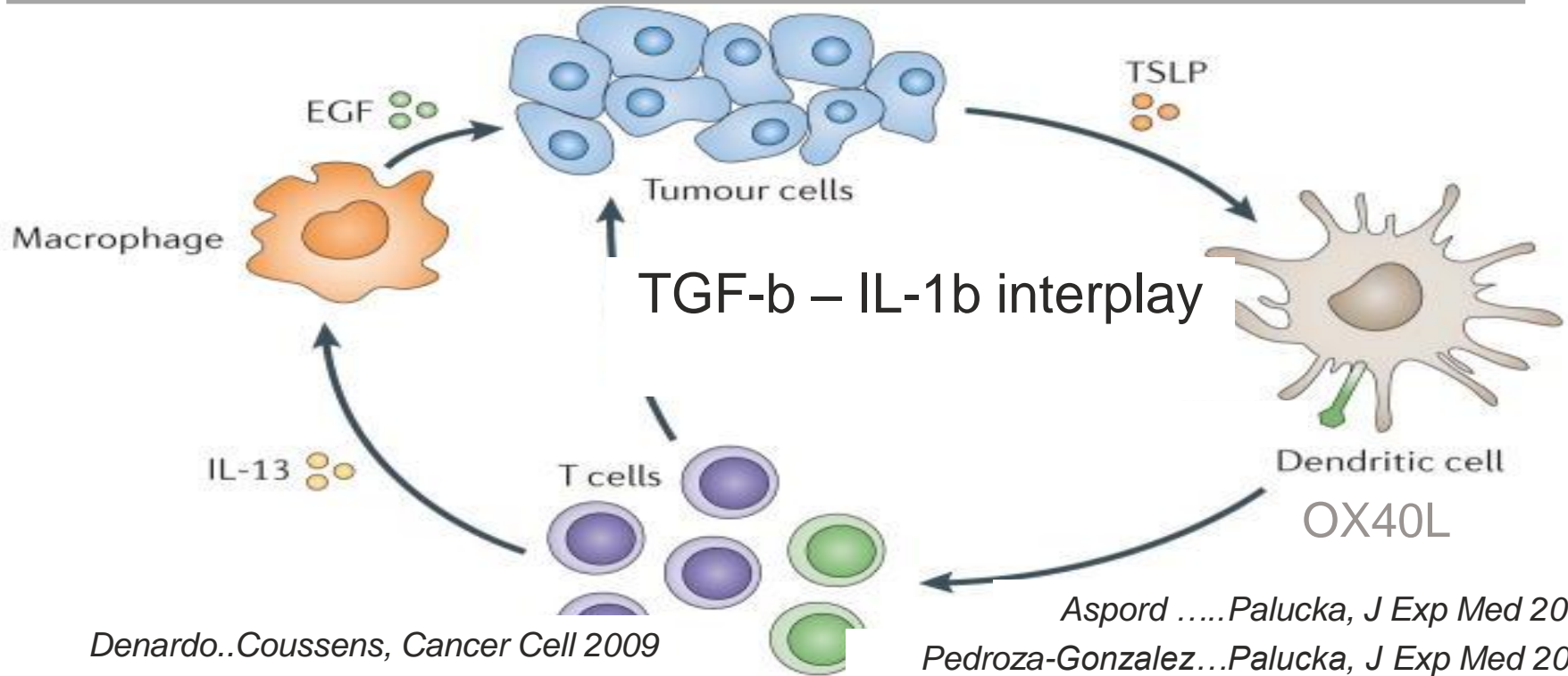
Steinman and Melman, Lanzavecchia et al,
Banchereau et al, Kalinski et al.....

Mature dendritic cells subvert T cells in breast cancers



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







Breast cancer subverts dendritic cell maturation to induce Th2 cells promoting cancer progression



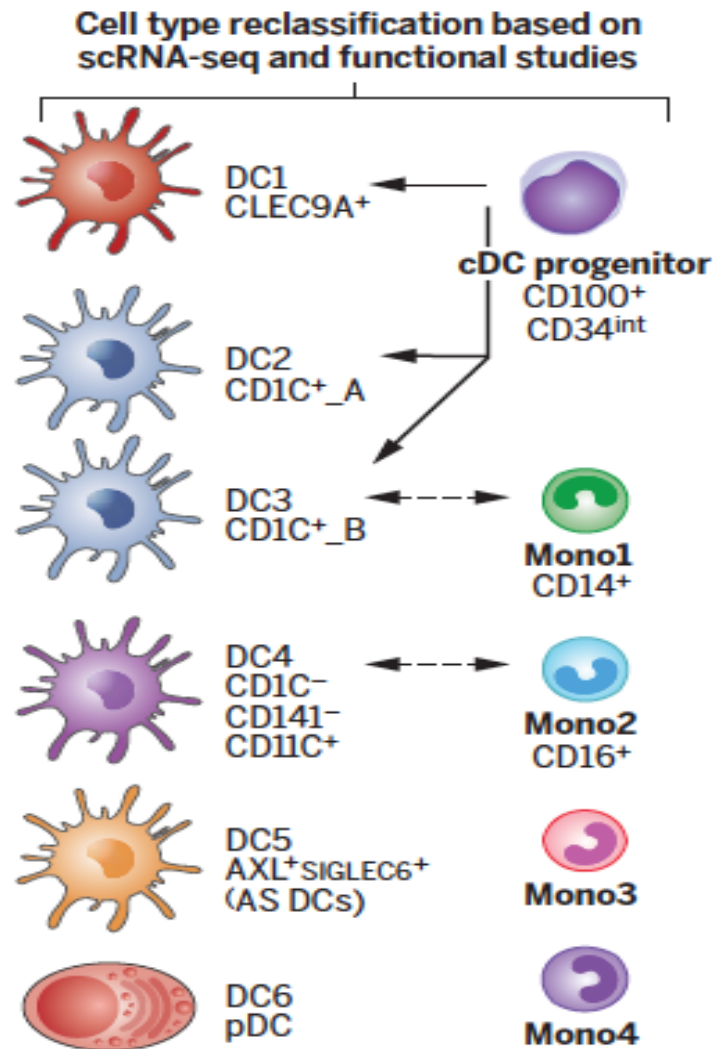
Denardo..Coussens, *Cancer Cell* 2009
Shiao...Coussens *Cancer Immunol Res*, 2015
Ruffell....Coussens, *Cancer Cell* 2014

AspordPalucka, *J Exp Med* 2007
Pedroza-Gonzalez...Palucka, *J Exp Med* 2011
Wu ...Yu...Palucka, *Cancer Immunol Res* 2014
Coussens, Zitvogel & Palucka *Science* 2013

The Human DC Compartment 2013

	<p>pDC</p> 	<p>BDCA1⁺ (CD1c)⁺</p> 	<p>BDCA3⁺ (CD141)⁺</p> 	<p>LC</p> 	<p>CD14⁺</p> 	<p>CD1a⁺</p> 
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 ⁺ Nec12 ⁺ Xcr1 ⁺ Clec9a ⁺ Dec205 ^{hi}	Lin ⁻ HLA-DR ⁺ CD11c ⁺ CD1a ⁺ CD14 ⁻ BDCA1 ⁺ Langerin ⁺ EpCAM ⁺ Sirpa ⁺ 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 ⁻ Sirpa ⁺ 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			Cutaneous tissue		
				Epidermis	Dermis	

The Human Blood DC Compartment in 2017

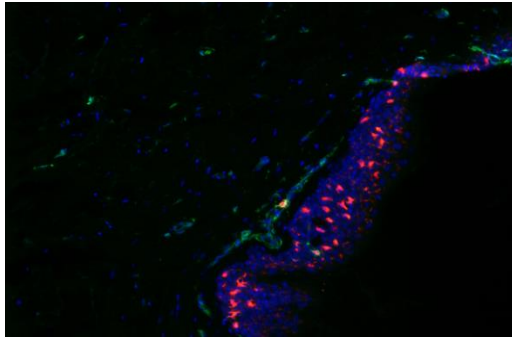
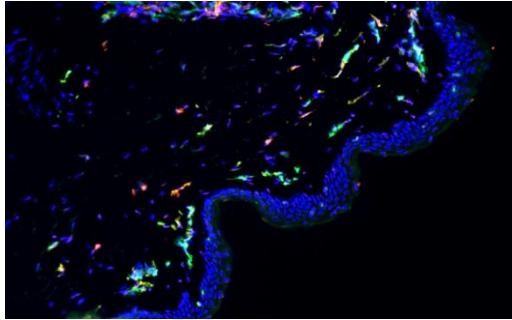


The Jackson

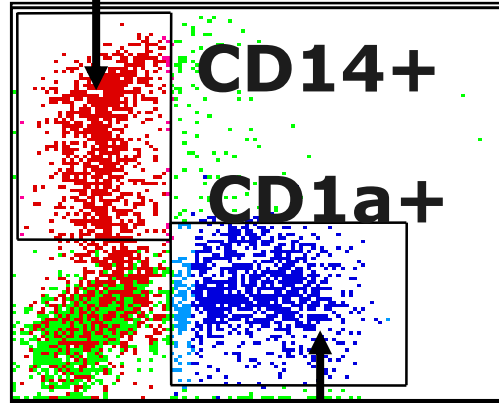
Villani *et al.*, *Science* **356**, 283 (2017)

21 April 2017

Distinct Human Dendritic Cell Subsets regulate different arms of immune responses



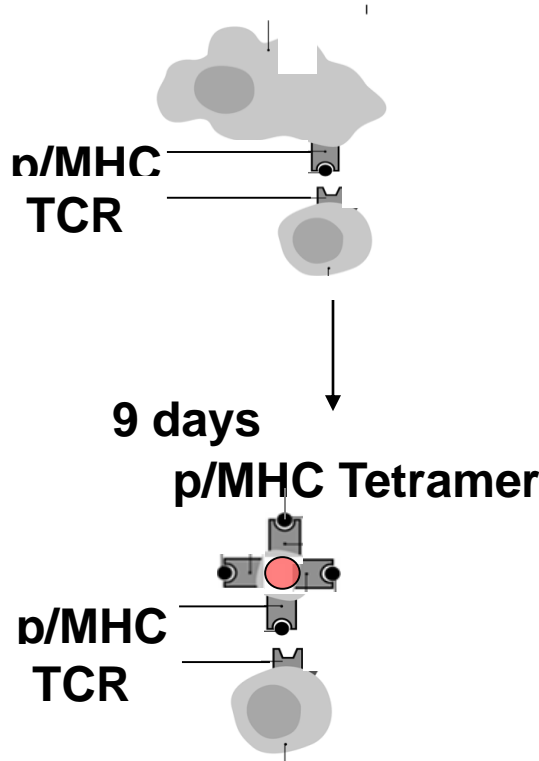
**Human Dermal DCs –
DC-SIGN positive**



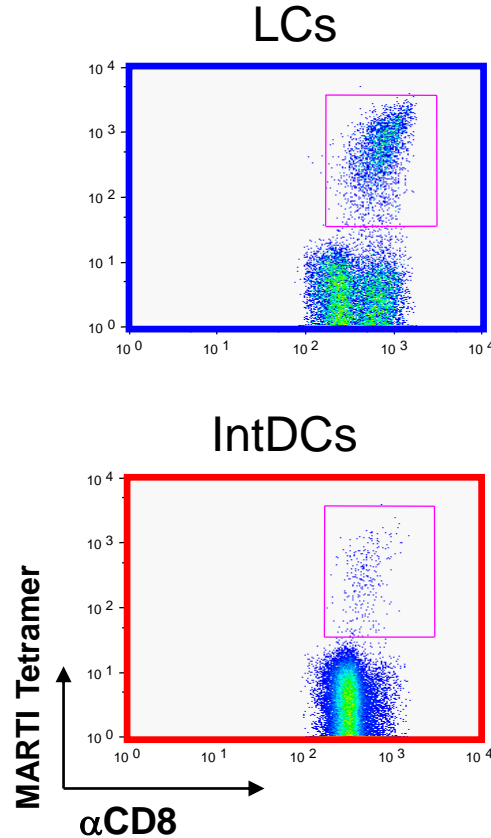
**Human Langerhans
Cells – Langerin
positive**

Caux et al, 1996, 1997, 1998

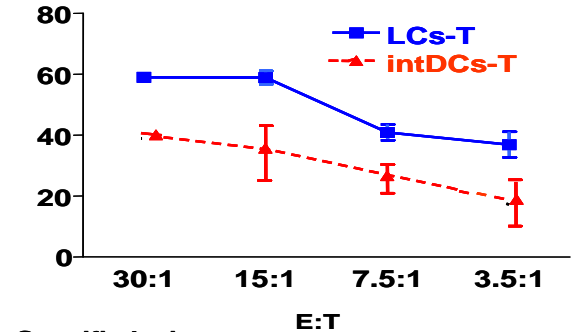
Langerhans Cells are More Efficient than CD14⁺ Dermal-DCs in CD8⁺ T Cell Priming



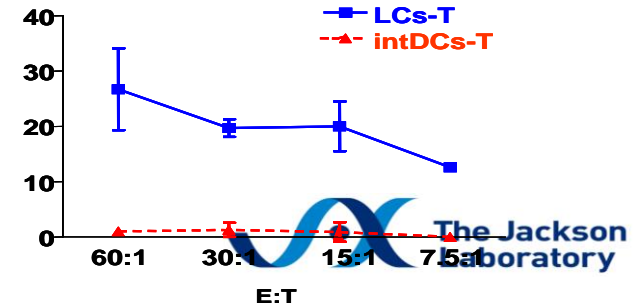
Klechevsky, Ueno,
Immunity, 2008



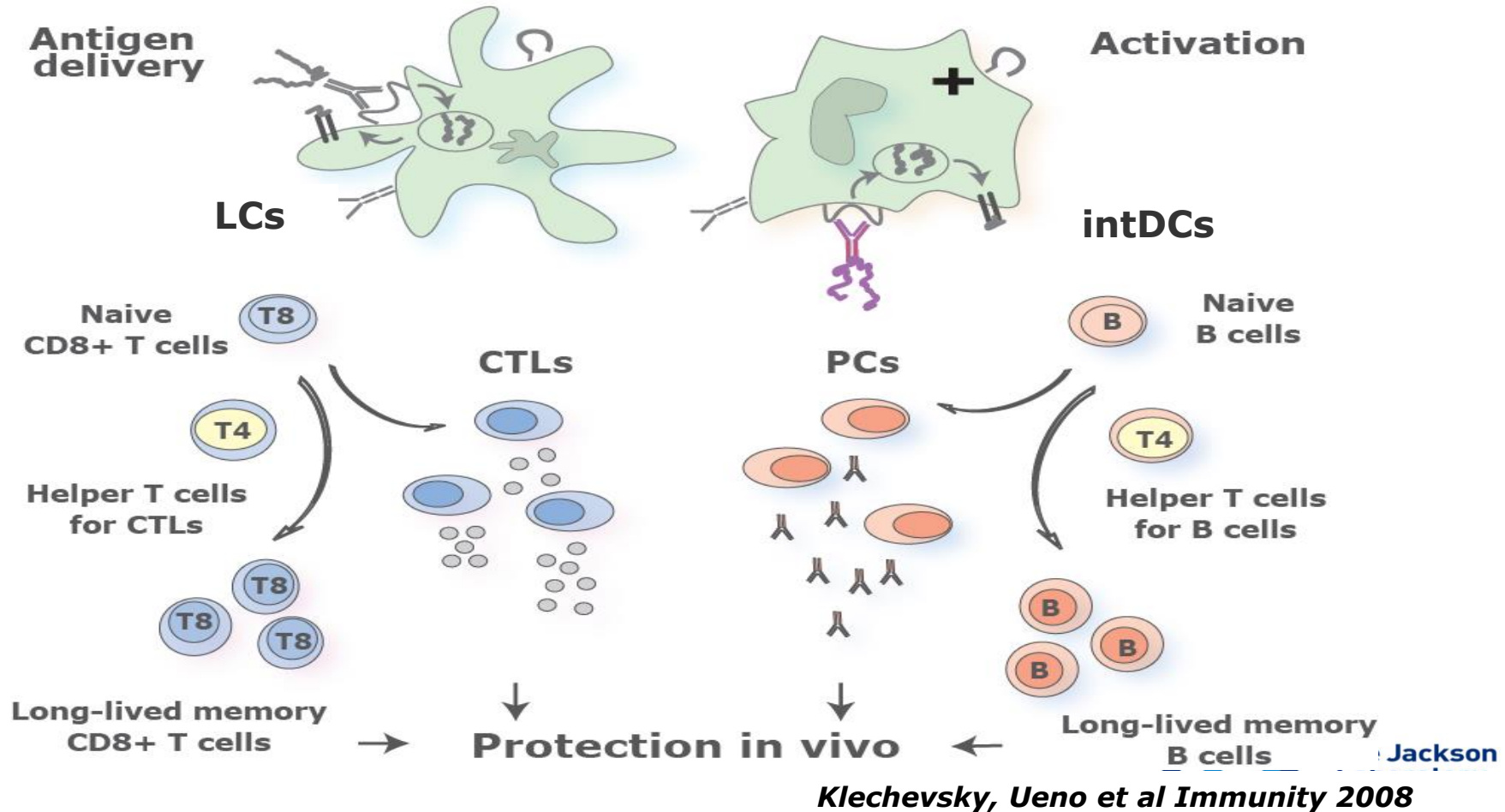
Peptide-pulsed T2 cells



HLA-A*0201+ melanoma cells

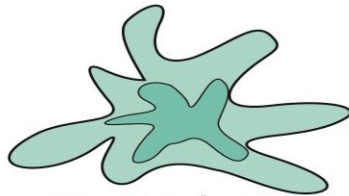


Distinct DC subsets elicit distinct immune responses

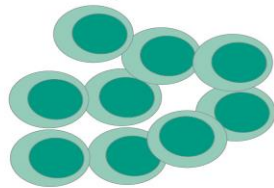


Distinct DC subsets elicit different CD8+ T cells

**Langerhans cells
CD141+ DCs**

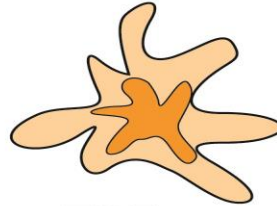


IL-15/ *XCL1*

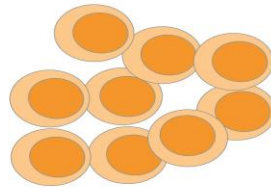


Potent CTLs

CD1c+ DCs



TGF- β



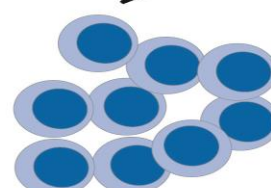
**Tissue resident
memory
CD8+ T cells**

Yu, Immunity, 2013

**CD14+ interstitial
DCs**



ILT2/ILT4

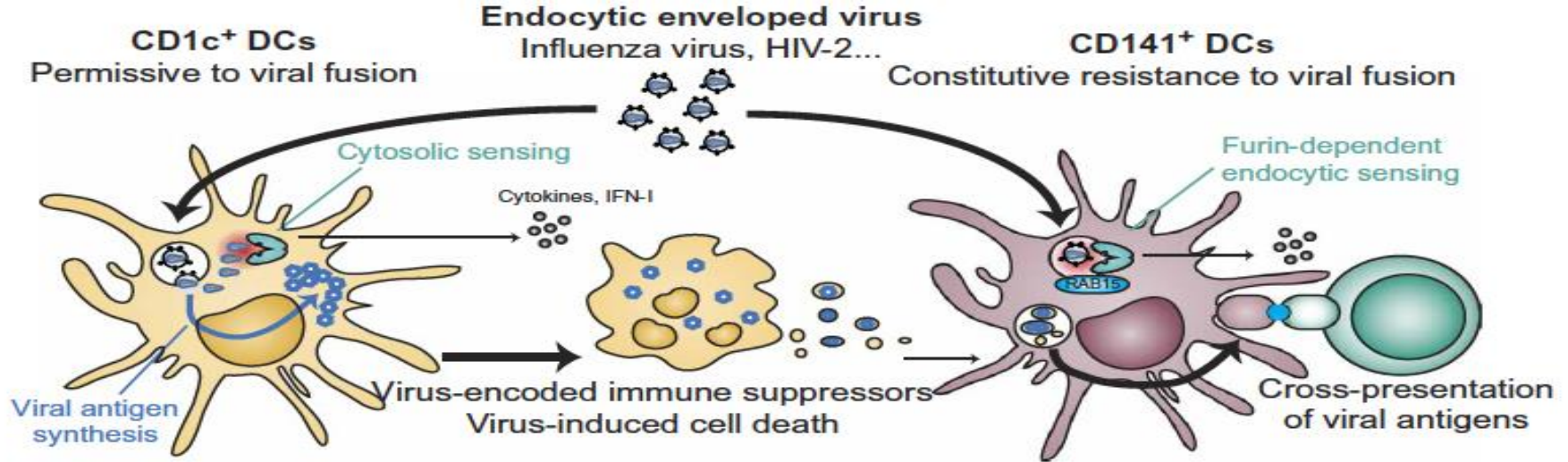


**Dysfunctional
CD8+ T cells**

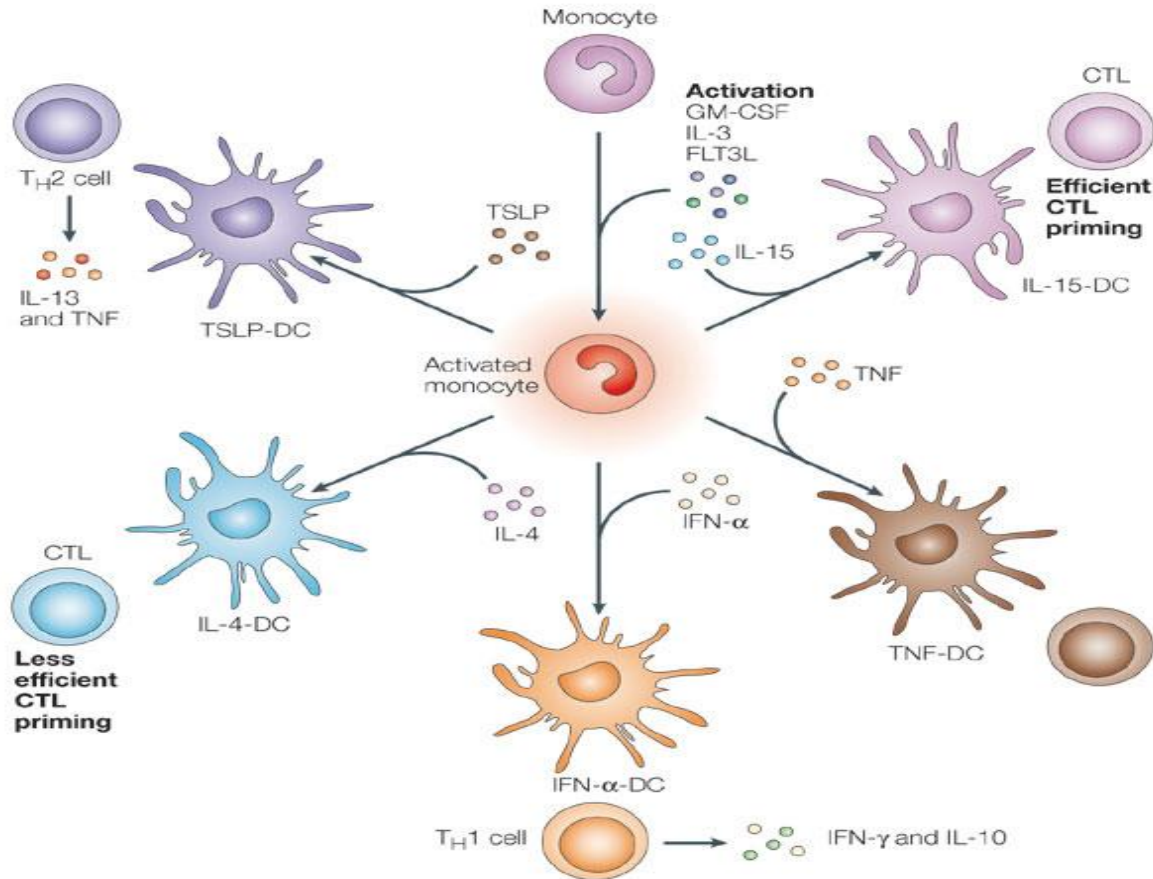
Klechevsky, Ueno, Immunity, 2008

Molecular mechanisms underlying functional specialization of human DC subsets

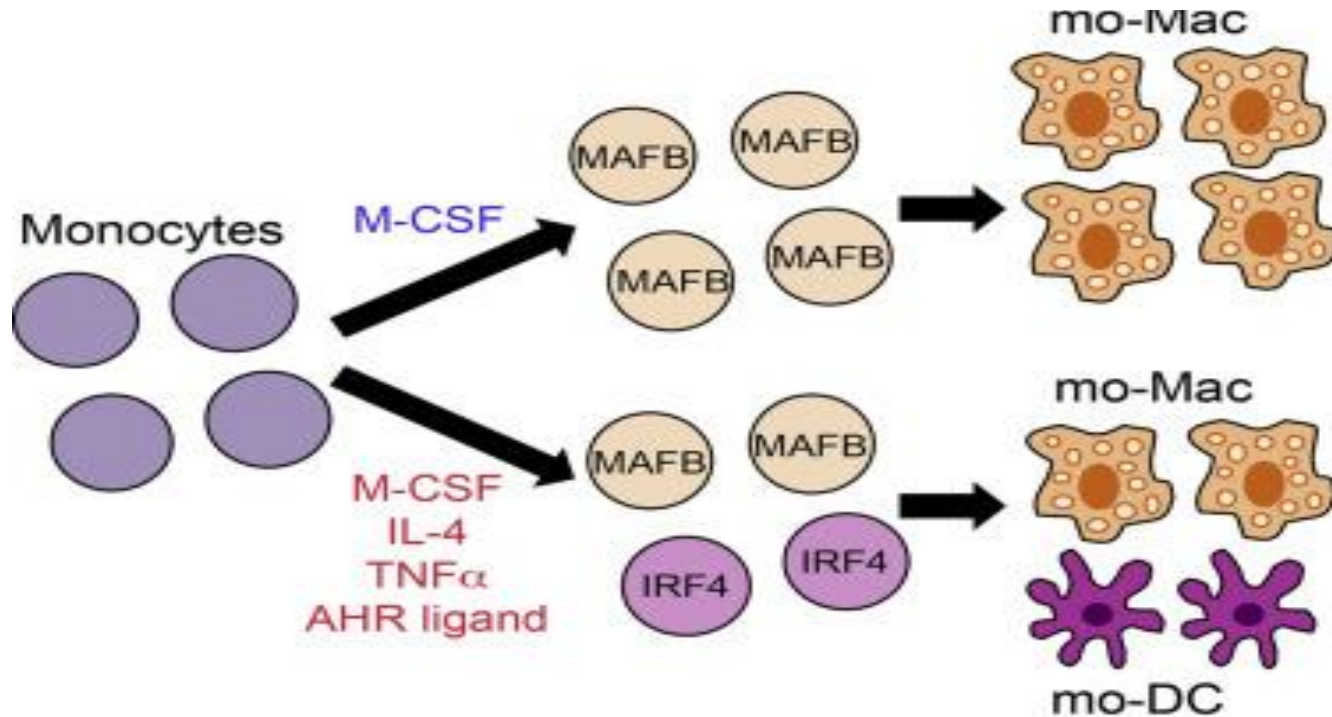
Constitutive resistance to viral infection in human CD141⁺ dendritic cells



Multiple monocyte-derived DCs



Aryl hydrocarbon receptor controls monocyte differentiation to DCs



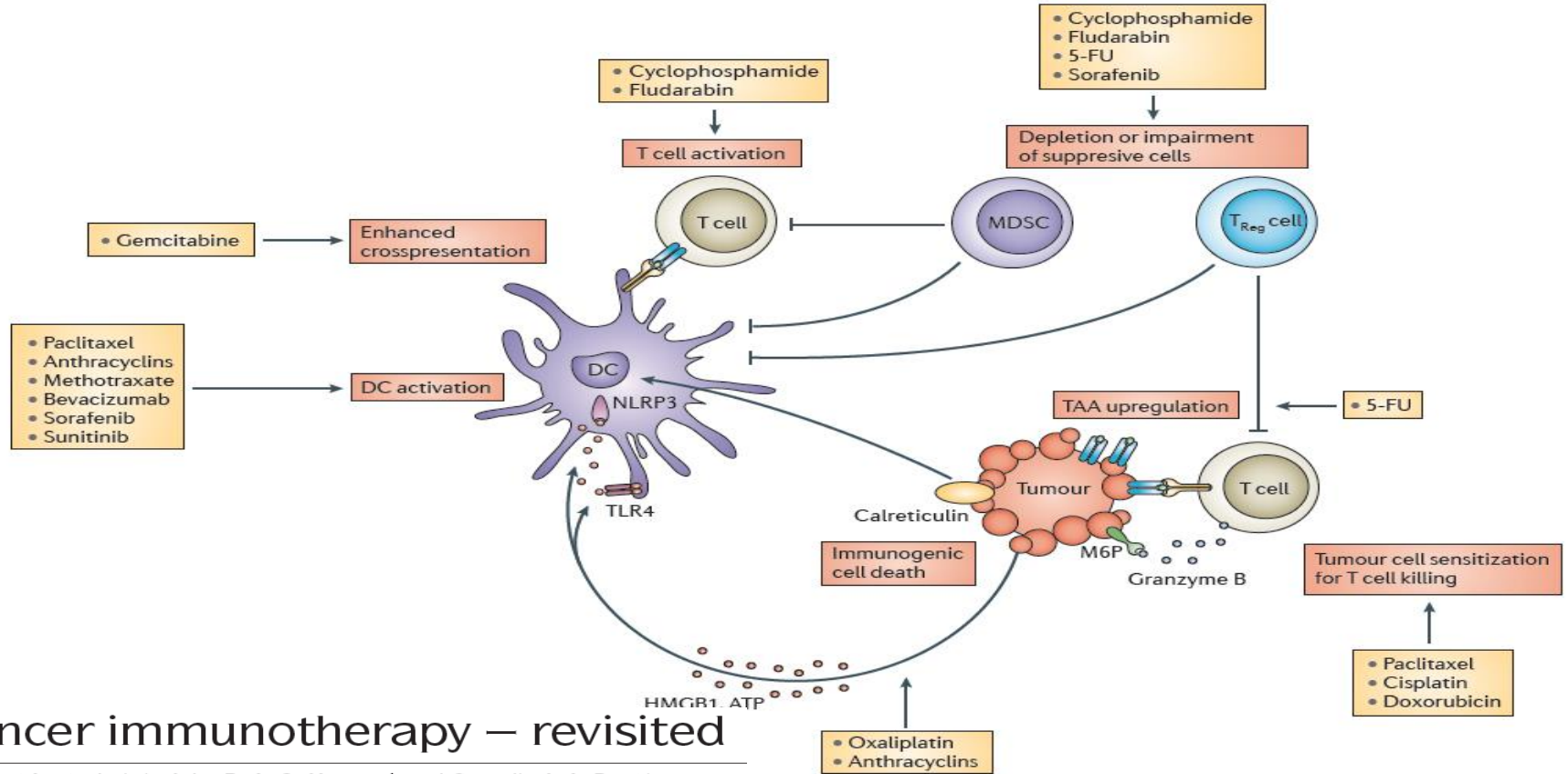
Christel Goudot, Alice Coillard, Alexandra-Chloé Villani, Paul Gueguen, Adeline Cros, Siranush Sarkizova, Tsing-Lee Tang-Huau, Mylène Bohec, Sylvain Baulande, Nir Hacohen, Sebastian Amigorena, Elodie Segura

Aryl Hydrocarbon Receptor Controls Monocyte Differentiation into Dendritic Cells versus Macrophages

null, Volume 47, Issue 3, 2017, 582–596.e6

<http://dx.doi.org/10.1016/j.immuni.2017.08.016>

Chemotherapy and targeted therapy meet immunology



Cancer immunotherapy – revisited

W. Joost Lesterhuis*, John B. A. G. Haanen* and Cornelis J. A. Punt*

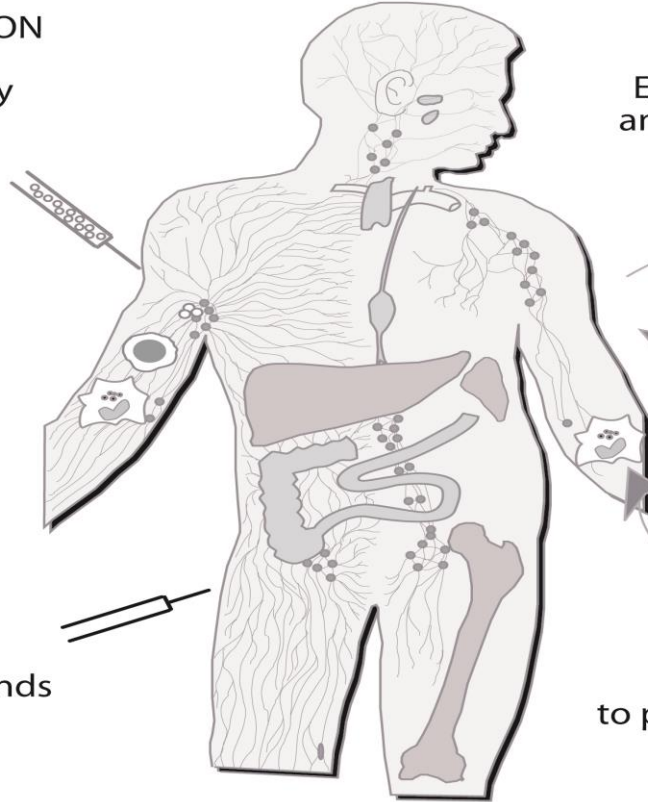
Dendritic cells in cancer therapy

ENDOGENOUS VACCINATION

Immunogenic chemotherapy
Radiotherapy
Anti-tumor antibodies
T cell checkpoint blockade

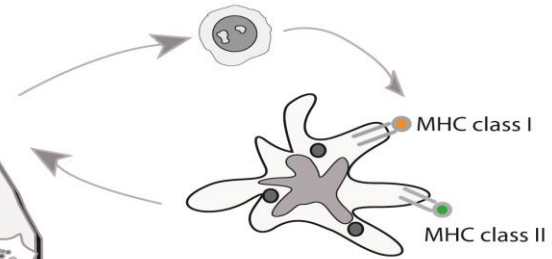
REPROGRAMMING INFLAMMATION

Targeting DCs with TLR ligands
Cytokine blockade



EX VIVO GENERATED CYTOKINE DRIVEN DCs

Ex vivo instruction to generate
and maintain cytotoxic effectors
and helper T cells

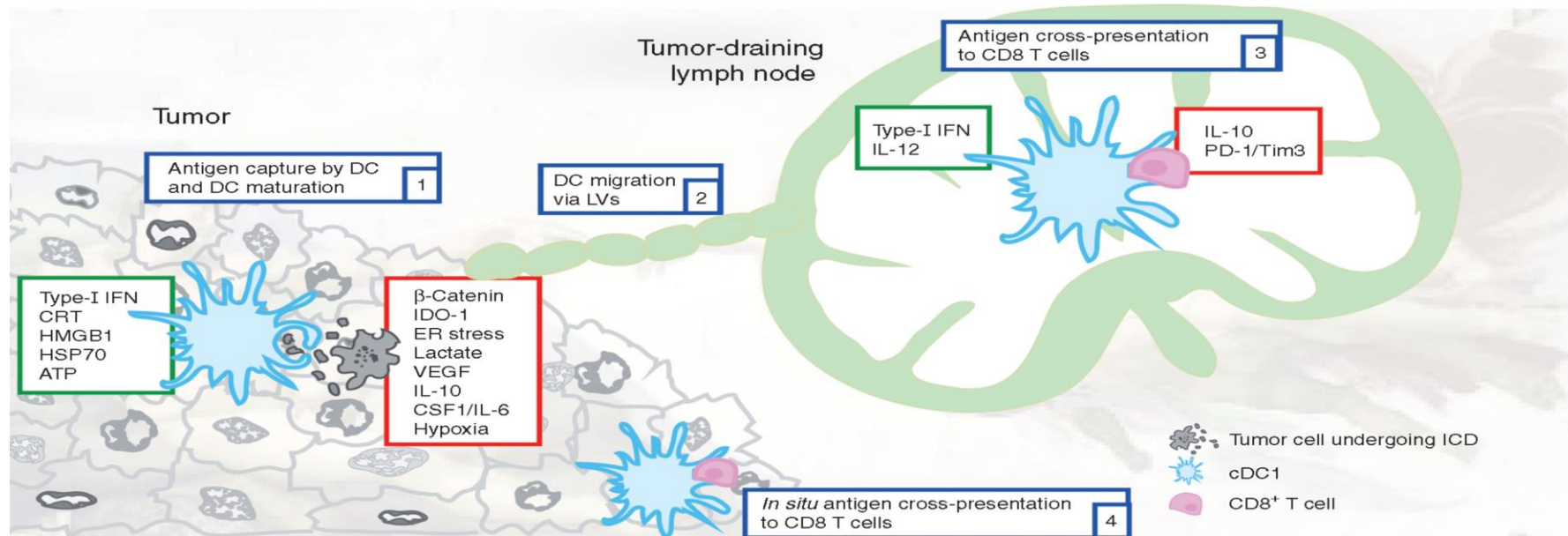


Anti-DC antibody linked
to pathogen and/or cancer antigens
and DC activators

TARGETING ANTIGENS TO
DC SUBSETS IN VIVO



Communication between tumor and lymph nodes

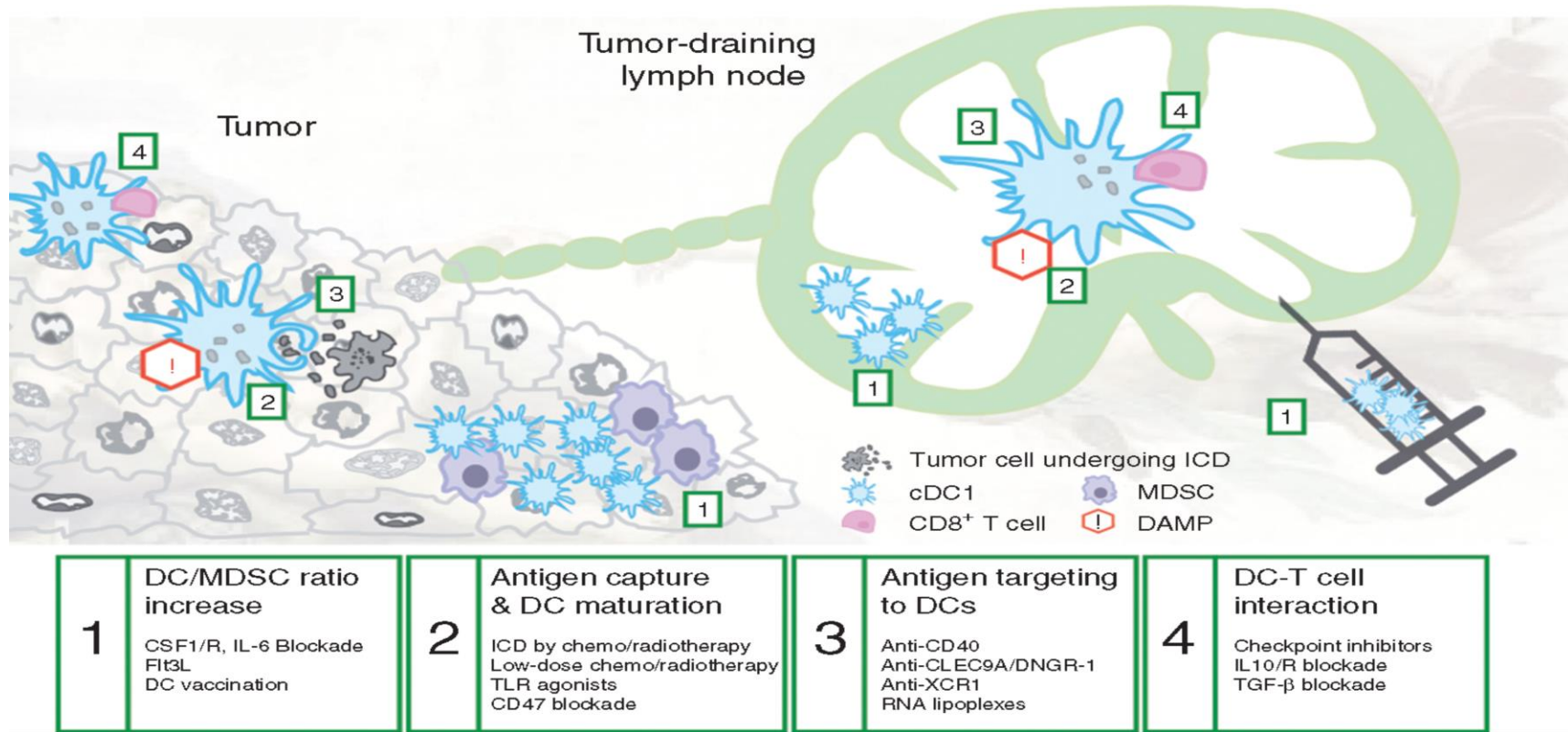


From: Antigen cross-presentation and T-cell cross-priming in cancer immunology and immunotherapy

Ann Oncol. Published online September 01, 2017. doi:10.1093/annonc/mdx237

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From: Antigen cross-presentation and T-cell cross-priming in cancer immunology and immunotherapy

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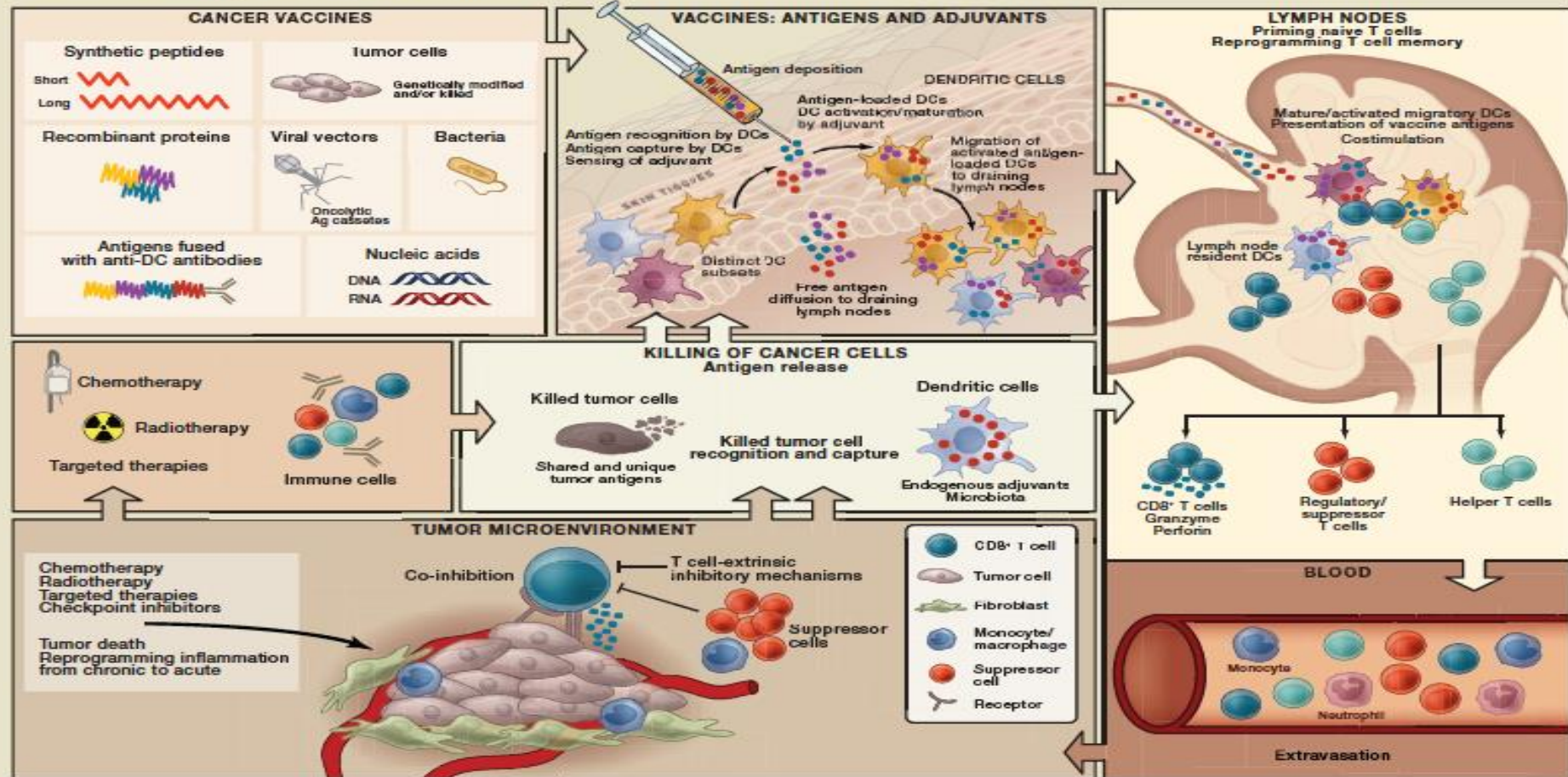
SnapShot: Cancer Vaccines

Karolina Palucka¹ and Jacques Banchereau²

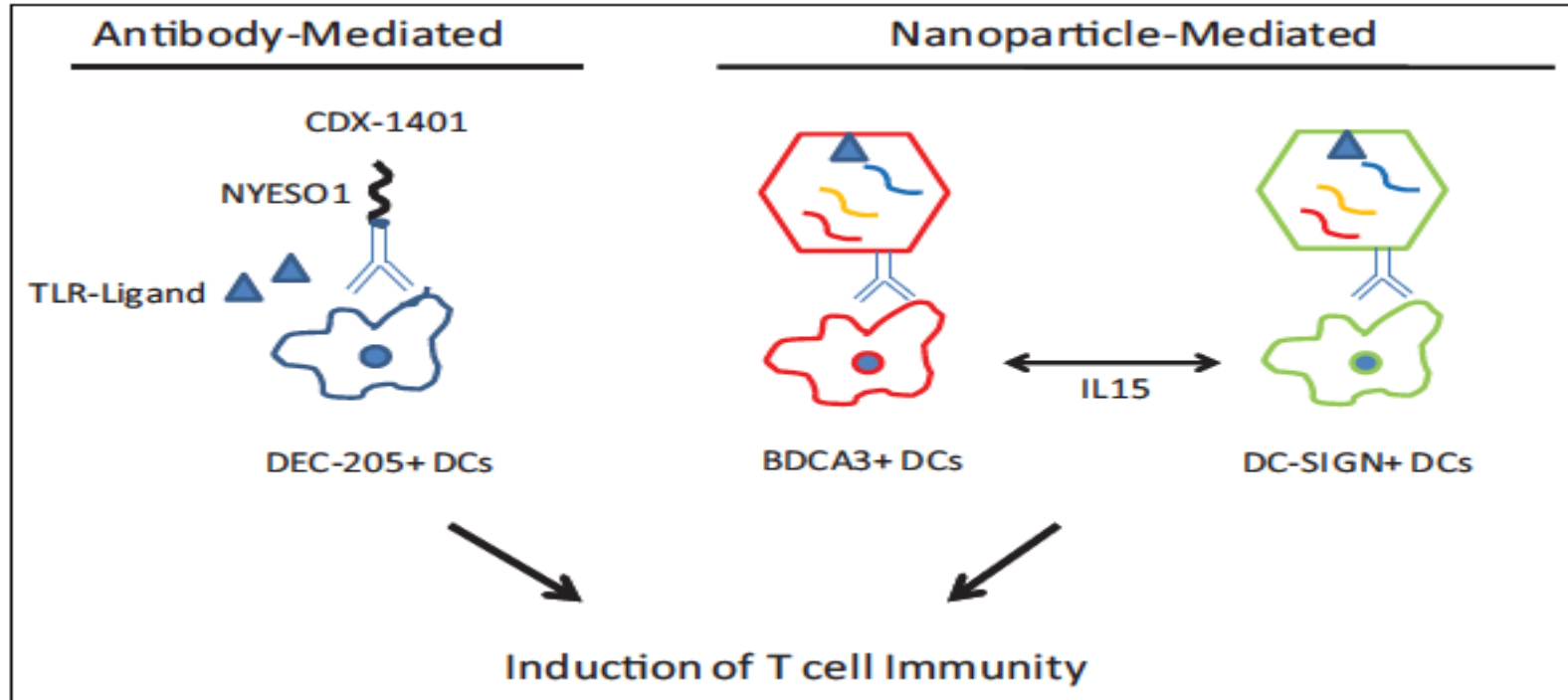
¹Ralph M. Steinman Center for Cancer Vaccines, Baylor Institute for Immunology Research, Baylor Research Institute, Dallas, TX 75204, USA

²The Jackson Laboratory, Farmington, CT 06030, USA

Cell

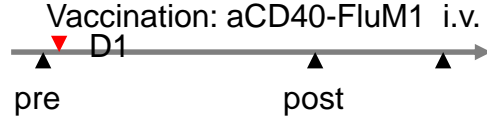


Emerging strategies for DC targeting in clinical trials



To cite this article: Madhav V Dhodapkar & Kavita M Dhodapkar (2014) Recent advances and new opportunities for targeting human dendritic cells in situ, *Oncolimmunology*, 3:8, e954832, DOI: [10.4161/21624011.2014.954832](https://doi.org/10.4161/21624011.2014.954832)

Specific CD8⁺ T cell expansion via CD40 targeting in humanized Mice

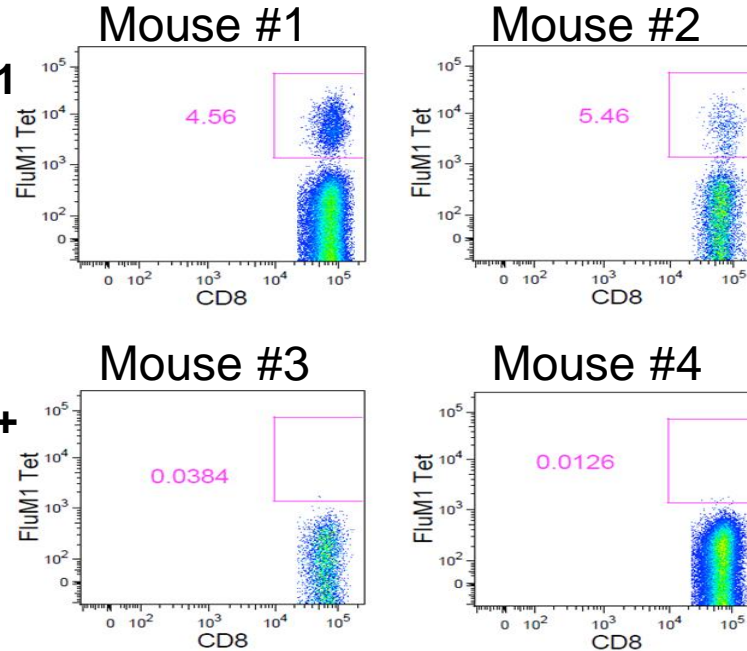


**CD40-FluM1
targeting Ab**

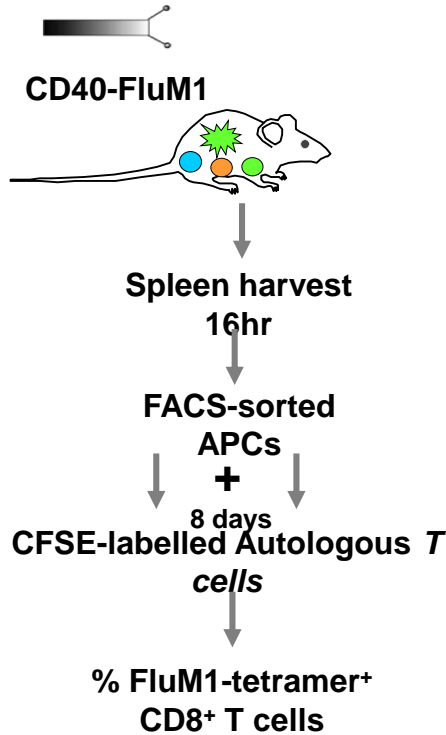
aCD40-FluM1

**IgG4-FluM1 +
aCD40**

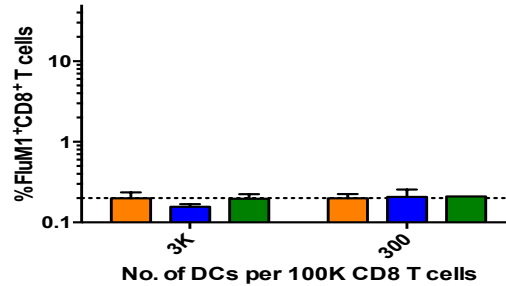
CD8 T cell Response in vivo



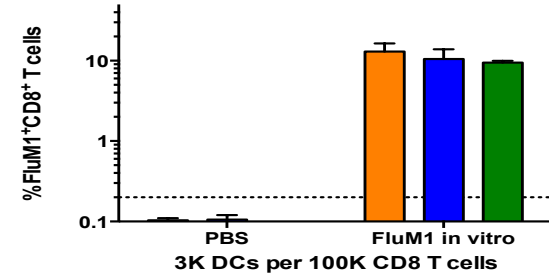
CD40 targeting antibody deliver antigens to both subsets of DCs in humanized Mice



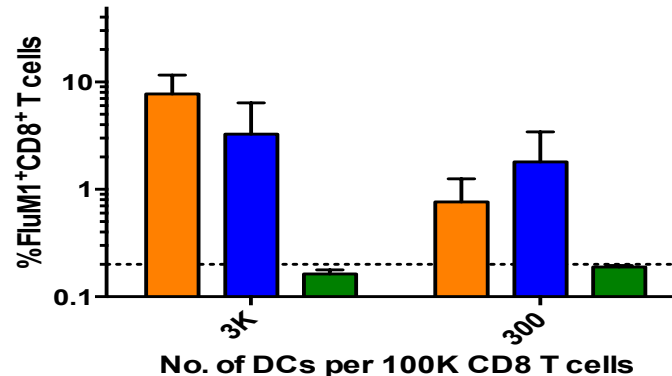
In vivo PBS control



In vitro FluM1-loaded control

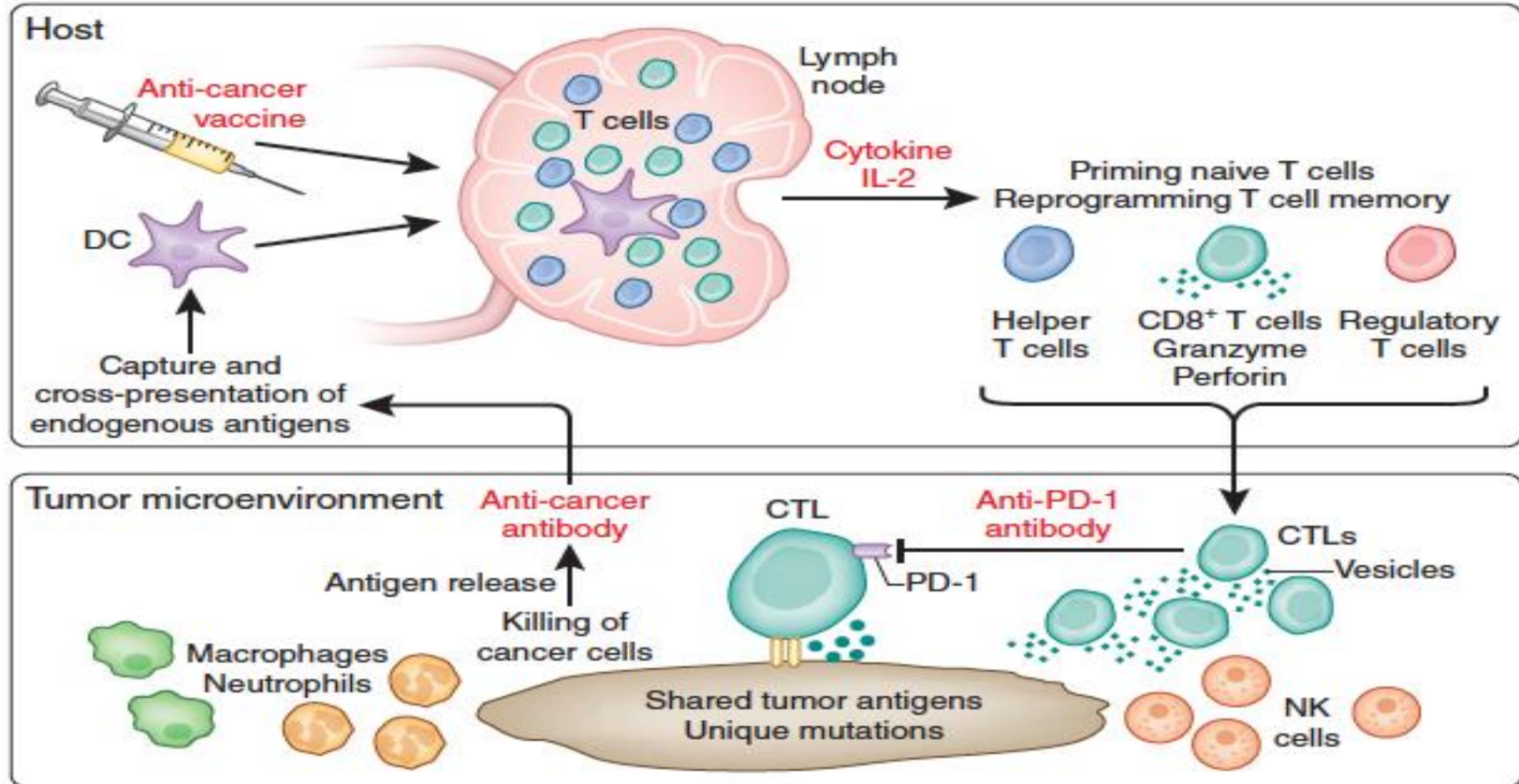


In vivo CD40-FluM1 Ab



CD1c+ DCs
CD141+ DCs
pDCs

Diversity and collaboration for effective immunotherapy



Thanks to our patients

Thanks to funding organizations

Chun Yu

Florentina Marches

Jan Martinek

Te-Chia Wu

Patrick Metang

John Graham

Pierre Authie

Clinical collaborators

Jacques Banchereau

Question 1

Which cells in tissue are professional antigen presenting cells?

- a. Macrophages**
- b. B cells**
- c. Dendritic cells**
- d. Epithelial cells**

Question 2

Which features are the most critical for DC ability to prime T cells?

- a. Antigen presentation**
- b. Localization in the lymph node**
- c. Maturation**
- d. DC subsets**
- e. All of the above**