Dendritic Cells

2012 SITC Primer

Madhav V. Dhodapkar, MD
Yale University,
New Haven, CT

The following relationships exist related to this presentation:

None

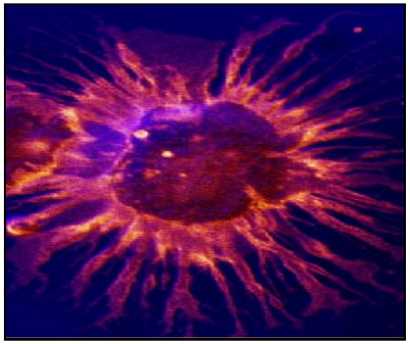
Funding: NIH, LLS, MMRF, Celgene, KHK
Advisory: Celgene, Shire, BMS
Co-inventor on some patents related to use of DCs

Outline: This Presentation

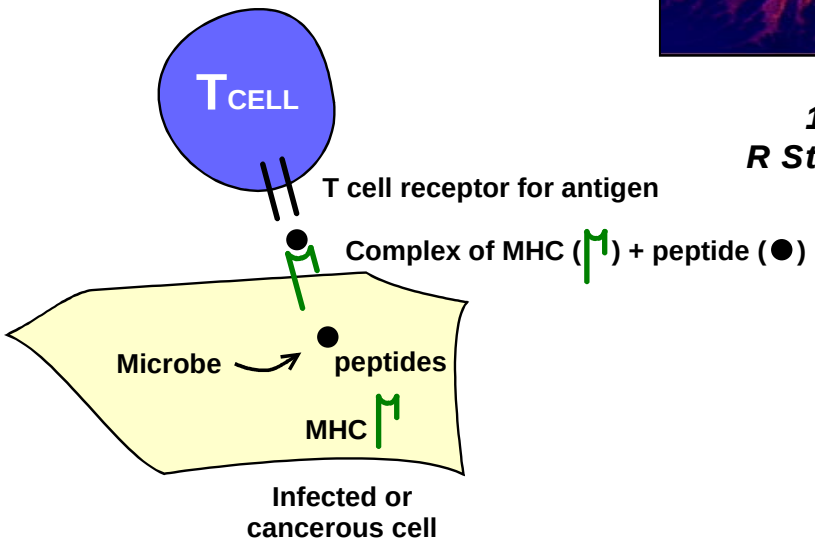
- Basic Biology of DCs
- DCs as targets for cancer immunotherapy
- Non-immunologic roles of DCs in cancer

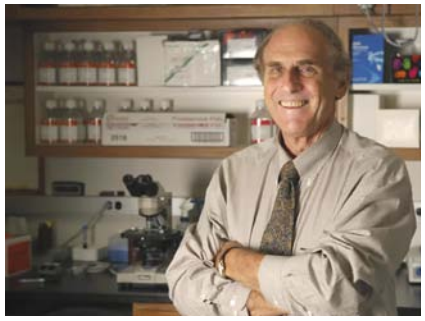
Accessory Cell

Antigen + T cell → Immunity / Tolerance

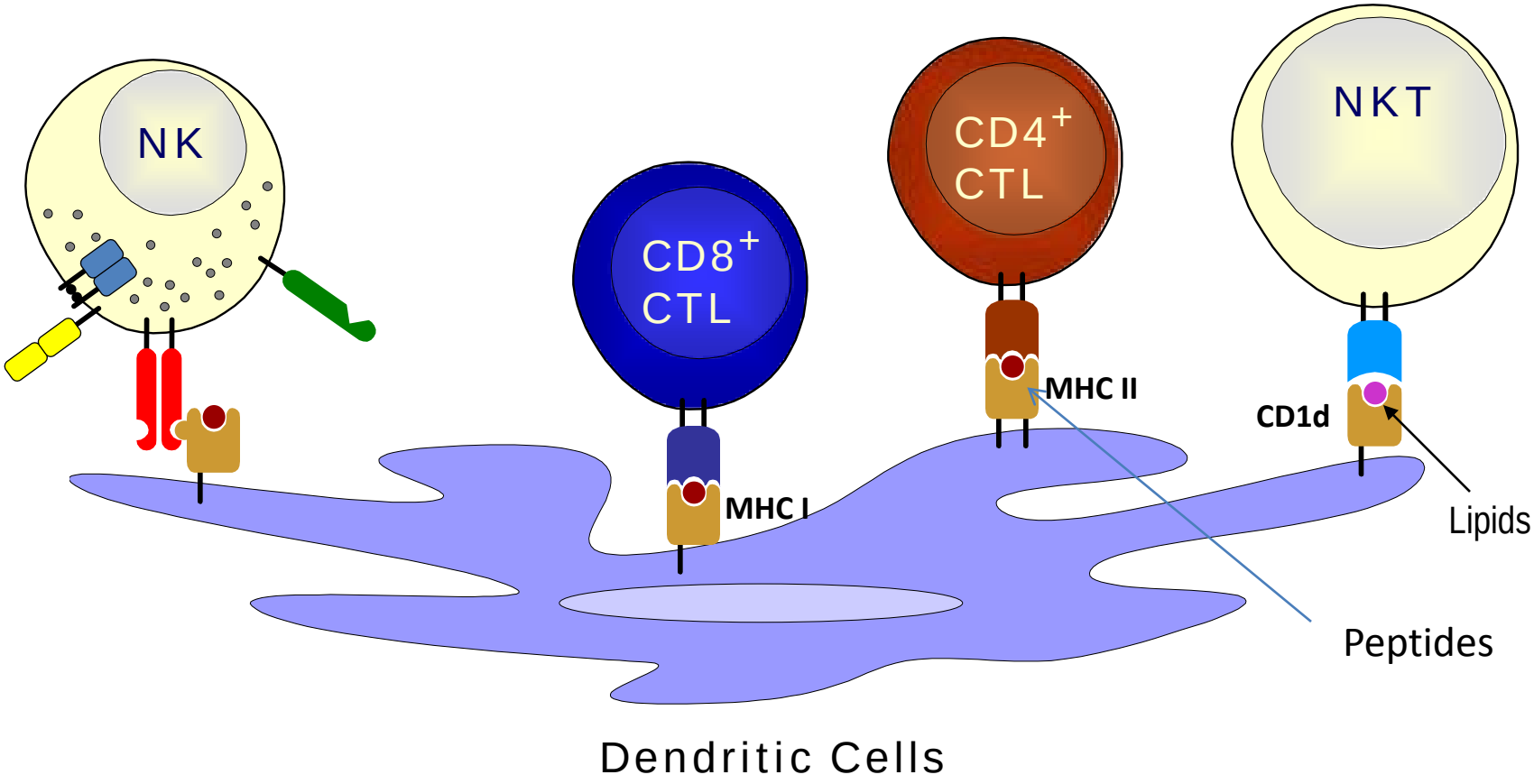


1973
R Steinman





DCs as the conductors of the immunologic orchestra



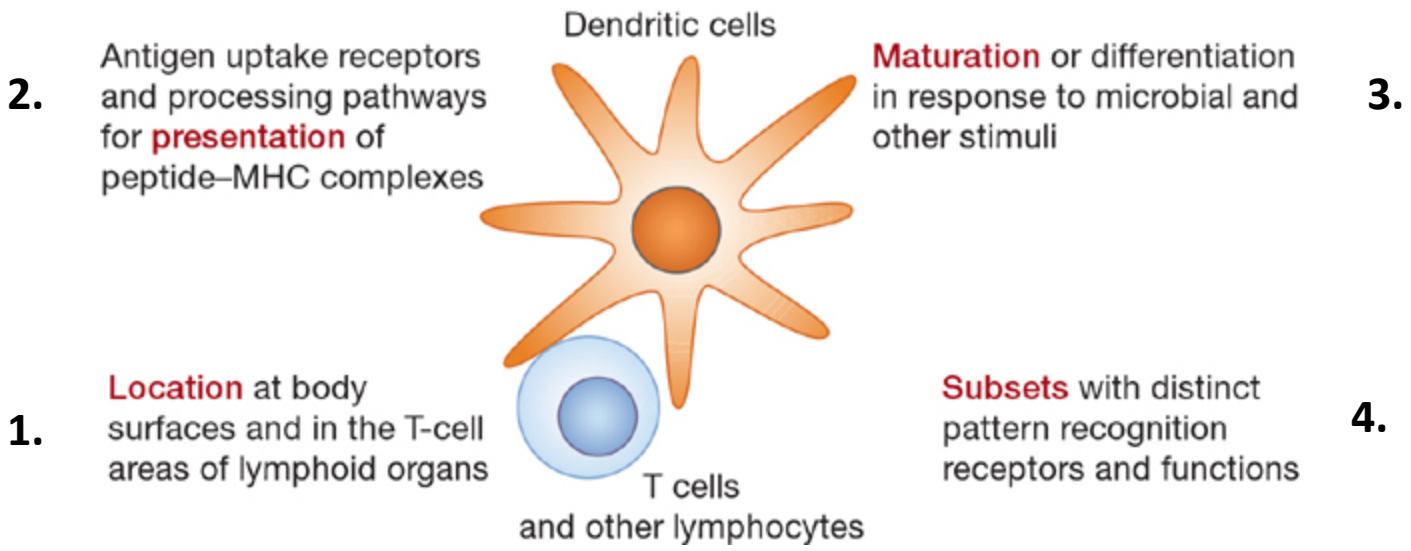
Why Should Cancer Immunologists and Biologists Care About Dendritic Cells ?

- Central role in immune regulation
  - Innate immunity
  - Adaptive immunity

……Targets of vaccines, adjuvants.

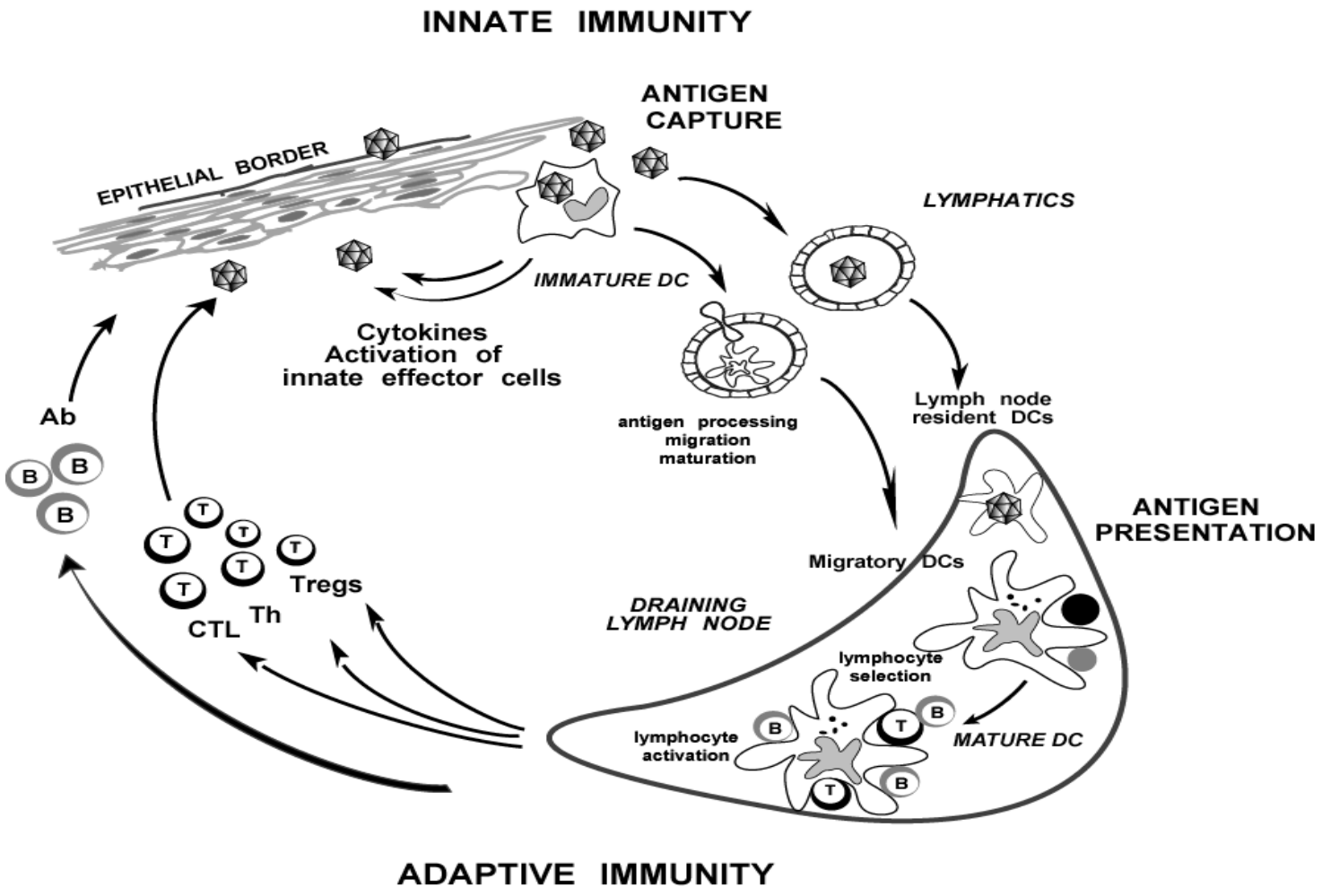
- An important component of the tumor microenvironment (non-immune effects)….more direct contributions to carcinogenesis.

Some Properties Of DCs Of Relevance To Their Application In Medicine



Steinman and Banchereau, Nature 2008

DENDRITIC CELLS AS NATURE's ADJUVANT

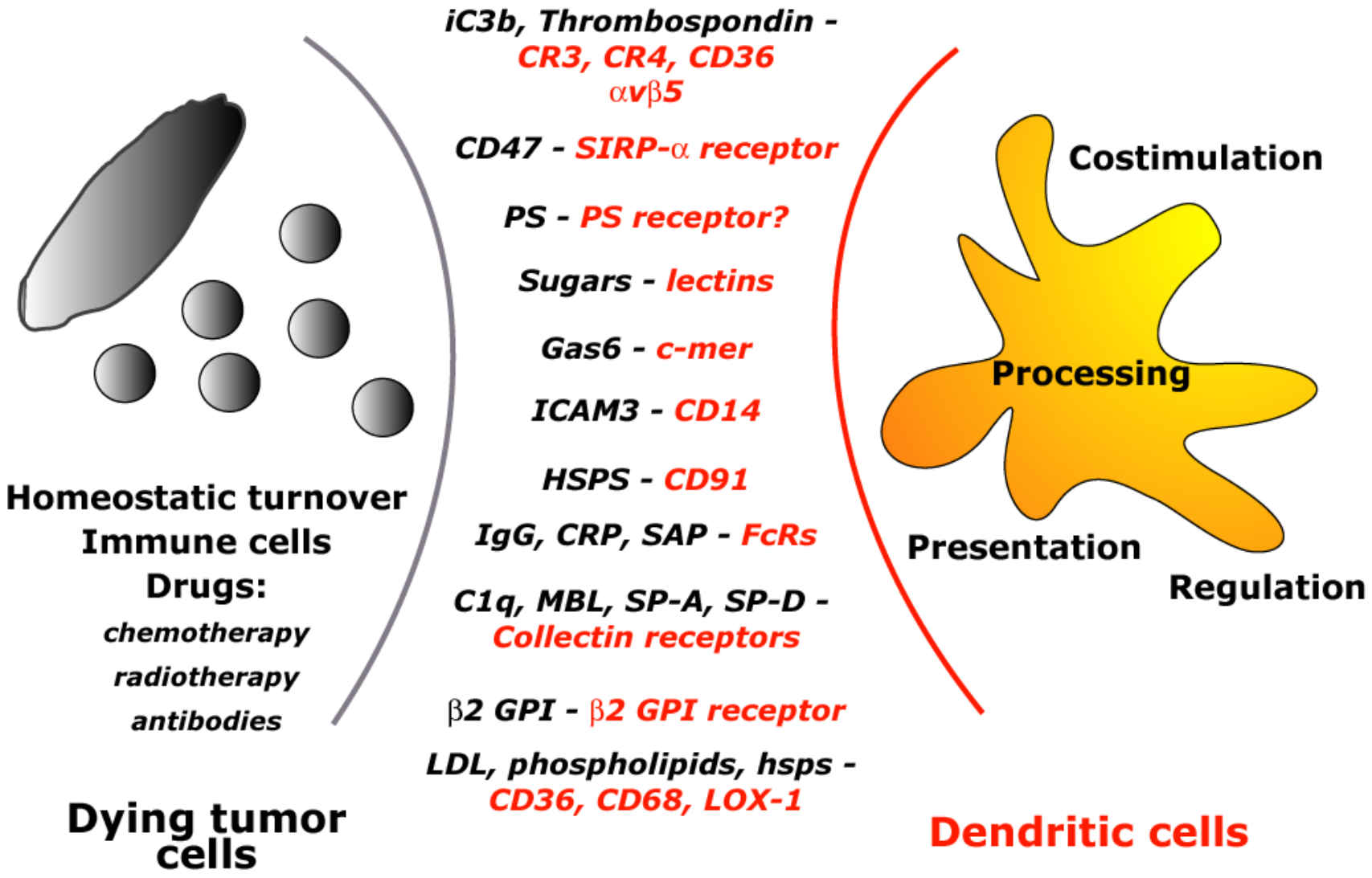


Palucka et al.

Antigen Uptake and Processing

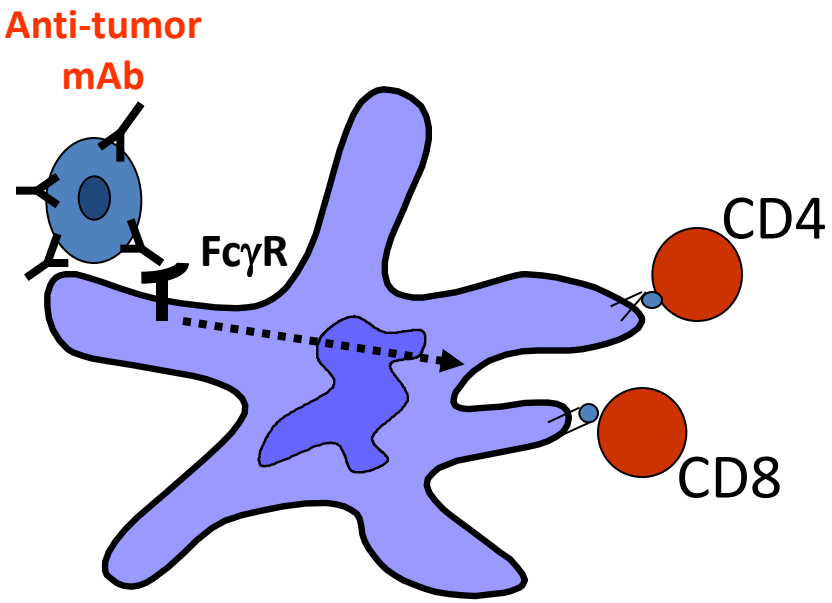
- DCs have several mechanisms of antigen uptake.
- Receptor-mediated uptake generally leads to more efficient Ag presentation.
- Both the mode of entry (specific receptor) and the nature of antigenic cargo can impact processing and presentation.

Dendritic cells express several receptors to recognize tumor and dying cells



Dhodapkar et al 2007 Cell Death Differ

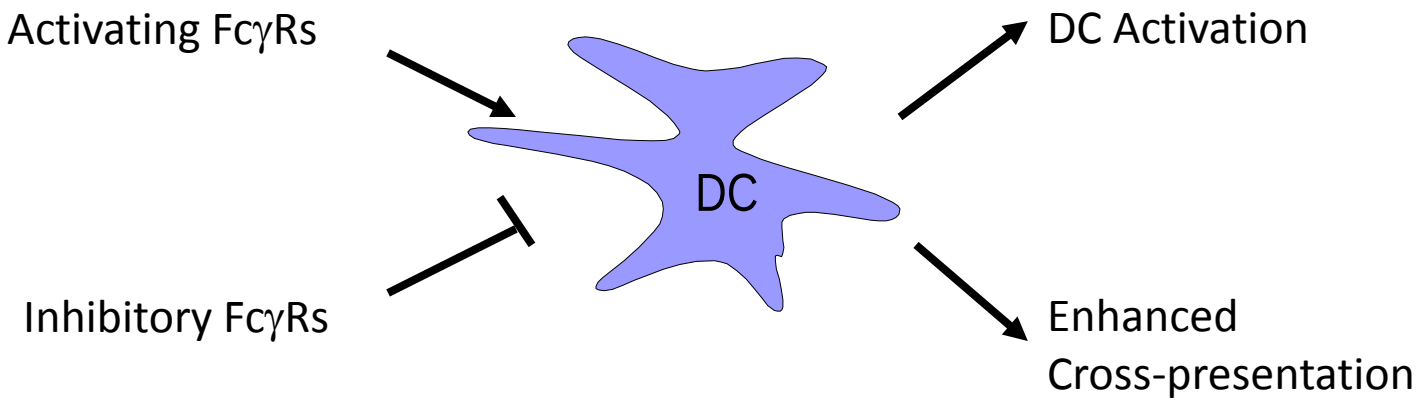
Targeting tumor antigens to Fcγ receptors of dendritic cells via anti-tumor monoclonal Ab enhances anti-tumor immunity



The enhanced presentation requires presence of Fcγ receptors on DCs.

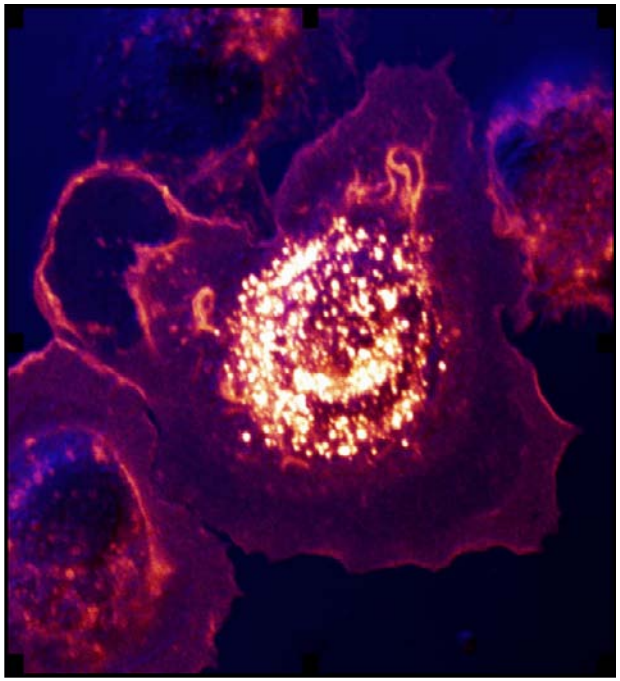
J Exp Med 195:125, 2002

Balance of Activating / Inhibitory FcγRs As A Checkpoint for Regulating Ag Presentation



DENDRITIC CELL MATURATION

The control point of cellular immunity

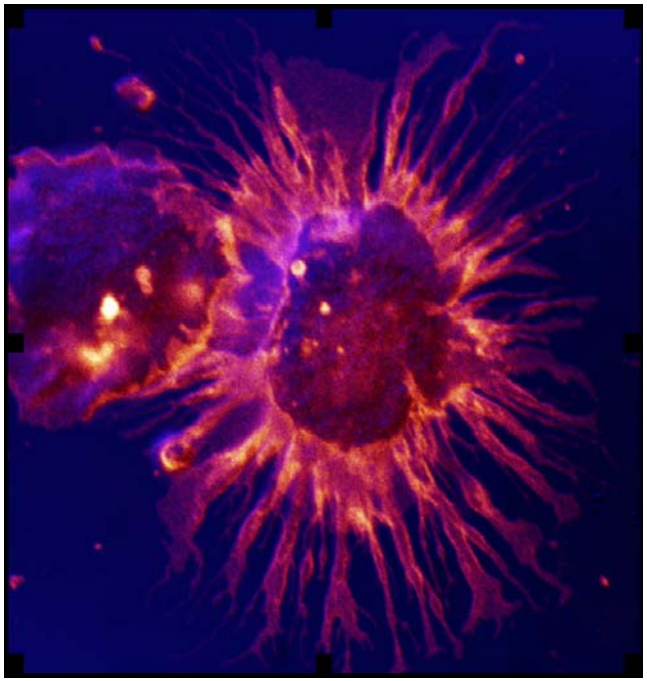


Microbial Products

Tissue damage

Cells of innate immunity

Cells of adaptive immunity



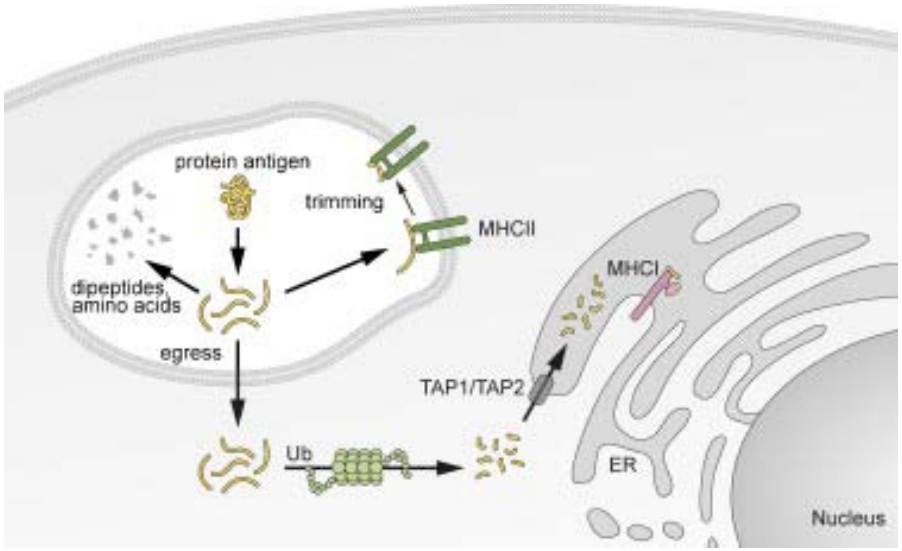
Immature DC → **Mature DC**

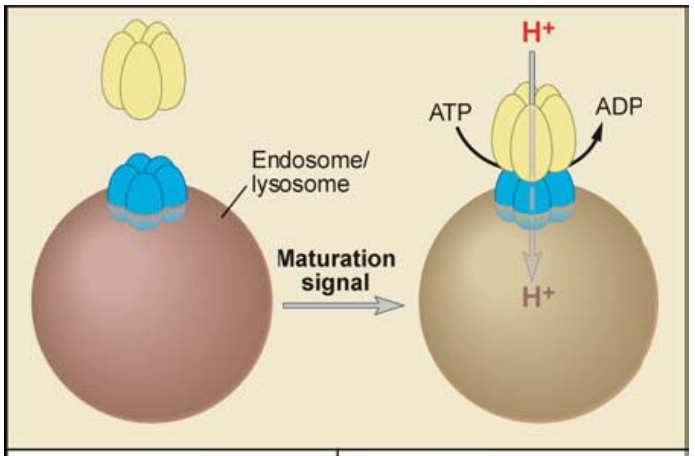
Antigen Capture

Immune Activation

Steinman & Mellman

Lysosomal Activation and Regulation of Antigen presentation



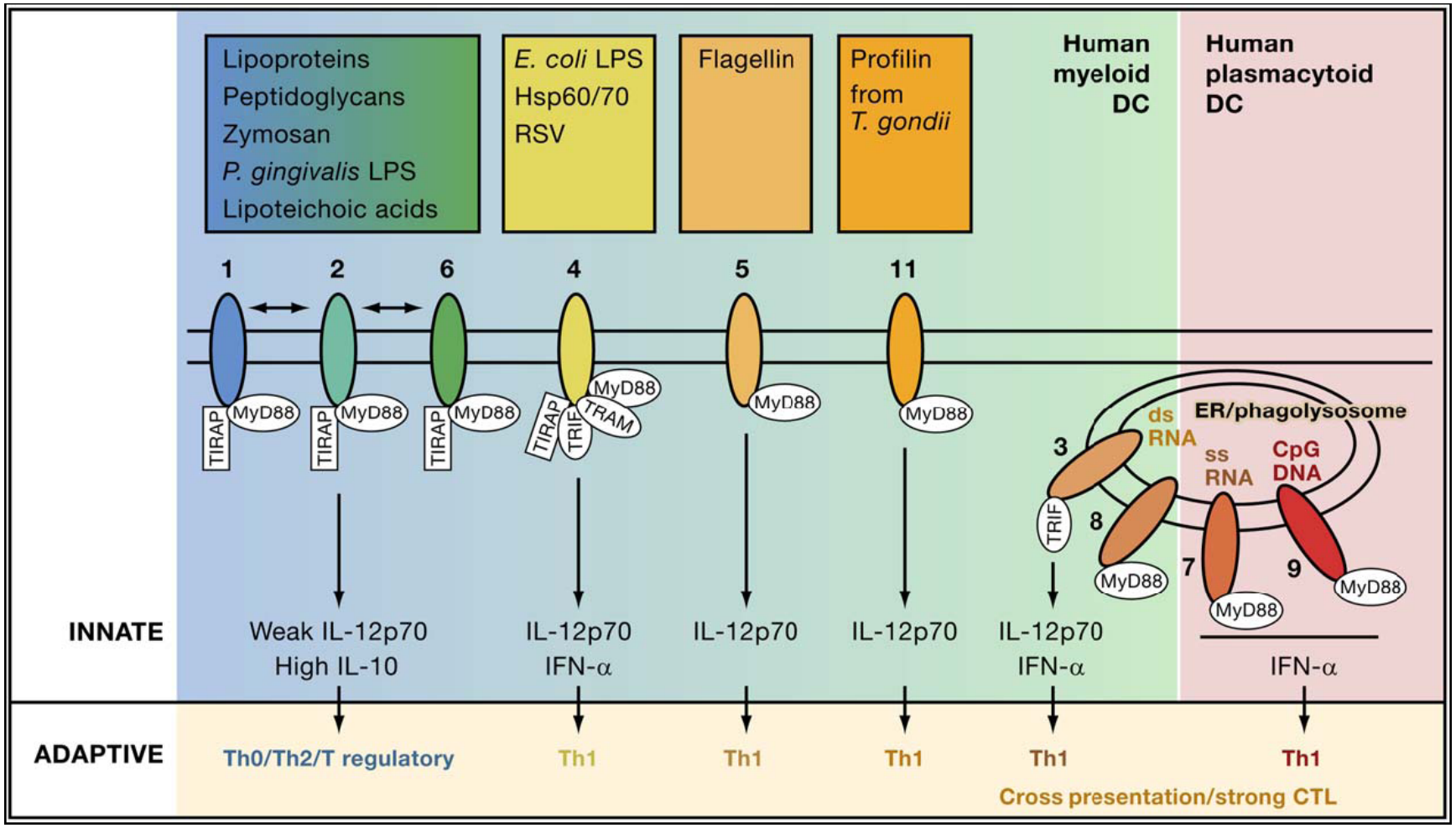


Immature DC	Mature DC
Reduced V-ATPase assembly	Enhanced V-ATPase assembly
Reduced acidification	Enhanced acidification
Higher pH	Lower pH

A distinctive property of DCs (relative to macrophages) is the limited lysosomal proteolysis, which favors presentation on MHC I.

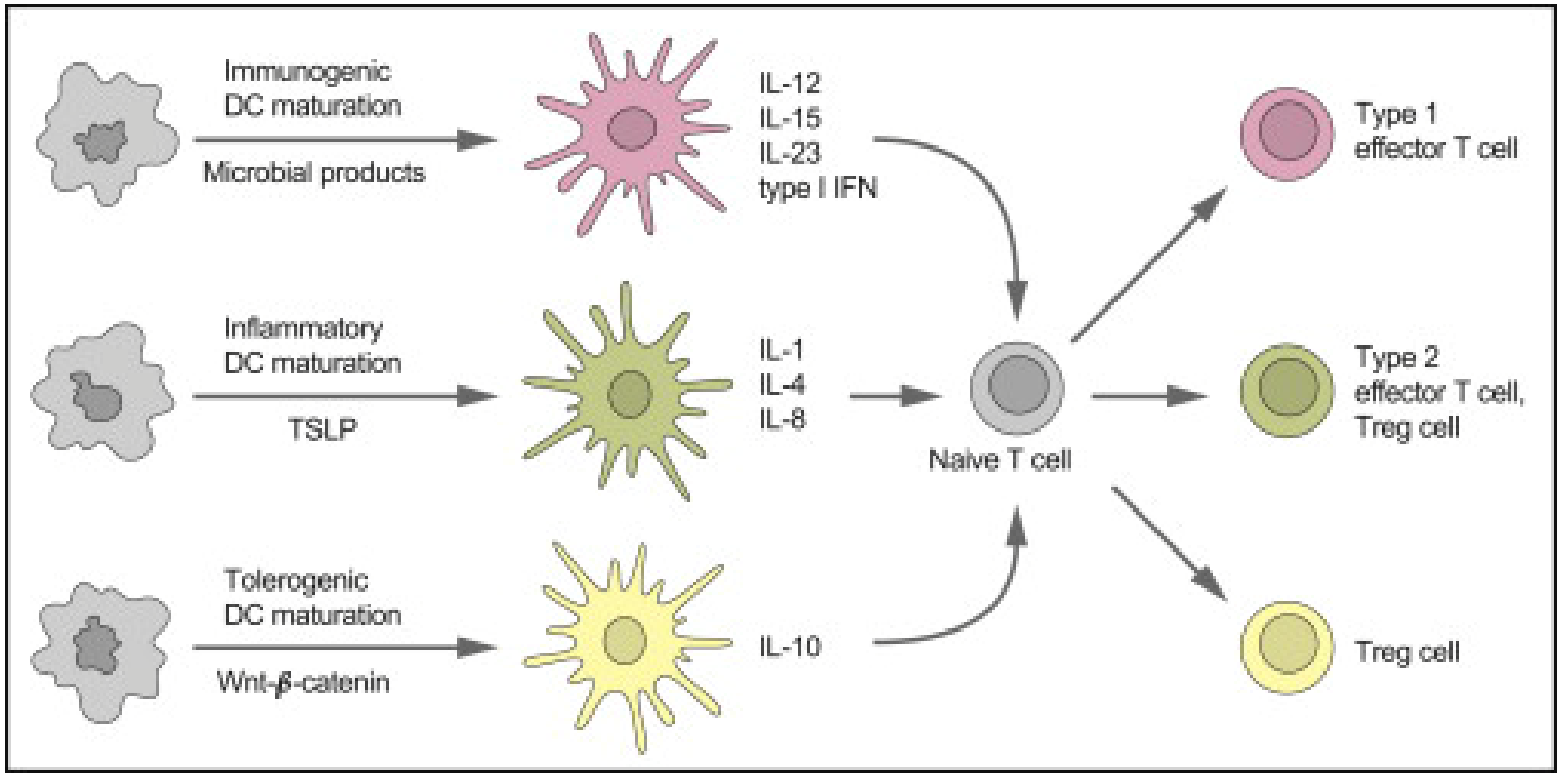
Trombetta & Mellman. 2005 Ann Rev Imm

TRIGGERING DISTINCT TLRs ON DCs ELICITS DIFFERENT CYTOKINE PROFILES AND DIFFERENT IMMUNE RESPONSES



Pulendran & Ahmed. 2006 Cell

Distinct Forms of DC maturation elicit different T cell responses

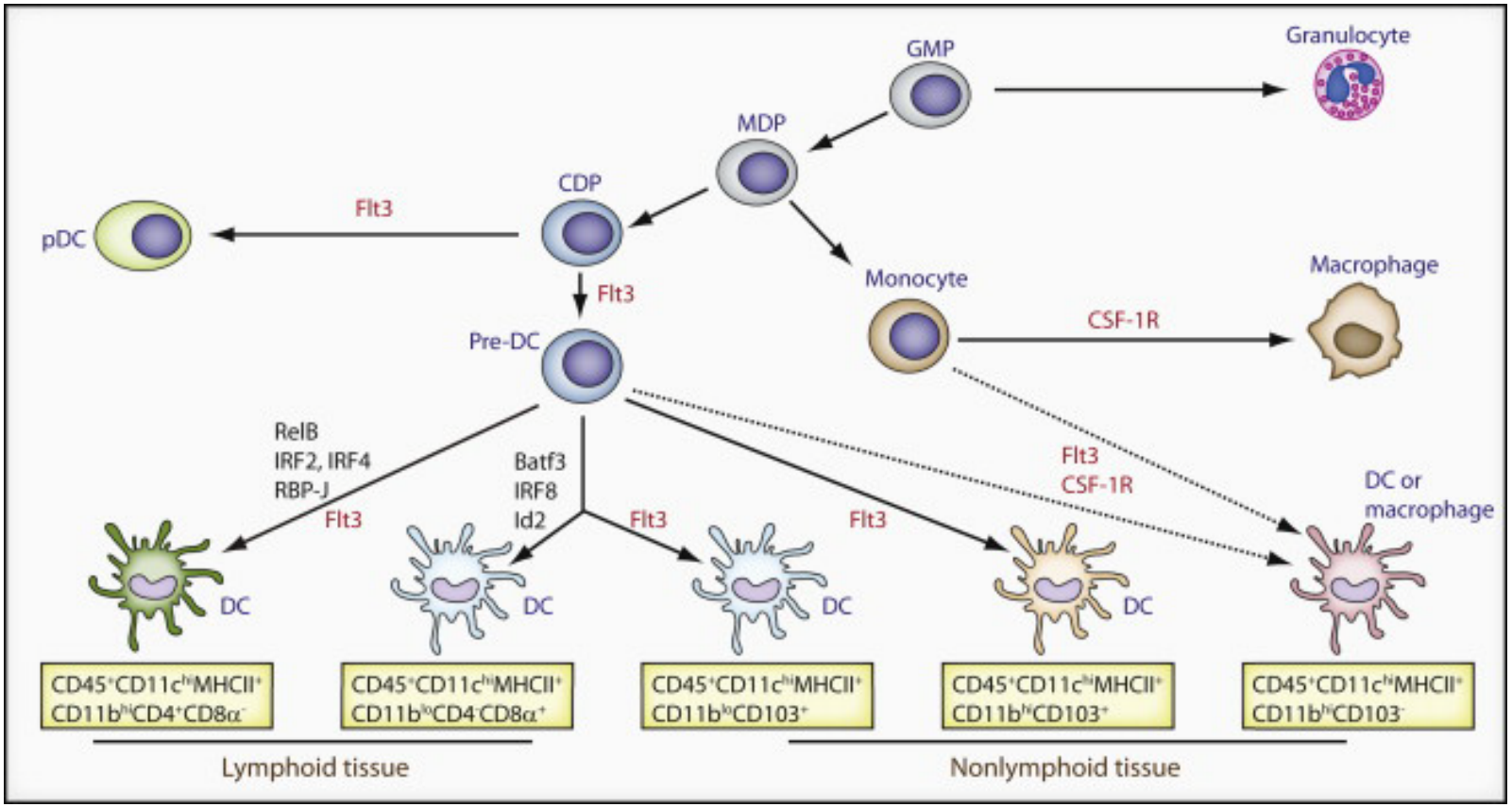


Palucka et al. Immunity 2010

DC Subsets and Diversity

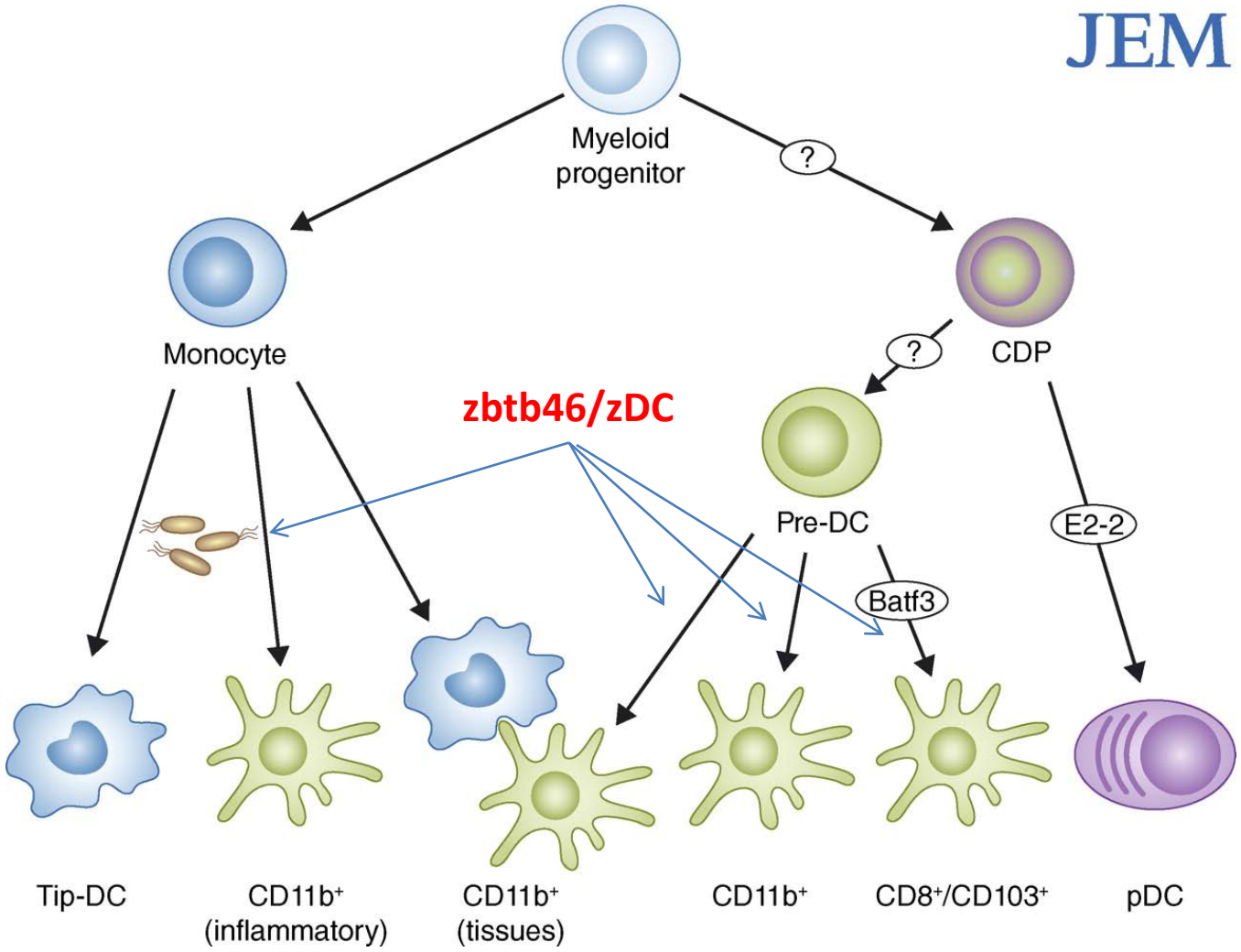
- Both lymphoid and non-lymphoid tissue resident, as well as recruited compartments.
- Some compartments capable of proliferation and self renewal in situ.
- Role of distinct transcription factors in developmental origin of distinct subsets.
- Distinct functional properties.

Developmental Origins of Mouse DC Subsets



Hashimoto et al. Immunity 2011

Transcriptional Specification of Dendritic Cell lineage in the mouse.

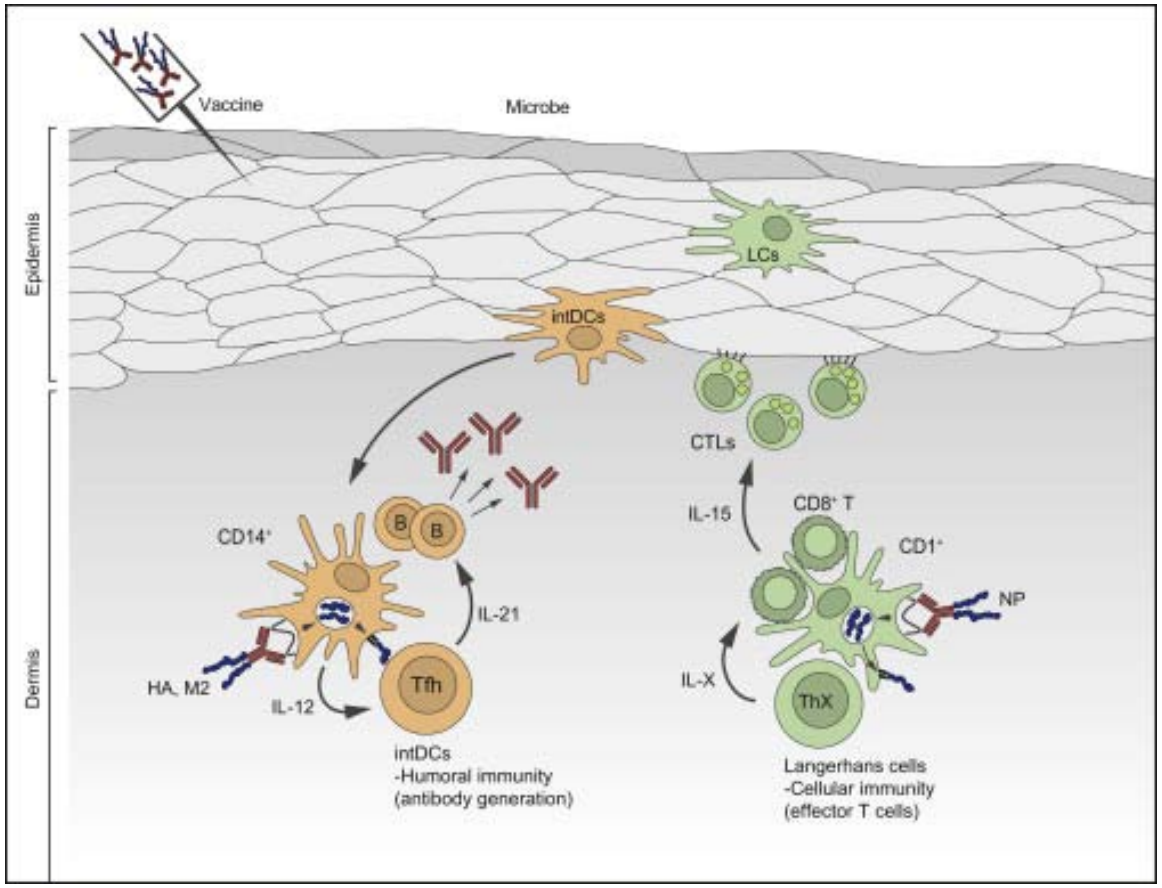


Reizis B J Exp Med 2012;209:1053-1056

Functional Specialization of Major Murine cDC Subsets

Subset	**Function**
Lymphoid DCs	
CD8a+	– Cross-presentation
CD8a-	– MHC II presentation
Tissue-resident DCs	
CD103+	– Cross presentation – ? Gut tolerance / Tregs
CD11b+ CD103-	– ? Amplify T cell immunity

Different DC Subsets mediate different functions



Palucka et al. Immunity 2010

Genomic Signatures of Murine DC Subsets

- Recent data from the Immunogen consortium suggest distinct gene expression profiles of defined murine DC subsets, including both tissue-resident cells and migratory DCs.

- Some genes in the core cDC signature
  - Zbtb46
  - Ccr7
  - Flt3
  - Kit
  - Btla

Miller et al. Nature Imm 13:888, 2012

Expression Of Pattern Recognition Receptors In DC Subsets

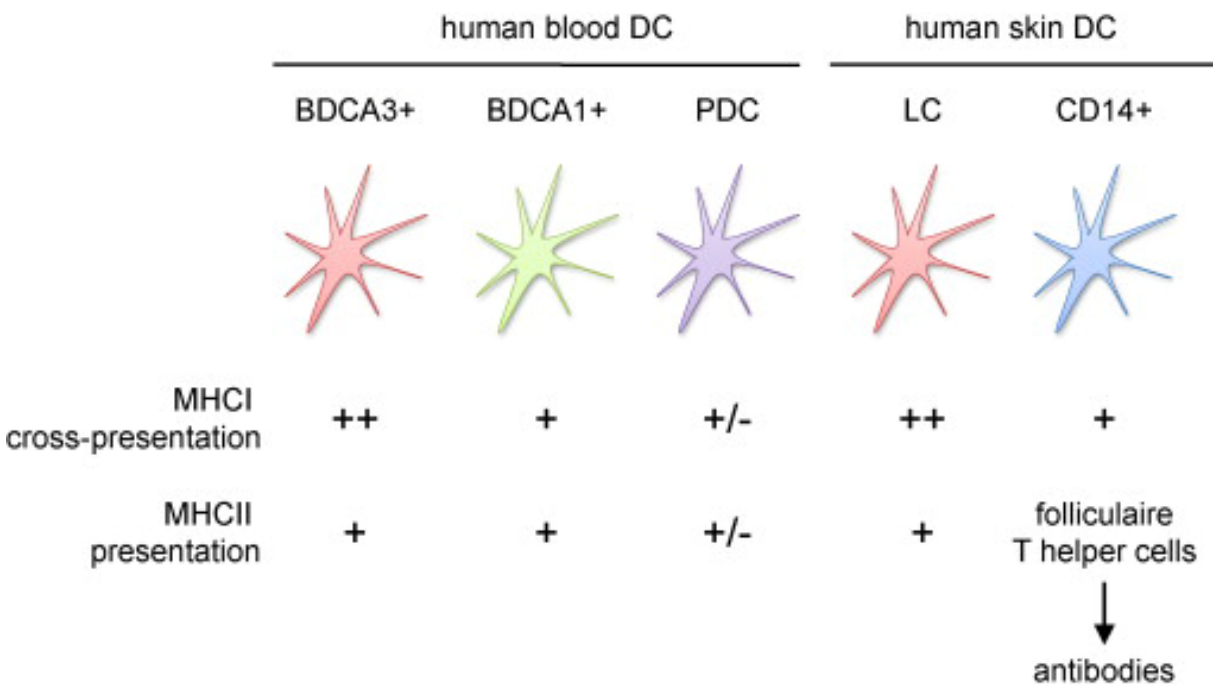
PRR	Human blood DC			Human skin DC		Murine splenic DC		
	BDCA3+	BDCA1+	PDC	LC	CD14	CD11b− CD8+	CD11b+ CD8−	PDC
TLR1	+	+	+	+/−	++	++	++	++
TLR2	+	++	+/−	−	++	++	++	++
TLR3	+++	+	−	+	+	+++	+	+/−
TLR4	−	+	−	−	++	+	+	+
TLR5	−	+	−	+/−	++	+	+++	++
TLR6	+	+	+	+/−	++	++	+++	+
TLR7	−	+	+++	+	+	−	++	+++
TLR8	+	+	−	−	++	++	++	++
TLR9	−	−	++	+	+	++	++	+++
TLR10	+/−	+	+	+/−	+/−	N/A	N/A	N/A
RIG-I	+	+	+/−	?	?	−	+	+
MDA5	+	+	+	?	?	−	+	+

Human CD141+ BDCA3+ DCs as possible equivalents for murine CD8+ DCs

Property	Mouse $CD8^+$ DCs	Human $CD141^+$ DCs
Surface markers	$CD8^+$, $CD11b^{low}$, $CD24^{hi}$, $CD36^+$ $CD205^+$ $CD172a^-$ $Clec9A^+$ $DCIR2^-$ $Necl2^+$, $XCR1^+$	$CD1^-$ $CD141^+$ $Clec9A^+$ $Necl2^+$ $XCR1^+$
Developmental transcription factors	$Batf3^+$, IRF-8^+, IRF-4^-	$Batf3^+$, IRF-8^+, IRF-4^-
Pathogen sensors	$TLR1^{-/low}$ $TLR2^+$ $TLR3^+$ $TLR4^+$ $TLR6^{-/low}$ $TLR7^-$ $TLR9^+$ $TLR11/12^+$ RIG^-	$TLR3^+$, $TLR7^-$, $TLR9^-$
IL-12 production	Yes	Yes
Dead cell uptake	Yes	Yes
Antigen cross-presentation	Yes	Yes

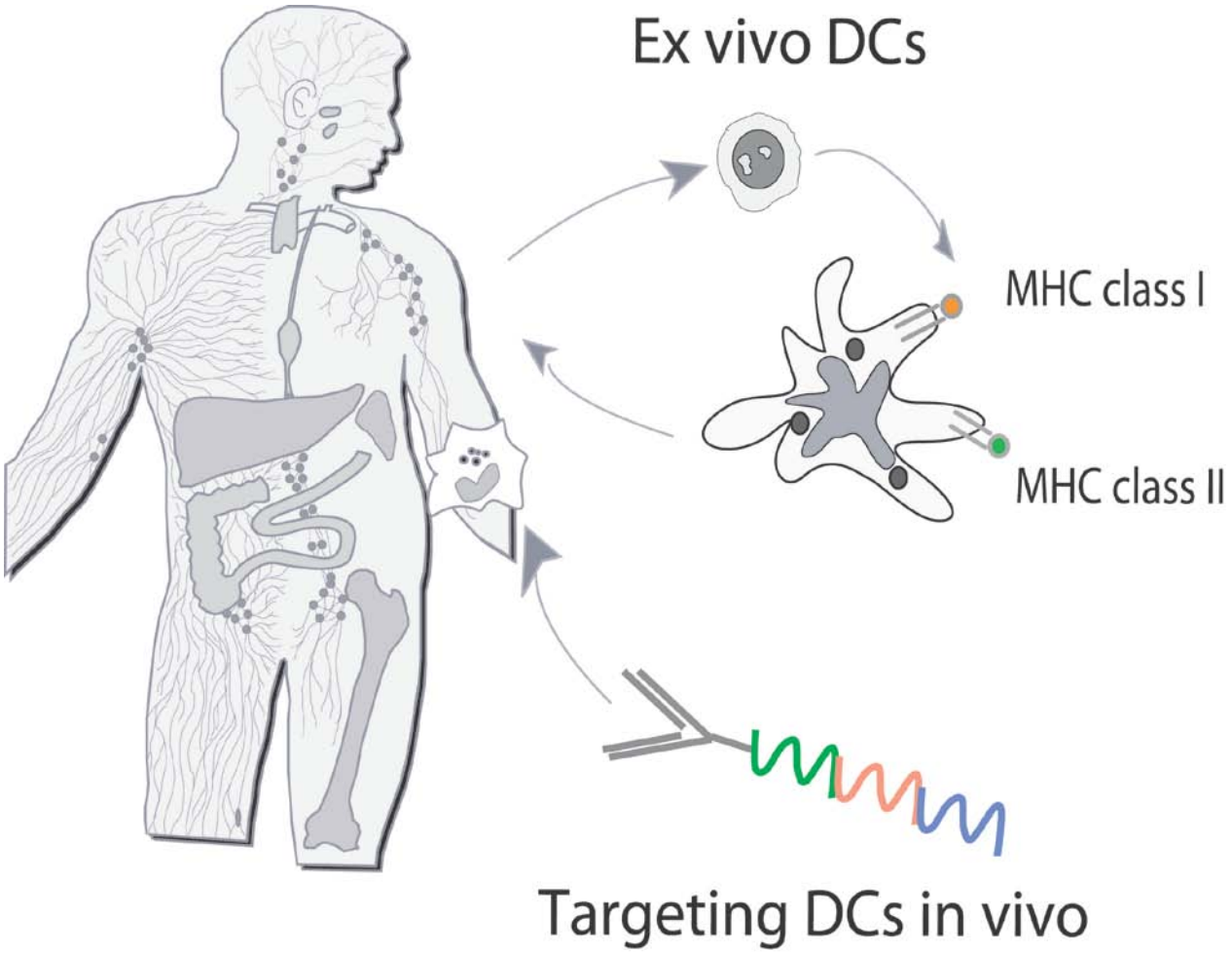
Bachem et al., 2010; Crozat et al., 2010; Jongbloed et al., 2010; Poulin et al., 2010

Functional Diversity in Human DC Subsets



Delamarre, Mellman; Sem Imm 2011

Two Paths to Harnessing DCs in Cancer

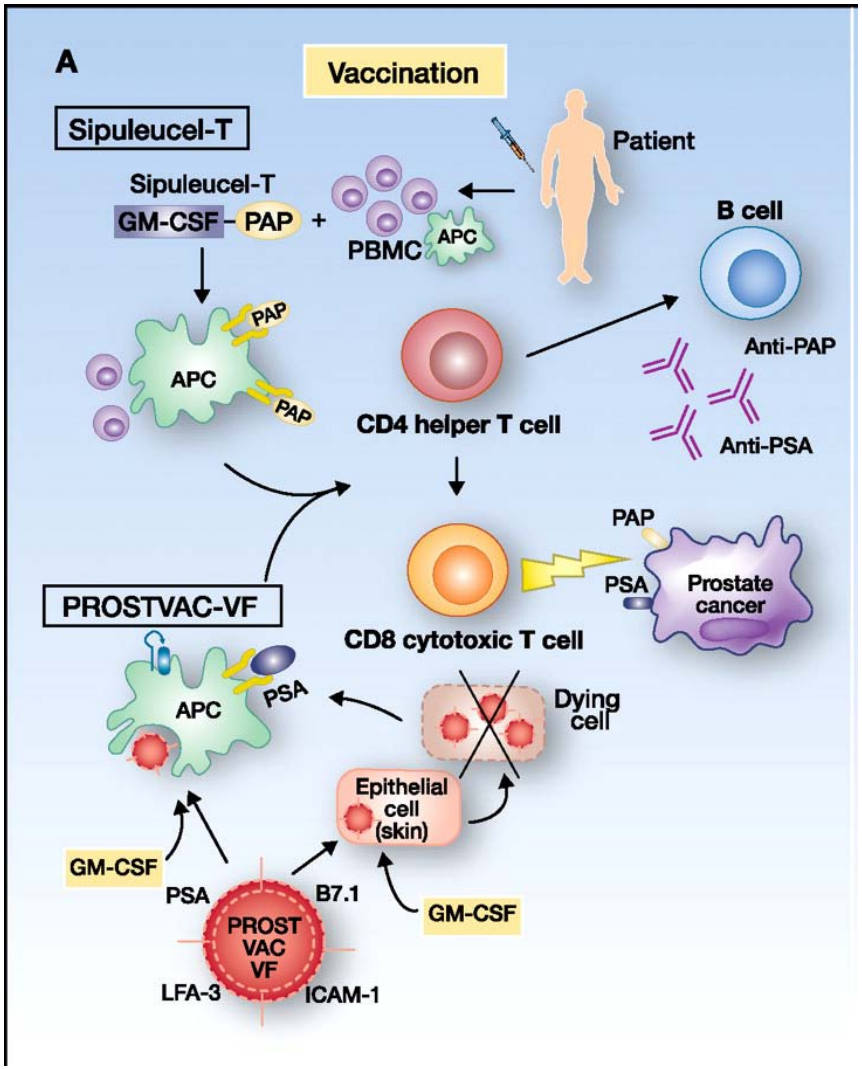


Palucka et al. Immunity 2010

Strategies for Adoptive Transfer of DCs

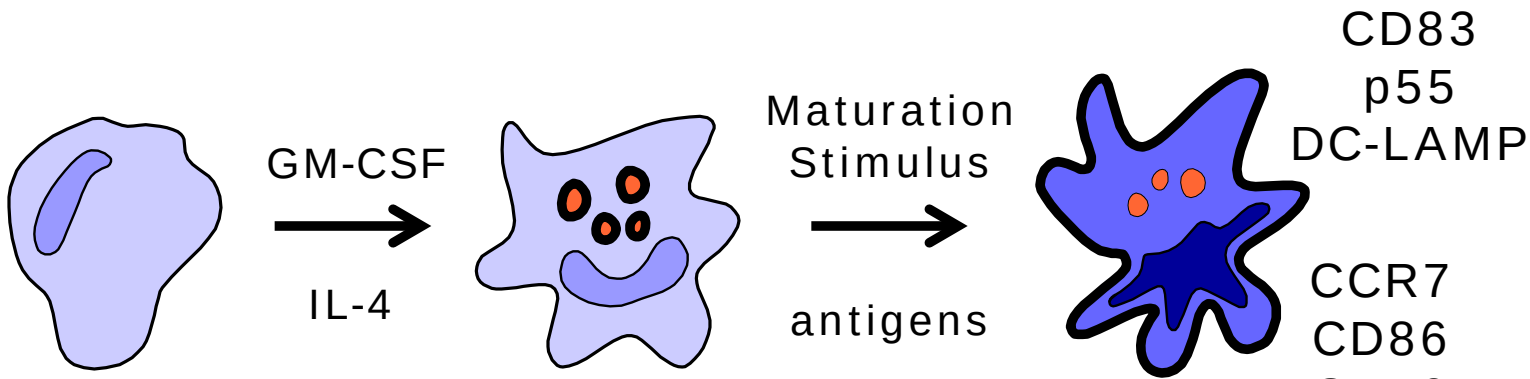
- Circulating blood derived DCs
  - Provenge
- Monocyte-derived DCs
- CD34+ HPC derived DCs

Sipuleucel-T as a Cellular Vaccine Against Cancer



May K F et al. Clin Cancer Res 2011;17:5233-5238

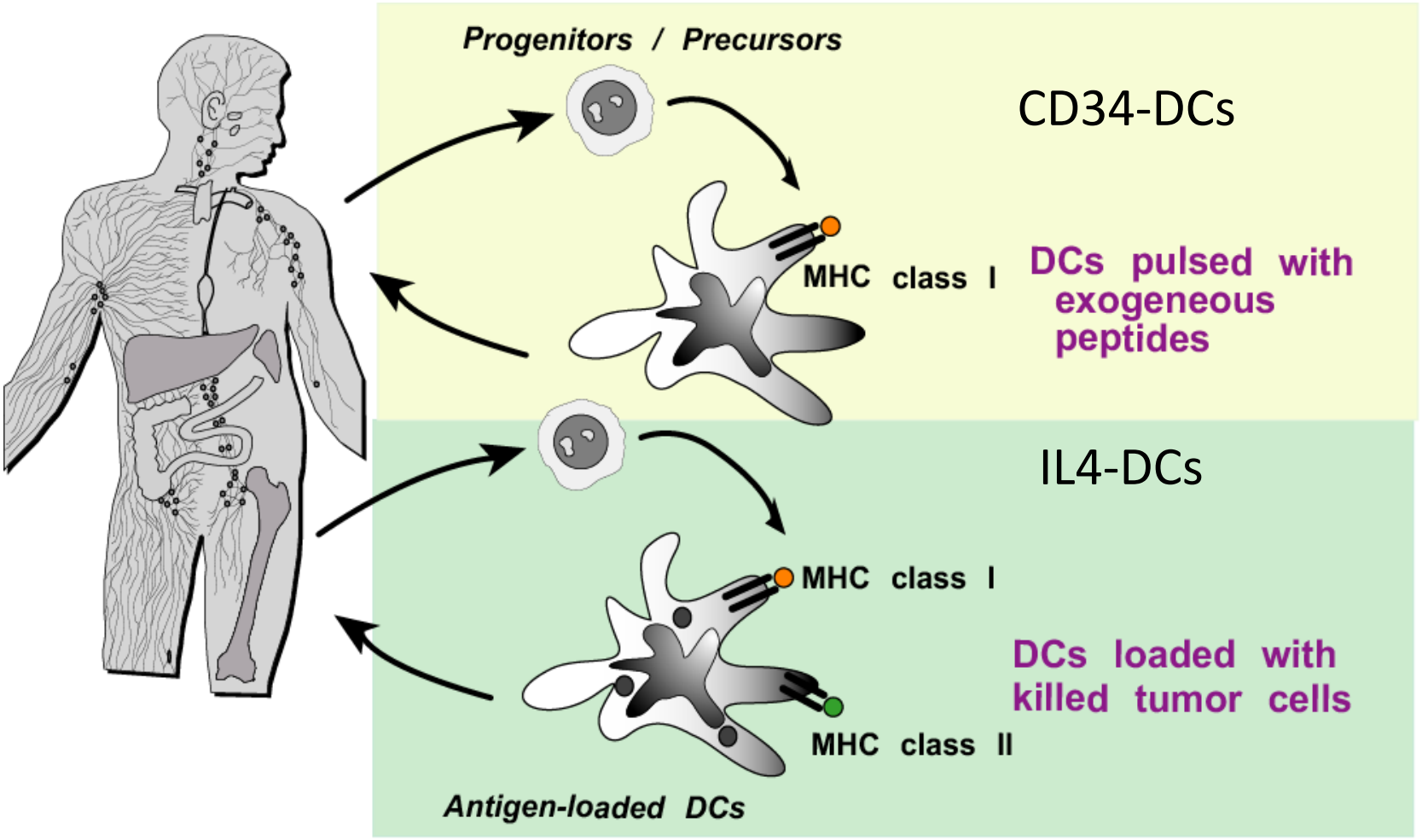
Generation of Monocyte-Derived DCs for DC vaccination



MONOCYTE IMMATURE DC MATURE DC

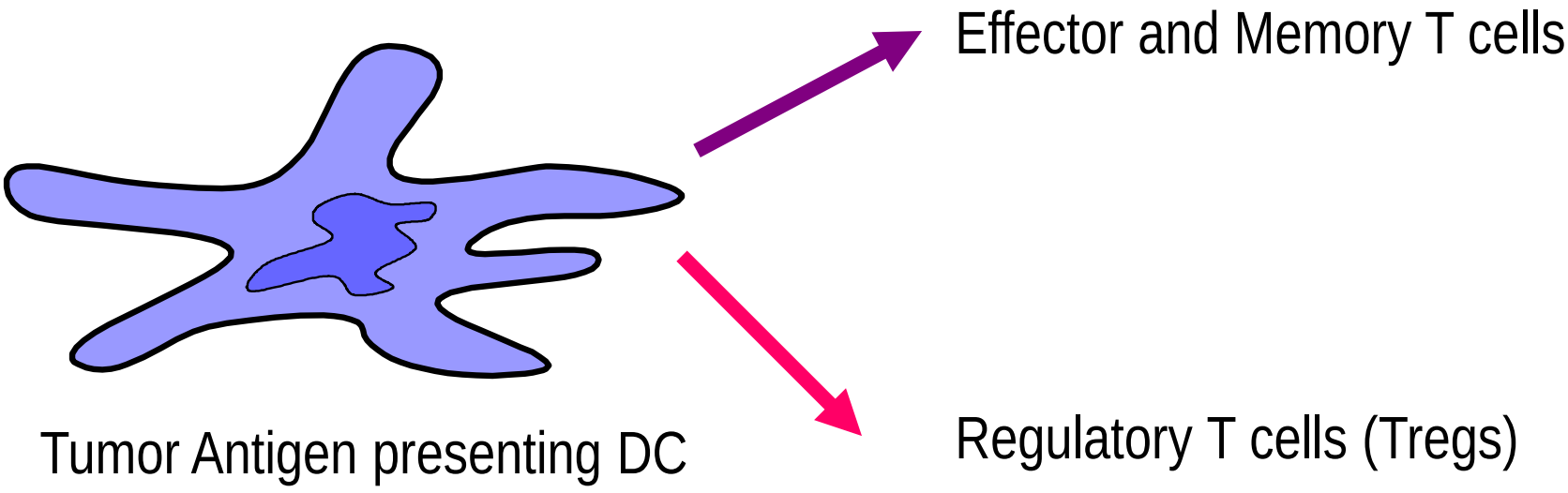
Dhodapkar et al
J. Clin. Invest. 104: 173-180 '99
J. Clin. Invest. 105: R9-R14 '00
J. Exp. Med. 193: 233-238 '01

Ex vivo generated DCs can be loaded with several antigens including peptides or tumor cells



Palucka and Fay

Balance Of Effector Versus Tregs As A Determinant Of Vaccine Efficacy



Conclusions from several trials of adoptive transfer of Ex-vivo DCs

- No dose limiting toxicity.
- Induction of immune responses.
- Some evidence for clinical activity, including regression of advanced disease
- ..but overall low rates of clinical responses

Need to develop approaches that enhance clinical activity.

Some Possible Reasons Behind Limited Efficacy of Therapeutic DC Vaccines

- Limited Potency of the vaccine
  - DC subtype, maturation stimulus, antigen, route, migration, targeting innate lymphocytes
- Tumor / Host related factors
  - Therapeutic versus preventive, Bulk disease vs MRD
  - Tumor associated immune-suppression
  - ? Need for combination approaches
  - ? Need to identify biomarkers predictive of regressions

In vivo targeting of DCs

- Targeting antigen in vivo to specific DC receptors
  - Antibodies– DEC205
  - Nanoparticles
  - Others

Advantages:

Efficiency, amenable to larger scale studies as an “off the shelf” reagent.

Large numbers of DCs can be targeted …? Greater efficacy

Early phase studies currently underway .

Challenges:

Which receptor, which antigen, which adjuvant, efficacy ?

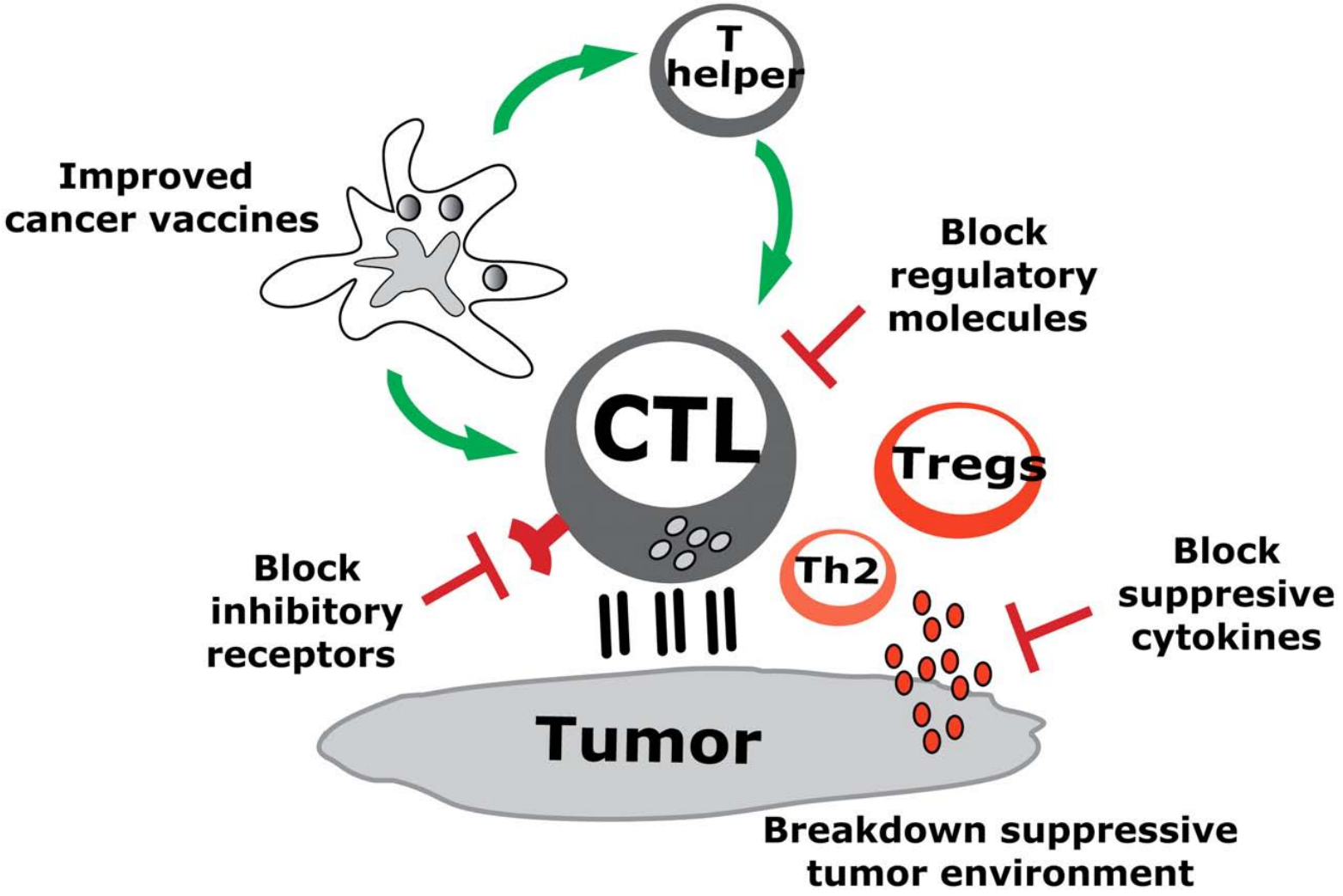
Some Examples of Targets for In-vivo Targeting of DCs

- MMR
- DEC-205
- DC-SIGN
- CD40

Need for concurrent administration of a DC maturation stimulus…e.g. TLR ligand.

Early phase studies show feasibility of this approach and its capacity to induce T cell immunity

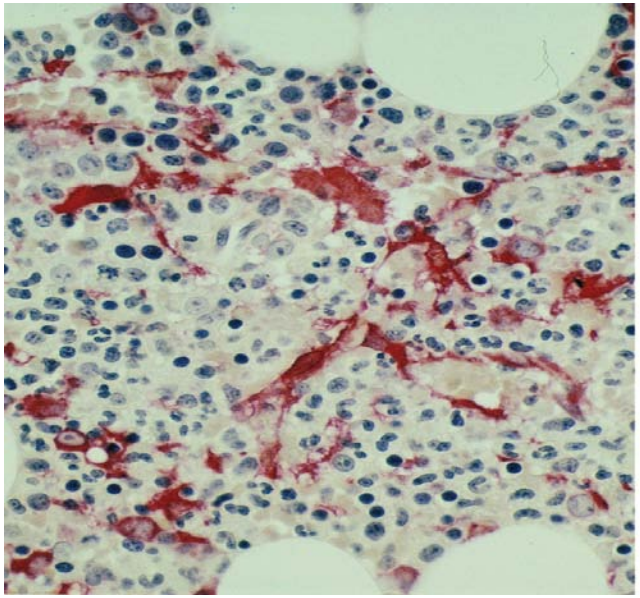
Combination Approaches to Improve Cancer Vaccines

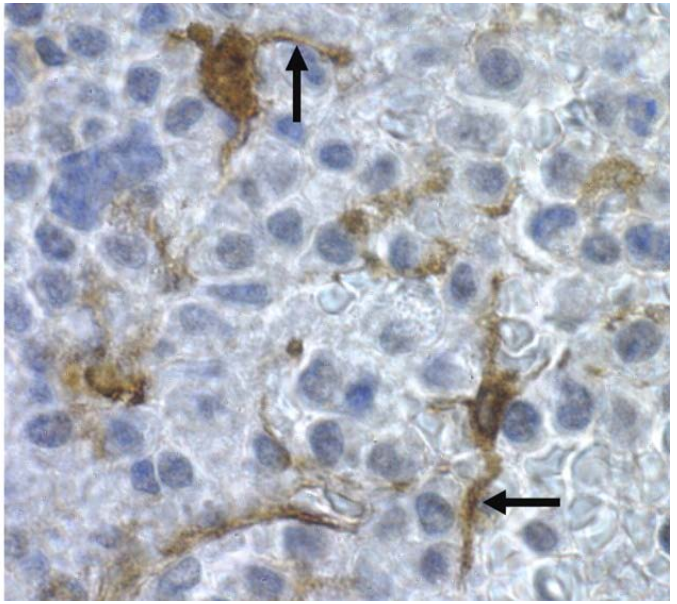


Palucka et al JI 2011

Non-Immune Effects of DCs in the Tumor Bed

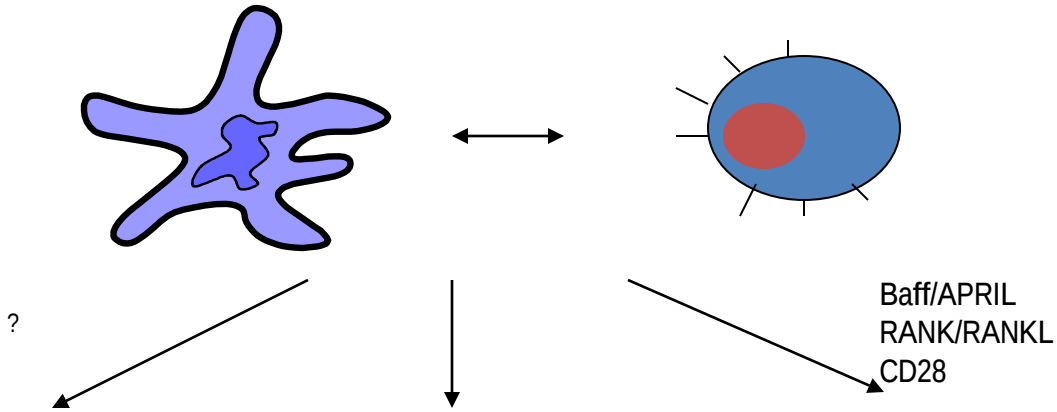
Enrichment of Dendritic Cells Within Tumor Lesions of Myeloma Patients





Rettig et al. Science 1997
Said et al, Blood 1997
Chauhan et al Blood 1998
Bahlis et al, Blood 2007

Cross-talk between myeloma cells and infiltrating DCs



Cell Fusion

↓

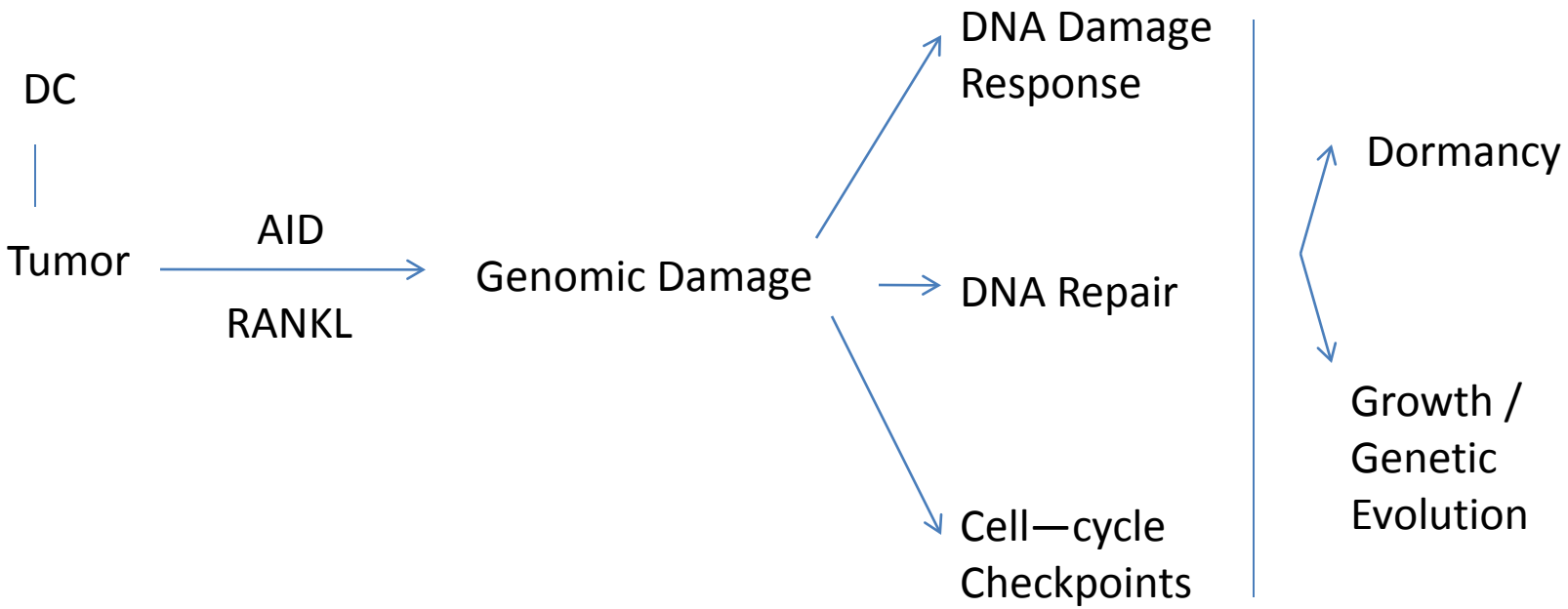
Osteoclastogenesis

Altered
T cell polarization

Enhanced clonogenicity
& dedifferentiation of
tumors

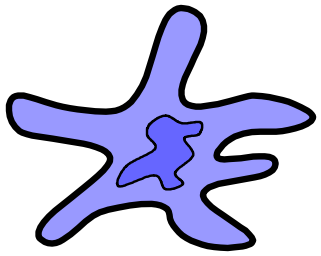
Kukreja et al JEM2007
Dhodapkar Blood 2008
Chauhan Cancer Cell 2009
Yaccoby et al. Clin Cancer Res 2005
Bahlis et al Blood 2007

DC-Tumor Interactions as contributors to genomic damage and genetic evolution of cancer



Koduru et al.

Possible Non-Immune Effects of DCs in Tumor Biology



Trophic Effects on Tumor Cells:
-Growth, Survival, ? niche

Modification of Tumor Microenvironment
-Angiogenesis, Osteoclastogenesis

? Other Effects
? Genomic instability, ? dormancy

Conclusions

- DCs serve as critical APCs for activation and regulation of the immune system.
- Harnessing the anti-tumor properties of DCs and targeting them will be essential to better harness immune system against cancer.
- DCs may also serve more active roles within TME to regulate carcinogenesis.

Acknowledgments

- Funding: NIH, LLS, MMRF

- Current and past members of Dhodapkar lab

- Kavita Dhodapkar
- Karolina Palucka, Jacques Banchereau, Joseph Fay
- Ralph Steinman, Jeff Ravetch

Thank You…

And now let us see what you remember out of this ?