

An agent-based model for investigation of immunological synapse patterns



Anastasios Siokis¹, Philippe A. Robert^{1,2}, Philippos Demetriou³, David Depoil³, Michael L. Dustin³, Michael Meyer-Hermann^{1,2}

¹Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Braunschweig, 38106, Germany ²Institute of Biochemistry, Biotechnology and Bioinformatics, Technische Universität Braunschweig, Braunschweig, 38106, Germany ³Kennedy Institute of Rheumatology, University of Oxford, Oxford OX3 7FY, UK



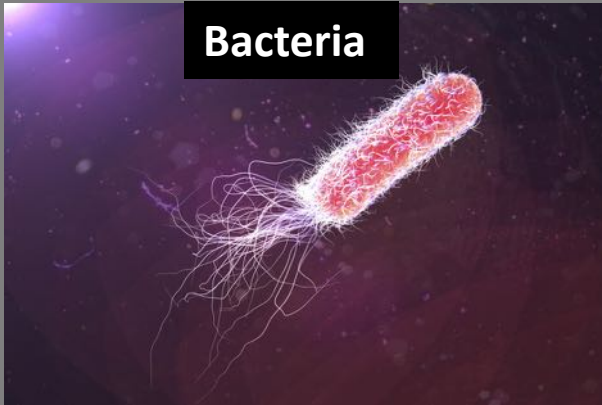
We are under attack by pathogens and cancer



KENNEDY
INSTITUTE OF RHEUMATOLOGY | NDORMS



Frontiers Science news |
<https://tinyurl.com/y57szcxb>



Bacteria

Health and Human Services |
NIH |
<https://tinyurl.com/yxon6s9f>

Pseudomonas aeruginosa



Viruses

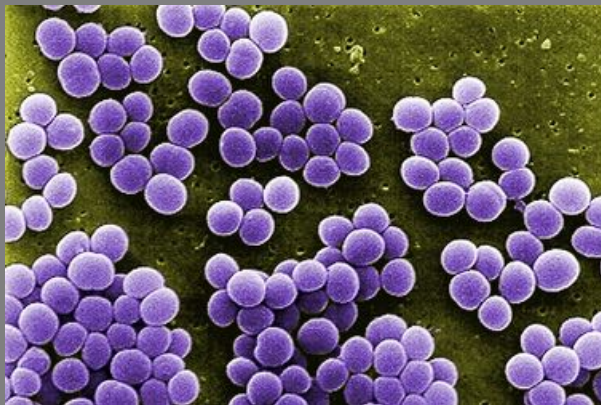
Ebola virus



Wikipedia

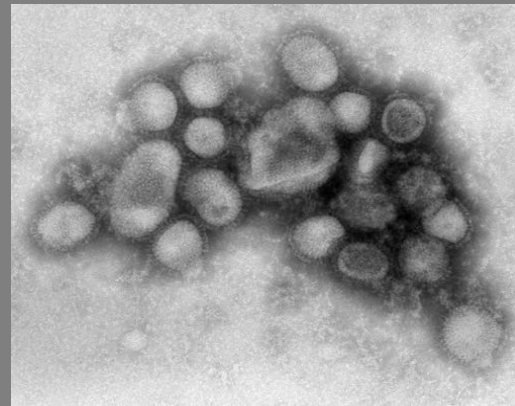
Leishmania major

Janice Haney Carr | CDC |
<https://tinyurl.com/j2wvqb2>



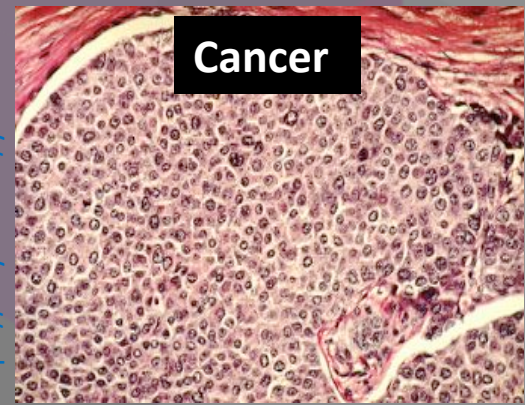
Centers for disease control and
prevention | CDC |
<https://tinyurl.com/yxd8euw8>

Staphylococcus aureus



H1N1 Influenza virus

Visuals online | NIH |
<https://tinyurl.com/y6ctnsiz>



Cancer

Breast cancer

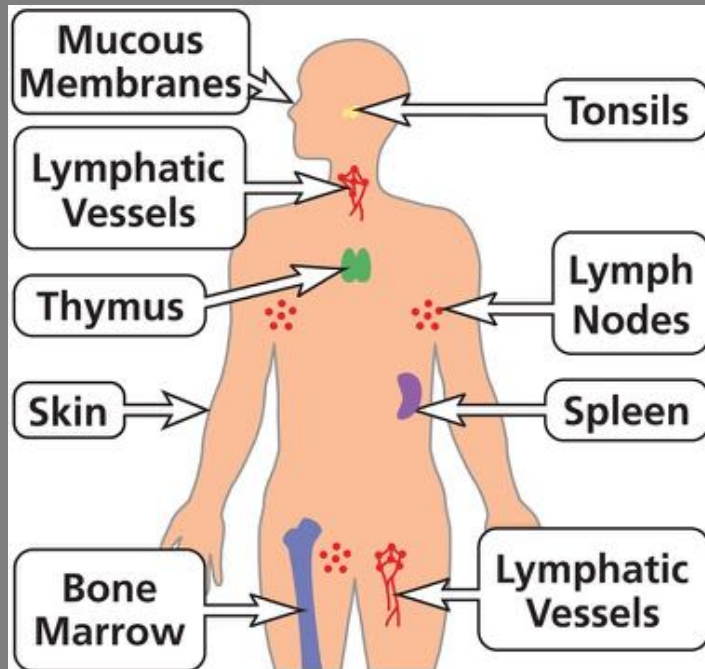
Immune defense and counter attack



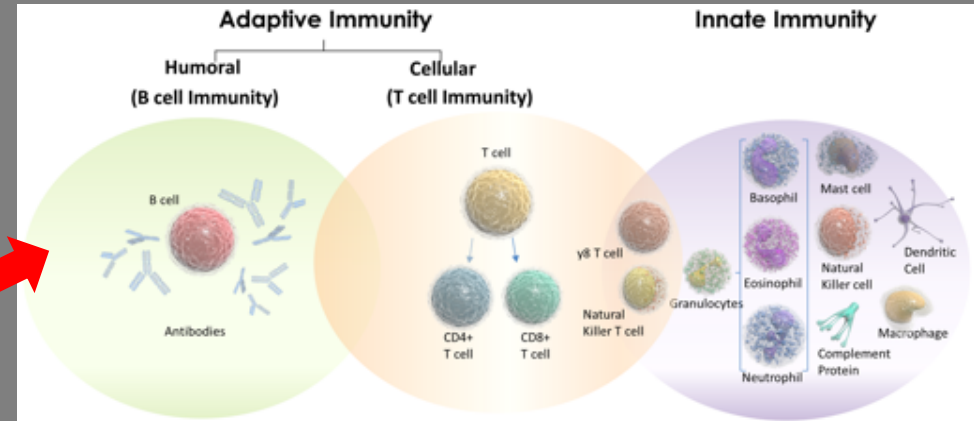
KENNEDY
INSTITUTE OF RHEUMATOLOGY | NDORMS



Organs of the Immune System



Health and Human Services | NIH |
<https://tinyurl.com/y78ejau3>



Oxford Immunotec | <https://tinyurl.com/y382unta>

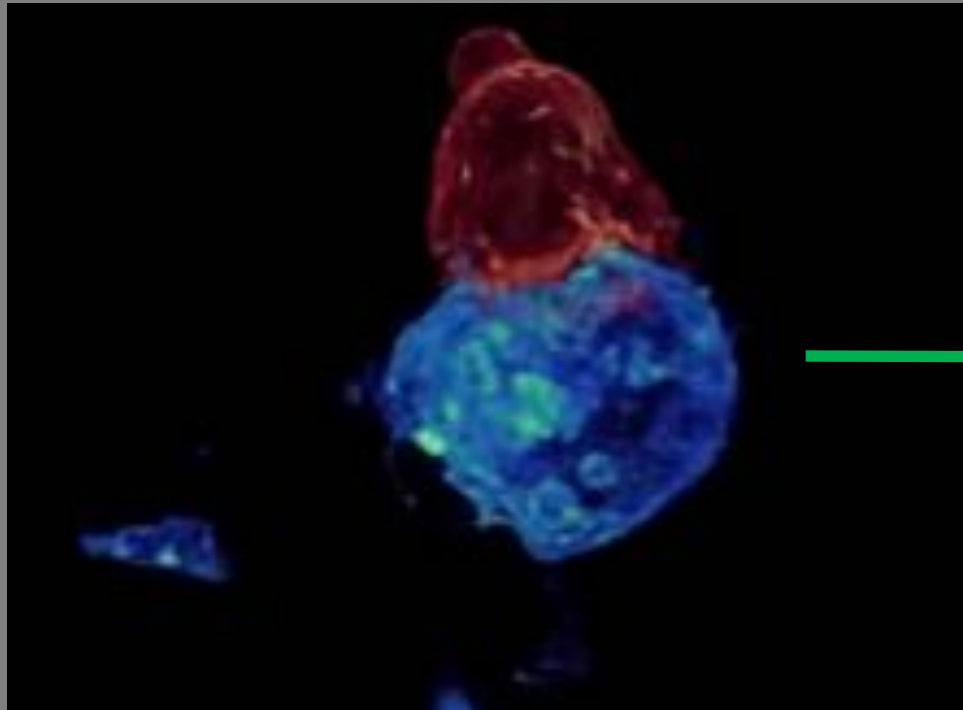
Innate immunity:

- immediate non-specific defense
- phagocytes kill or inactivate foreign objects
- information transfer to adaptive immunity

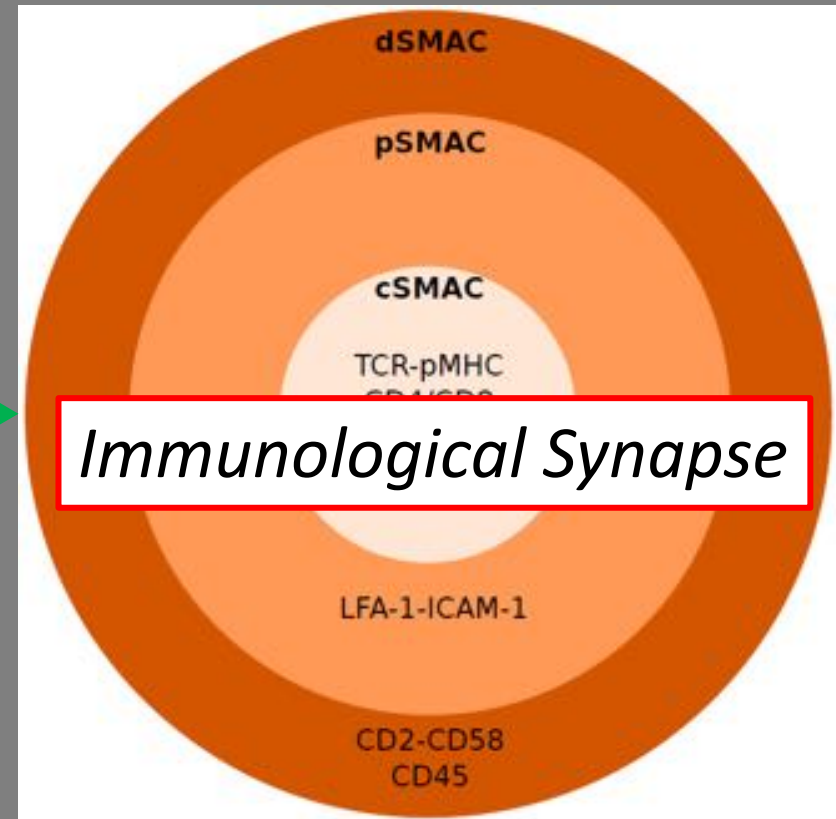
Adaptive immunity:

- **Humoral:** B cell mediated, antibody production
- **Cellular:** T cell mediated, interaction of T and antigen presenting cells (APCs)

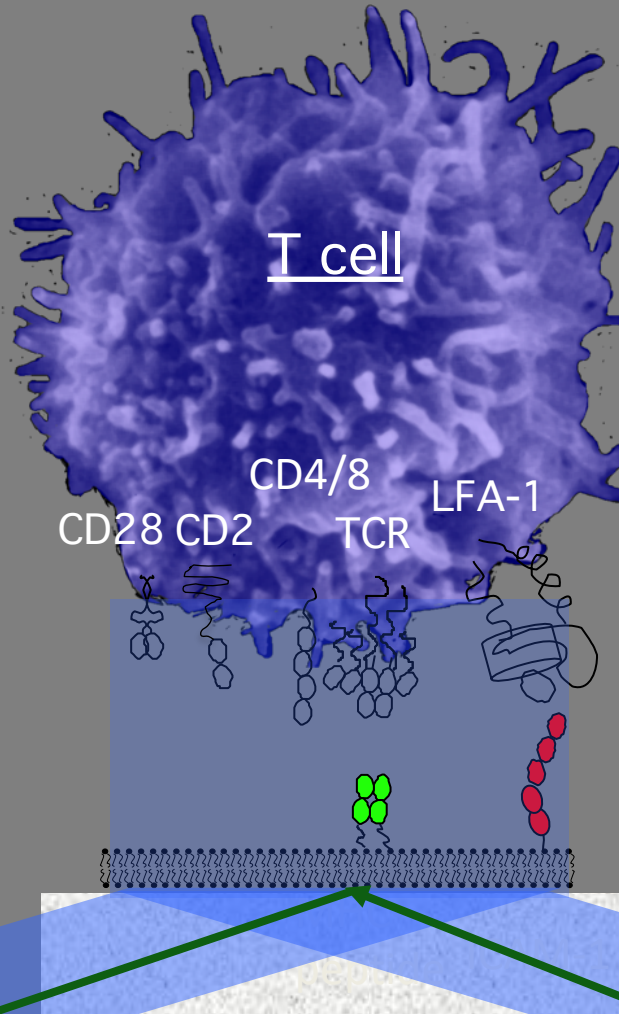
Dynamic process of



Ritter et al. *Immunity*. 2015;42(5):864-76.

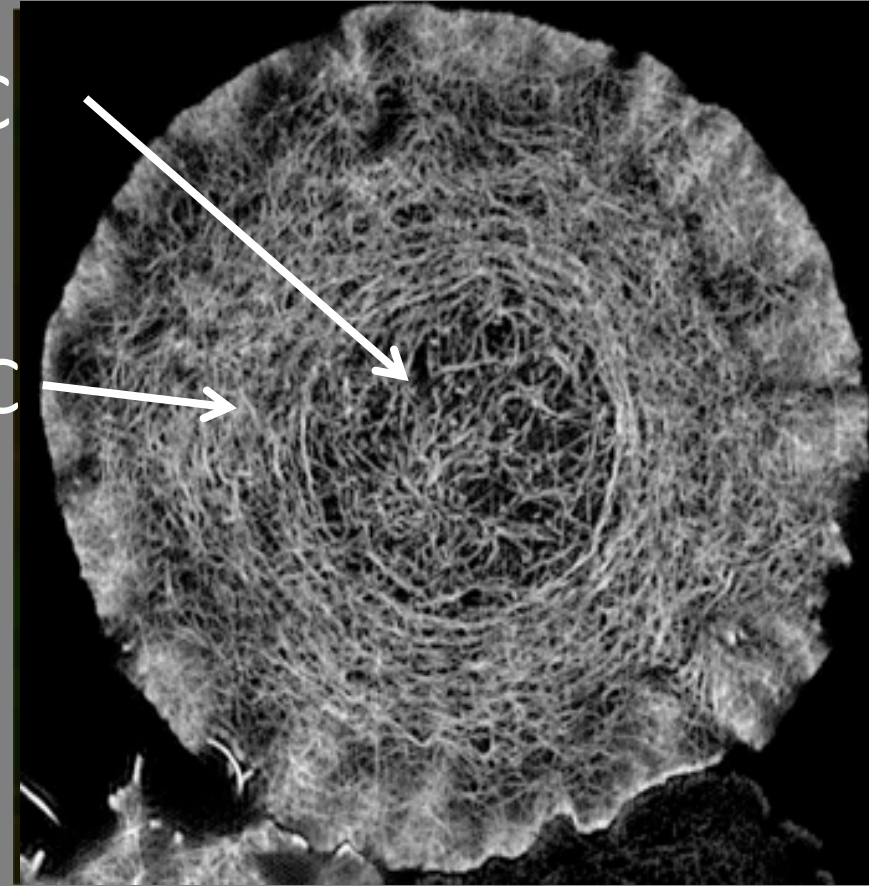


LFA-1 gradient in the immune synapse

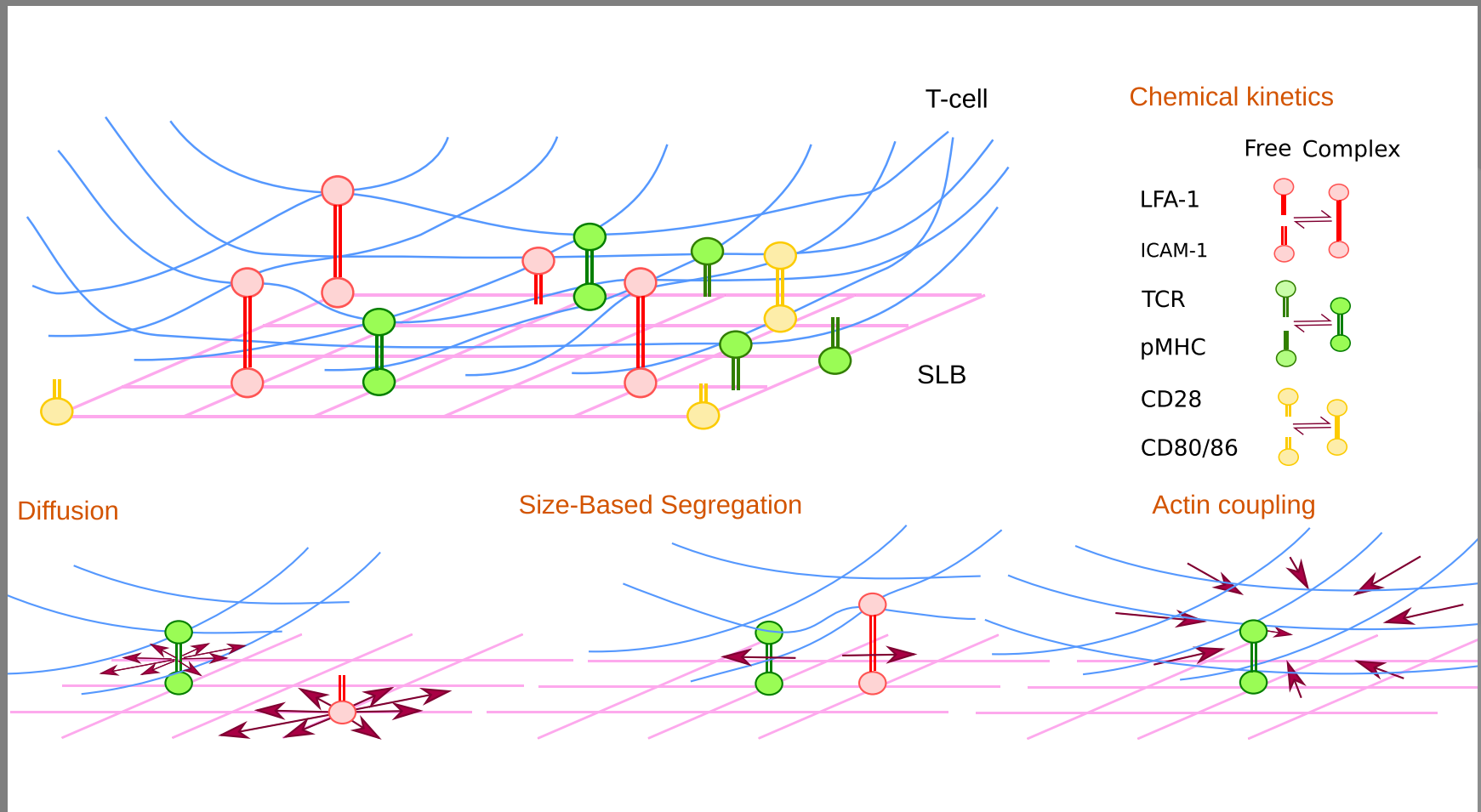


cSMAC

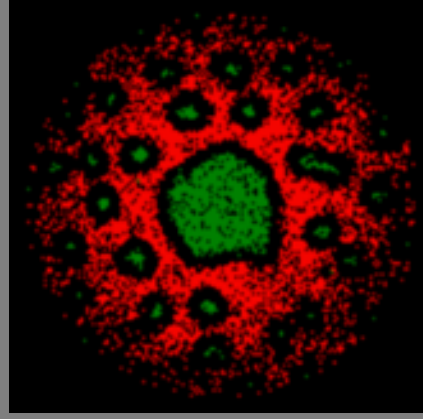
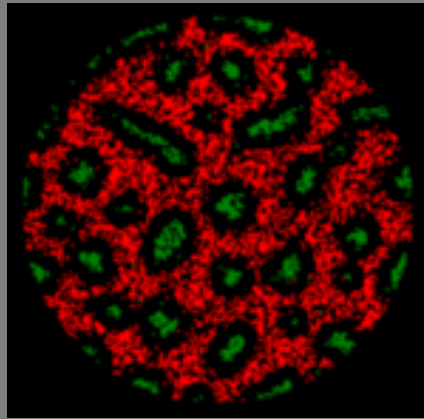
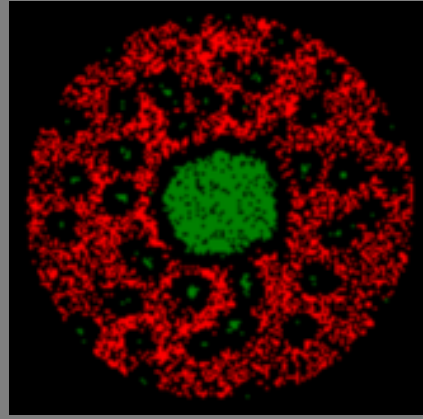
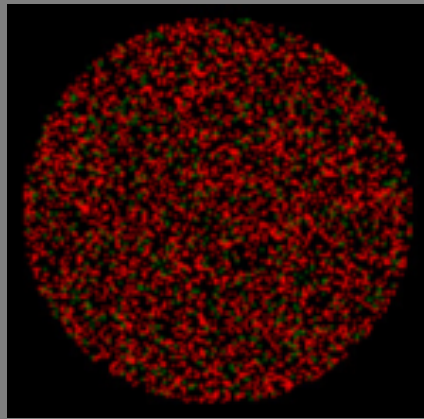
pSMAC



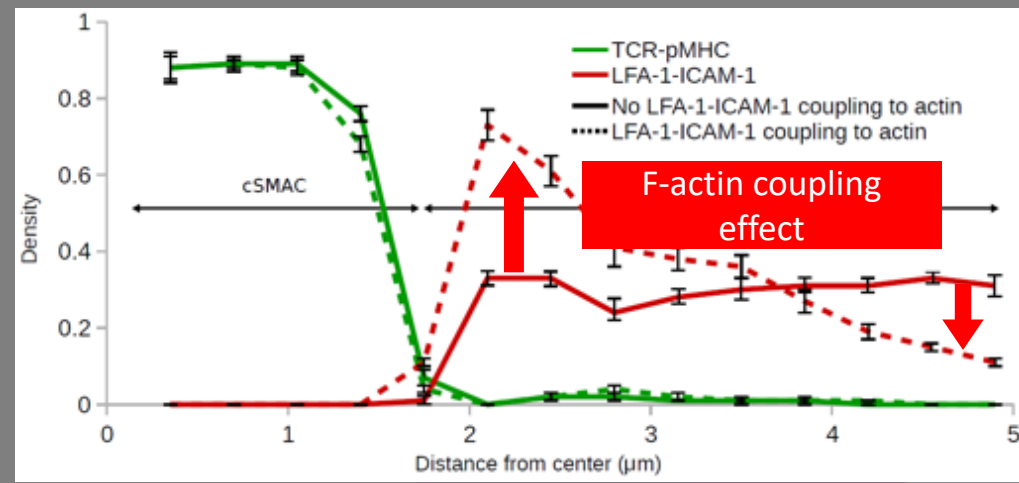
Synapse simulation



Immunological synapse simulation



— No F-actin coupling
- - - F-actin coupling



TCR-pMHC

LFA-1-ICAM-1

Differential F-actin coupling for CD28 ring

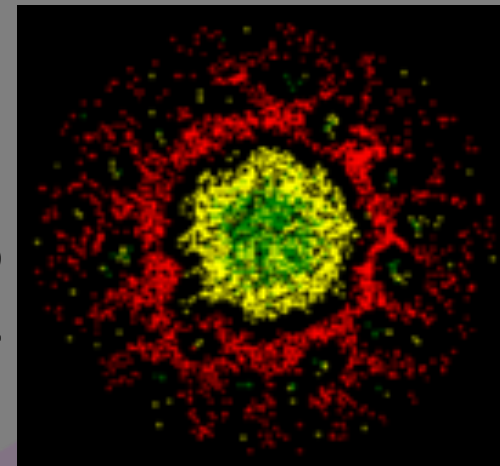
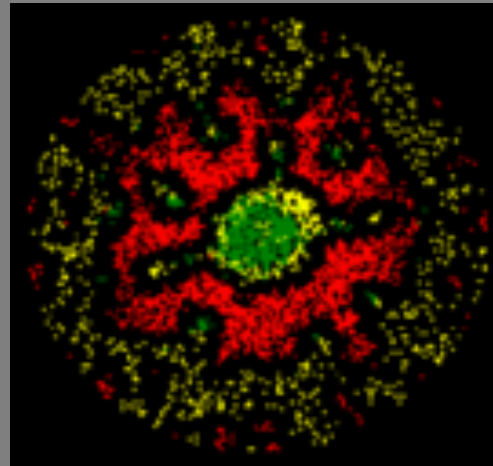
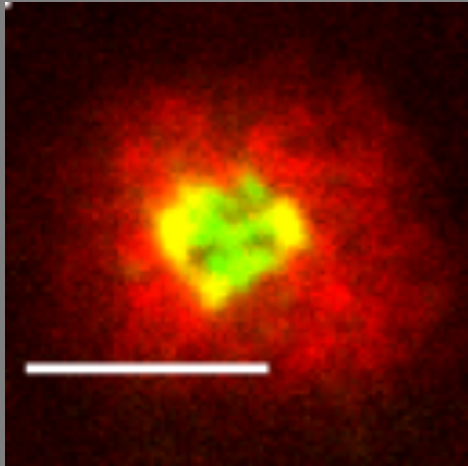


KENNEDY
INSTITUTE OF RHEUMATOLOGY | NDORMS



CD28-LFA-1 SBS

CD28-LFA-1 SBS



CD28-CD80
coupling to actin

Demetriou | Dustin lab | 2018 | Oxford | UK

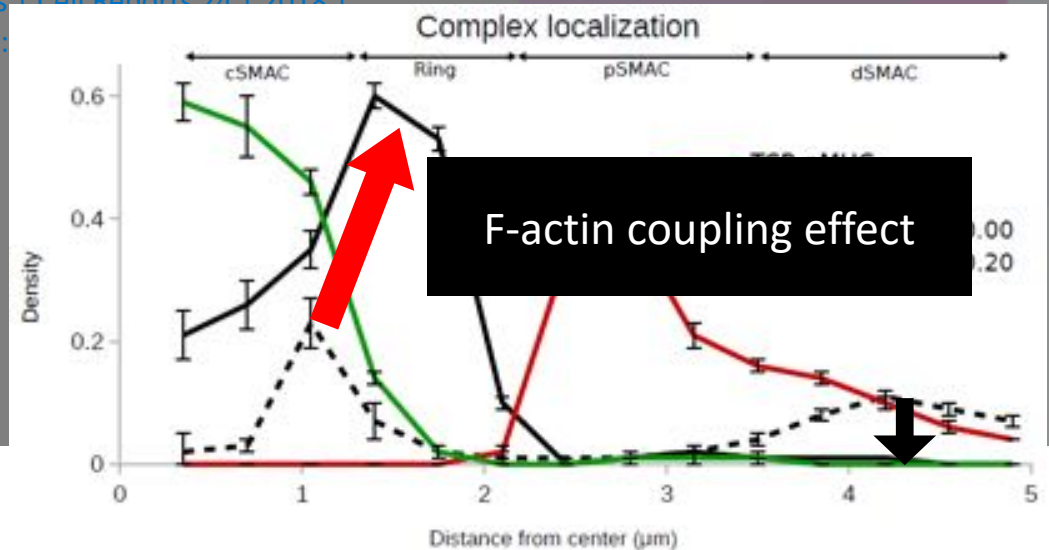
CD28 passive followers

Siokis | Cell Reports 24 | 2018 | <https://doi.org/10.1016/j.celrep.2018.04.014>

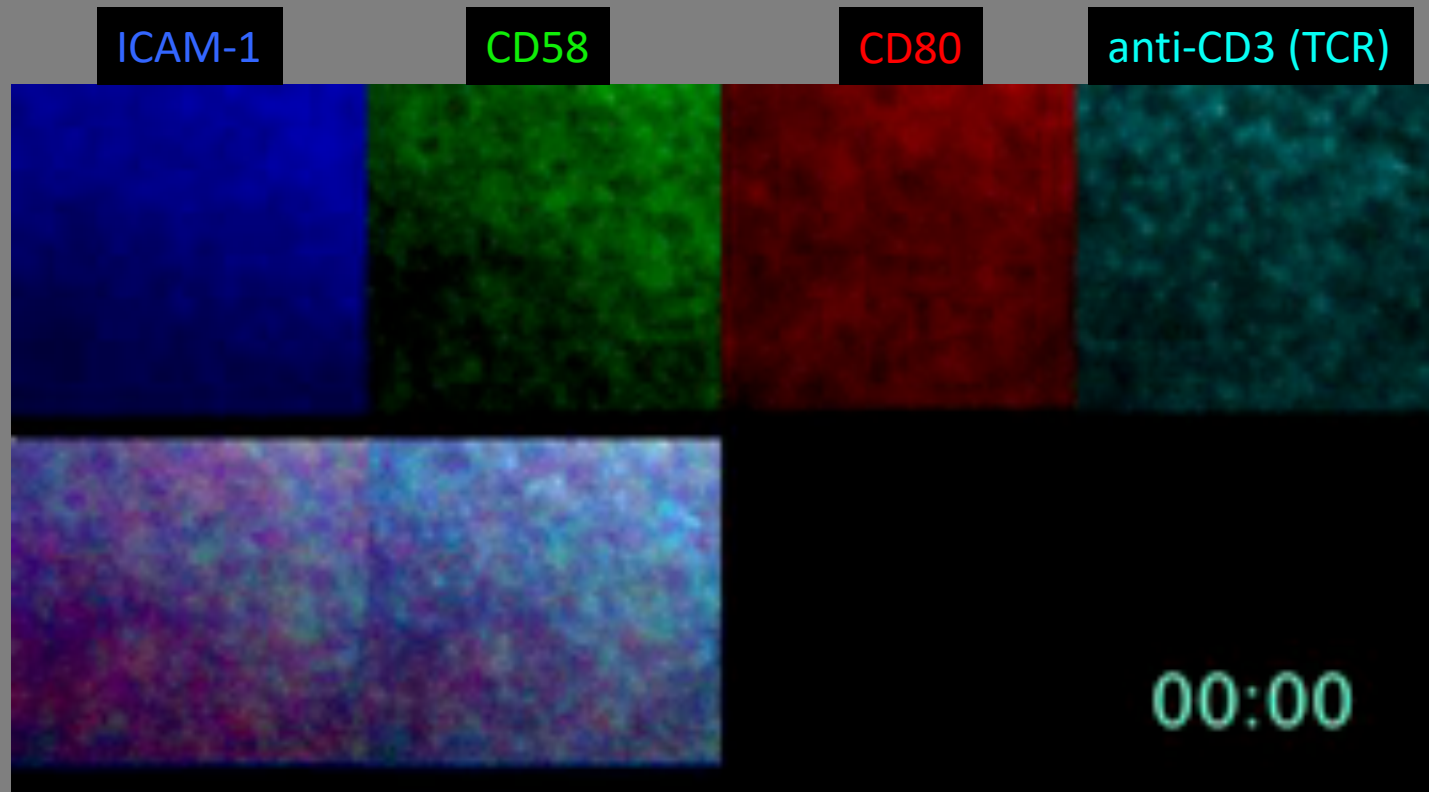
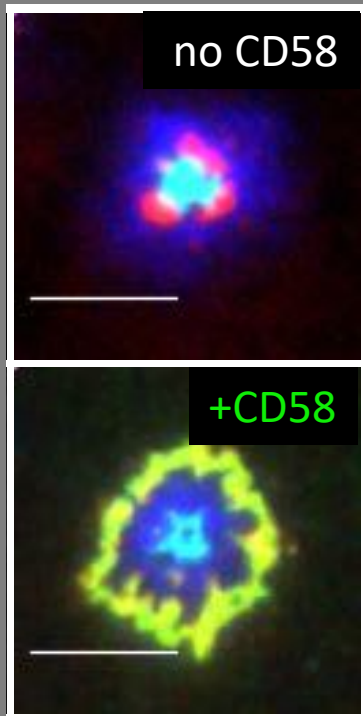
TCR-pMHC

LFA-1-ICAM-1

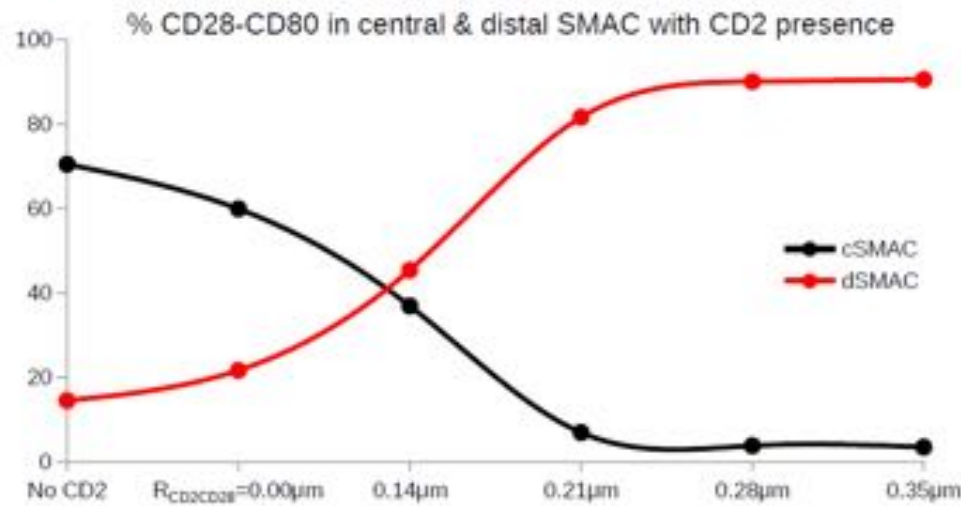
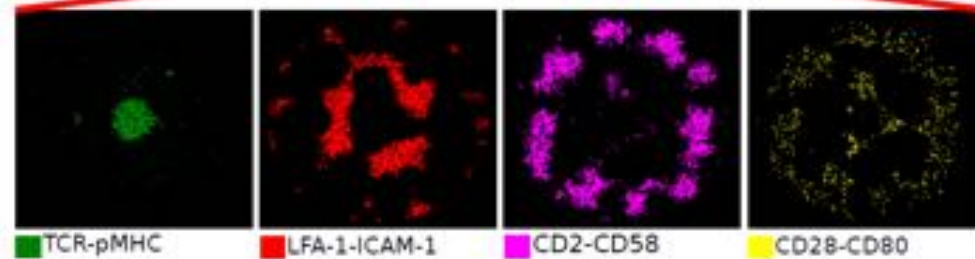
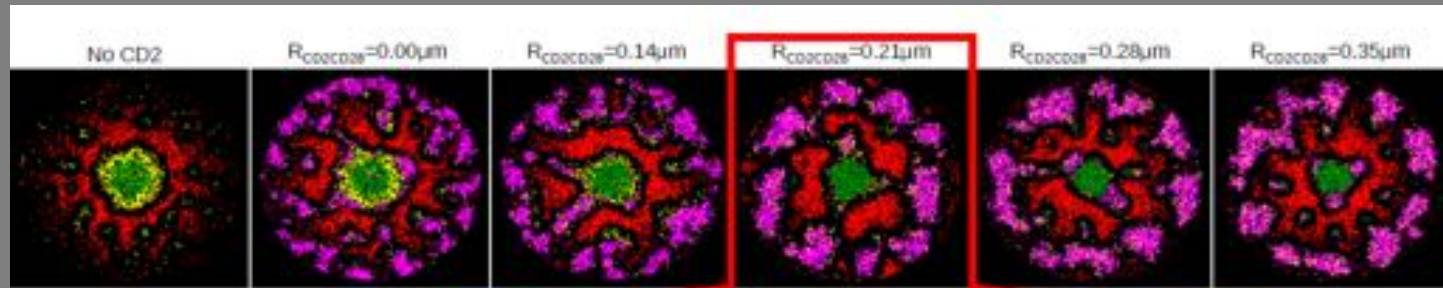
CD28-CD80



Costimulators (\pm) are captured in the corolla



CD2-CD28 attractoin can account for Corrola



TCR-pMHC

LFA-1-ICAM-1

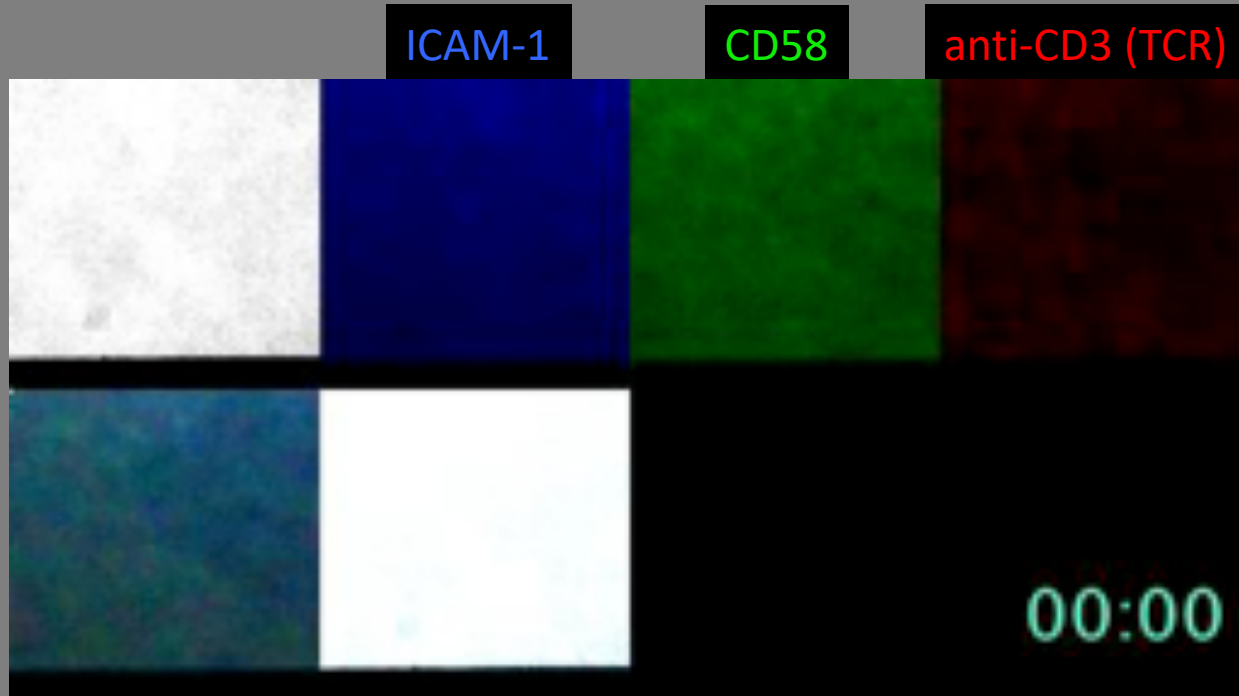
CD2-CD58

CD28-CD80

CD2-CD28 overlay

CD2-CD28 attraction

CD2 corolla formation



Self attraction promotes corolla with no CD28



KENNEDY
INSTITUTE OF RHEUMATOLOGY | NDORMS

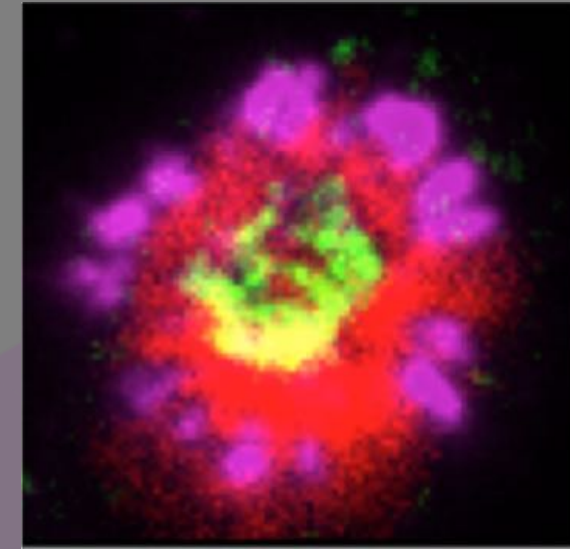
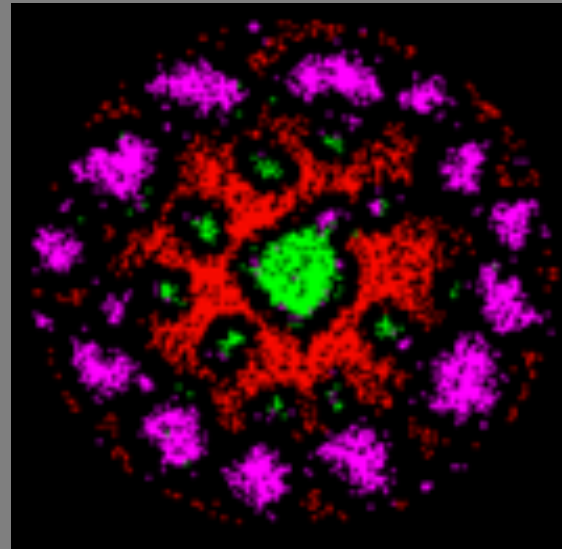
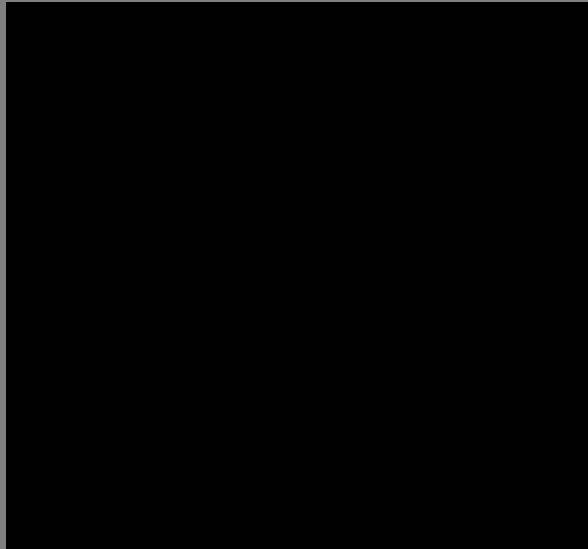


Gowrishankar | Cell | 2012 |
10.1016/j.cell.2012.05.008

t = 30 minutes

t = 30 minutes

0-30 minutes



Demetriou | Nat Immunol |
2019 | Revision

TCR-pMHC

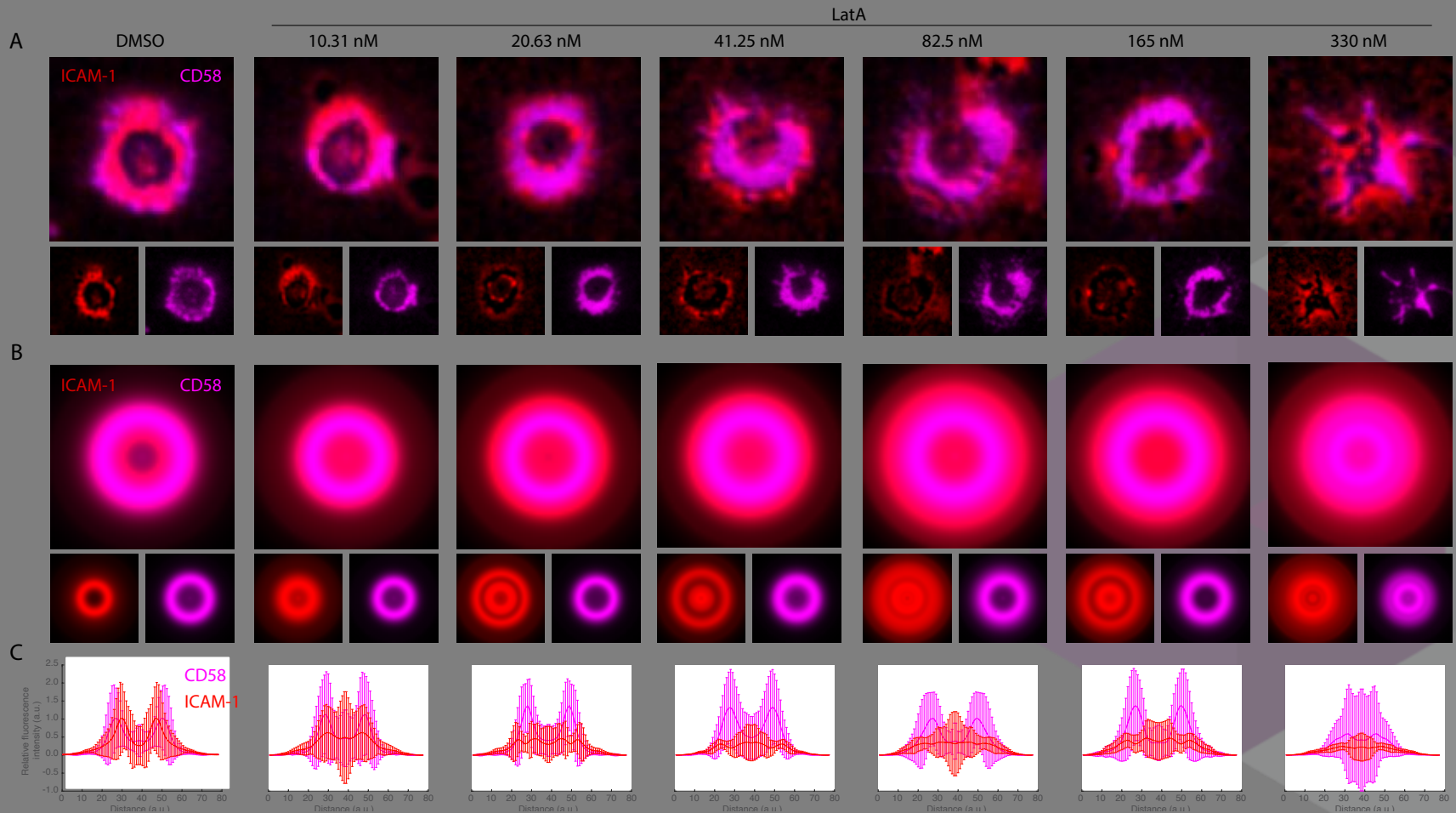
LFA-1-ICAM-1

CD2-CD58

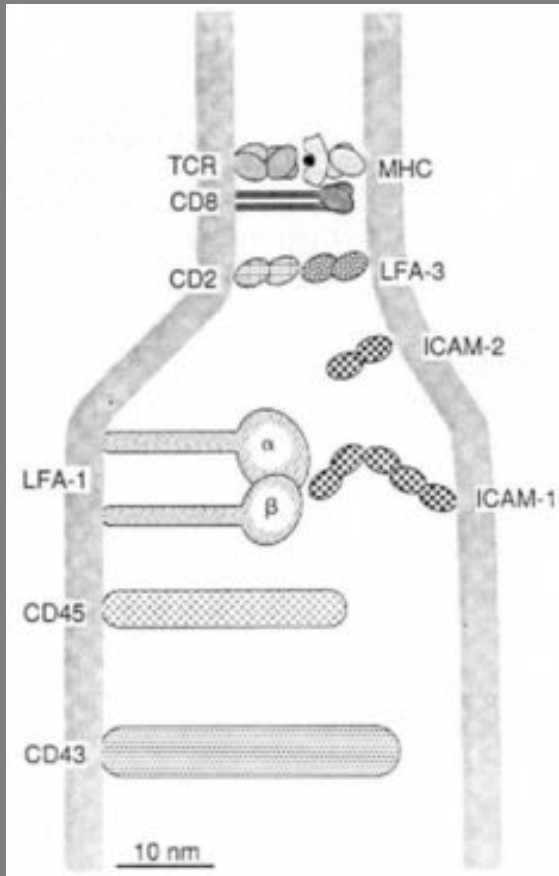
F-actin controls position of CD2 and LFA-1 rings



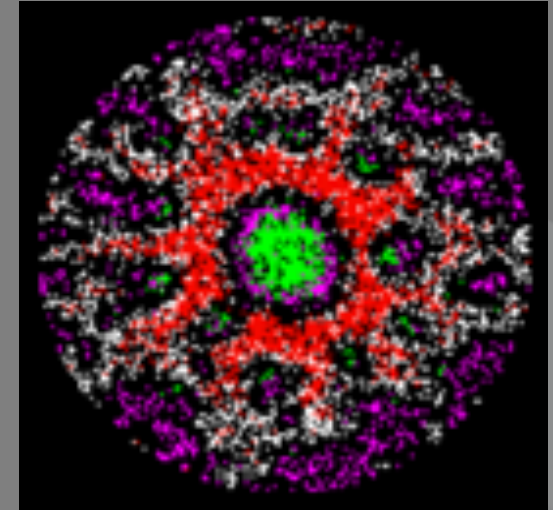
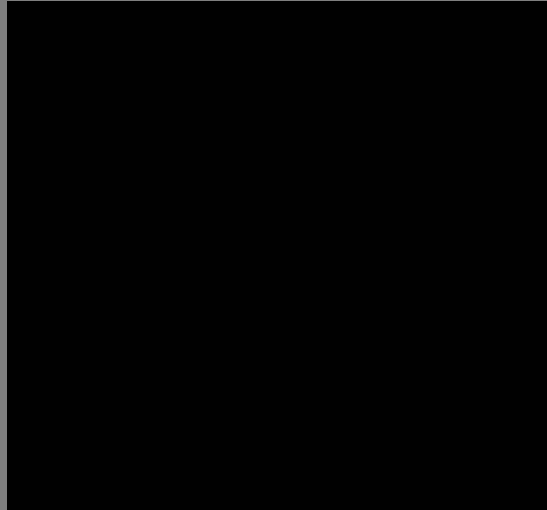
KENNEDY
INSTITUTE OF RHEUMATOLOGY | NDORMS



CD45 can also promote corolla formation



0-30 minutes



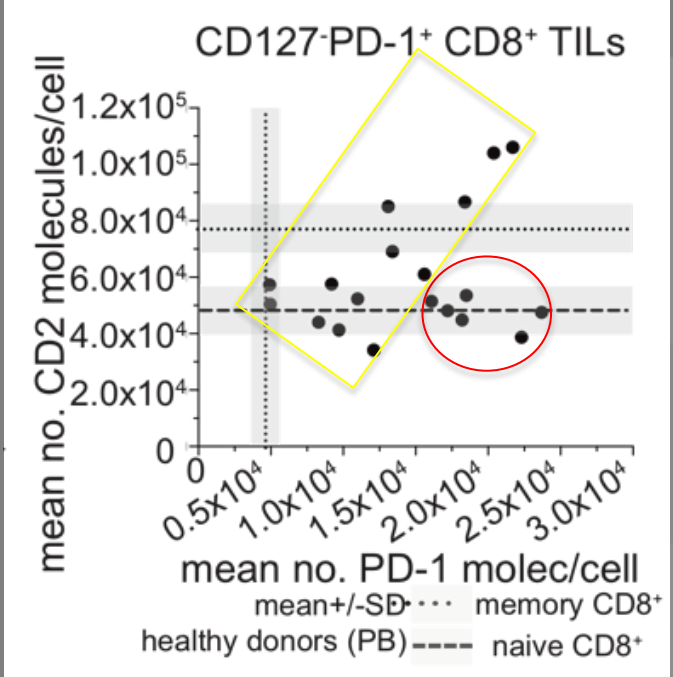
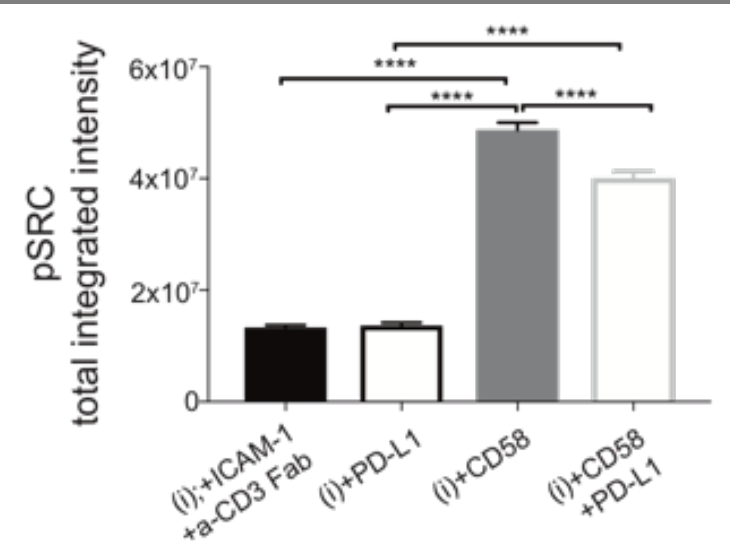
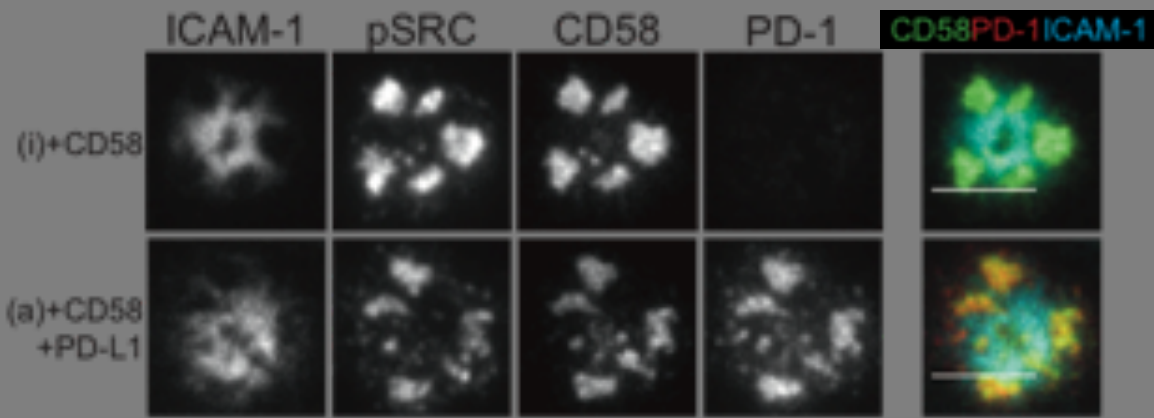
TCR-pMHC

LFA-1-ICAM-1

CD2-CD58

CD45

Low CD2 is a checkpoint



Conclusion- low CD2 checkpoint

- CD2 expression can be down-regulated on TIL.
- CD2 expression is tightly controlled on T-cell subsets.
- CD2-CD58 interactions localize to a corolla-making space for many interactions.
- Low CD2 expression limits TCR amplification.
- Low CD2 and high PD-1/PD-L1 interaction have a similar impact on TCR signaling.

Acknowledgements



Enas Abu Shah
Stefan Balint
Pablo Cespedes
Liliana Cifuentes
Ewaldus Compeer
James Felce
Elke Kurz
Audun Kvalvaag
Alessio Lanna
Viveka Mayya
David Saliba
Salvatore Valvo

Maria Harkiolaki (Diamond)

Mark Wallace (Kings)

Andrew Turberfield

Paul Bowness

Graham Ogg

Peter Taylor



Omer Dushek
Christian Eggeling
Marco Fritzsche
Simon Davis

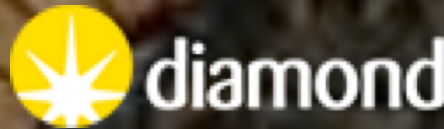
Anastasios Siokis
Michael Meyer-Hermann
Ilenia Papa
Gabriel Victora
Carola Vinuesa



Andrew McMichael
Persephone Borrow
Suzanne Campion

Recent Alumni

Kaushik Choudhuri (U. Mich)
Durga Dandamudi (Abbvie)
Philippos Demetriou (Weizmann)
David Depoil (Immunocore)
Sudha Kumari (MIT)
Jungeun Jang (Genetech)
James Muller (MSKCC)
Hila Novak (Technion)
Alexandra Zanin-Zhorov (Kadmon)



U Minn

Bruce Blazar
Cam Hyman-McDonald



Elena Brenna

NYULMC

Juan Lafaille
David Stokes
Jaime Llodra
Dan Littman
Wenbiao Gan

Columbia

Lance Kam
Chirag Sachar
Edward Judokusumo

