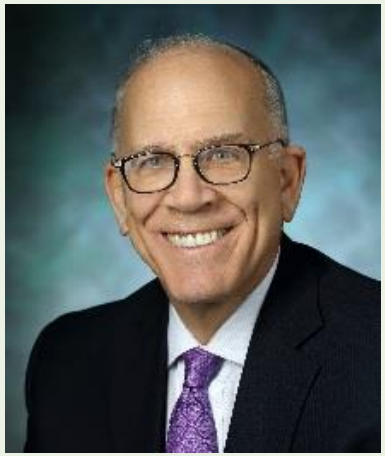
Immune System Basics

Engineering the Immune System to Fight Cancer



Jonathan Schneck, M.D., Ph.D.

Professor of Pathology and Oncology

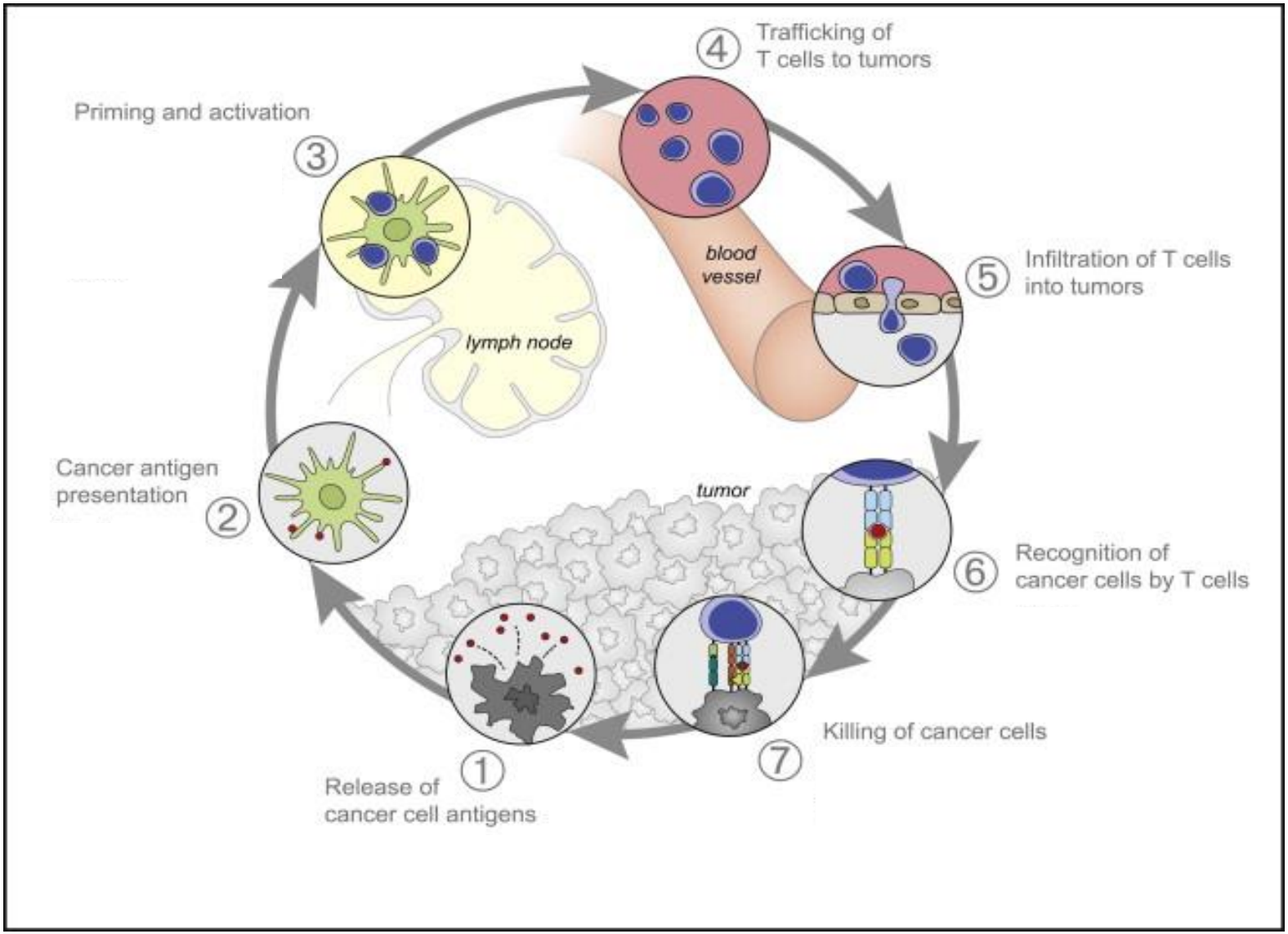
- Disclosures
  - NexImmune- Scientific Founder and SAB Chair
  - DimerX (MHC-Ig) product line sold by BD

Cancer Immunotherapy

Cancer **Immunotherapy**

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark

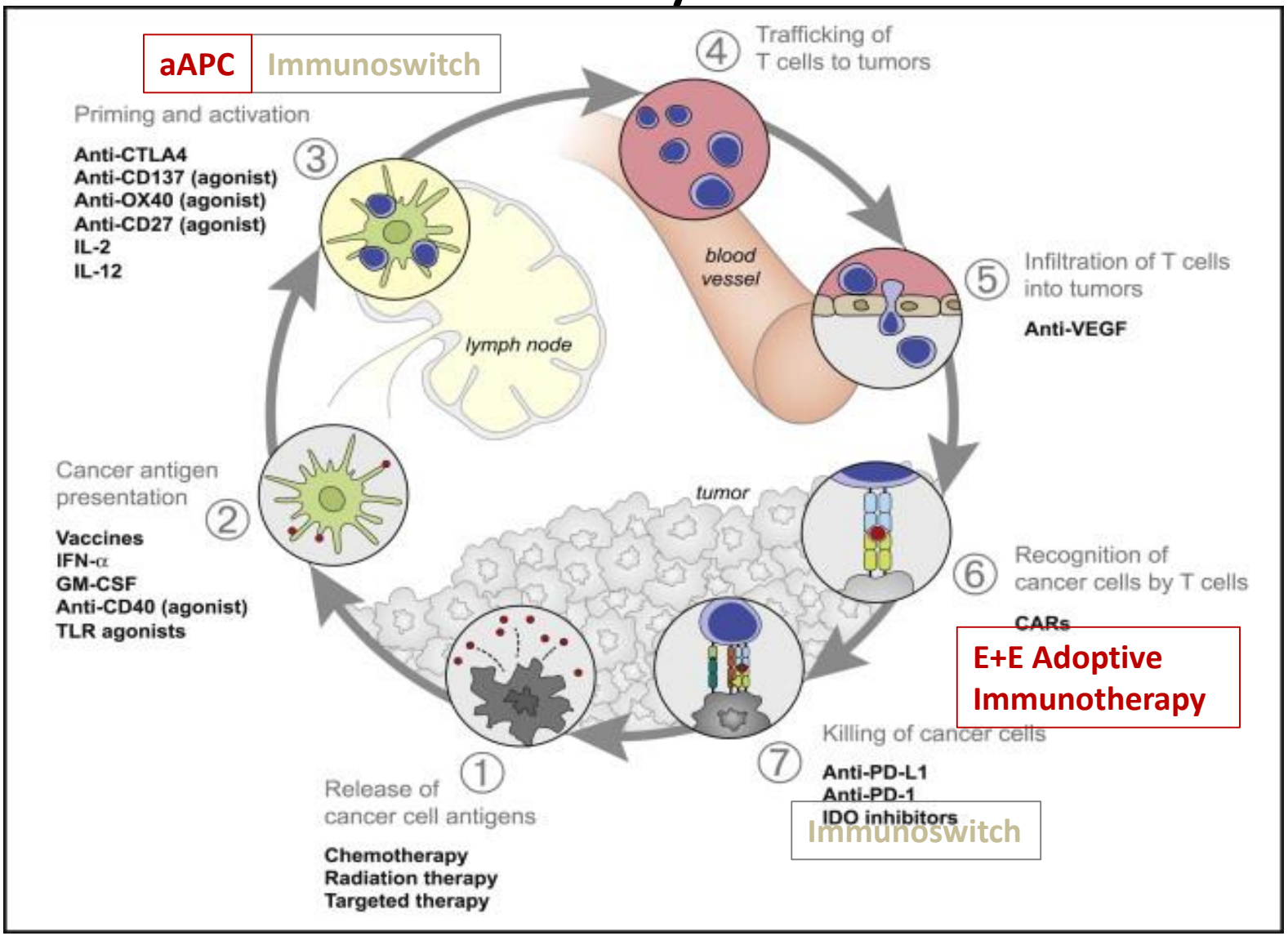
Cancer-Immunity Cycle



Oncology Meets Immunology: The Cancer-Immunity Cycle

http://dx.doi.org/10.1016/j.immuni.2013.07.012

Cancer-Immunity Cycle: Ability to Disrupt at Multiple Critical Points in the Cycle



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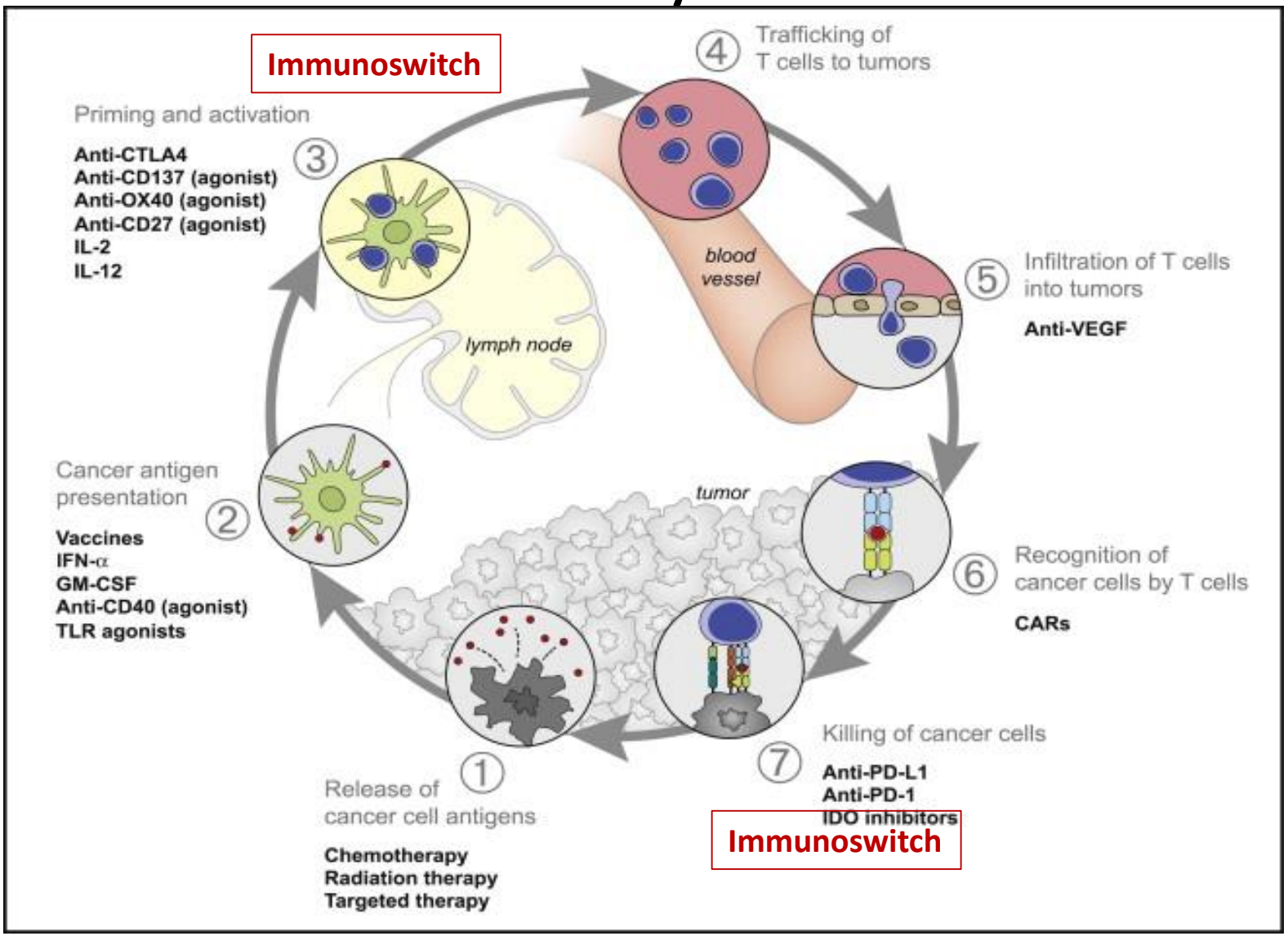

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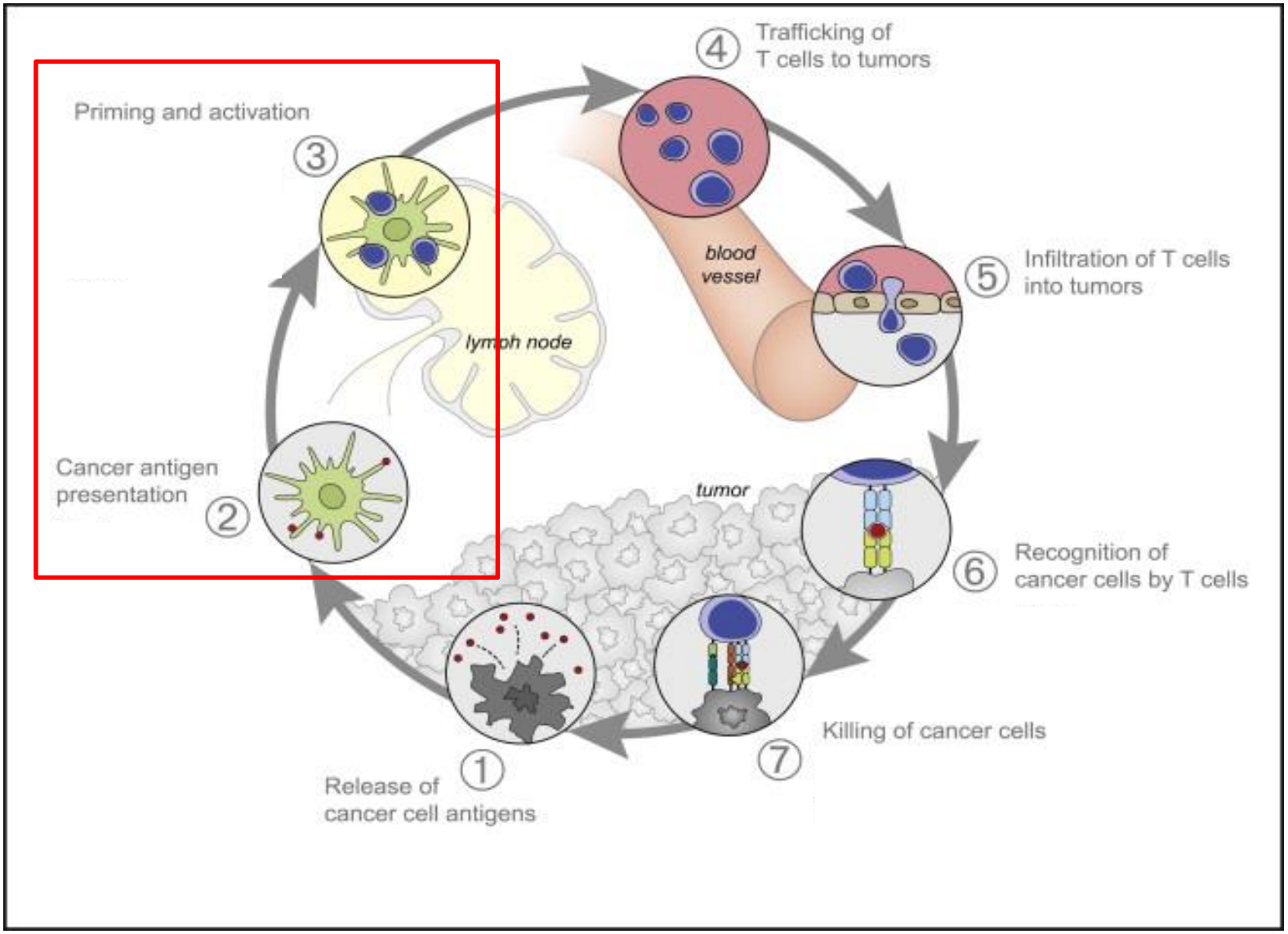

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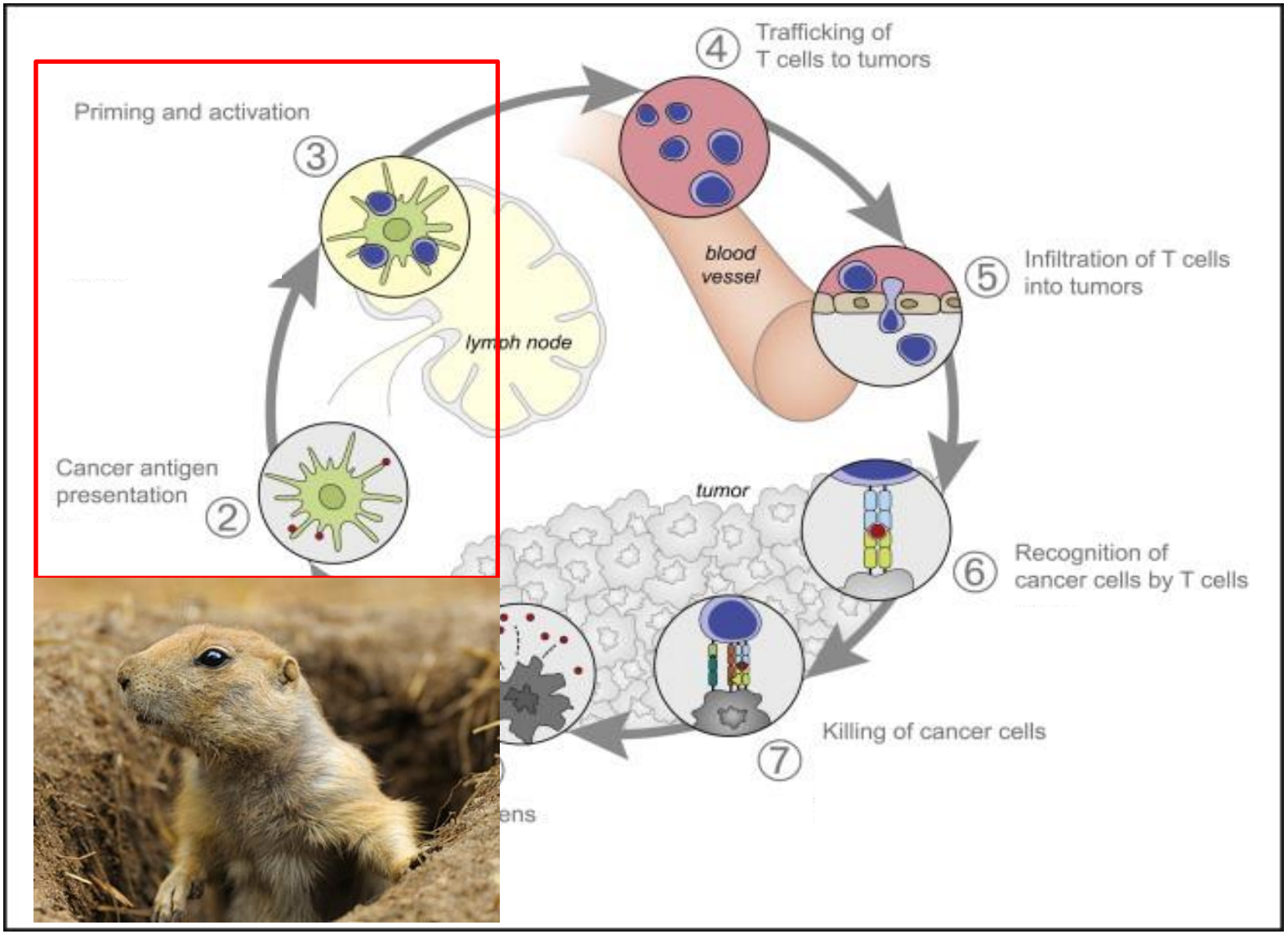

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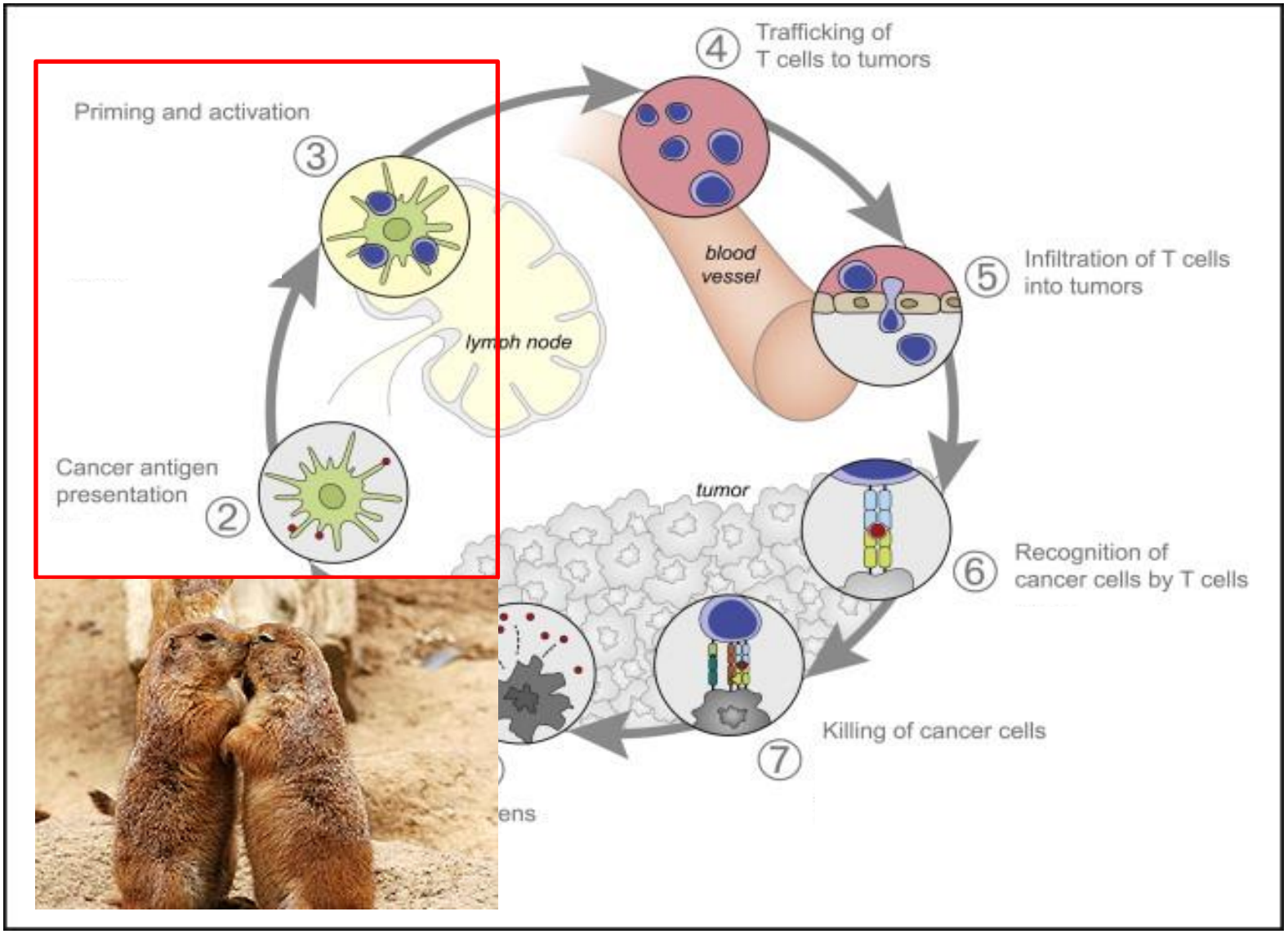
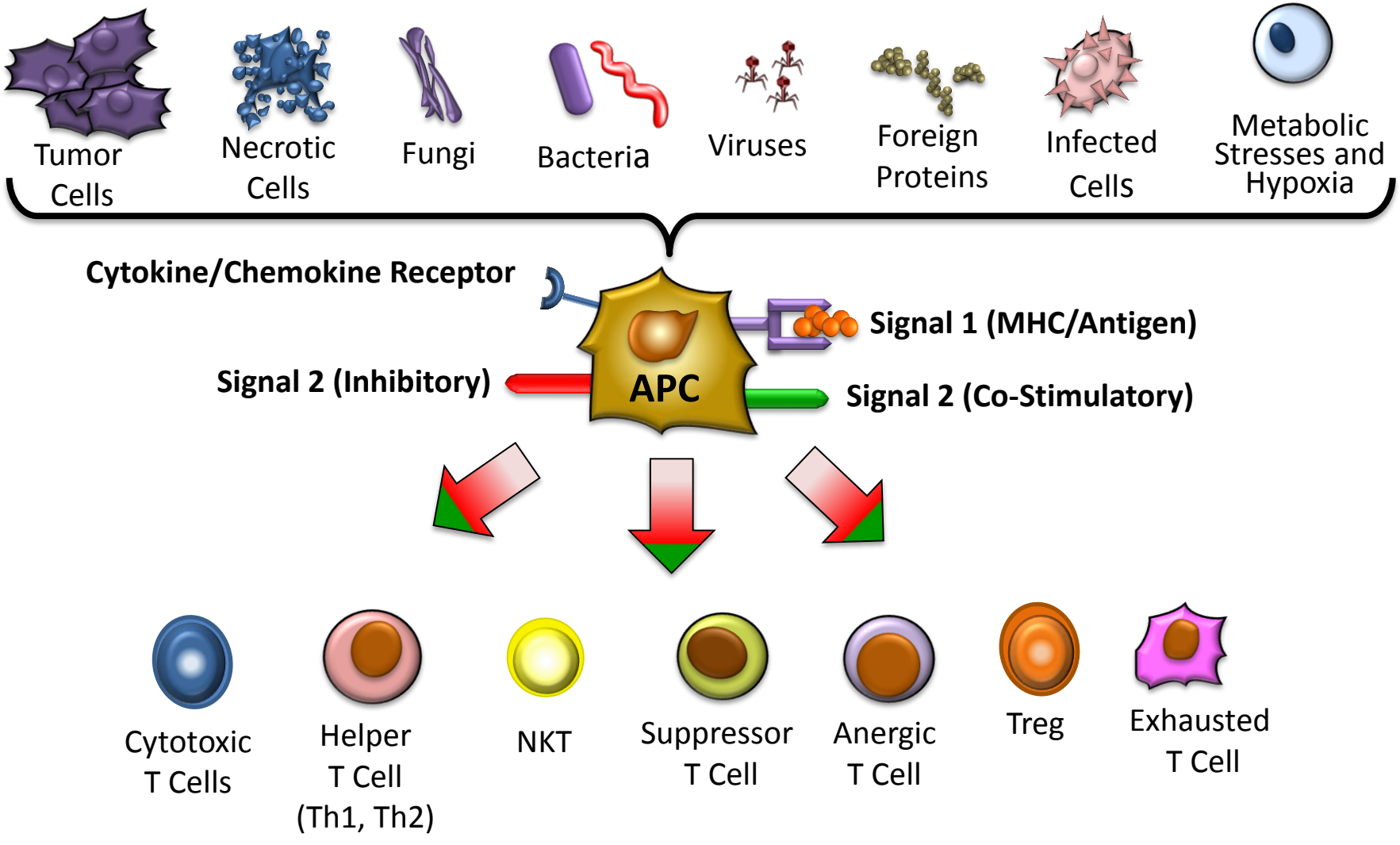
Cancer-Immunity Cycle



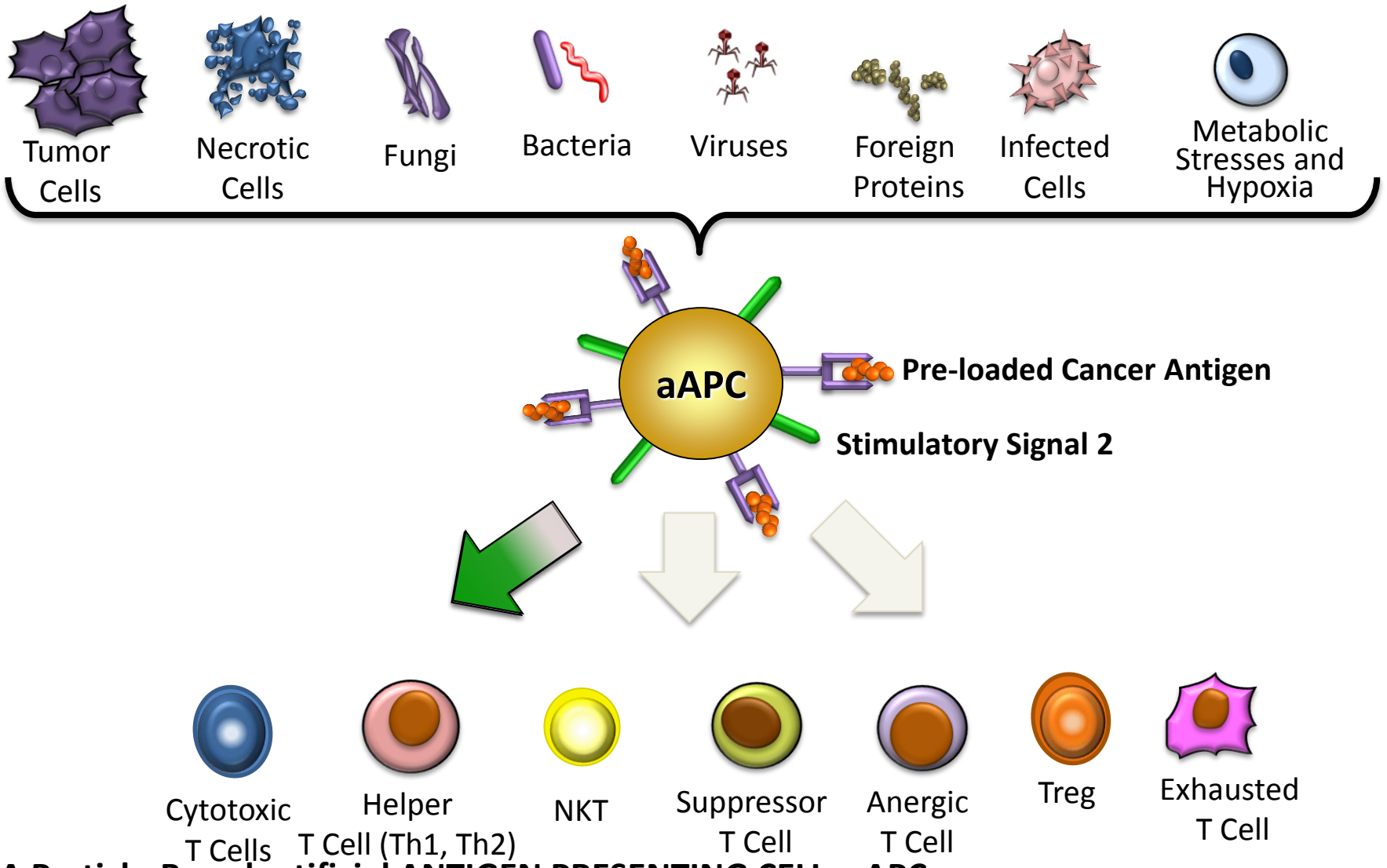
Oncology Meets Immunology: The Cancer-Immunity Cycle

http://dx.doi.org/10.1016/j.immuni.2013.07.012

Antigen Presenting Cells Orchestrate Immune Responses



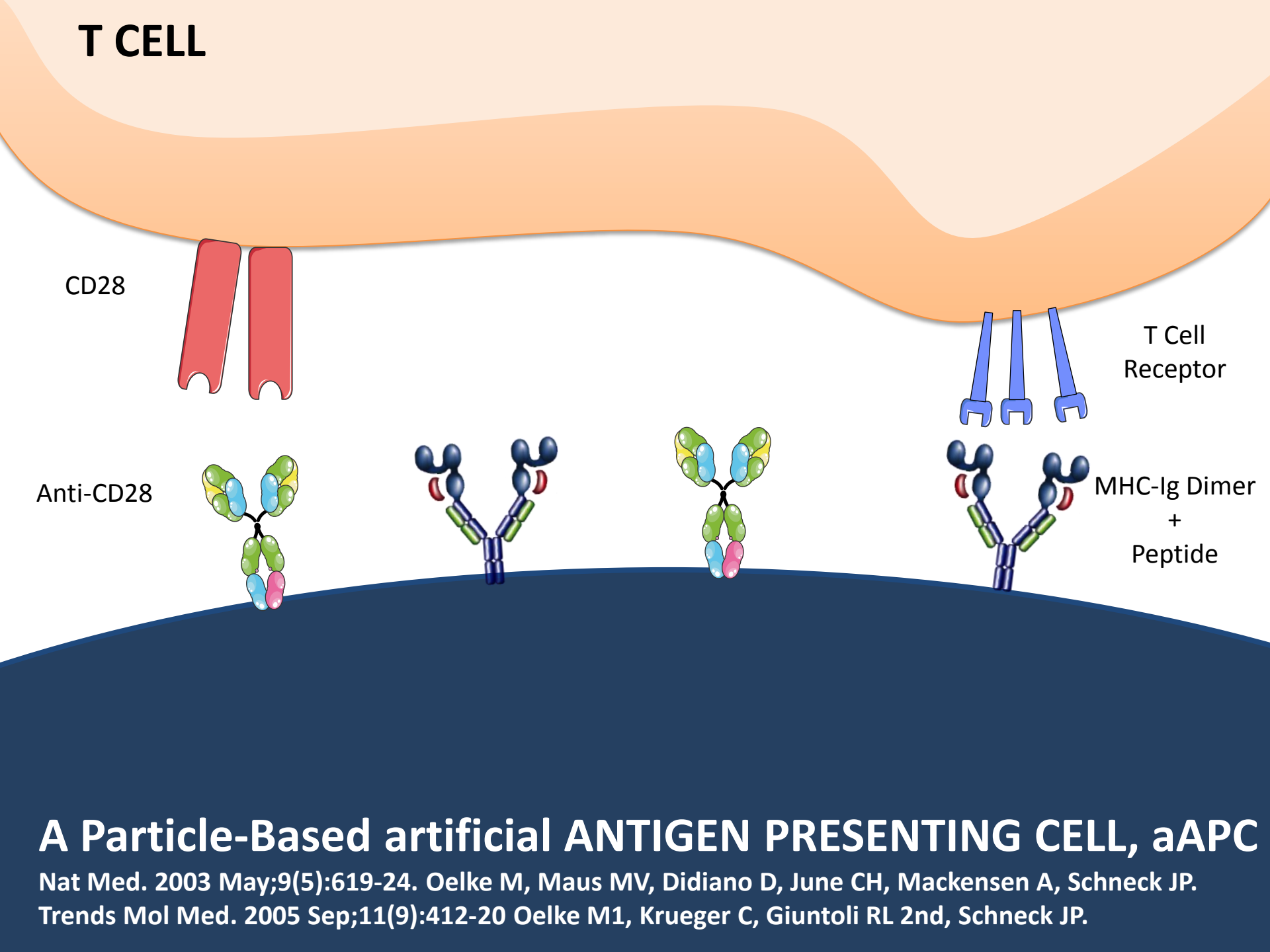
artificial Antigen Presenting Cell (aAPC) for Treating Cancer



A Particle-Based artificial ANTIGEN PRESENTING CELL, aAPC

Nat Med. 2003 May;9(5):619-24. Oelke M, Maus MV, Didiano D, June CH, Mackensen A, Schneck JP.

Trends Mol Med. 2005 Sep;11(9):412-20 Oelke M1, Krueger C, Giuntoli RL 2nd, Schneck JP.



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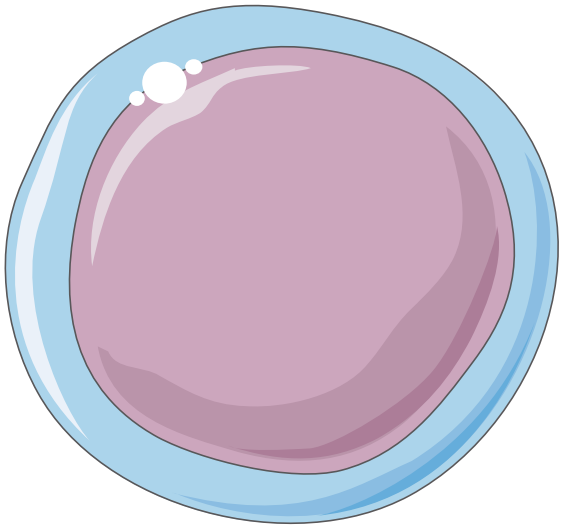
Immunoengineering:
It's all about the bass, about the bass, about the bass no treble

Size
Composition
Geometry

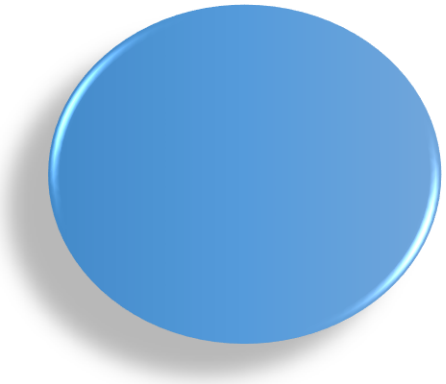
Immunoengineering:
It's all about the bass, about the bass, about the bass no treble

Microparticles vs. Nanoparticles



T Cell

7μm



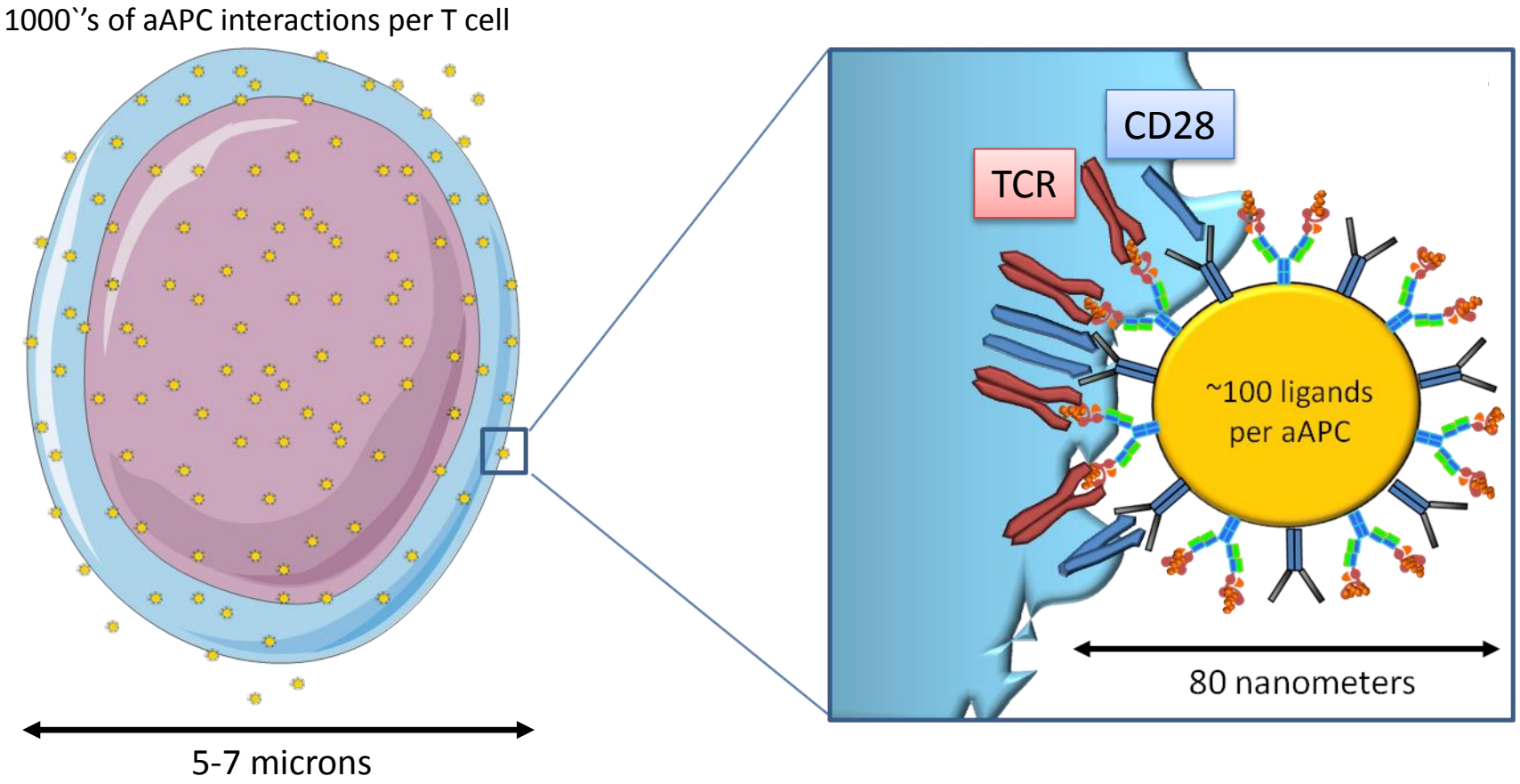
Microbead

4.5μm

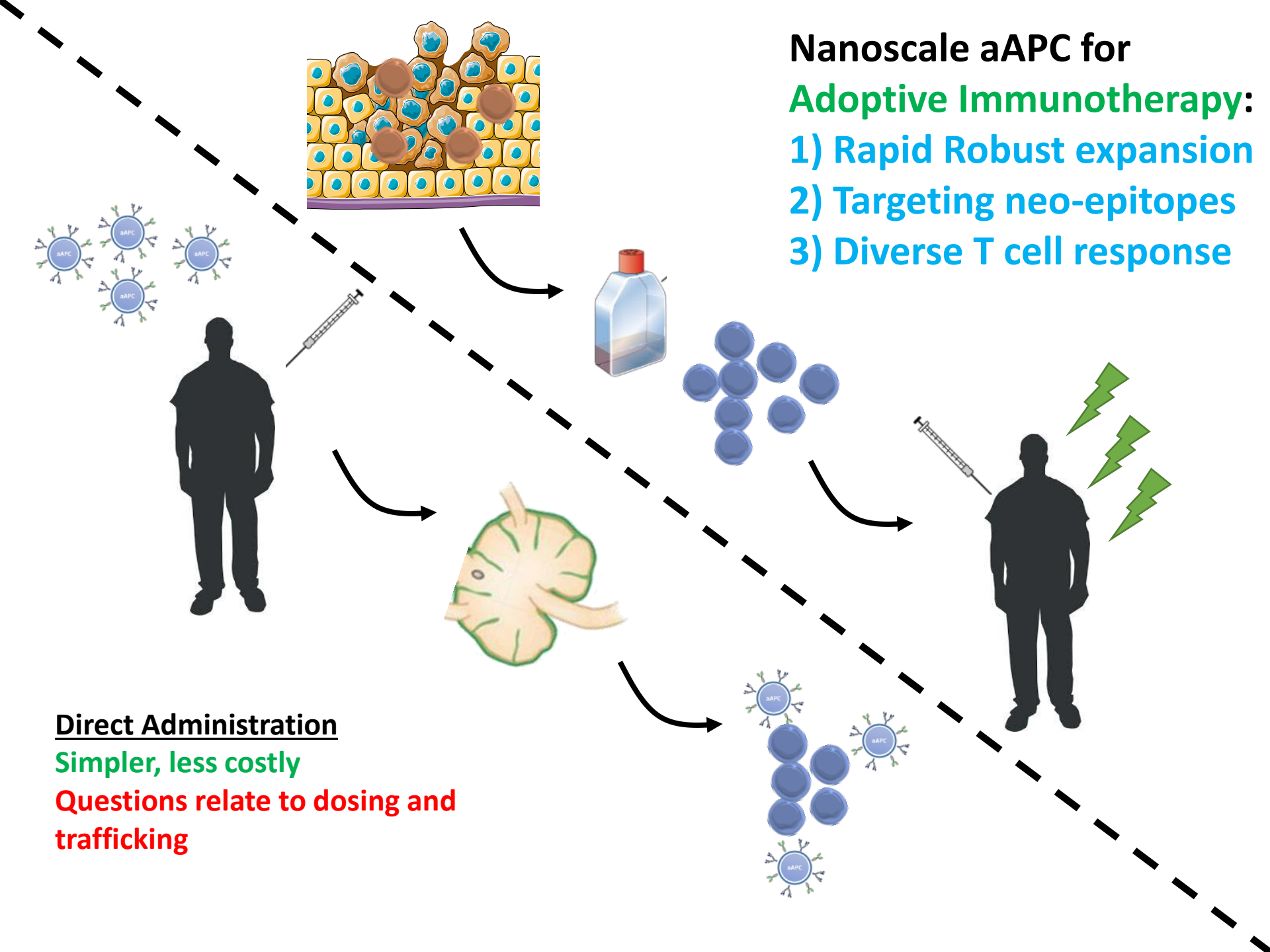
Nanobead

50-100nm

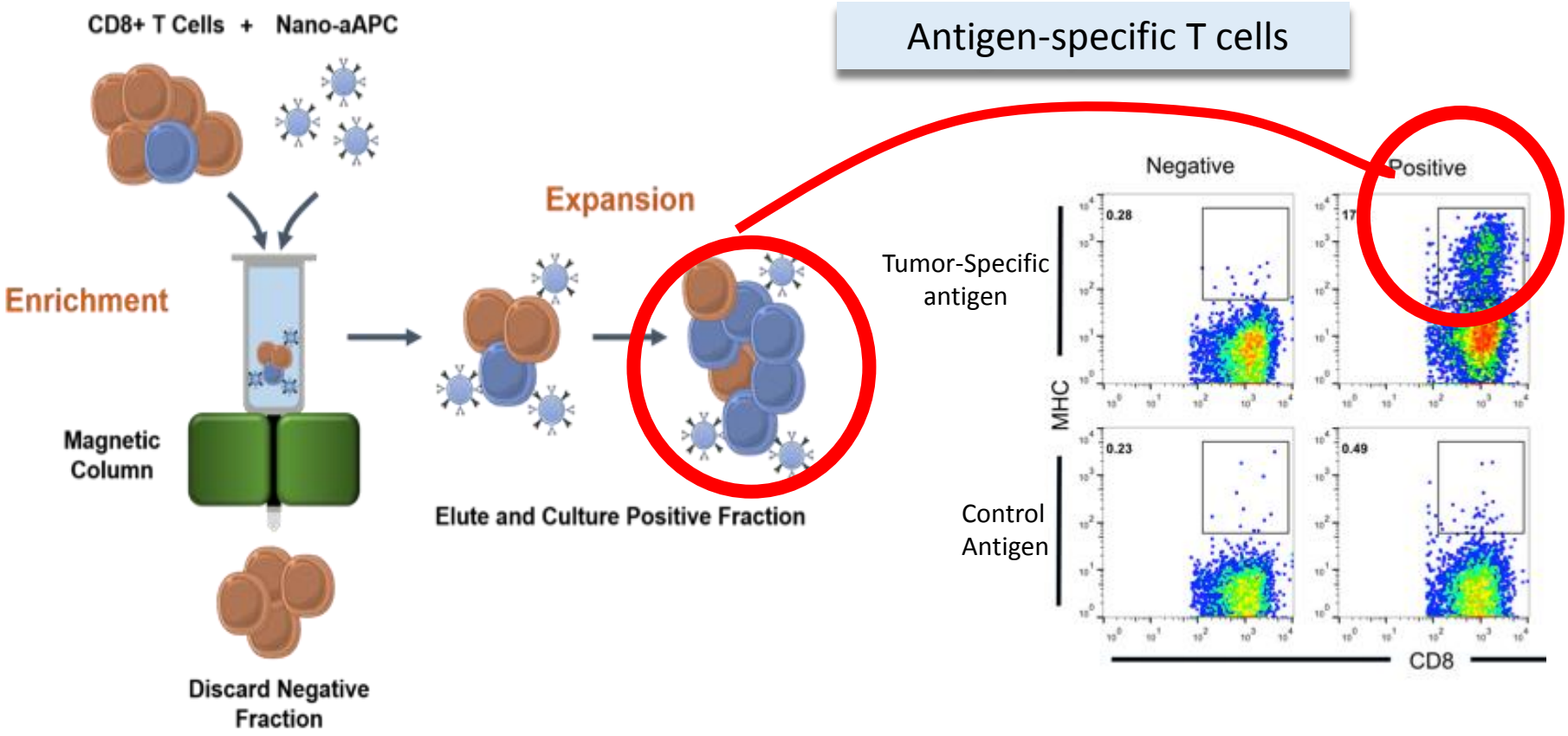
Nano-aAPC – Overcoming Activation Threshold and Expanding Targeted T cell Populations via Naturally Occurring Mechanisms



Multiple aAPCs simultaneously delivering specific, polarized signals to activate and expand antigen-specific T cells

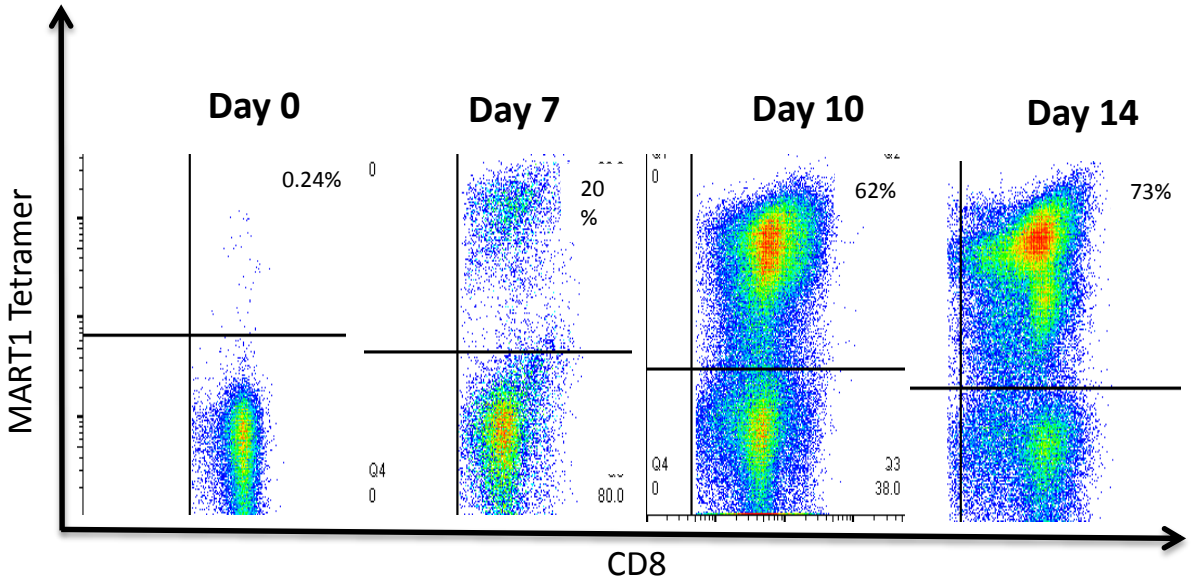

Nanoscale aAPC for
Adoptive Immunotherapy:
1) Rapid Robust expansion
2) Targeting neo-epitopes
3) Diverse T cell response
Direct Administration
Simpler, less costly
Questions relate to dosing and trafficking

E+E Enables Rapid Antigen-Specific *in vitro* T cell Expansion



ACS Nano. 2015 Jul 28;9(7):6861-71
Enrichment and Expansion with Nanoscale aAPC;
Perica K, Bieler JG, Schütz C, Varela JC, Douglass J,
Skora A, Chiu YL, Oelke M, Kinzler K1, Zhou S, Vogelstein B, Schneck JP.

E+E MART1-T cells: Stimulate Robust T Cell Expansion



Total number of cells: 5x10⁴
Viability: 93%
CD8+%: 99%
Number MART1+ CD8+ Cells: 46

Total number of cells: 7.9x10⁴
Viability: 72%
CD8+%: 91%
Number MART1+ CD8+ Cells: 10.5k

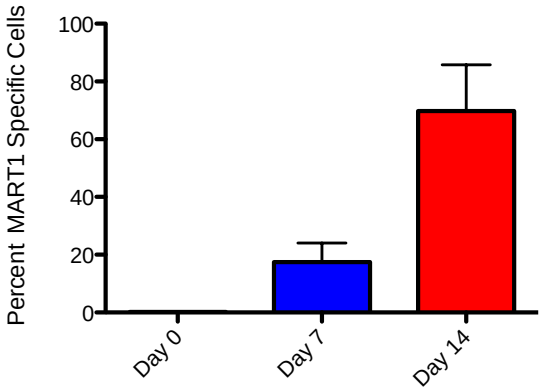
Fold expansion – 120-210x

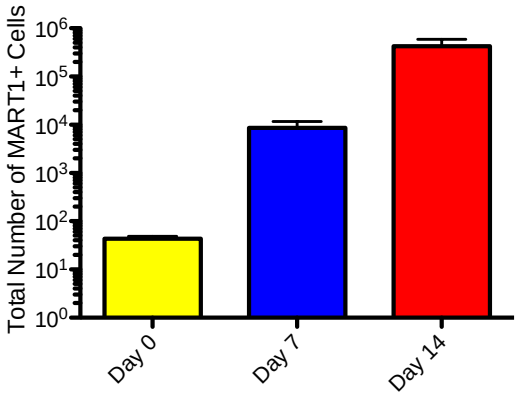
Total number of cells: 1.97x10⁵
Viability: 88%
CD8+%: 99%
Number MART1+ CD8+ Cells: 106k

Fold expansion – 1000-2100x

Total number of cells: 1.3x10⁶
Viability: 80%
CD8+%: 98%
Number of MART1+ CD8+ Cells: 750k

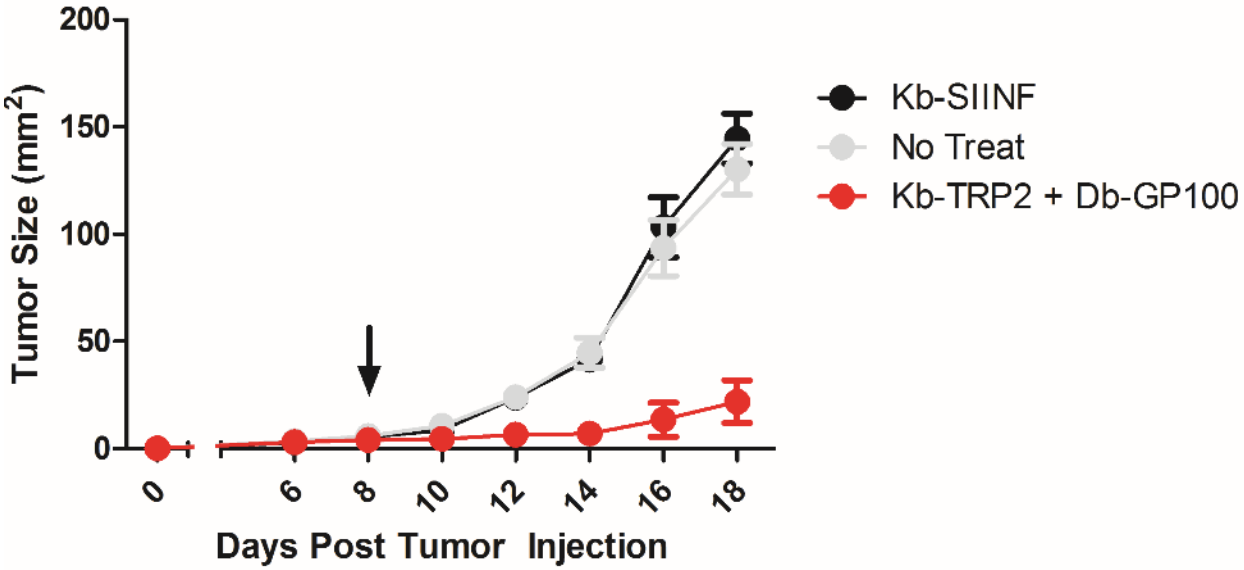
Fold expansion – 6400-14,000x

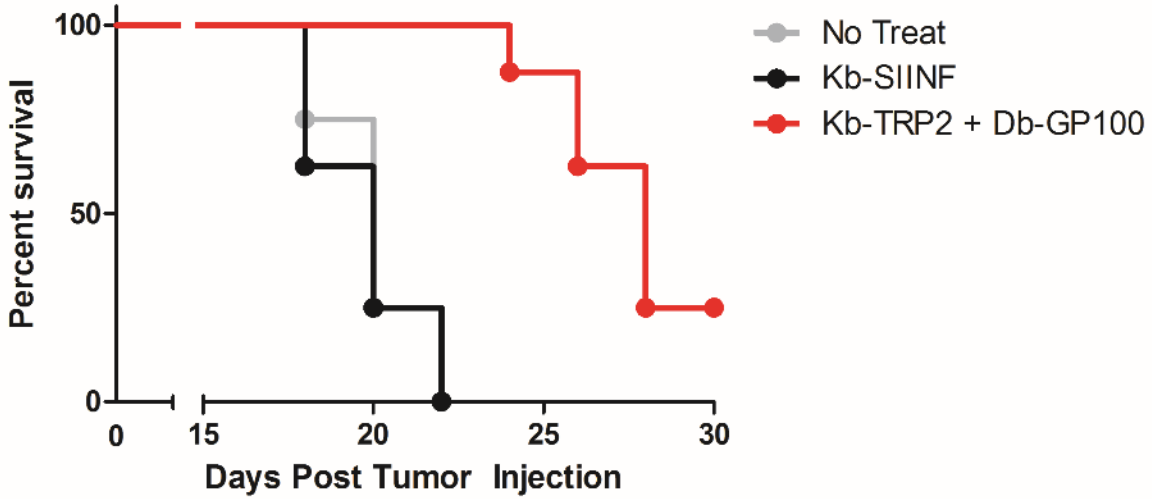




Varela and Schneck et al., UNPUBLISHED CONFIDENTIAL DATA

Adoptive Transfer of E+E Stimulated T cells Treats Established B16 Melanoma



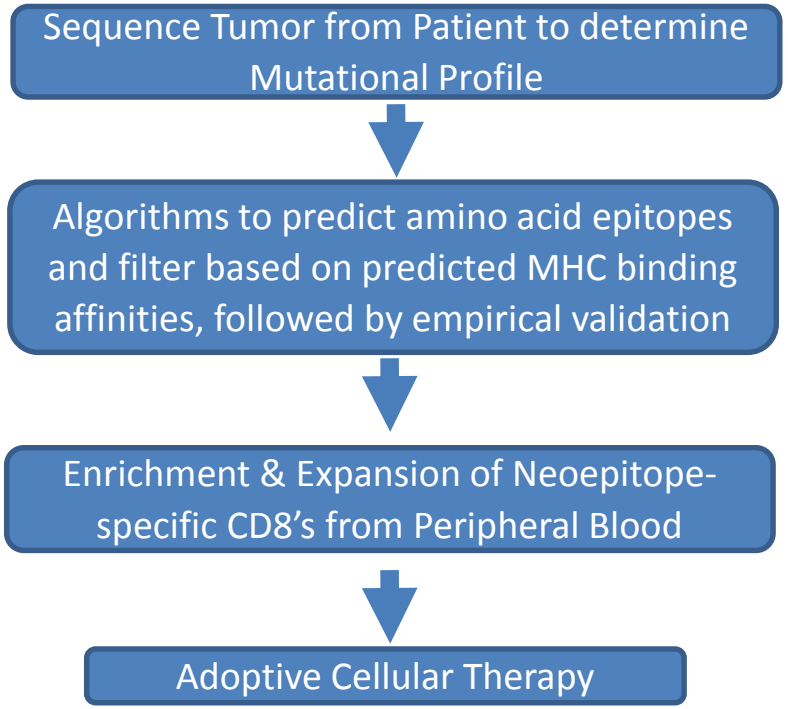


ACS Nano. 2015 Jul 28;9(7):6861-71

Perica K, Bieler JG, Schütz C, Varela JC, Douglass J,
Skora A, Chiu YL, Oelke M, Kinzler K1, Zhou S, Vogelstein B, Schneck JP.

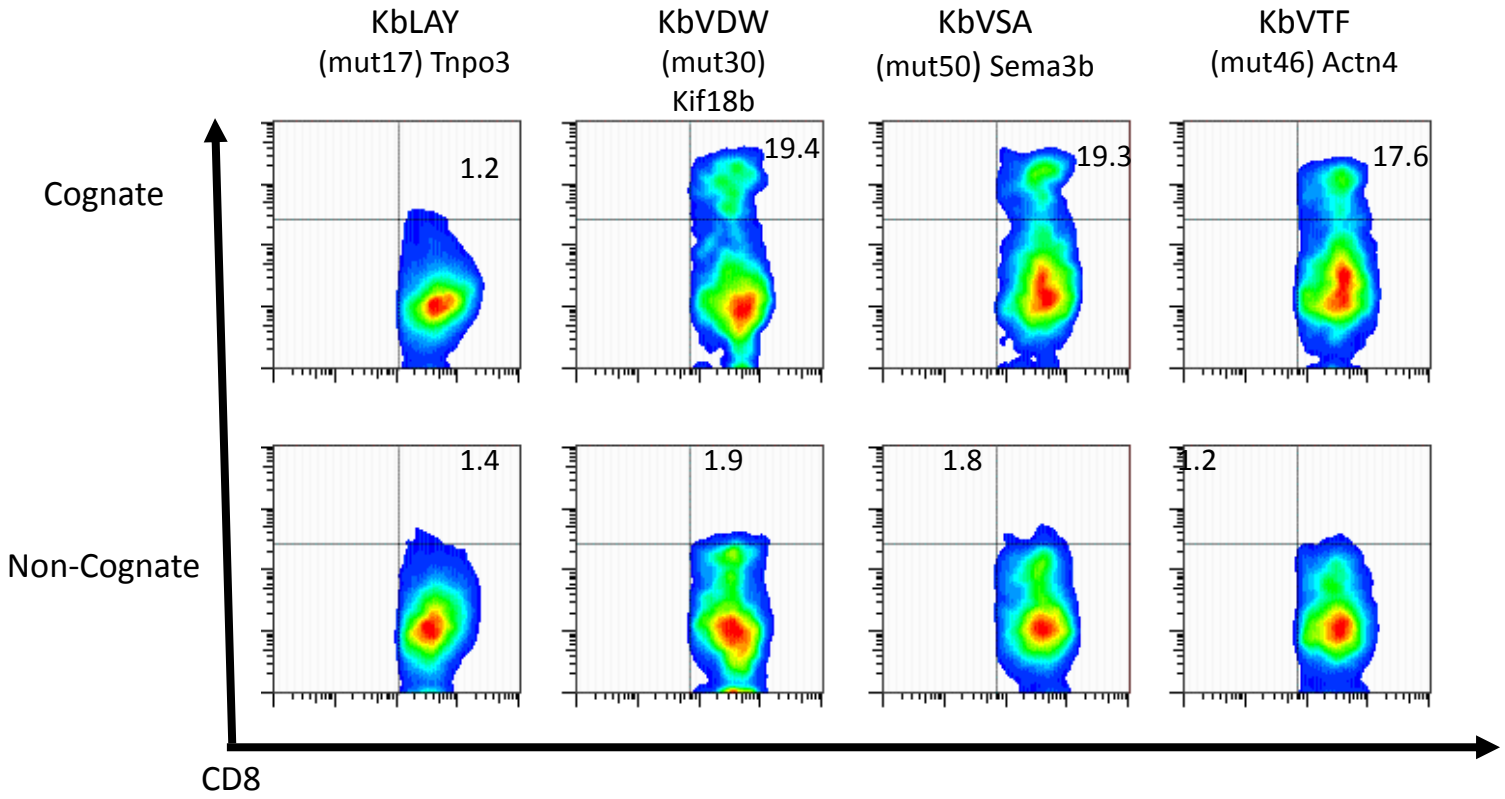
Targeting Neoepitopes

- Mutations in tumor provide patient-specific targets
  - Single Amino Acid Substitutions (AAS) lead to novel MHC-I epitopes
  - 'Non-Self' → High Avidity TCR's
  - Personalized Targeted Cellular Therapy



Comprehensive Pipeline for Personalized Adoptive Cellular Therapy

E+E Validation of Predicted Neo-Epitope Responses from Naïve CD8+ Repertoire



Predicted Affinity nM	69	9066	1487	210
RMAS MHC Stability %	24	1.9	3.4	8.2

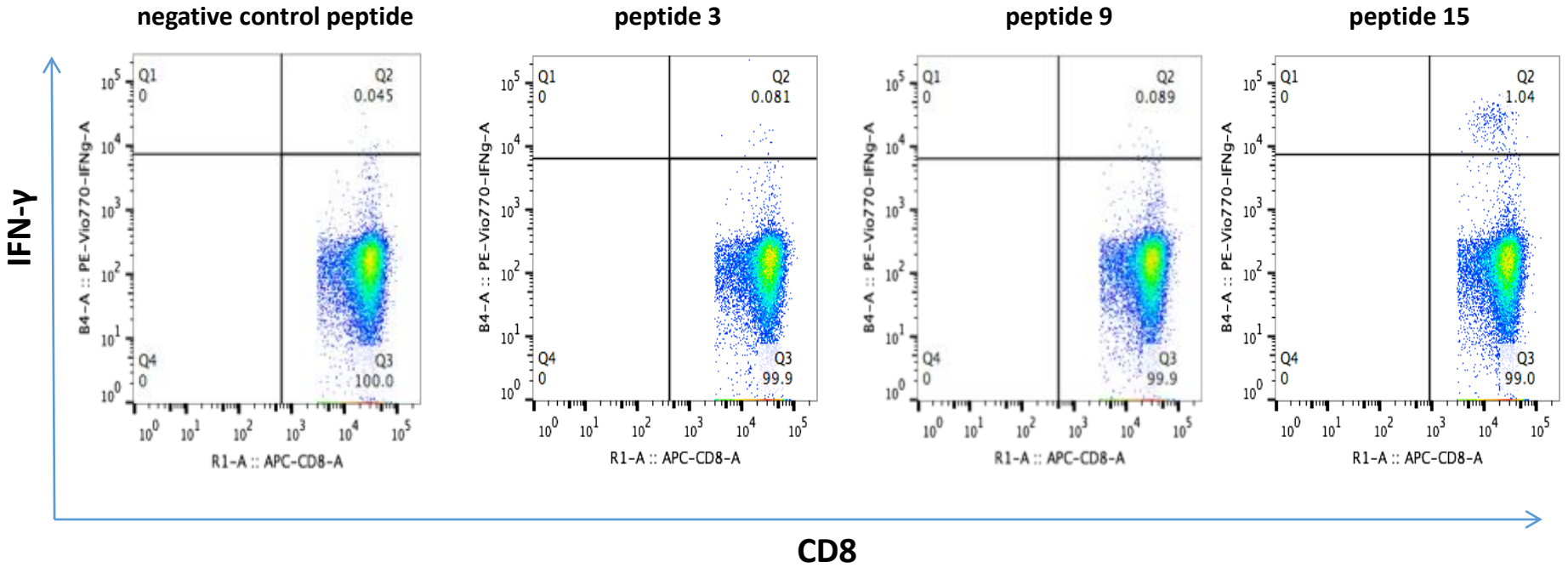
ACS Nano. 2015 Jul 28;9(7):6861-71

Enrichment and Expansion with Nanoscale aAPC; Perica K, Bieler JG, Schütz C, Varela JC, Douglass J, Skora A, Chiu YL, Oelke M, Kinzler K1, Zhou S, Vogelstein B, Schneck JP.

Advancing Neo-Antigen approach to Patient-Specific Therapy

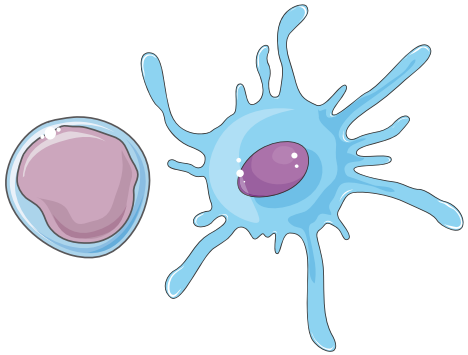
Generation of functionally active human neo-antigen-specific CD-8^{+} T cells from a healthy donor

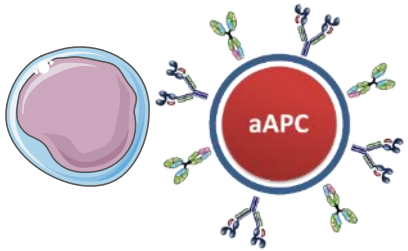
POC "Batching" 3 neo-epitopes simultaneously using AIM E+E

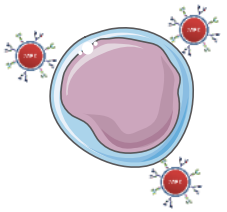


*E+E was performed simultaneously in **multiplex mode** with 3 neo-epitopes identified from MCF-7 breast cancer cells. Intracellular staining analysis was performed using stimulation with single peptides (3, 9 or 15). M Oelke Neximmune confidential information*

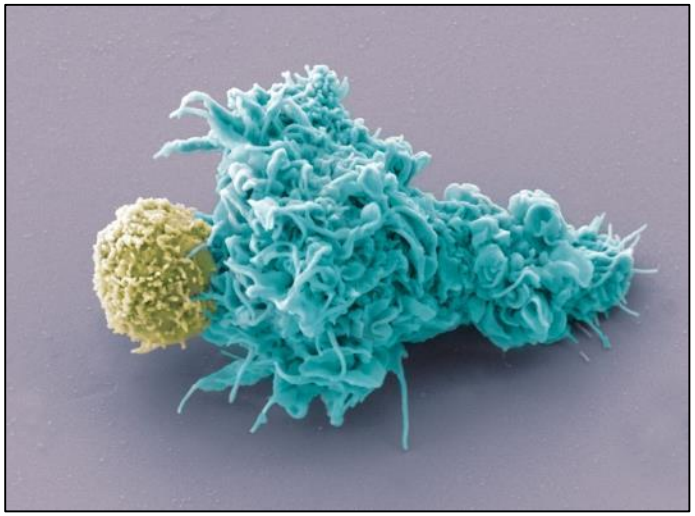
Shape in aAPC Design







Thoulouze et al. (2006).

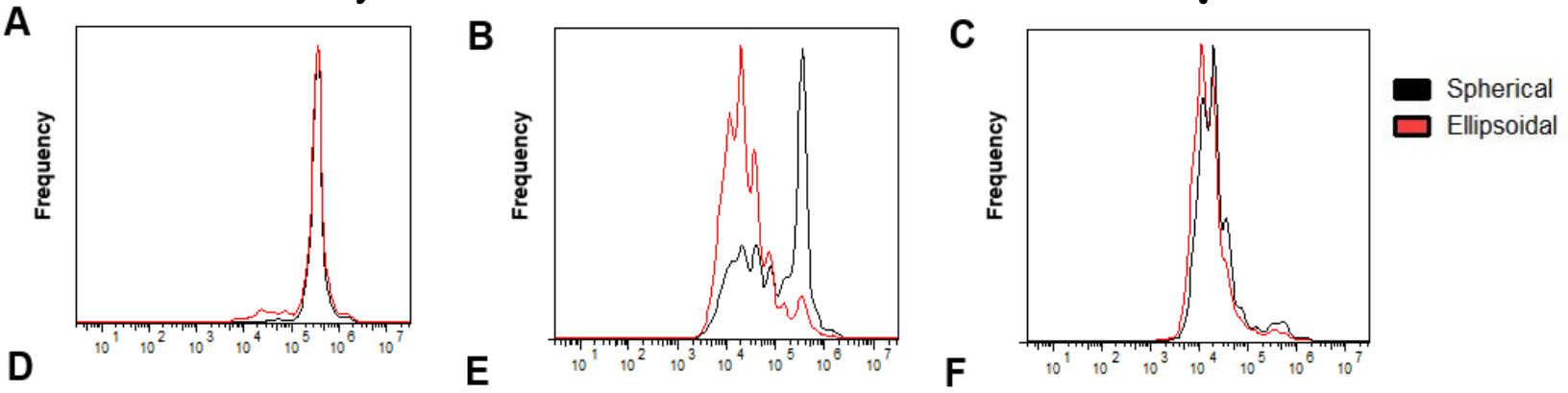


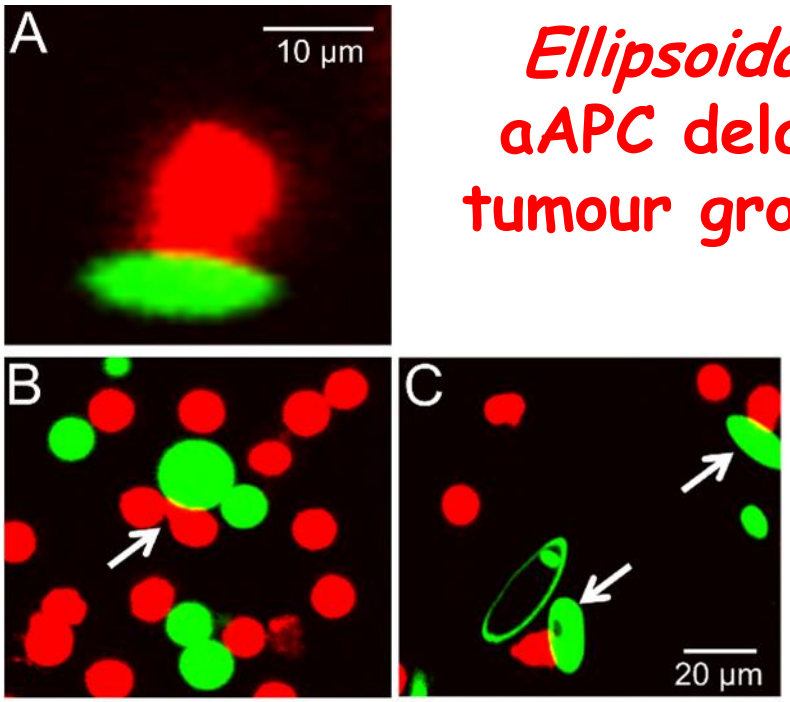
APC have large surface area and planar surface area of contact for T cells

aAPC are synthesized from spherical particles, which minimize surface and contact area

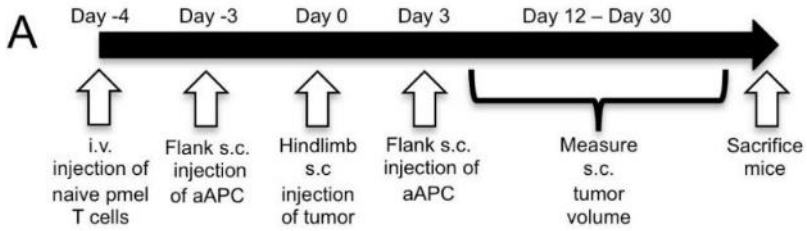
Sunshine JC, Perica K, Schneck JP, Green JJ. Particle shape dependence of CD8+ T cell activation by artificial antigen presenting cells. Biomaterials. 2013 Oct 4. [Epub ahead of print].

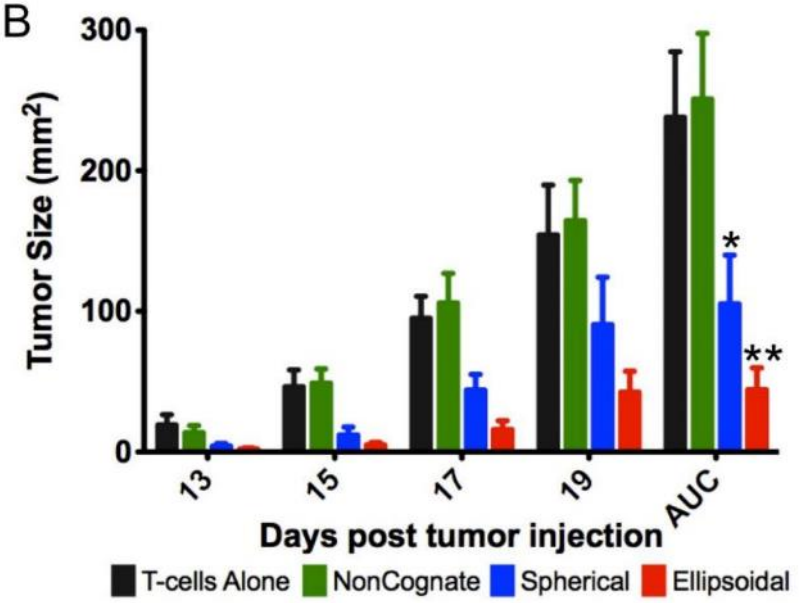
Football-shaped aAPC are better than spherical aAPC





Ellipsoidal aAPC delay tumour growth





aAPC Platform – Differentiating Attributes

1. Engage directly with targeted T cell receptors – do not require processing and presentation by host DCs and cannot be down-regulated
   - Activate and expand both foreign and self tumor-specific T cells
2. E+E allows for batching: Target multiple tumor-specific antigens simultaneously minimizing potential for tumor escape
3. Target naïve and memory T cell repertoire
   – Results in robust, persistent anti-tumor activity and immunologic memory
   – Minimizes potential for on-target, off-tissue auto-immunity
4. Mechanistically, complements other IO approaches, CPI, that break tolerance
5. Shape: A design parameter that recapitulates biology and impacts on efficacy
6. Validates 'predicted' neo-antigens and deliver immunogenic neo-antigens in clinical practice setting
7. Manufacturing flexibility and precision of 'off-the-shelf' components provide rapid path to new product design and production

Life After aAPC?

What if we could harness a tumor's own signal 1 antigens to allow for a polyclonal response and no required *a priori* knowledge of these peptides?

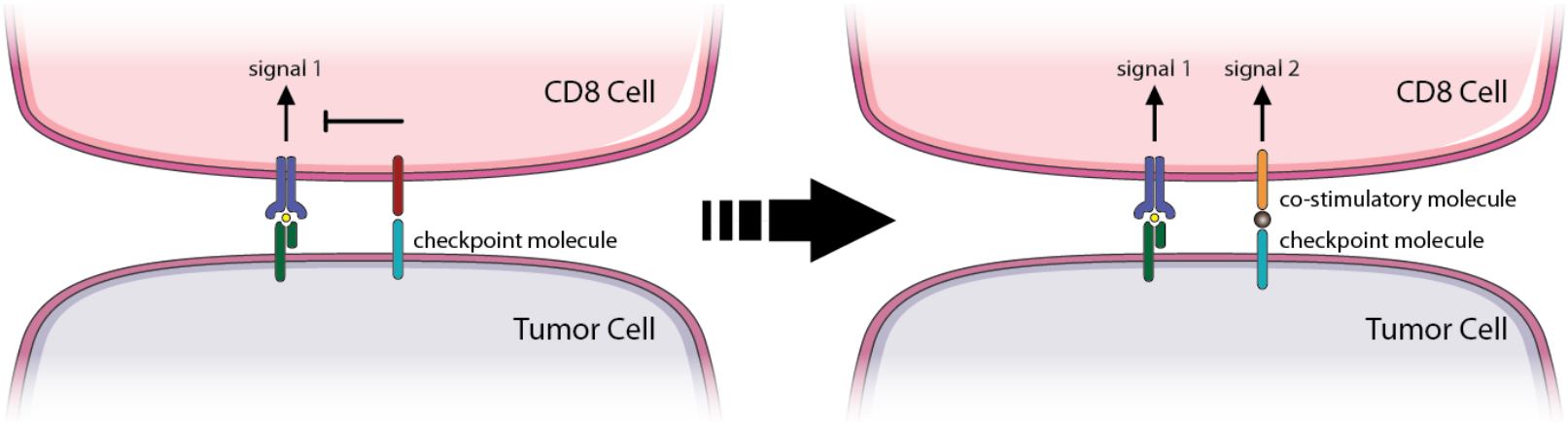
Immunoswitch particles target conserved molecules on tumor cells and T cells to turn an immunoinhibitory environment into an immunostimulatory one

-**Implications are:**

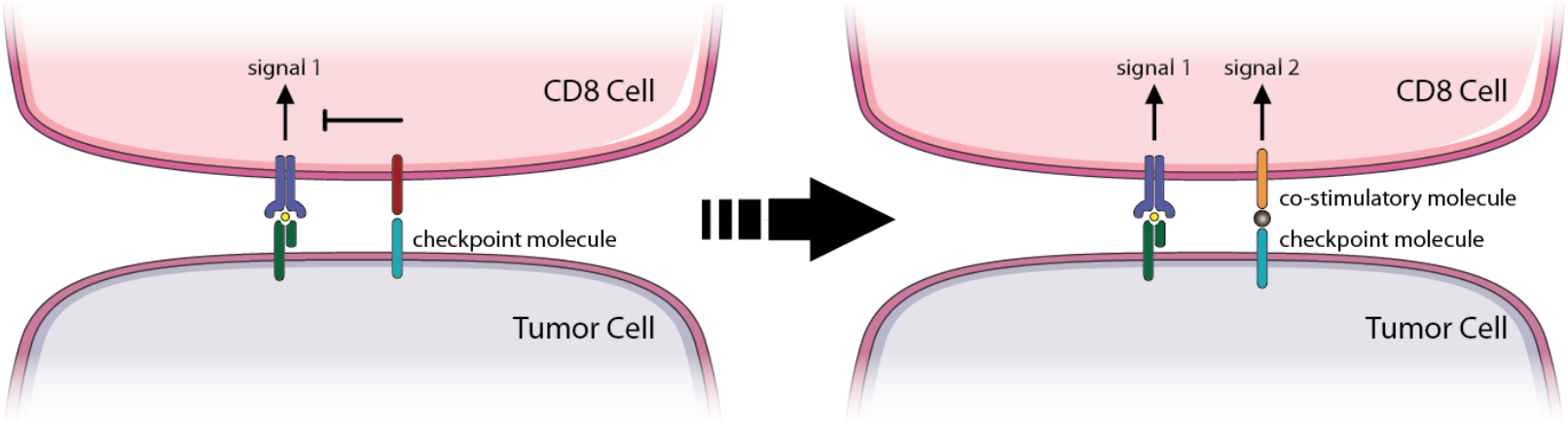
1) independent of HLA restriction- 1 particle good for all people

2) independent of known tumor antigens- 1 particle good for all antigens

3) Only need tumors with T cells

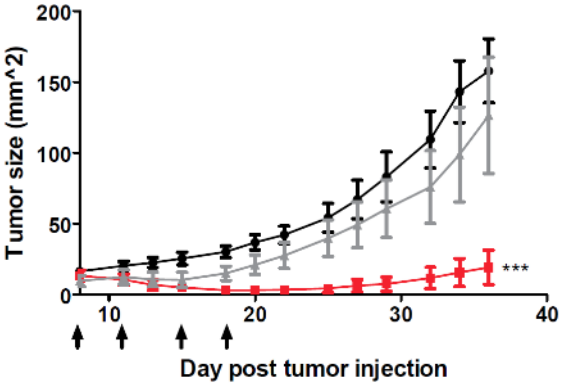


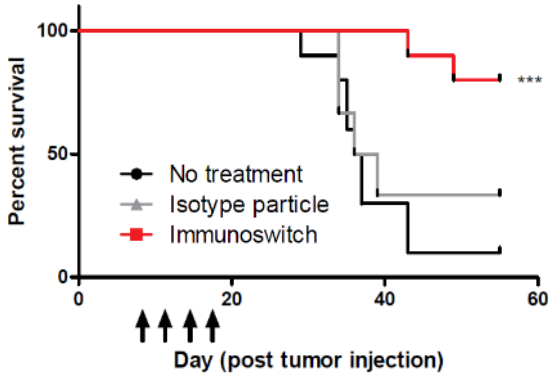
Immunoswitch particles convert inhibitory checkpoint signal into CD8+ T cell co-stimulation



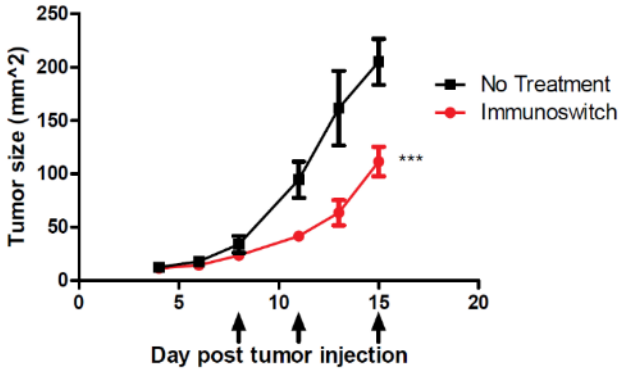
Immunoswitch particles delay tumor growth in multiple tumor models and in the absence of a foreign antigen

MC38-OVA colon cancer





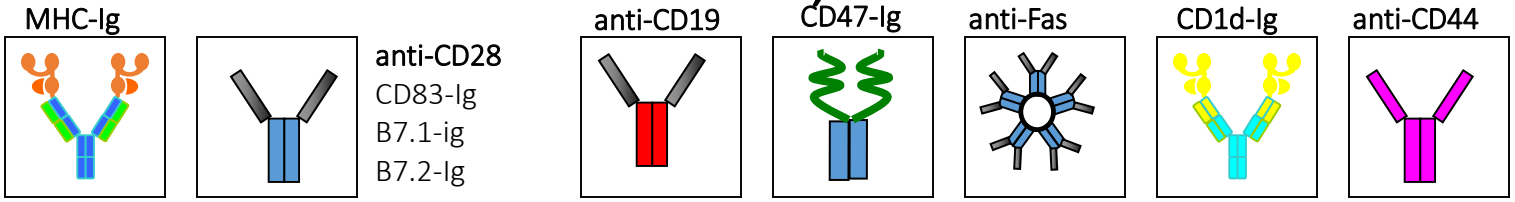
B16-F10 melanoma



Summary

- Immunoswitch particles link checkpoint blockade with co-stimulation more effectively than soluble antibodies in multiple tumor models
- Immunoswitch particles have an anti-tumor response in the absence of adoptively transferred cells
- Increased effector-target cell conjugation may drive immunoswitch anti-tumor response
- Immunoswitch particles alter the TCR repertoire within the tumor microenvironment

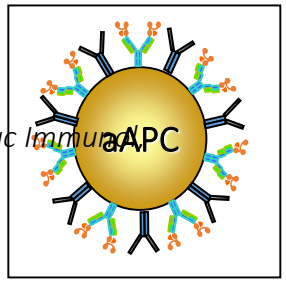
Immunoengineering: All about the bass, about the bass about about the bass, no treble

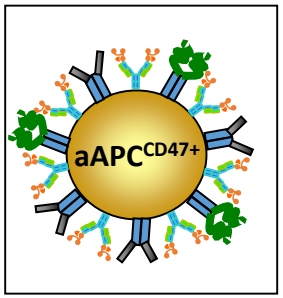


1)Immunotherapy
Oelke et al, Nat Med 9;5:619-24
Perica et al ACS Nano 2014
Perica et al ACS Nano 2015 in press (almost)

micro-, nano-bead/quantum dot

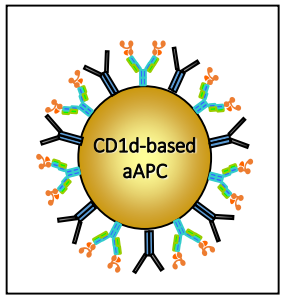
2) Diagnostic tool
Ndhlovu et al. *Clini Vac Immunol* 16:1066-73 (2009)

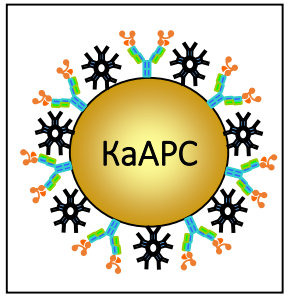


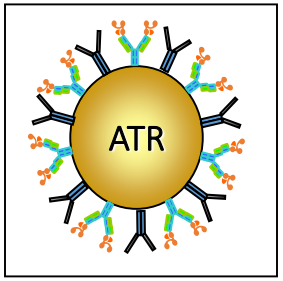


"don't eat me" aAPC for enhanced in vivo functionality
Bruns et al, Clin Cancer Res. (2015

3) Regulation of Polyfunctionality in CTL
Ndhlovu et al. (2010) *PNAS*







Antigen-specific T cell Redirectors
redirection of antigen-specific T cells to tumor cells

NKT cell activation
Identification of an inhibitory substance in ovarian cancer ascites that suppresses immune responses
Webb et al, Clin Cancer Res 14:23 (2008)
Webb et al, JIM 31;346:38-44 (2009)

Treatment of T cell mediated autoimmune diseases
Schütz et al, Blood 111:3546 (2008)

ACKNOWLEDGEMENTS

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