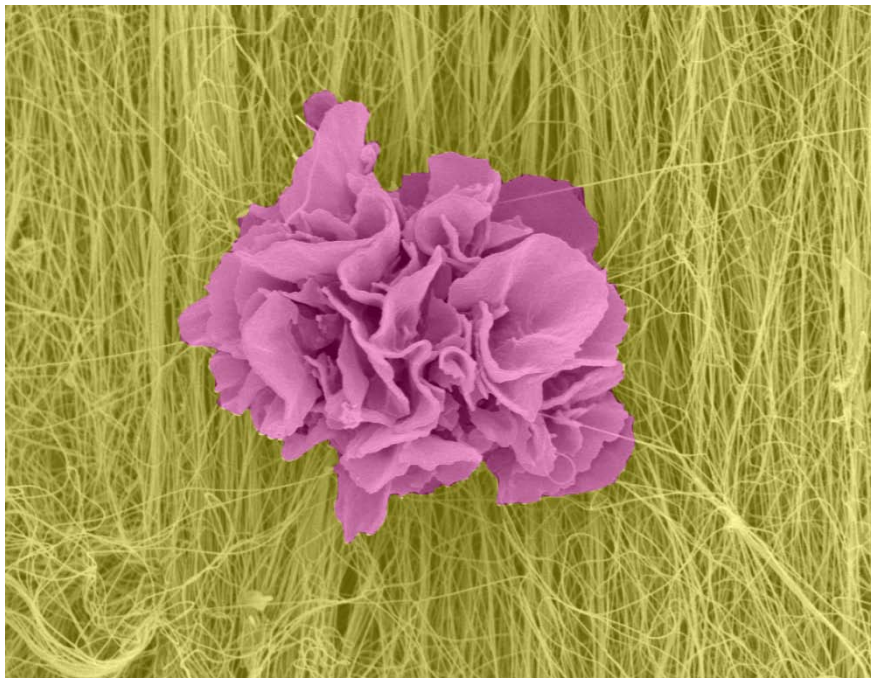
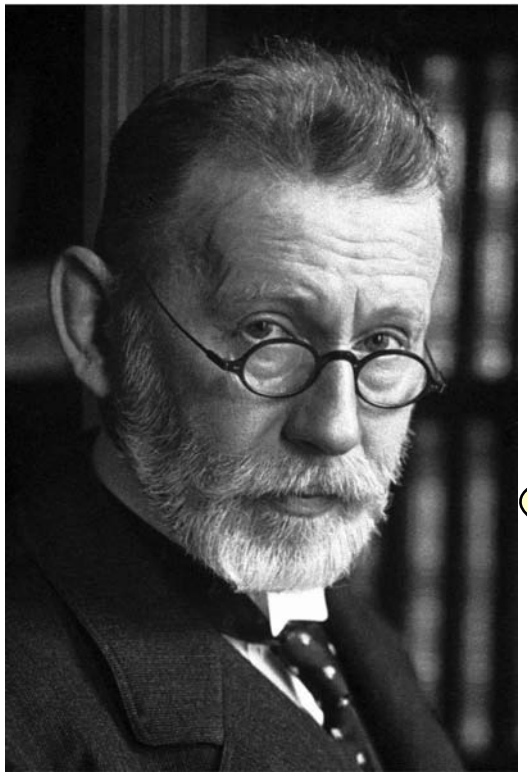
Ralph Steinman and the Discovery of Dendritic Cells
Dec. 7th, 2011



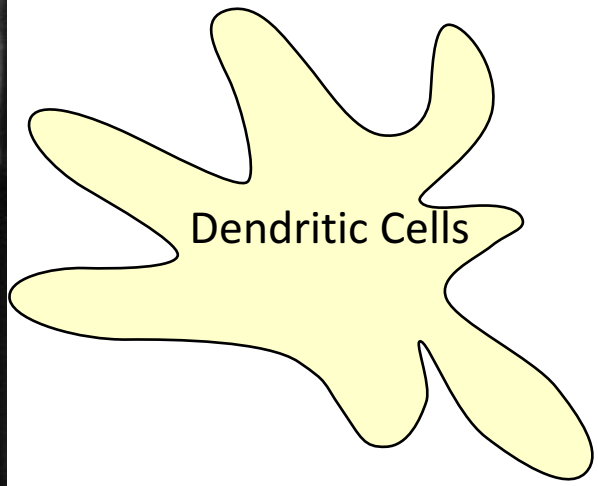
Dendritic cell in human dermis (collagen fibers)
Patti Stoitzner, Kristian Pfaller, Nikolaus Romani -- Innsbruck

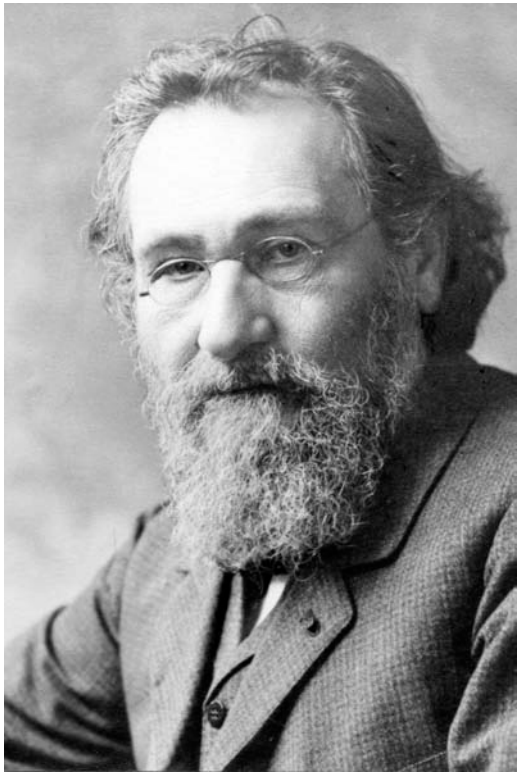
RMS

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

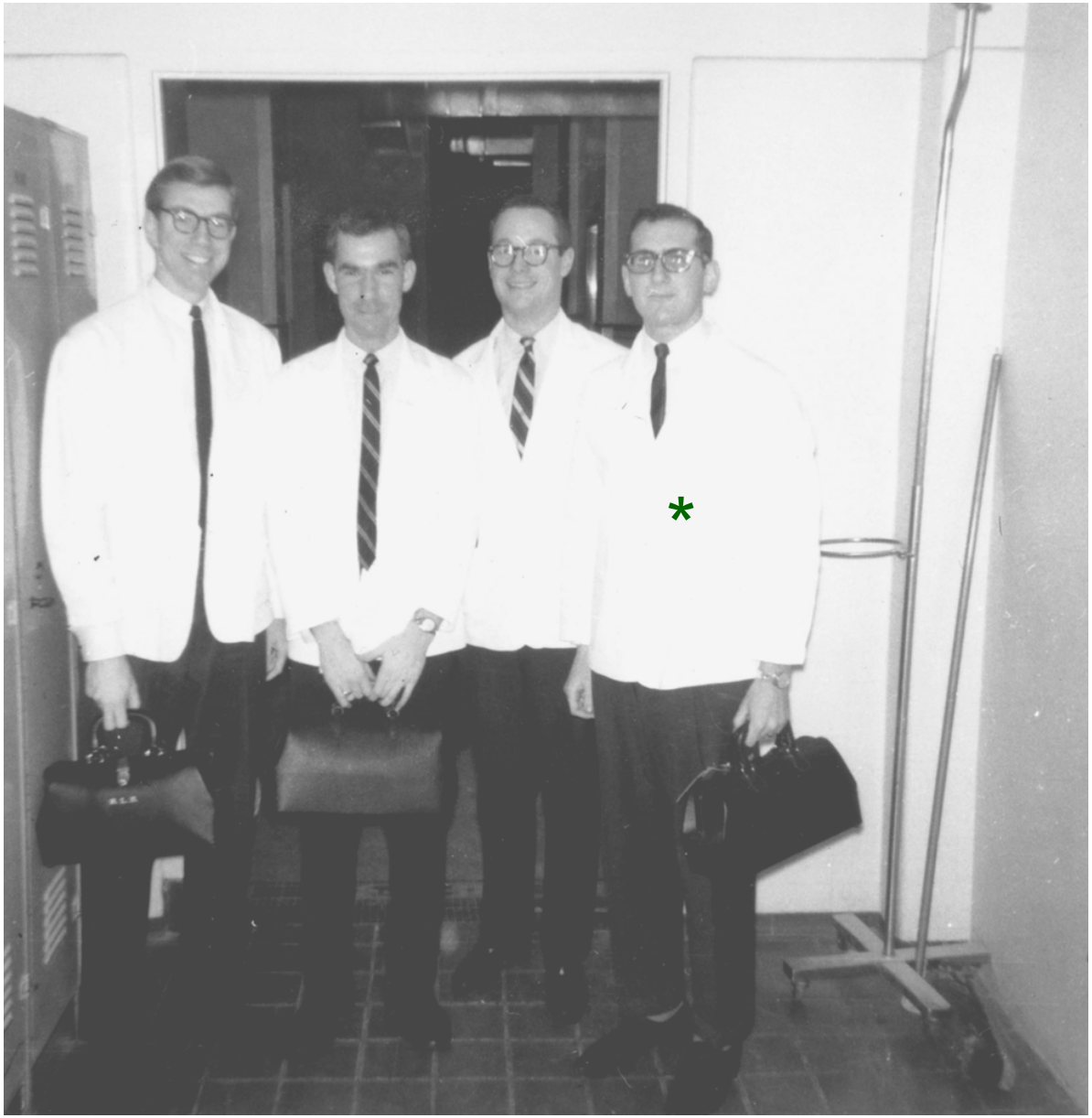


Paul Ehrlich
Adaptive Immunity





Ilya Ilyich Metchnikov
Innate Immunity

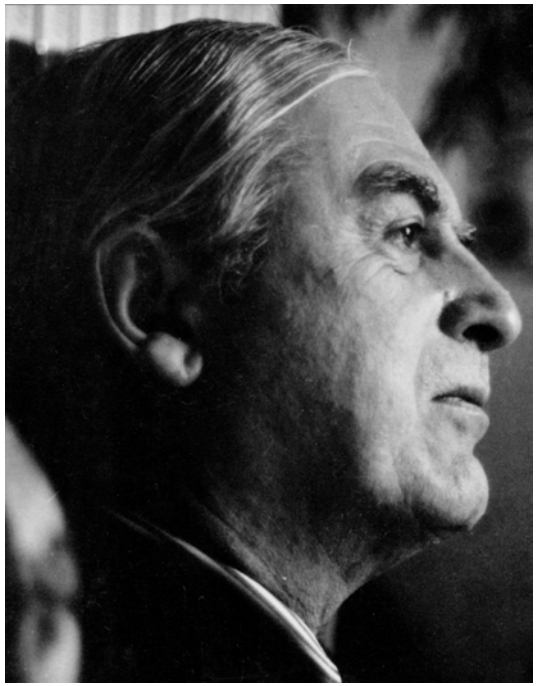


Ralph's (*) first day of physical diagnosis, Harvard Medical School 1964

RMS

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

Macfarlane Burnet
Clonal Selection



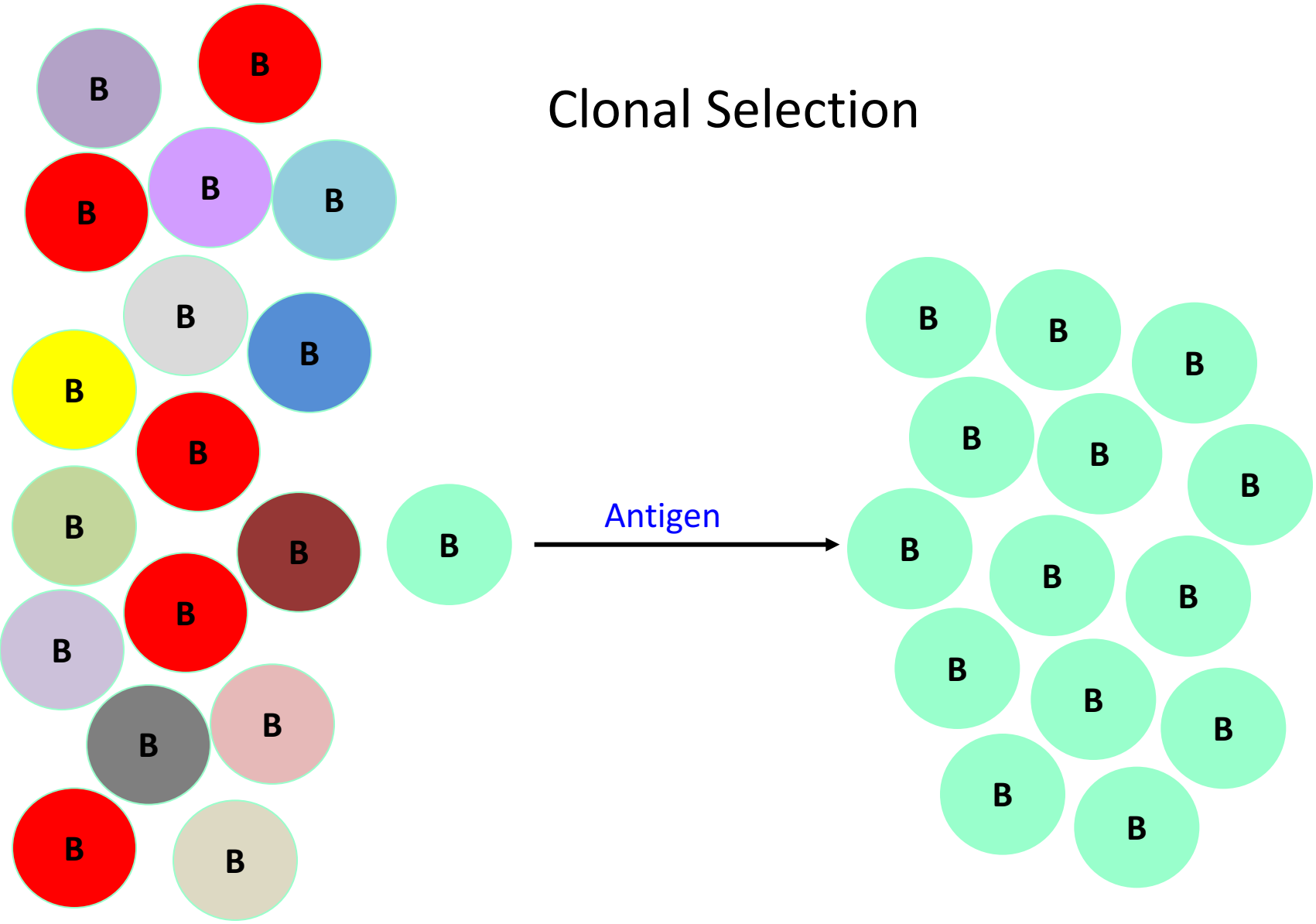
Peter Medawar
Immune Tolerance

RMS

Properties of Immune Responses

1. Specificity
2. Diversity
3. Memory

Clonal Selection



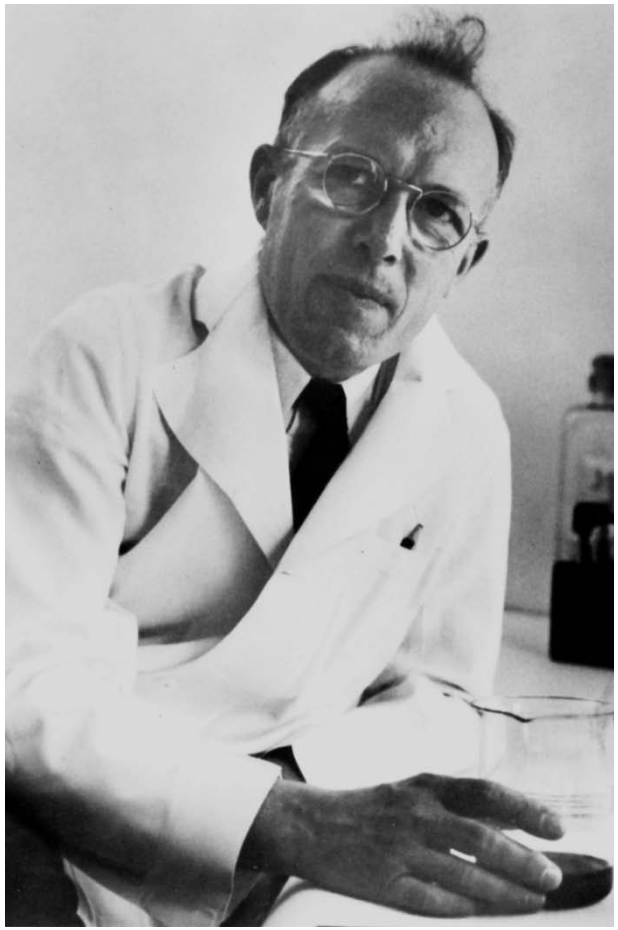
V(D)J Recombination

Clonal Expansion

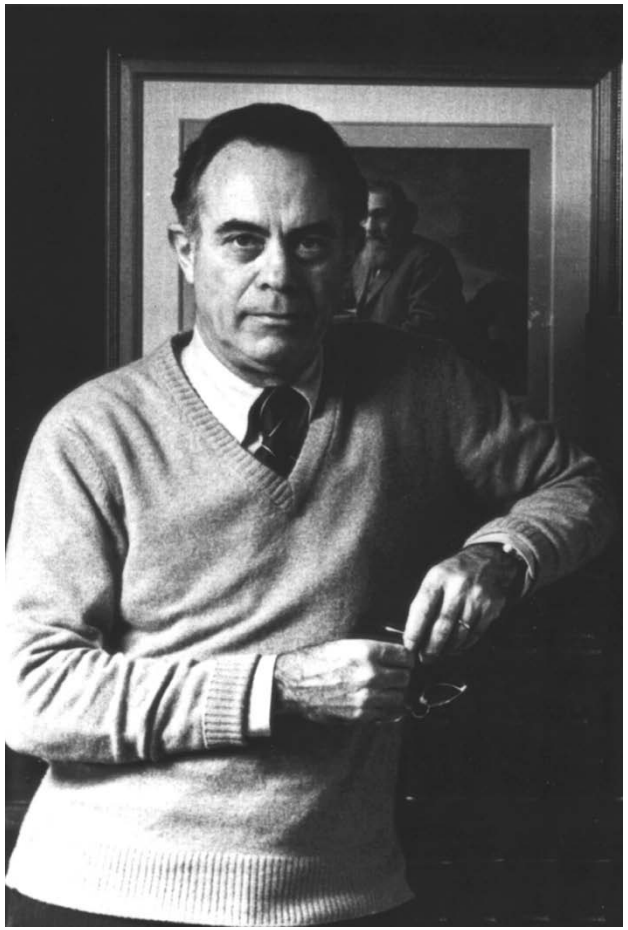
Burnet, Lederberg, Talmage

Ralph Steinman's mentors at Rockefeller University

Zanvil Cohn

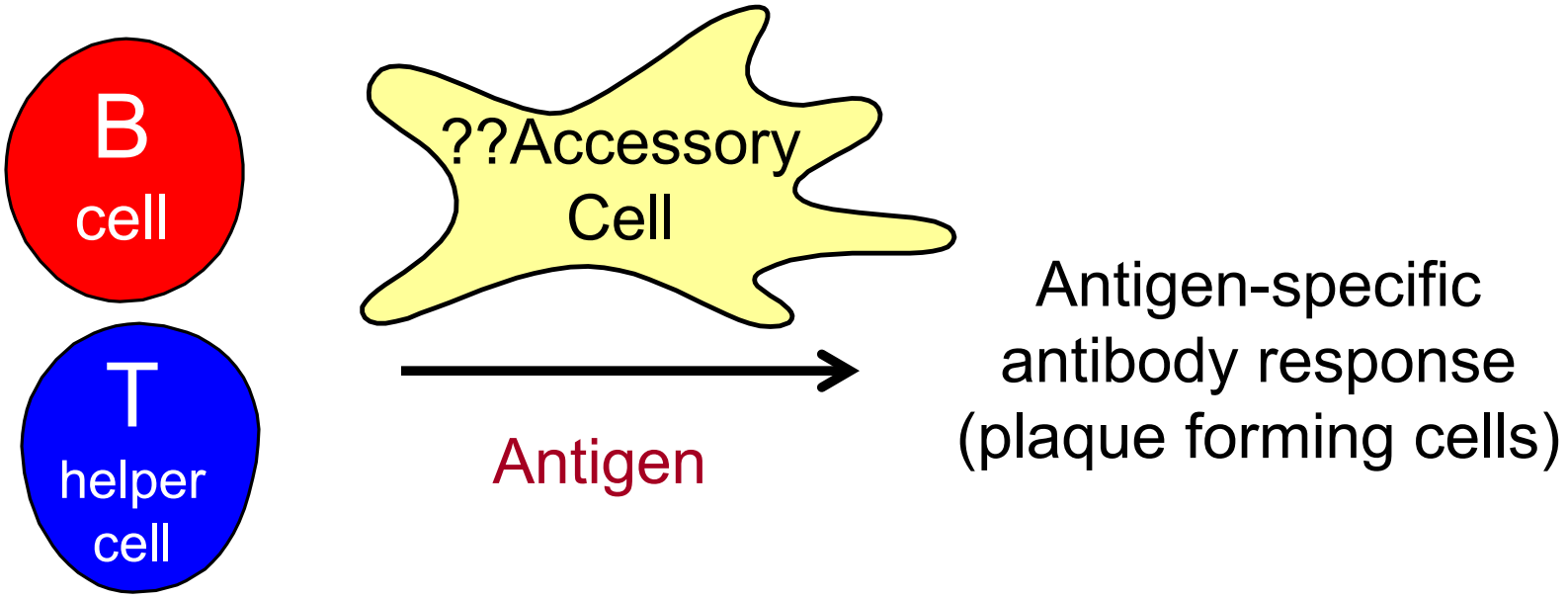


René Dubos

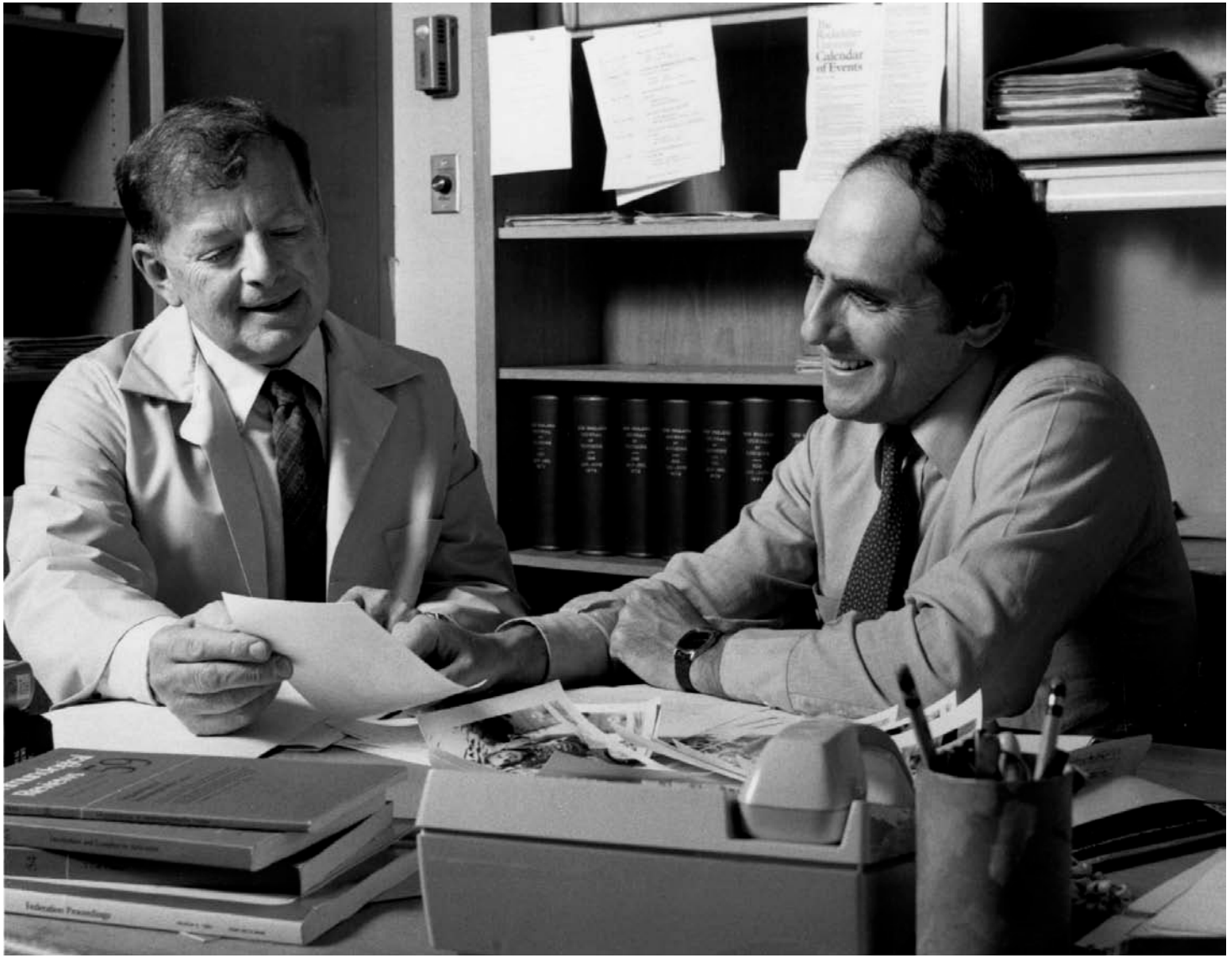


James Hirsch

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

RMS

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)

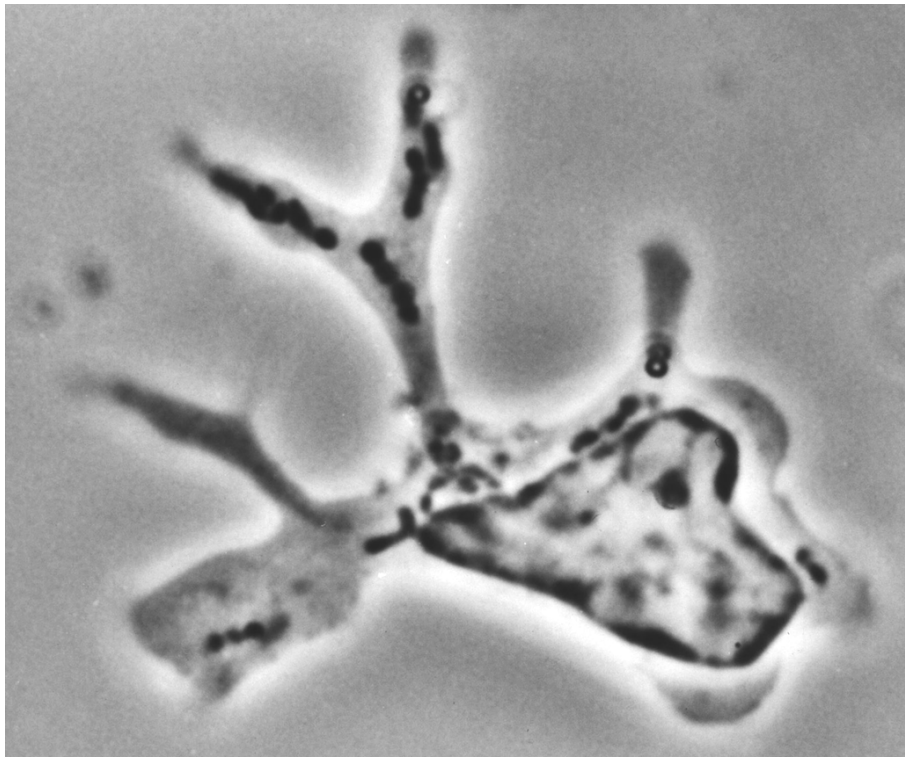
3. Steinman R.M., and Cohn, Z.A. The interaction of particulate horseradish peroxidase immune complexes with mouse peritoneal macrophages in vitro. JCB (1972)

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)

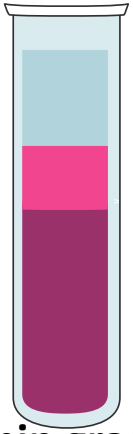


Steinman, R.M., and Cohn, Z.A. Identification of a novel cell type in peripheral lymphoid organs of mice. J. Exp. Med. 137:1142-1162 (1973)

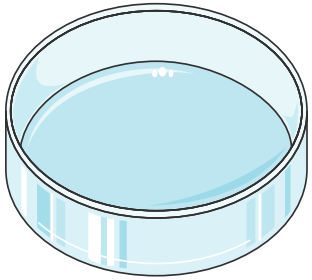
RMS

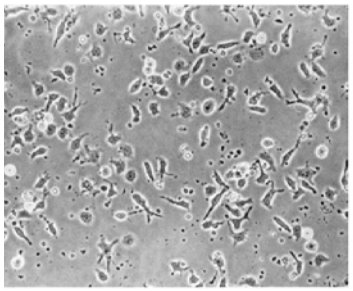
Dendritic Cell Purification

Spleen



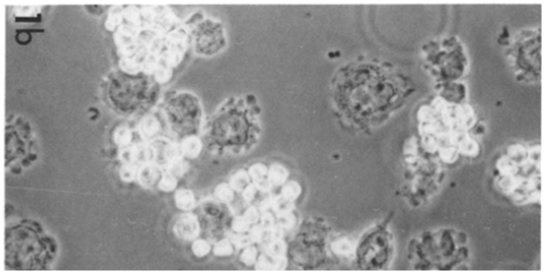
Albumin gradient



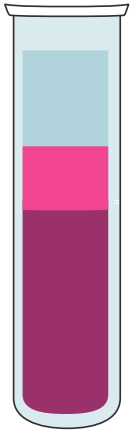


Low Density
Adherent Cells

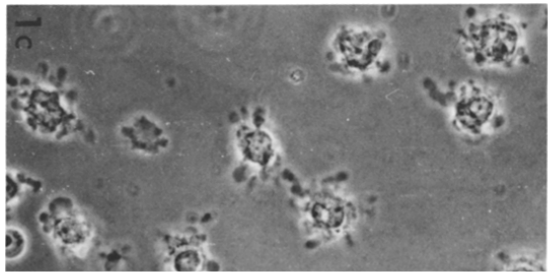
Overnight Culture



EA Rosettes



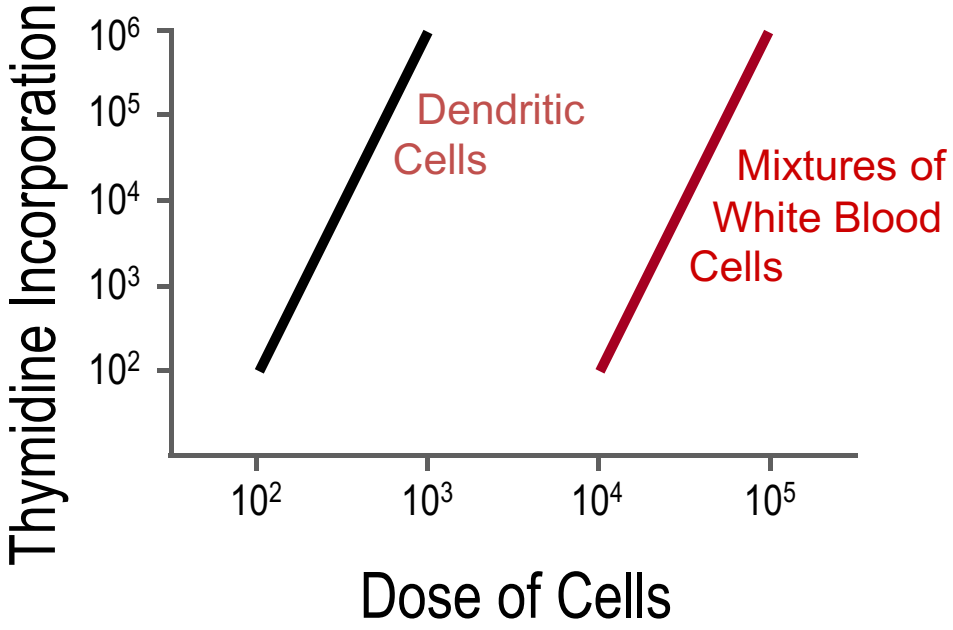
Albumin gradient



Purified DC!

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*

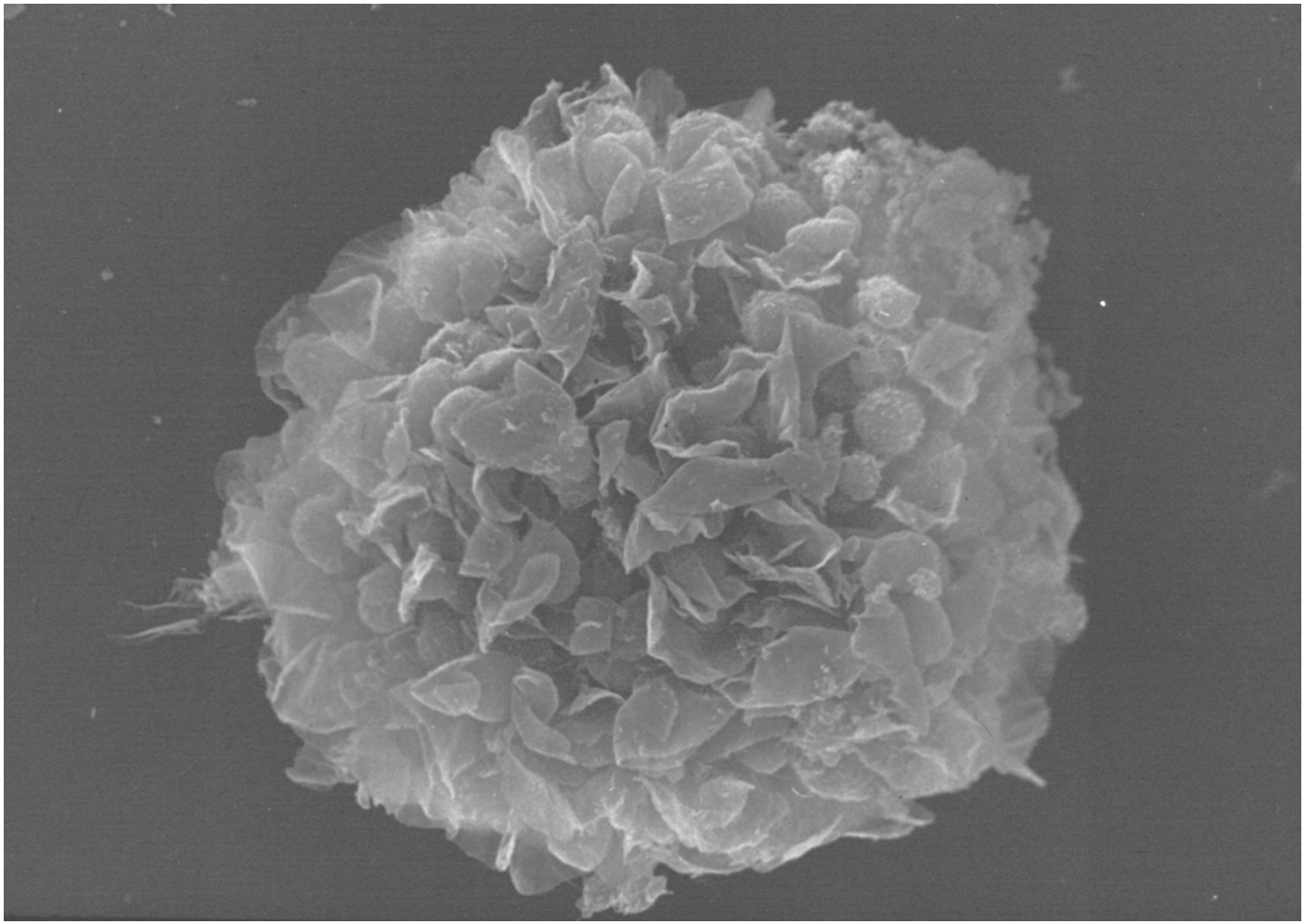
By MICHEL C. NUSSENZWEIG, RALPH M. STEINMAN,‡ BODMA GUTCHINOV, AND ZANVIL A. COHN

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."

JEM 1980

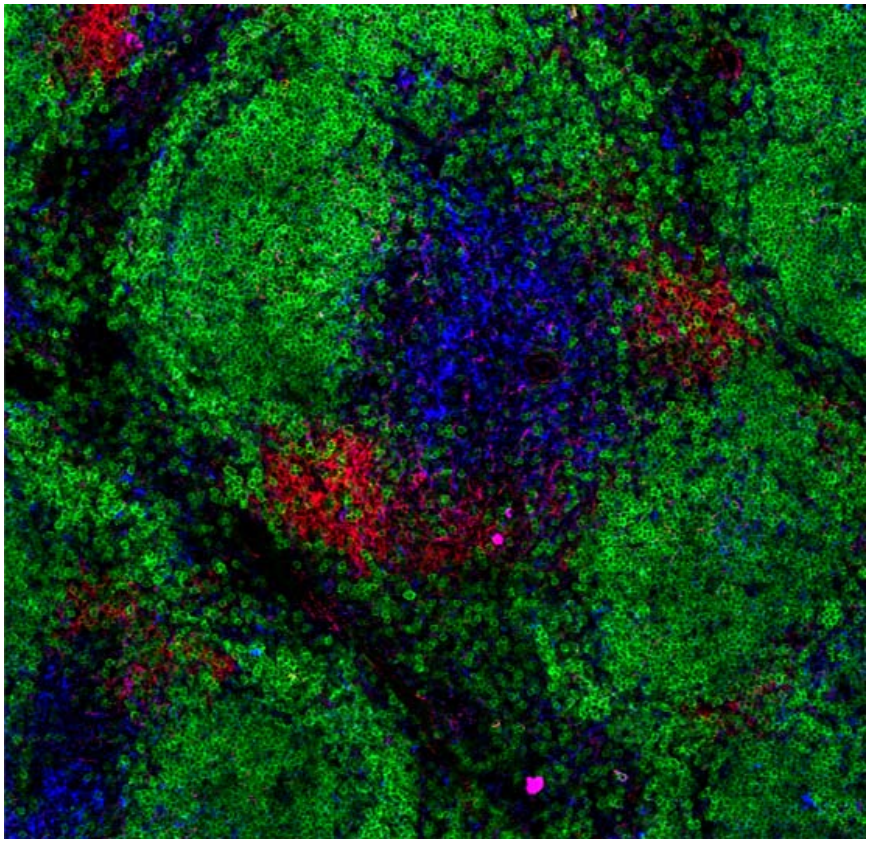
RMS



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

RMS

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)

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Collaborators on Initial Experiments on Antigen Presentation and Human DCs

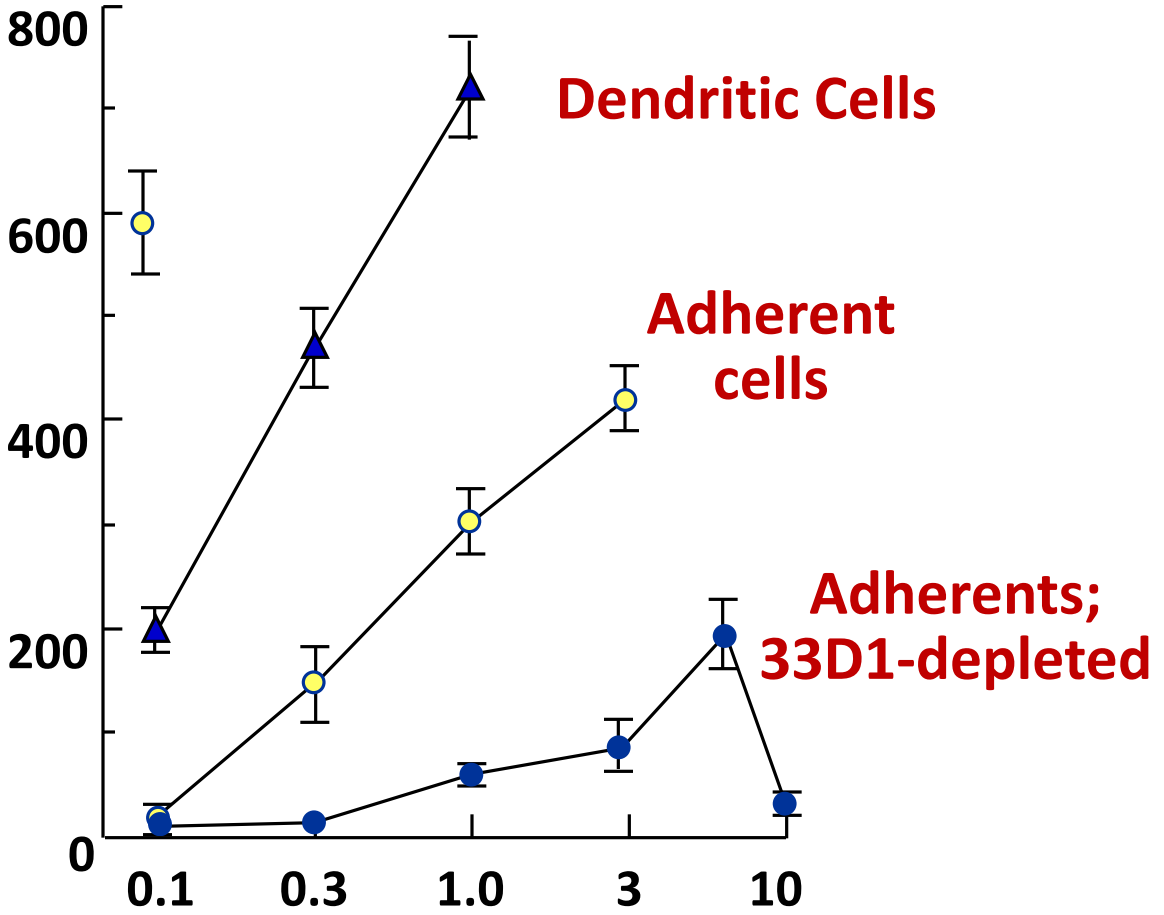
Kayo Inaba

Wesley van Voorhis

RMS

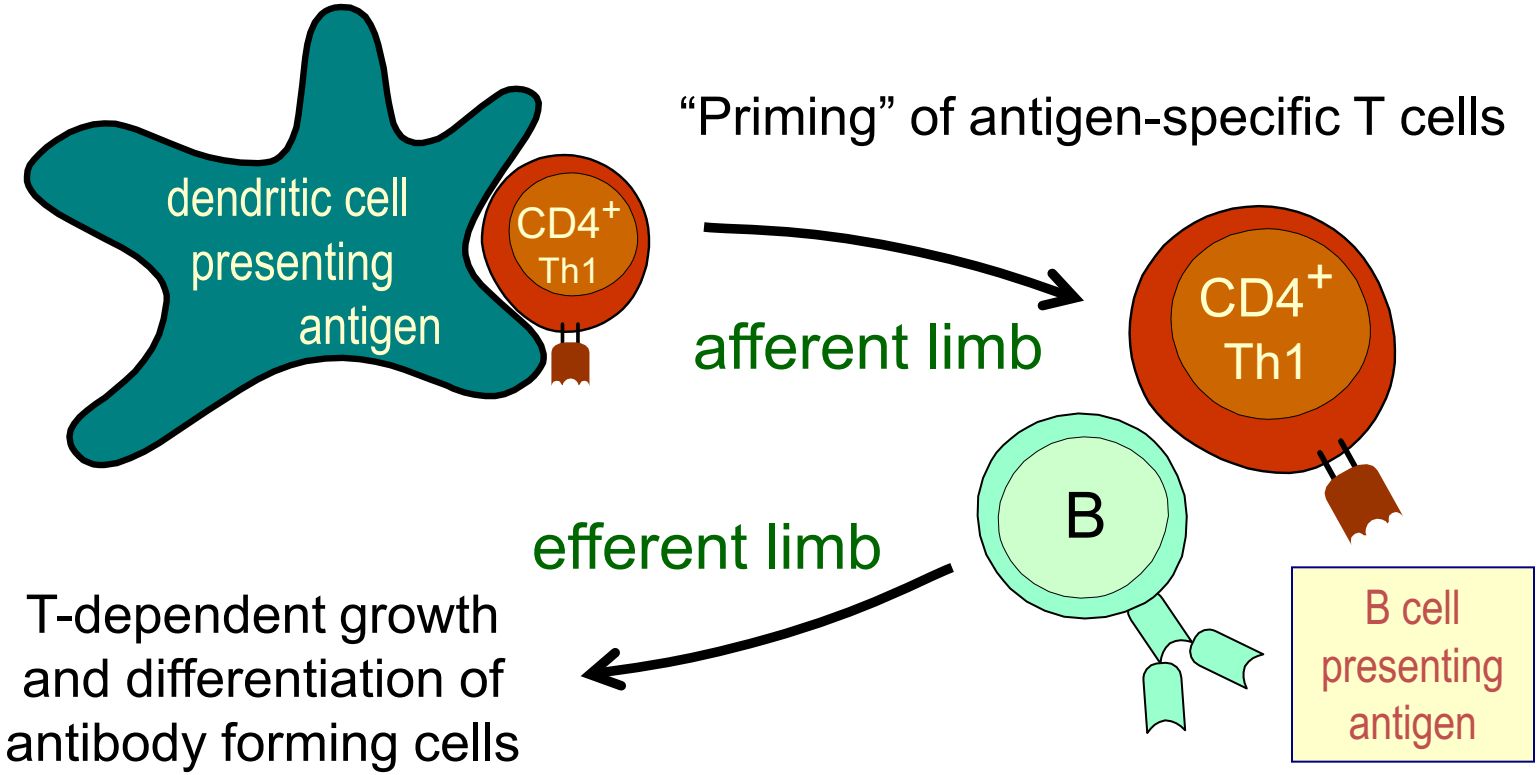
Dendritic Cells Are Potent Accessory Cells to Induce Antibody Forming Cells in Spleen B & T cell Cultures

Kayo Inaba



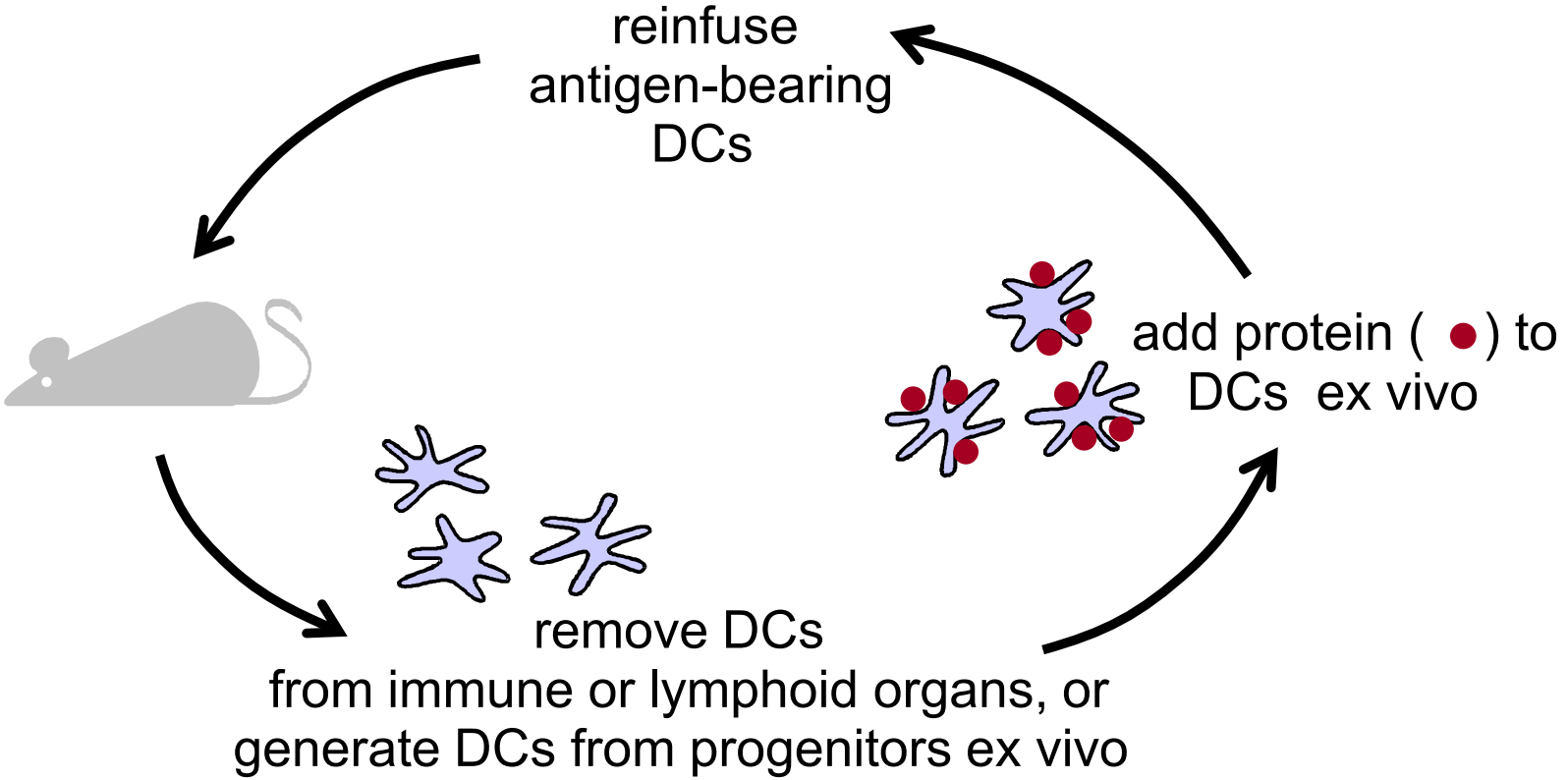
Inaba et al, Proc. Natl. Acad. Sci. 1983

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)

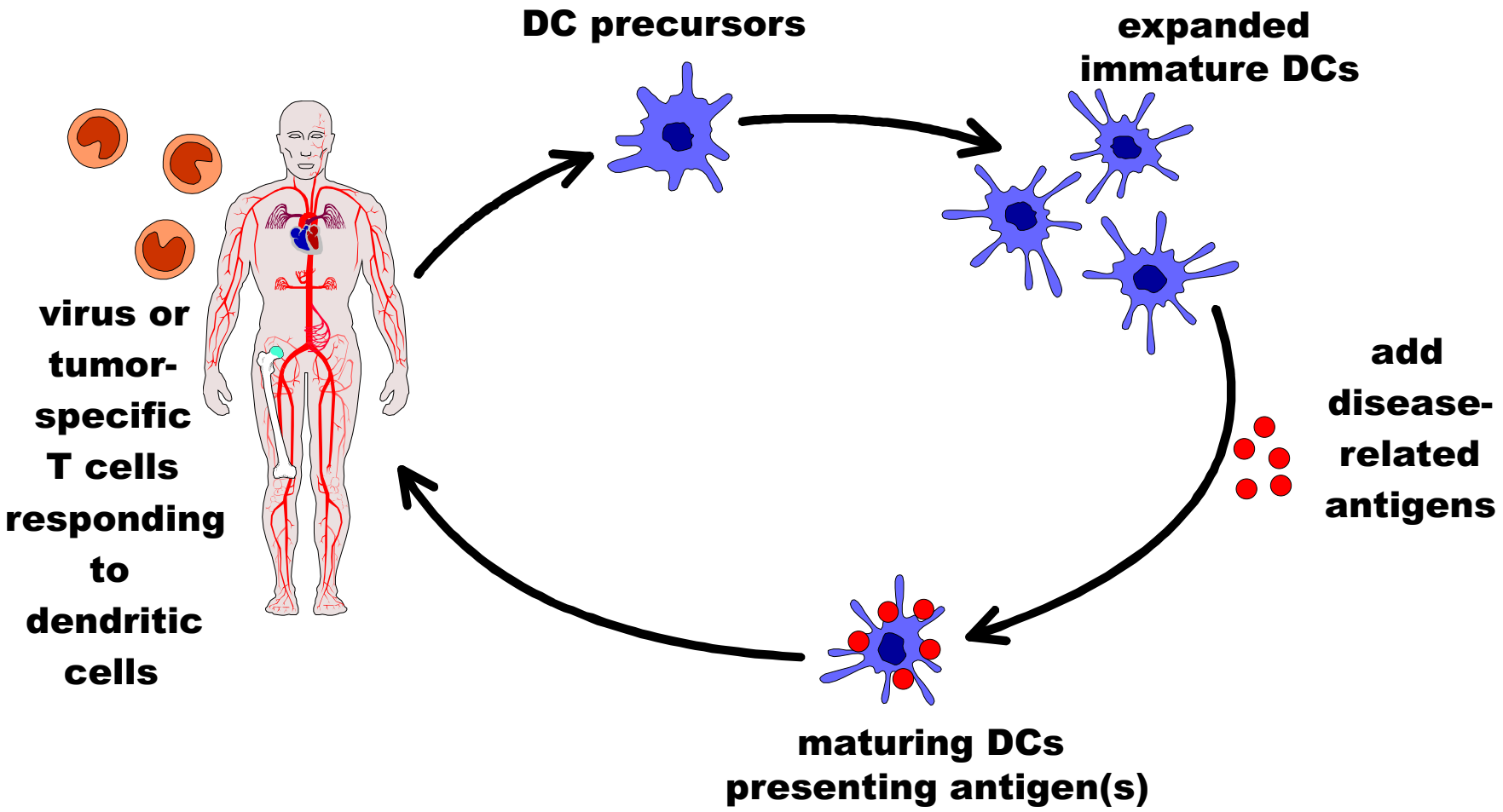
Dendritic Cells (DCs) Are “Nature's Adjuvants”



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

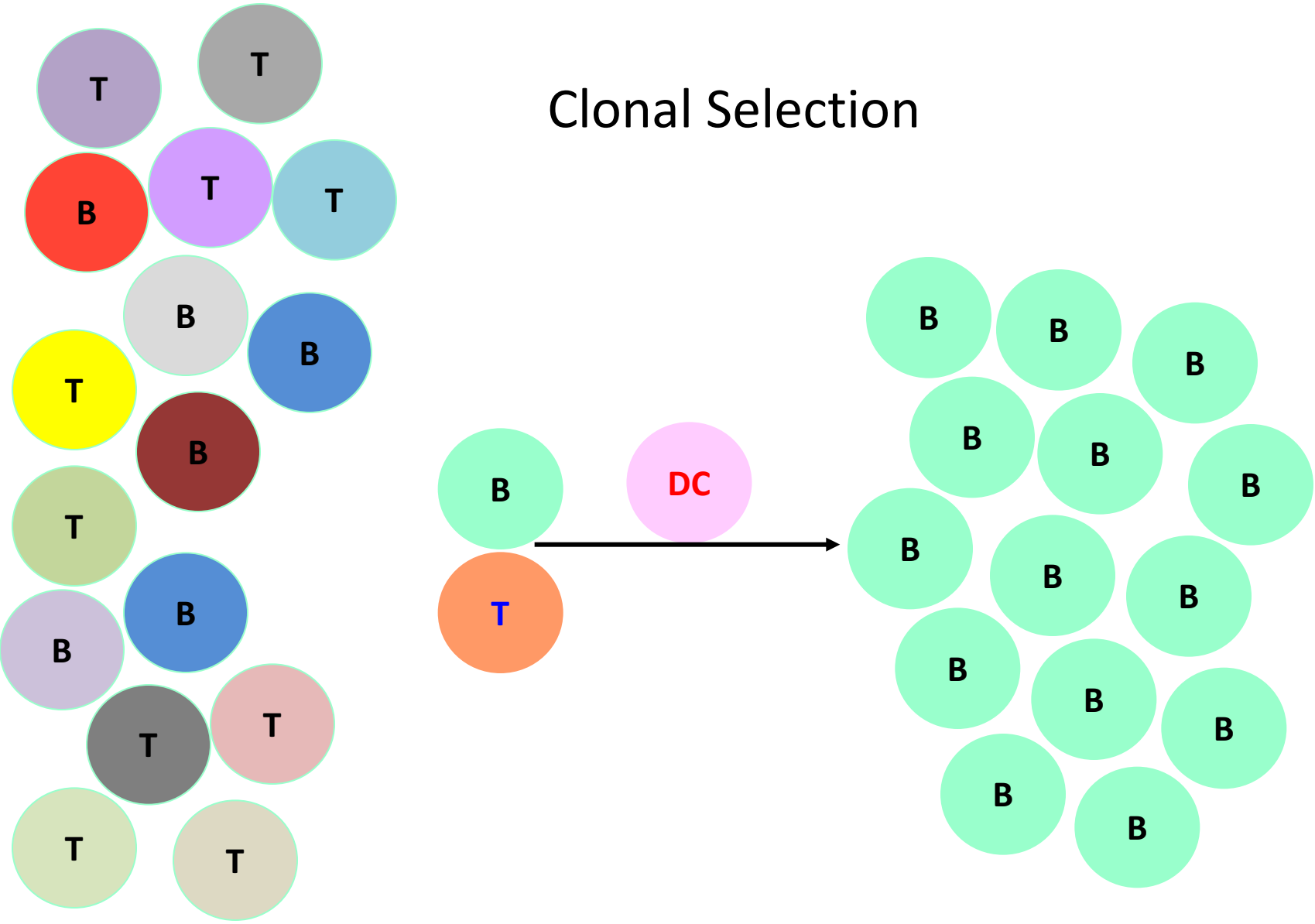
RMS

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



* Schuler, Thurner; Dhodapkar; Banchereau, Palucka

Clonal Selection

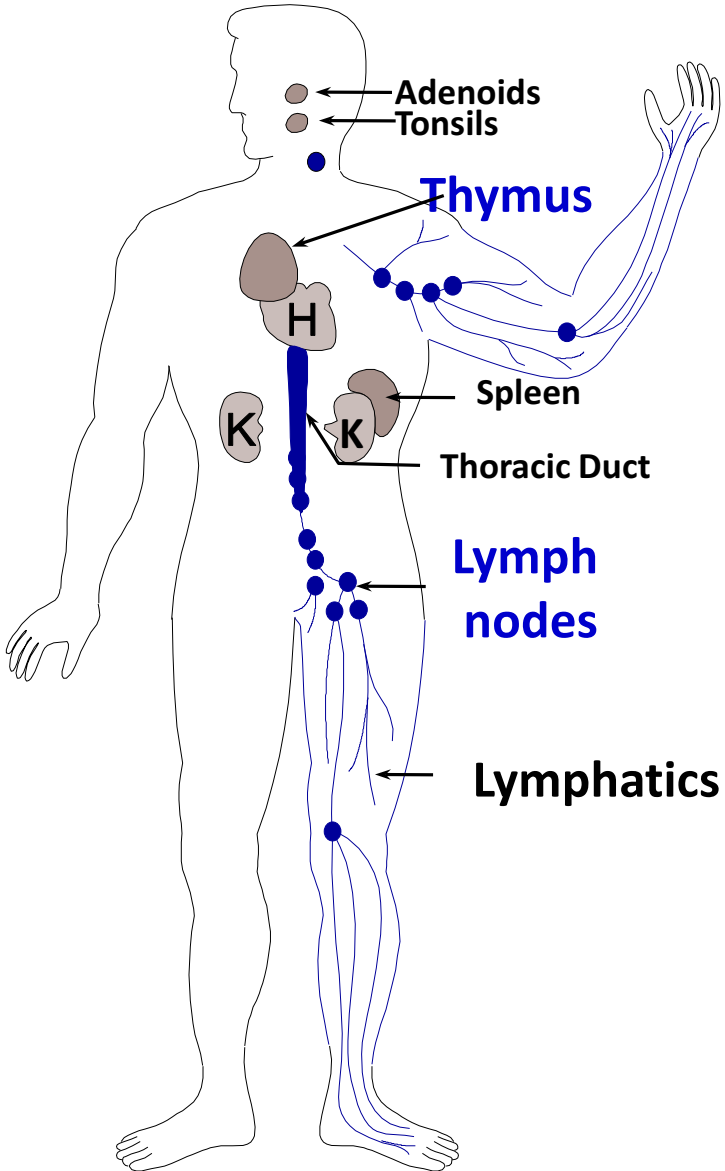


V(D)J Recombination

Clonal Expansion

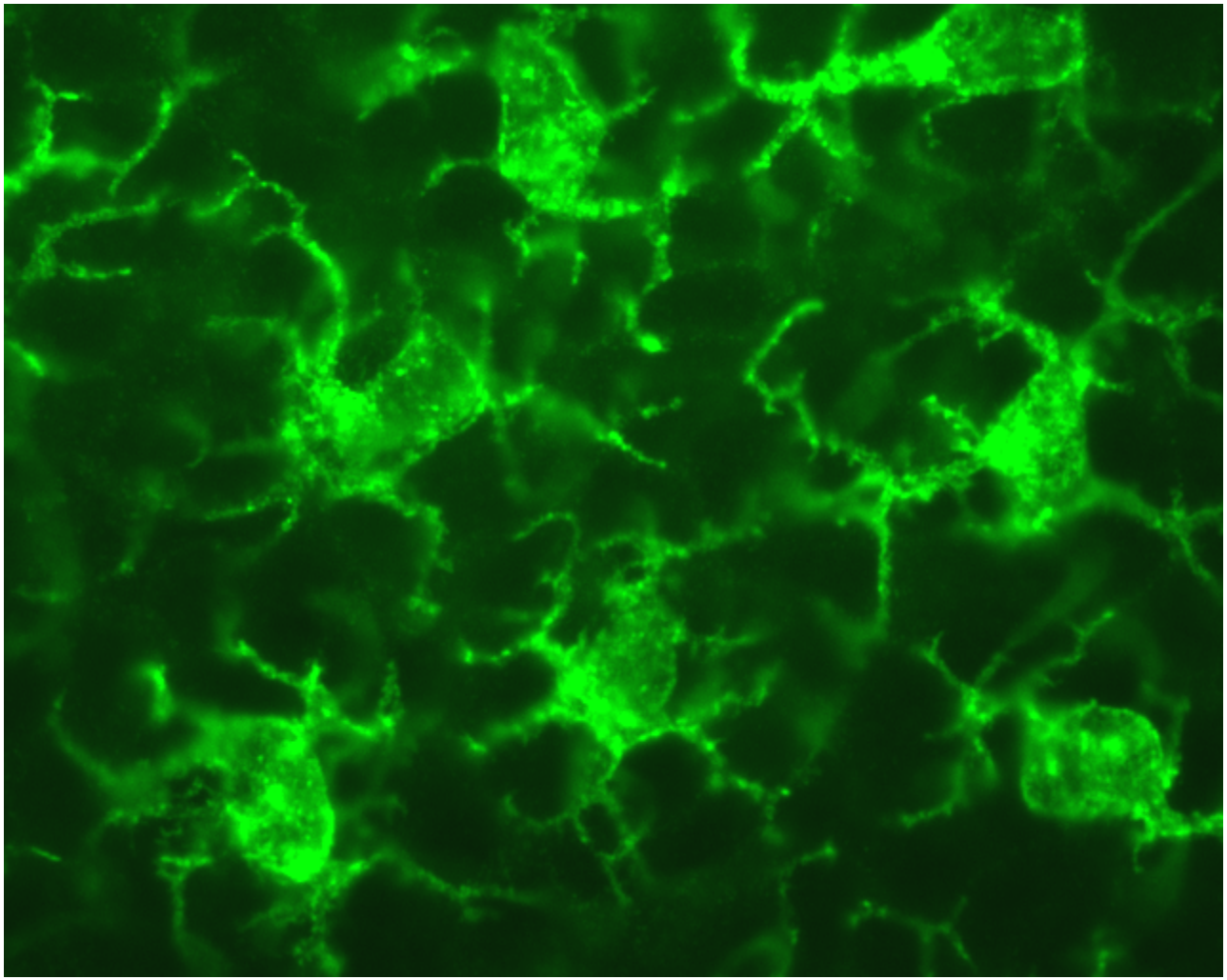
Burnet, Lederberg, Talmage

Initiating Immunity and Tolerance *In Vivo*



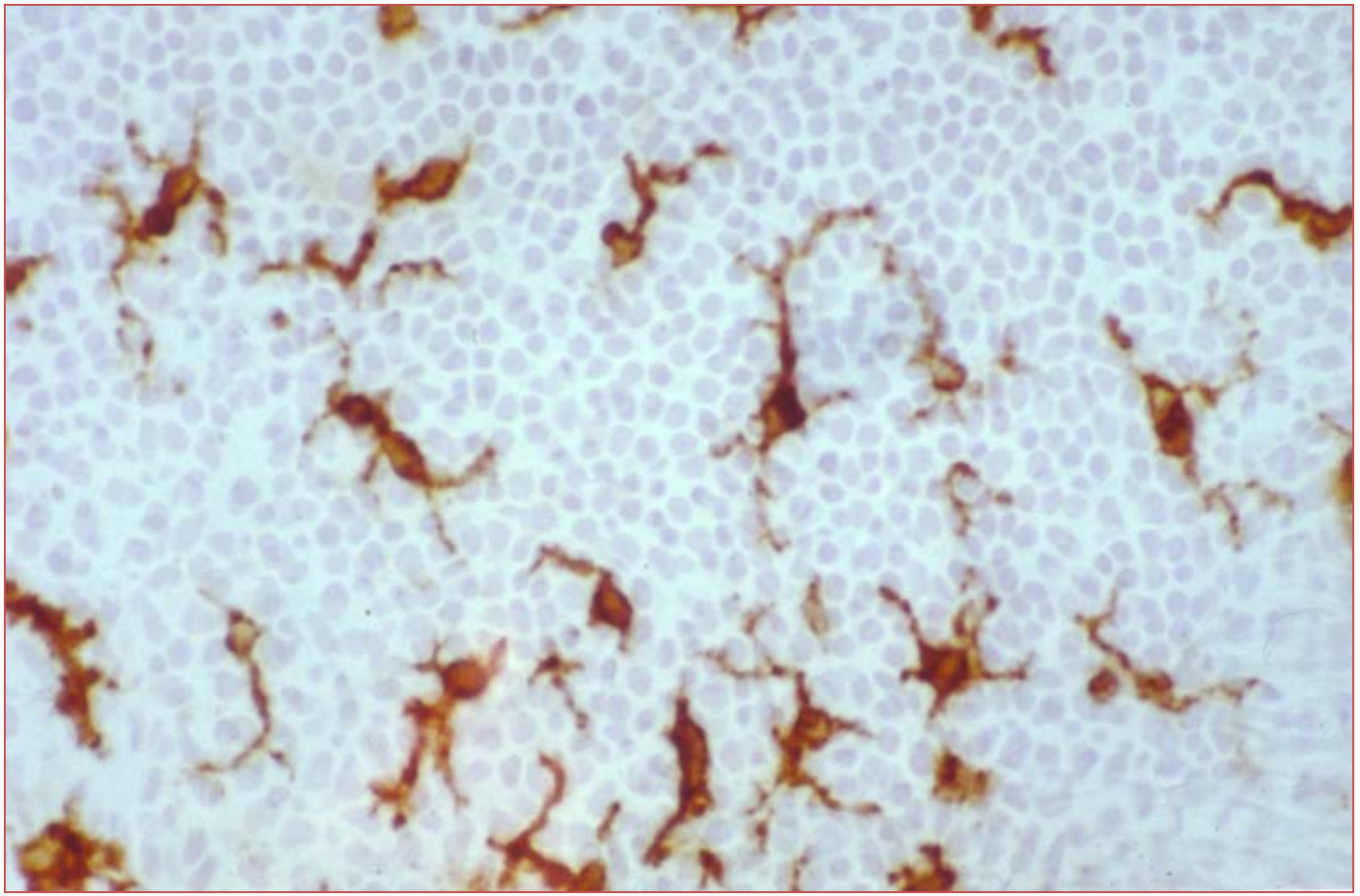
RMS

Dendritic Cells in Skin

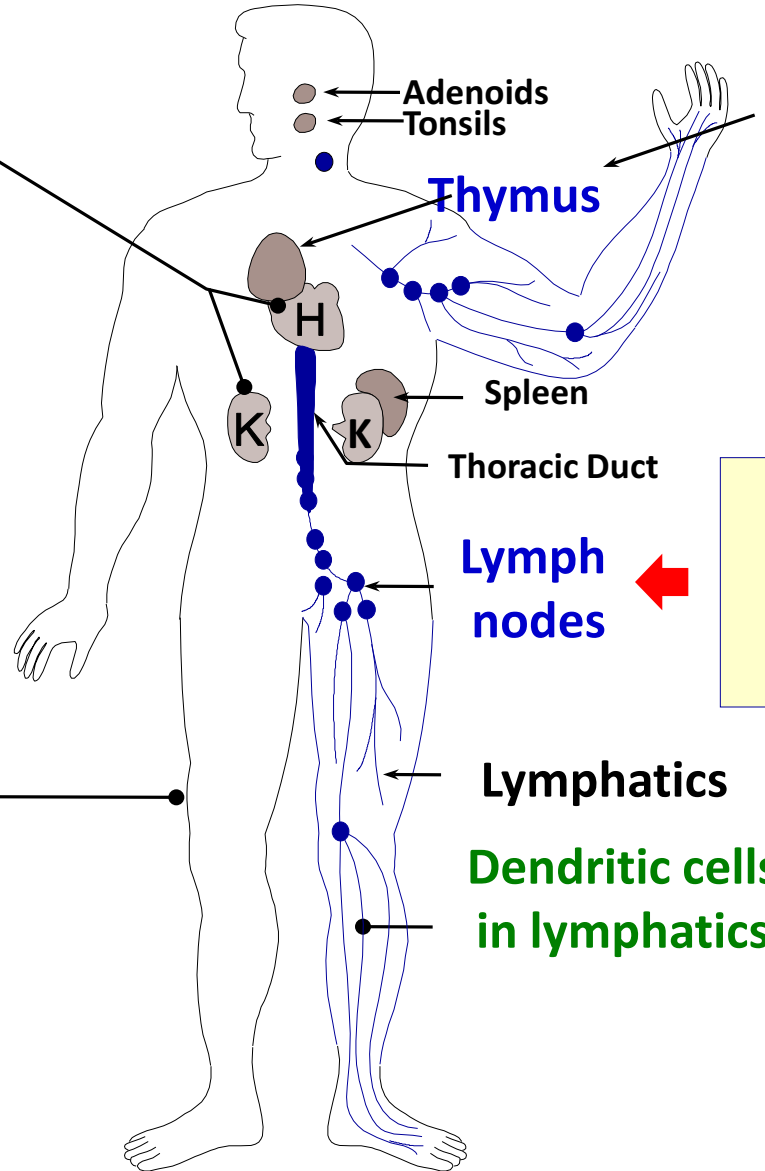


Courtesy of Juli Idoyaga, Cheolho Cheong, Chae Gyu Park

Dendritic Cells in Airway Epithelium (P. Holt)



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



Dendritic cells in interstitial spaces of most organs

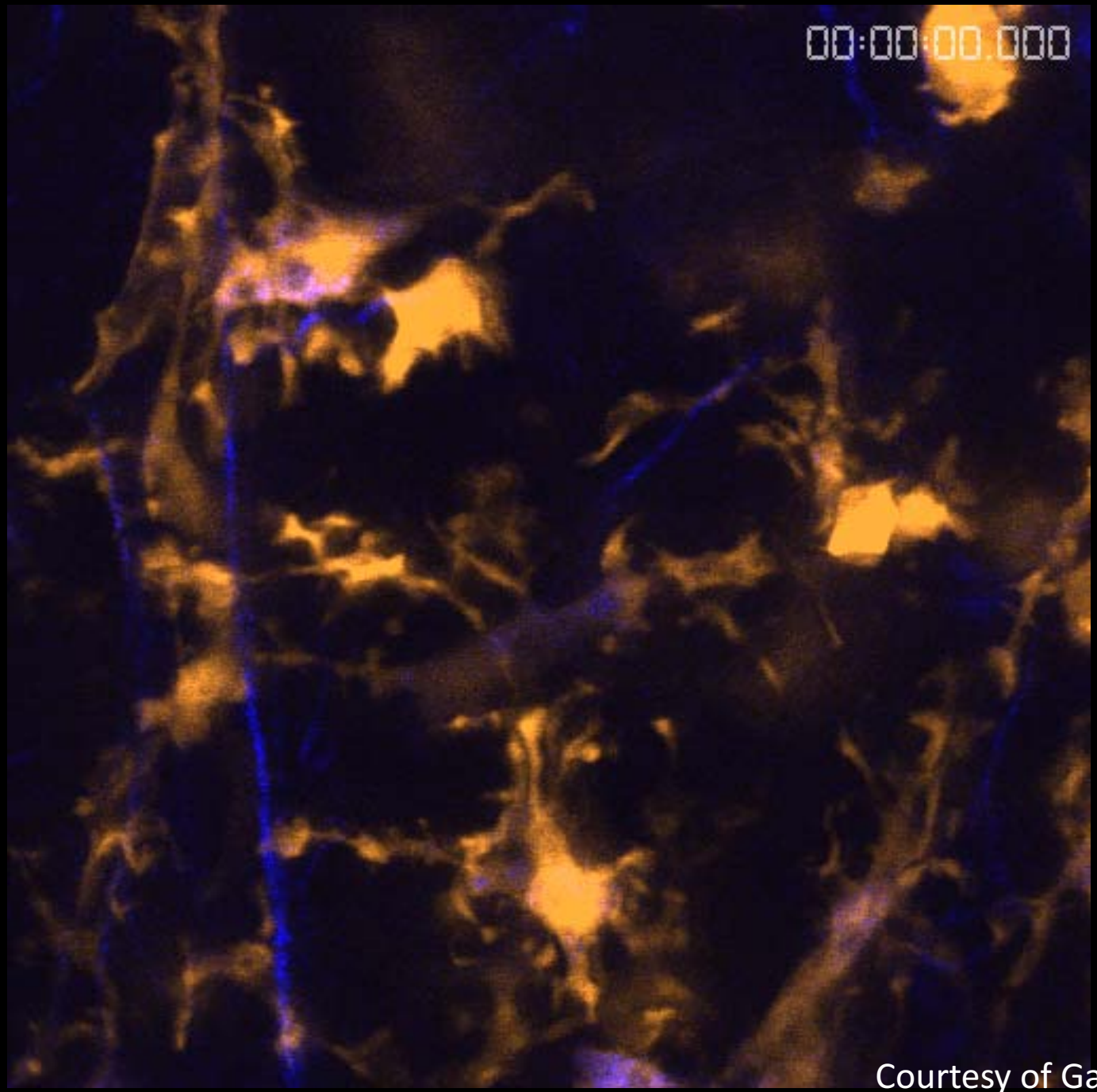
Dendritic cells for central tolerance

Generation of B &T cell immunity

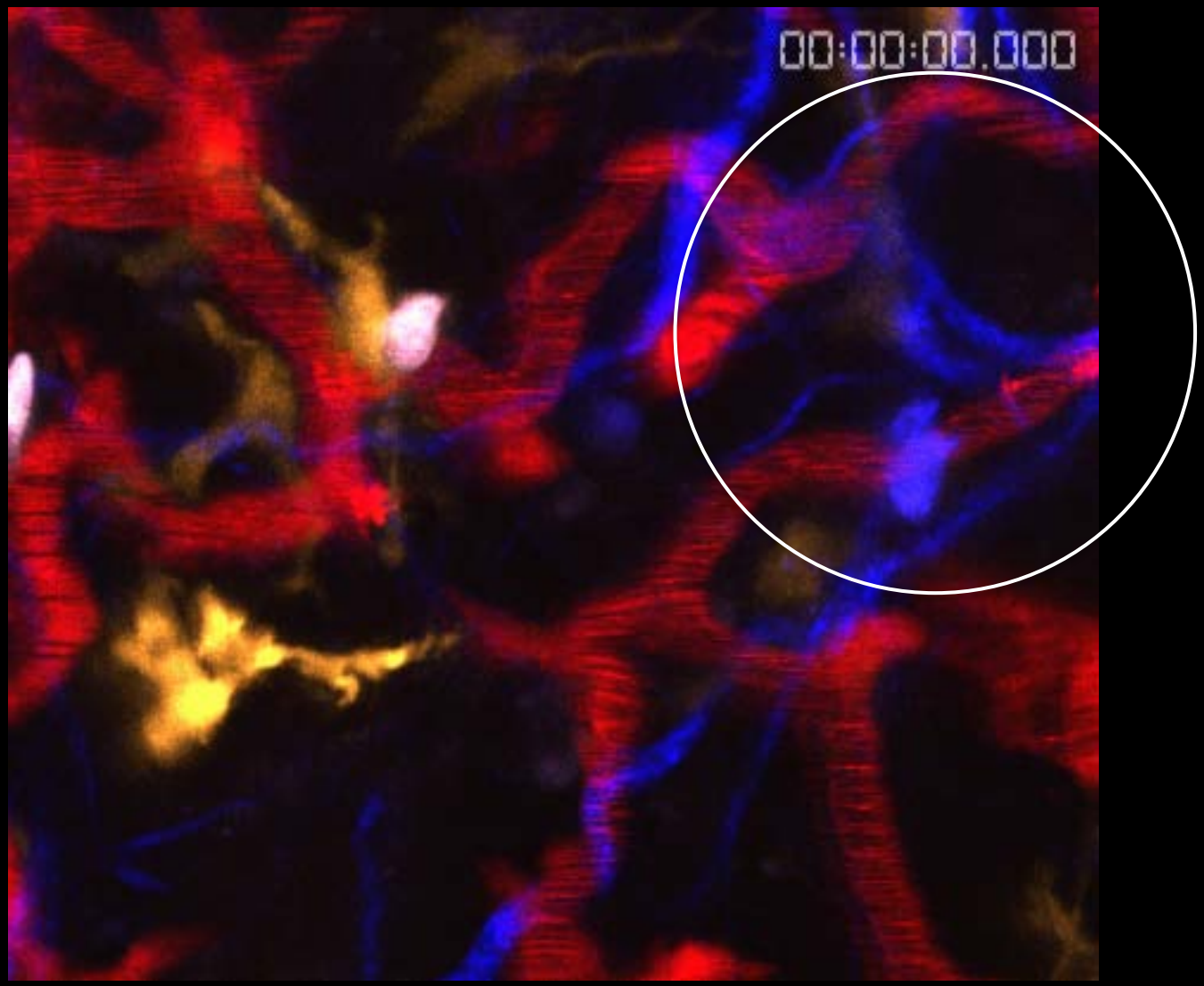
Dendritic cells in skin and other internal mucosal surfaces

Dendritic cells in lymphatics

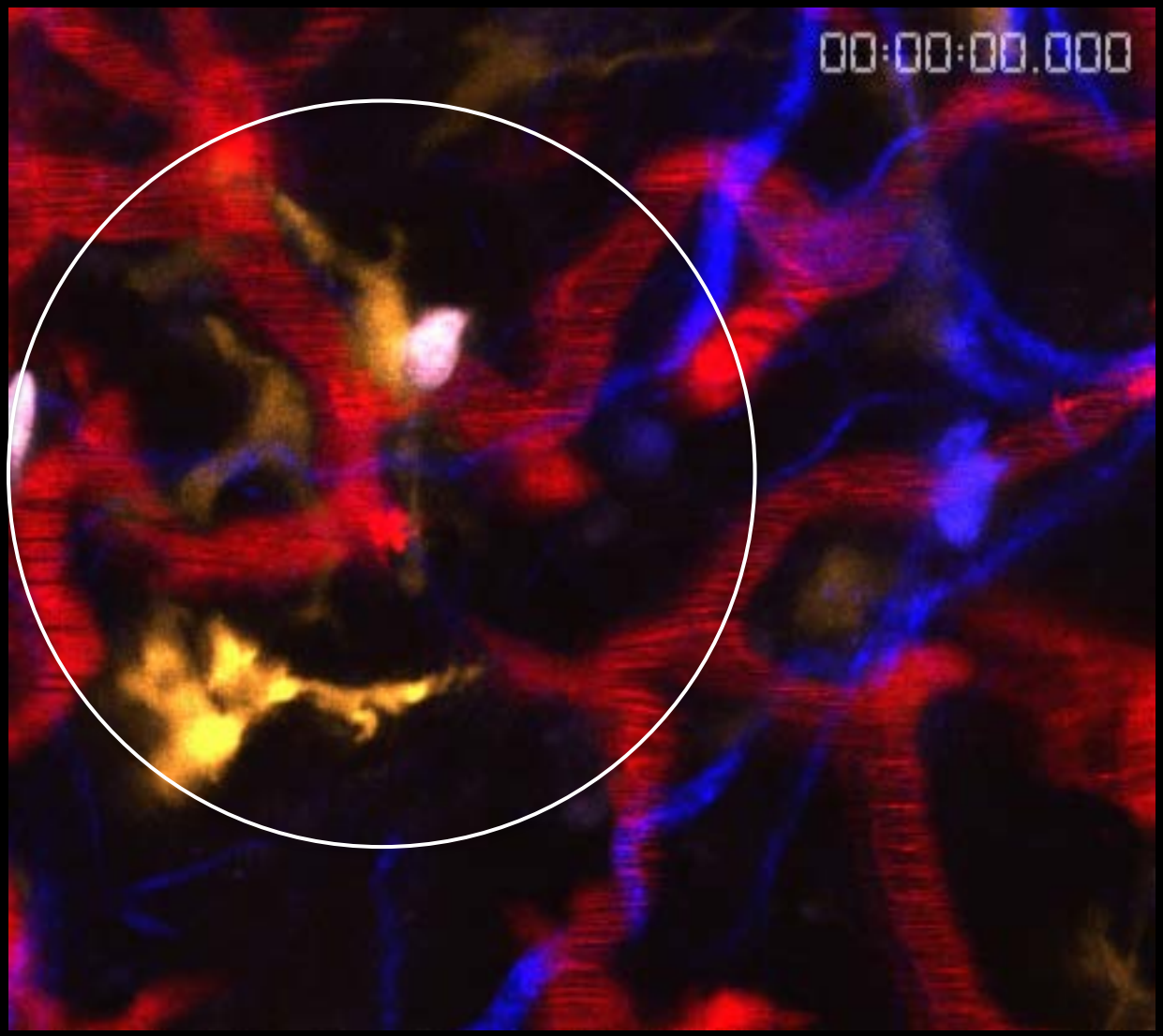
RMS



Courtesy of Gabriel Victora

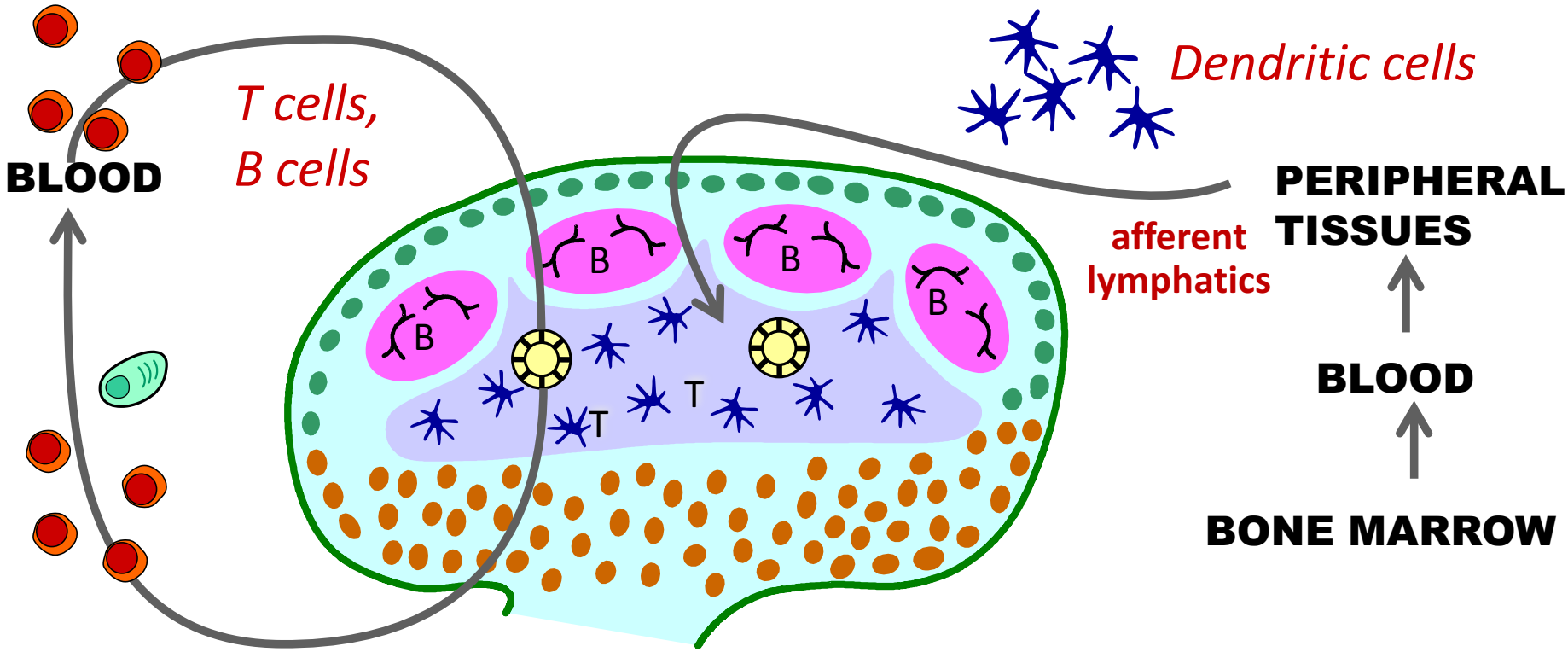


Courtesy of Gabriel Victora



Courtesy of Gabriel Victora

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



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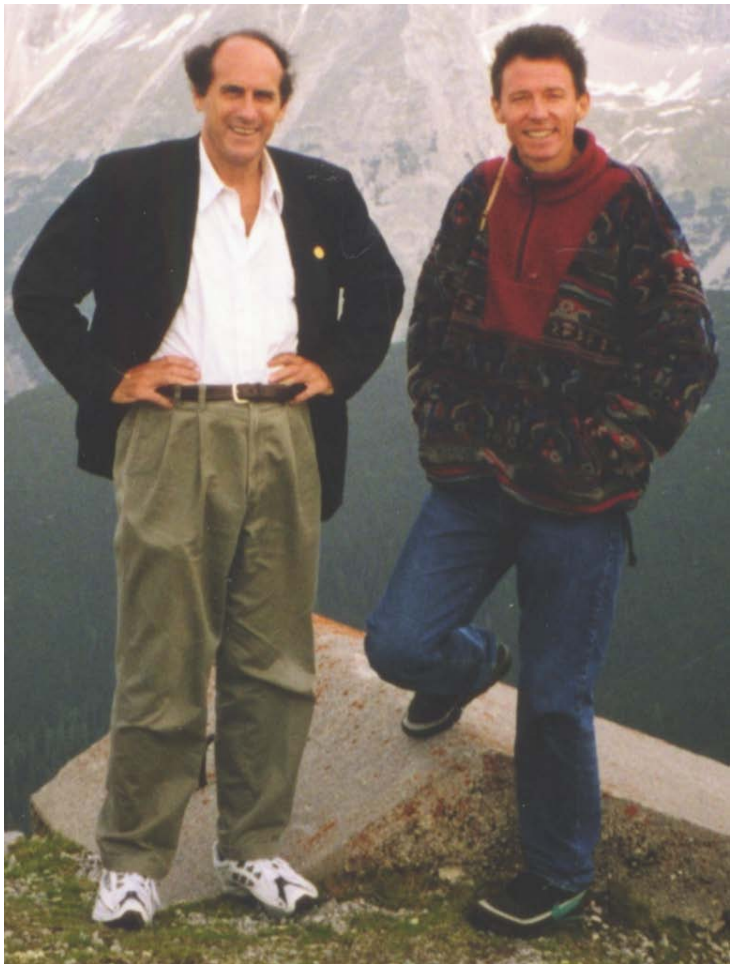
Maturation Allows Dendritic Cells to Initiate Immunity



Nikolaus Romani

Gerold Schuler

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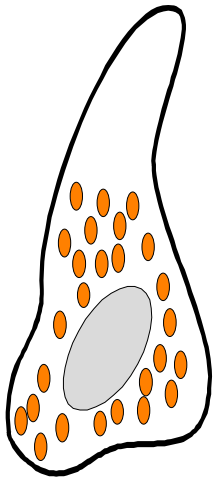
Dendritic Cell as Sensors

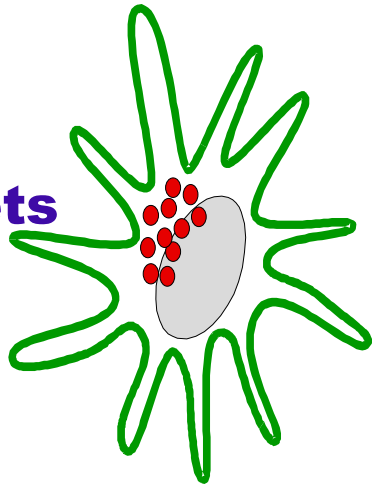
IMMATURE DC
(Steady state)

Lysosome **MHC II**

MATURE DC
(Infection)



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



Antigen capture

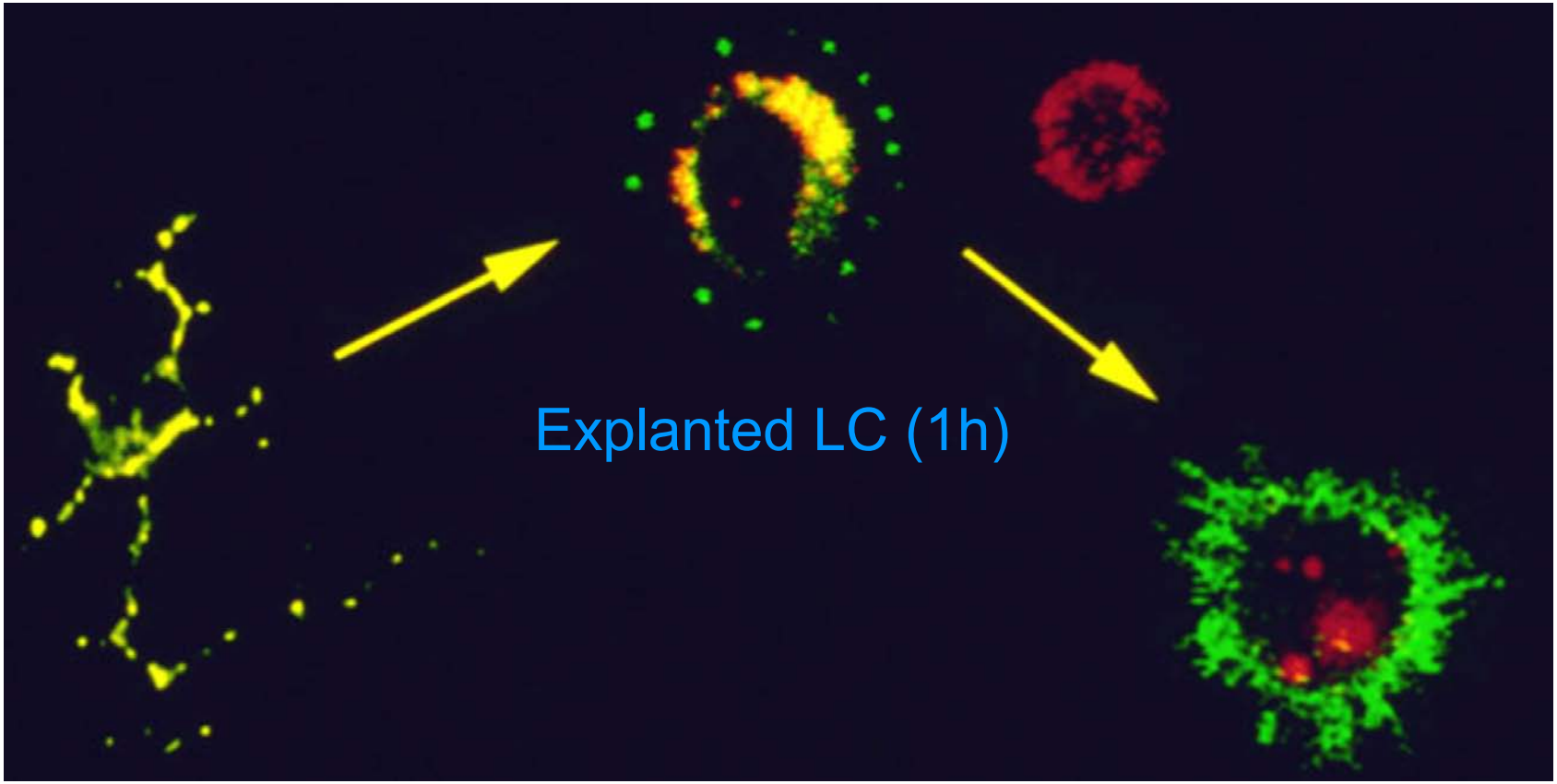
receptors for antigen uptake and maturation stimuli

Costimulation, immunity

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

RMS

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

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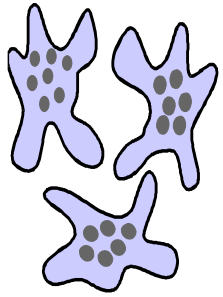
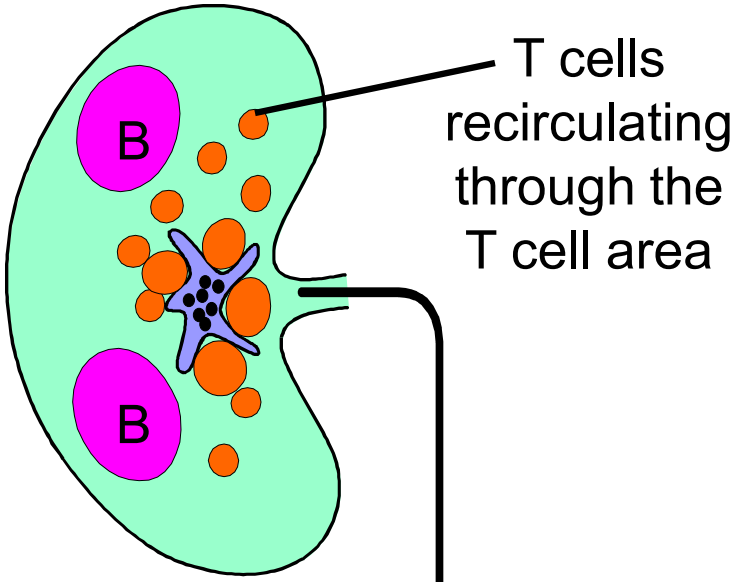
Initiating Antigen-Specific Immune Responses In Vivo

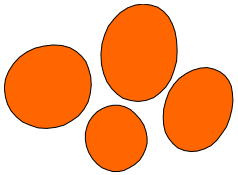


AFFERENT

LYMPHATIC



Mature peripheral dendritic cells
with captured antigen

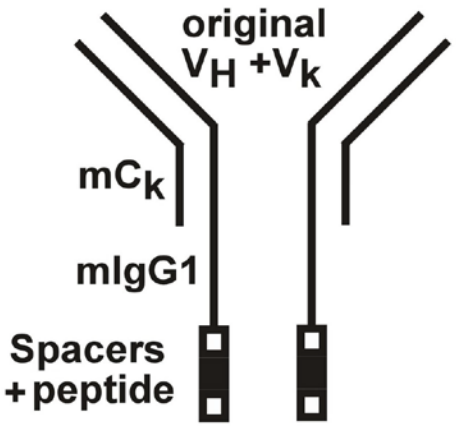


EFFERENT

LYMPHATIC

Activated, antigen-specific,
Th1 helper and T killer cells

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

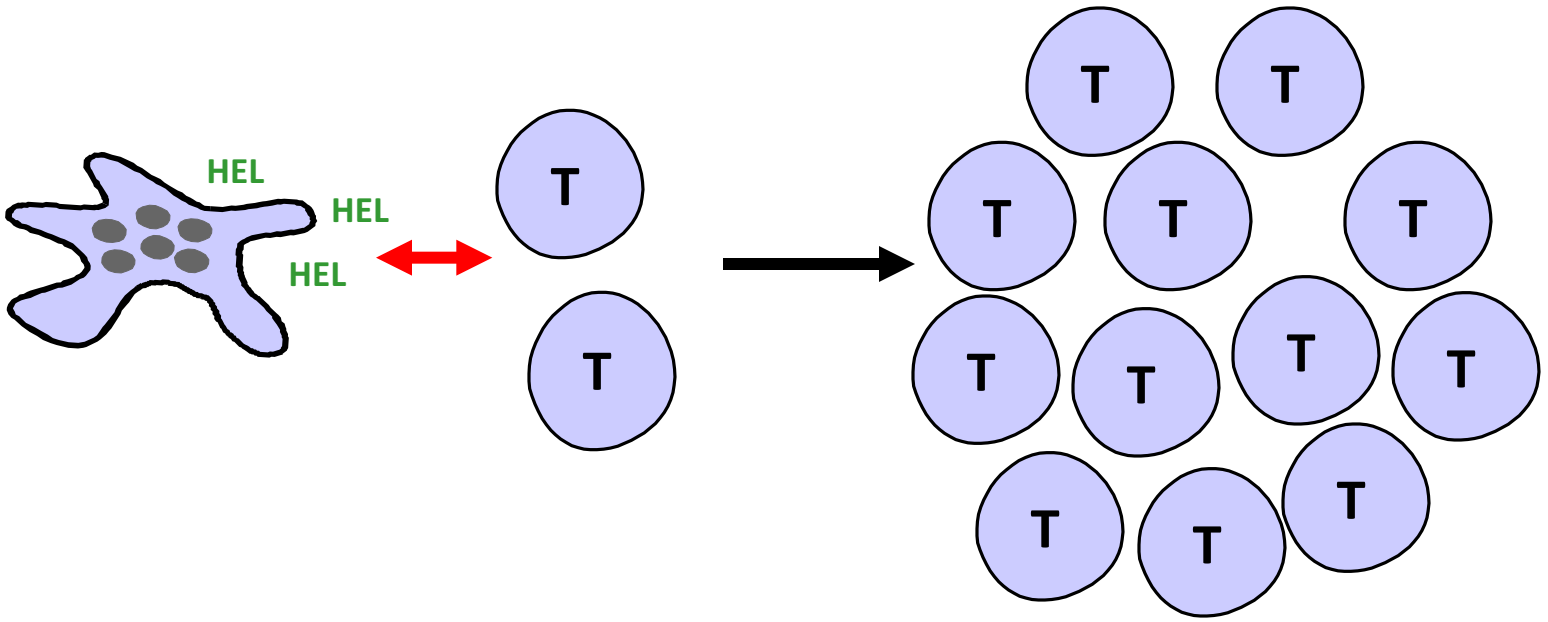


Engineer peptide or protein sequences into the C-terminus of the heavy chain

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

RMS

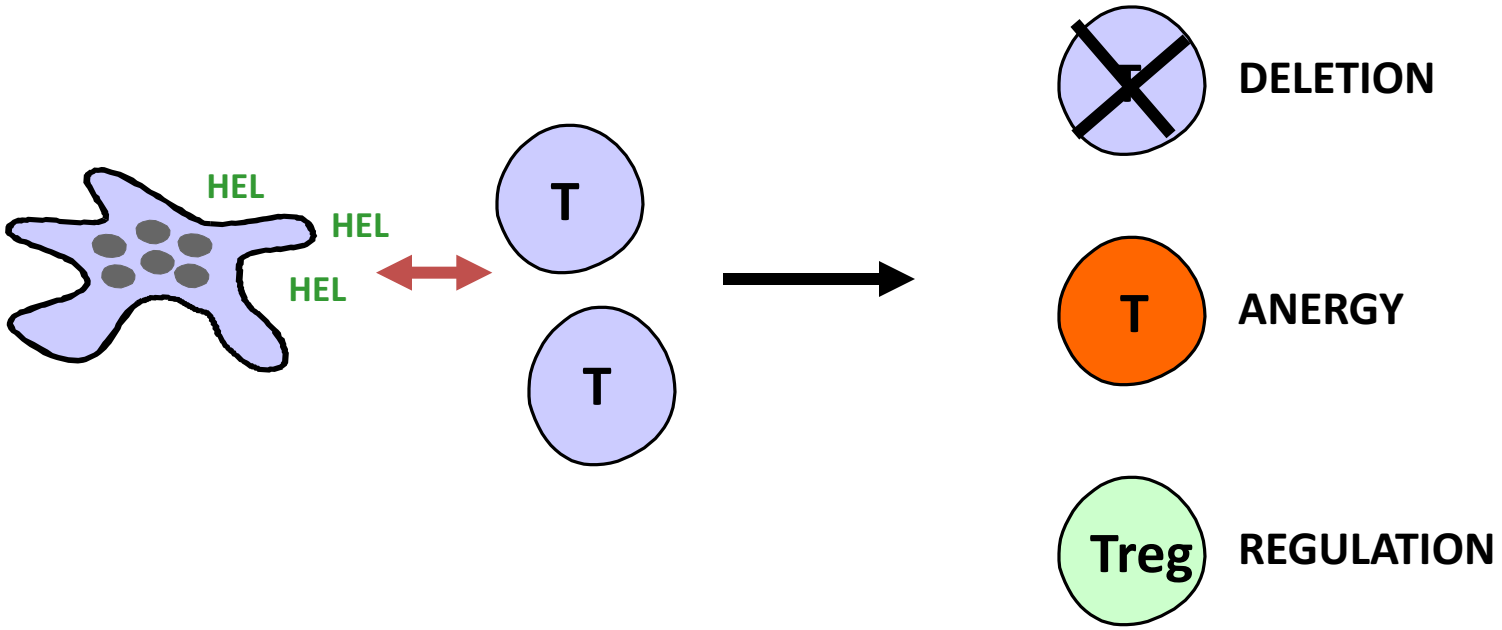
DC activation by TLR or CD40 ligation or other activators and induces prolonged T cell effector responses



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)

RMS

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

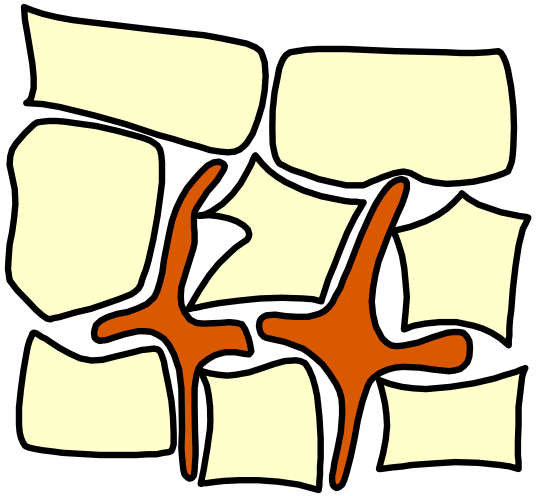


Hawiger et al, JEM 2001
Hawiger et al, Immunity 2003
Kretchmer et al Nat Imunol 2005

RMS

During the Steady State, Dendritic Cells Induce Tolerance

Self and harmless environmental antigens

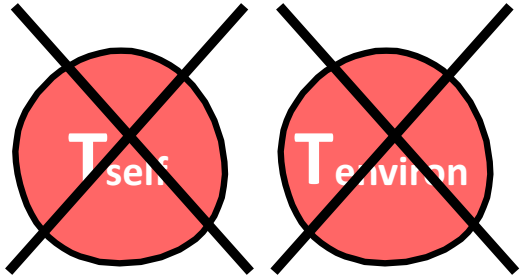


an epithelium with dendritic cells

STEADY STATE

immature DCs

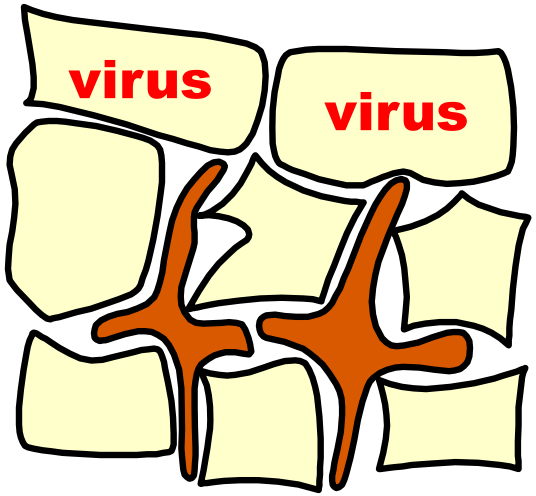
Deletion, anergy



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

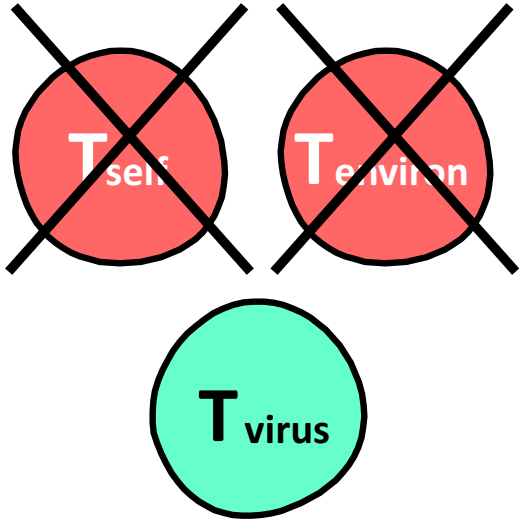


an epithelium with dendritic cells

INFECTION

mature DCs

Deletion, anergy



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

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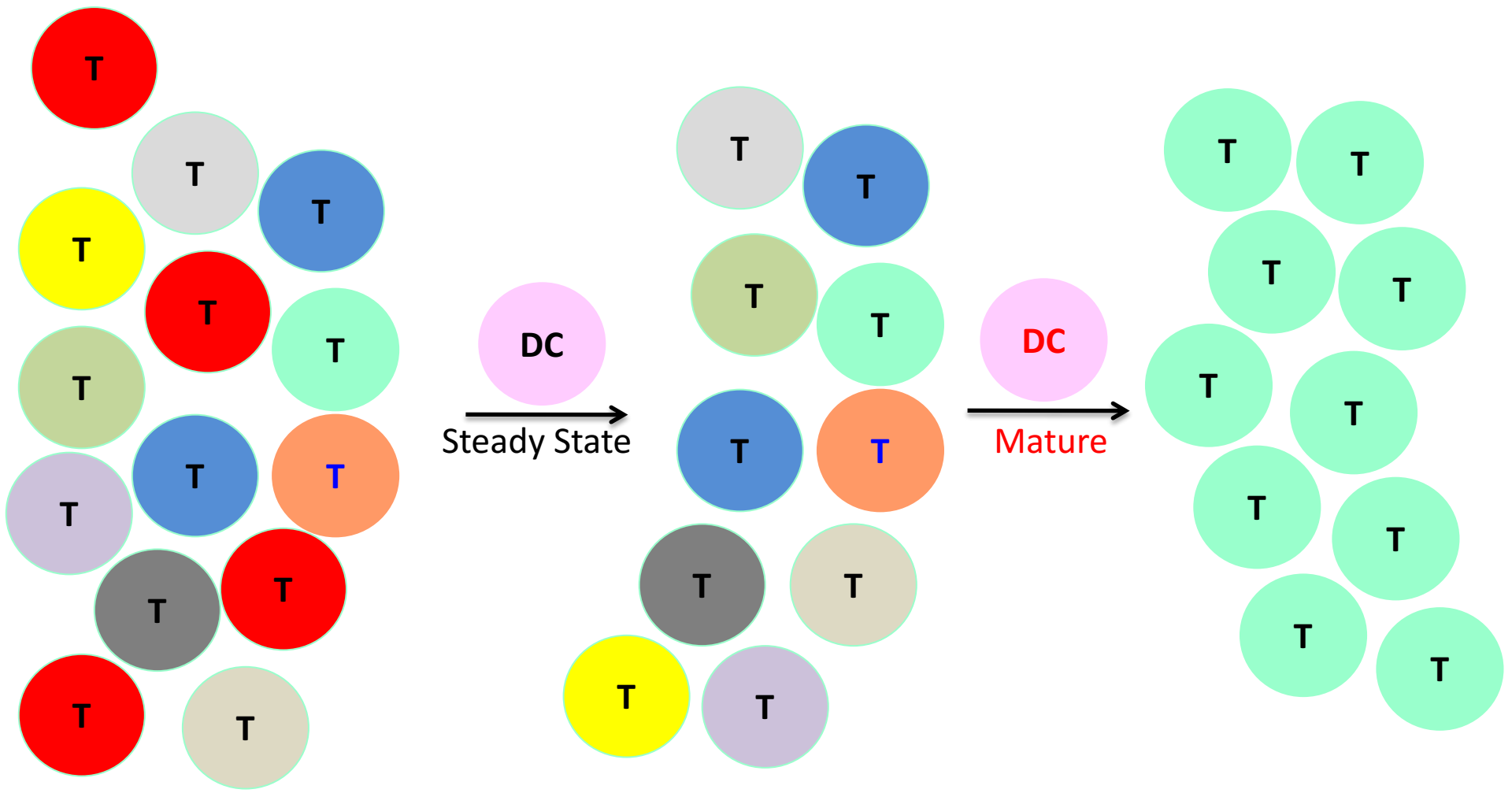
Clonal Selection



V(D)J Recombination

Self tolerance

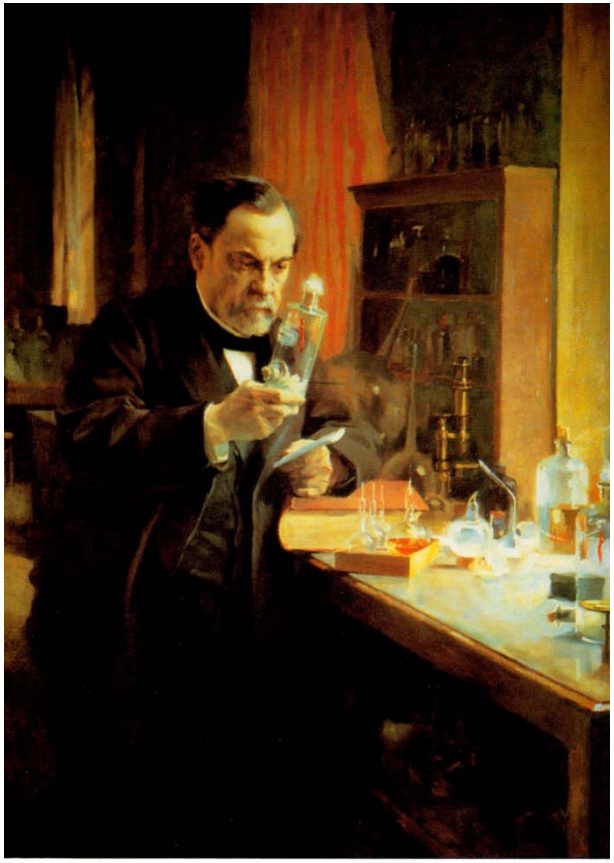
Clonal Expansion

Burnet, Lederberg, Talmage

Dendritic Cell Development Pathway

Liu and Nussenzweig, Science 2009

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)**

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Dendritic Cells Initiate Immunity and Control its Quality

Can Dendritic Cells Be Harnessed to Discover Vaccines?

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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

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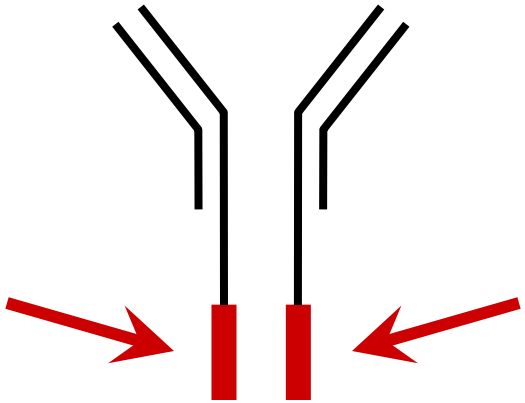
New Protein Vaccines Based on Defined Antigens, Adjuvants and Dendritic Cells

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)

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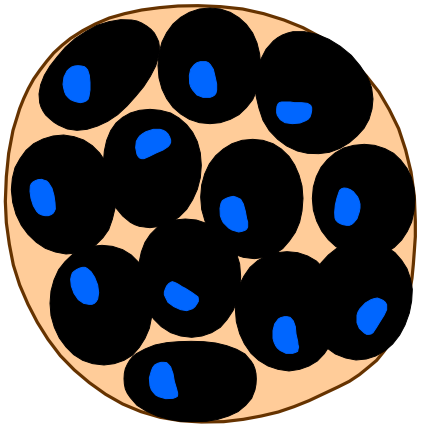
New Vaccines Based on Defined Antigens and Adjuvants to Elicit *Appropriate* T Cell Resistance and Silencing

MELANOMA

MAGE
MART
tyrosinase
TRP's



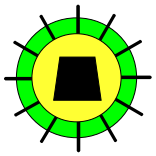
MYCOBACTERIUM TUBERCULOSIS

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

ALLERGY

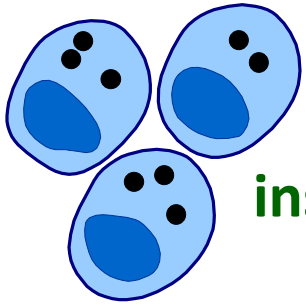
Pollens, e.g., Bet v1
Mites, e.g., Der p1
Cow's milk

HIV-1



env
pol
gag
nef

TYPE I DIABETES



insulin

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Proof of Concept Studies in Human Subjects

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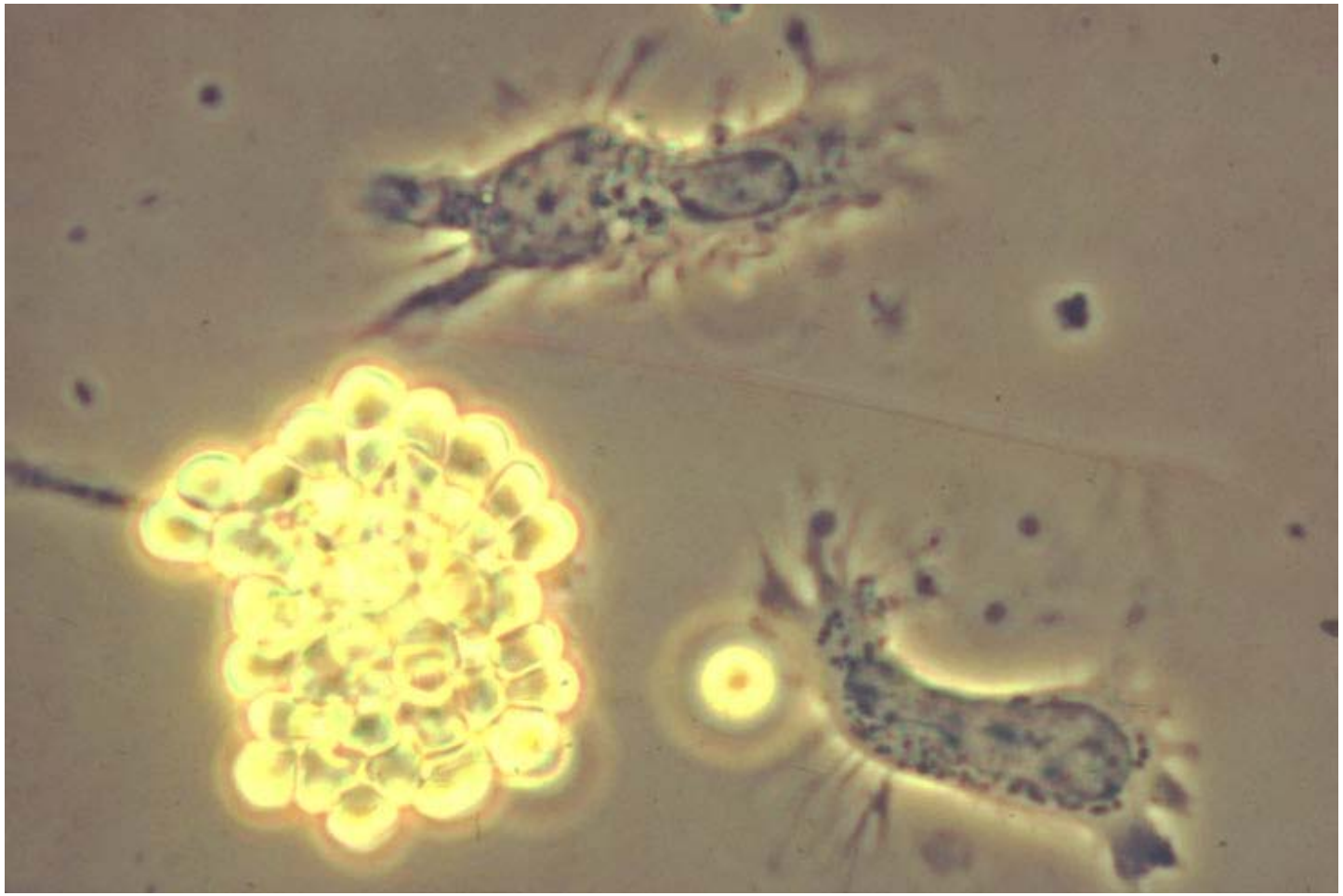
Dendritic Cells



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

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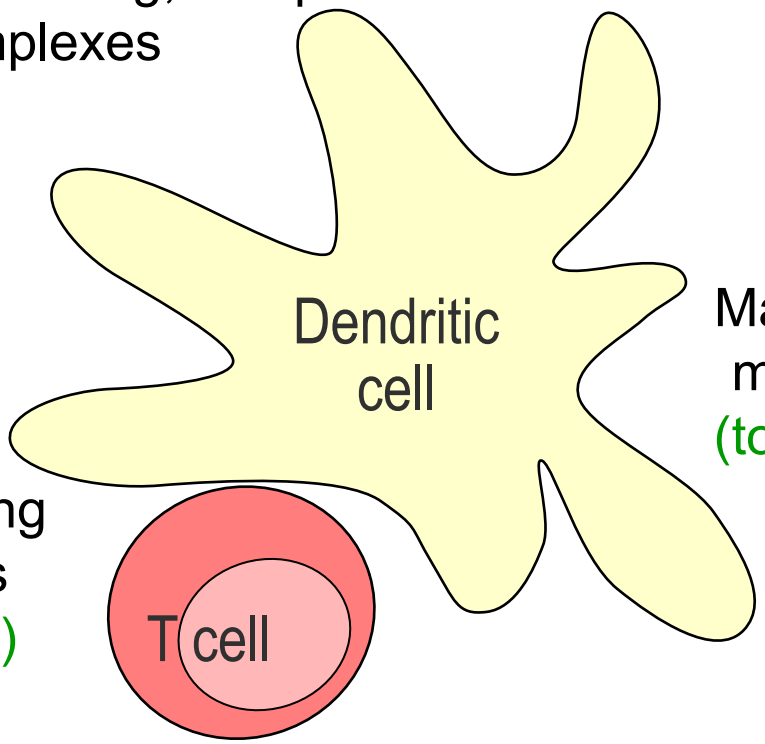
Dendritic Cells: Some Biological Features

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)

And other lymphocytes

"Conductors of the immune Symphony"

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CONGRATULATIONS RALPH!

&

THANK YOU FROM COLLABORATORS STUDENTS AND FELLOWS

&

THANK YOU NOBEL ASSEMBLY