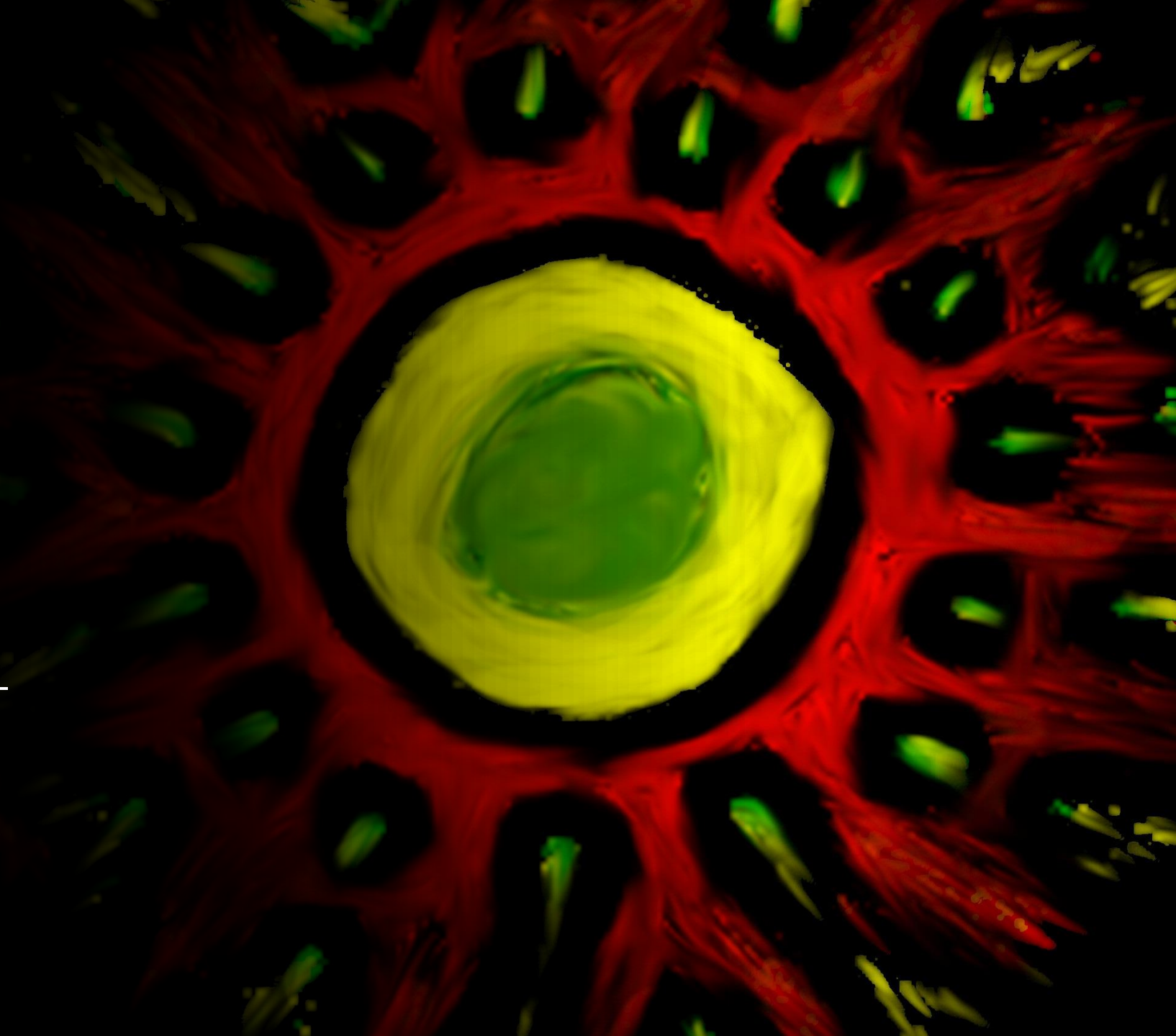
Agent-based Modeling of Immunological Synapse Dynamics

Anastasios Siokis, PhD

9th June 2021

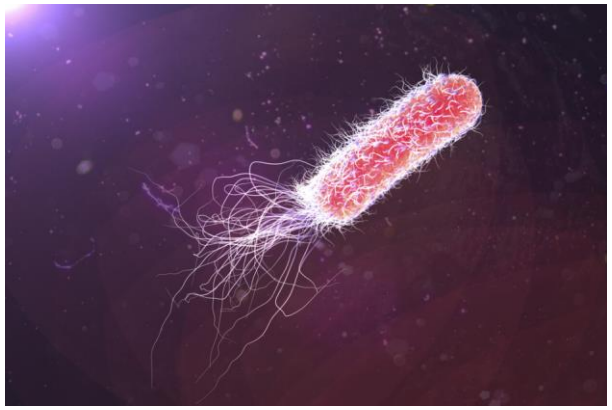
Rosa Webinar



Under attack

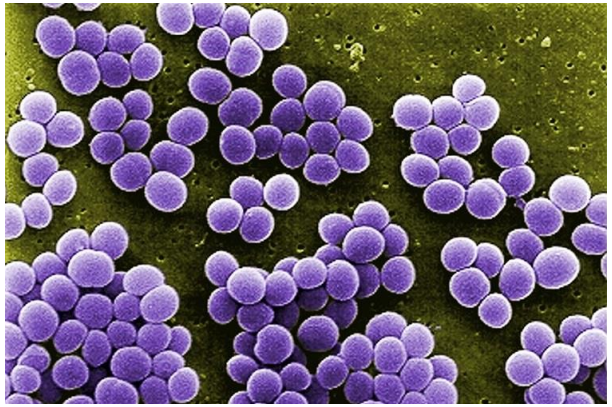
Bacteria

Frontiers Science news | https://tinyurl.com/y57szcbx



Pseudomonas aeruginosa

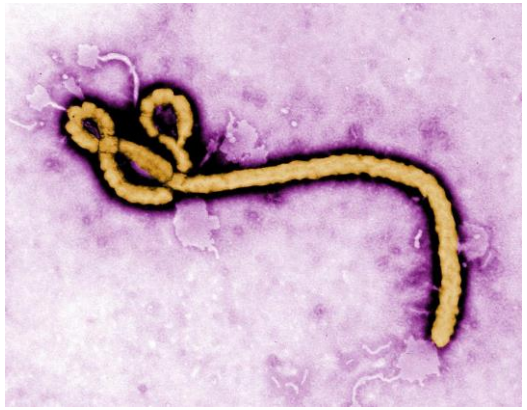
Janice Haney Carr | CDC | https://tinyurl.com/j2wvqb2



Staphylococcus aureus

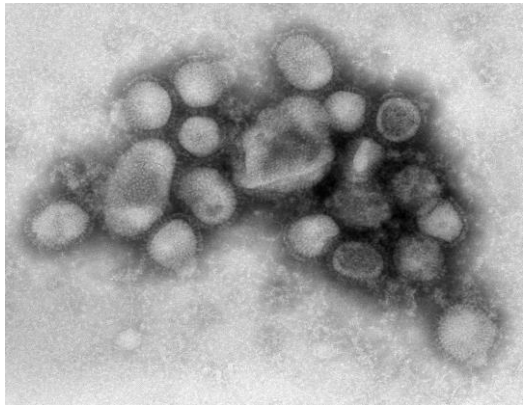
Viruses

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



Ebola virus

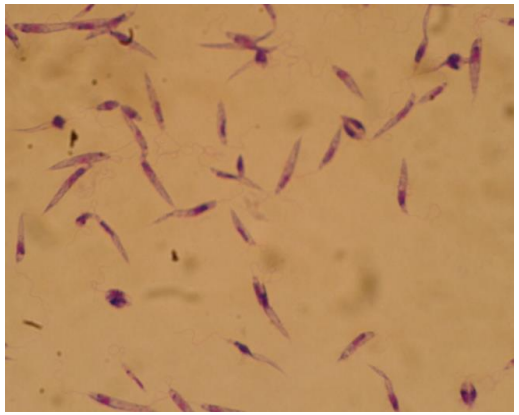
Centers for disease control and prevention | CDC | https://tinyurl.com/yxd8euw8



H1N1 Influenza virus

Parasites

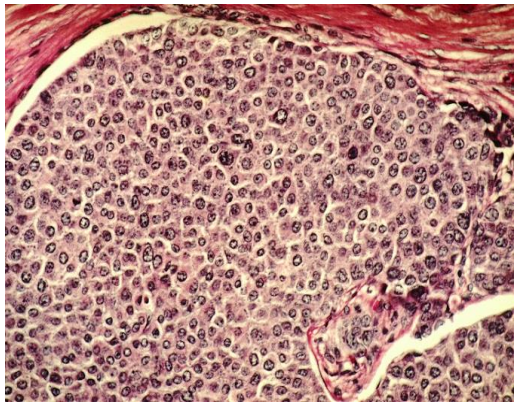
Wikipedia



Leishmania major

Cancer

Visuals online | NIH | https://tinyurl.com/y6ctnslz



Breast cancer

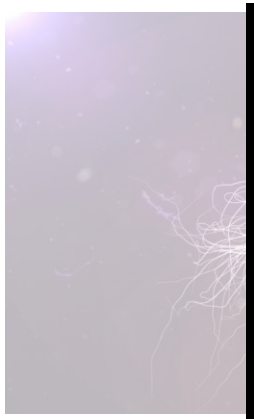
Under attack

Bacteria

Viruses

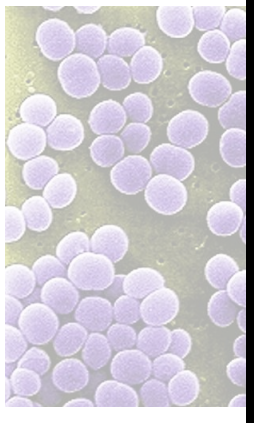
Parasites

Frontiers Science news | https://tinyurl.com/y57szcbx



Pseudomo

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

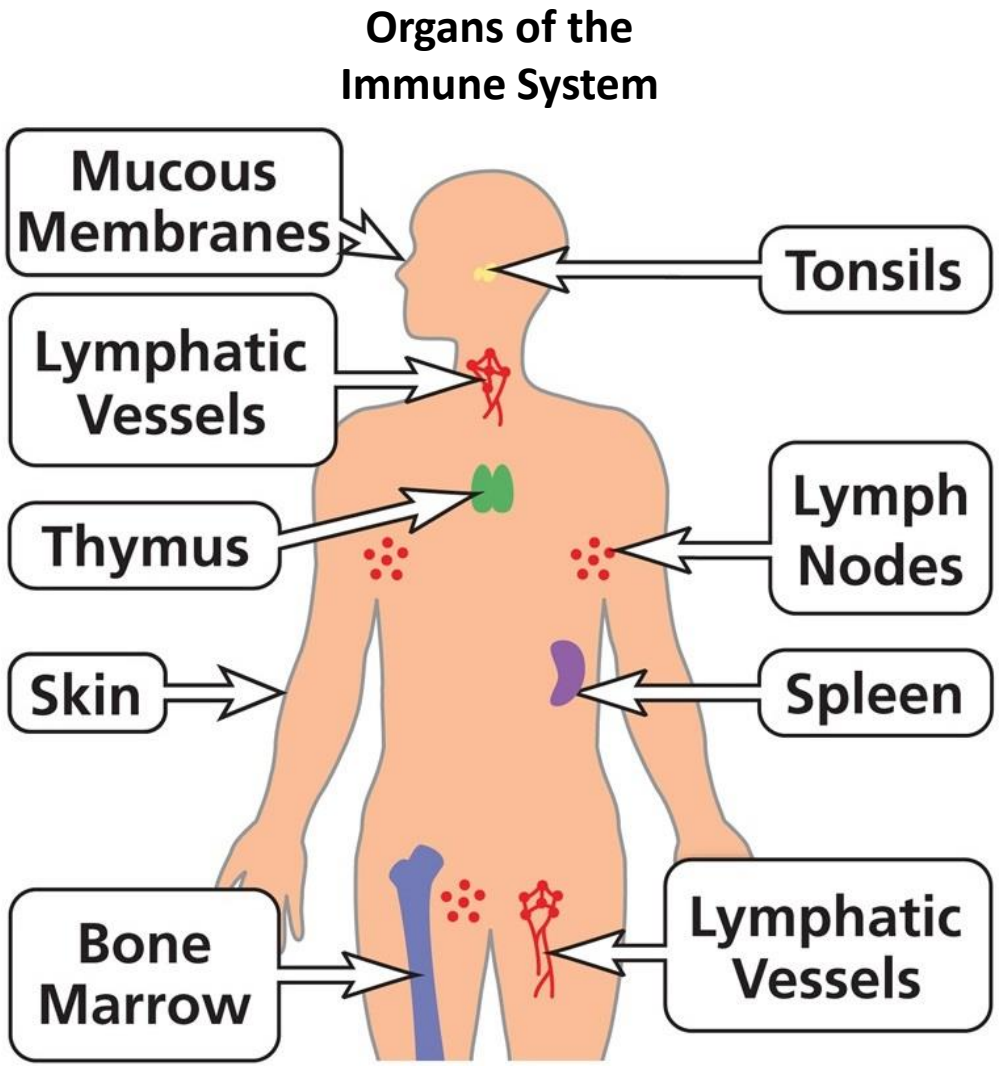


Staphylococcus aureus

H1N1 Influenza virus

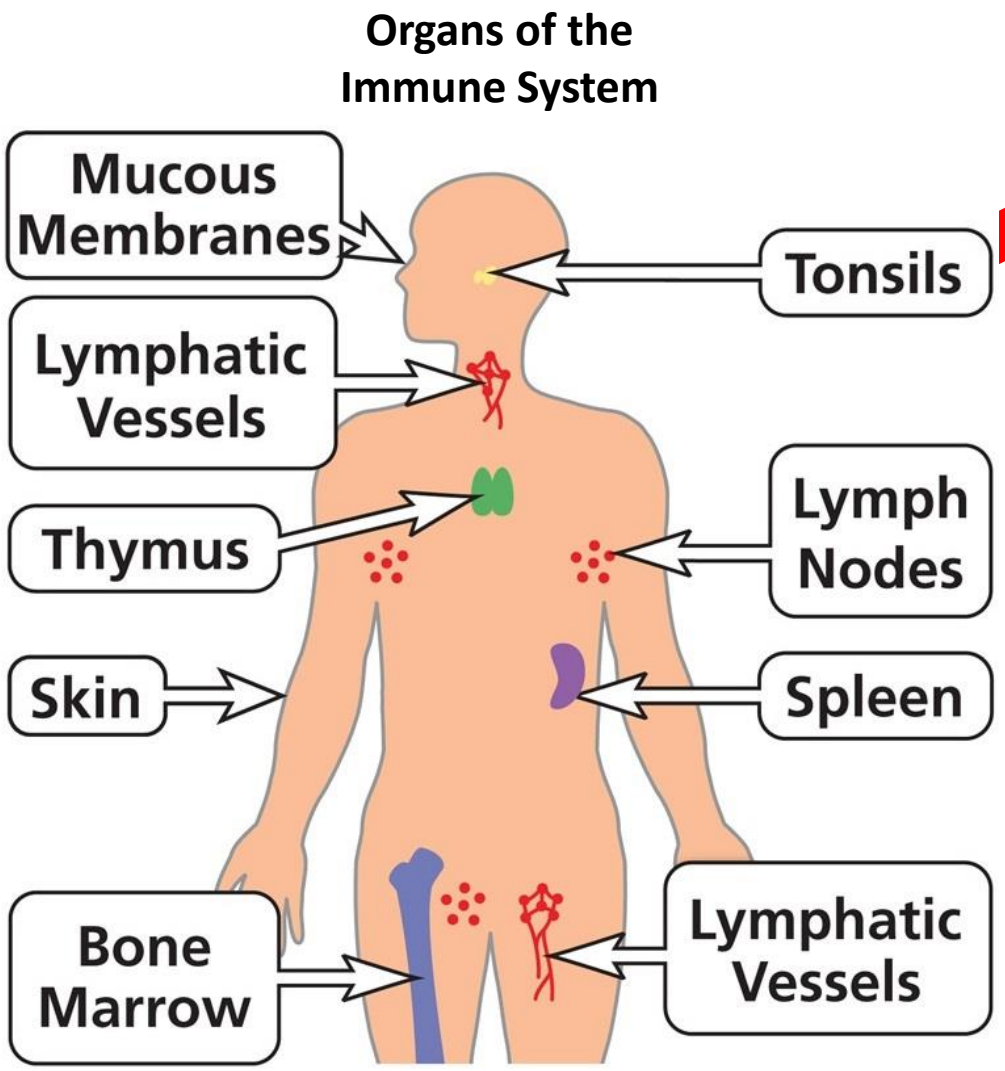
Breast cancer

Defense and counterattack



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

Defense and counterattack



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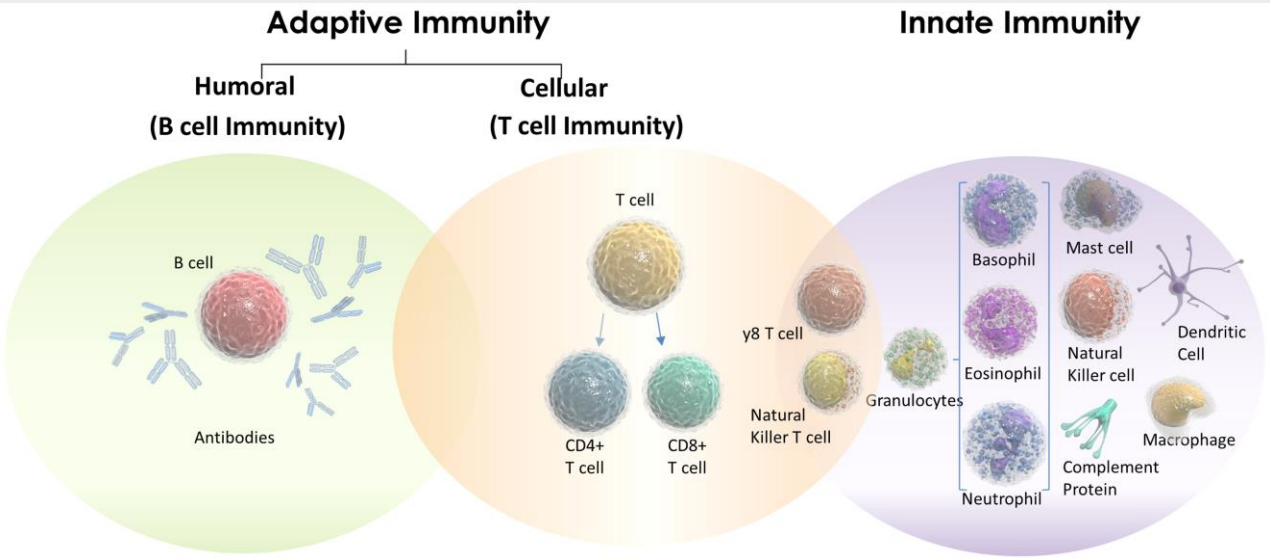
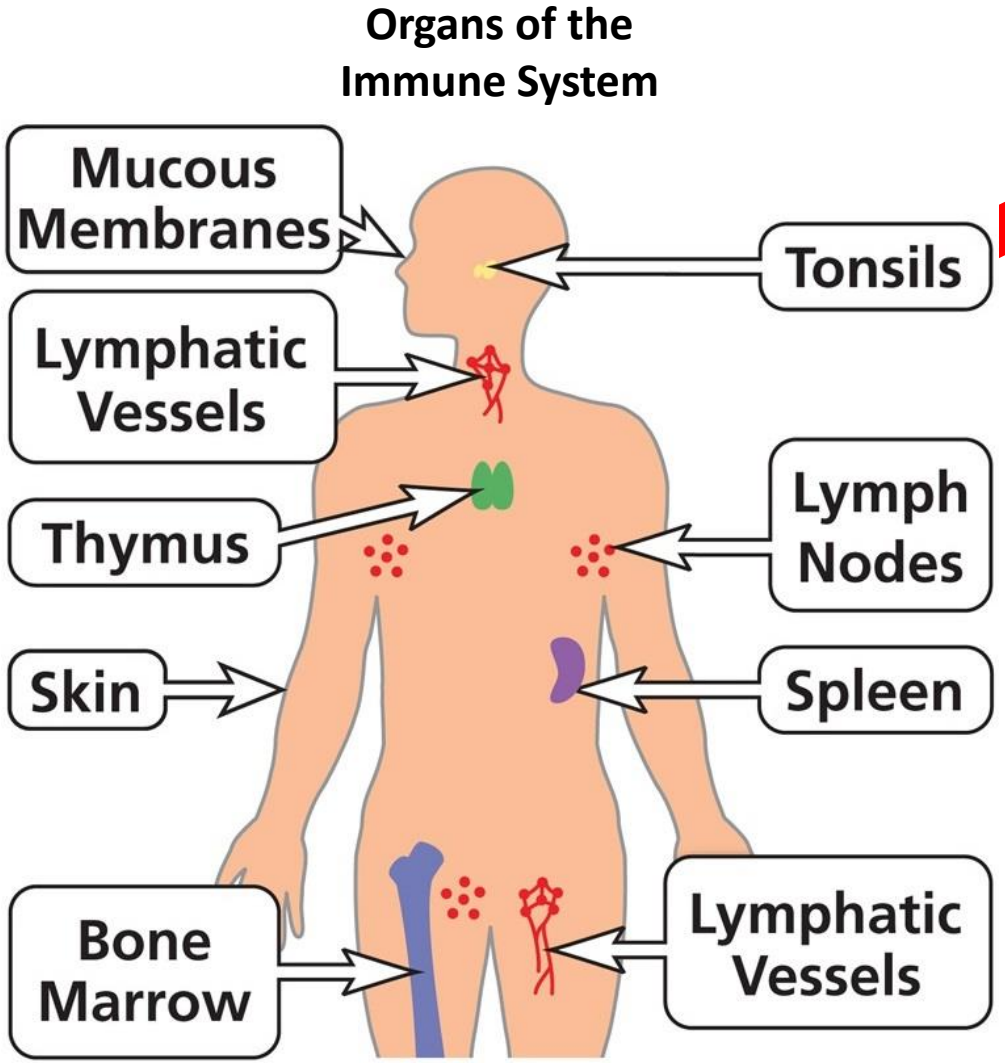


Oxford Immunotec | https://tinyurl.com/y382unta

Defense and counterattack



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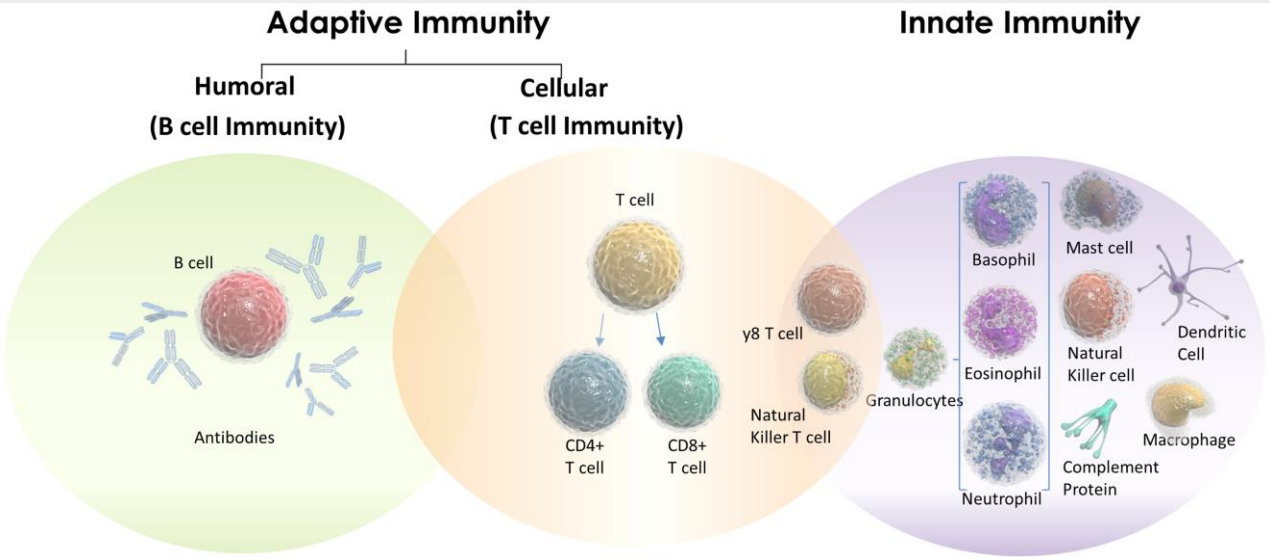

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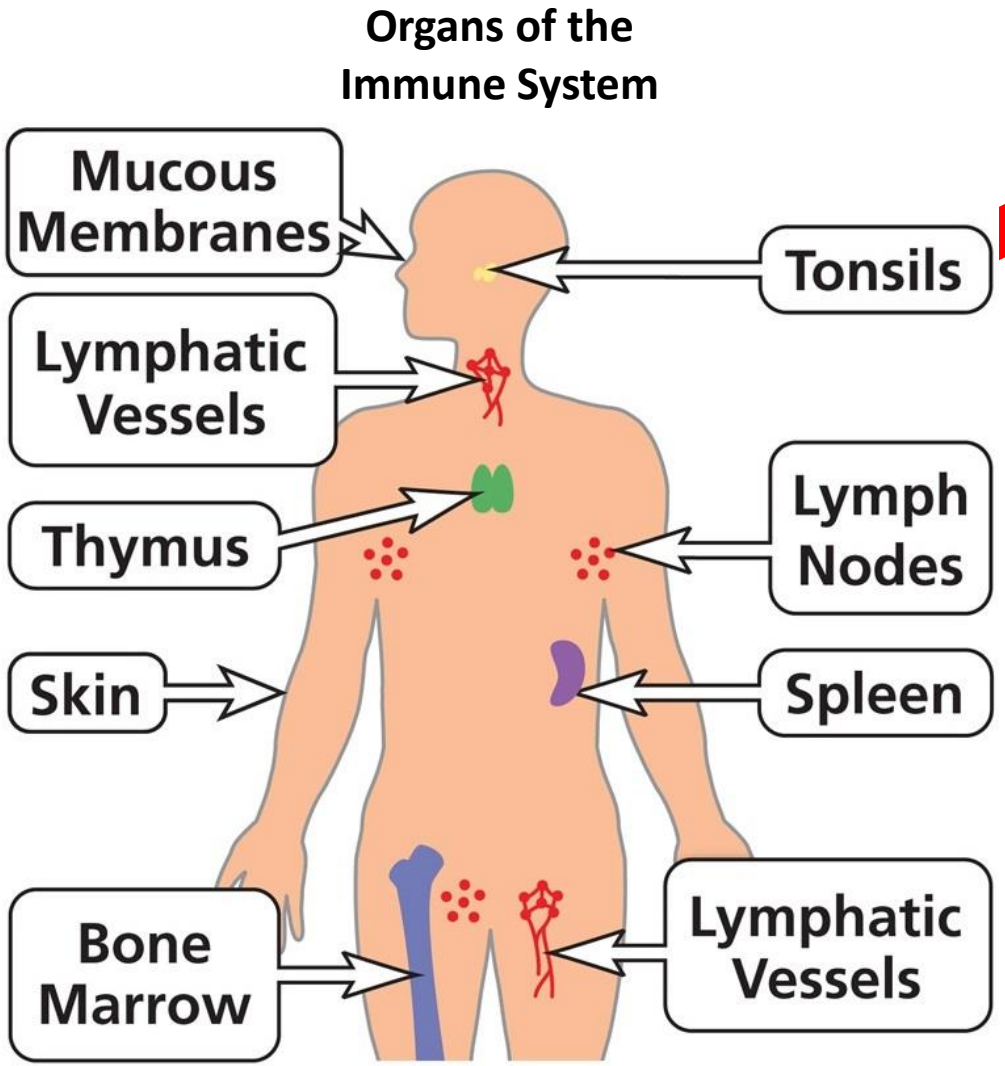
Innate immunity:

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

Defense and counterattack



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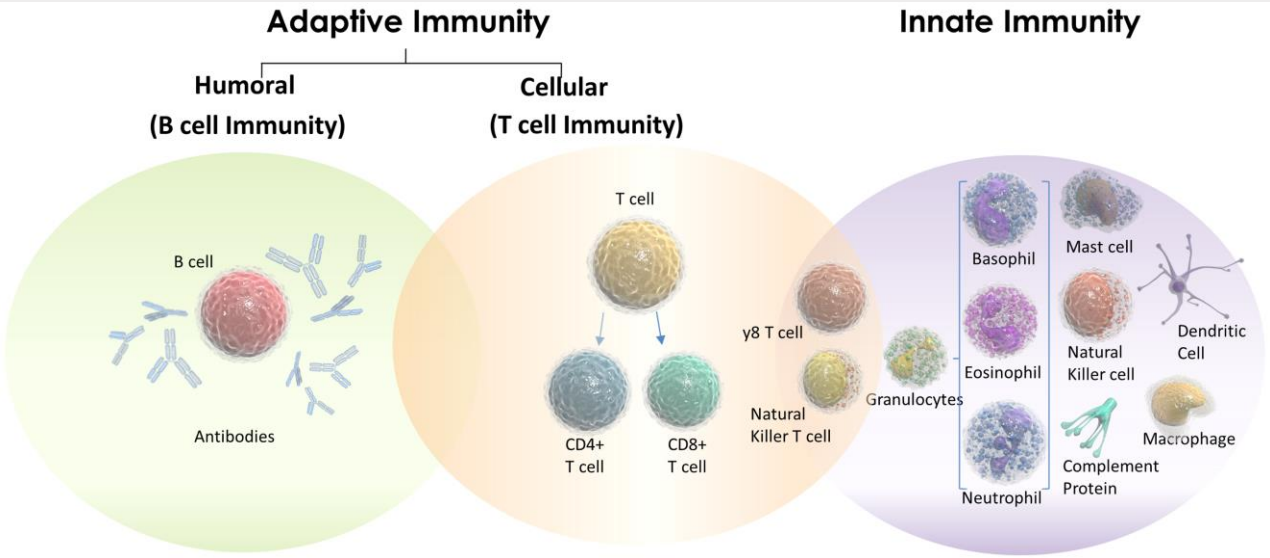

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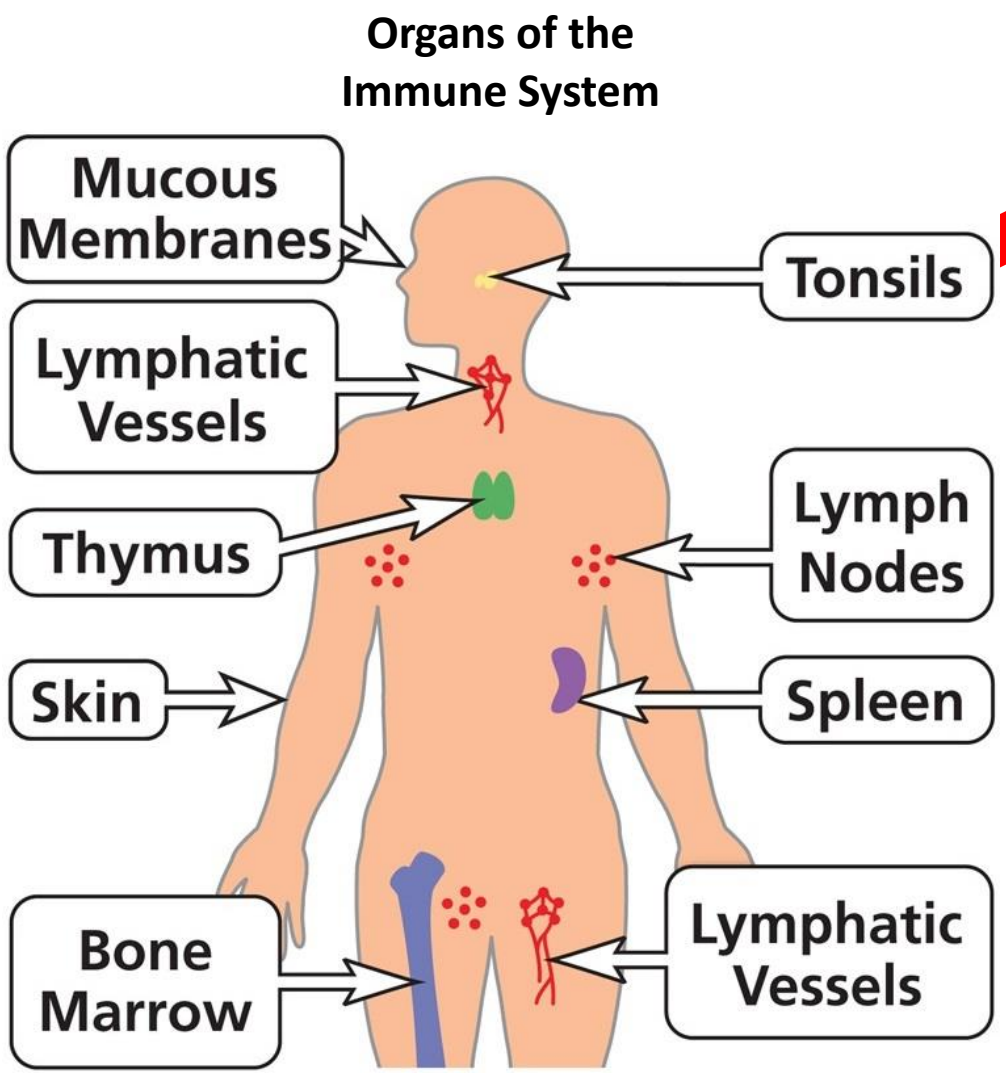
Innate immunity:

- 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)

Defense and counterattack



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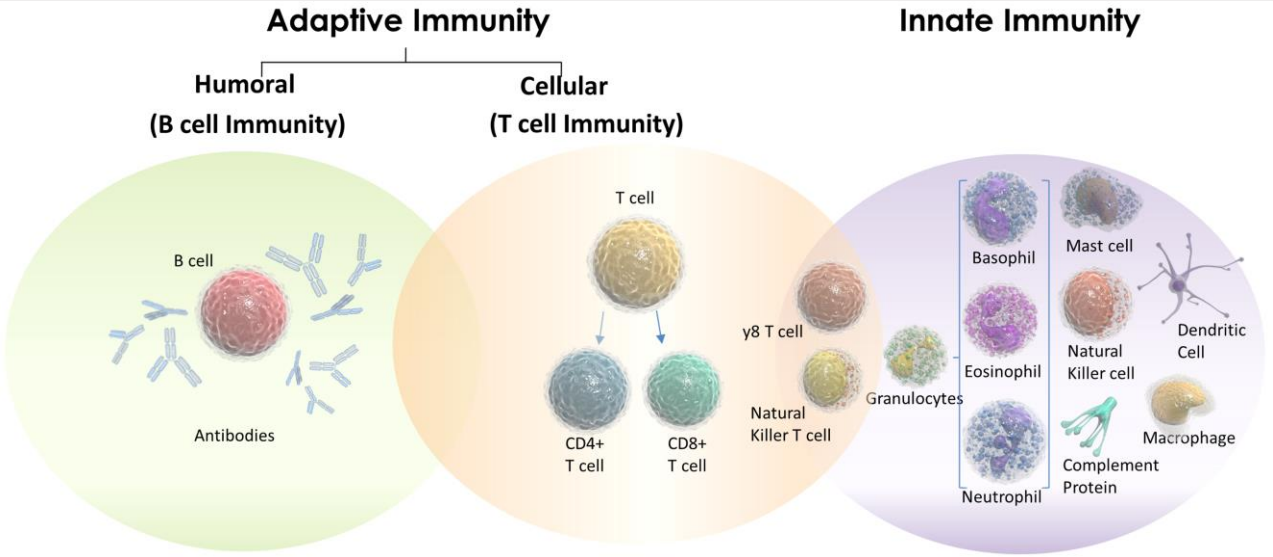

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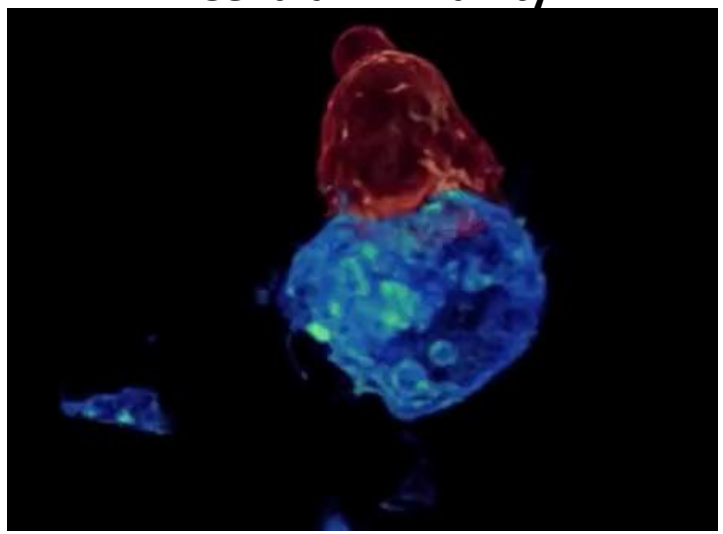
Cellular immunity

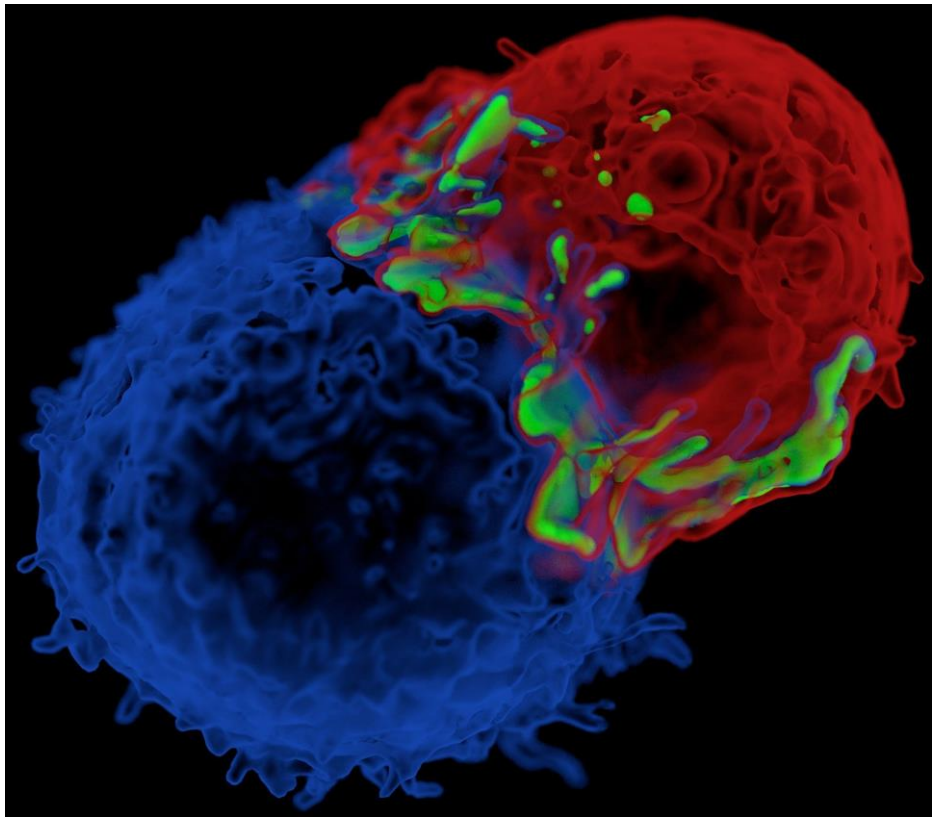


James and Vale | Nature 487 | 2012 | https://doi.org/10.1038/nature11220

T cell

Dendritic cell
Macrophage
B cell

Characteristic pattern formation



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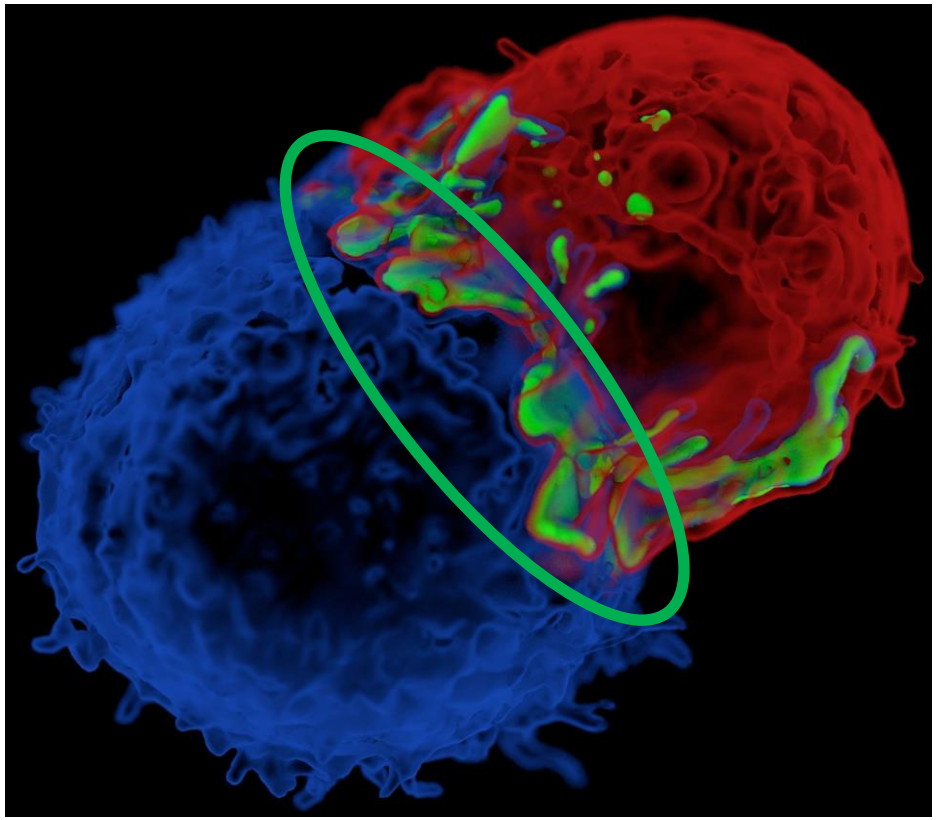

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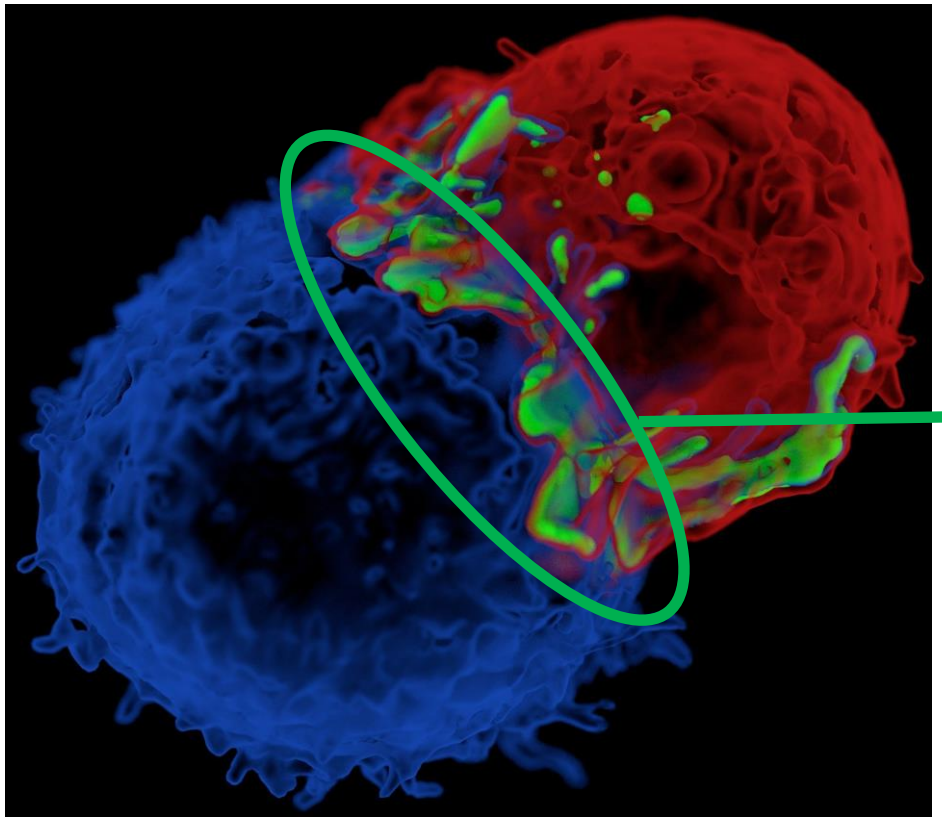

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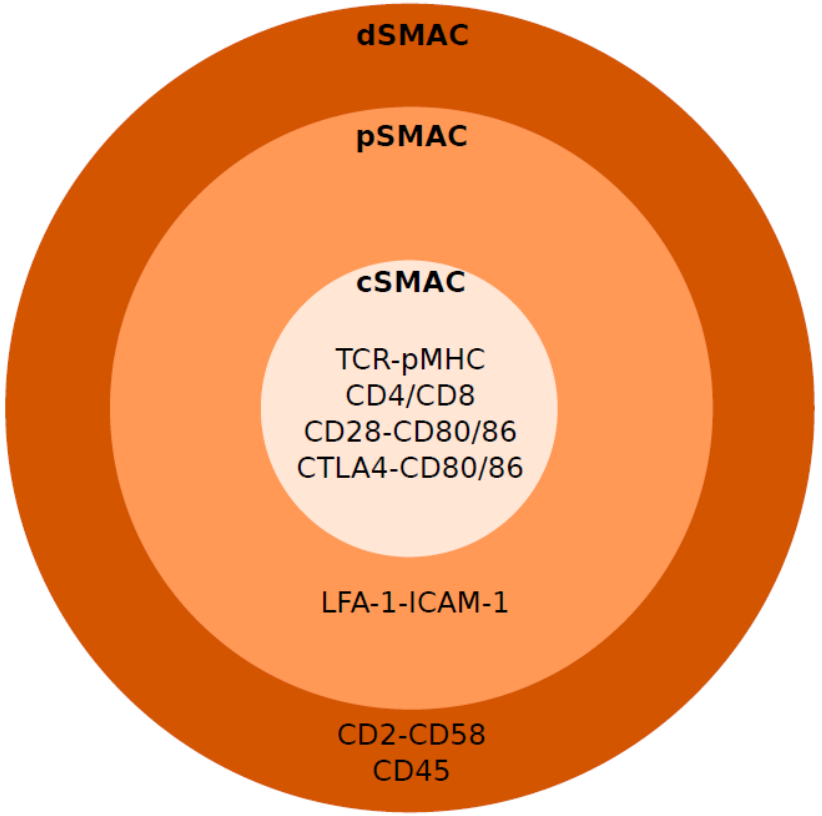
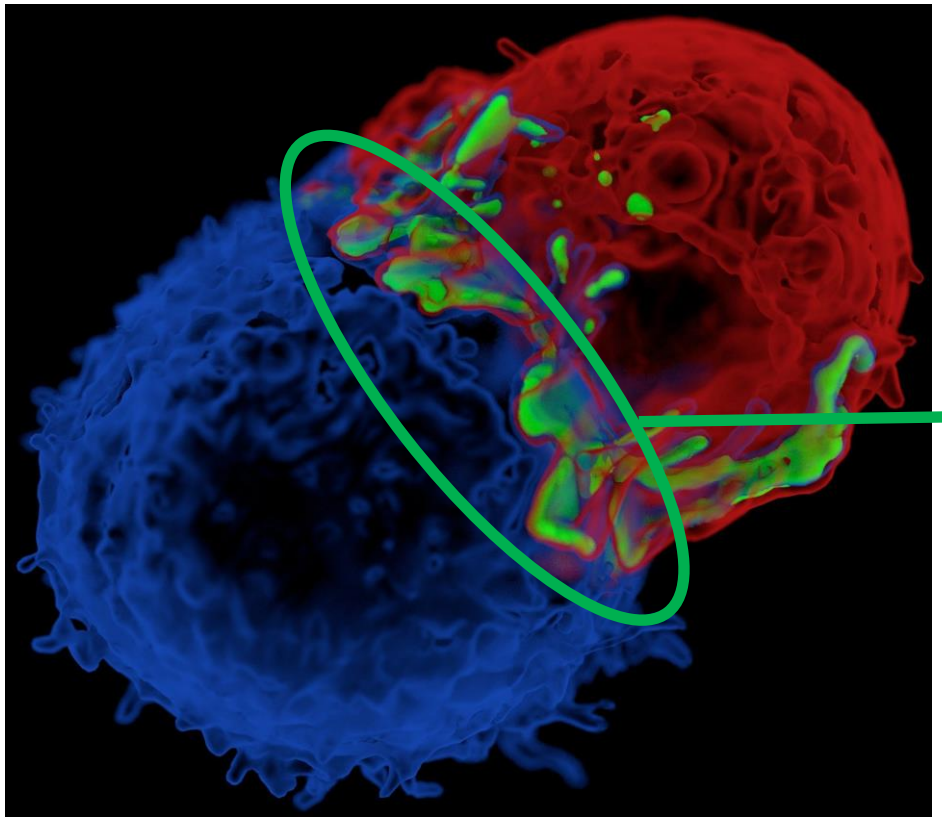


SMAC - supramolecular activation cluster
TCR - T cell receptor
pMHC - Antigen peptide bound to major histocompatibility complex
LFA-1 - Lymphocyte function-associated antigen 1
ICAM-1 - Intercellular Adhesion Molecule 1
CD - Cluster of differentiation XX

Characteristic pattern formation



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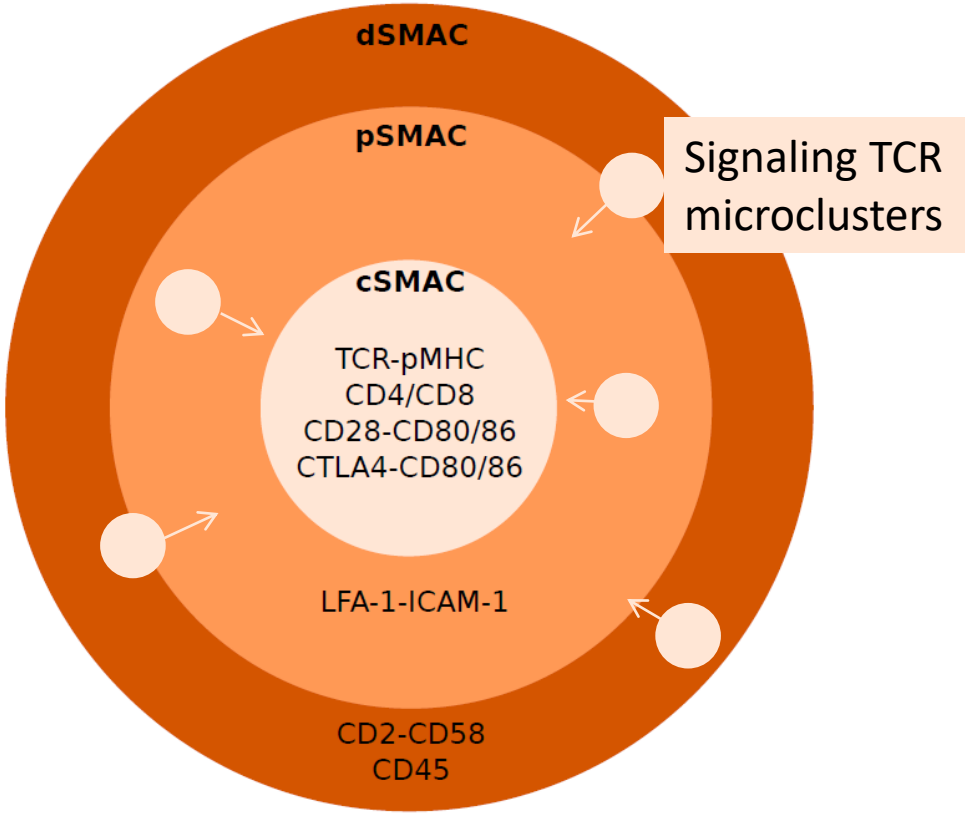

Signaling TCR microclusters

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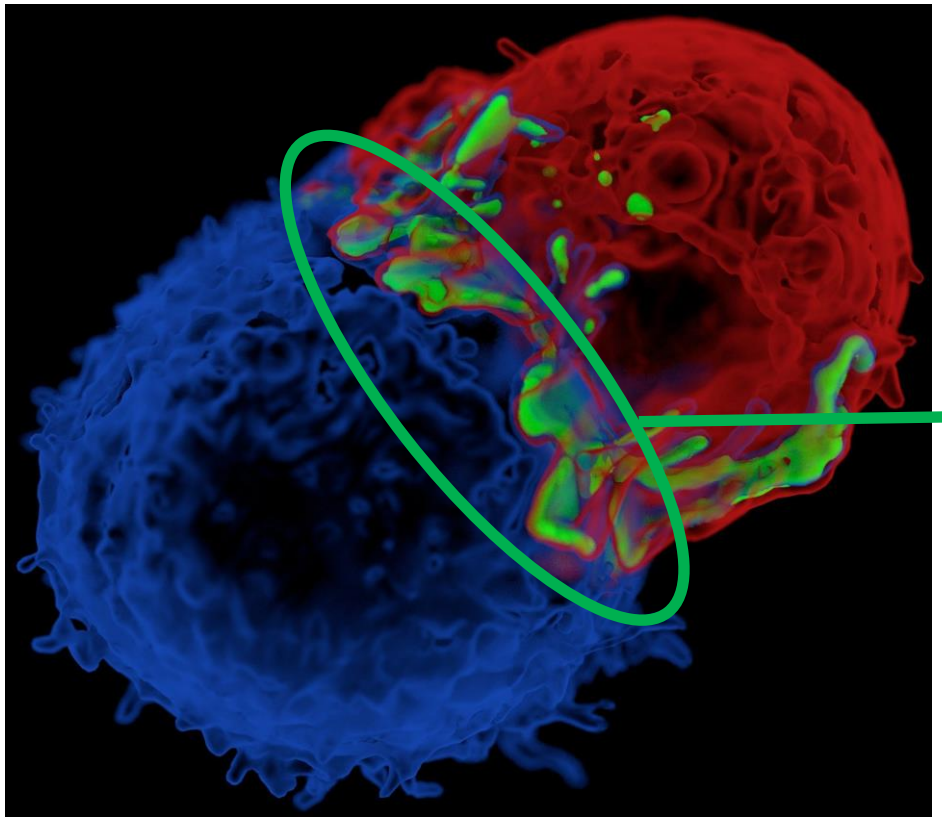

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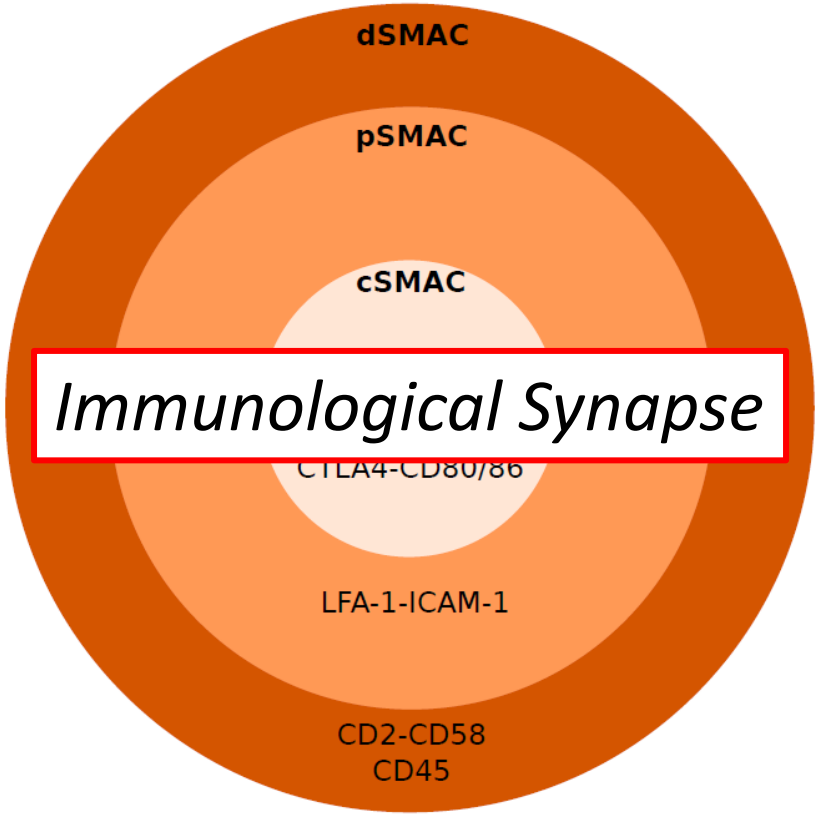

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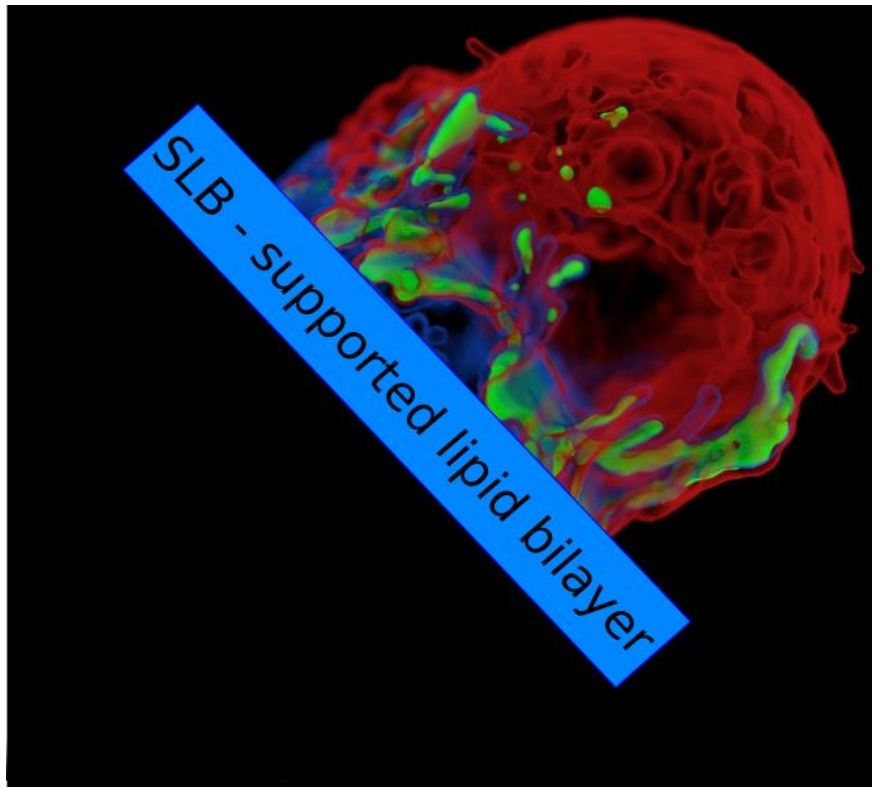

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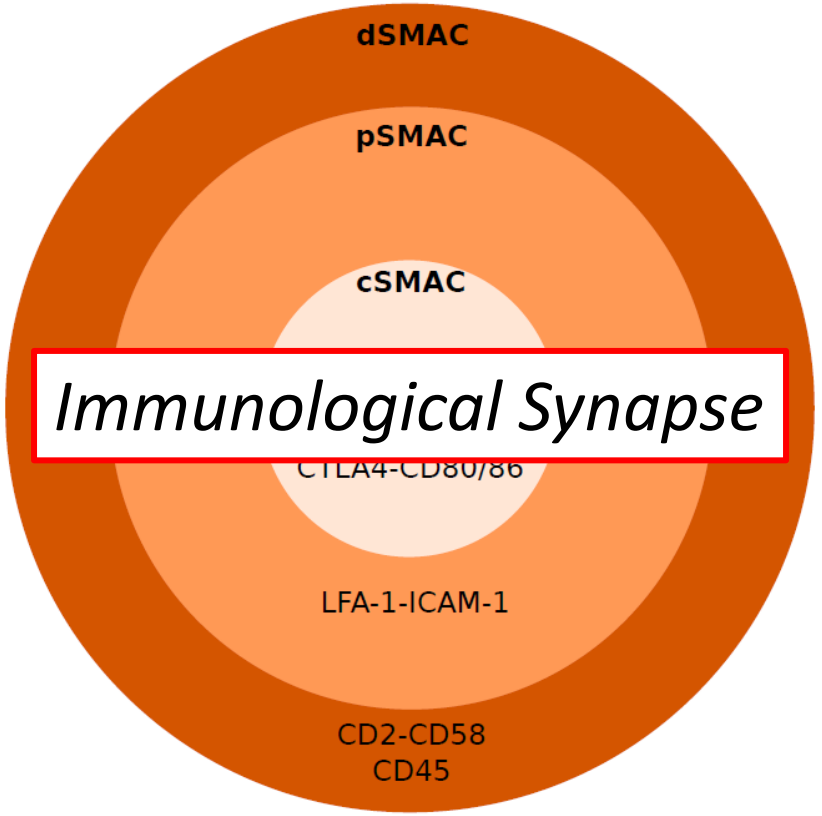

Most experiments performed on SLBs

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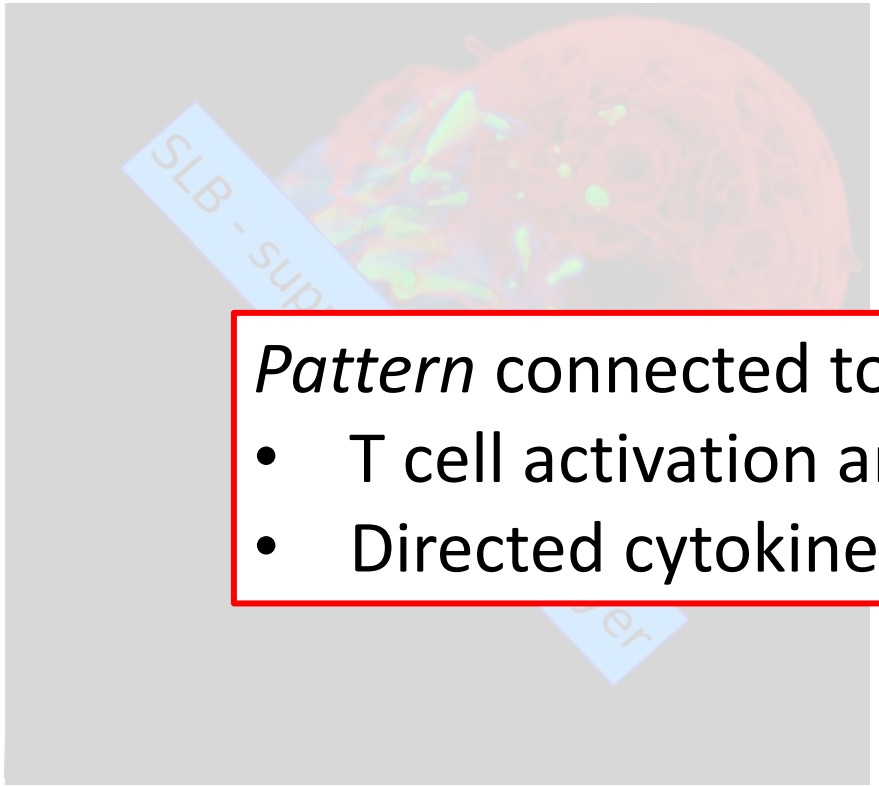

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Pattern connected to *Function*:

- T cell activation and fate decision
- Directed cytokine/lytic granule secretion

Most experiments performed on SLBs

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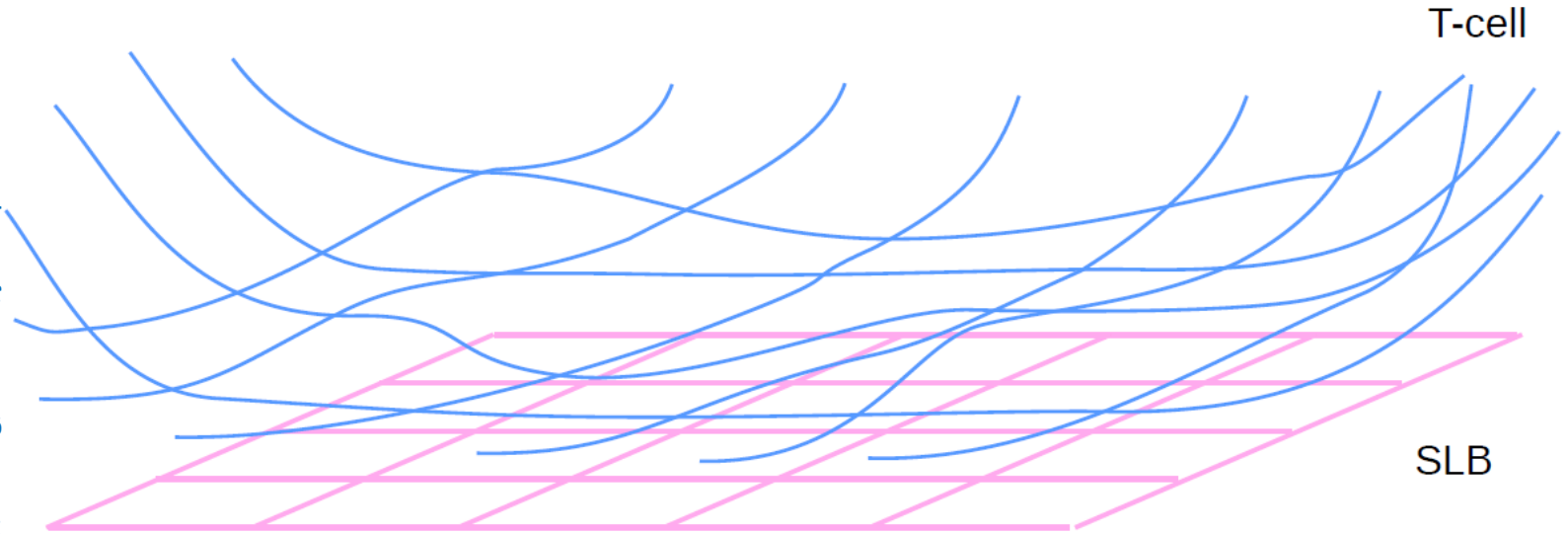
Understand the mechanisms leading to immune synapse formation

Coming up next

1. What are the mechanisms leading to Immune Synapse formation?
2. What is the effect of LFA-1 gradient?
3. What are the mechanisms of CD28 costimulatory molecule localization?
4. Is CD28 localization affected by the presence of other costimulatory molecules?
5. How does the CD2 corolla pattern form?
6. Is there active modulation of TCR-pMHC association rate, k_{on}?

Agent-based model



Siokis | Cell Reports 24 | 2018 | https://doi.org/10.1016/j.celrep.2018.06.114

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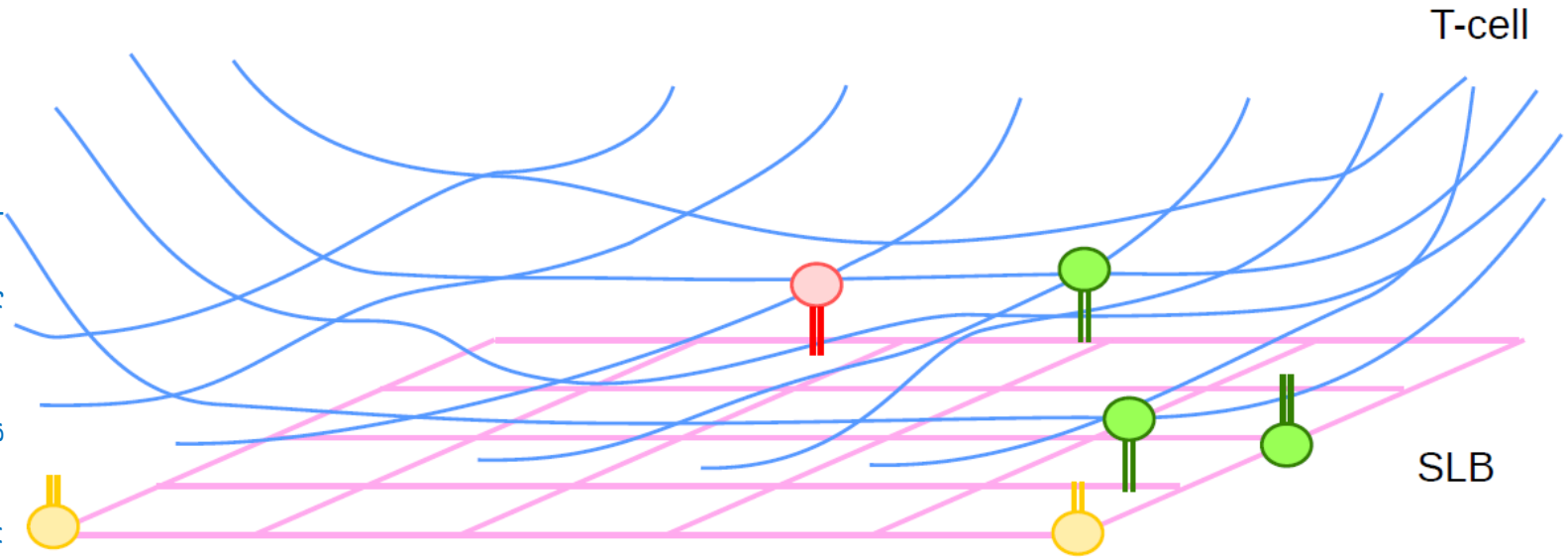

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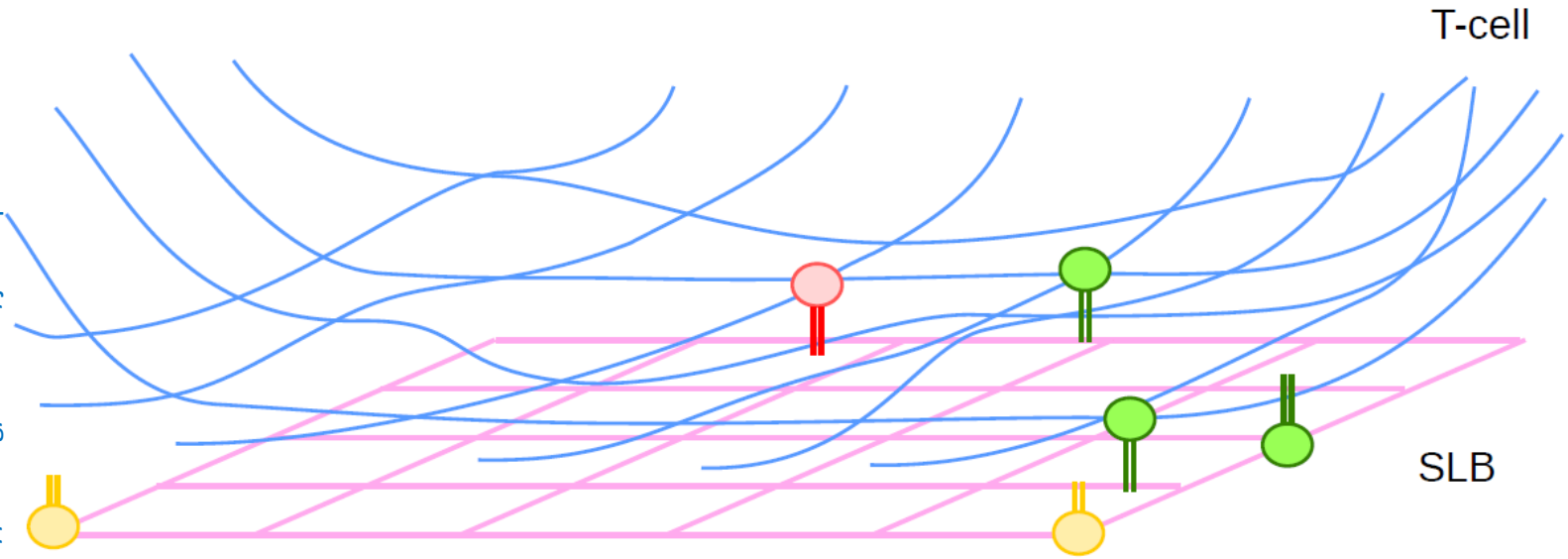

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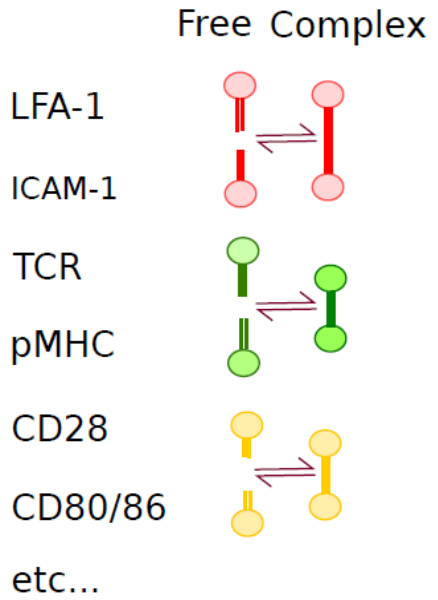
Chemical kinetics



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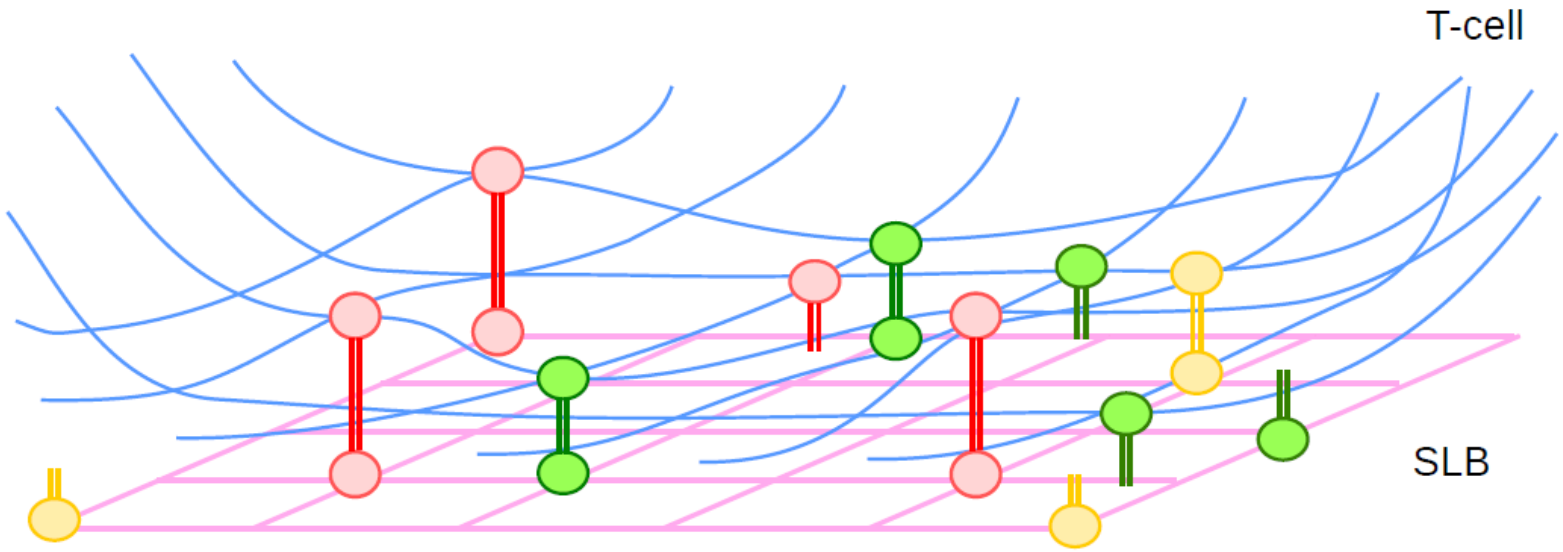

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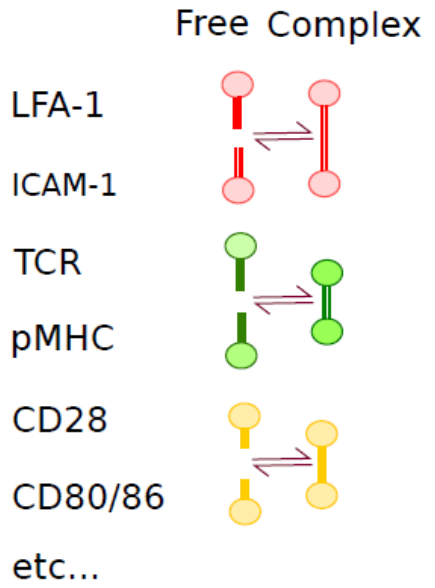

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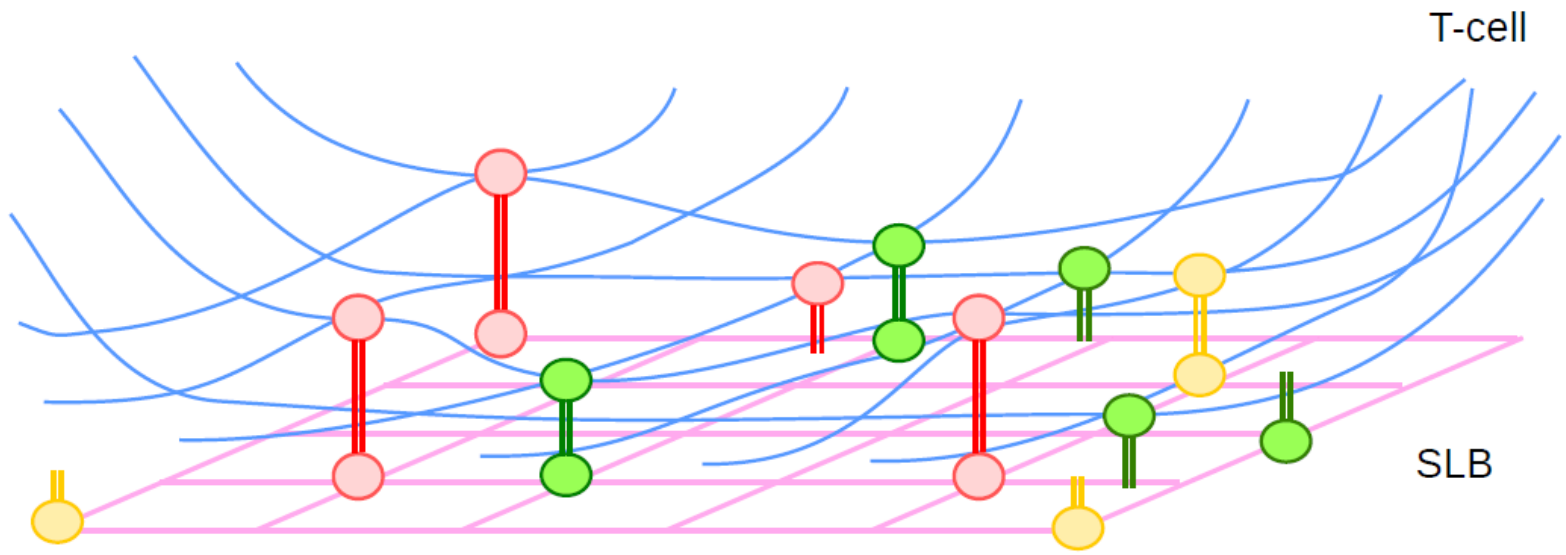

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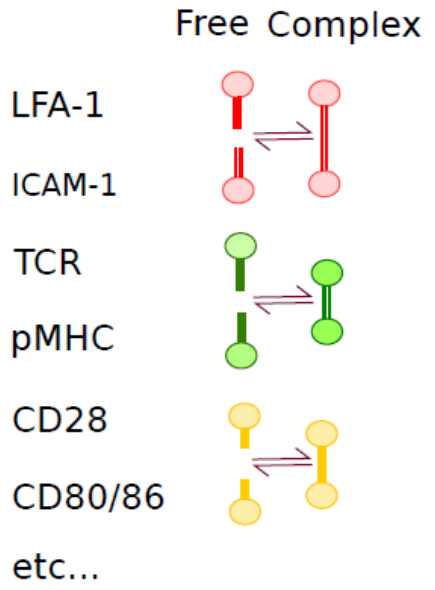
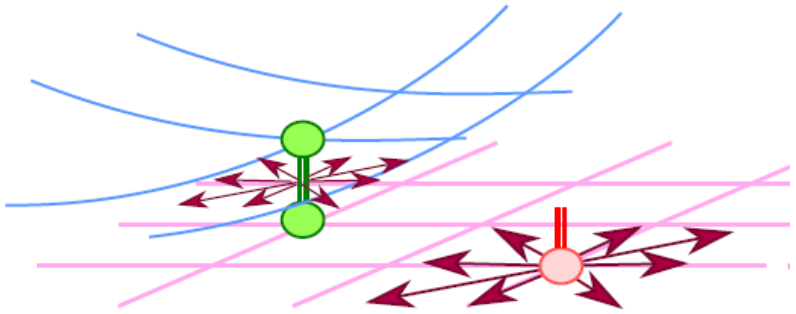


Diffusion



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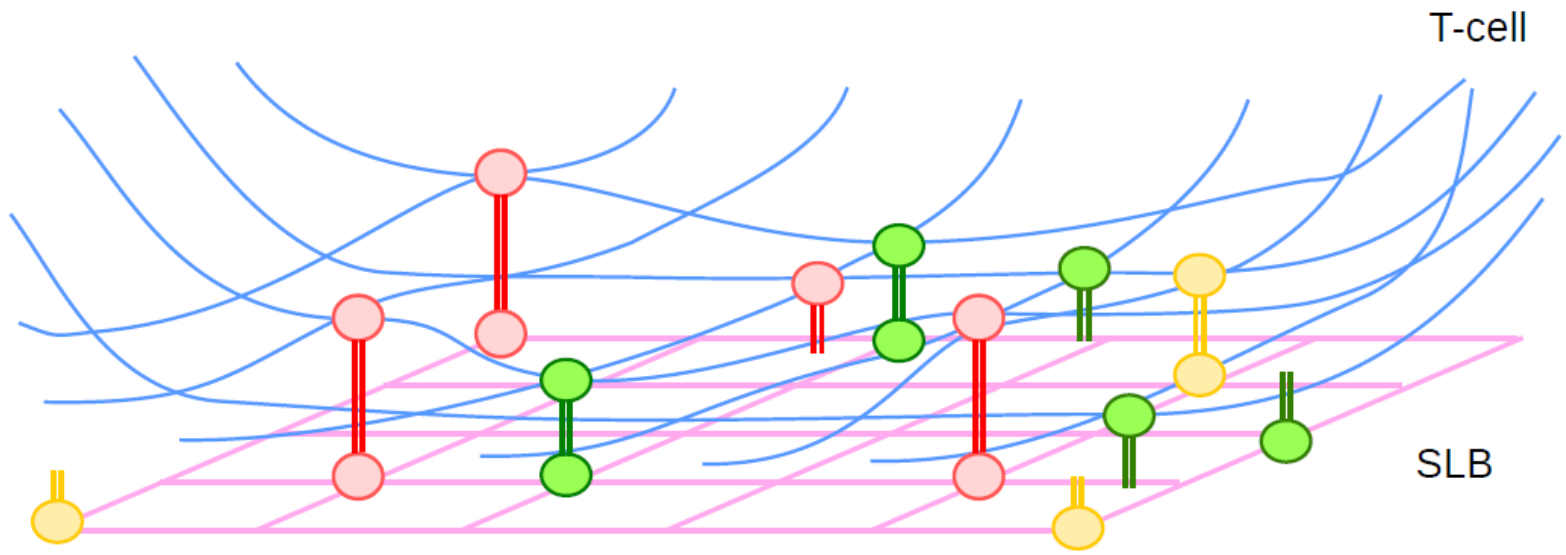

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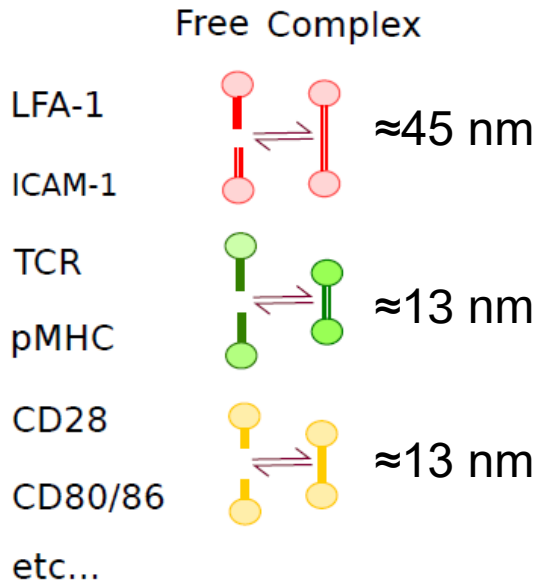

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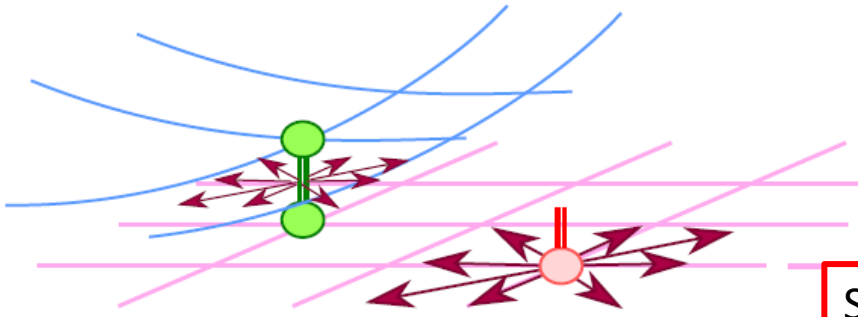
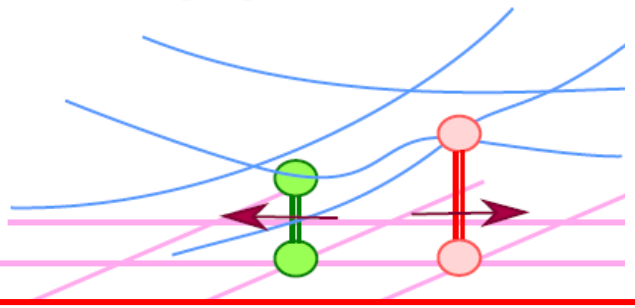
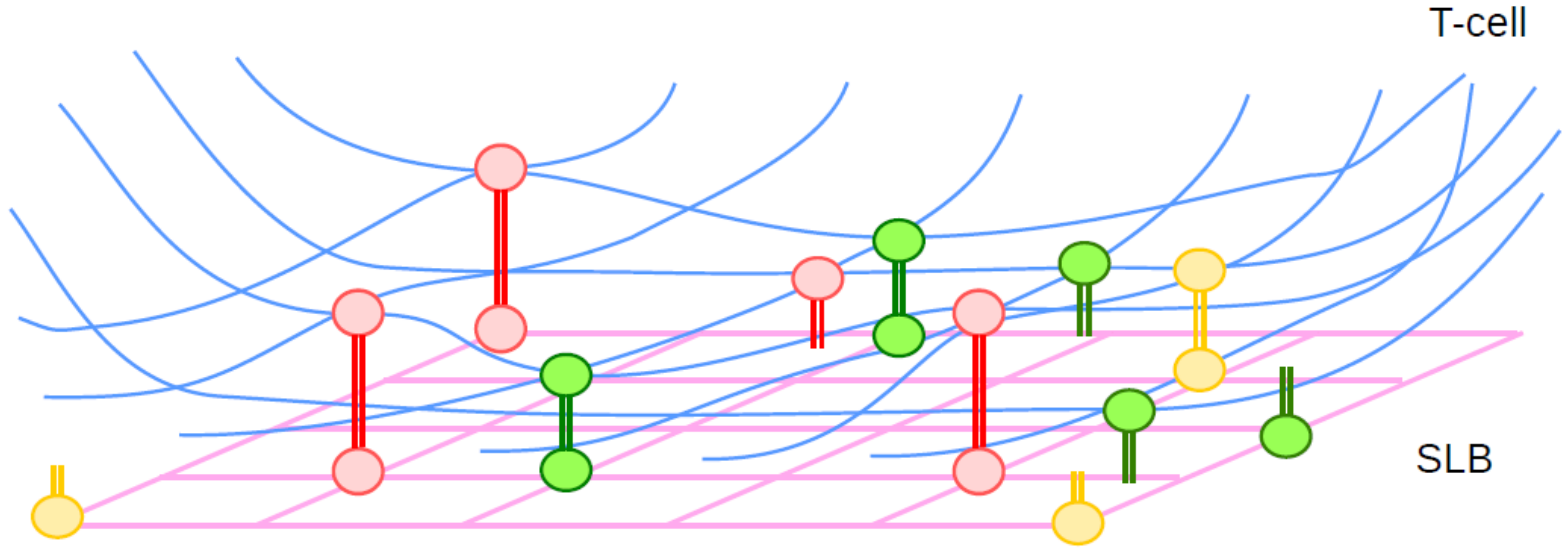


Size-Based Segregation



Summation of weighted vectors
Resulting vector points to new position

Agent-based model



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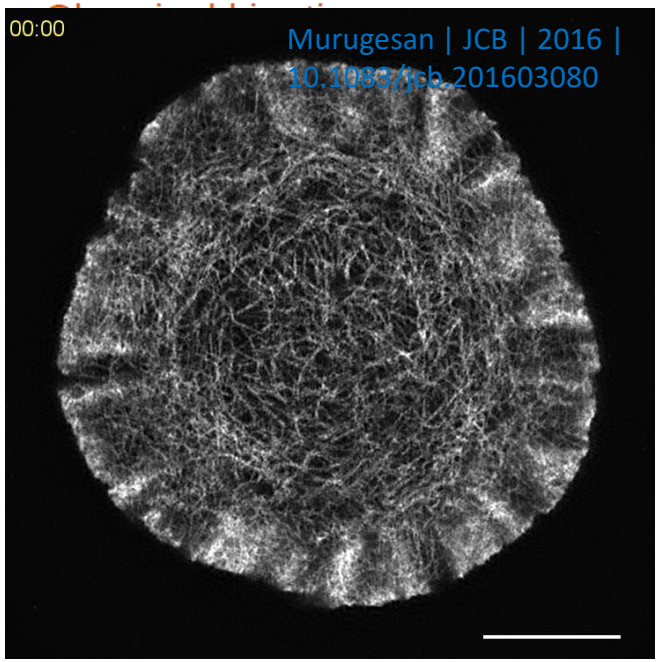

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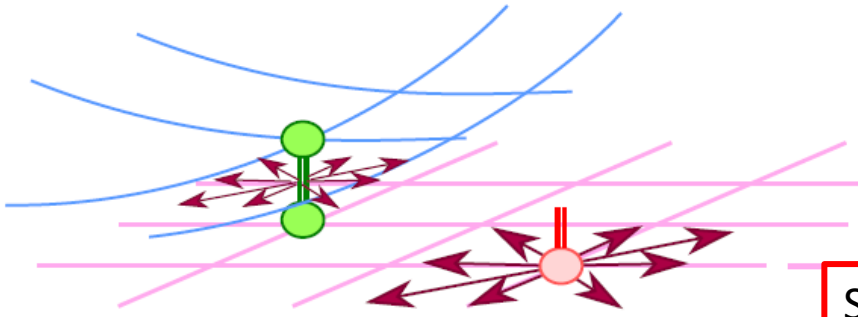

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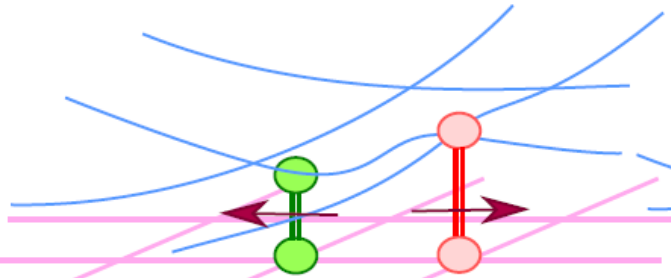
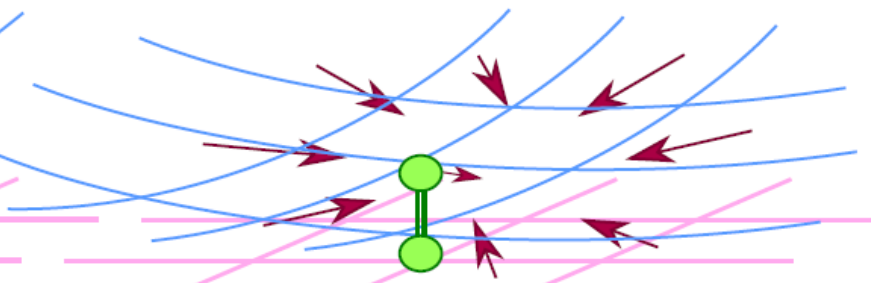


Actin coupling



Summation of weighted vectors
Resulting vector points to new position

+

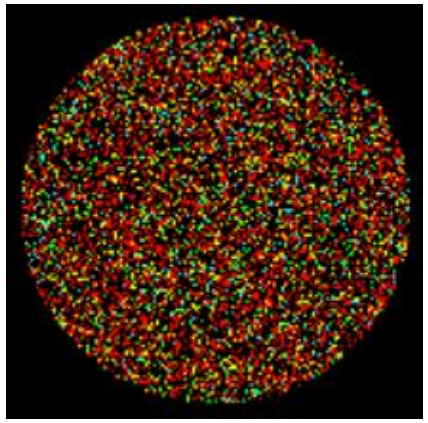
Vector added to the forces vector

Answer-seeking questions

1. What are the mechanisms leading to Immune Synapse formation?

Immunological Synapse Formation

Chemical kinetics
Diffusion



TCR LFA-1

TCR-pMHC LFA-1-ICAM-1

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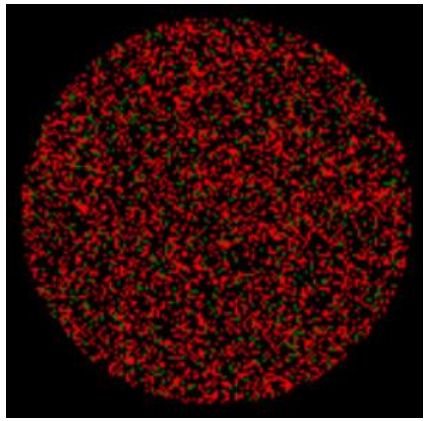
Immunological Synapse Formation

Chemical kinetics
Diffusion

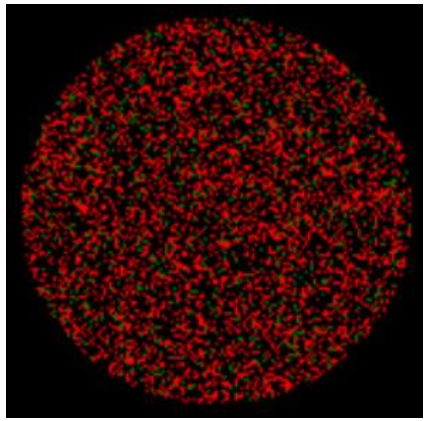


Siokis | Cell Reports 24 | 2018 | https://doi.org/10.1016/j.celrep.2018.06.114

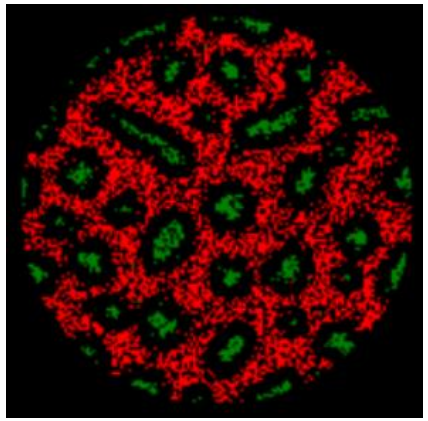
TCR-pMHC LFA-1-ICAM-1

Immunological Synapse Formation

Chemical kinetics
Diffusion



plus TCR-LFA-1 SBS



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Immunological Synapse Formation

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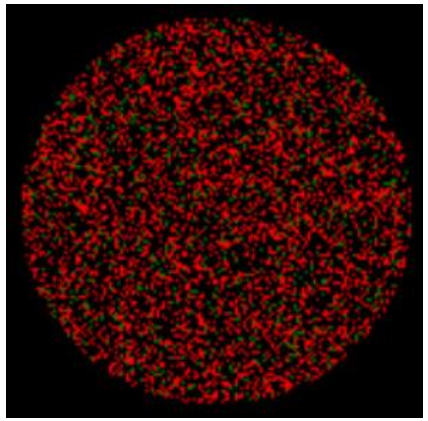
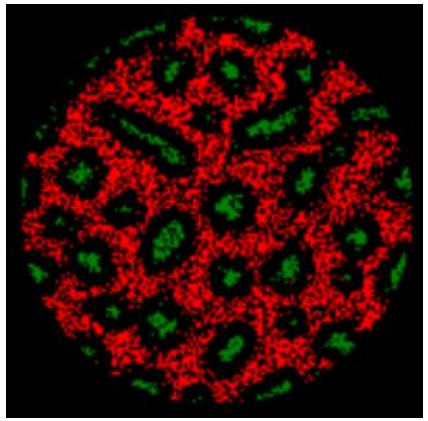


plus TCR centripetal
transport

0-20 minutes

plus TCR-LFA-1 SBS



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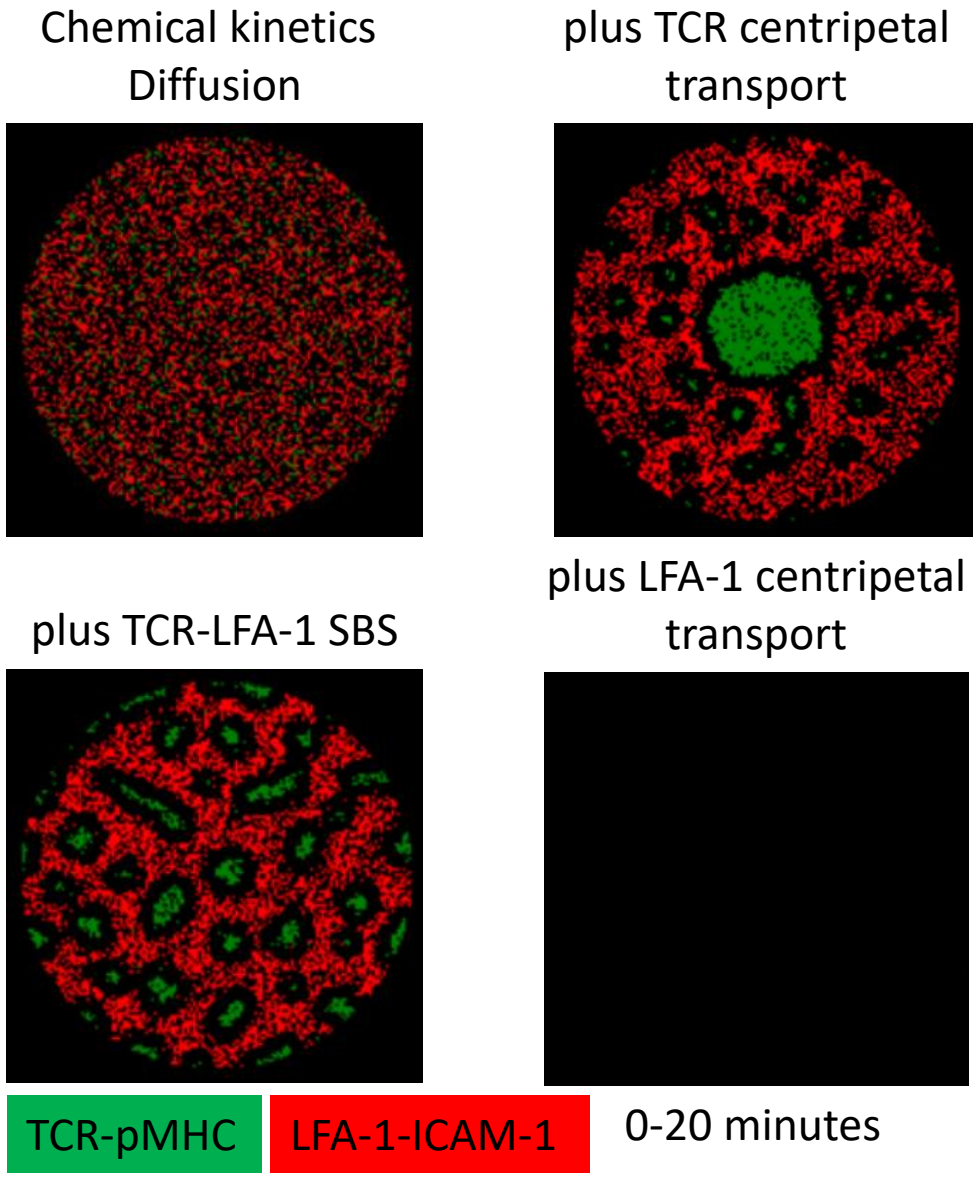
Siokis | Cell Reports 24 | 2018 | https://doi.org/10.1016/j.celrep.2018.06.114

Answer-seeking questions

1. What are the mechanisms leading to Immune Synapse formation?
   - ✓ Chemical kinetics, diffusion, size-based segregation & centripetal transport

Immunological Synapse Formation



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Immunological Synapse Formation

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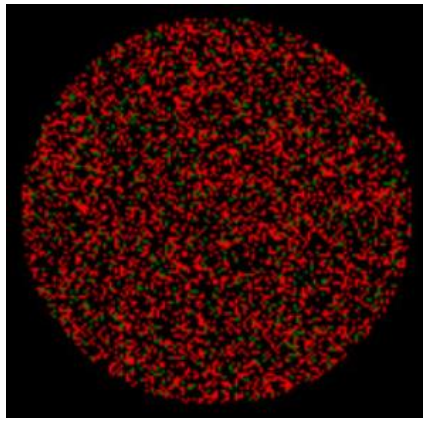

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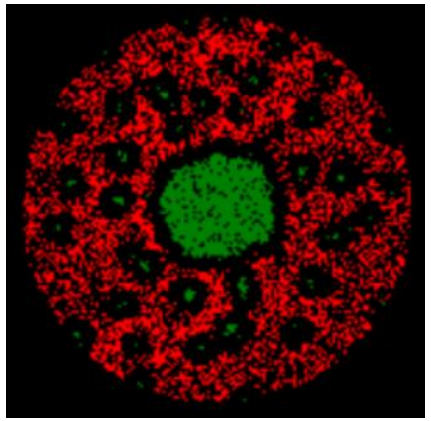

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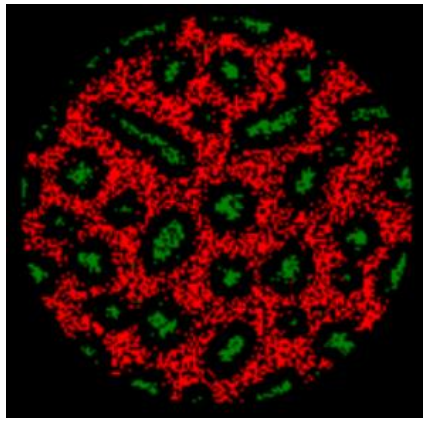

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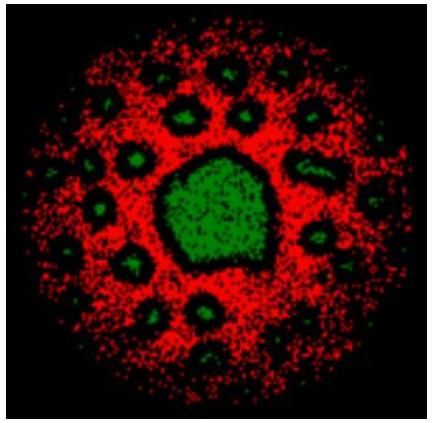

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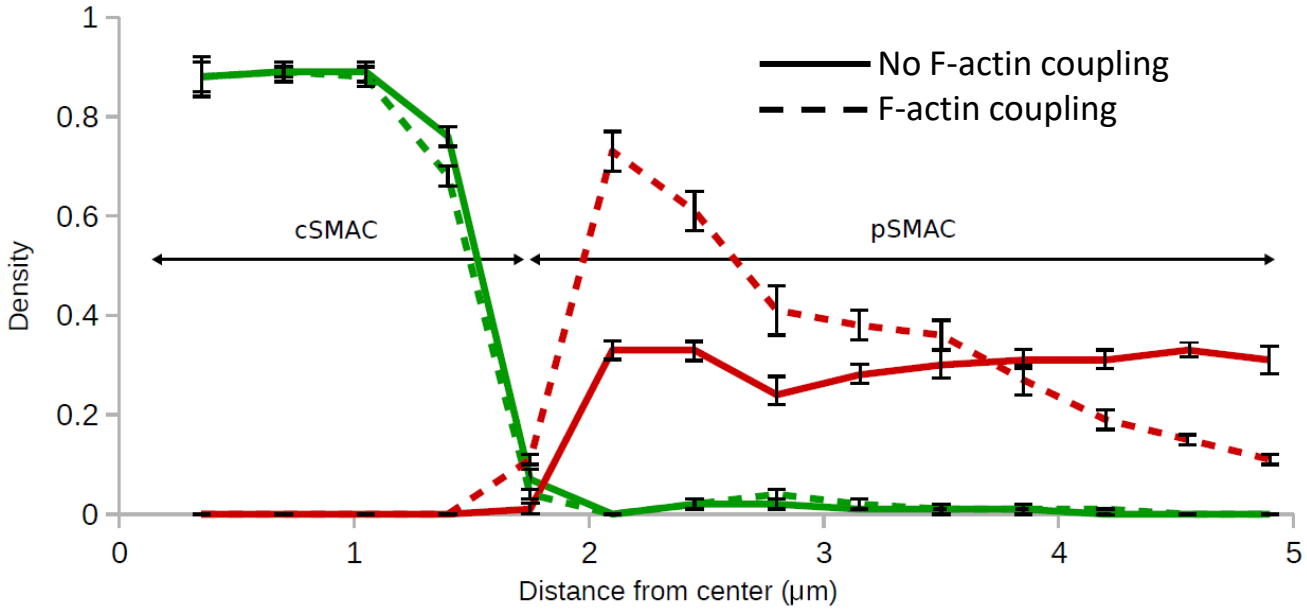

Immunological Synapse Formation

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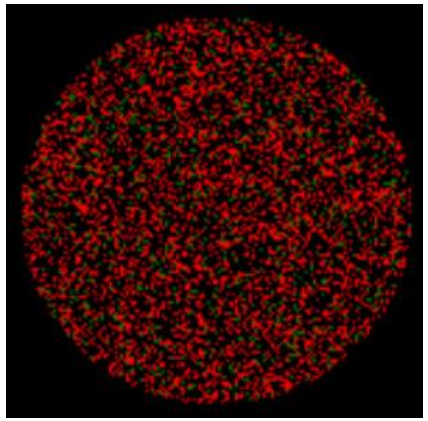

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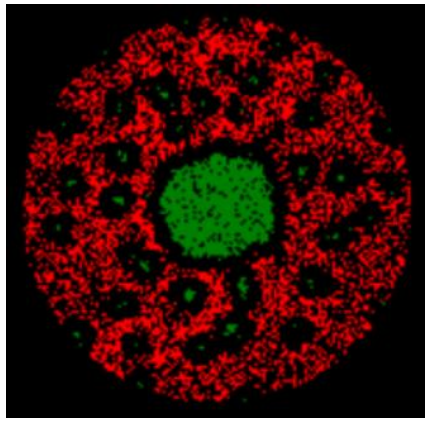

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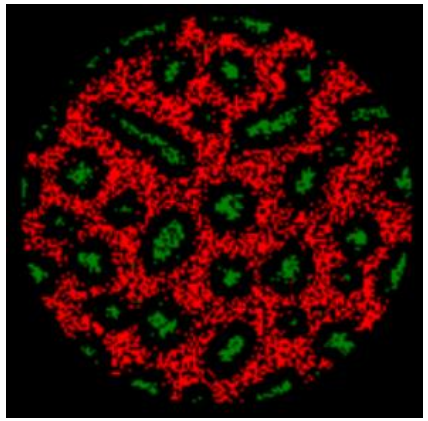

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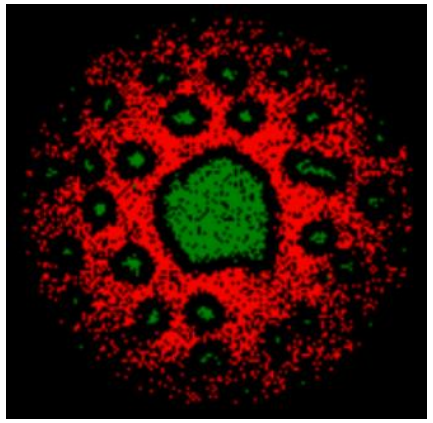

TCR-pMHC | LFA-1-ICAM-1

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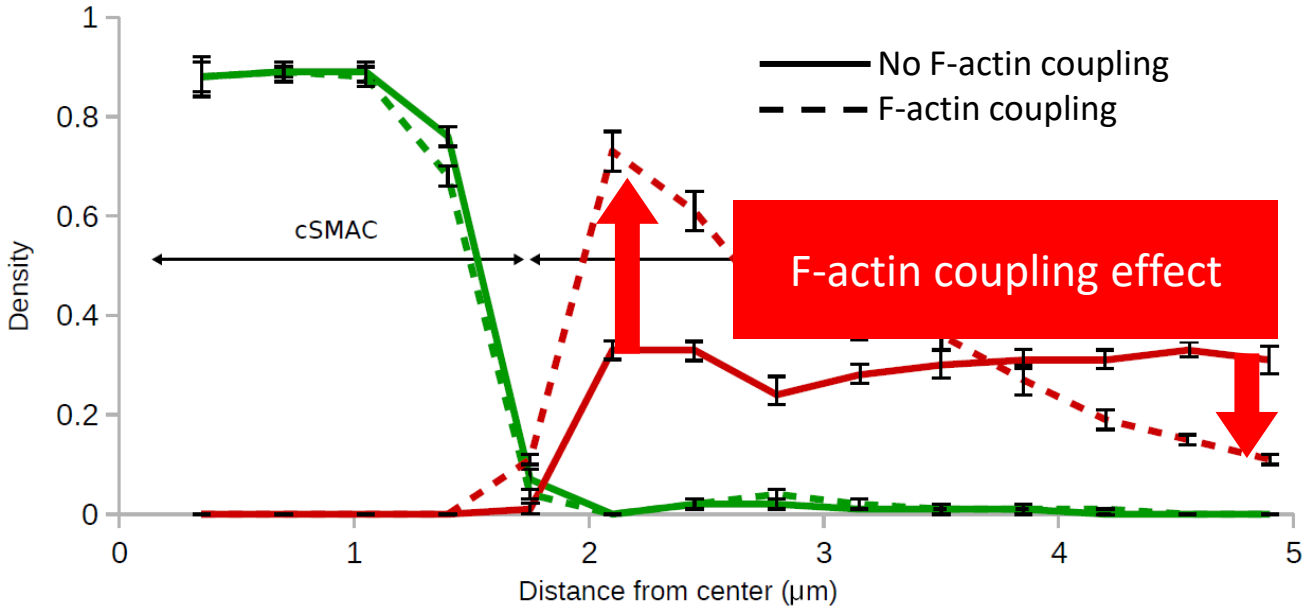

LFA-1 gradient reported (not further examined):
Yokosuka | Immunity | 2008
Comrie | J Cell Biology | 2015
Demetriou | Nature Immunology | 2020

Answer-seeking questions

1. What are the mechanisms leading to Immune Synapse formation?
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2. What is the effect of LFA-1 gradient?

LFA-1-ICAM-1 gradient affects the localization of free molecules

CD28 not interacting with neighbors

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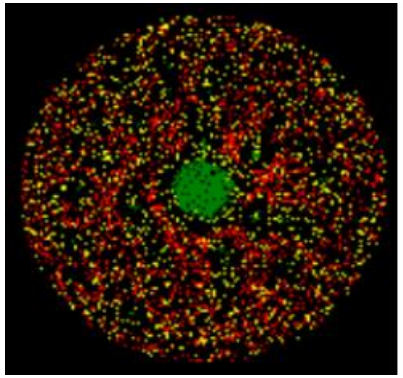
CD28 not interacting with neighbors

TCR-pMHC

LFA-1-ICAM-1

CD28



No LFA-1-actin interaction

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LFA-1-ICAM-1 gradient affects the localization of free molecules

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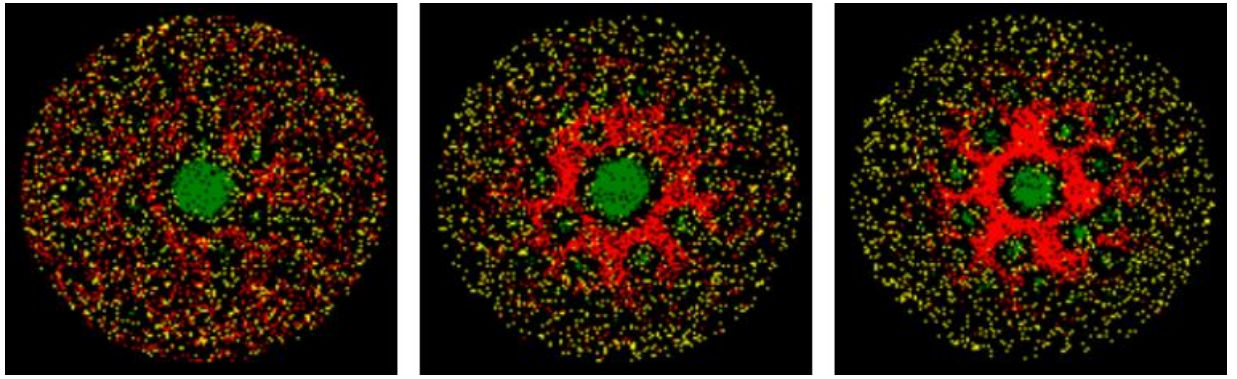
LFA-1 actin coupling

TCR-pMHC

LFA-1-ICAM-1

CD28



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Presence of costimulatory molecules

CD28 costimulation

- Expressed on naive and effector T cells
- Binds to CD80 & CD86
- Promotes actin polymerization
- Recruits Filamin-A (FLNa) - actin binding protein
- Recruits PKC-θ
- Size similar to TCR-pMHC (≈13 nm)
- **Ring structure around cSMAC**

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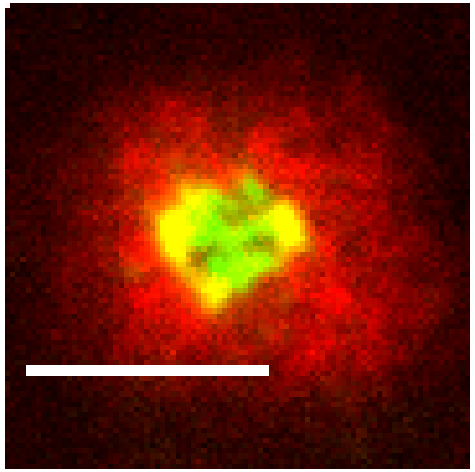

TCR-pMHC

LFA-1-ICAM-1

CD28-CD80

Demetriou | Dustin lab | 2018 | Oxford | UK

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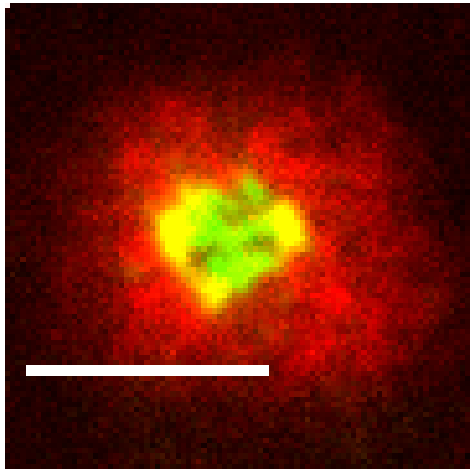

TCR-pMHC

LFA-1-ICAM-1

CD28-CD80

Demetriou | Dustin lab | 2018 | Oxford | UK

CD2 costimulation & adhesion

- Expressed on T & NK cells
- Binds to CD58 (humans) & CD48 (rodents)
- Augment & sustain antigen induced Ca2+ increase
- Synergize with TCR to activate PLCγ1
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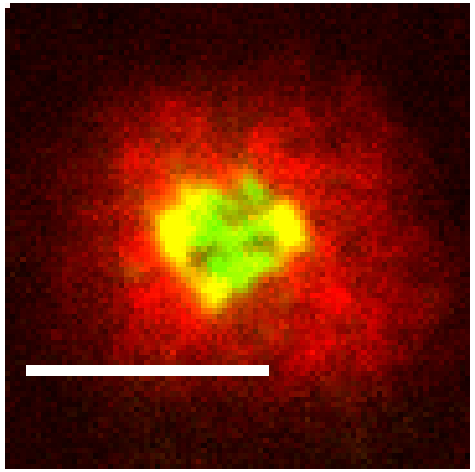

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CD28-CD80

CD2-CD58

Demetriou | Dustin lab | 2018 | Oxford | UK

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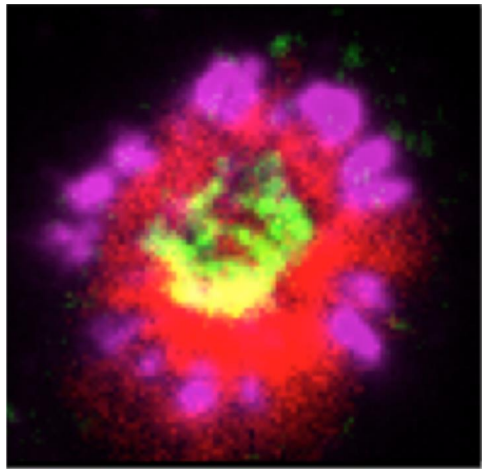
- **Flower petal-like corolla pattern in dSMAC**



Demetriou | Nat Immunol | 2020 | https://www.nature.com/articles/s41590-020-0770-x

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Absence of costimulation leads to T cell anergy

TCR-pMHC

LFA-1-ICAM-1

CD28-CD80

CD2-CD58

Demetriou | Dustin lab | 2018 | Oxford | UK

Demetriou | Nat Immunol | 2020 | https://www.nature.com/articles/s41590-020-0770-x

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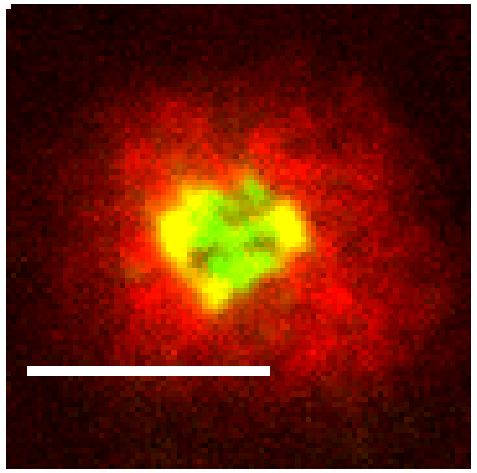
F-actin driven CD28-CD80 localization

TCR-pMHC

LFA-1-ICAM-1

CD28-CD80



Demetriou | Dustin lab | 2018 | Oxford | UK

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TCR-pMHC

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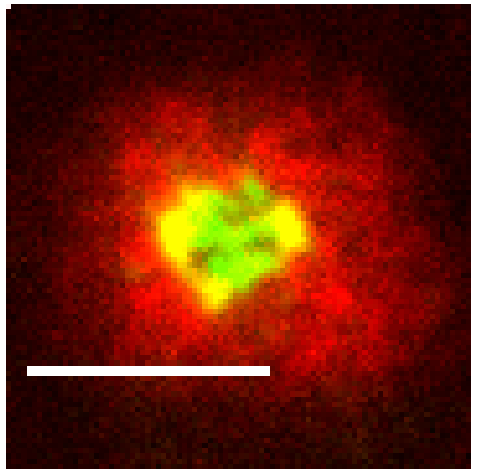


Demetriou | Dustin lab | 2018 | Oxford | UK

Siokis | Cell Reports 24 | 2018 | https://doi.org/10.1016/j.celrep.2018.06.114

CD28-LFA-1 SBS

0-20 minutes

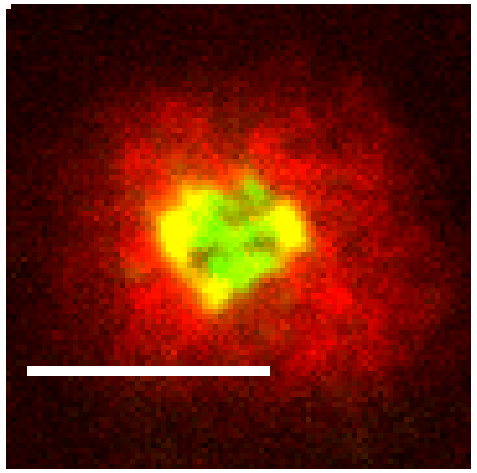
CD28 passive followers

F-actin driven CD28-CD80 localization

TCR-pMHC

LFA-1-ICAM-1

CD28-CD80



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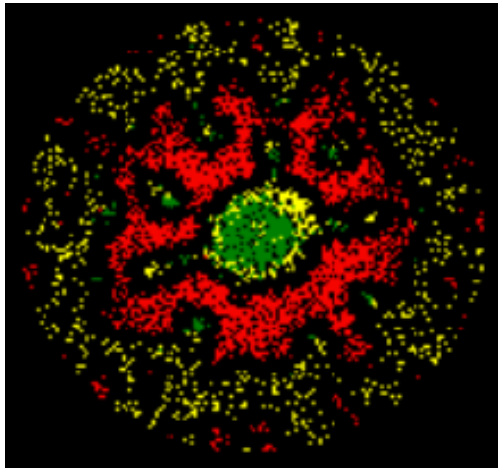


CD28 passive followers

CD28-LFA-1 SBS

CD28-CD80 coupling to actin

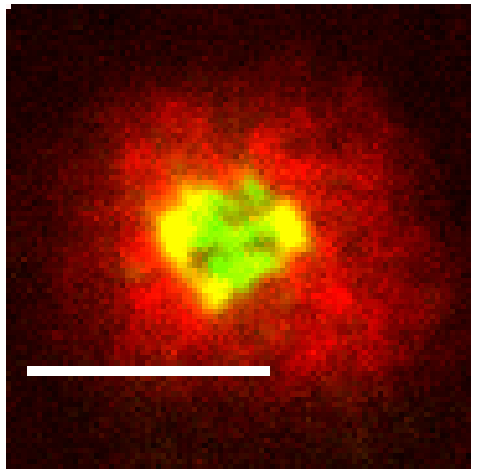
0-20 minutes

F-actin driven CD28-CD80 localization

TCR-pMHC

LFA-1-ICAM-1

CD28-CD80



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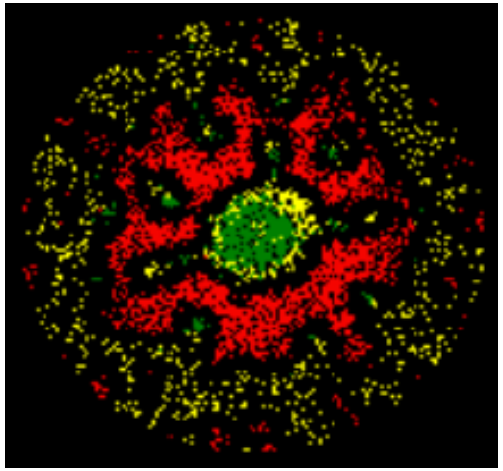

CD28 passive followers

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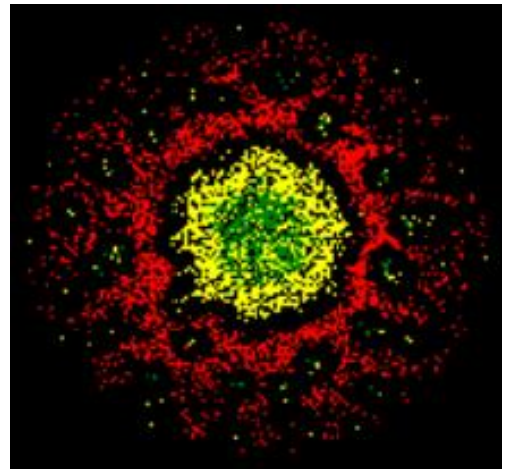

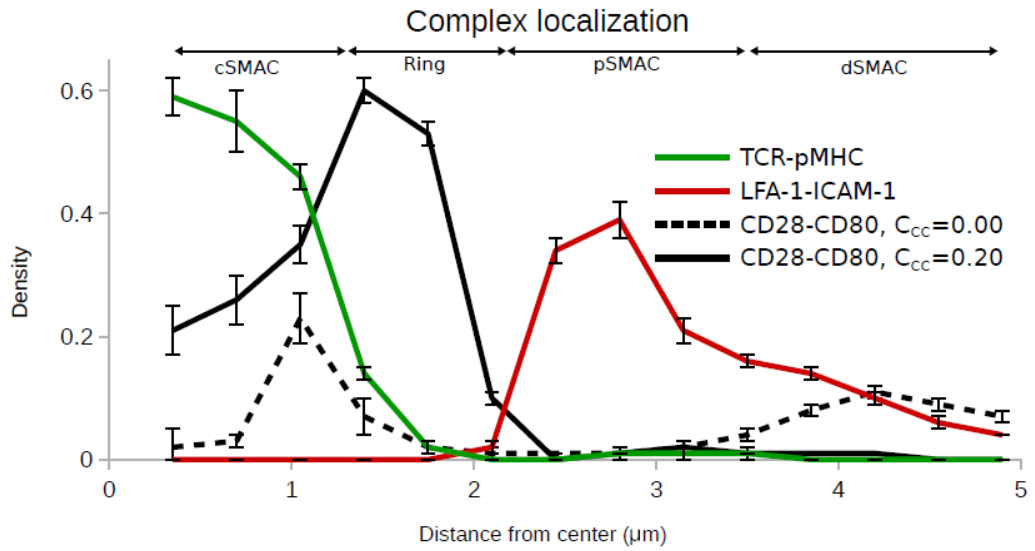

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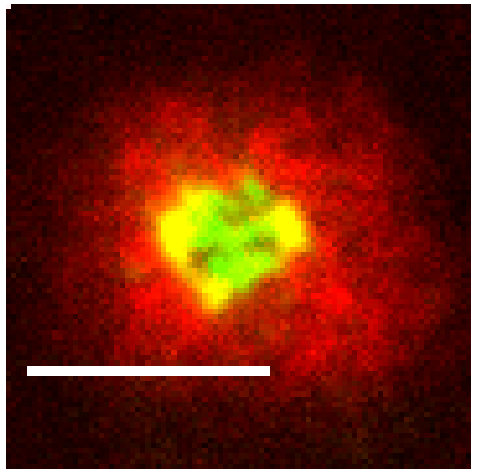

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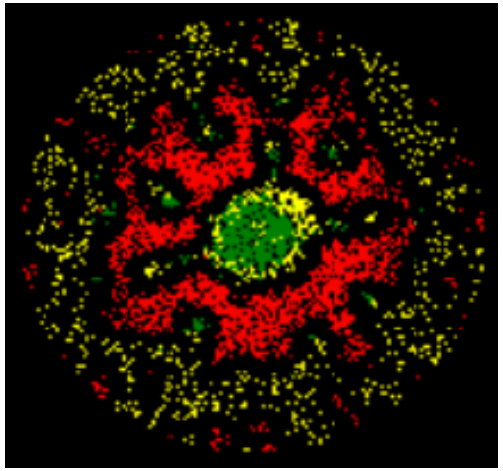

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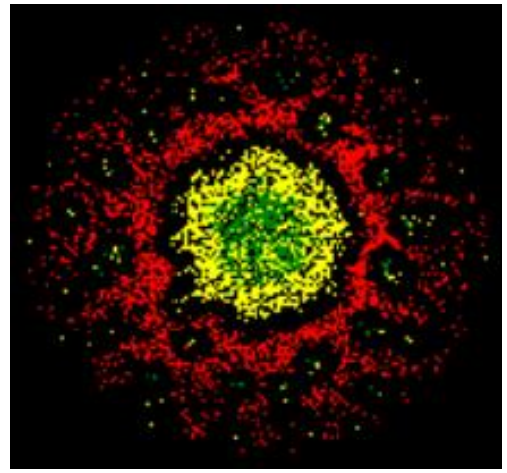
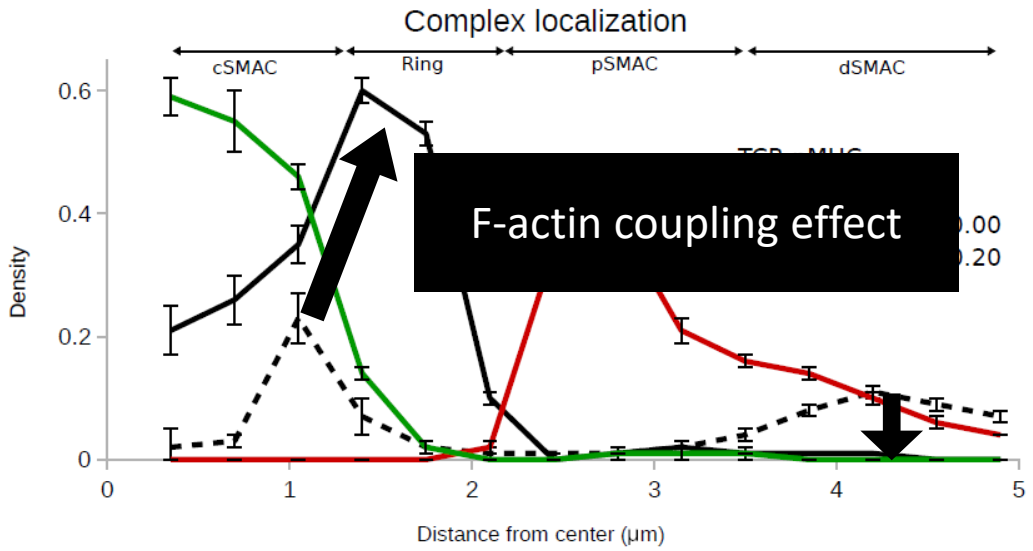
CD28-LFA-1 SBS

CD28-CD80 coupling to actin





Answer-seeking questions

1. What are the mechanisms leading to Immune Synapse formation?
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2. What is the effect of LFA-1 gradient?
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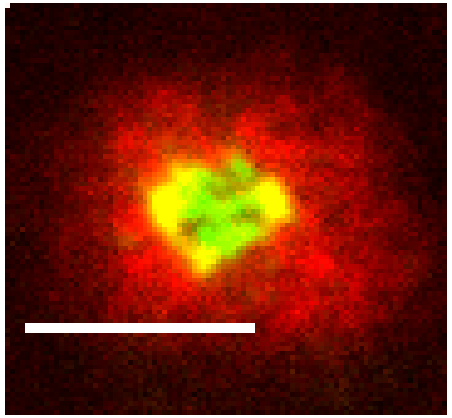
4. Is CD28 localization affected by the presence of other costimulatory molecules?

CD2 presence alters CD28 localization



Demetriou | Nat Immunol | 2020 | https://www.nature.com/articles/s41590-020-0770-x

TCR-pMHC

LFA-1-ICAM-1

CD2-CD58

CD28-CD80

CD2-CD28 overlay

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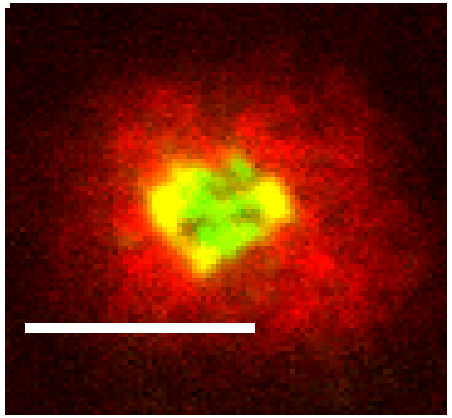

+ CD58

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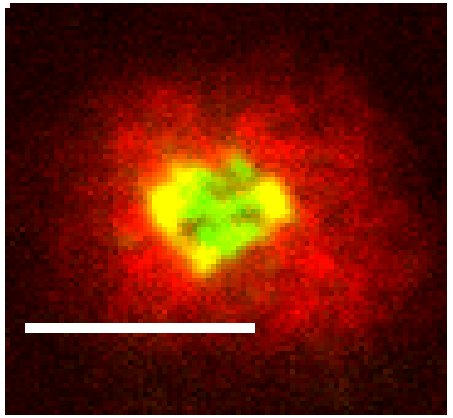

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CD2-CD28 corolla

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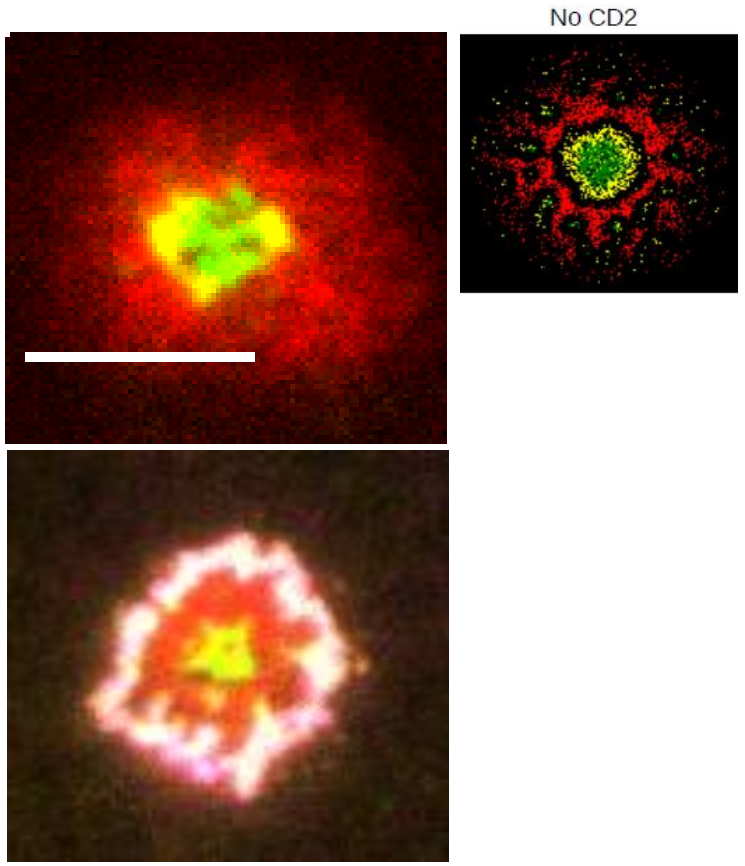

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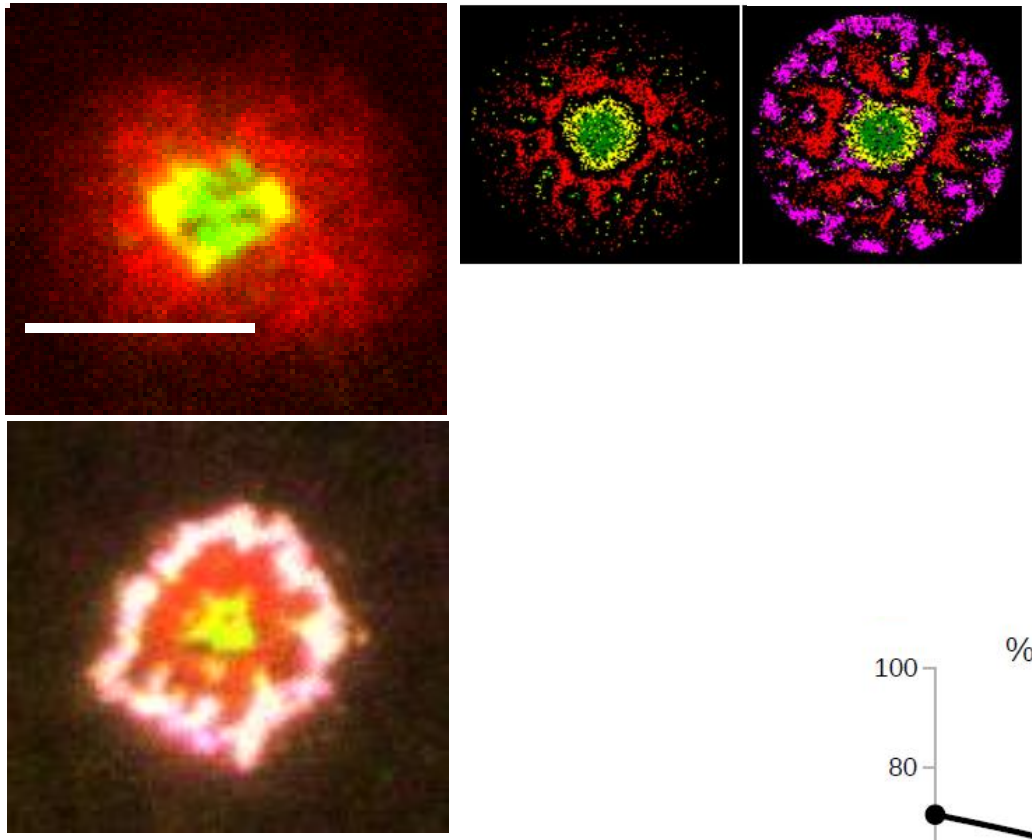
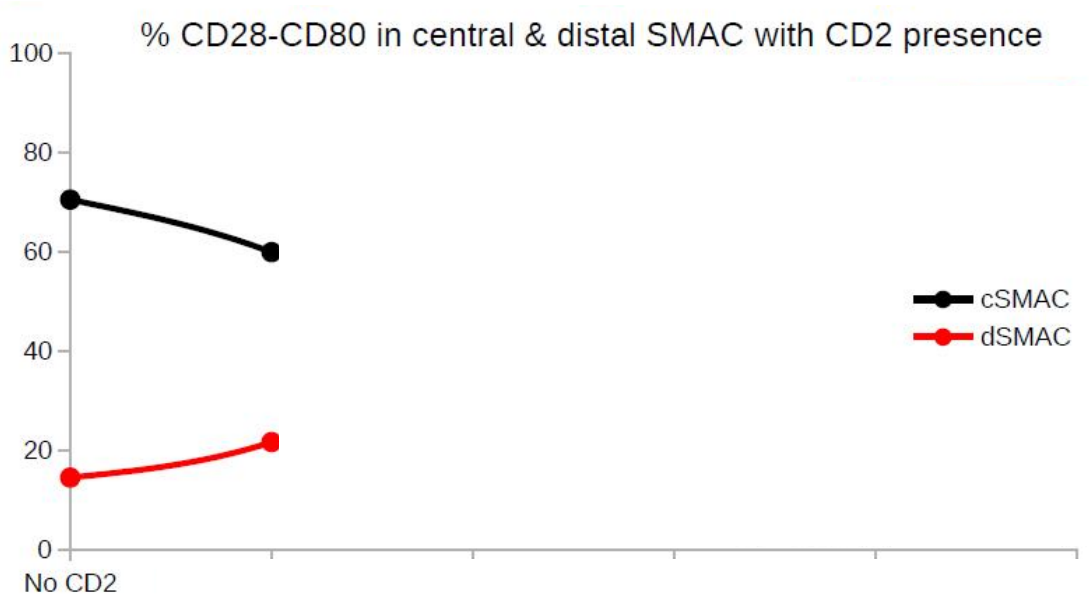
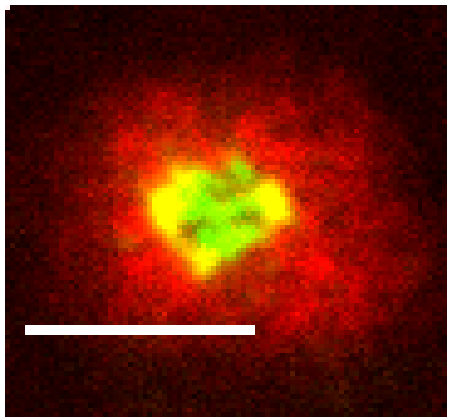


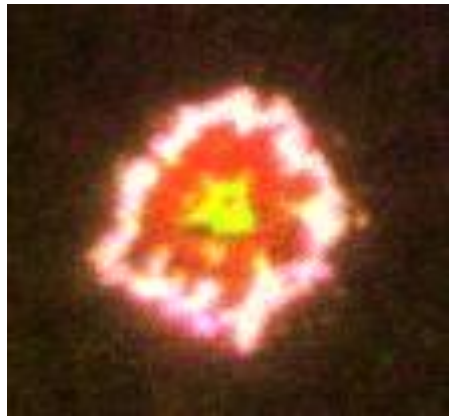


Demetriou | Nat Immunol | 2020 | https://www.nature.com/articles/s41590-020-0770-x

Siokis | bioRxiv | 2020 | https://doi.org/10.1101/2020.01.16.908723

CD2 presence alters CD28 localization





TCR-pMHC | LFA-1-ICAM-1

CD2-CD58 | CD28-CD80

CD2-CD28 overlay

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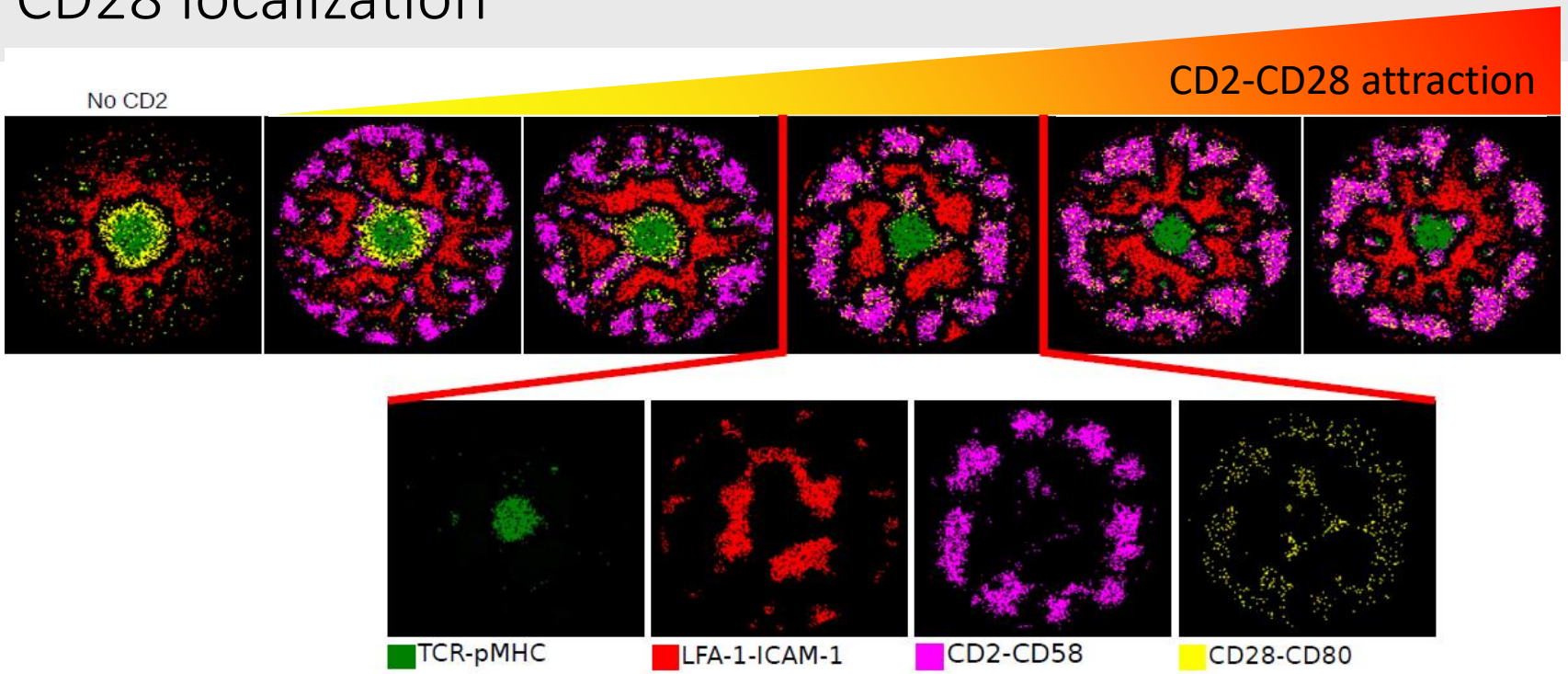

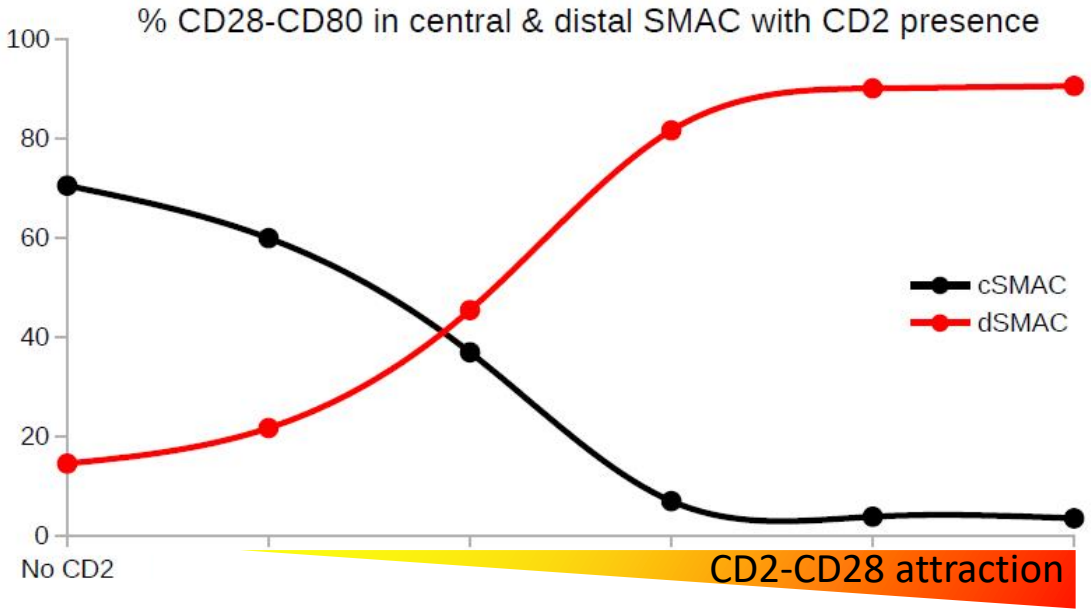

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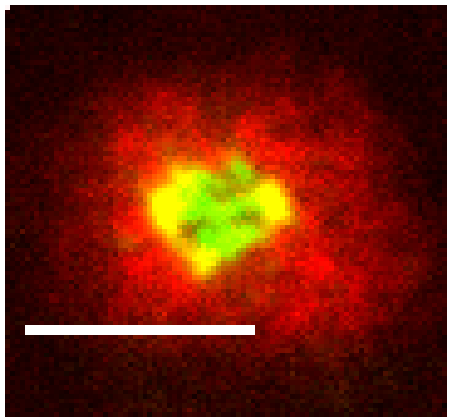

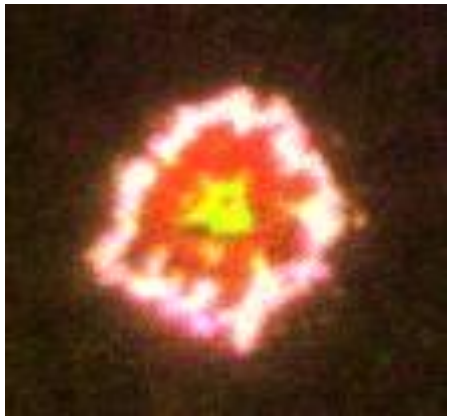

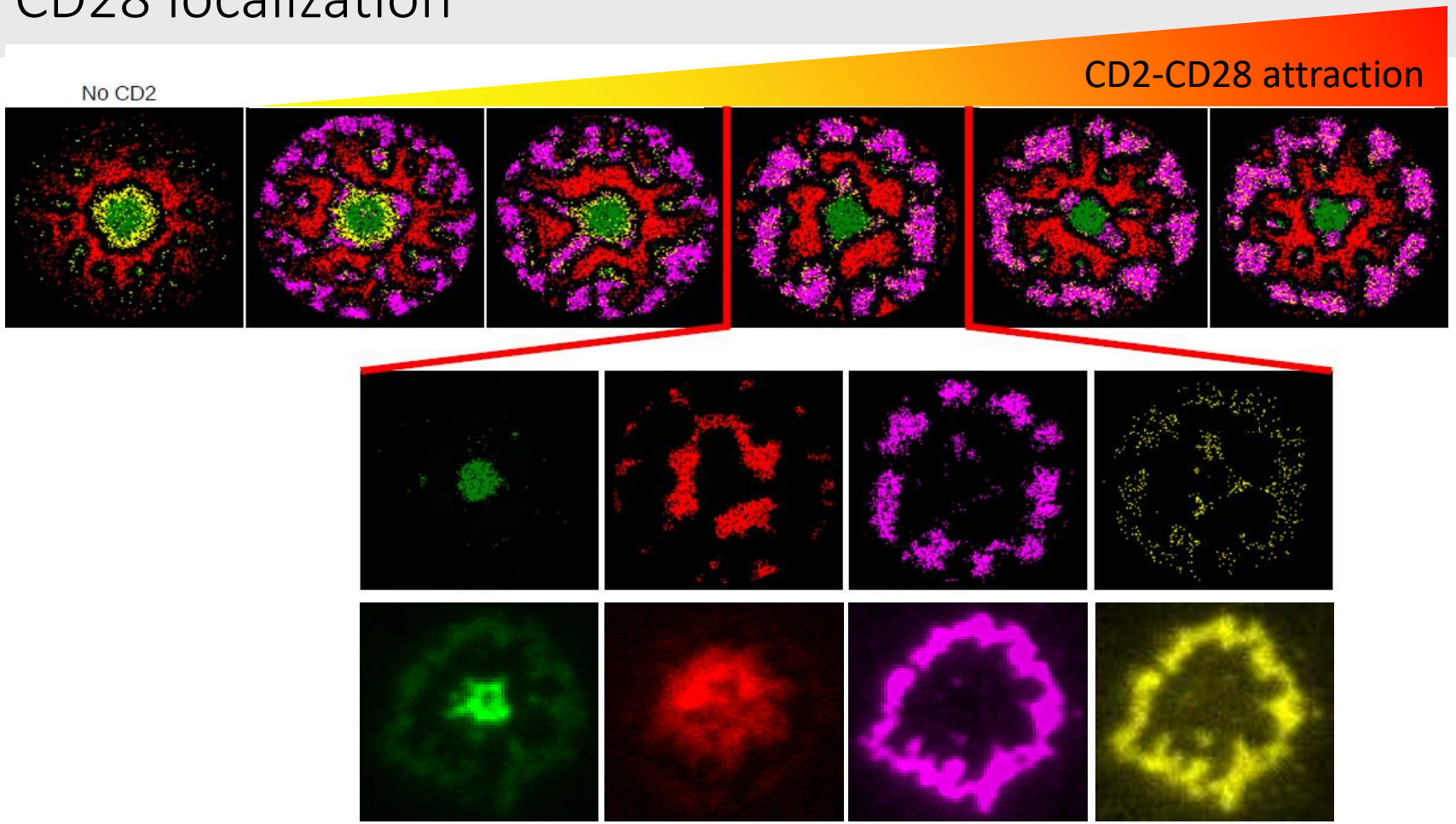

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CD2-CD58 localization in the synapse

TCR-pMHC

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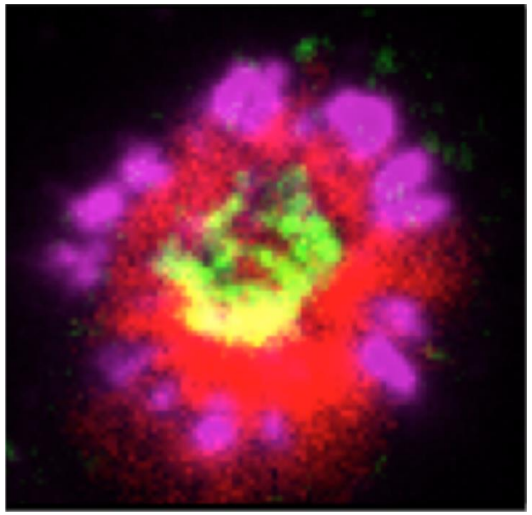

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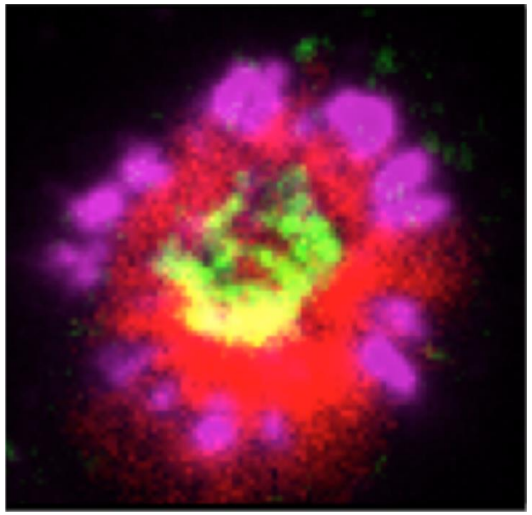

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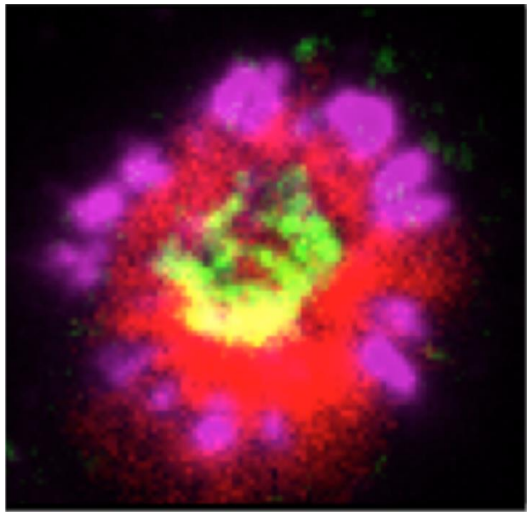

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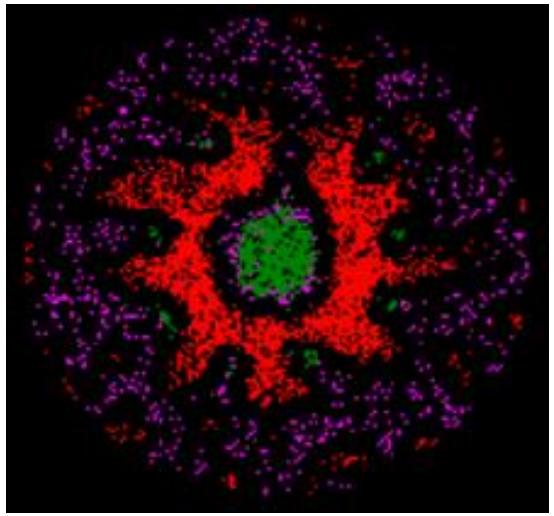

CD2 Passive followers

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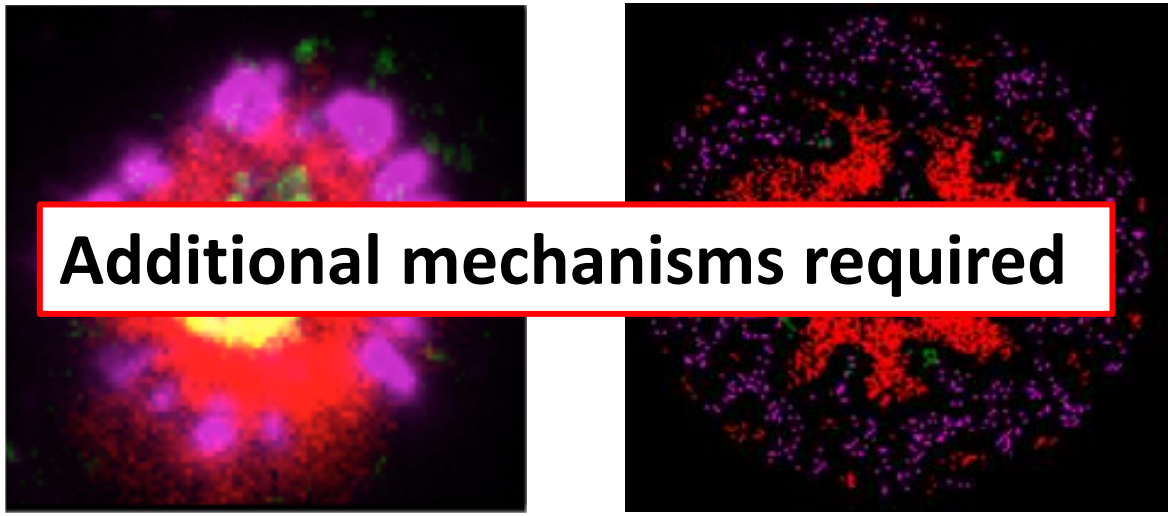

Additional mechanisms required

CD2 Passive followers

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Presence of CD45 can induce CD2 corolla pattern formation

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→ CD45-CD2 repulsion
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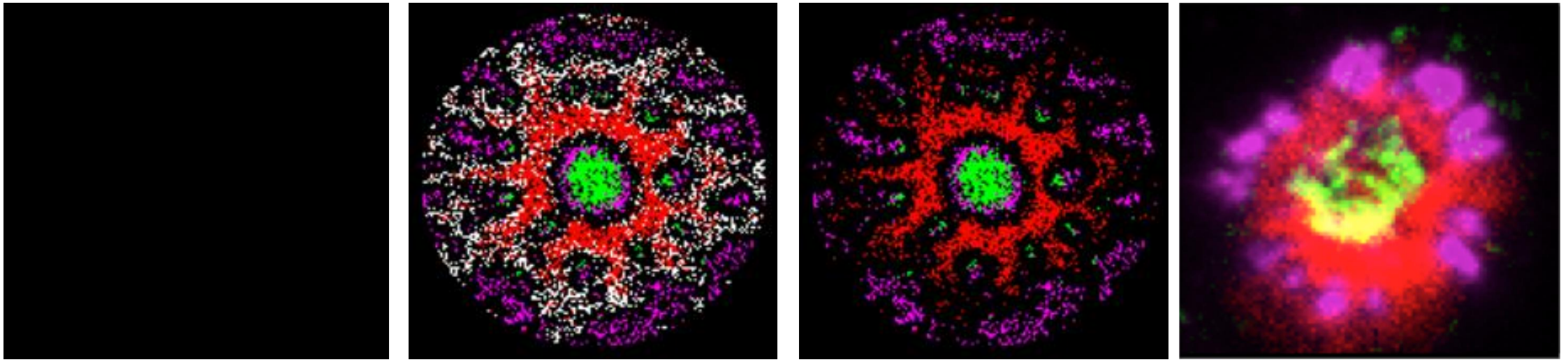


Siokis | bioRxiv | 2020 | https://doi.org/10.1101/2020.01.16.908723

CD45 not shown

Demetriou | Nat Immunol | 2020 | https://www.nature.com/articles/s41590-020-0770-x

Presence of CD45 or any other molecule that interacts with CD2 in the dSMAC can induce corolla formation

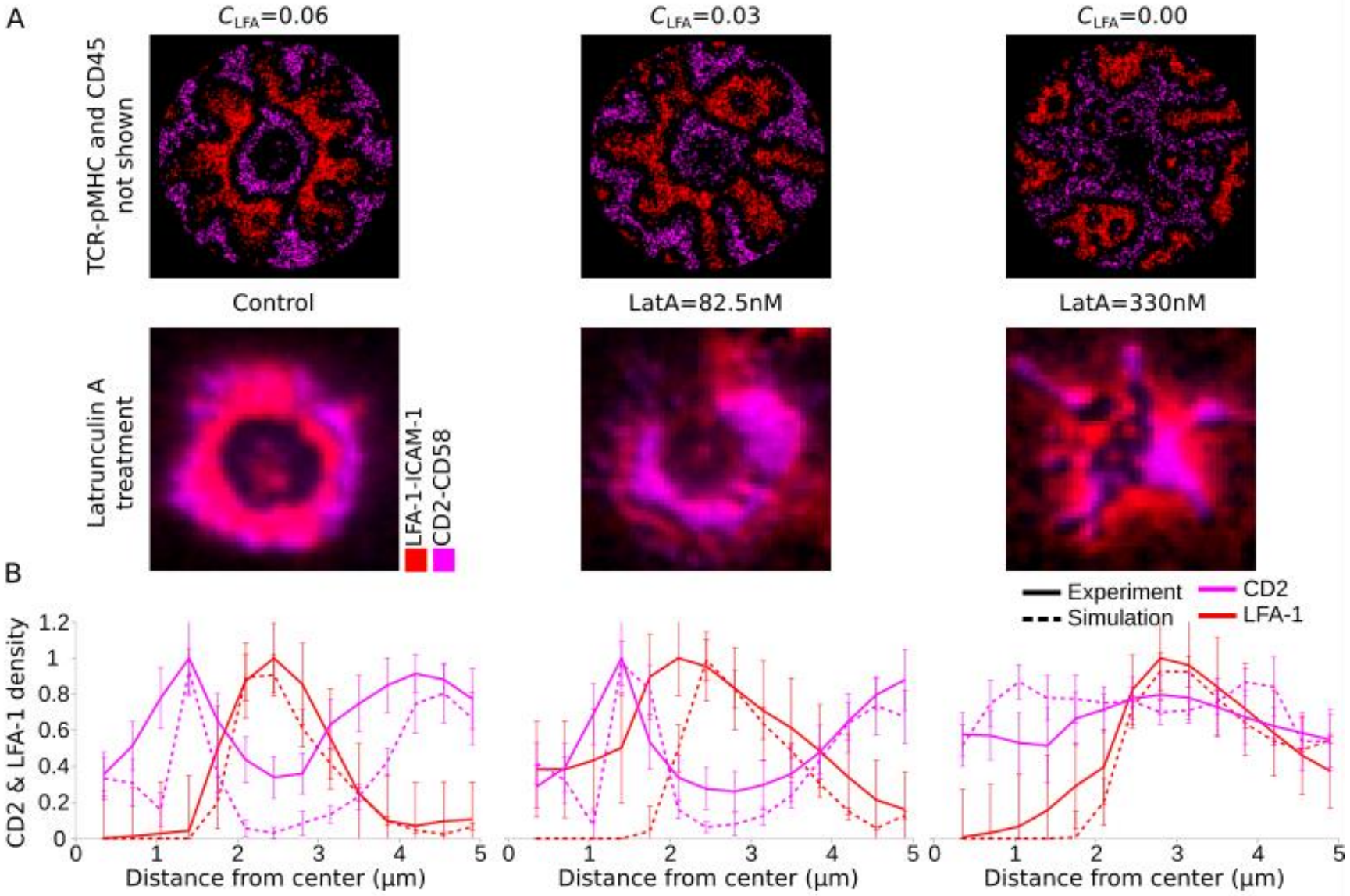
TCR-pMHC

LFA-1-ICAM-1

CD2-CD58

CD45

Lantraculin A treatment disrupts the corolla pattern



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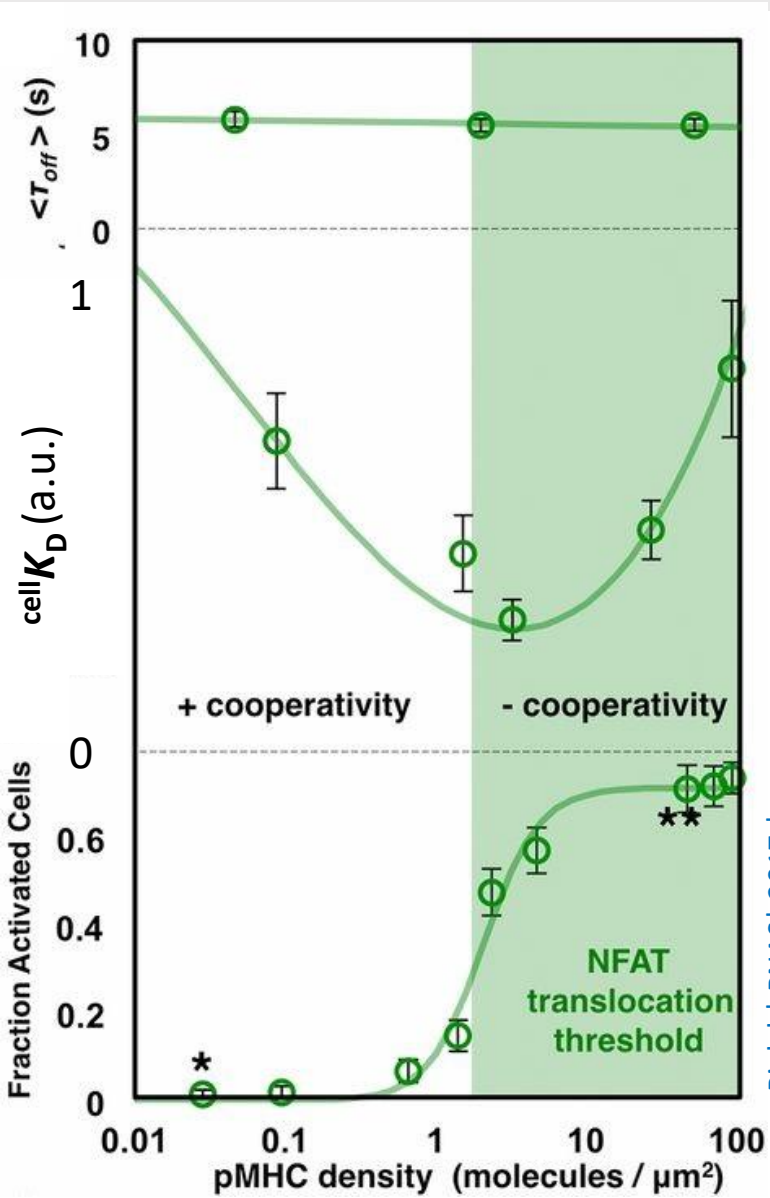
T cell receptor cooperativity



Pielak| PNAS| 2017 | 10.1073/pnas.1613140114

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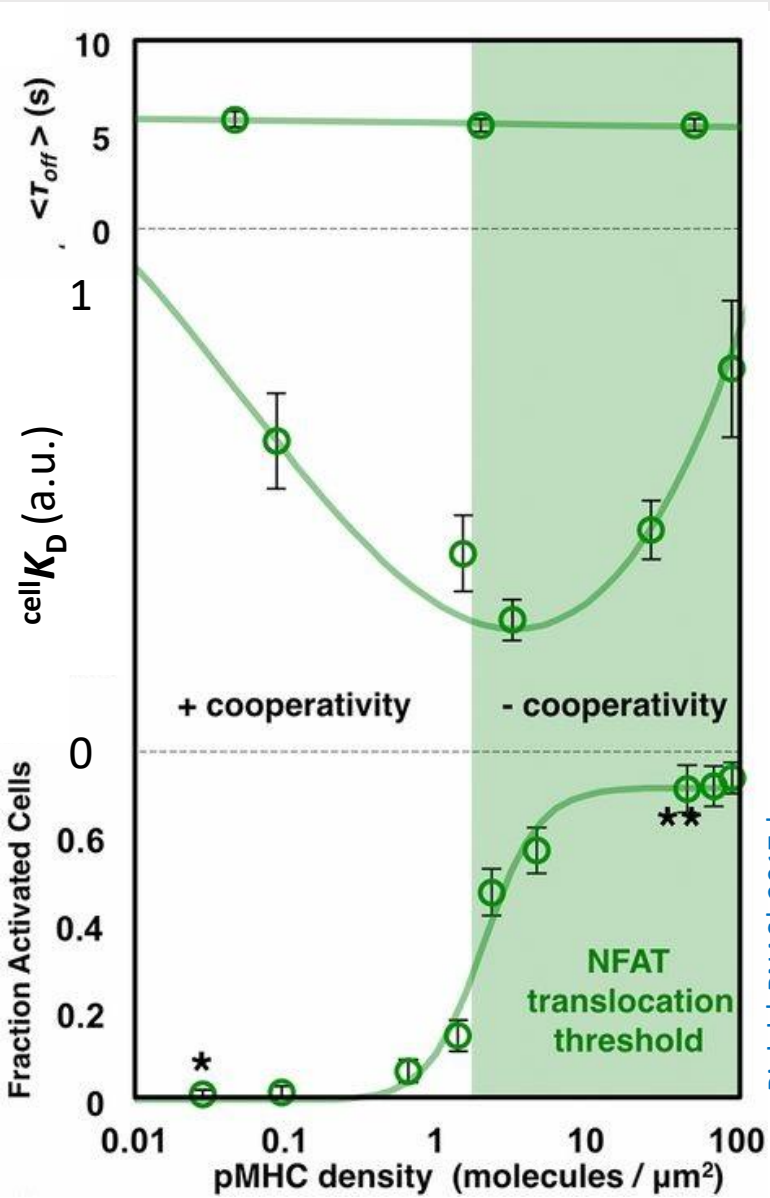

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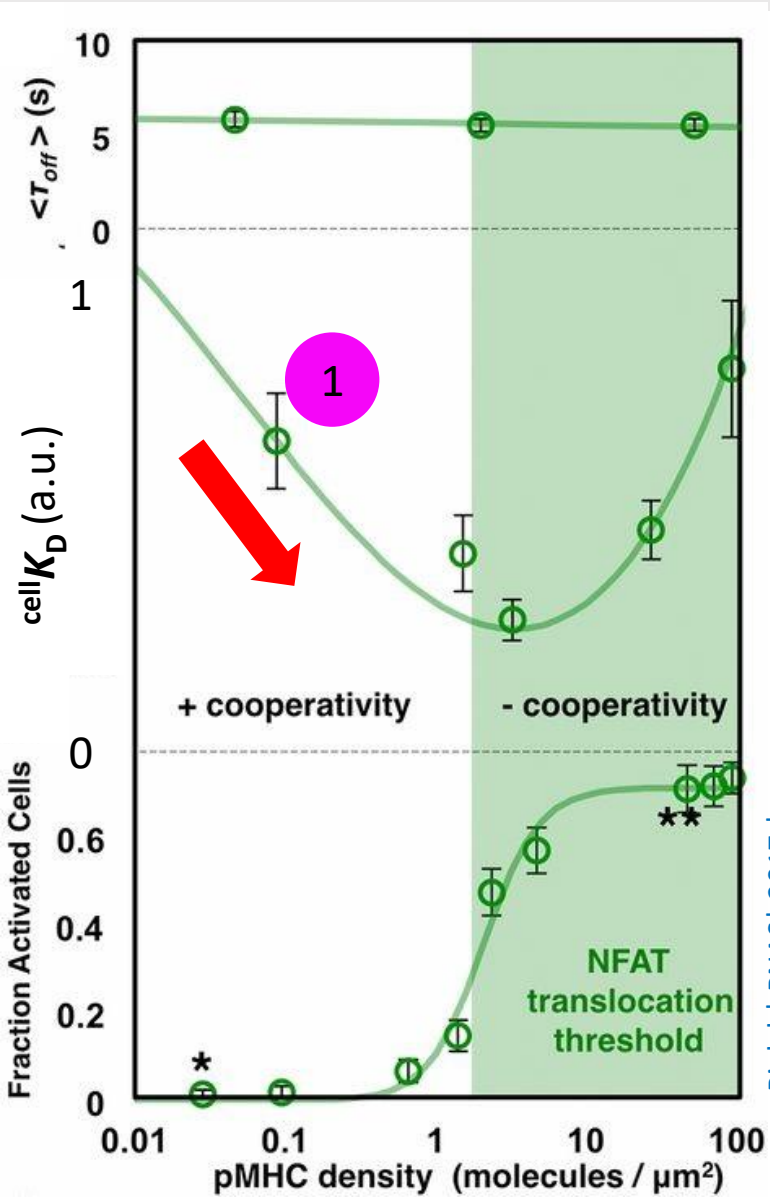

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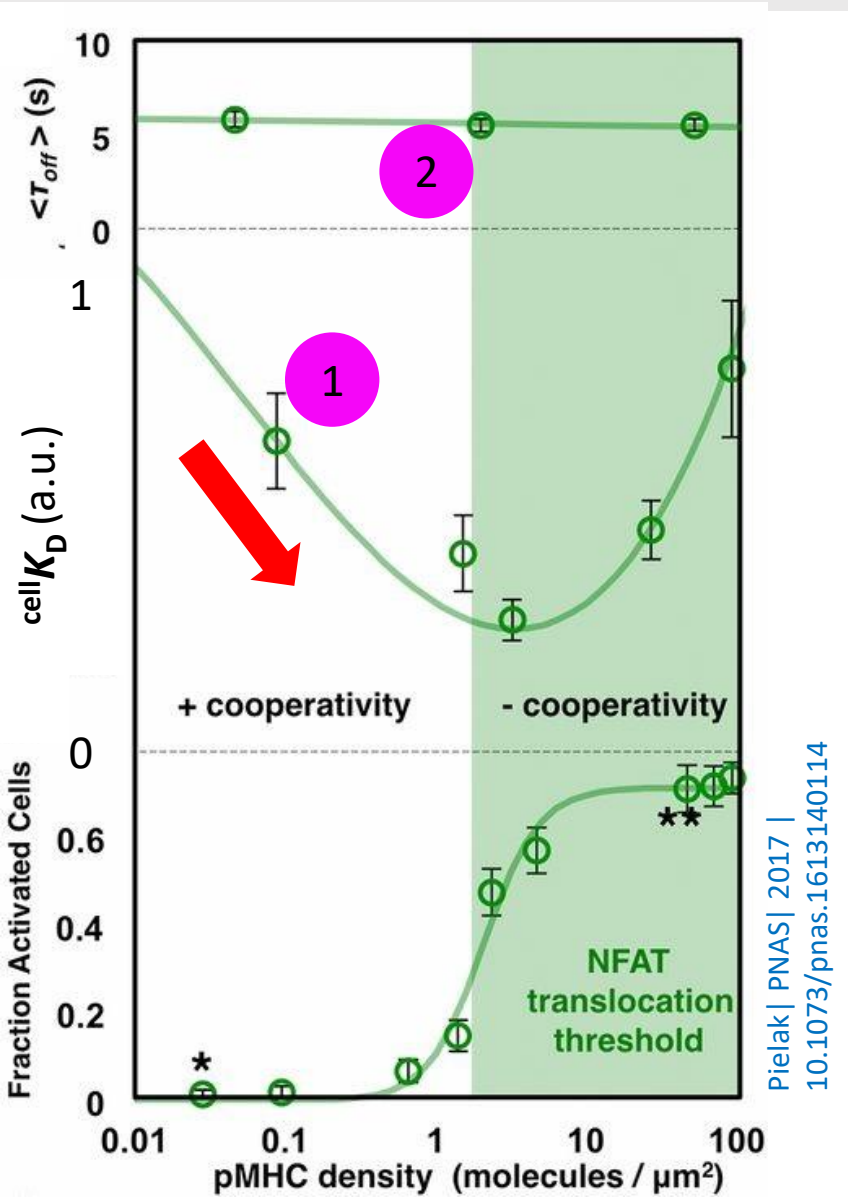

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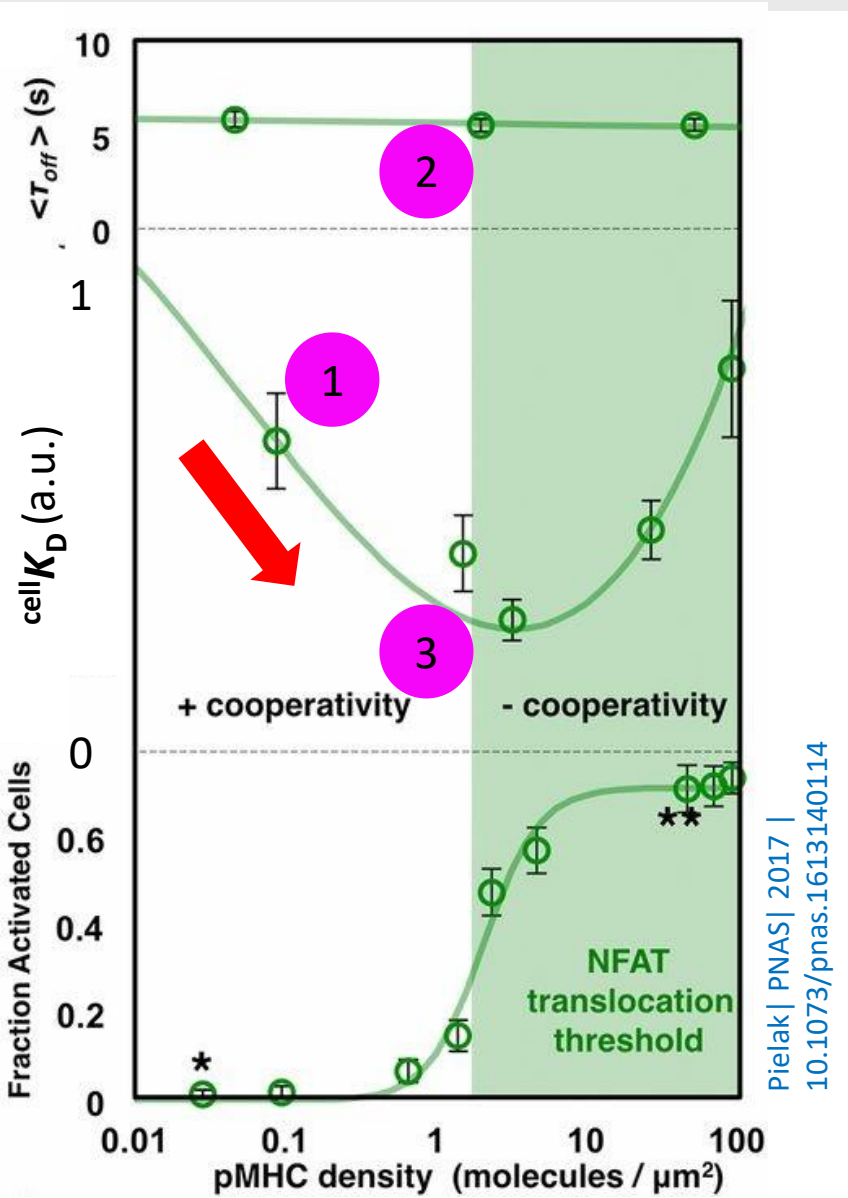

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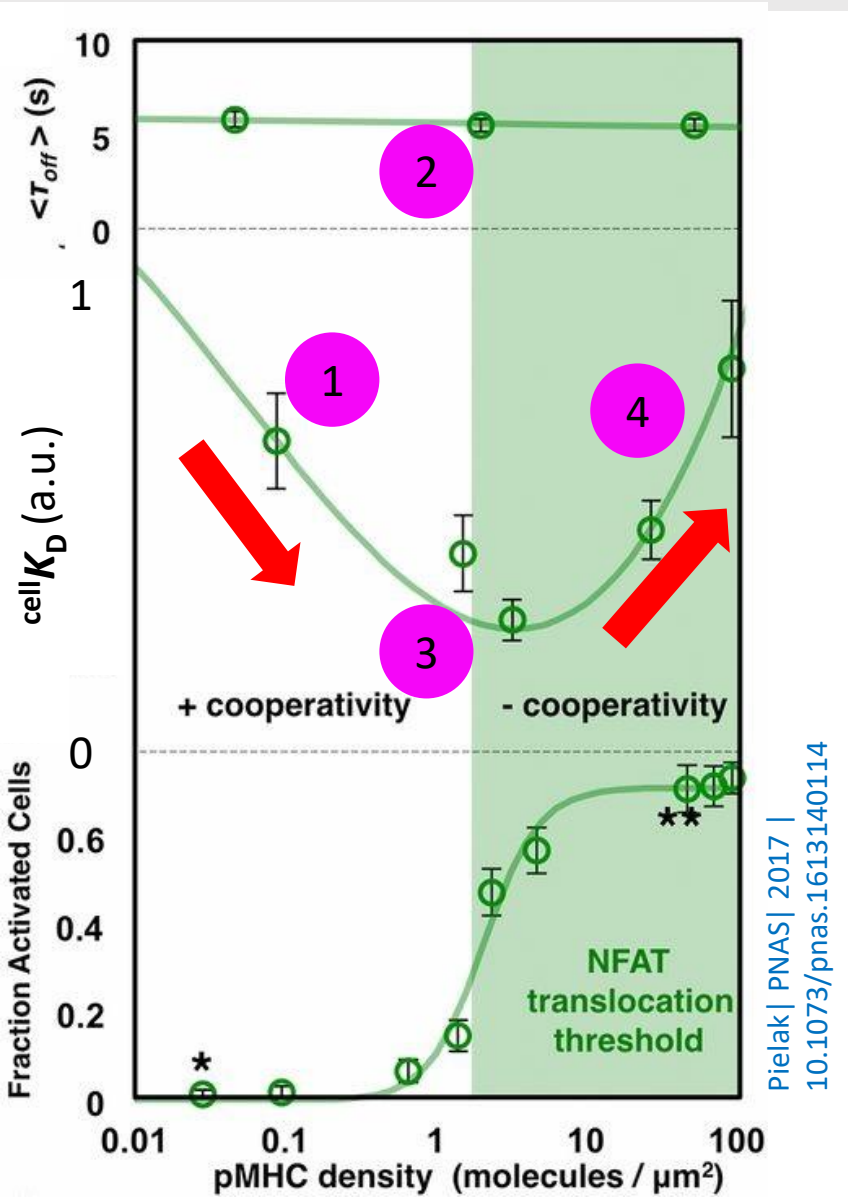

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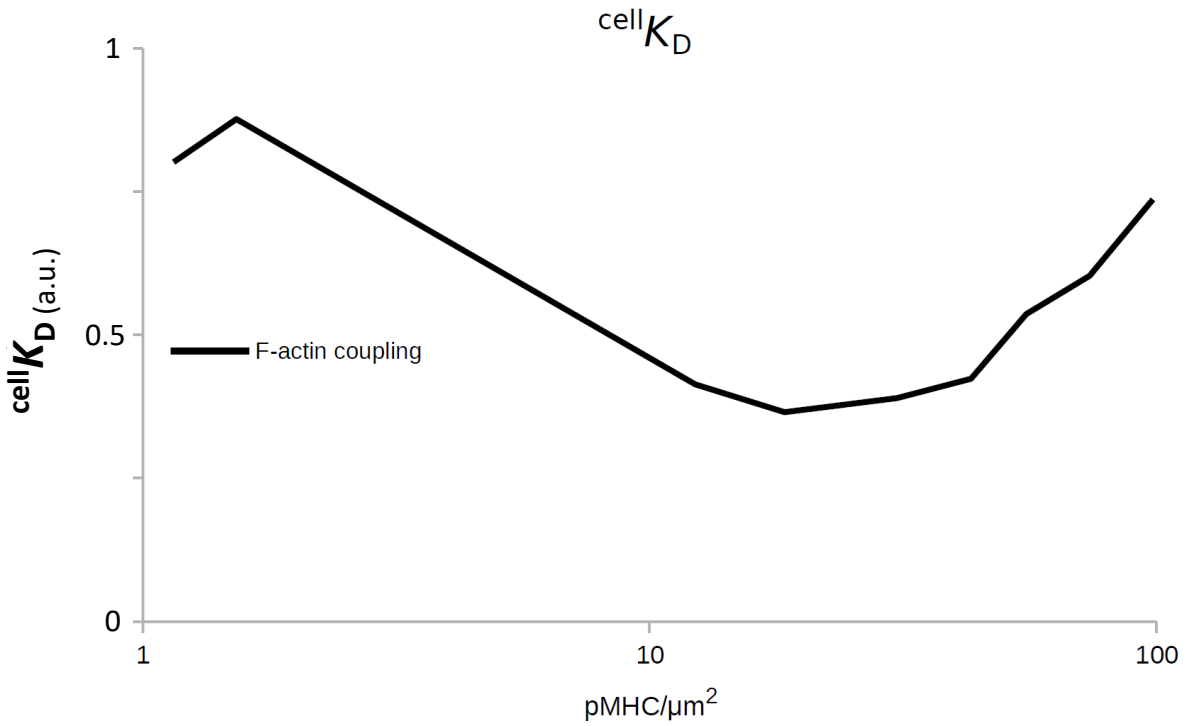

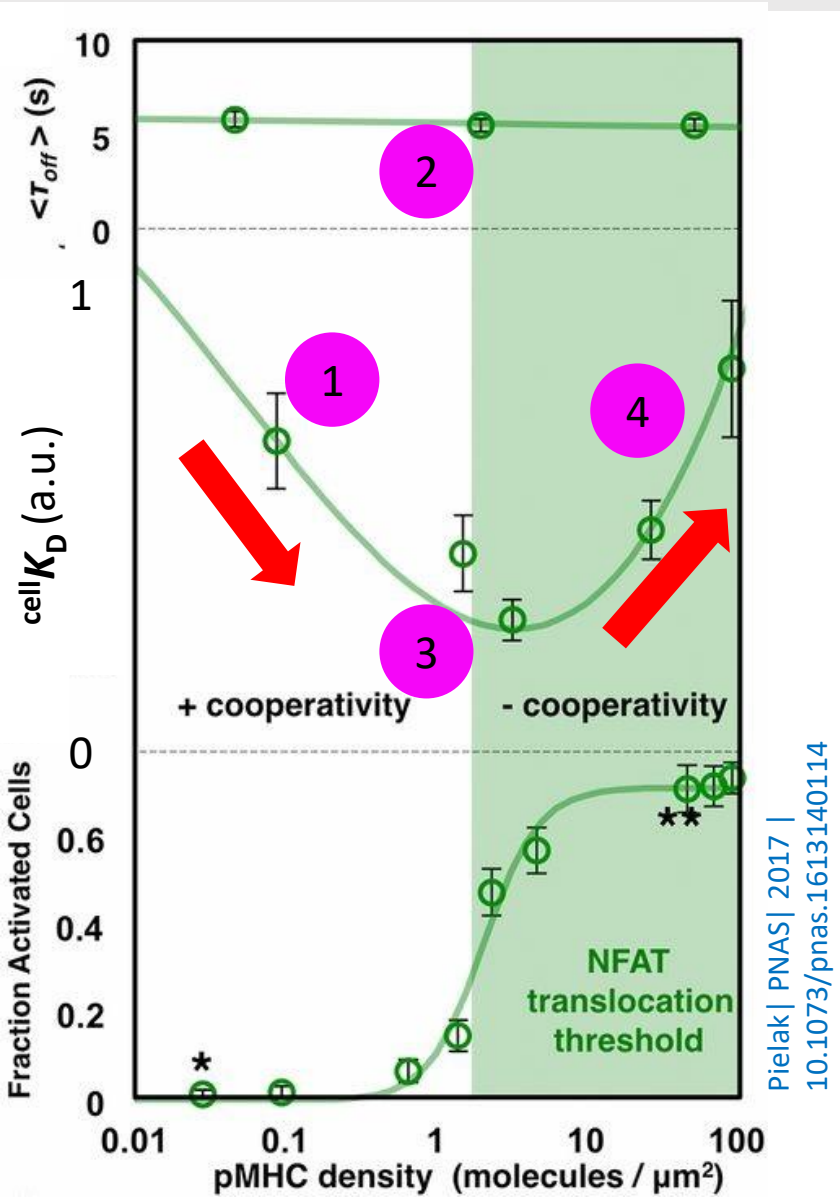

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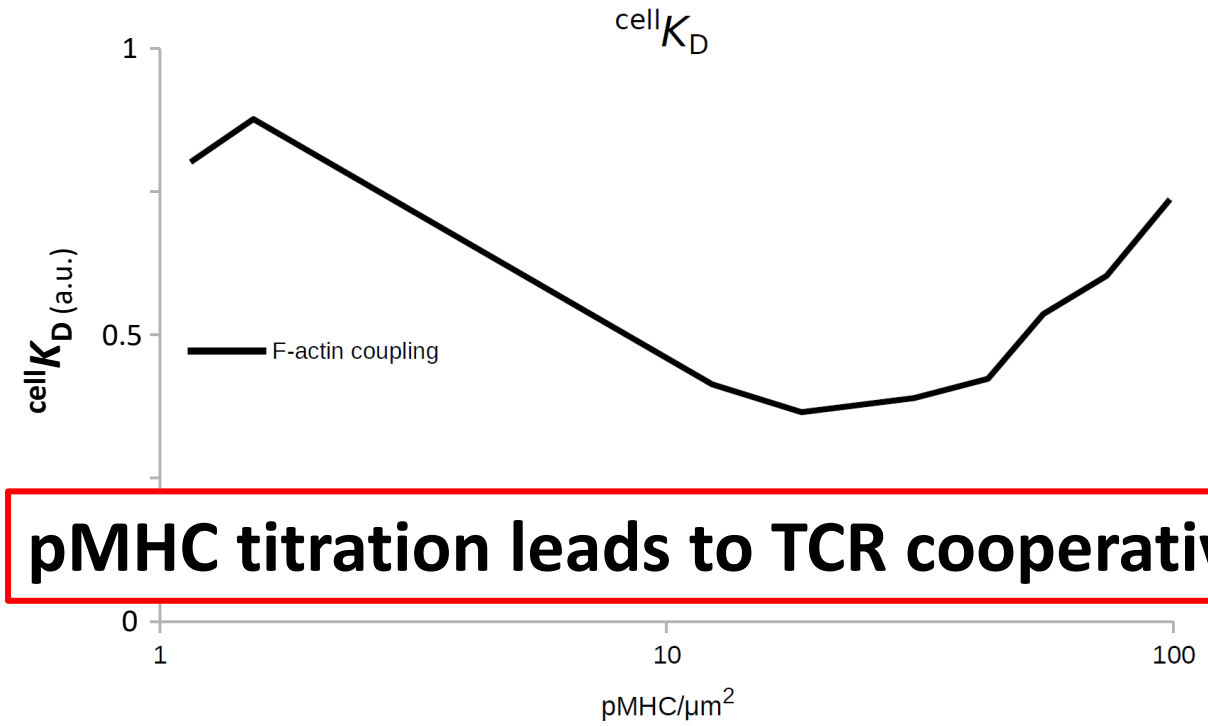

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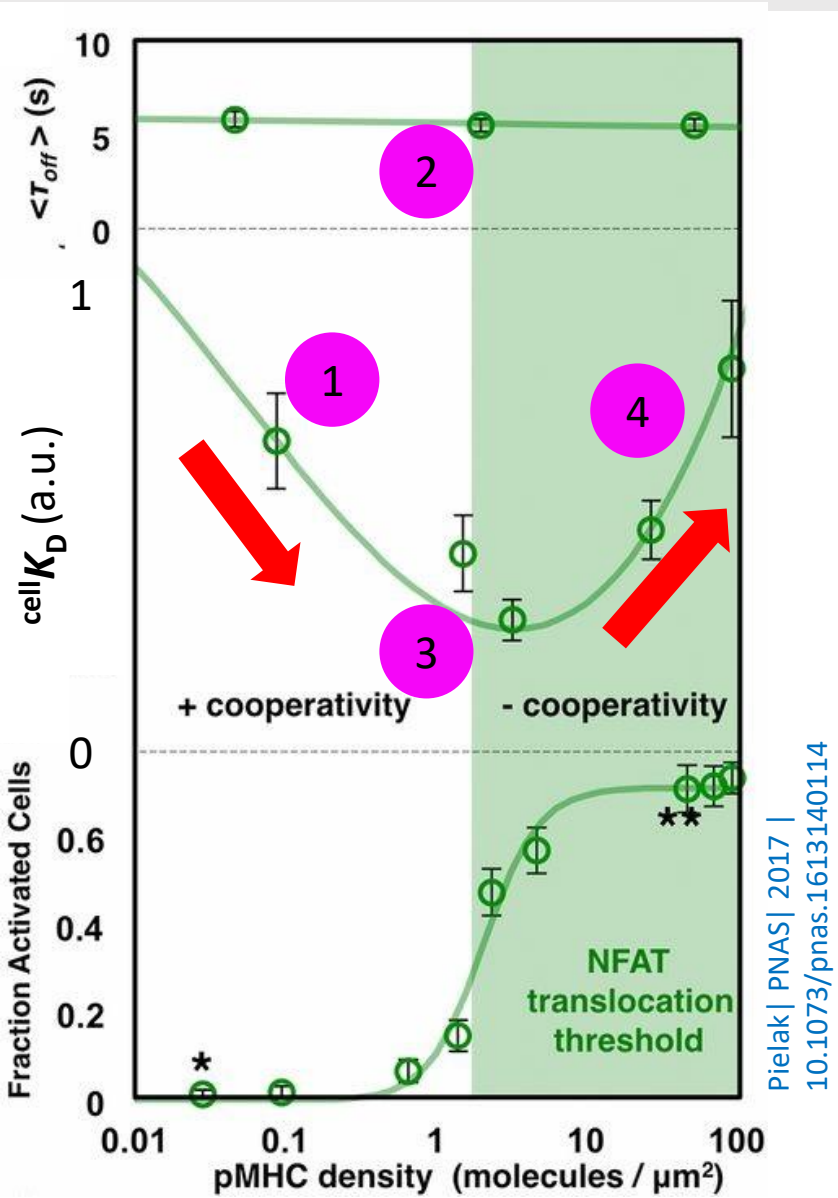

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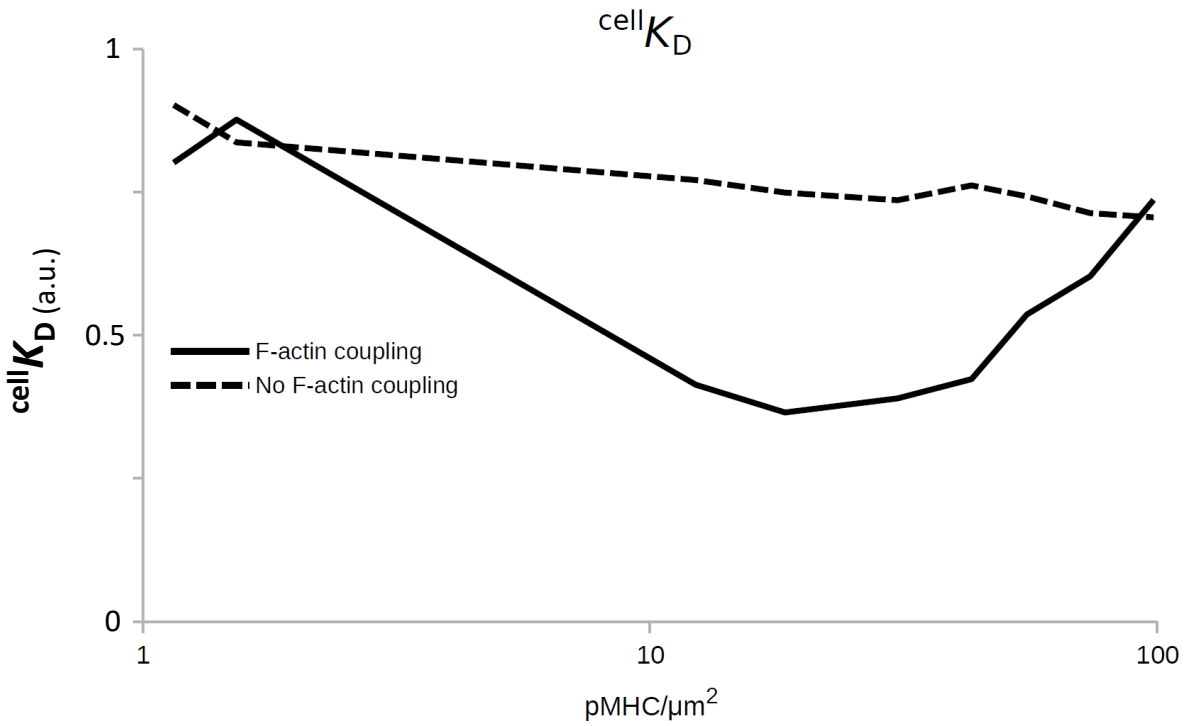

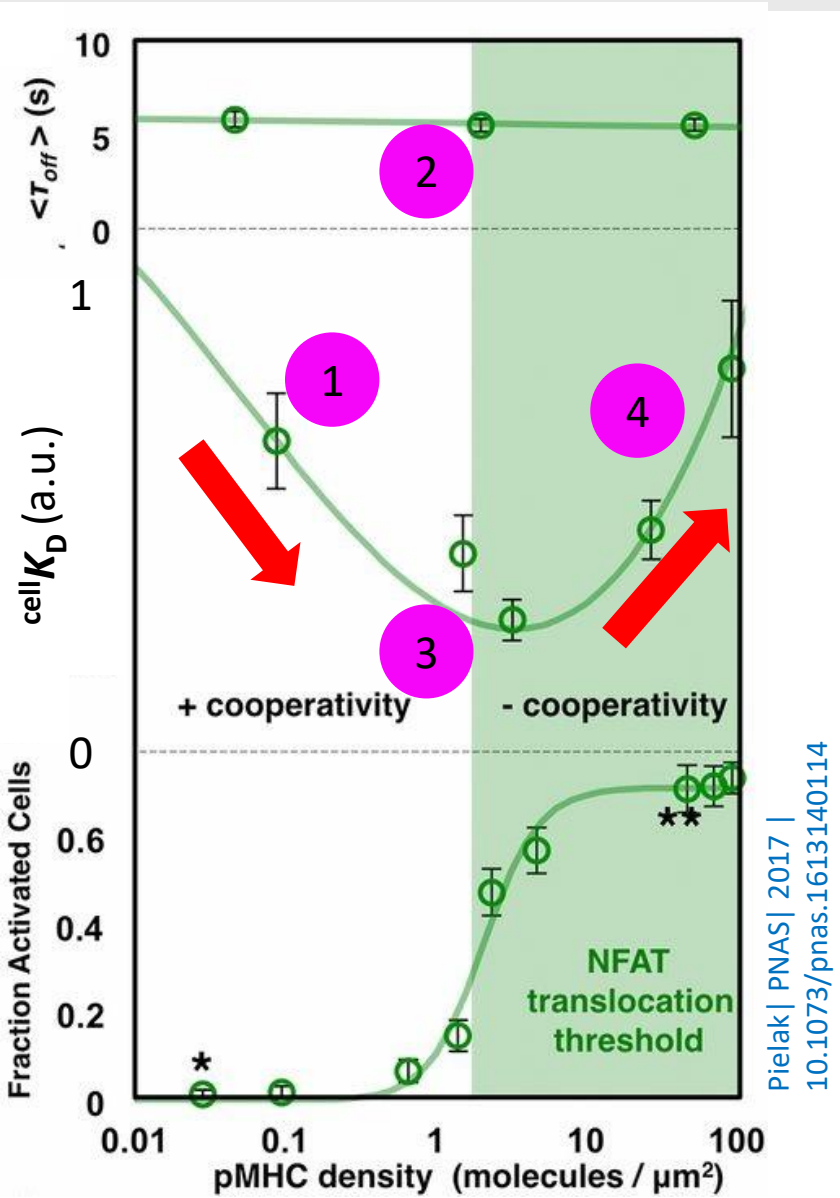

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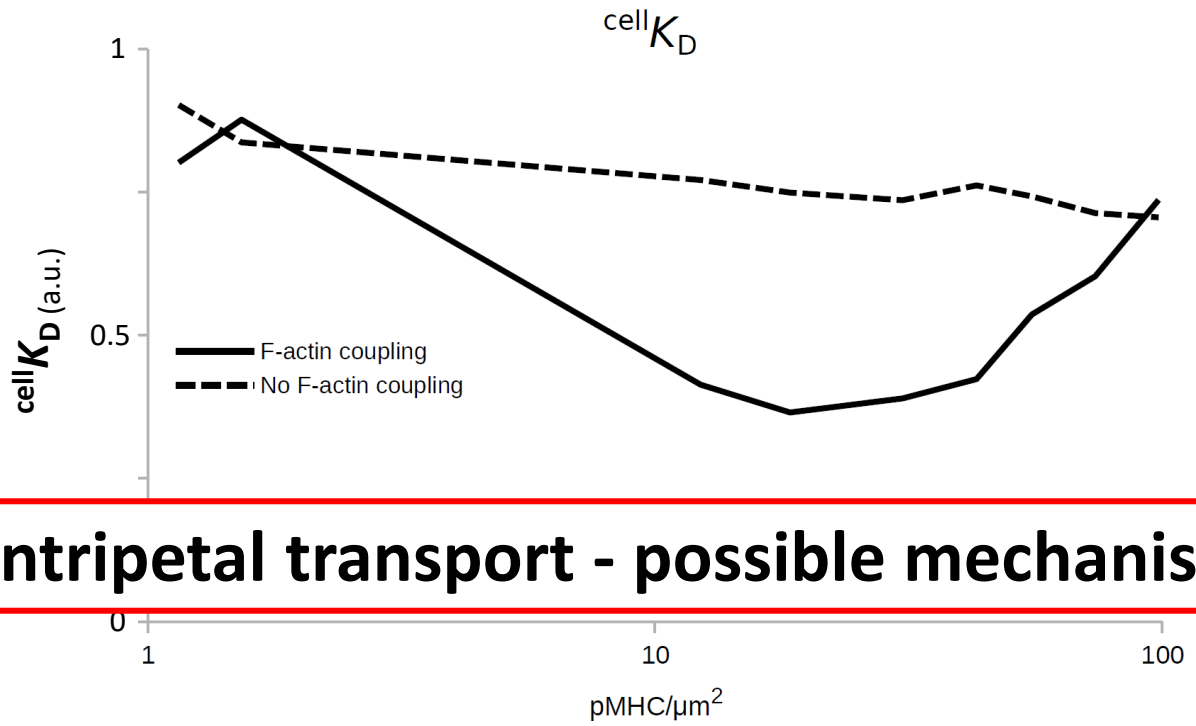

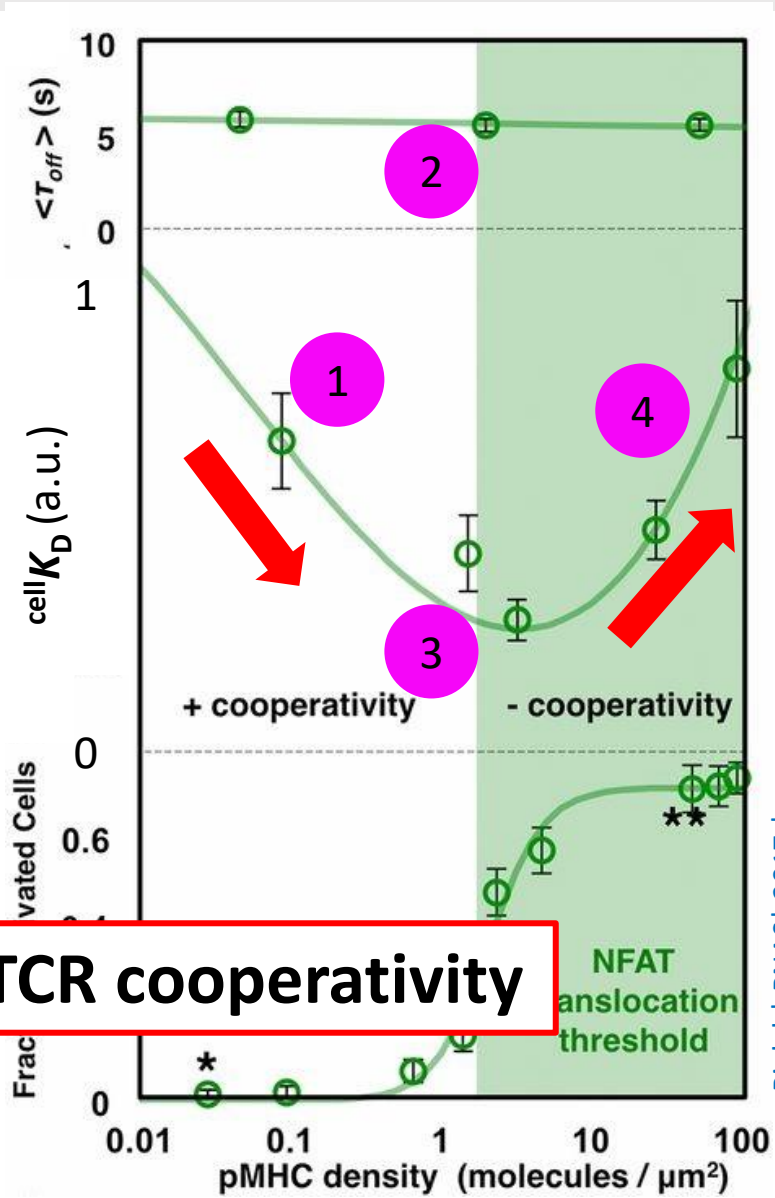

Centripetal transport - possible mechanism of TCR cooperativity

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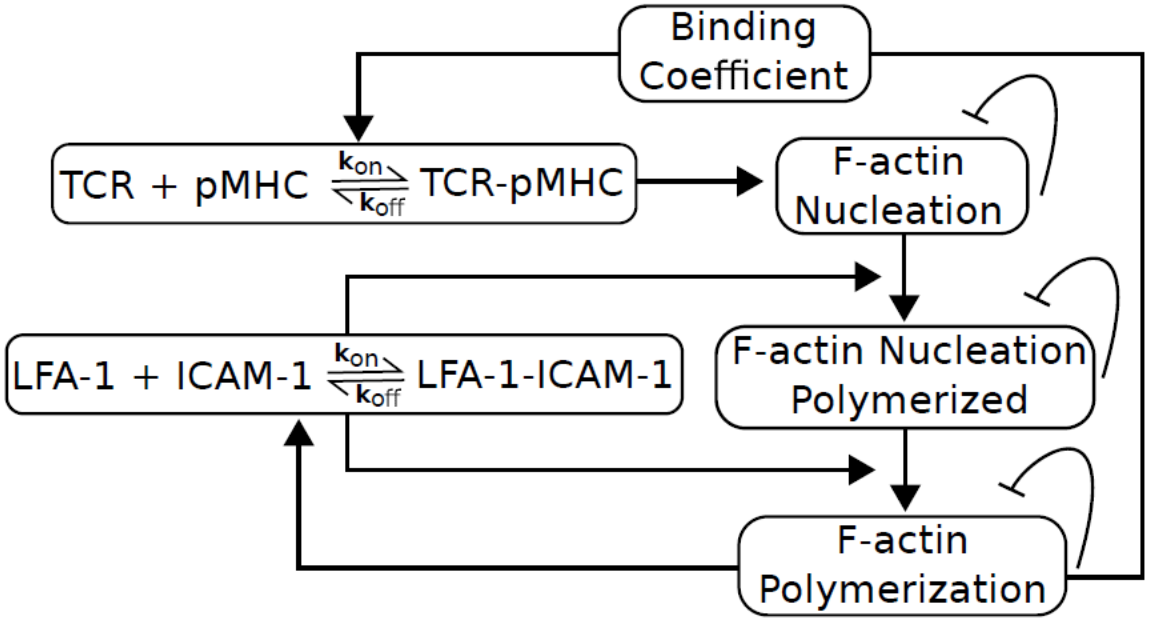
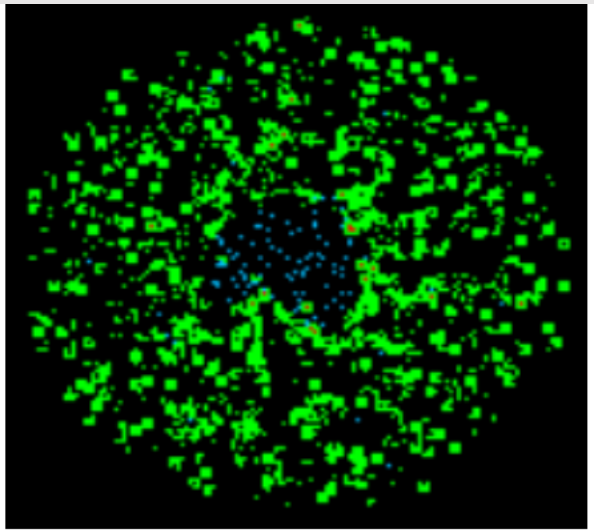
F-actin foci - active modulation of k_{on}





Nucleation points
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Polymerization points

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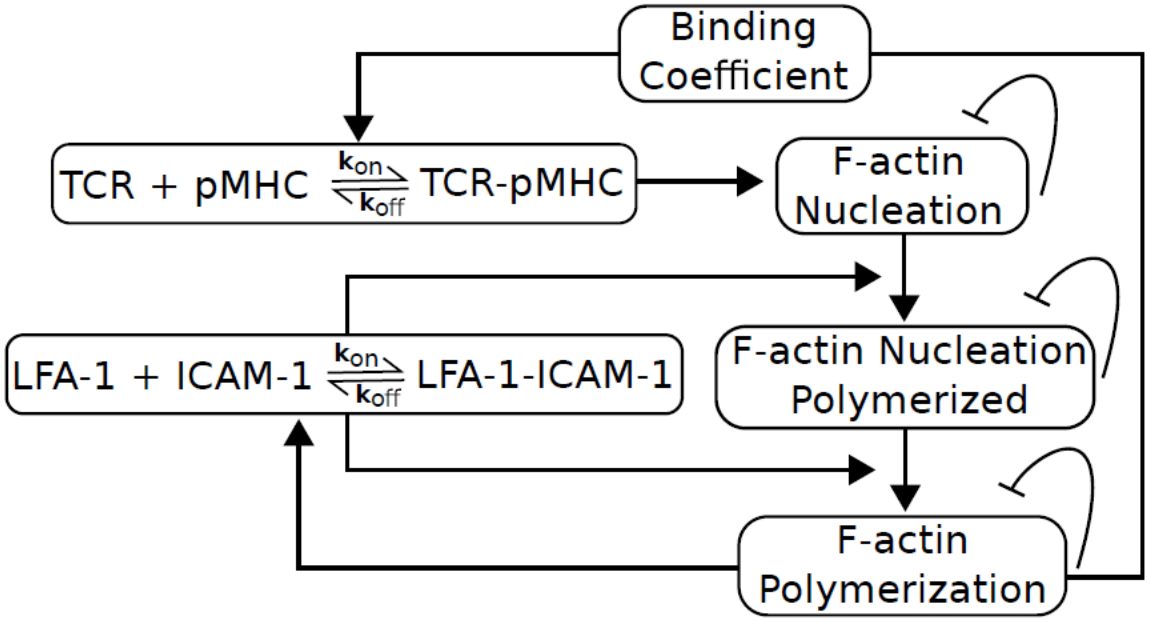

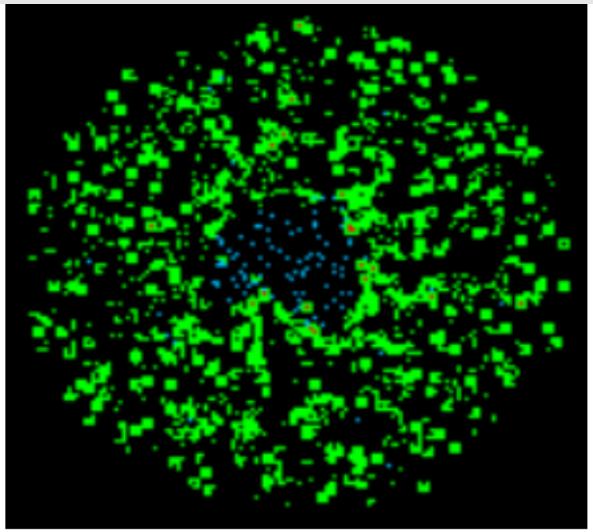

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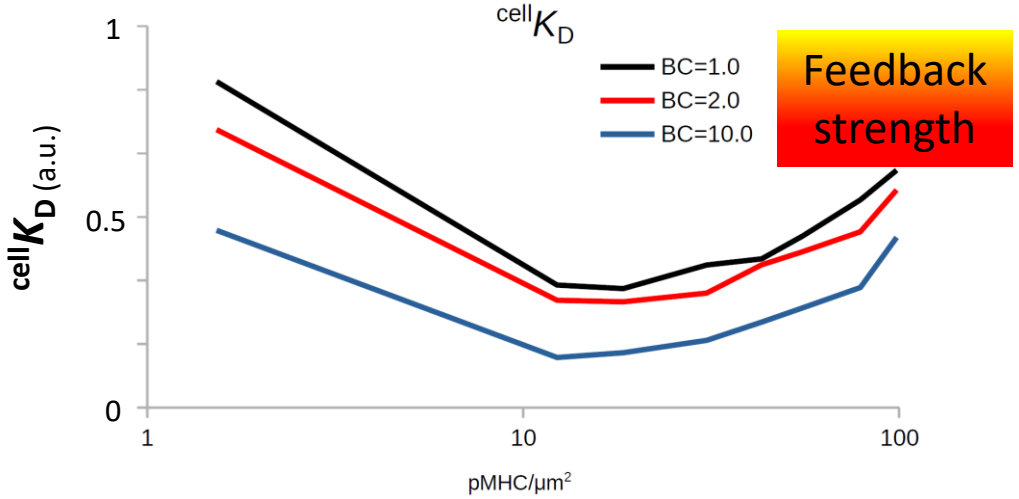

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synapse formation is the cornerstone of adaptive immunity and therefore, understanding the mechanisms leading to different characteristic patterns is pivotal

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