

# Johns Hopkins Engineering

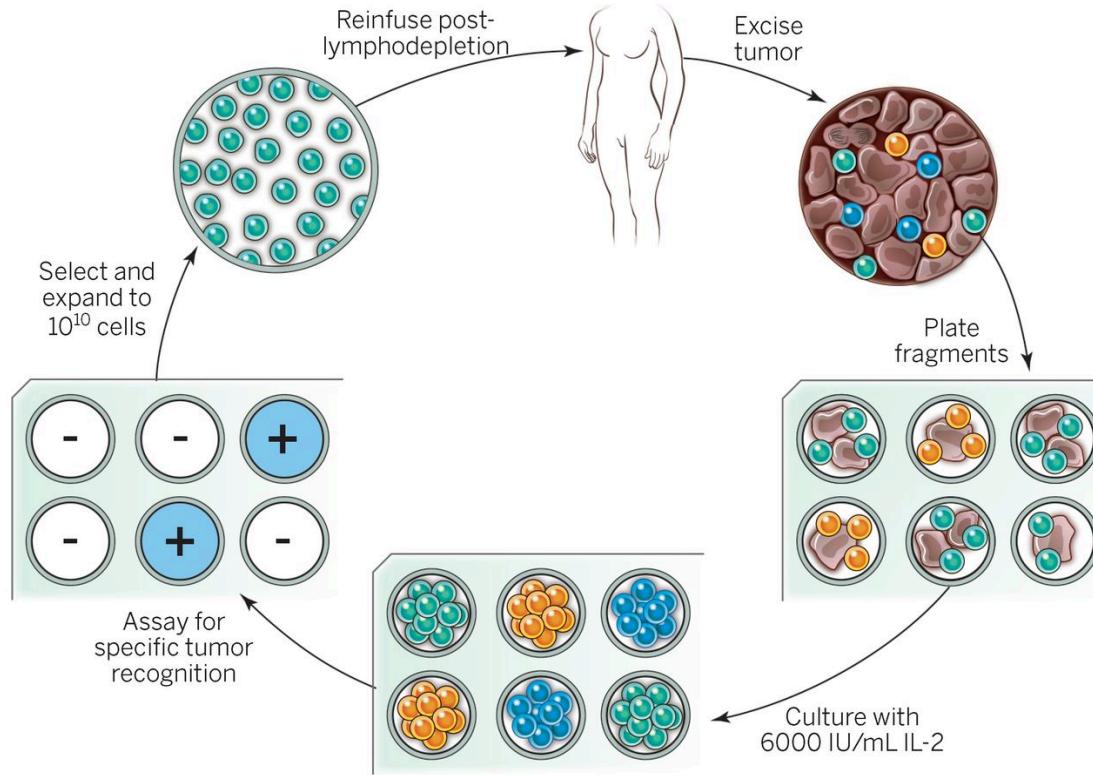
## Immunoengineering

### Immunoengineering Cancer: T Cell Therapies

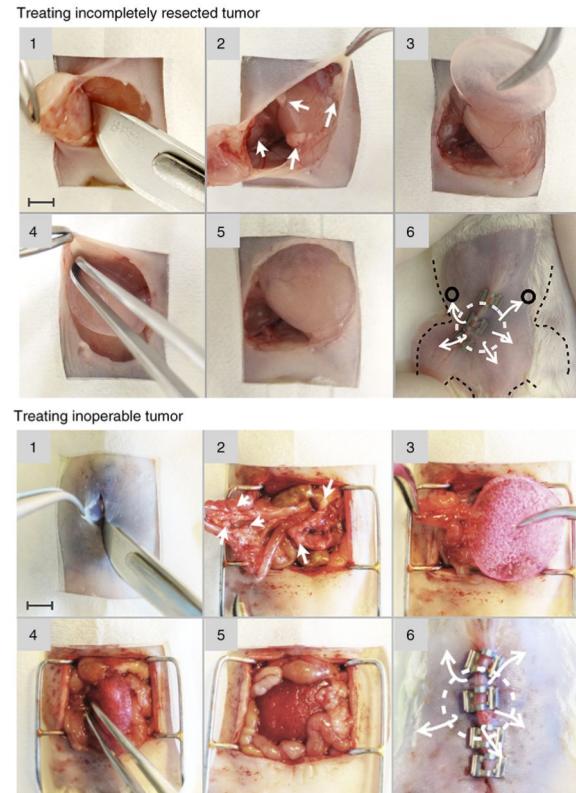
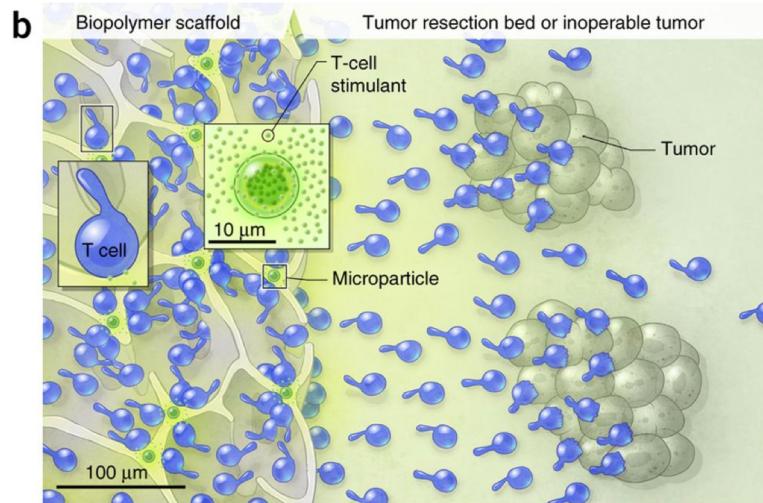


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# Adoptive T Cell Transfer

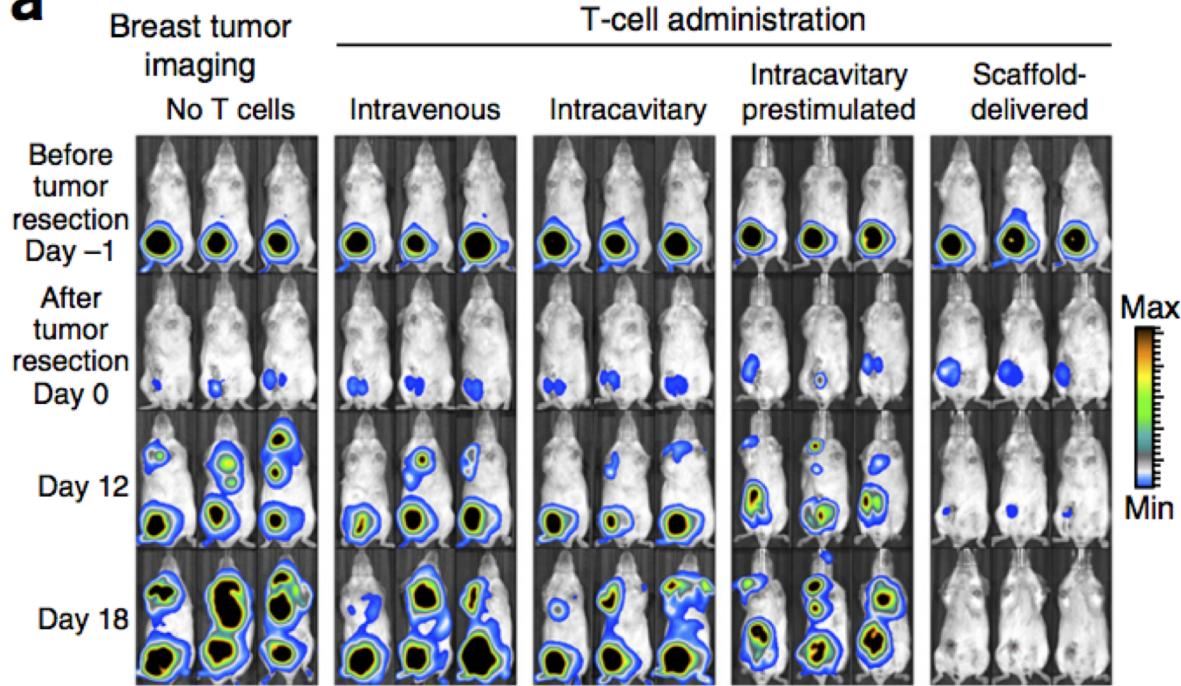


# Enhancing Adoptive Therapy: Scaffolds



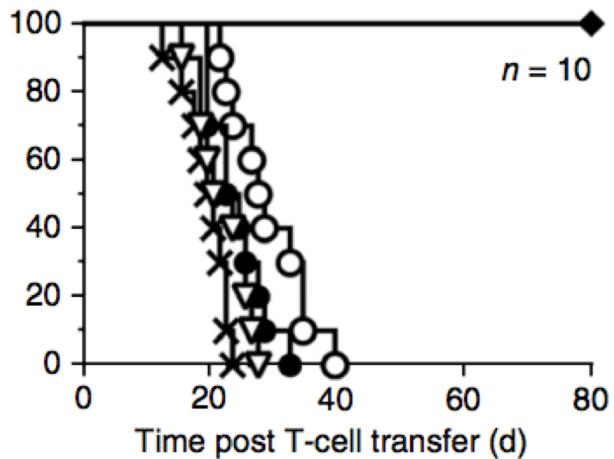
# Enhancing Adoptive Therapy: Scaffolds

a

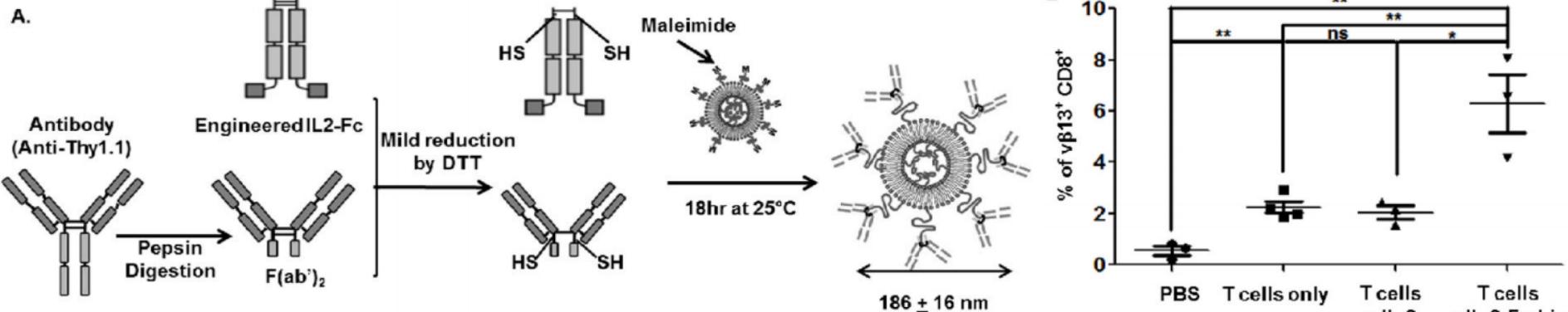


b

- No T cells (ms = 19 d)
  - Intravenous (ms = 21 d)
  - Intracavitary (ms = 25 d)
  - Intracavitory, prestimulated (ms = 30 d)
  - Scaffold-delivered
- $P = 0.21$
- $P = 0.03^*$
- $P = 0.048^*$
- $P < 0.0001^*$

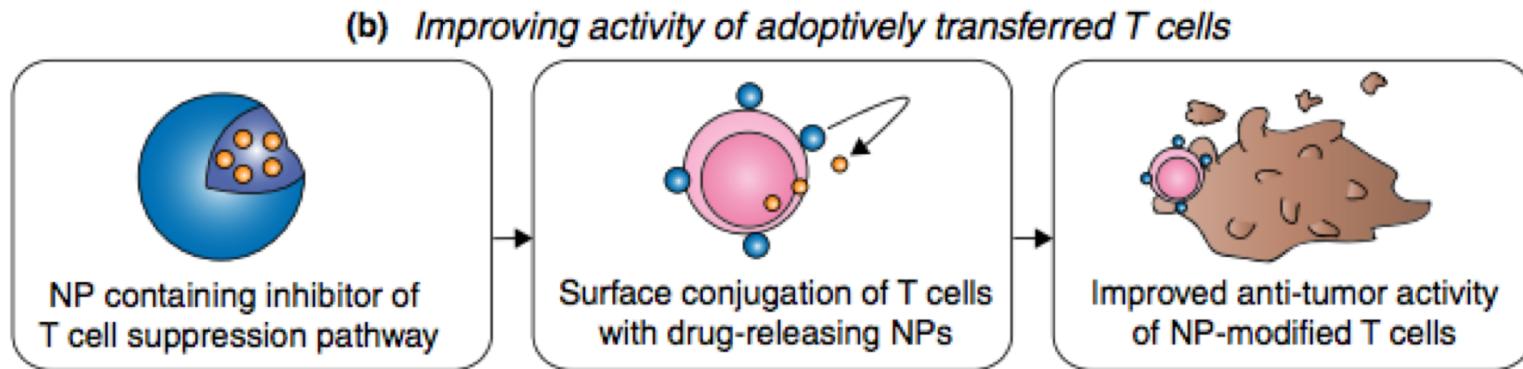


# Enhancing Adoptive Therapy: T-cell targeted drug delivery



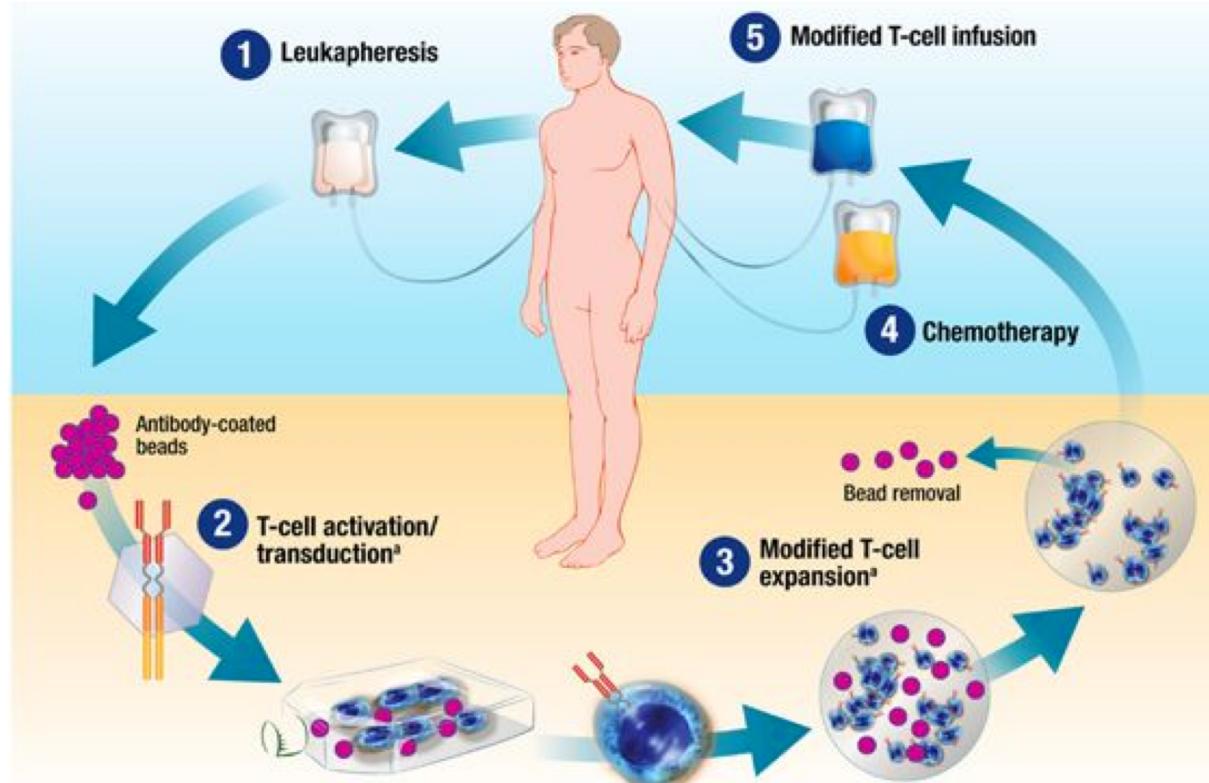
- Two targeting strategies
  - anti-Thy1.1: antibody against cell surface antigen expressed only on adoptively transferred T cells → highly specific targeting but lower stimulation
  - Recombinant IL-2: binds IL-2 receptor expressed by activated T cells → less specific targeting but direct stimulatory signal

# Other Methods for Enhancing Adoptive Therapy



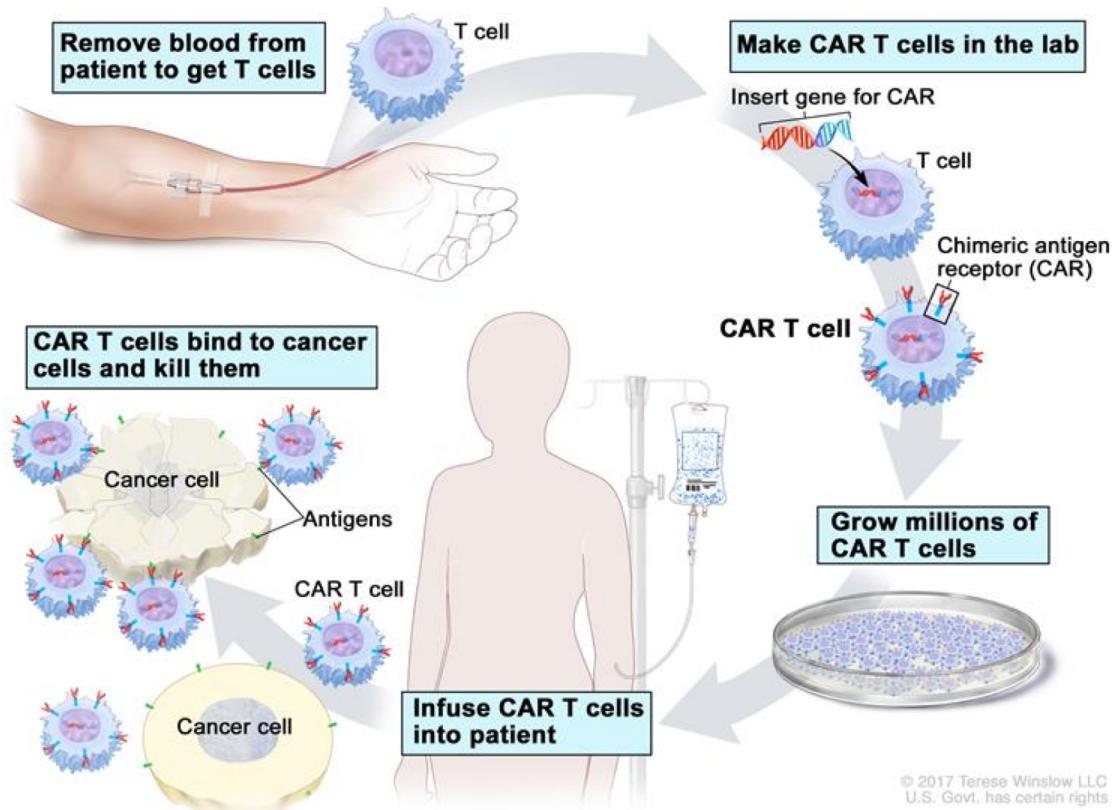
- Combination therapy with checkpoint blockade
- *Ex vivo* conjugation of T cells with NPs locally releasing immunomodulators
- Particles that release inhibitors of immunosuppressive pathways (e.g. TGF- $\beta$ )

# Ex vivo Modification of T Cells



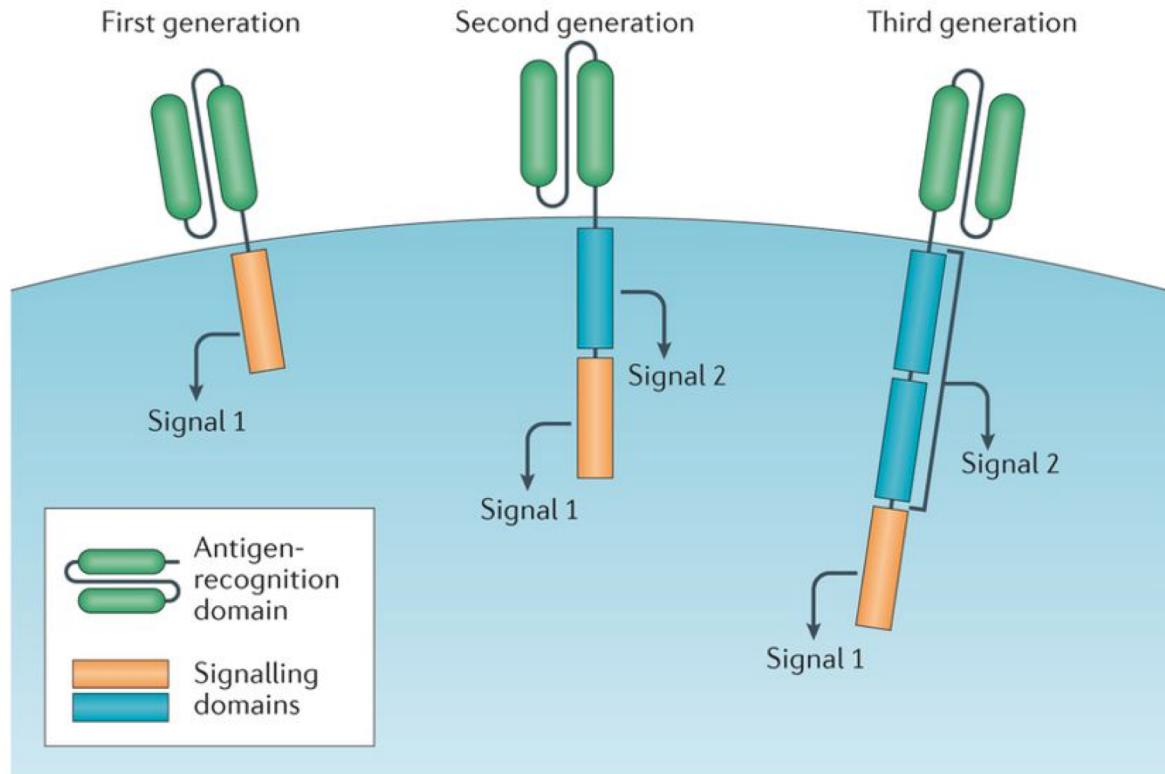
Levine. "Performance-enhancing drugs: design and production of redirected chimeric antigen receptor (CAR) T cells". *Cancer Gene Therapy*

# Chimeric Antigen Receptor (CAR) T Cell Therapy

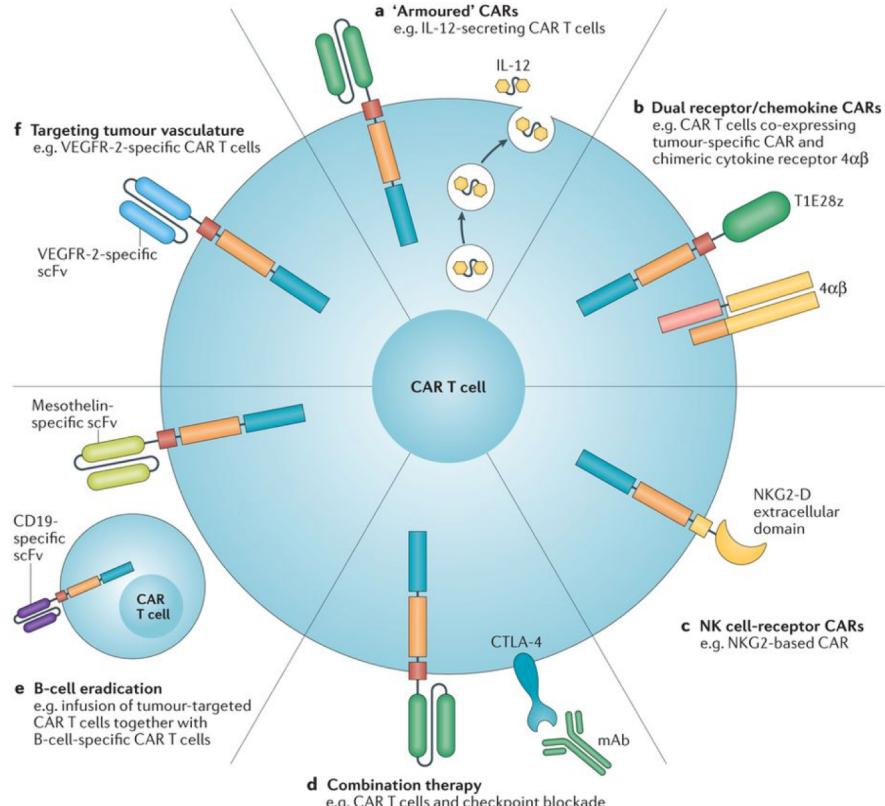


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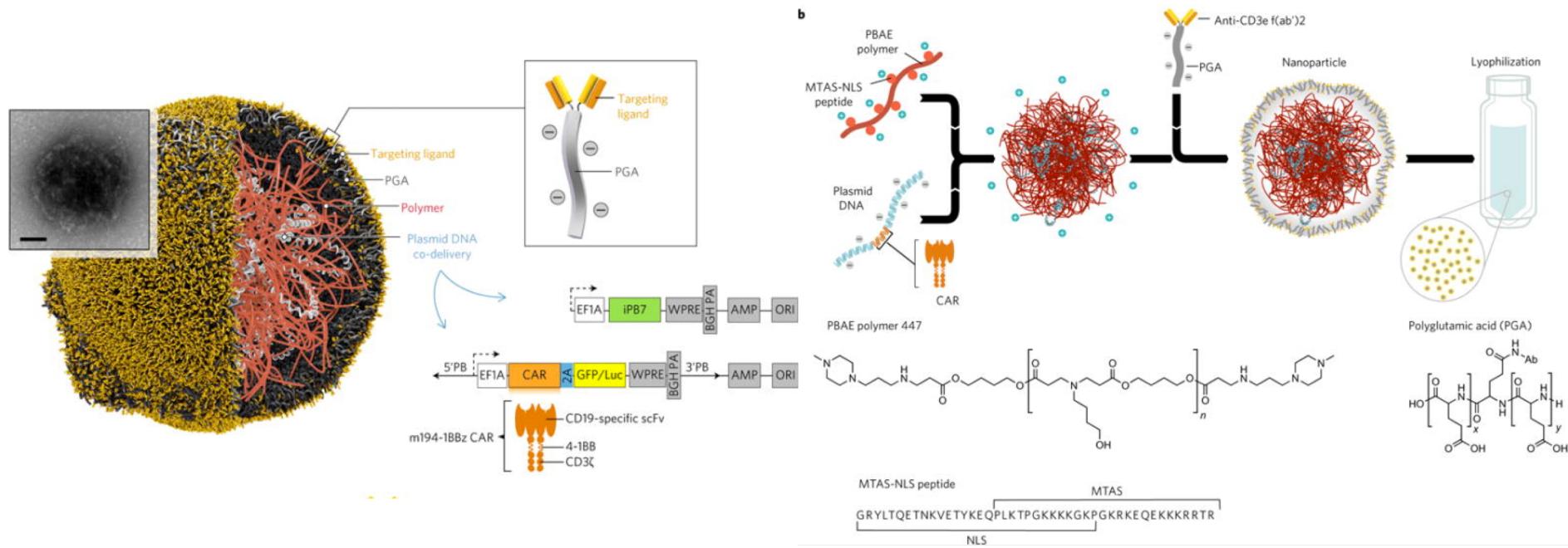
# CAR Constructs



# Improvements to CAR T Cell Therapy

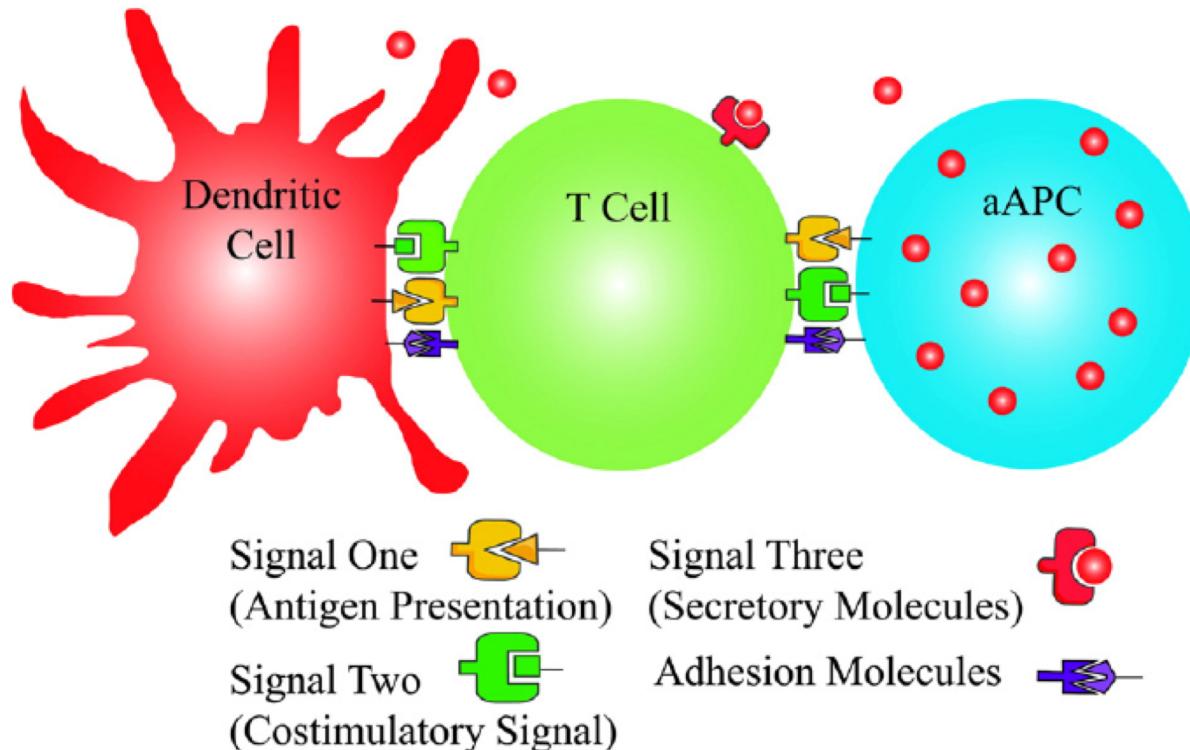


# In vivo T Cell Programming

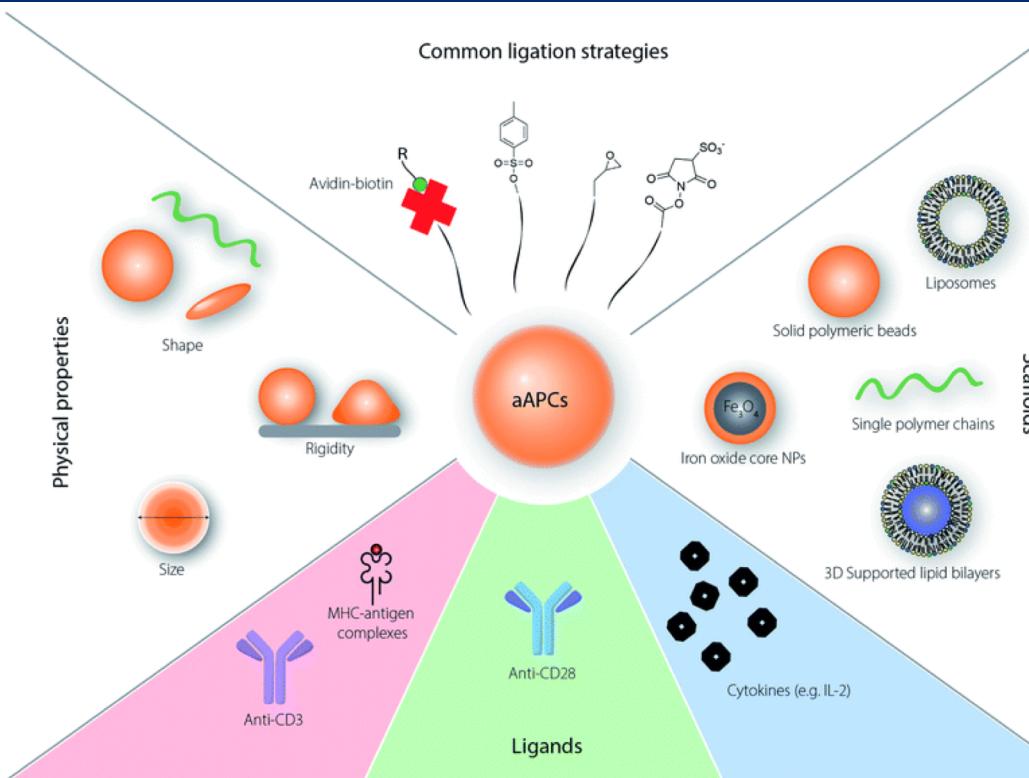


Smith et al. "In situ programming of leukaemia-specific T cells using synthetic DNA nanocarriers" *Nature Nanotechnology* 12(8), (2017): 813-820.

# Artificial Antigen Presenting Cells (aAPCs)

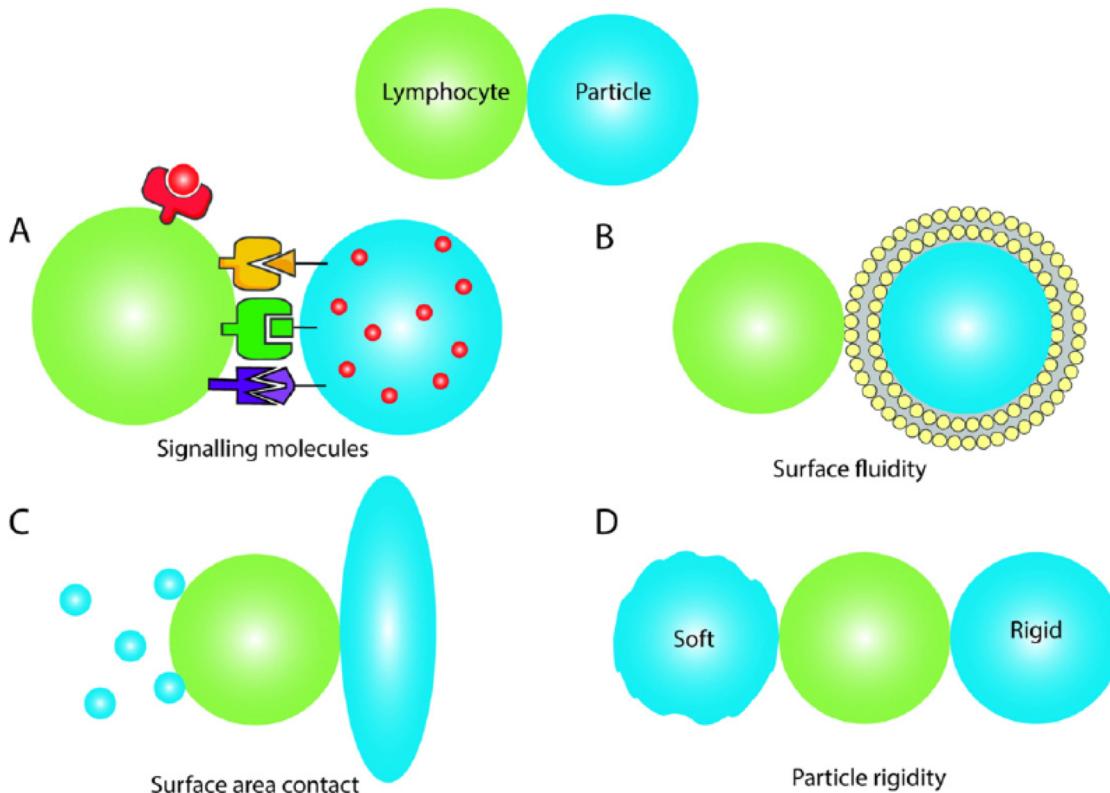


# aAPC Engineering Approaches



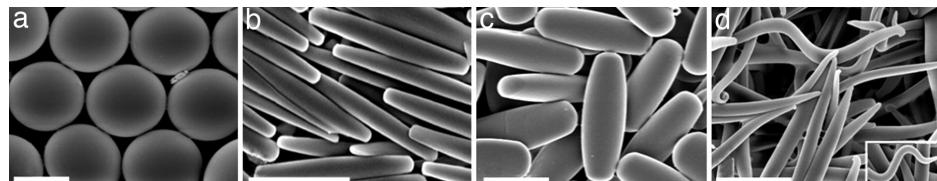
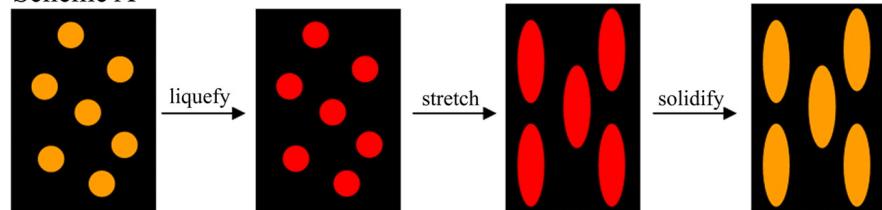
Van der Wijden et al. "The right touch: design of artificial antigen-presenting cells to stimulate the immune system" *Chem. Sci.* 5, (2014): 3355-3367.

# aAPC Surface Engineering Parameters

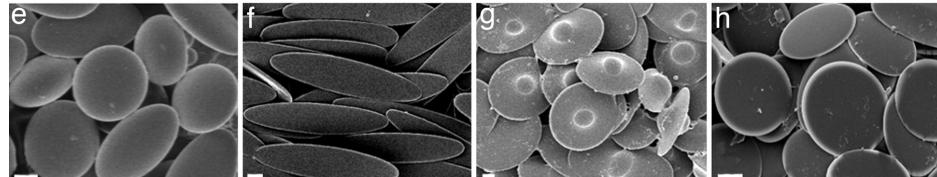
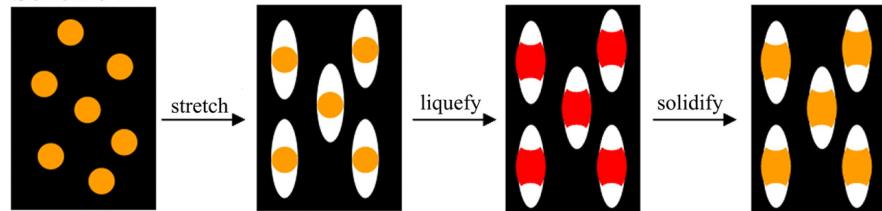


# Particle Shape Engineering

Scheme A

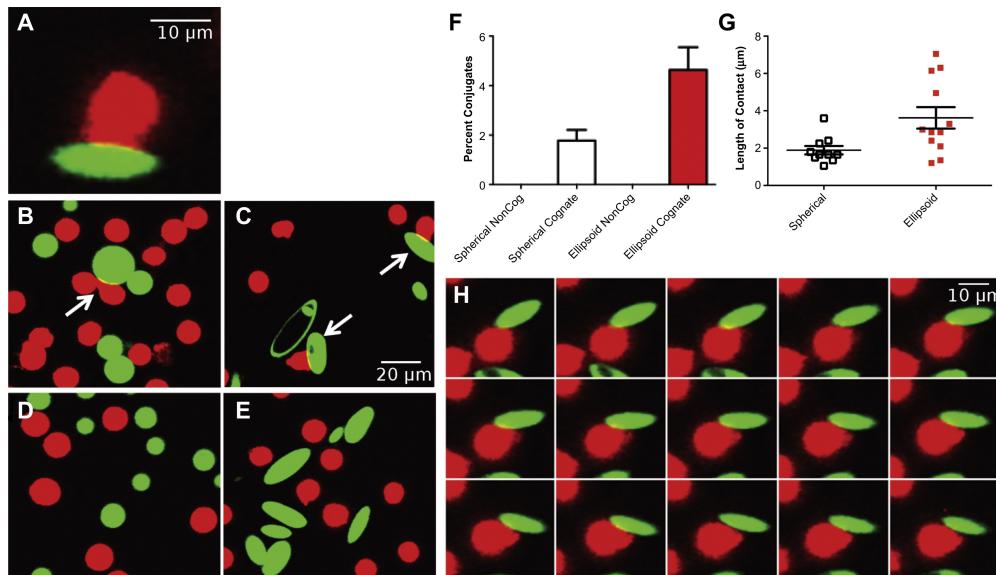
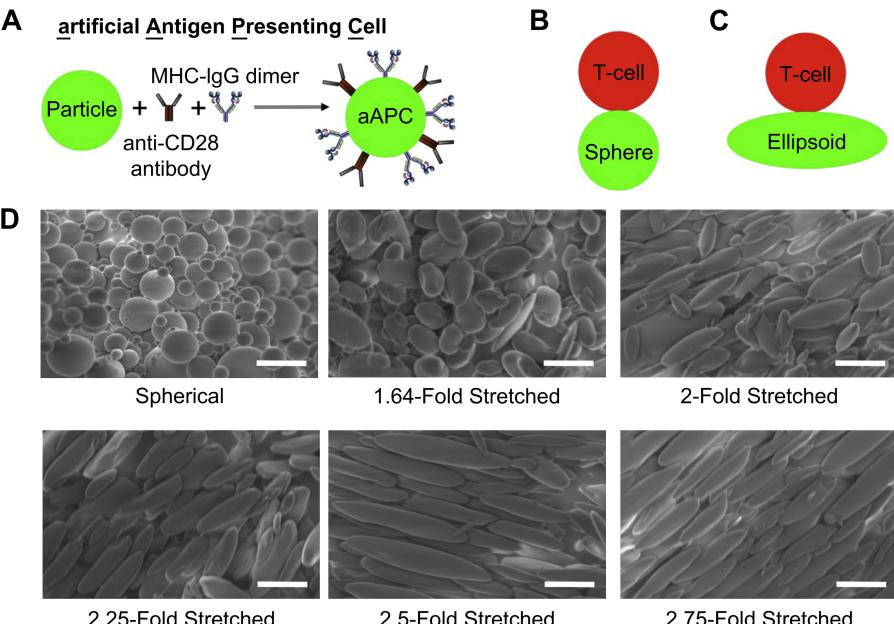


Scheme B

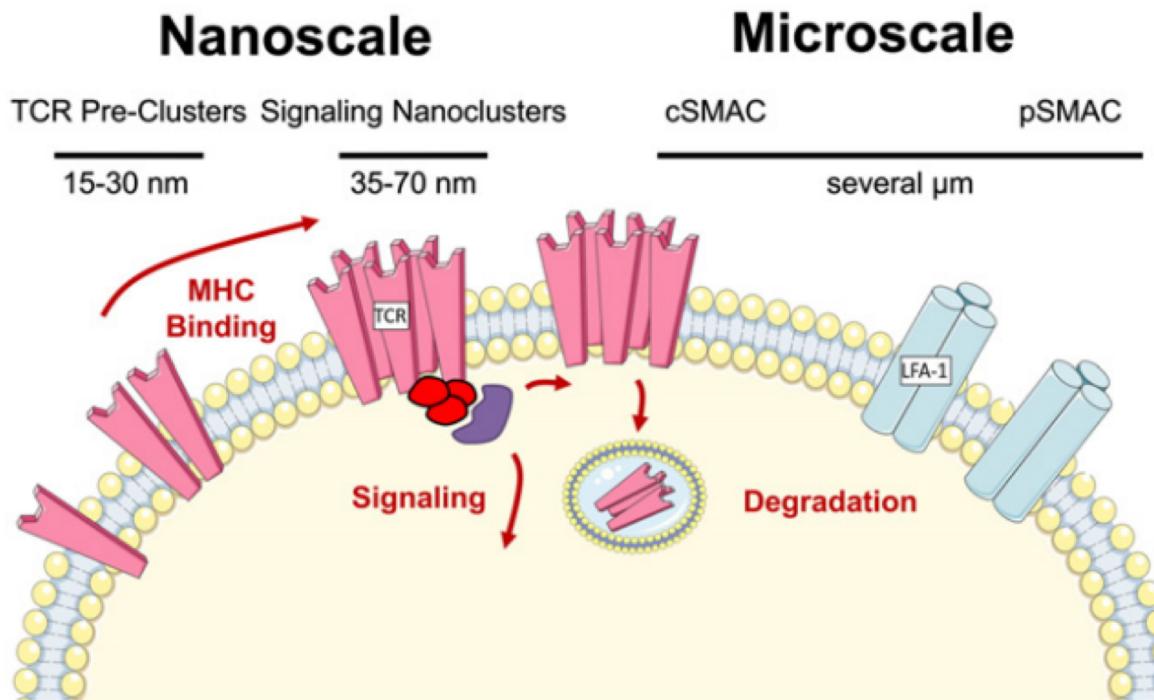


- Spherical polymeric particles (e.g. PLGA, PCL, polystyrene) are cast into a thin plastic film and stretched to generate diverse particle shapes

# aAPC Shape Effects



# Membrane Reorganization in T cell-APC Interaction



# Microscale: Immunological Synapse Formation

Green: MHC-peptide

Red: ICAM-1 (adhesion molecule)

Time (min)

0.5

1.5

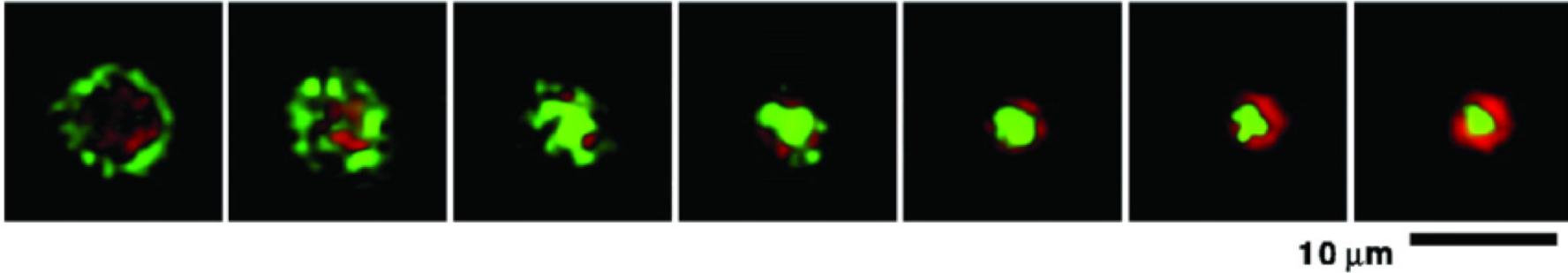
3

5

10

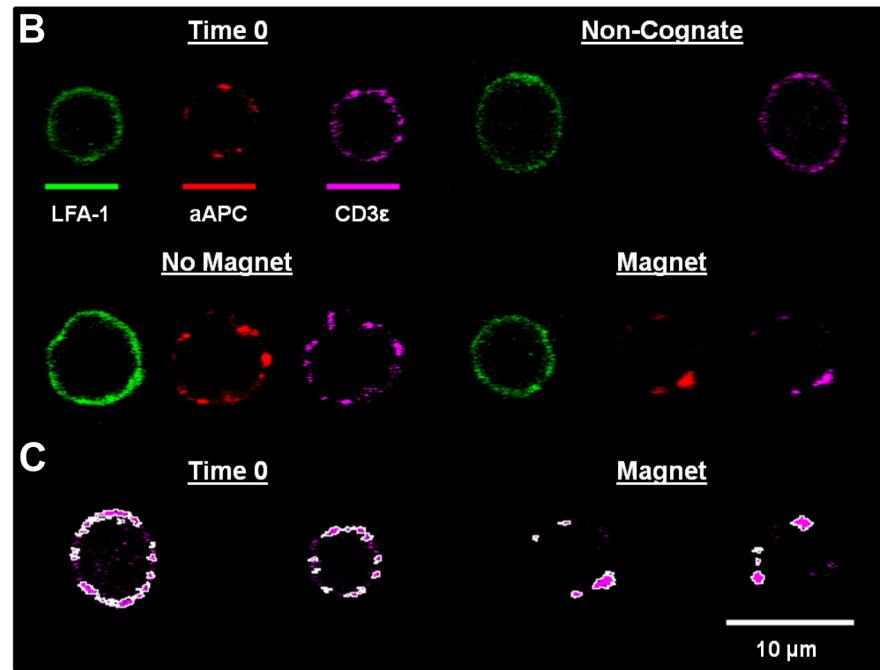
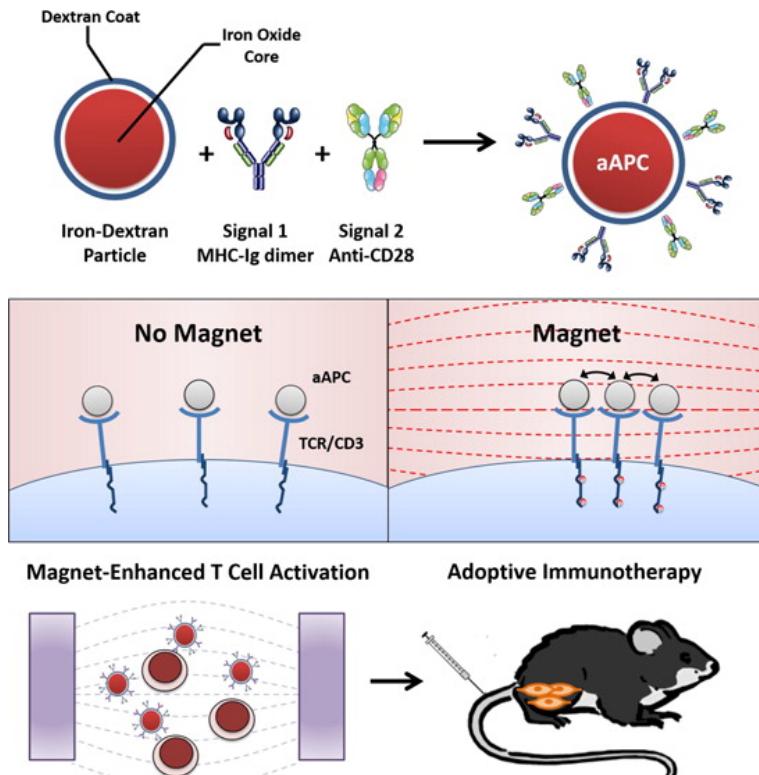
30

60



- T cell interaction with a supported lipid bilayer shows receptor clustering and eventual formation of immunological synapse
- Conventional aAPCs with immobilized proteins cannot induce clustering

# Nanoscale: Receptor Clustering



Perica et al. "Magnetic Field-Induced T Cell Receptor Clustering by Nanoparticles Enhances T Cell Activation and Stimulates Antitumor Activity" *ACS Nano* 8(3), (2014): 2252-2260.



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