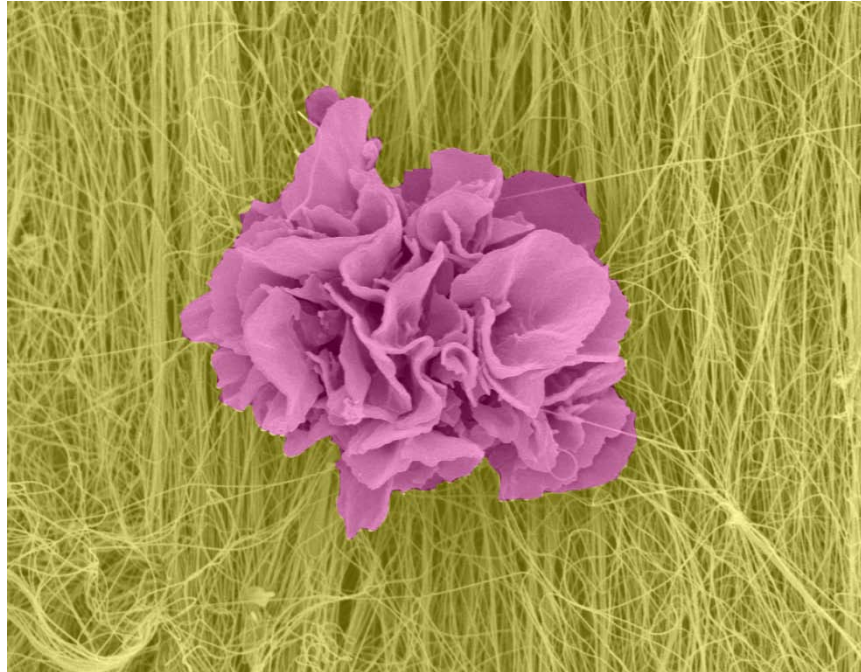


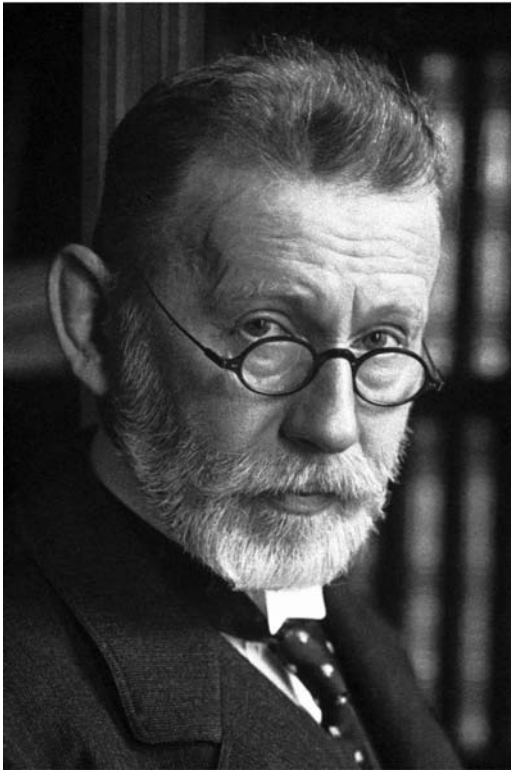
Ralph Steinman and the Discovery of Dendritic Cells

Dec. 7th, 2011

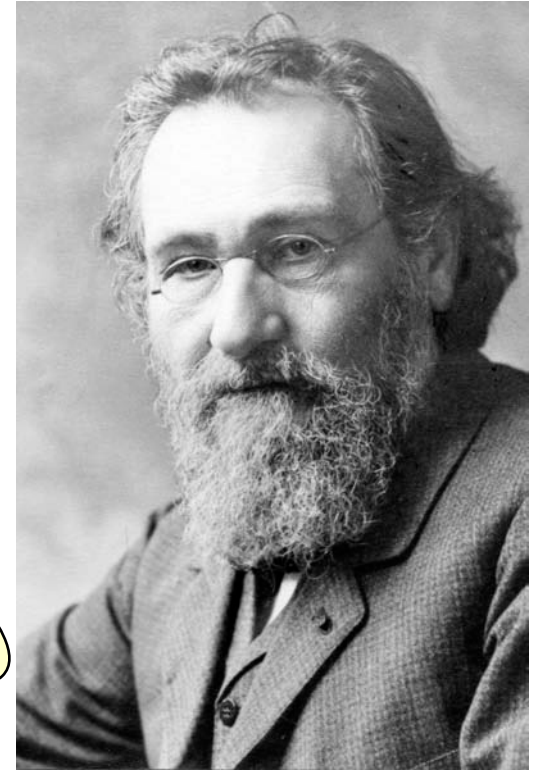
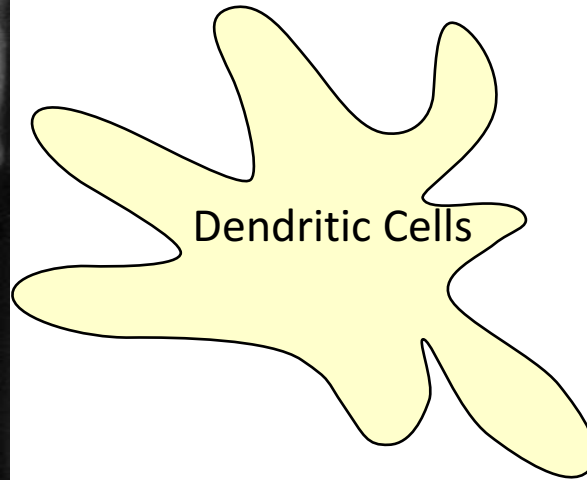


Dendritic cell in human dermis (collagen fibers)
Patti Stoitzner, Kristian Pfaller, Nikolaus Romani -- Innsbruck

1908 Nobel Prize “in recognition of their work on immunity”



Paul Ehrlich
Adaptive Immunity



Ilya Ilyich Metchnikov
Innate Immunity

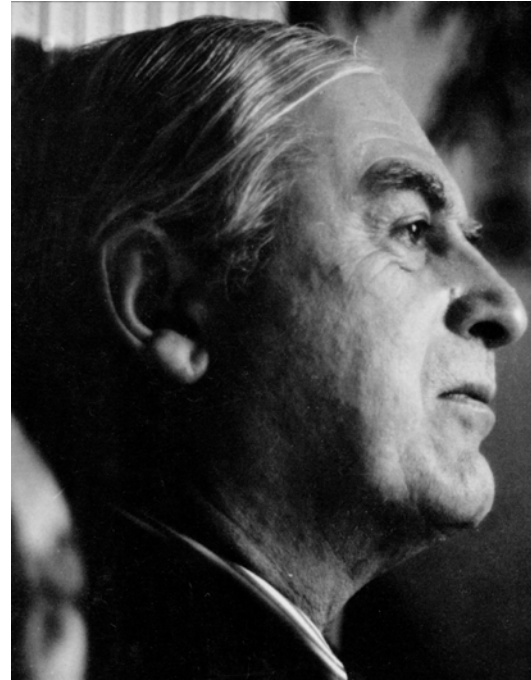


Ralph's (*)
first day of
physical
diagnosis,
Harvard
Medical
School 1964

1960 Nobel Prize “for the discovery of acquired immunological tolerance”



Macfarlane Burnet
Clonal Selection



Peter Medawar
Immune Tolerance

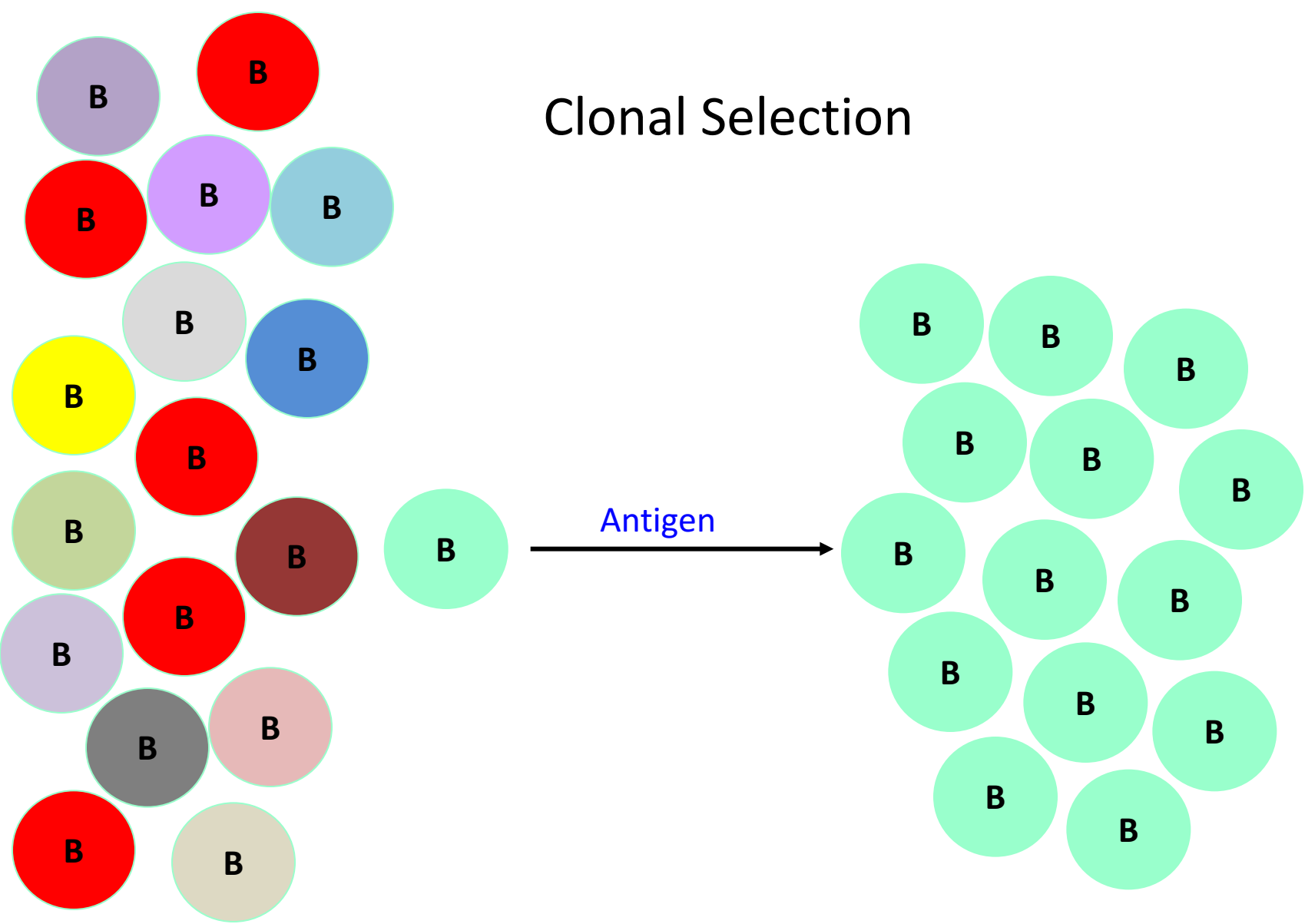
Properties of Immune Responses

1. Specificity

2. Diversity

3. Memory

Clonal Selection



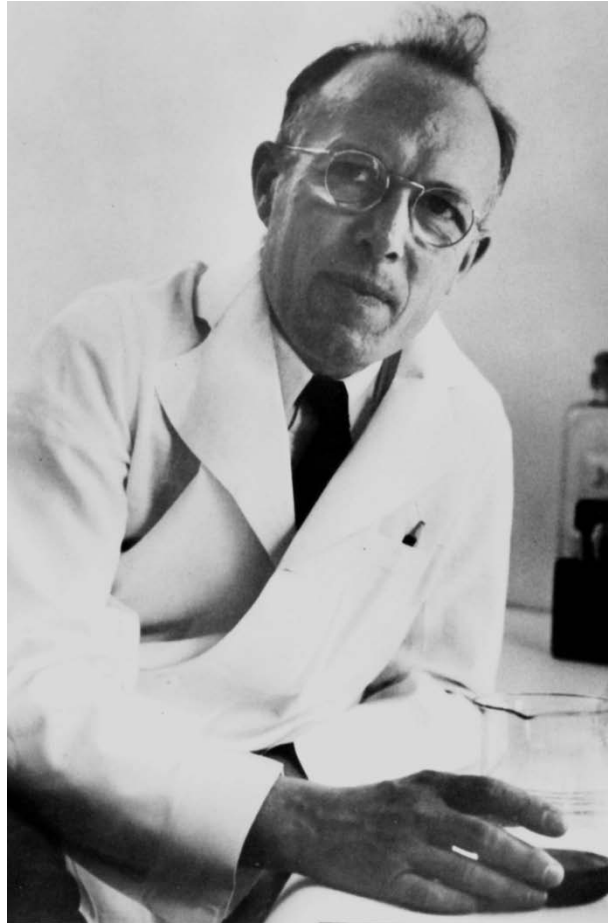
V(D)J Recombination

Clonal Expansion

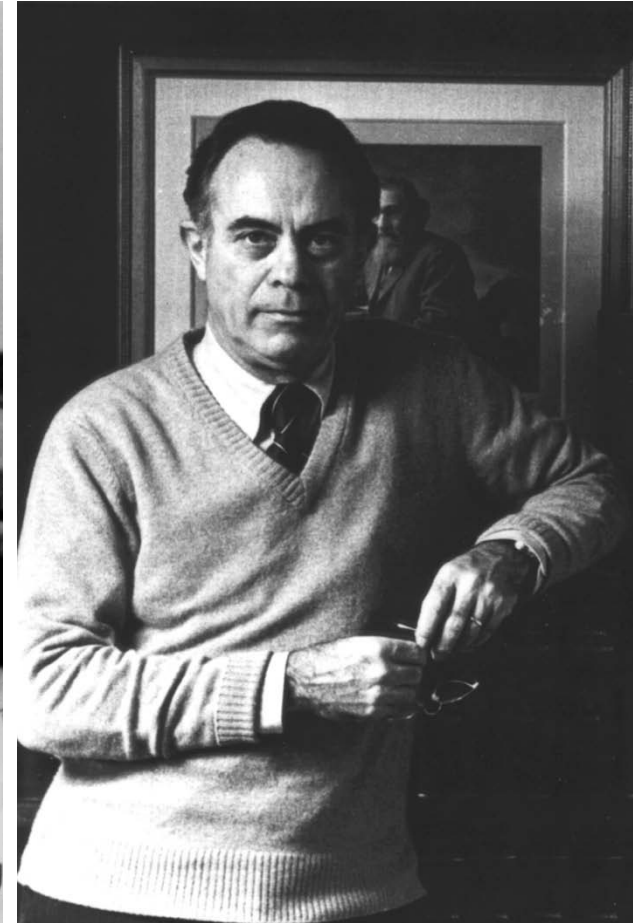
Ralph Steinman's mentors at Rockefeller University



Zanvil Cohn

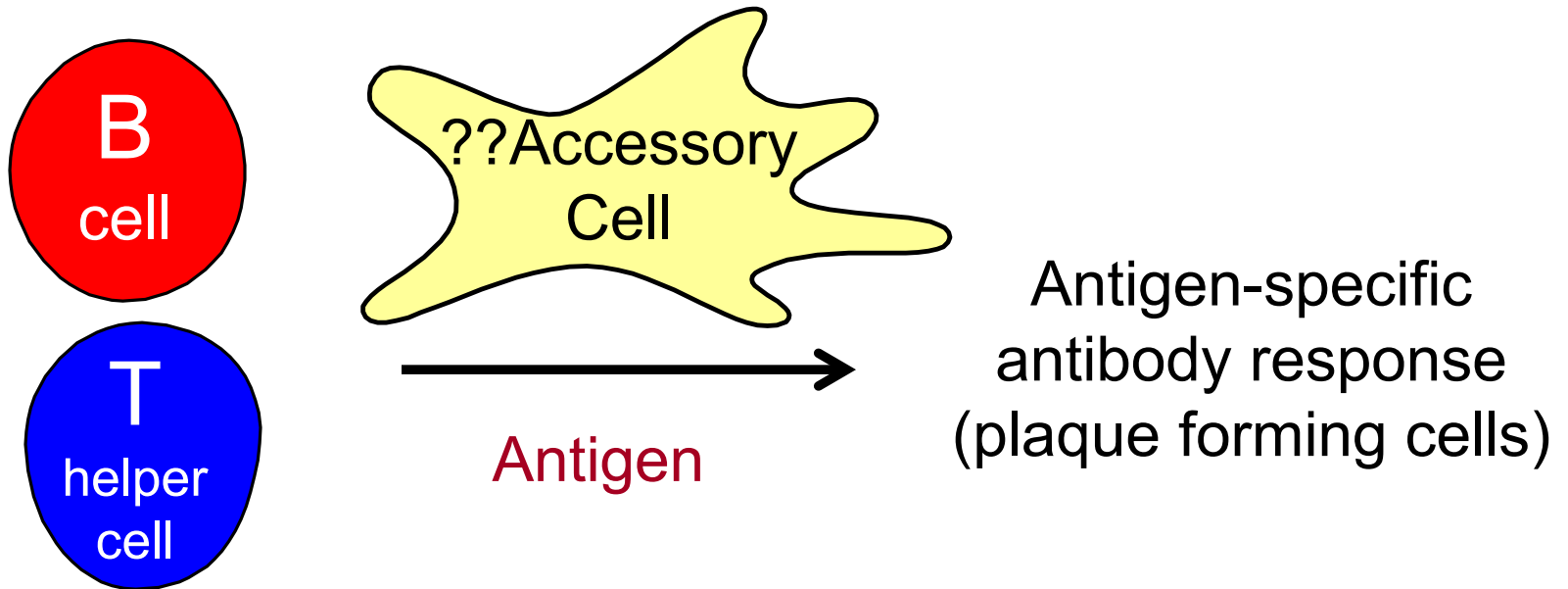


René Dubos



James Hirsch

Mouse Spleen Cell Mishell-Dutton Cultures: the Need for Accessory Cells



Mishell, R.I. and Dutton, R.W., J. Exp. Med. 126: 423 (1967)



Zanvil A. Cohn and Ralph M. Steinman

Reports Concluding that Macrophages Retain Intact Antigen on Their Cell Surfaces

Nossal, G. J. V., Abbot, A., Mitchell, J. and Lummus, Z., Antigen in immunity. XV. Ultrastructural features of antigen capture in primary and secondary lymphoid follicles. *J. Exp. Med.* 1968. 127: 277-296.

Unanue, E. R. and Cerottini, J.-C., The immunogenicity of antigen bound to the plasma membrane of macrophages. *J. Exp. Med.* 1970. 131: 711-726.

Antigen Degradation by Peritoneal Macrophages

1. Ehrenreich B.A., and Cohn, Z.A. The uptake and digestion of iodinated serum albumin by macrophages in vitro. JEM (1967)
2. Steinman R.M., and Cohn, Z.A. The interaction of soluble horseradish peroxidase with mouse peritoneal macrophages in vitro. JCB (1972)
3. Steinman R.M., and Cohn, Z.A. The interaction of particulate horseradish peroxidase immune complexes with mouse peritoneal macrophages in vitro. JCB (1972)

1974 Nobel Prize “for their discoveries concerning the structural and functional organization of the cell”

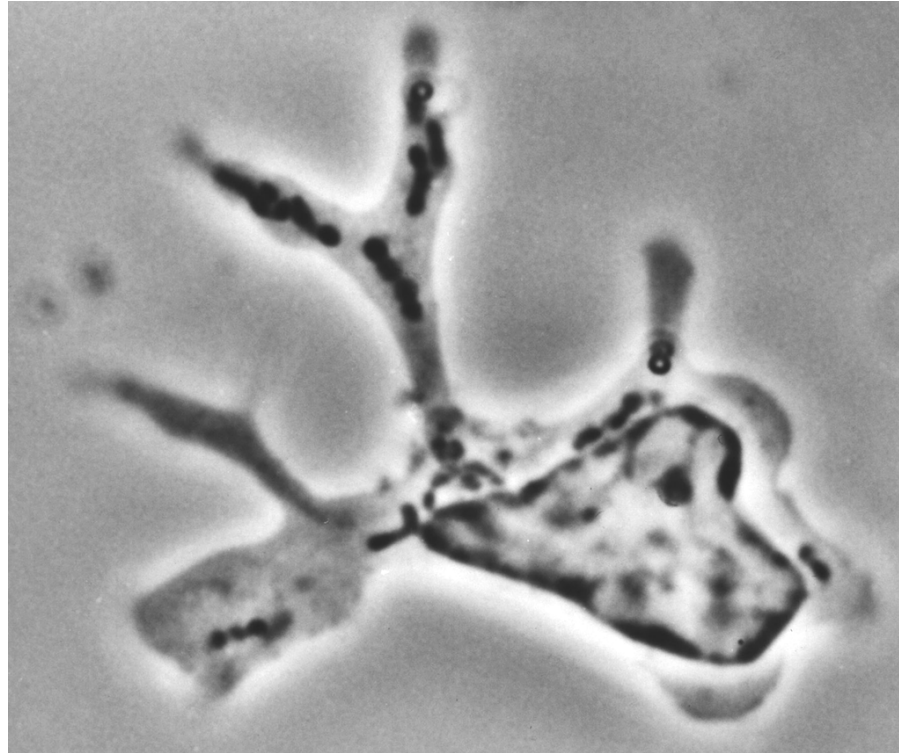


George Palade
Microscopy and
Fixation Methods



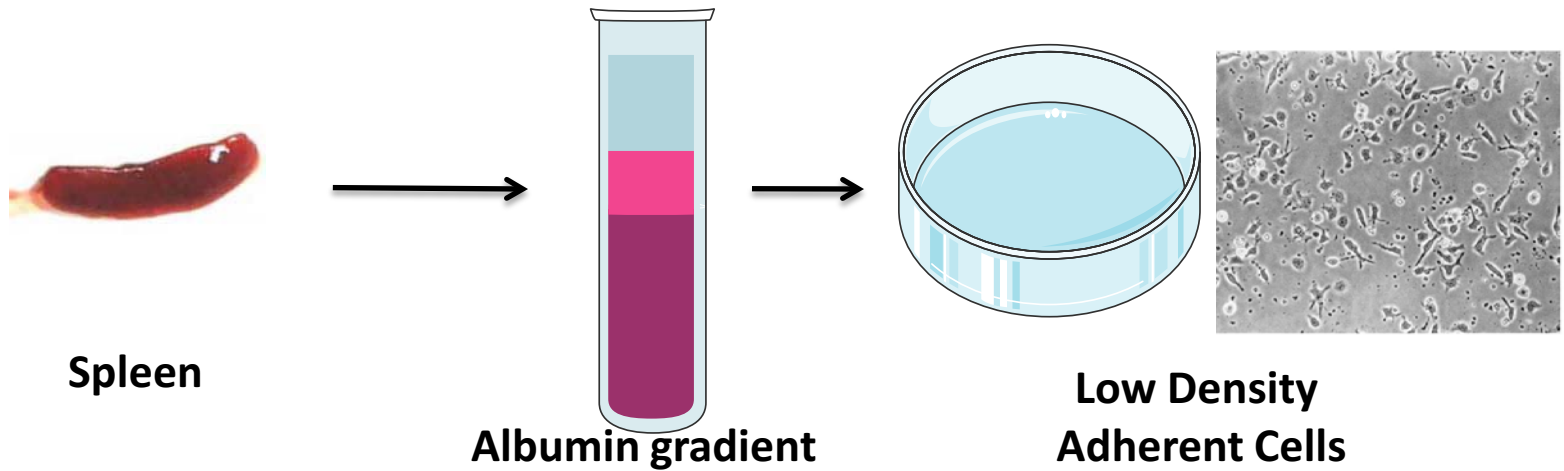
Christian De Duve
Gradients for DC
Purification

Dendritic Cell (“dendreon,” tree)

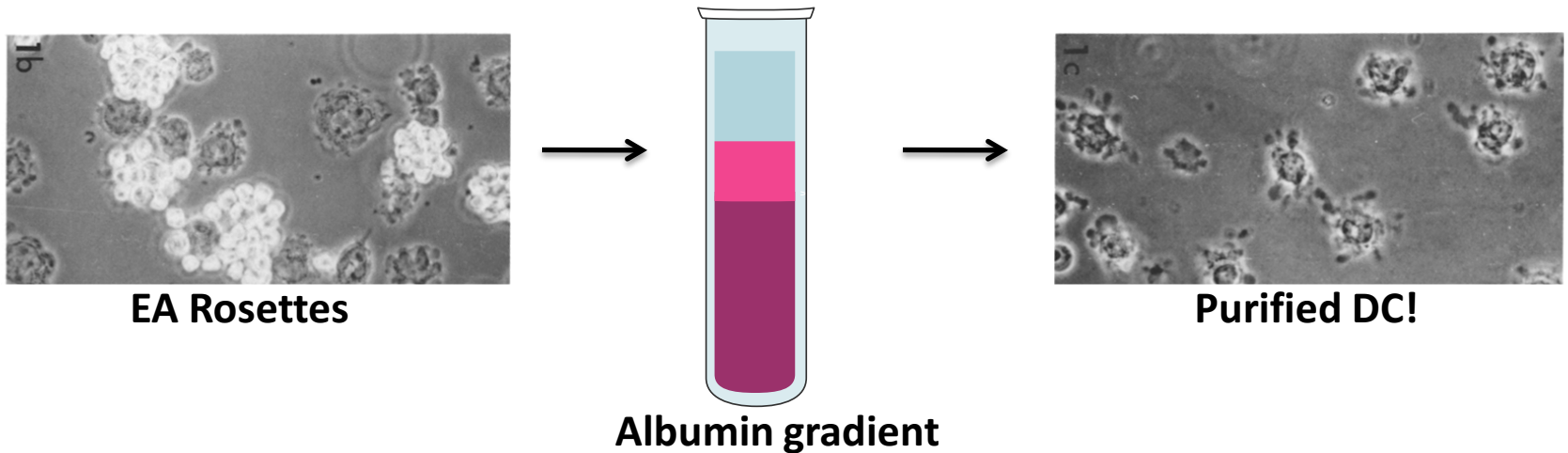


Steinman, R.M., and Cohn, Z.A. Identification of a novel cell type in peripheral lymphoid organs of mice. J. Exp. Med. 137:1142-1162 (1973)

Dendritic Cell Purification

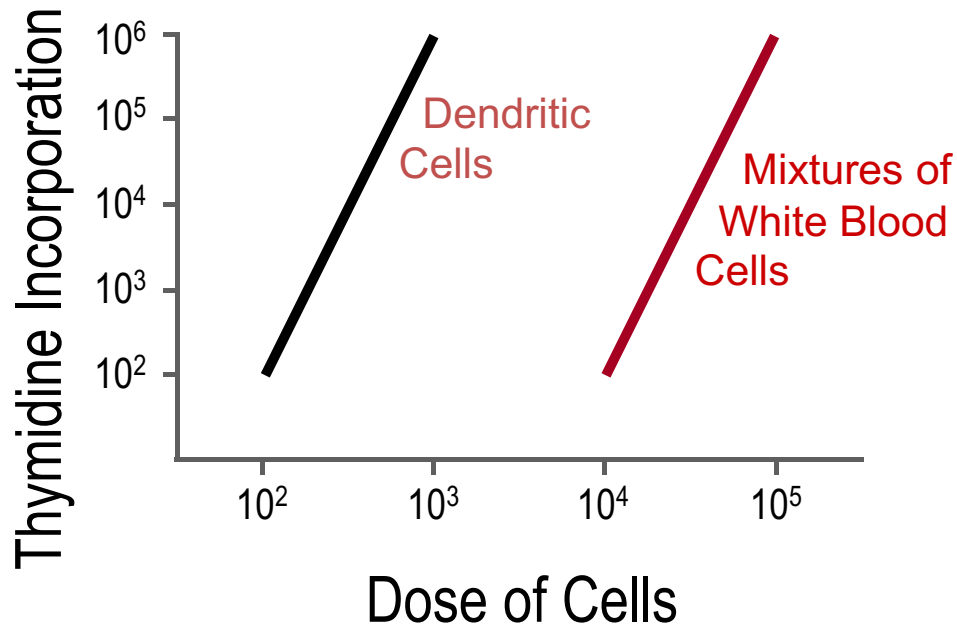


Overnight Culture



Steinman, R.M., and Cohn, Z.A. JEM (1974)

Mixed Leukocyte Reaction



Steinman and Witmer, PNAS 75: 5132-5136 (1978)

“This report was initially received with some skepticism, based on the widely held view that the major antigen presenting cells were the far more numerous macrophages and on the uncertainty that many immunologists had about the assay that Steinman and Cohn used to establish the function of their dendritic cells. “

William Paul Cell 2011

Antigen Presentation



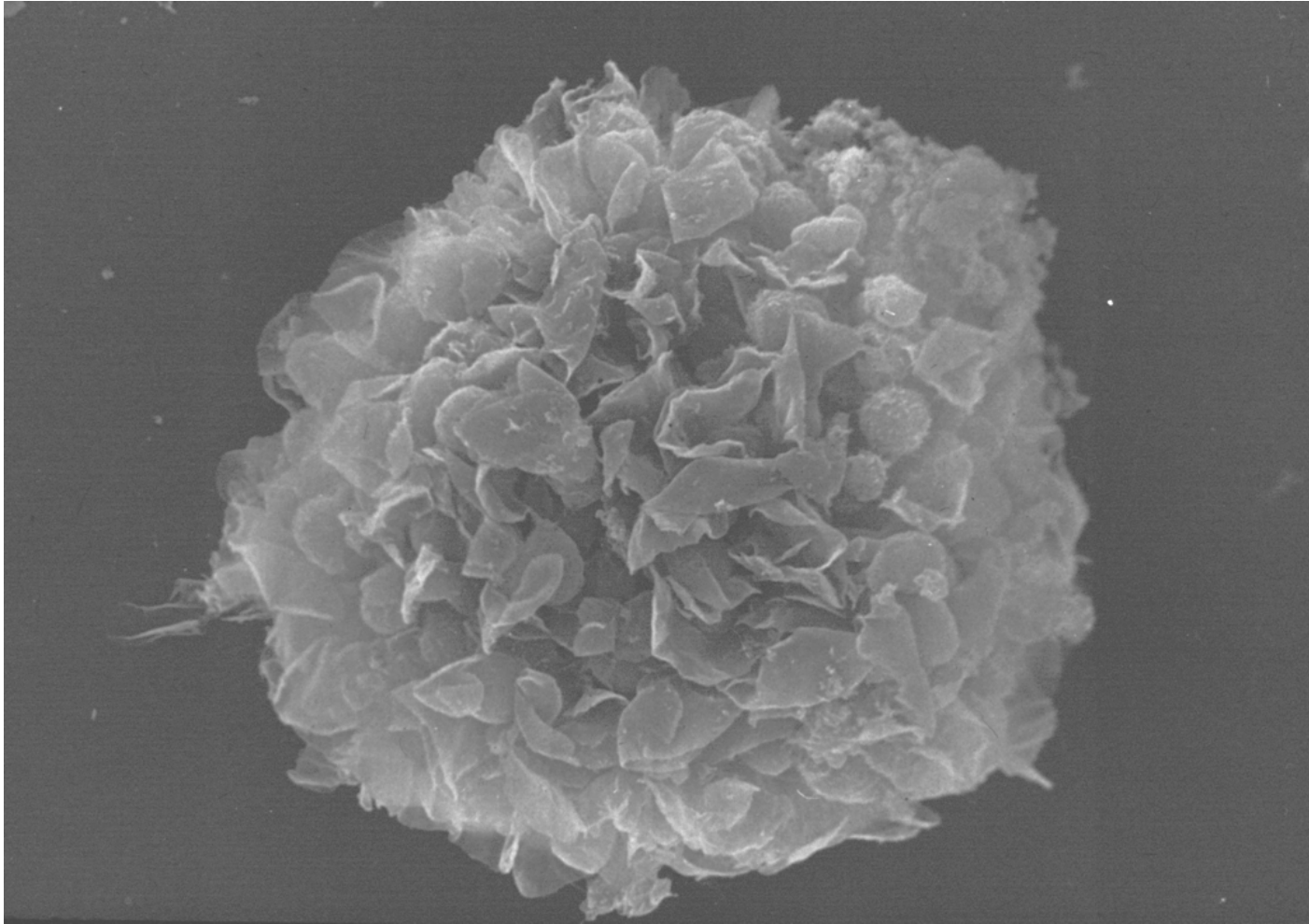
Michel Nussenzweig Bodma Gutchinov Maggi Pack Ralph Steinman 1980

DENDRITIC CELLS ARE ACCESSORY CELLS FOR THE
DEVELOPMENT OF ANTI-TRINITROPHENYL CYTOTOXIC T
LYMPHOCYTES*

By MICHEL C. NUSSENZWEIG, RALPH M. STEINMAN,[‡] BODMA GUTCHINOV,
AND ZANVIL A. COHN

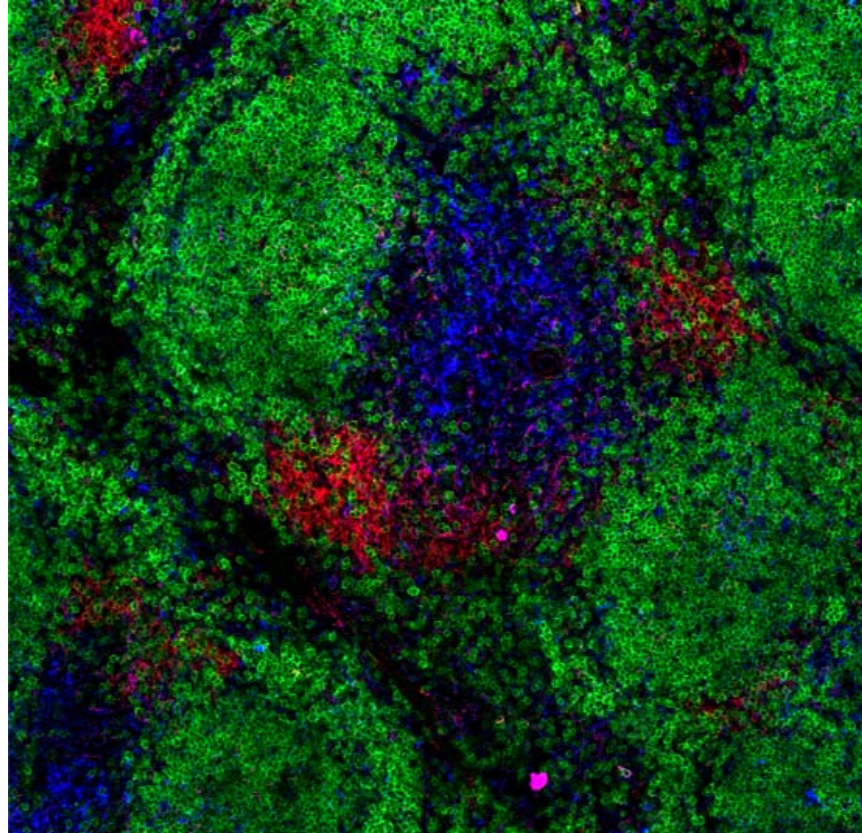
From The Rockefeller University, New York 10021

“DC are the critical accessory cells, whereas macrophages regardless of source or expression of Ia (MHC II) are without significant activity.”



Scanning EM of DC-T Cell Cluster, Courtesy of Gilla Kaplan

DC localization with Monoclonal Antibodies



Nussenzweig M.C., Steinman, R.M., Witmer, M., Gutchinov, B. [PNAS](#) (1982)
Steinman R.M, Gutchinov B., Wittmer, M. and Nussenzweig [JEM](#) (1983)

Collaborators on Initial Experiments on Antigen Presentation and Human DCs



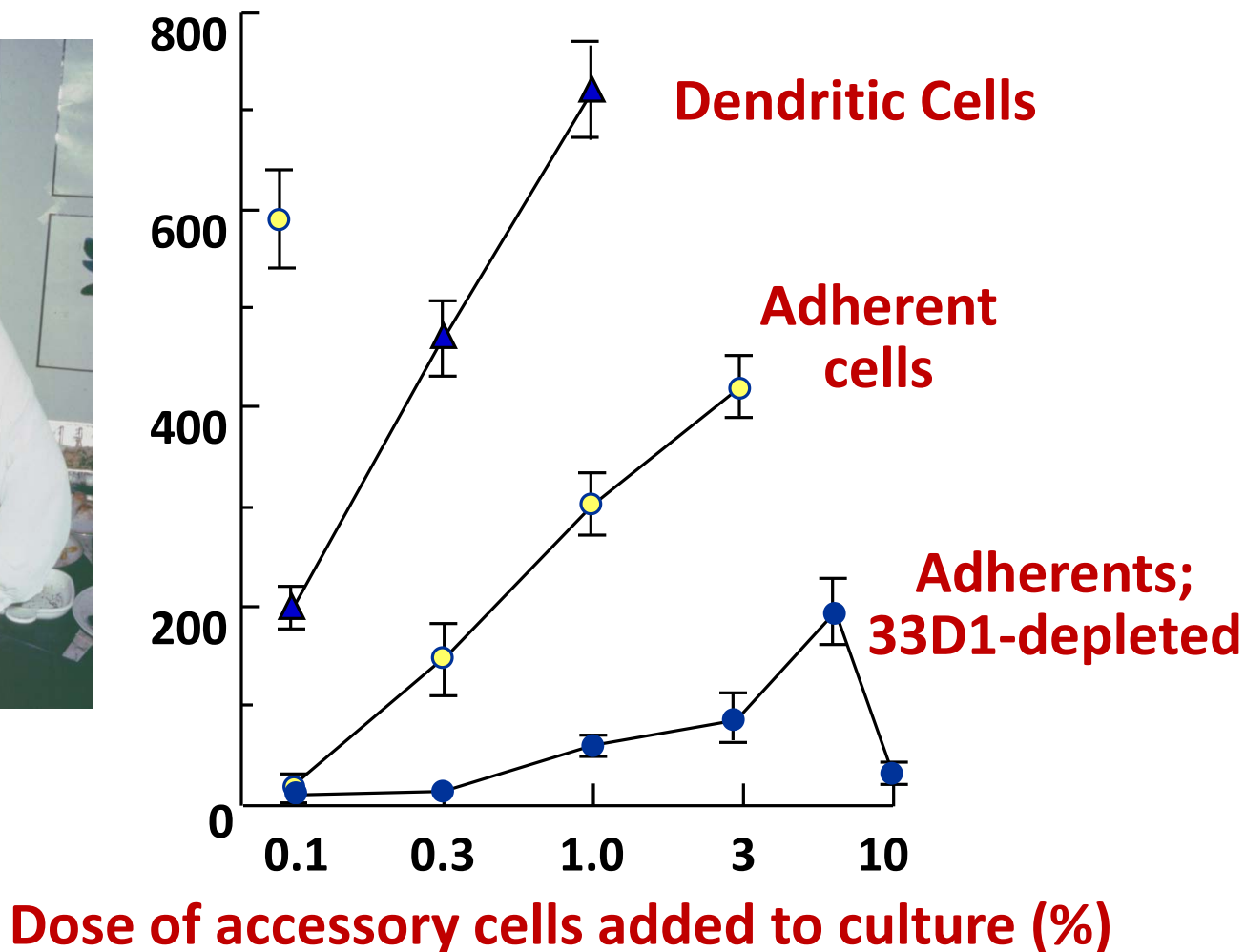
**Kayo
Inaba**

**Wesley
van Voorhis**

Dendritic Cells Are Potent Accessory Cells to Induce Antibody Forming Cells in Spleen B & T cell Cultures

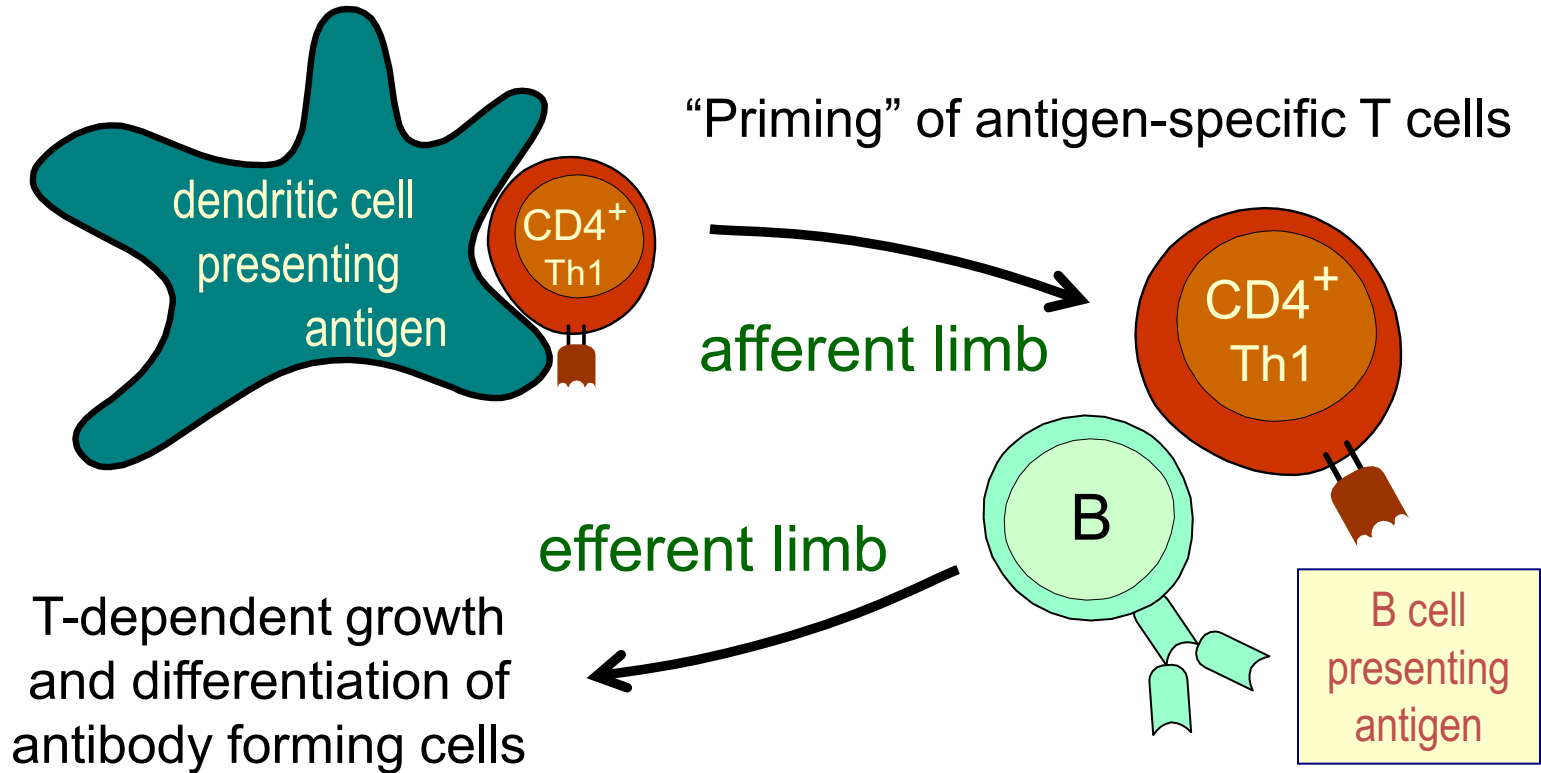


Kayo Inaba



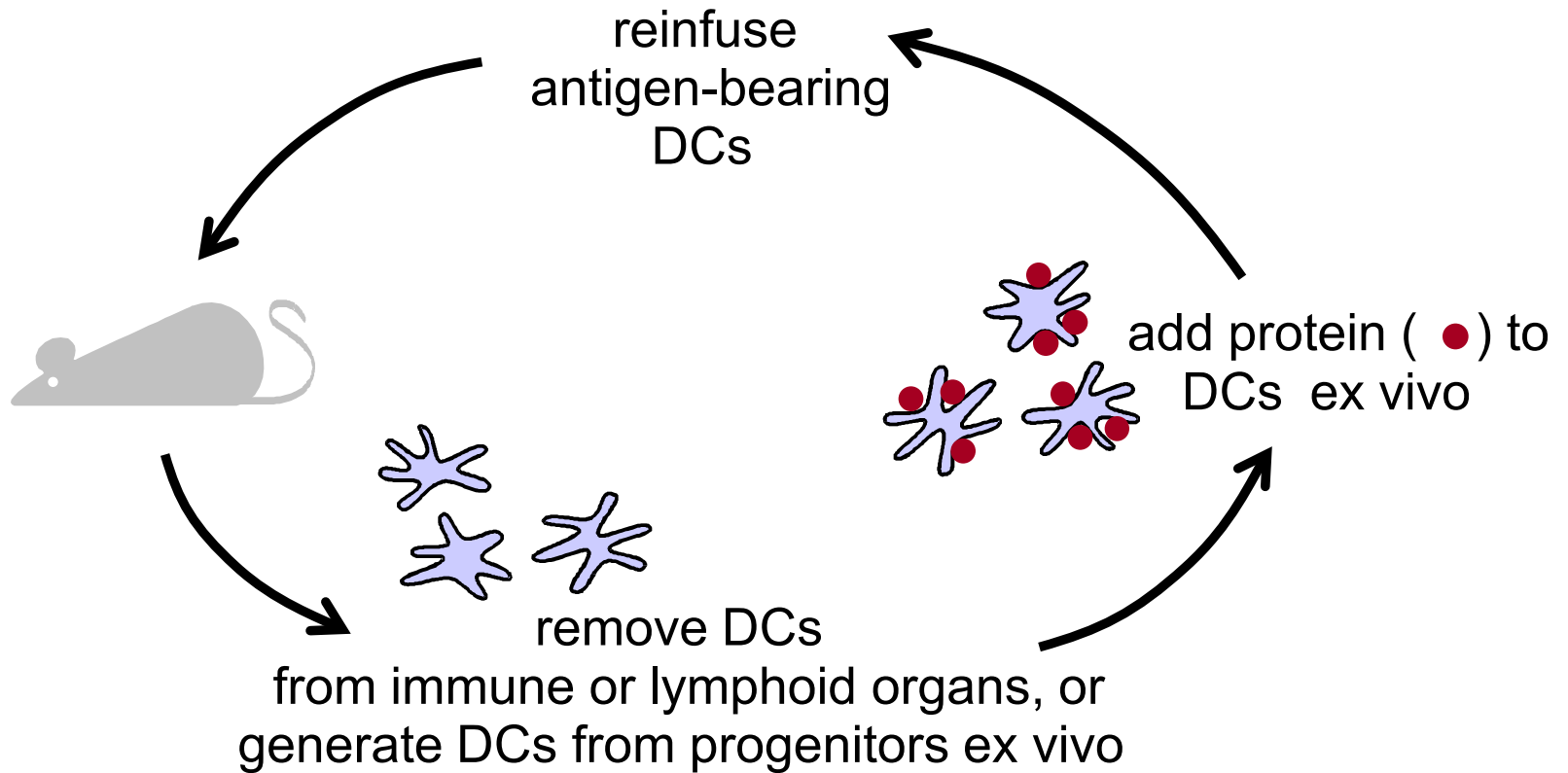
Inaba et al, Proc. Natl. Acad. Sci. 1983

Two Stages for Antigen Presentation During Immunity e.g., T Helper-Dependent, Antibody Production



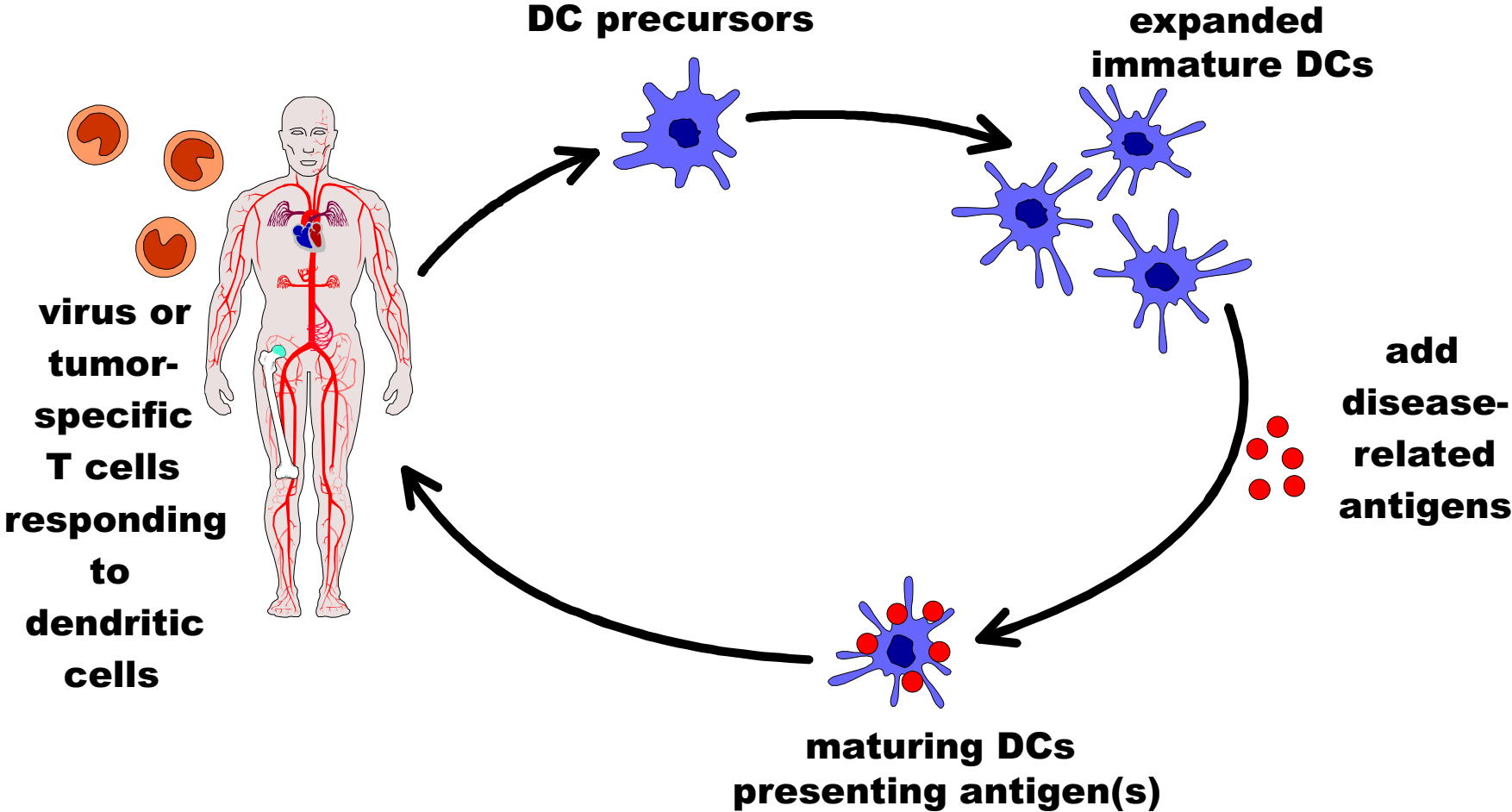
Inaba and Steinman, J. Exp. Med. 160: 1717-1735 (1984)
Inaba and Steinman, Science 229: 475-479 (1985)

Dendritic Cells (DCs) Are “Nature's Adjuvants”



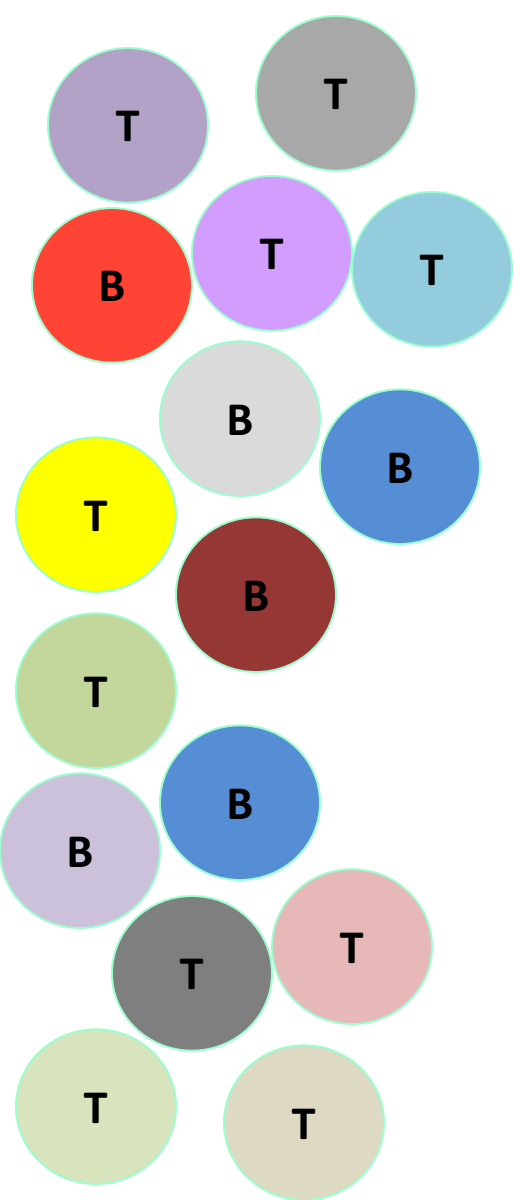
Inaba et al, J.Exp.Med. 1990 and 1993

An Approach to Initiating Immunity to Cancer*: Dendritic Cells Loaded with Tumor Antigens *ex vivo*

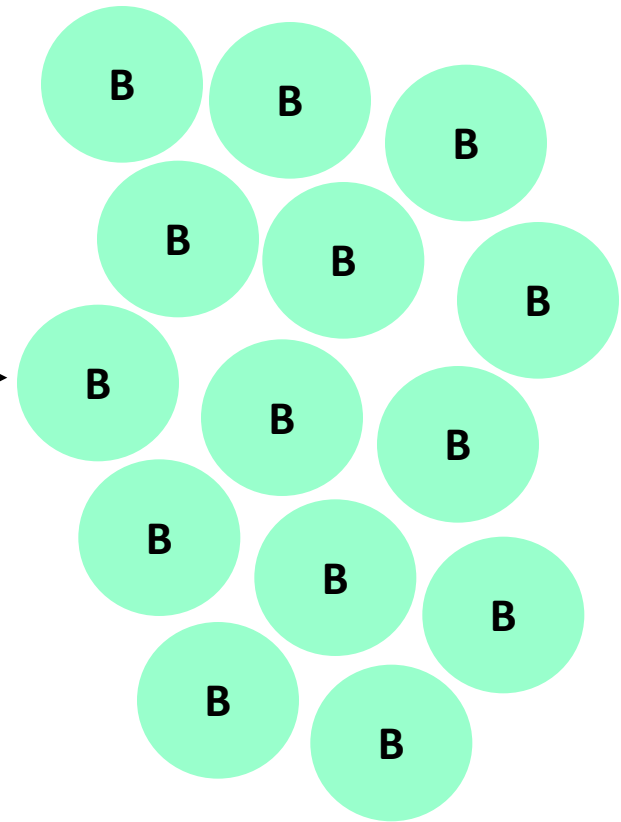
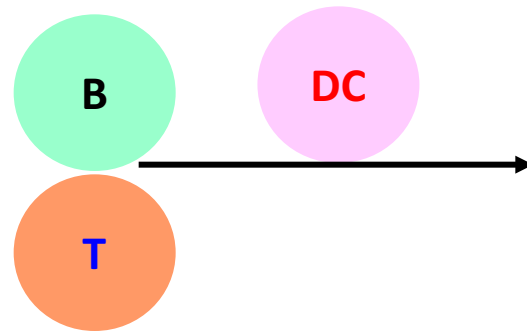


* Schuler, Thurner; Dhodapkar; Banchereau, Palucka

Clonal Selection

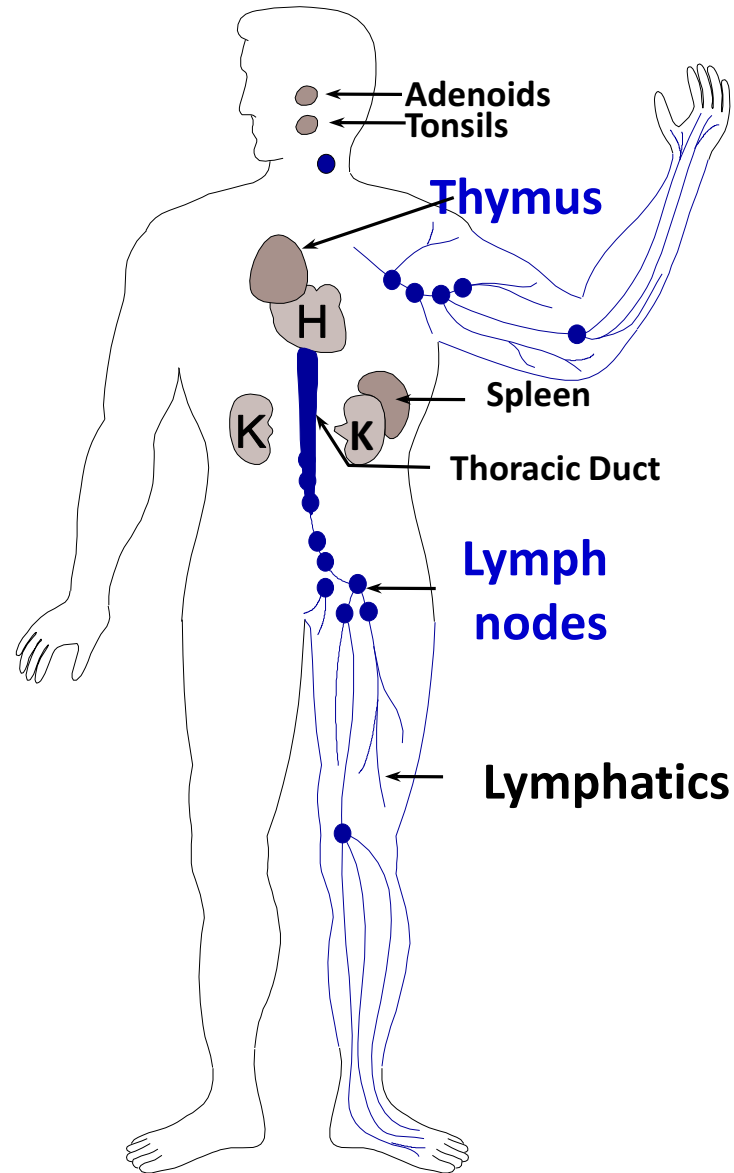


V(D)J Recombination

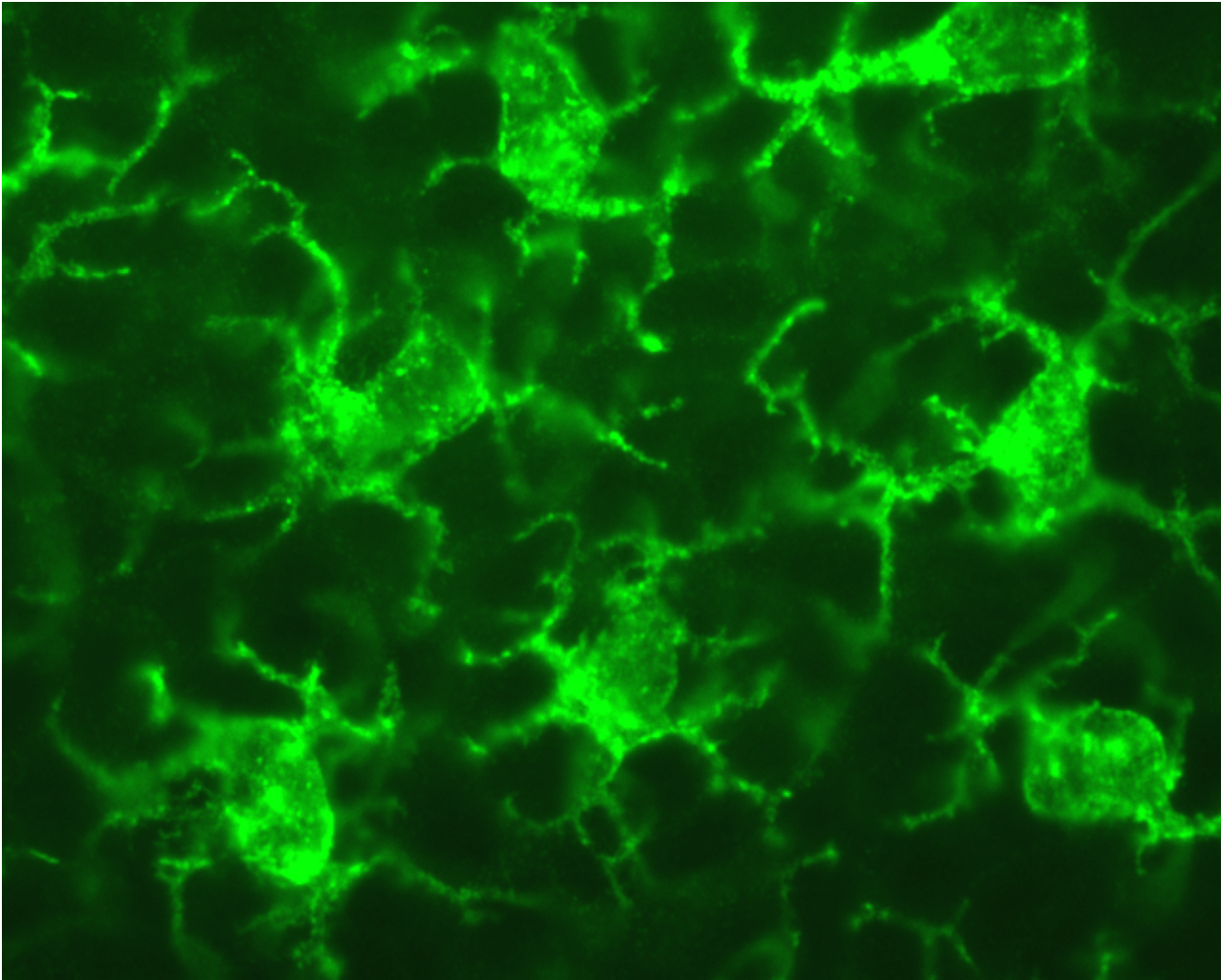


Clonal Expansion

Initiating Immunity and Tolerance *In Vivo*

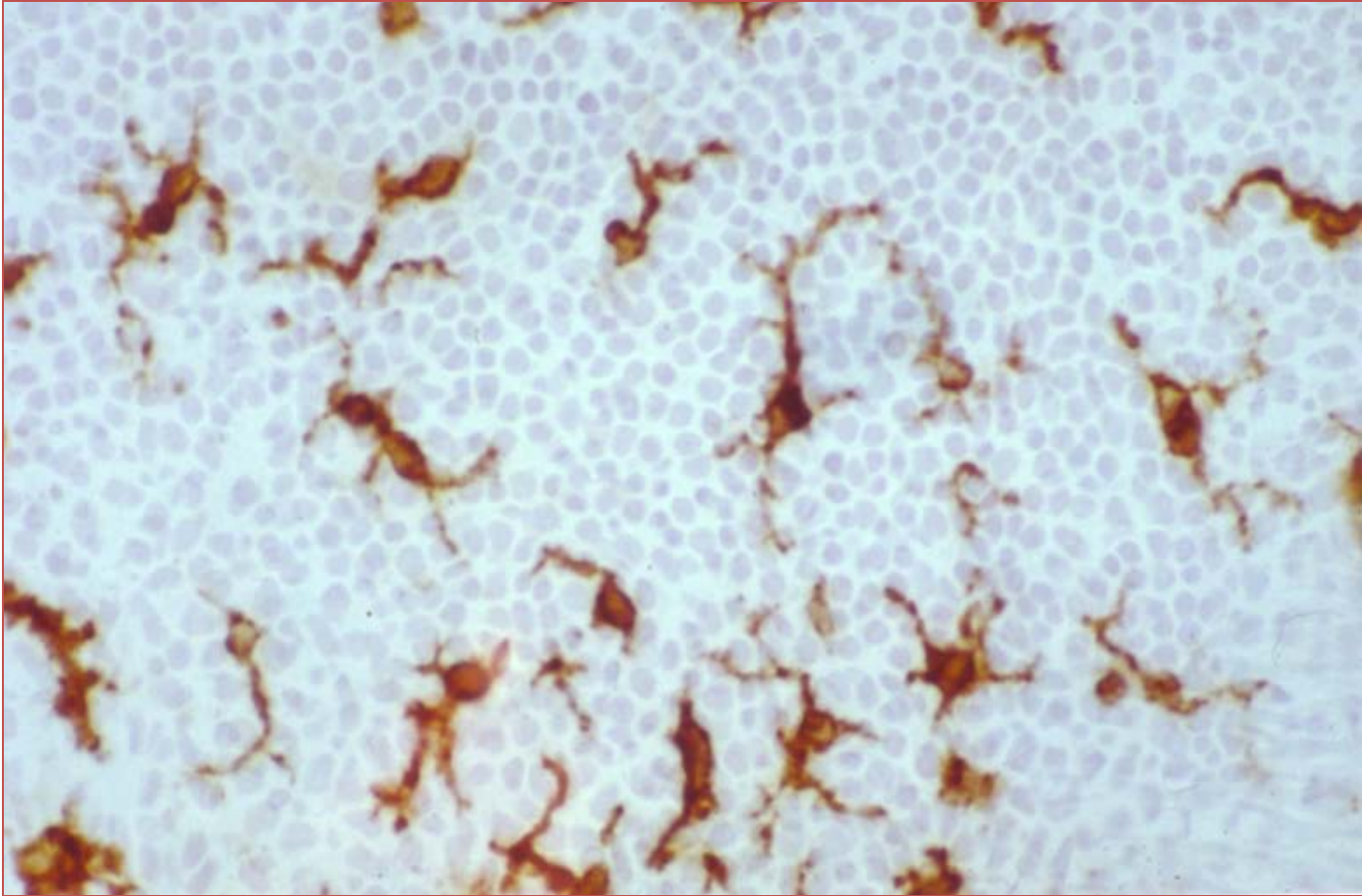


Dendritic Cells in Skin

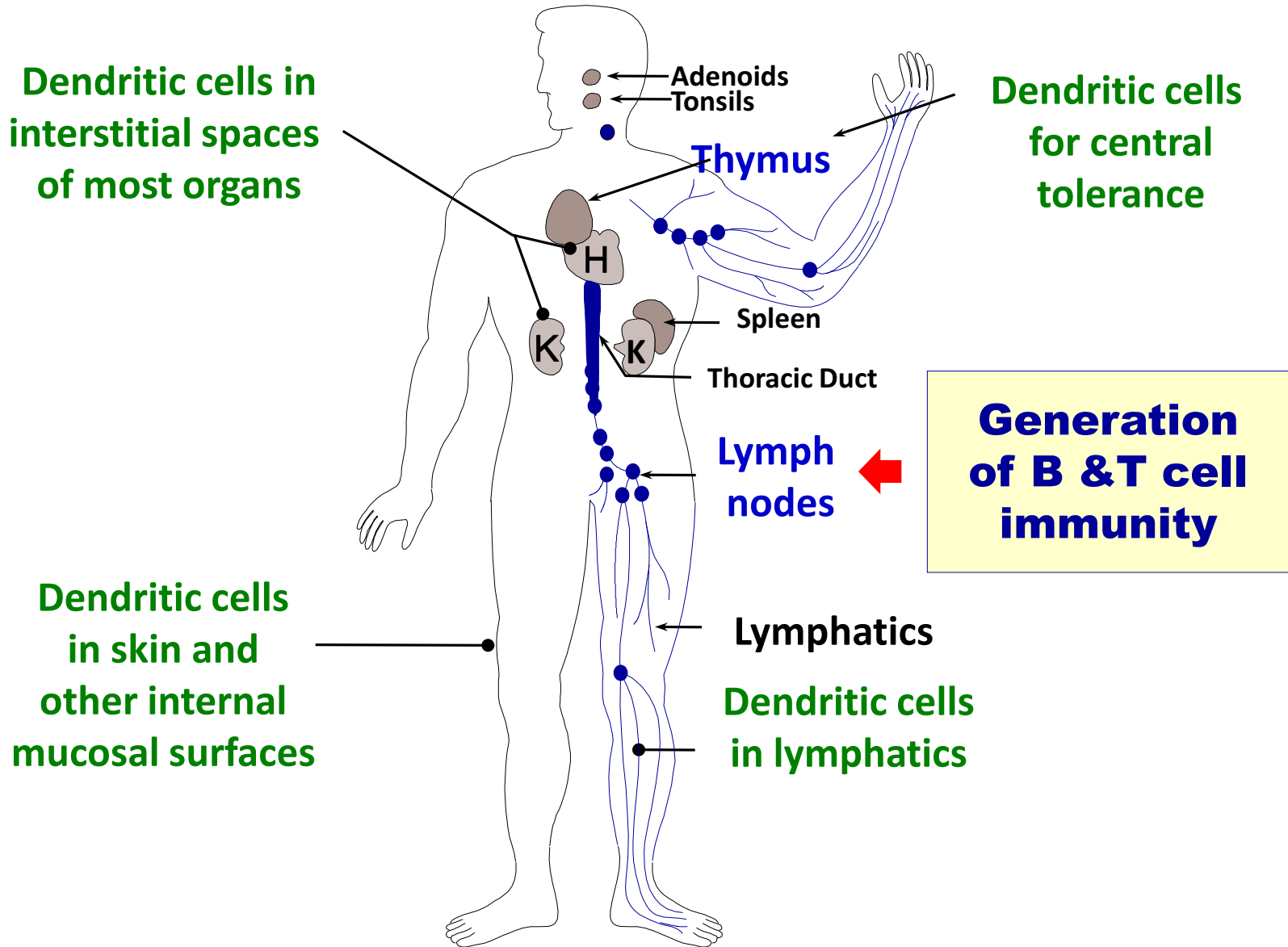


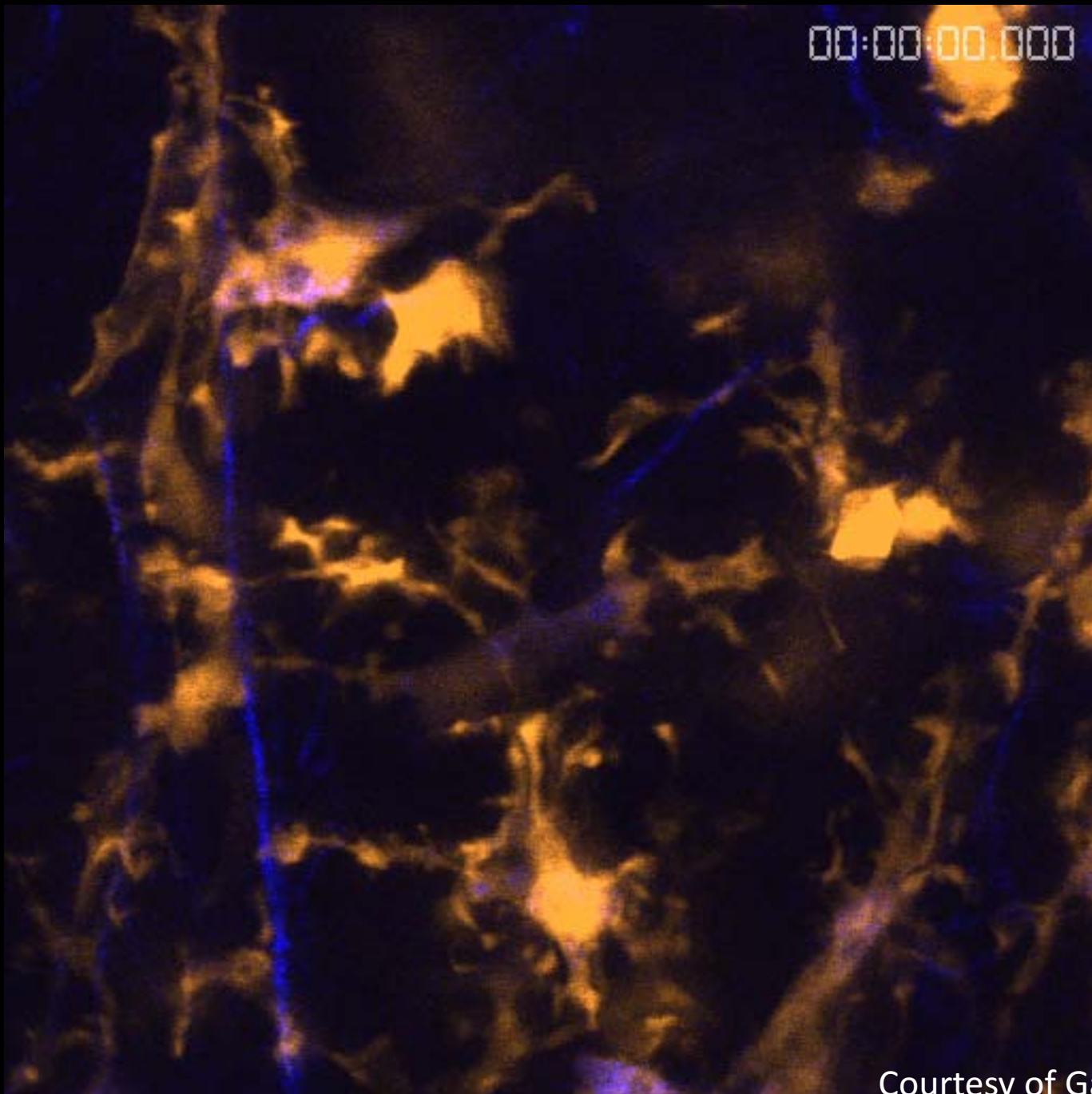
Courtesy of Juli Idoyaga, Cheolho Cheong, Chae Gyu Park

Dendritic Cells in Airway Epithelium (P. Holt)

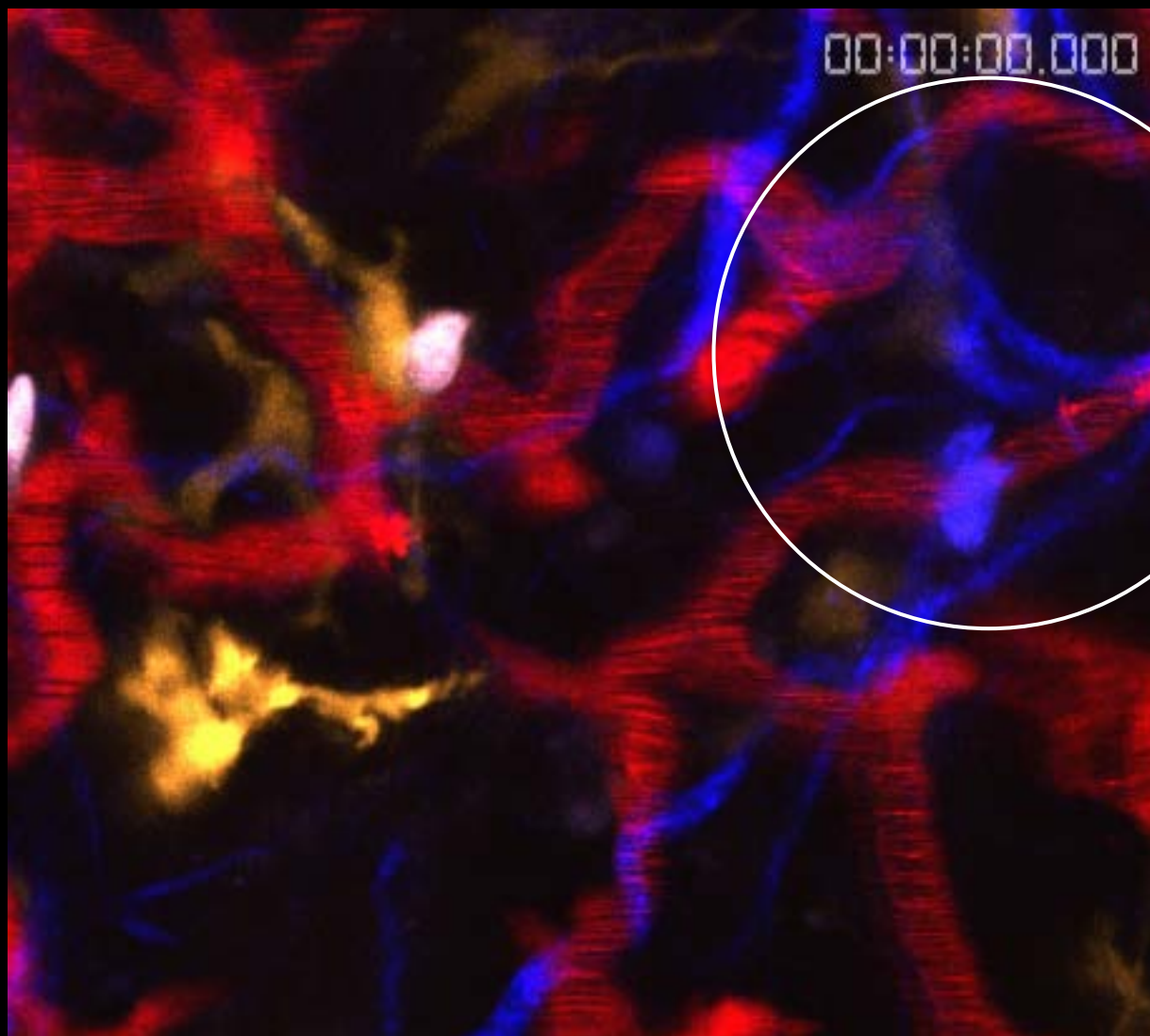


Initiating Immunity and Tolerance *In Vivo*: the Location of Antigen Capturing Dendritic Cells

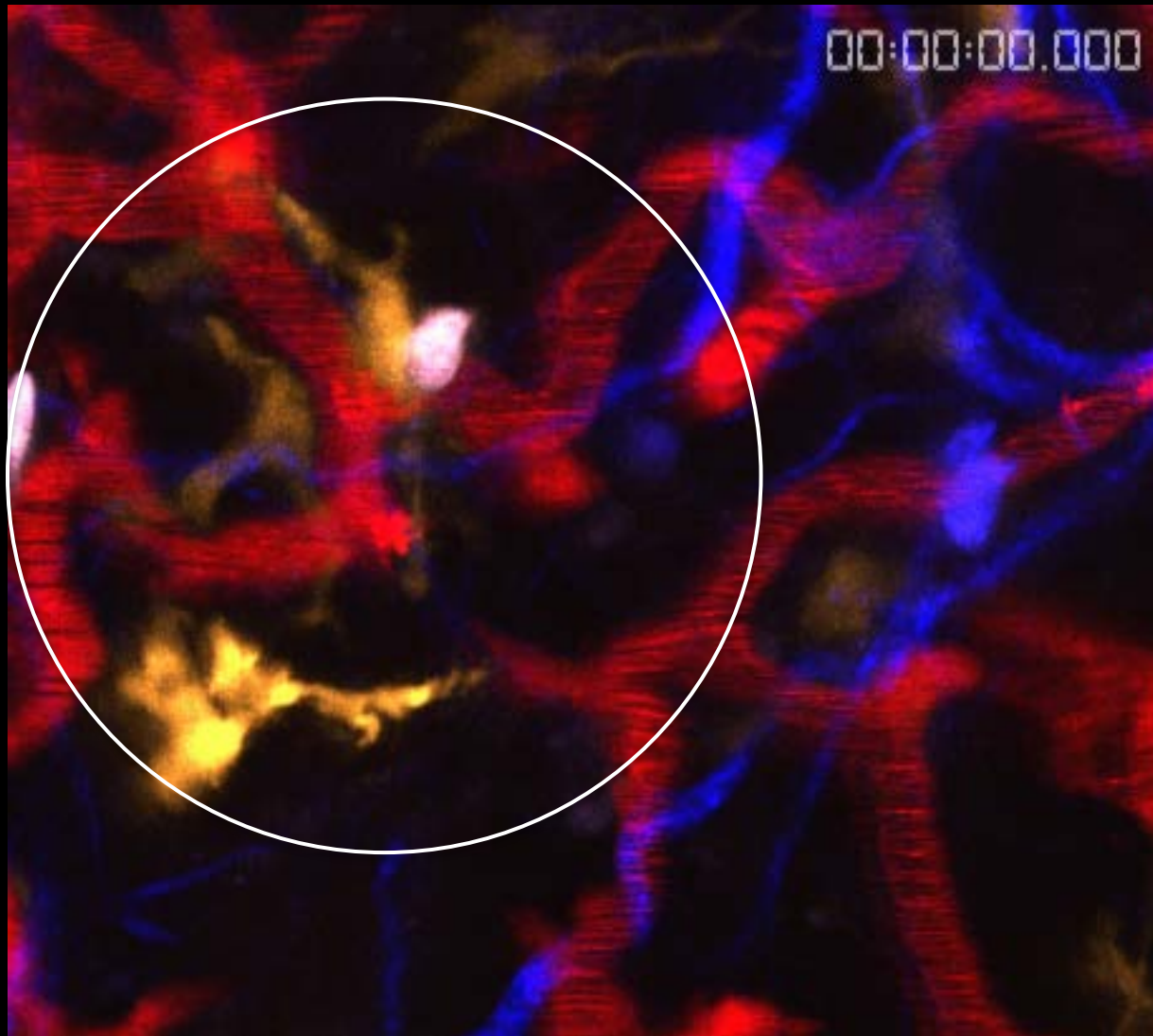




Courtesy of Gabriel Victora

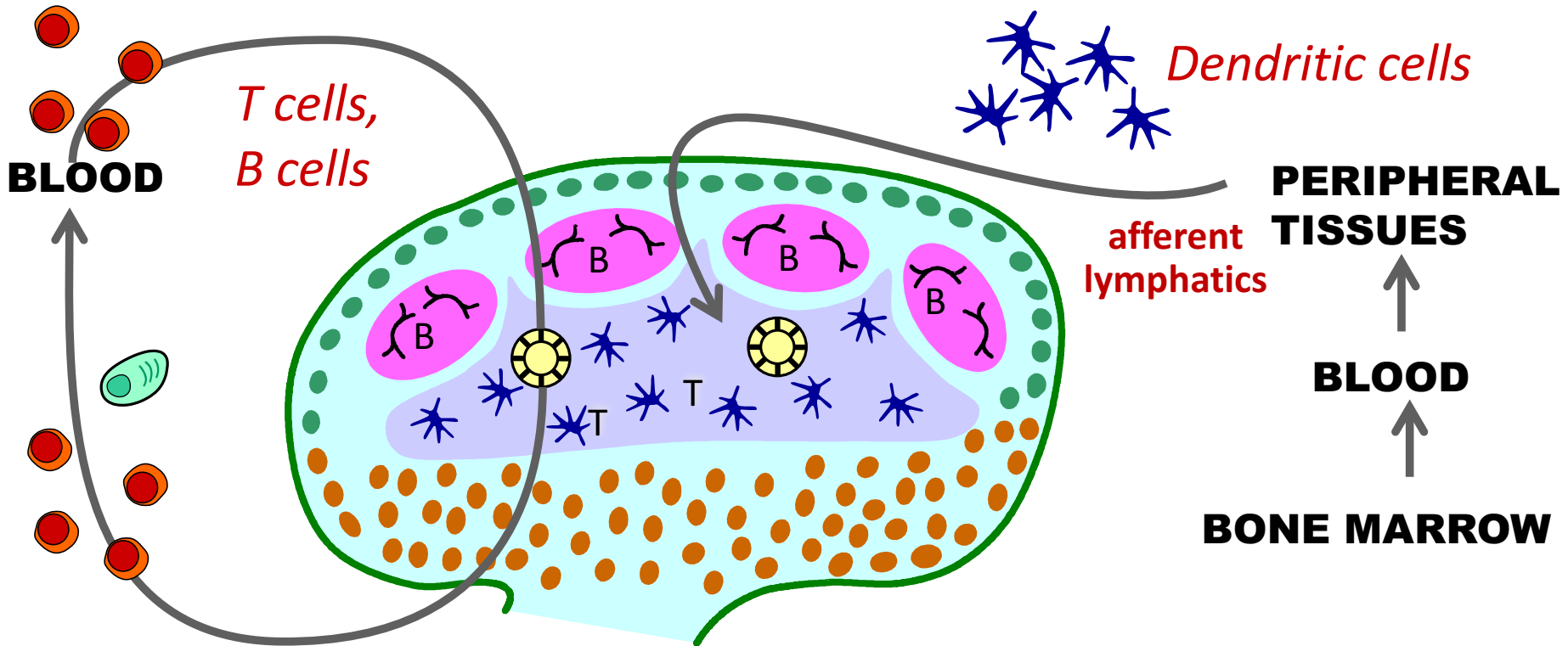


Courtesy of Gabriel Victora



Courtesy of Gabriel Victora

Dendritic Cells are Positioned in the T Cell Areas to Initiate Immunity



Maturation Allows Dendritic Cells to Initiate Immunity



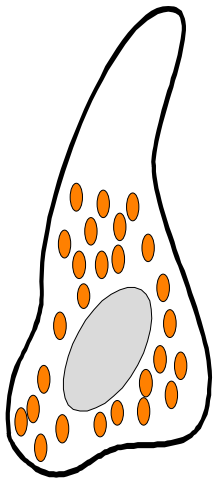
Nikolaus Romani



Gerold Schuler

Dendritic Cell as Sensors

IMMATURE DC
(Steady state)



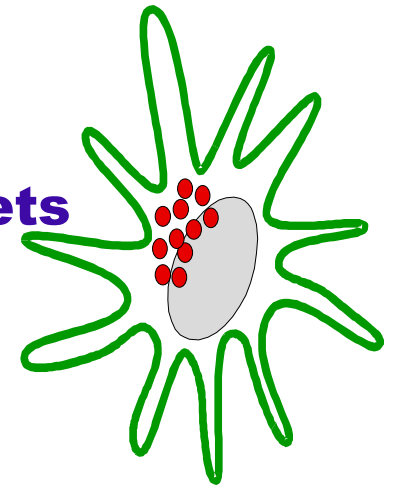
Antigen capture

receptors for antigen uptake
and maturation stimuli

Lysosome MHC II

Toll receptor ligands
cytokines, e.g, IFN's, TSLP
CD40 ligation, e.g., mast cells, platelets
innate lymphocytes, e.g., NK, NKT
HMGB1, Fc γ R

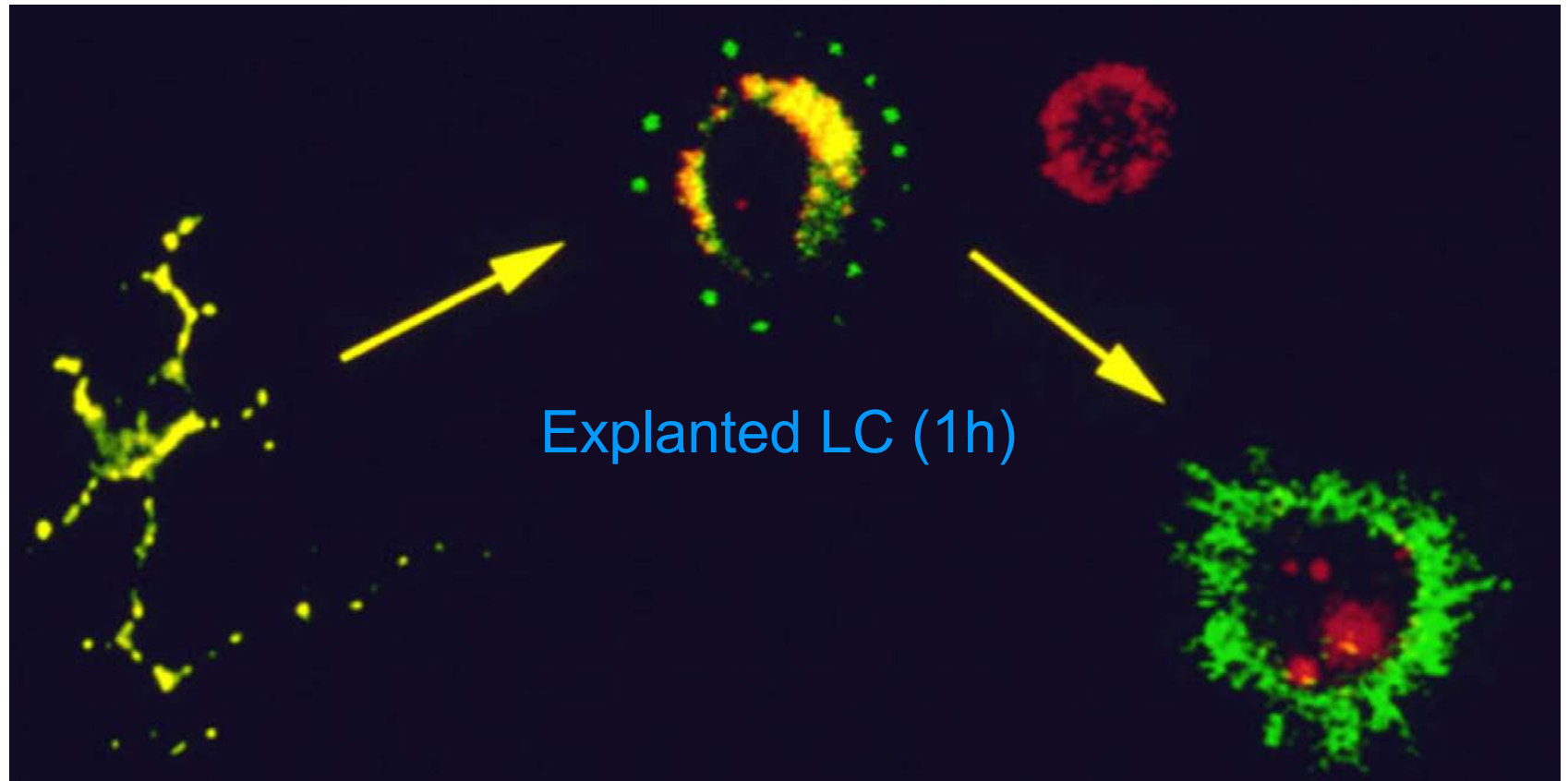
MATURE DC
(Infection)



Costimulation, immunity

cytokines, chemokines; CD40;
B7's, TNF's, Notch costimulators

Redistribution of MHC II From Lysosomes to the Cell Surface During Maturation of Langerhans Cells



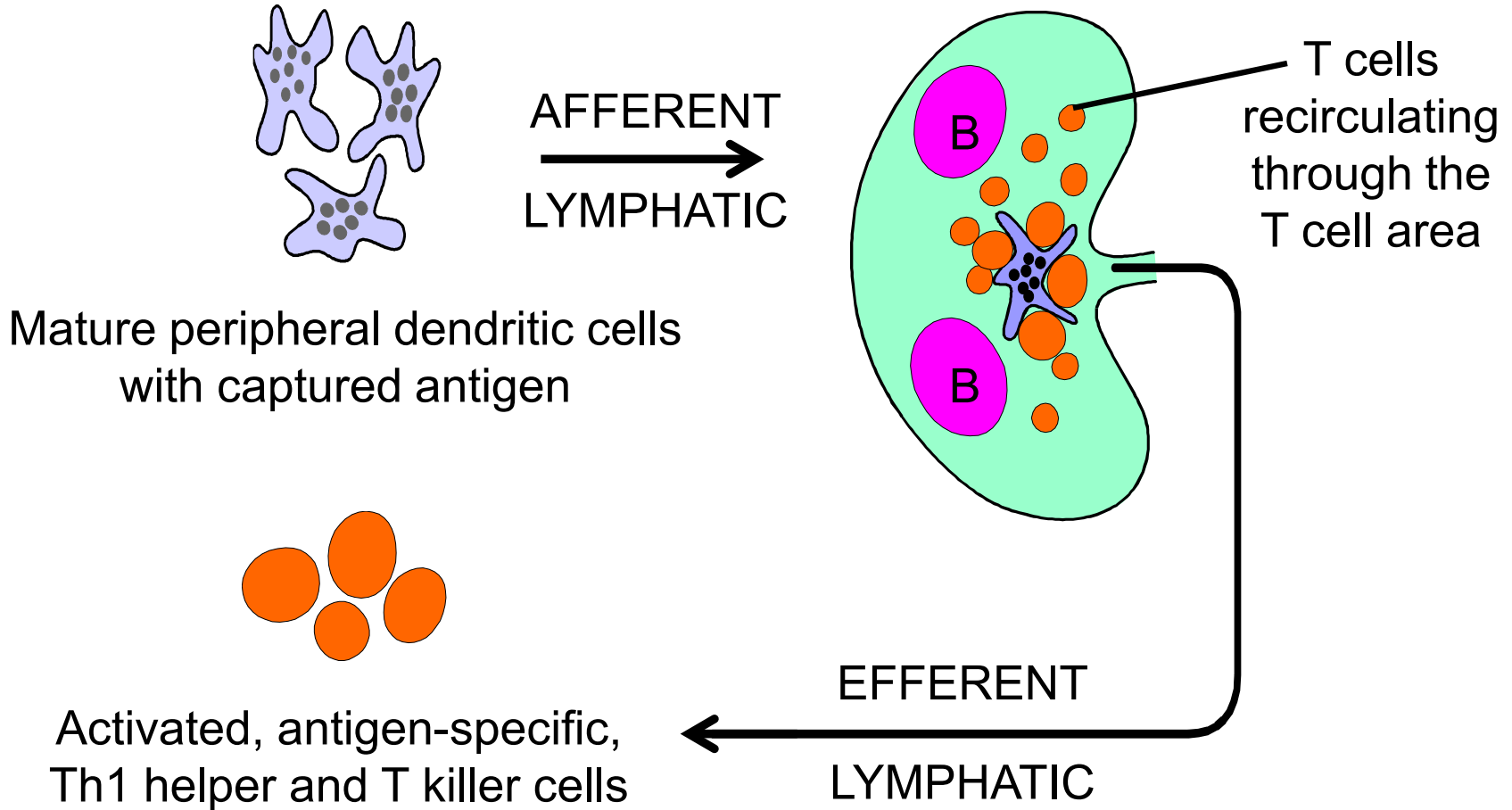
LC in the skin

MHC Class II / LGP

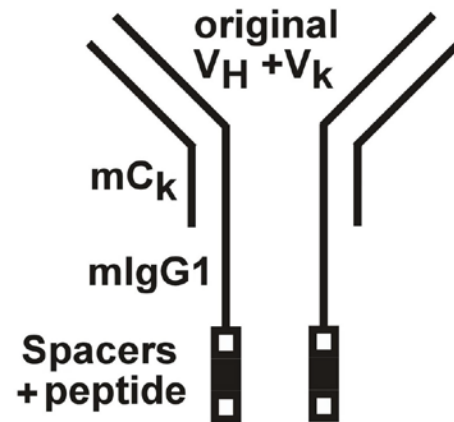
Explanted LC (24h)

Ira Mellman

Initiating Antigen-Specific Immune Responses In Vivo



Delivery of Defined Antigens to Dendritic Cells *In Situ* In Association With α -DEC Monoclonal Antibody

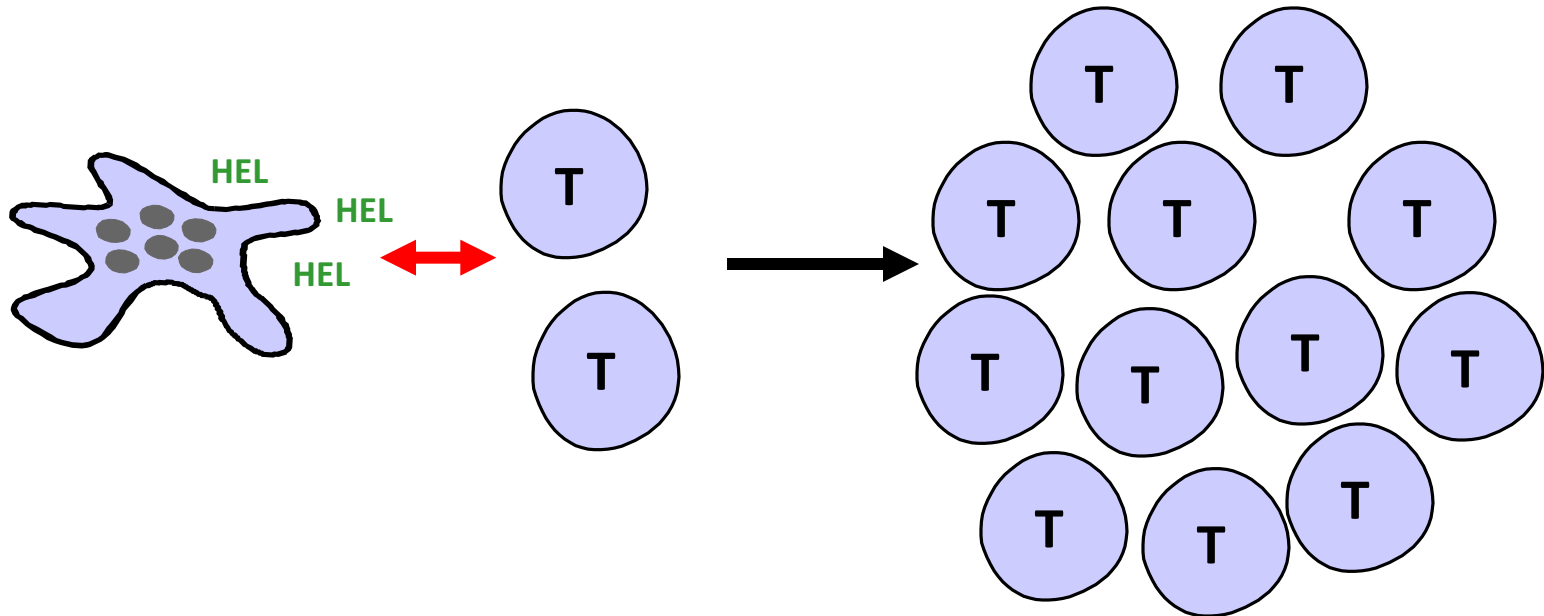


**Engineer peptide or
protein sequences into
the C-terminus of
the heavy chain**



Jiang WP, Swiggard, W Steinman RM, and Nussenzweig MC Nature 1995
Hawiger D, Steinman RM, and Nussenzweig MC, J. Exp. Med. (2001)

DC activation by TLR or CD40 ligation or other activators and induces prolonged T cell effector responses



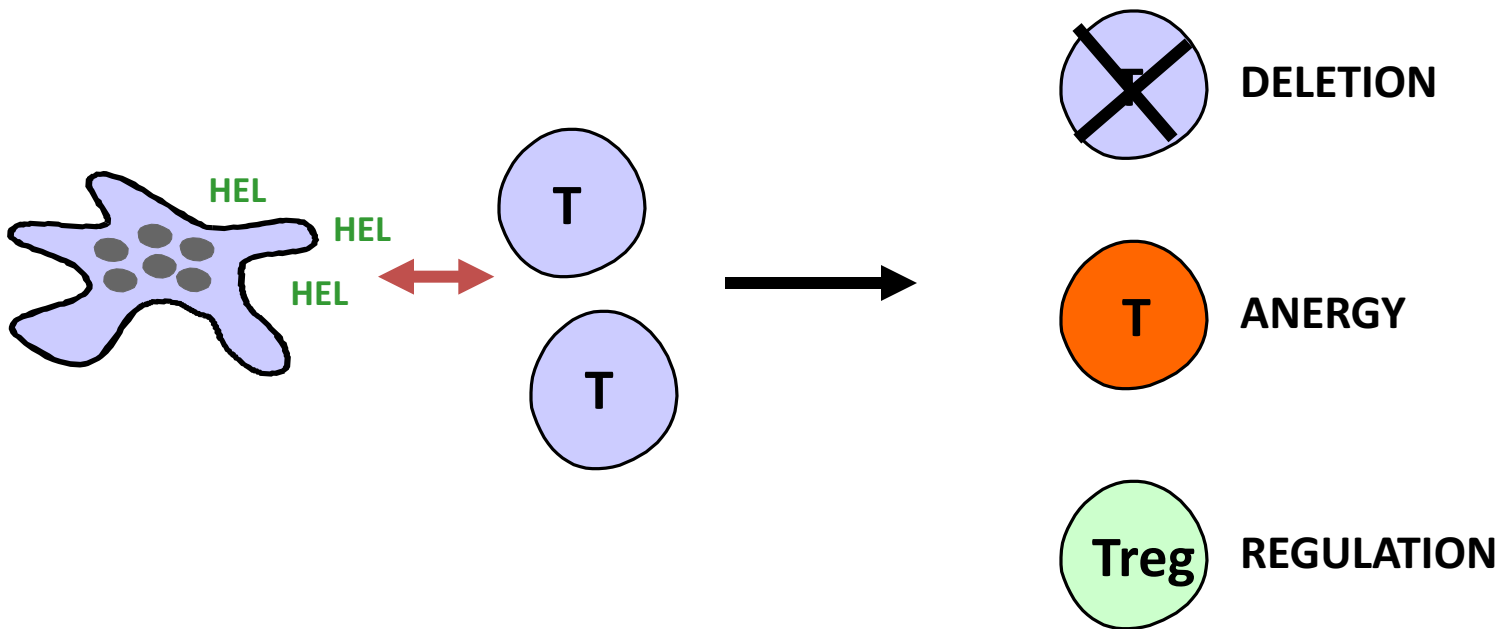
Hawiger et al, J. Exp. Med. (2001)

Bonifaz et al, J. Exp. Med. (2002)

Hawiger et al, Immunity (2004)

Bonifaz et al, J. Exp. Med. (2004)

Antigens presented by DCs in the steady state induce tolerance by several mechanisms



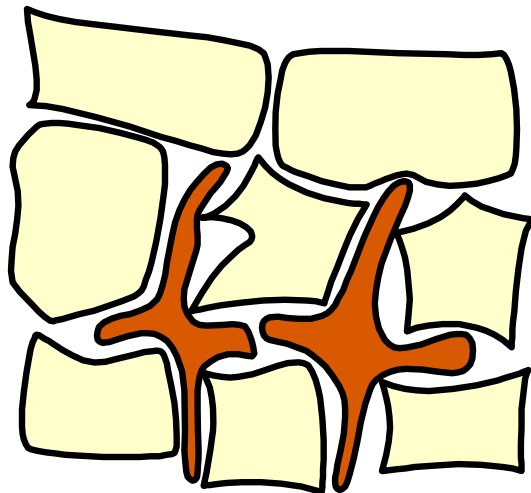
Hawiger et al, JEM 2001

Hawiger et al, Immunity 2003

Kretchmer et al Nat Immunol 2005

During the Steady State, Dendritic Cells Induce Tolerance

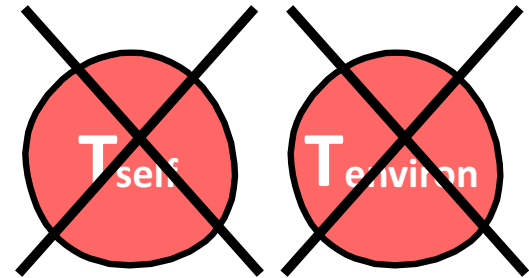
Self and harmless environmental antigens



an epithelium with dendritic cells

STEADY STATE
→
immature DCs

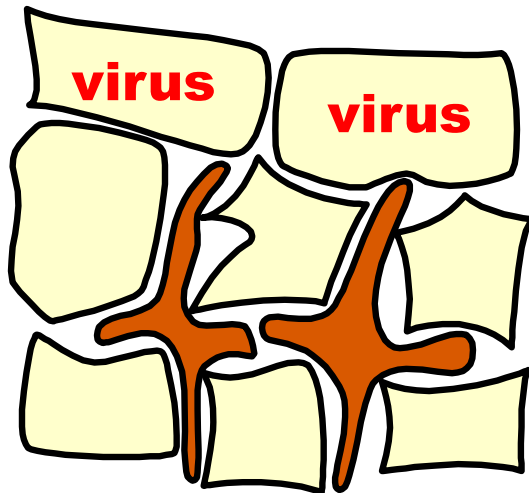
Deletion, anergy



Hawiger, Steinman, and Nussenzweig JEM 2001
Nussenzweig and Steinman PNAS 2002

During the Steady State, Dendritic Cells Induce Tolerance, So That During Infection, Dendritic Cell Maturation Does Not Lead to Autoimmunity and Chronic Inflammation

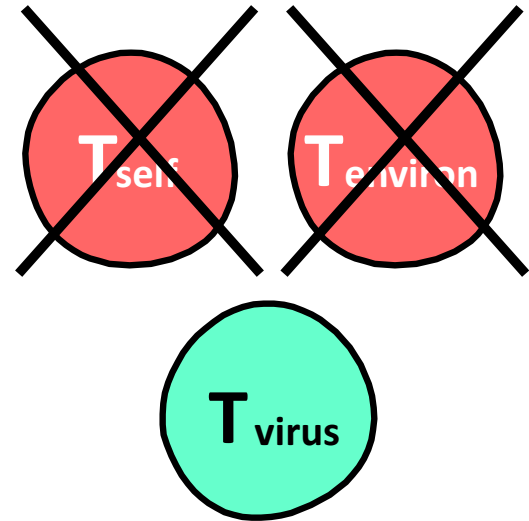
Self and harmless environmental antigens



an epithelium with dendritic cells

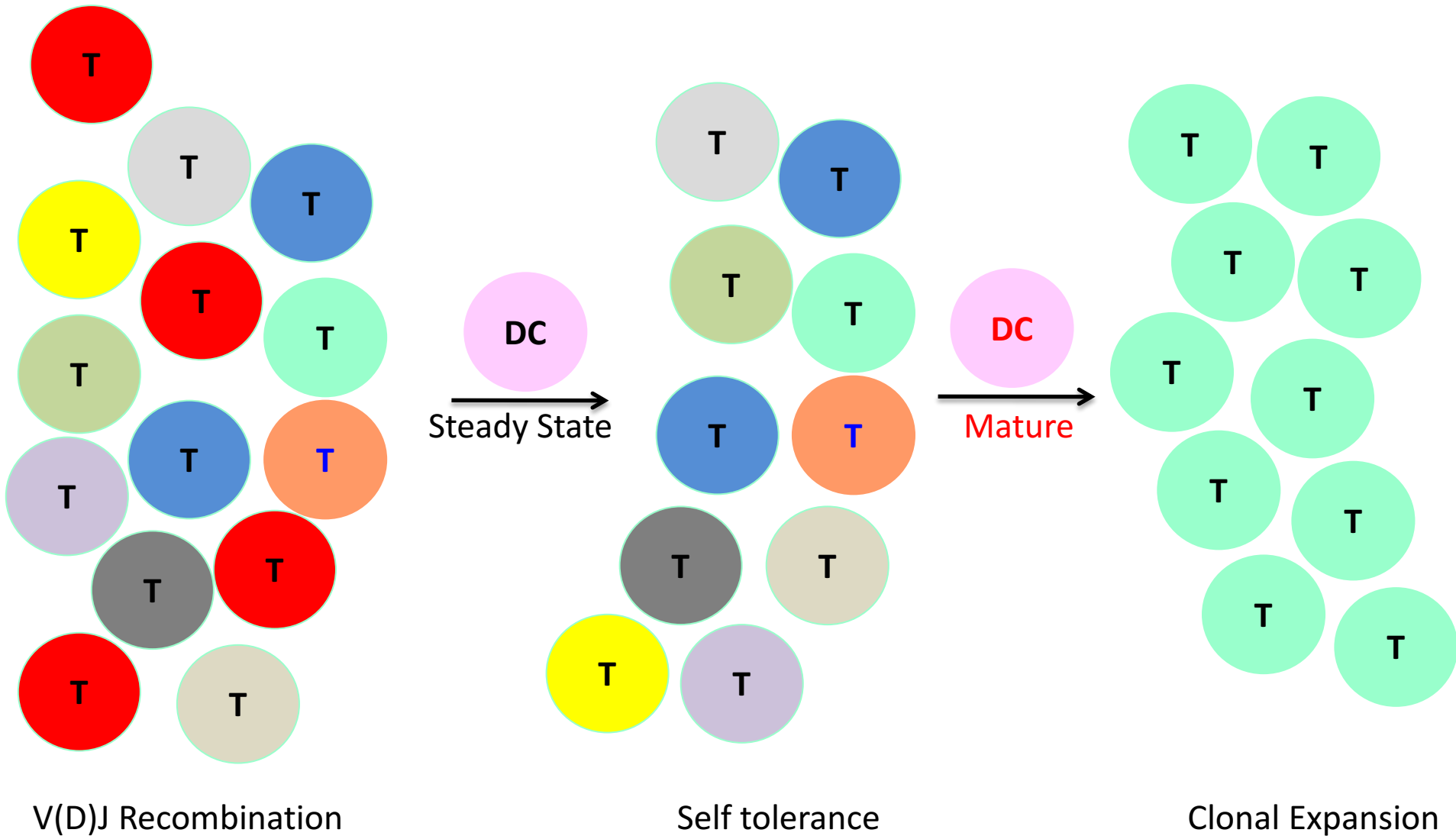
INFECTION
→
mature DCs

Deletion, anergy

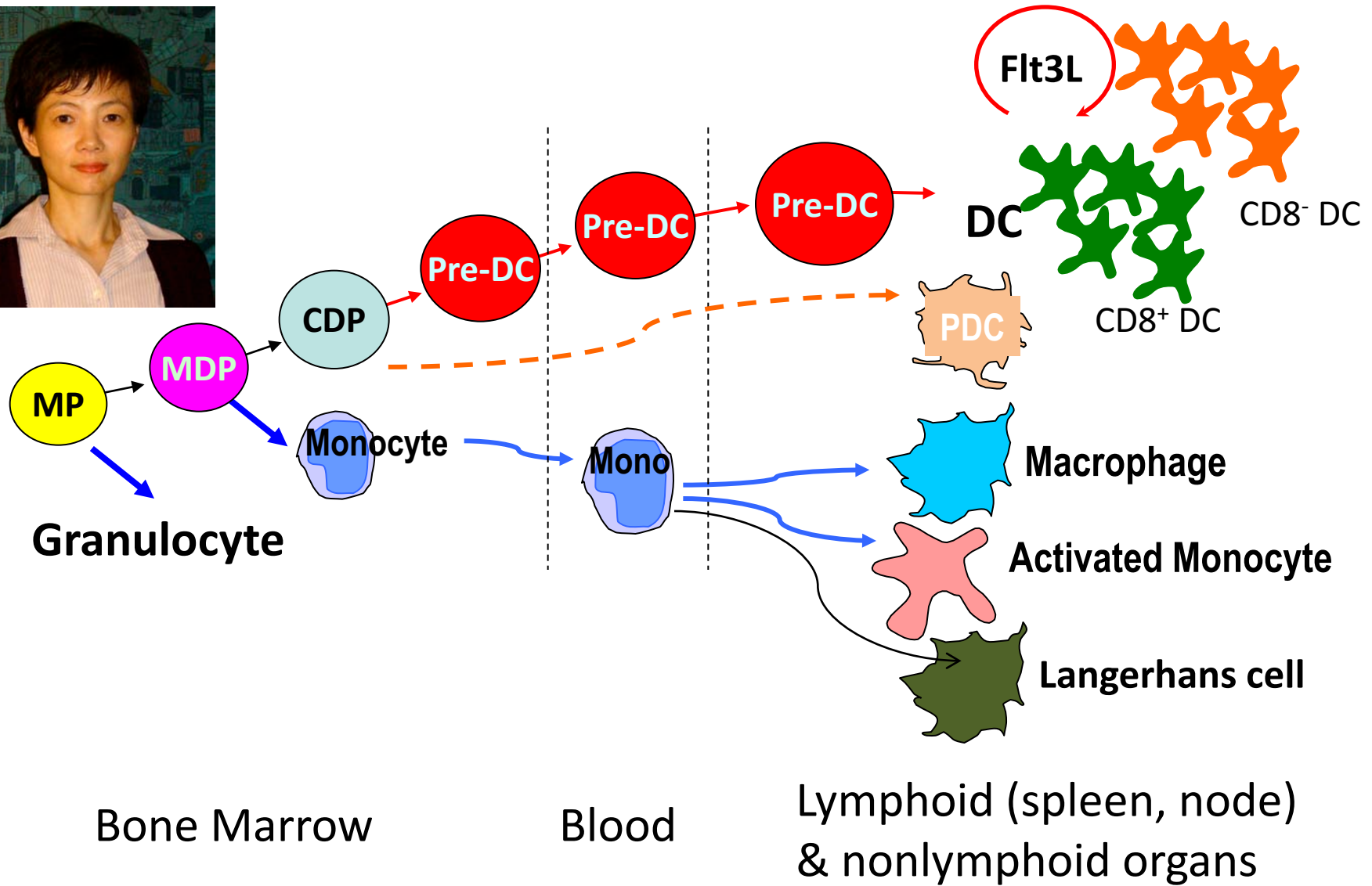


Hawiger, Steinman, and Nussenzweig JEM 2001
Nussenzweig and Steinman PNAS 2002

Clonal Selection



Dendritic Cell Development Pathway



Vaccines, A Medical Success Story



Portrait of Louis Pasteur studying rabies in his laboratory painted in 1887 by Edelfelt.

Since L. Pasteur, vaccine science has depended upon microbiology, to identify microbes and attenuate them to produce vaccines.

- Rabies (Pasteur)
- Yellow fever (Theiler)
- Polio (Enders, Weller, Robbins)

Dendritic Cells Initiate Immunity and Control its Quality

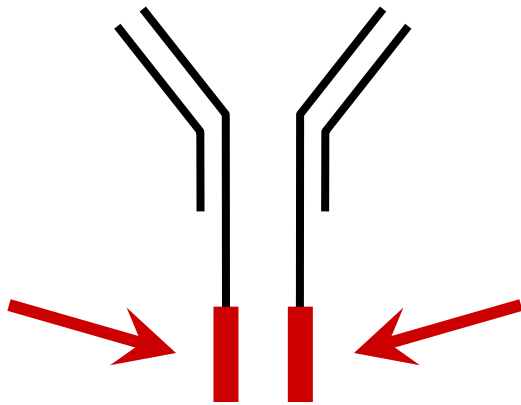
**Can Dendritic Cells Be
Harnessed to Discover Vaccines?**

Improving Protein Vaccines By Harnessing Several Features of Dendritic Cells

- **Receptors for antigen uptake/processing (including cross presentation) on DCs**
- **Pattern recognition receptors for DC maturation**
- **Pathways of DC development including DC subsets**

New Protein Vaccines Based on Defined Antigens, Adjuvants and Dendritic Cells

antibody that targets an uptake receptor on dendritic cells

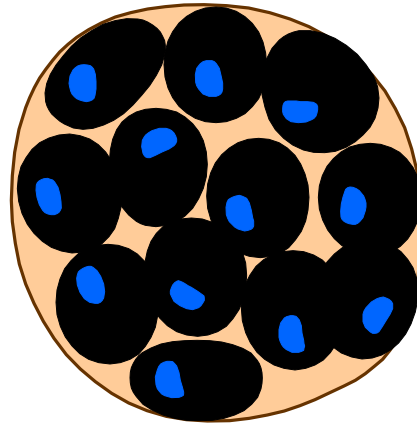


and “adjuvants” or agonists for innate signaling receptors to teach the dendritic cell the type of challenge it must prevent, e.g., synthetic dsRNA for viral vaccines

Protective antigens for AIDS, cancer, autoimmunity (e.g., multiple sclerosis)

New Vaccines Based on Defined Antigens and Adjuvants to Elicit *Appropriate* T Cell Resistance and Silencing

MELANOMA



MAGE
MART
tyrosinase
TRP's

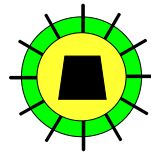
MYCOBACTERIUM TUBERCULOSIS



Esat-6 (in PPD skin test)
Antigens 85A,B

ALLERGY

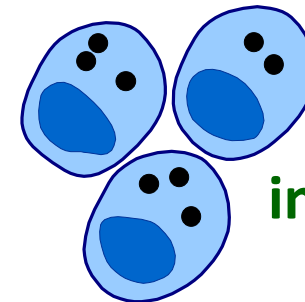
Pollens, e.g., Bet v1
Mites, e.g., Der p1
Cow's milk



HIV-1

env
pol
gag
nef

TYPE I DIABETES

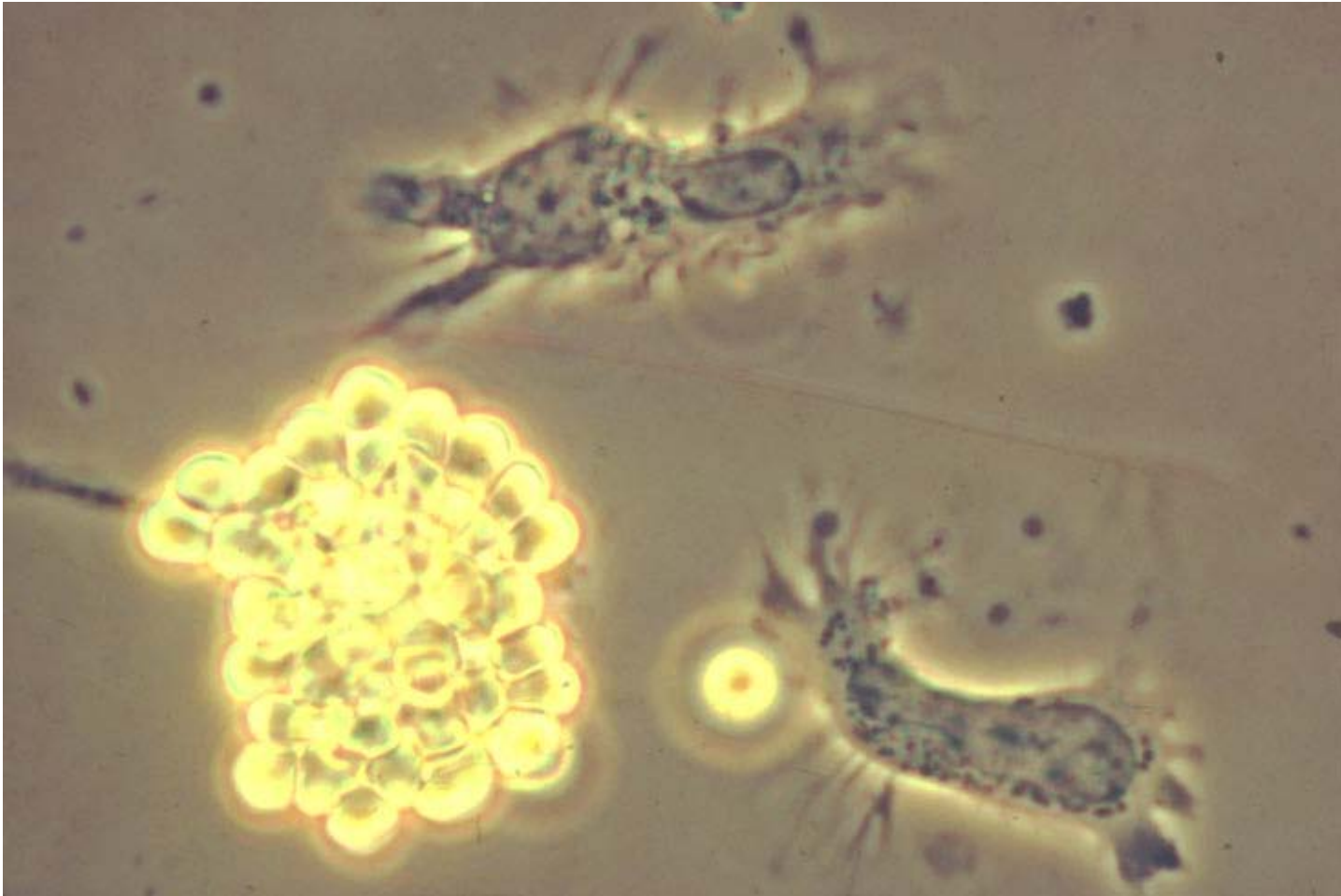


insulin



Proof of Concept Studies in Human Subjects

Dendritic Cells



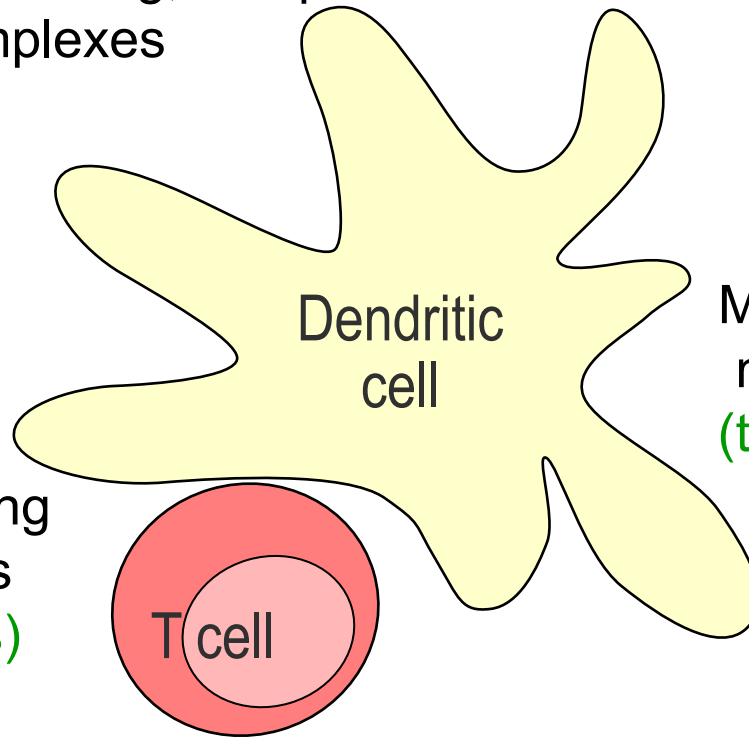
Steinman, R.M., and Cohn, Z.A. J. Exp. Med. (1973)

Dendritic Cells: Some Biological Features

Antigen uptake, processing, and presentation of peptide-MHC complexes
(endocytic system)

“Sensors”

“Sentinels”



Maturation in response to microbial & other stimuli
(toll like receptors, CD40)

Migration and homing to the T cell areas
(e.g., chemokines)

“Conductors of the immune Symphony”

And other lymphocytes

CONGRATULATIONS RALPH!
&
THANK YOU FROM COLLABORATORS STUDENTS AND FELLOWS
&
THANK YOU NOBEL ASSEMBLY

