Engineering Artificial Antigen Presenting Cells, aAPC, for Cancer Immunotherapy: From Bench to Bedside

Discussion with David Avigan and BIDC group

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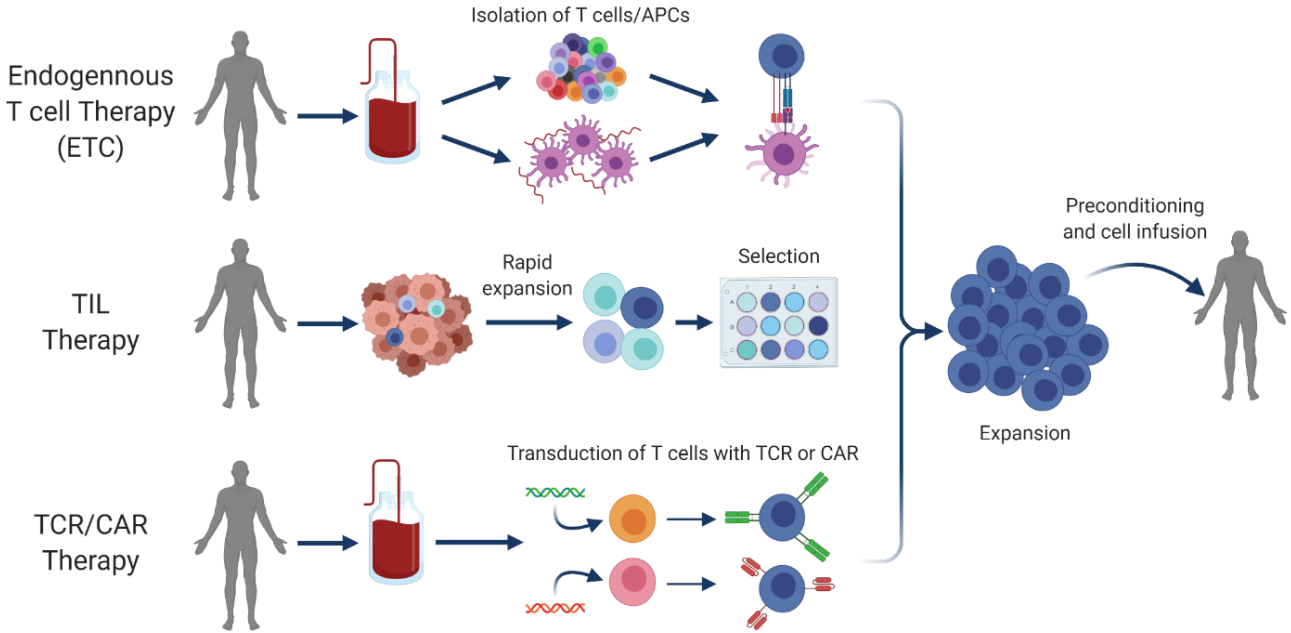
Adoptive Cellular Therapy, ACT, targets cancer cells by harnessing the immune system but current approaches are cumbersome…..and scalability limited



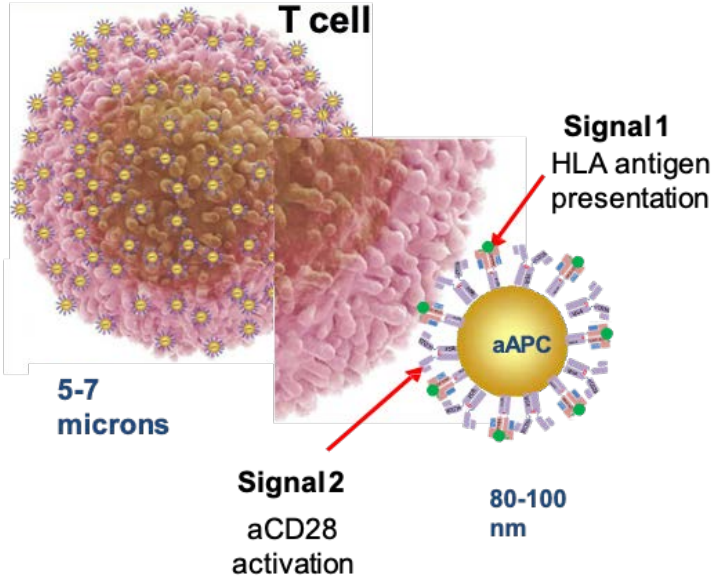
Isser, Livingston and Schneck, 2020 Dec 5;268:120584. doi: 10.1016/j.biomaterials.2020.120584

Cell Therapy Landscape

Why ETC? Sourcing naturally present tumor-specific T cells from PBMCs presents a number of potential opportunities for adoptive cellular therapy (ACT)

- First and foremost, the simplicity and modularity of this approach makes it amenable to personalization.
- The minimal requirements of clinical grade peptide or RNA and patient PBMCs present few regulatory hurdles or complex pipelines for targeting specific antigens, allowing for rapid, ad hoc targeting of patient-specific tumor antigens
- The importance of modularity is further highlighted by studies which have shown optimal antitumor responses may require simultaneous targeting of multiple tumor antigens
- Additionally, by targeting endogenous and at times naive T cells, ETC inherently provides flexibility over the memory phenotype of the final T cell product.
- The resulting T cells also tend to be relatively safe, as these naturally present cells have gone through negative selection.

Artificial Antigen Presenting Cells, aAPC: A simplified approach to T cell stimulation



Artificial Antigen Presenting Cells, aAPC: A simplified approach to T cell stimulation

Ex vivo induction and expansion of antigen-specific cytotoxic T cells by HLA-Ig–coated artificial antigen-presenting cells

MATHIAS OELKE[1], MARCELA V. MAUS[2], DOMINIC DIDIANO[1], CARL H. JUNE[2], ANDREAS MACKENSEN[3] & JONATHAN P. SCHNECK[1]
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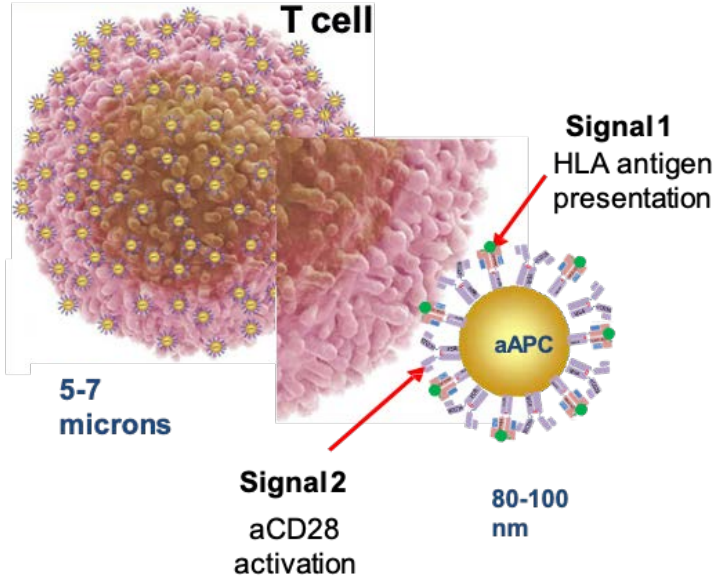
Published online 21 April 2003; doi:10.1038/nm869

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



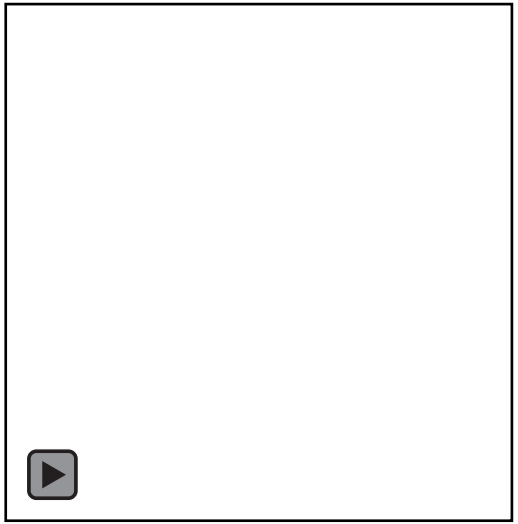
Co-stimulation

Tumor Specific

Activation

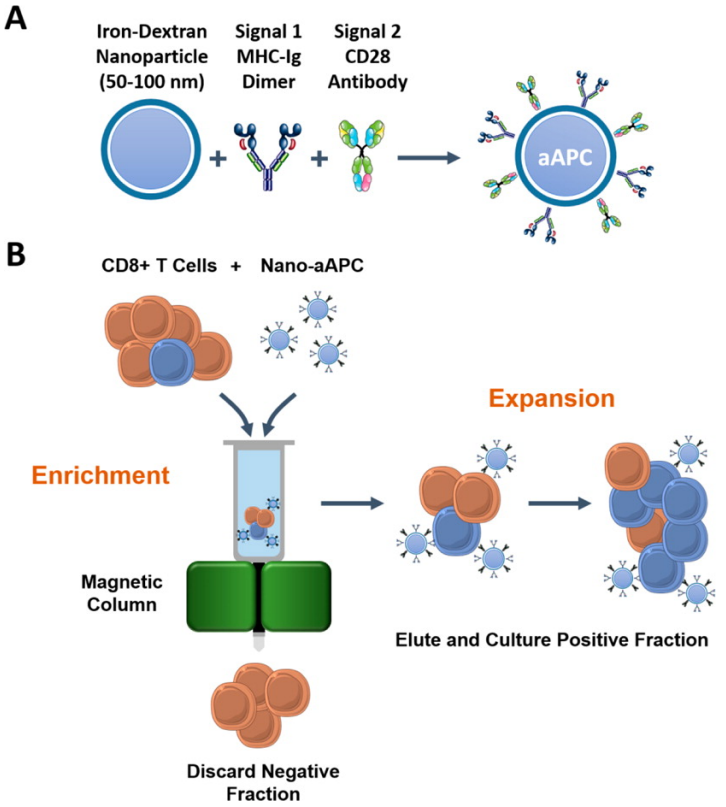
E+E: Enrichment & Expansion of aAPC-stimulated T cells

Tumor-specific T Cells

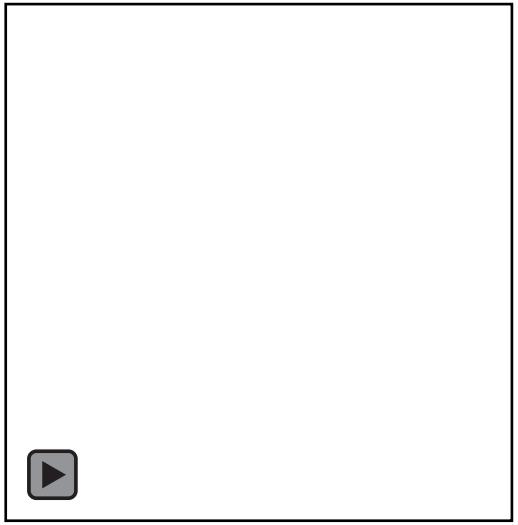


Perica et al. ACS Nano, 2015 Jul 28;9(7):6861-71. doi: 10.1021/acsnano.5b02829.
Hickey et al, Nano Lett 2020 Sep 9;20(9):6289-6298. doi: 10.1021/acs.nanolett.0c01511.

E+E: Enrichment & Expansion of aAPC-stimulated T cells



Tumor-specific T Cells



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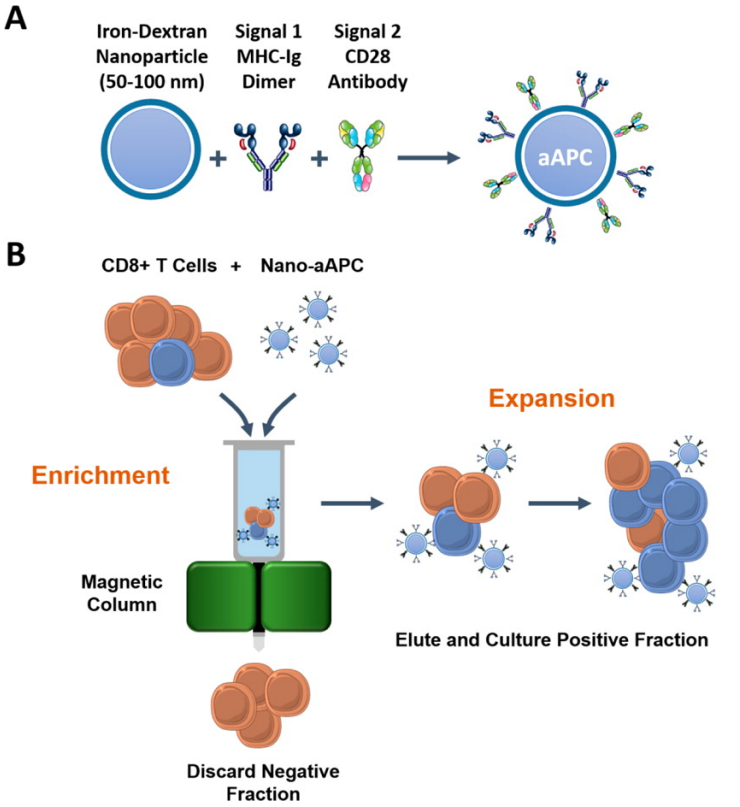

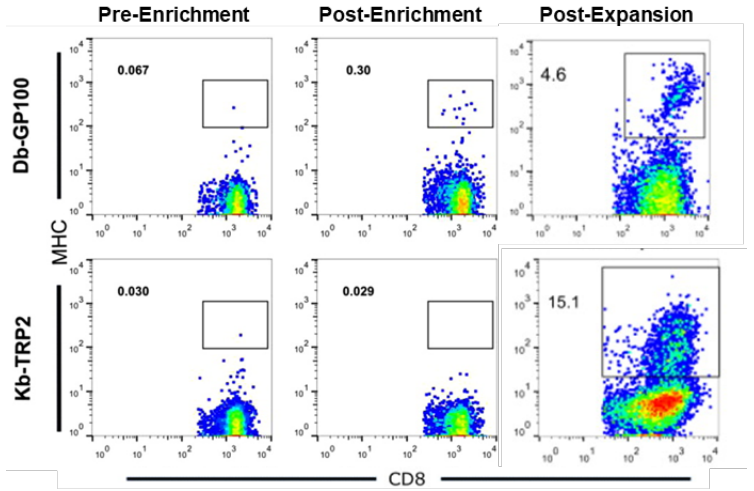

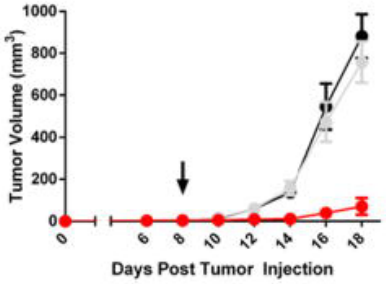

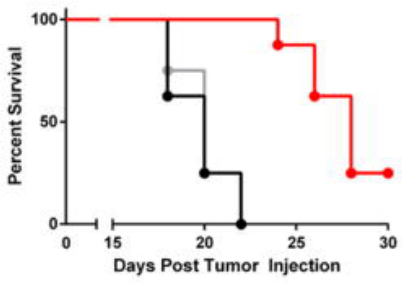

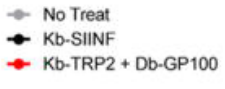

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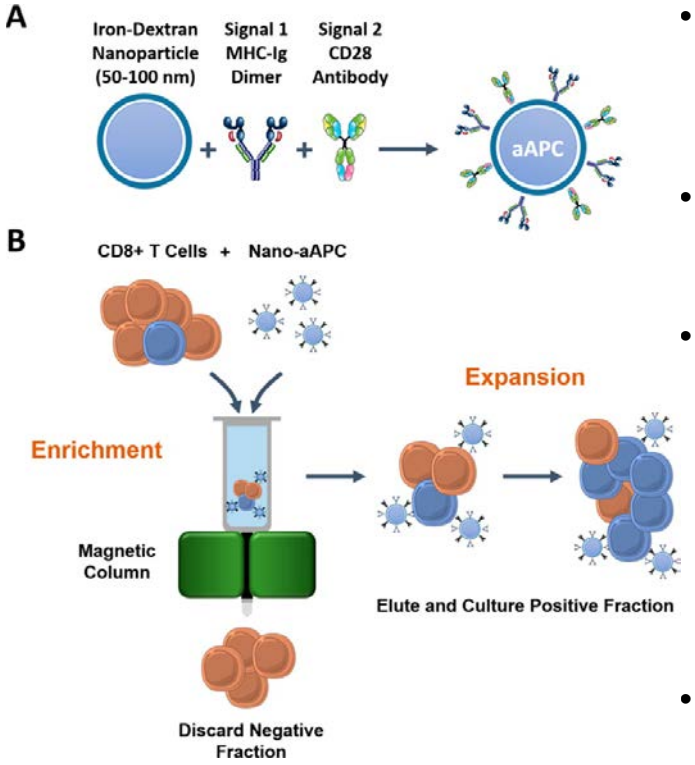
CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Rapid Expansion of Highly Functional Antigen-Specific T Cells from Patients with Melanoma by Nanoscale Artificial Antigen-Presenting Cells

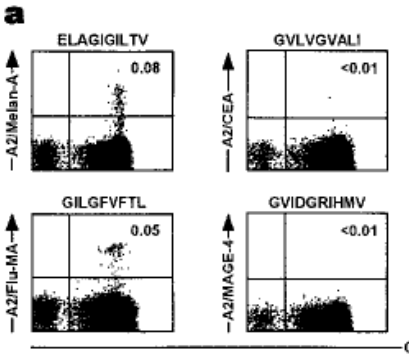
Junya Ichikawa[1], Tatsuya Yoshida[1], Ariel Isser[2], Andressa S. Laino[1], Melinda Vassallo[1], David Woods[1], Sojung Kim[3], Mathias Oelke[3], Kristi Jones[3], Jonathan P. Schneck[2], and Jeffrey S. Weber[1]

Ichikawa, *Clinical Cancer Research*, 2020

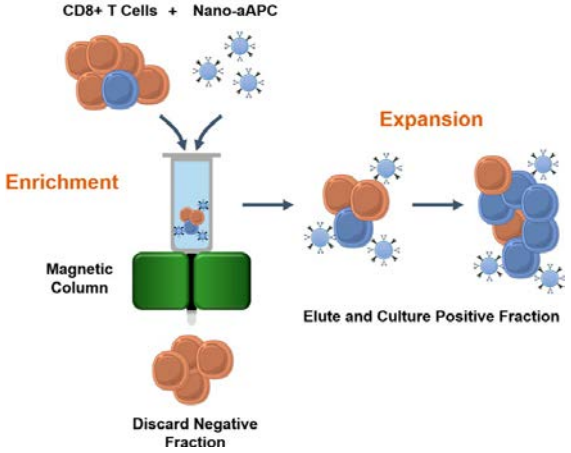
Application to Human CTL: Expansion of Mart-1 and GP-100 specific CTL from melanoma patients

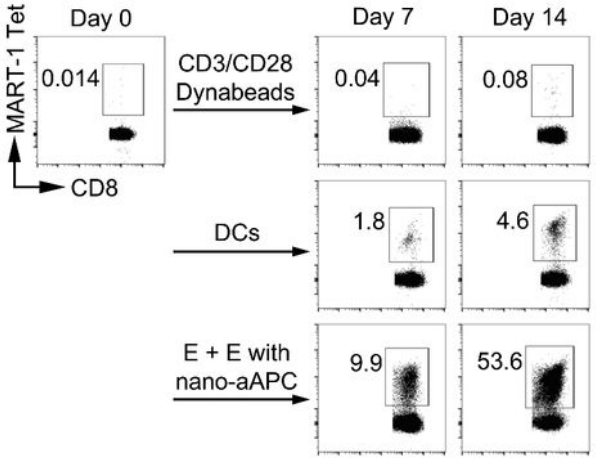


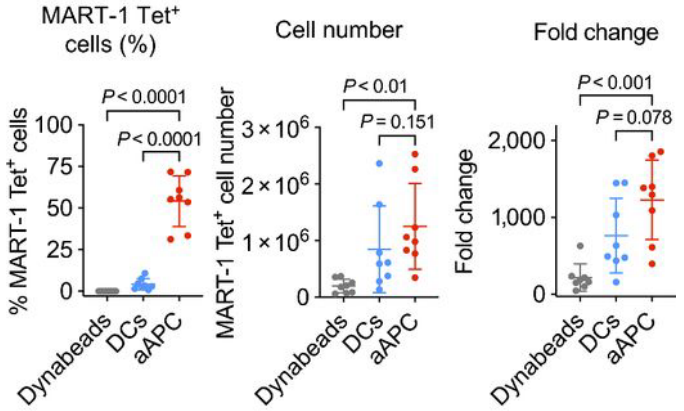
- MART-1 is a protein antigen found on the surface of healthy melanocytes and is involved in regulation of mammalian pigmentation.
- It is overexpressed in melanoma tumor cells and been targeted in a number of melanoma clinical trials
- MART-1_{26-35} is recognized by CD8+ T cells in the context of HLA-A*0201 and has a high precursor frequency (1:1000) in healthy donors. Nevertheless, precursor cells seem to be naïve, in contrast to virus-specific CD8+ T cells, suggesting the population is a result of thymic selection.
- GP-100 is another HLA-A*0201 well defined melanoma specific antigen

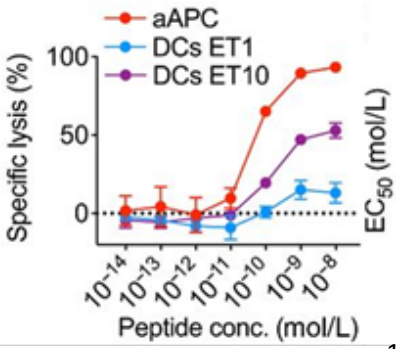


Nanoscale aAPCs can be used to expand highly functional tumor-specific CD8+ T cells from melanoma patients









Ichikawa, *Clinical Cancer Research*, 2020

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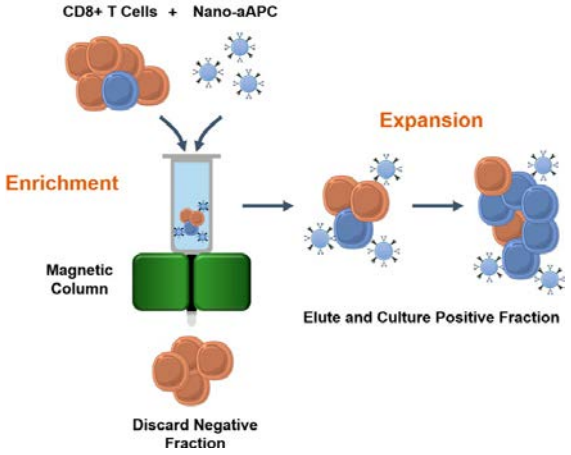
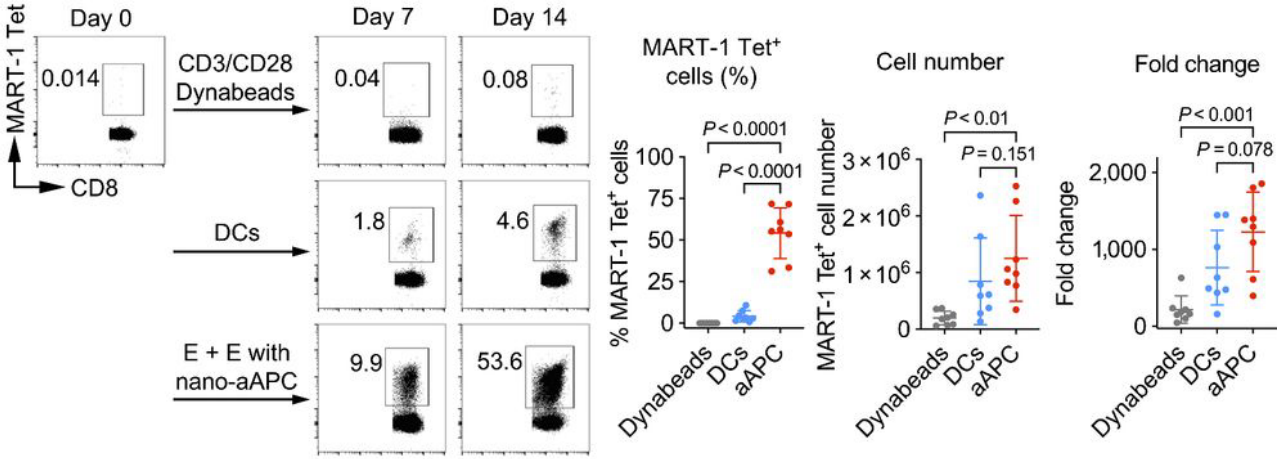
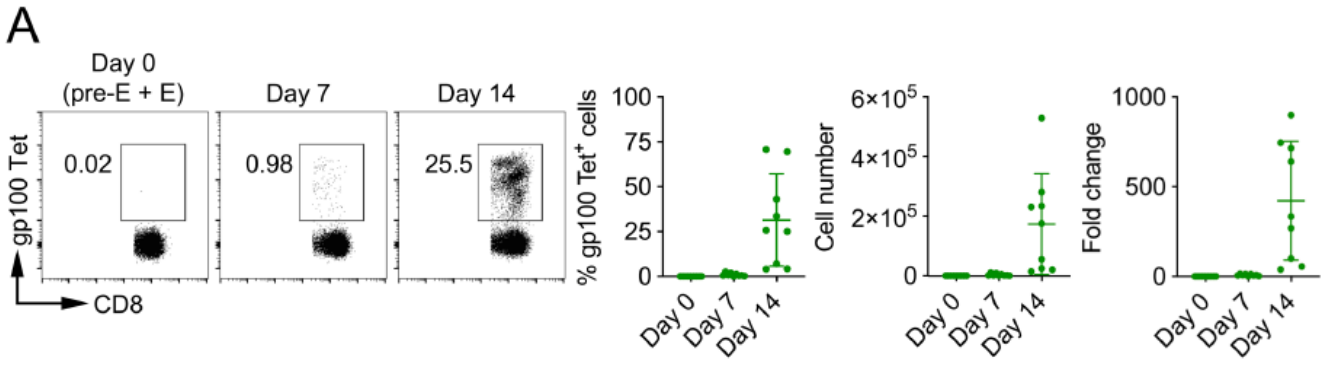
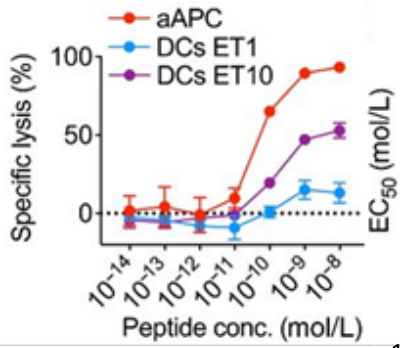


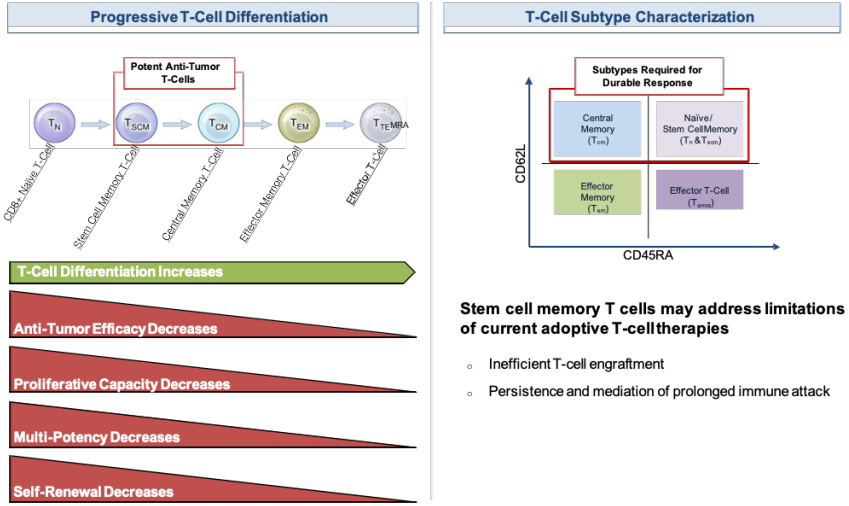






Optimal T Cell Phenotype Consists of Central Memory and Stem Cell Memory T cells

Central Memory (T_{cm}) and Stem Cell Memory (T_{scm}) T-cells represent key anti-tumor T-cells



Stem cell memory T cells may address limitations of current adoptive T-cell therapies

- Inefficient T-cell engraftment
- Persistence and mediation of prolonged immune attack

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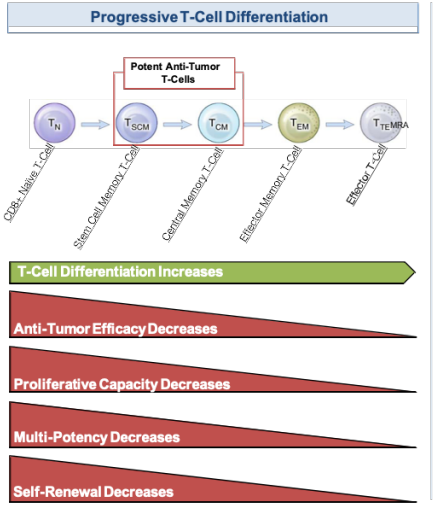

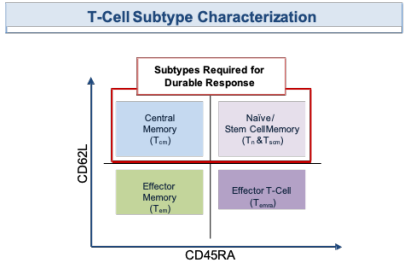

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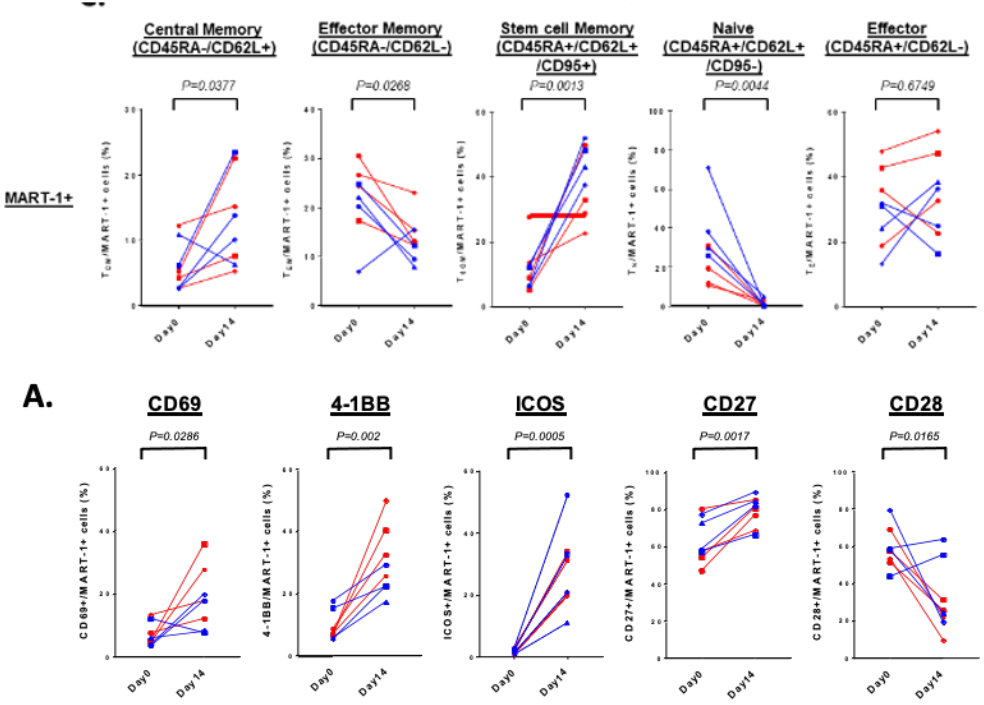

Ichikawa, *Clinical Cancer Research*, 2020

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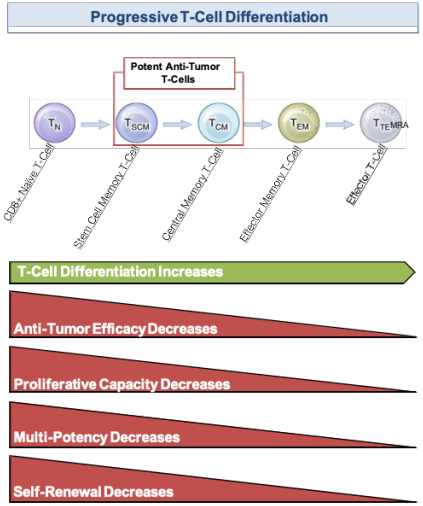

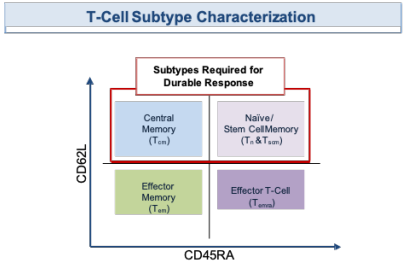

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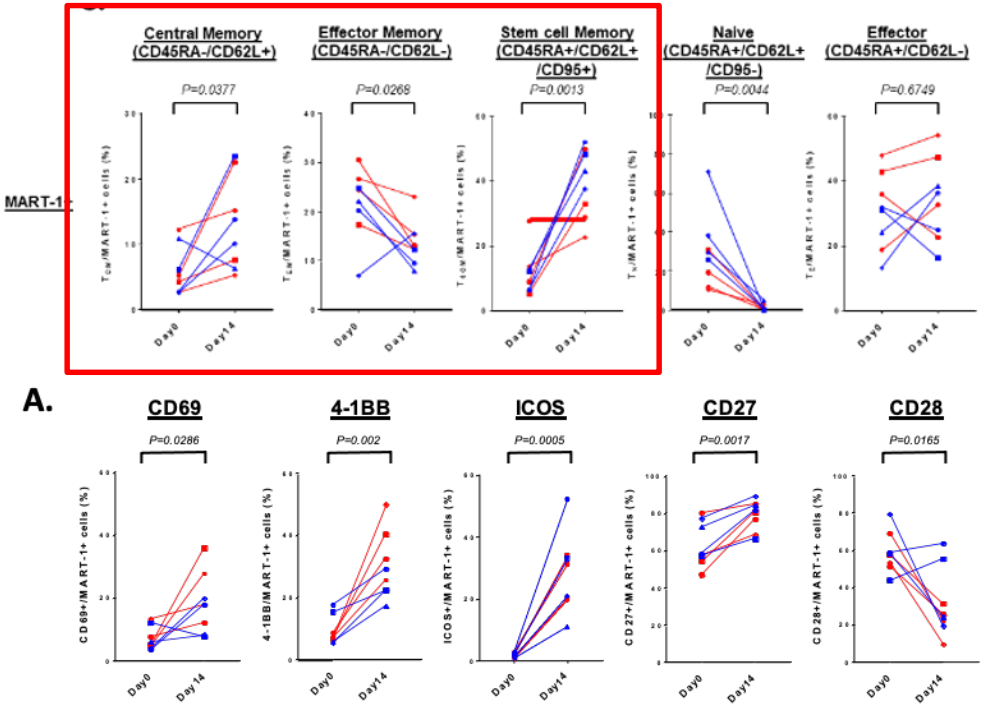
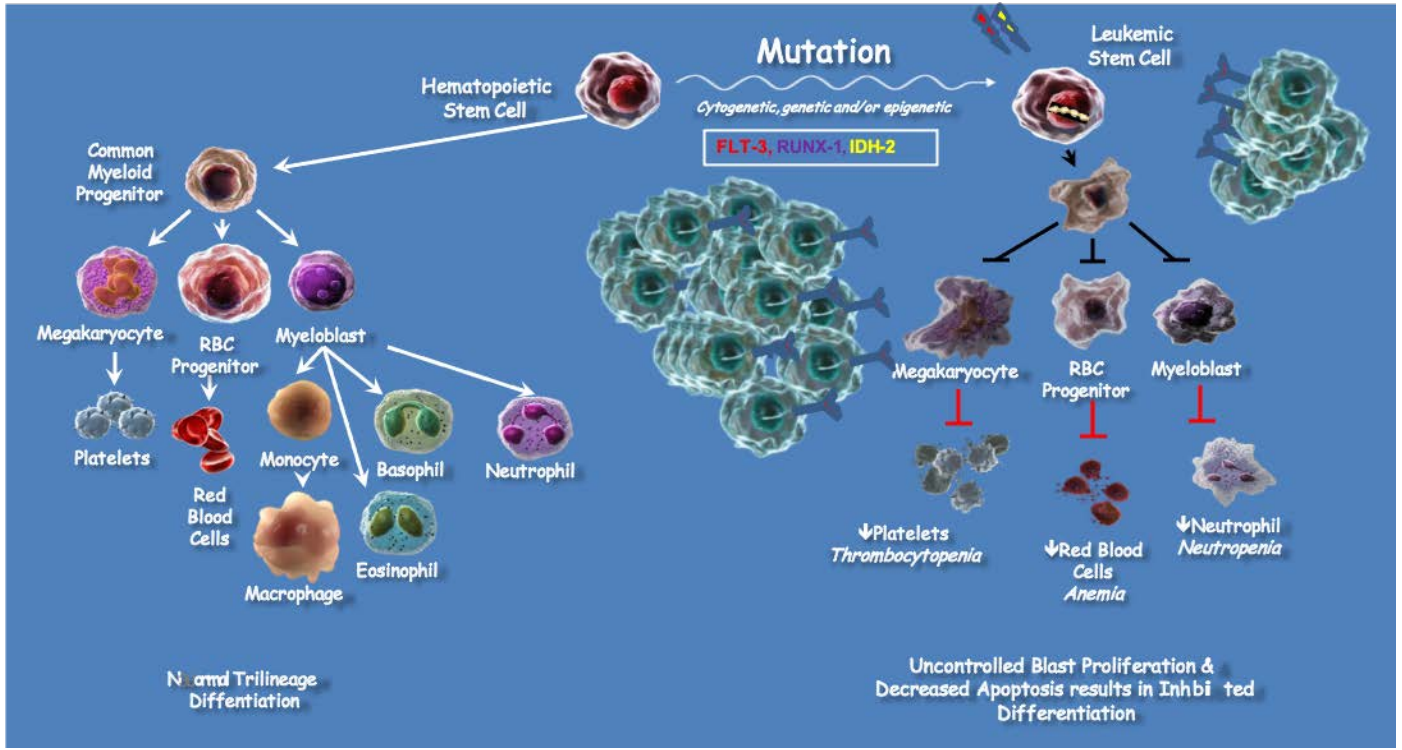
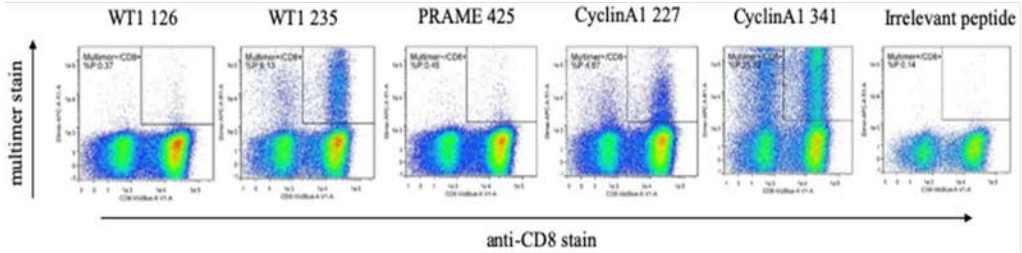


Ichikawa, *Clinical Cancer Research*, 2020

NEXI-001 Clinical Promise: Restore Normal Donor by Killing Both Leukemic Blasts and Leukemic Stem Cells Hematopoiesis



aAPC stimulated T cells can be directed against multiple AML antigen targets and grown to clinically relevant numbers



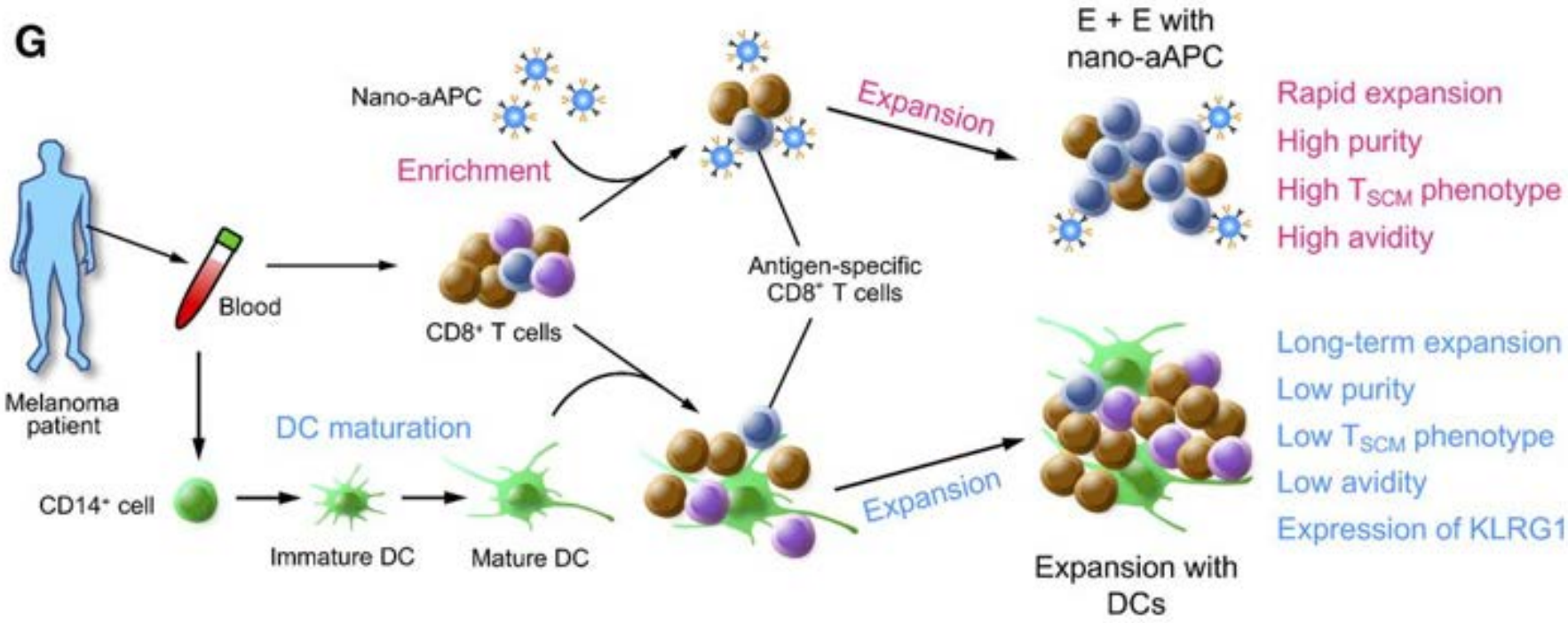
Total Antigen Specificity
38%

Enrichment and Expansion (E+E) system generates T-cell products that are highly antigen specific

	$WT1_{126}$	$WT1_{235}$ $CA1_{341}$		$PRAME_{425}$ Control	$CA1_{227}$		Total Specificity (%)
L132-2	0.5	21.4	0.6	3.7	12.0	1.4	32.8
L133-1	0.1	27.7	0.0	13.4	4.9	0.6	44.3
L139-1	0.7	31.6	0.4	7.2	6.6	0.4	44.6
L147-1	0.5	9.5	0.6	5.2	22.5	0.2	37.2

Reproducibility – variability is donor-dependent, not process-related

Summary

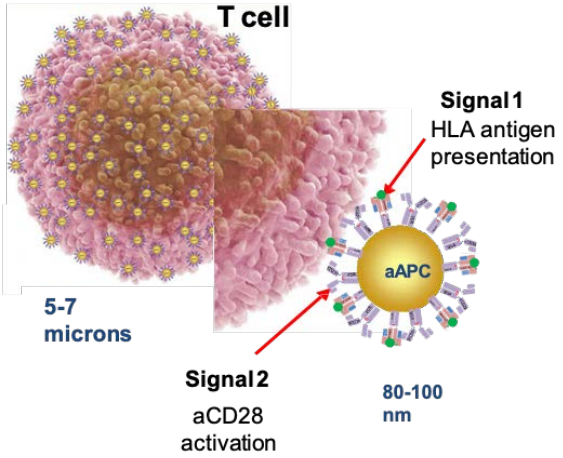


Ichikawa, *Clinical Cancer Research*, 2020

Summary

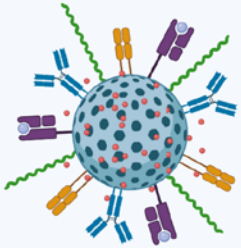
1. aAPC directly engage tumor-specific T cells for ACT – does not require processing and presentation by host DCs and cannot be down-regulated
   - Activate and expand both foreign and self tumor-specific T cells
2. E+E allows for batching: Target multiple tumor-specific antigens simultaneously minimizing potential for tumor escape
3. Target naïve and memory T cell repertoire
   – Results in robust, persistent anti-tumor activity and immunologic memory
4. Mechanistically, complements other IO approaches, CPI, that break tolerance
5. Scalable and flexible ‘off-the-shelf’ based approach: Cassette-able components provide rapid path to new product design and production
6. Can be used to detect and stimulate T cells from a complex mixture of tumor-specific peptides: Potential to validate ‘predicted’ neo-antigens in clinical settings

The Design Space



Modality

A *Particles*

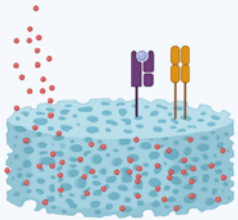


Incorporation of
Signal 1 Signal 2 Signal 3

Improvement of PK
- PEG
- CD47

Targeting moieties
- DC targeting
- LN targeting
- Tumor targeting

B *Scaffolds*



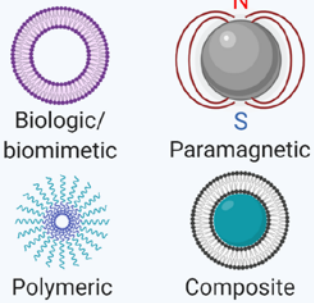
Incorporation of
Signal 1 Signal 2 Signal 3

Macroporous for cell infiltration

Release of soluble molecules
- Attractants
- Stimulants
- Antigen

Composition

C *Material choice*



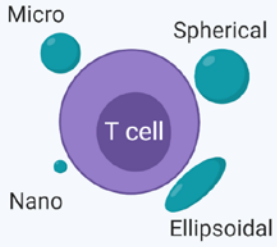
Biologic/ biomimetic

Paramagnetic

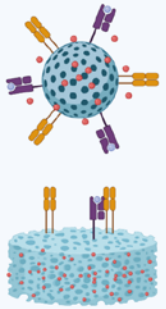
Polymeric

Composite

D *Size and shape*



E *Ligand choice*



T cell activation (Signal 1)
- pMHC multimers, αCD3

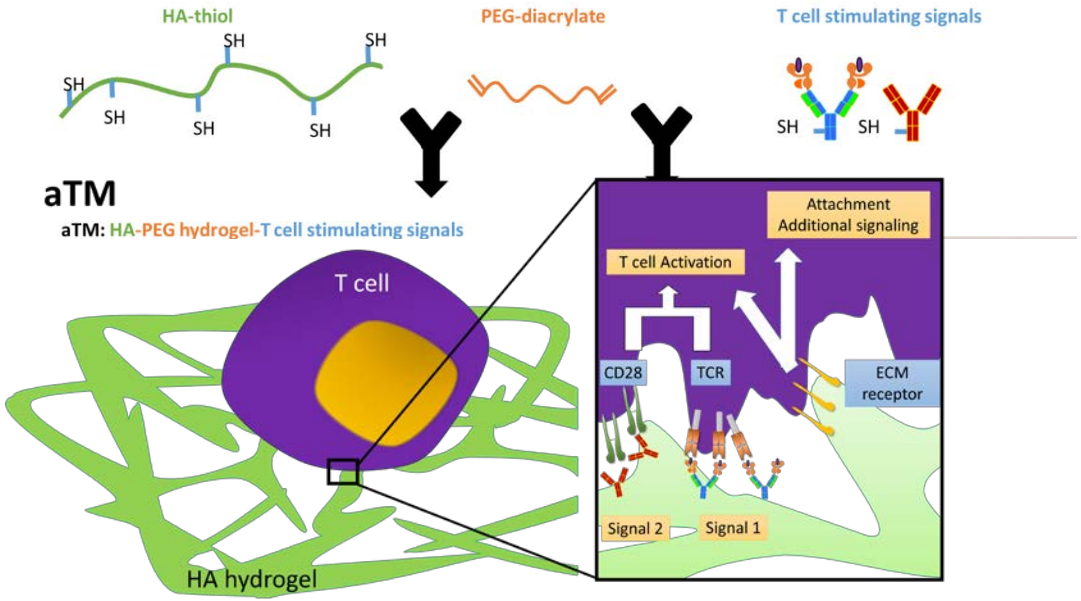
Costimulatory molecules (Signal 2)
- B7.1, αCD28, 41BBL,

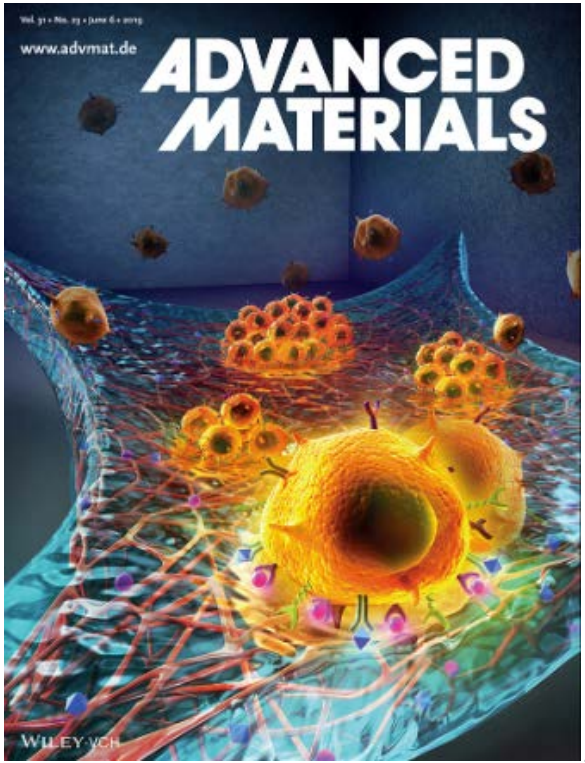
Cytokine support (Signal 3)
- IL-2, IL-7, IL-12, IL-15

Isser, Livingston and Schneck, 2021 Jan;268:120584. doi: 10.1016/j.biomaterials. 2020.120584. Epub 2020 Dec 5.

Biomaterials can be used to recapitulate the signals provided by endogenous antigen presenting cells

- Hyaluronic acid hydrogel conjugated with signals 1 and 2 for development of aTM platforms





Hickey, J. W., *Advanced Materials* (2019)

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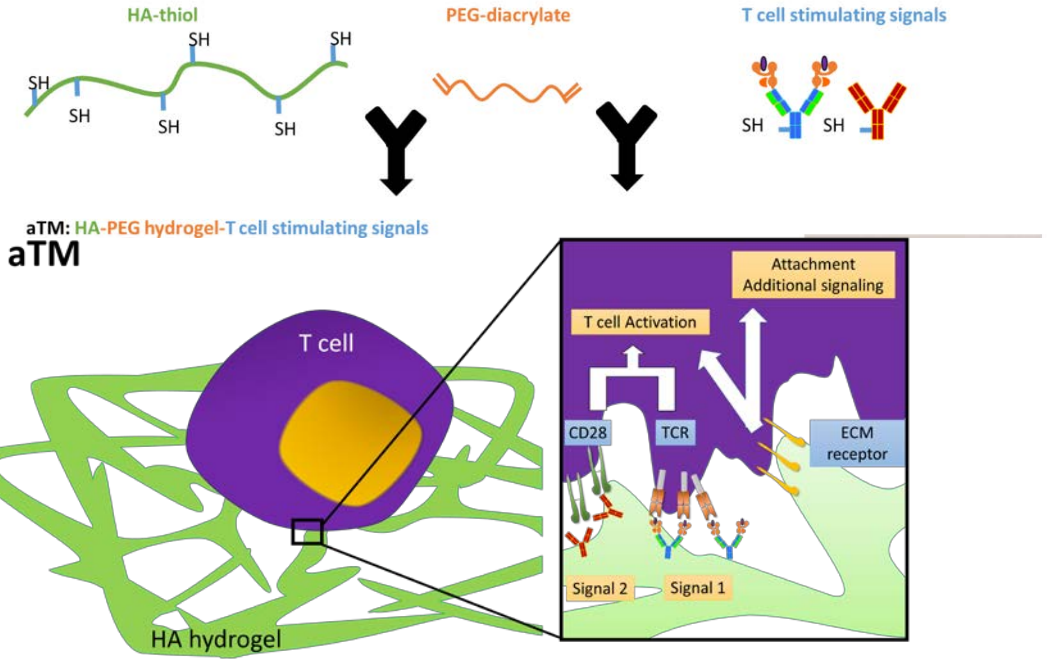
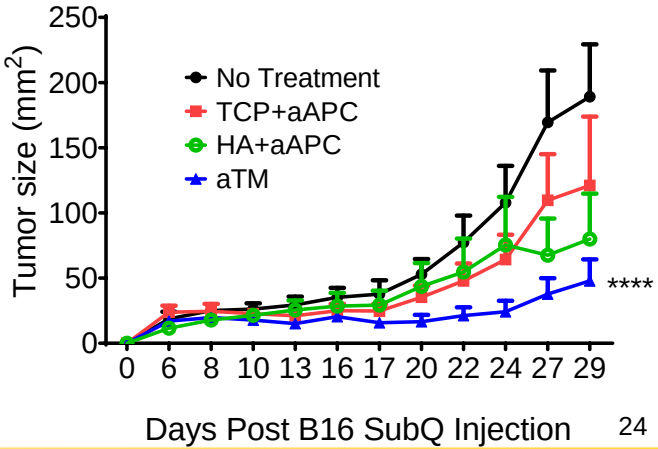
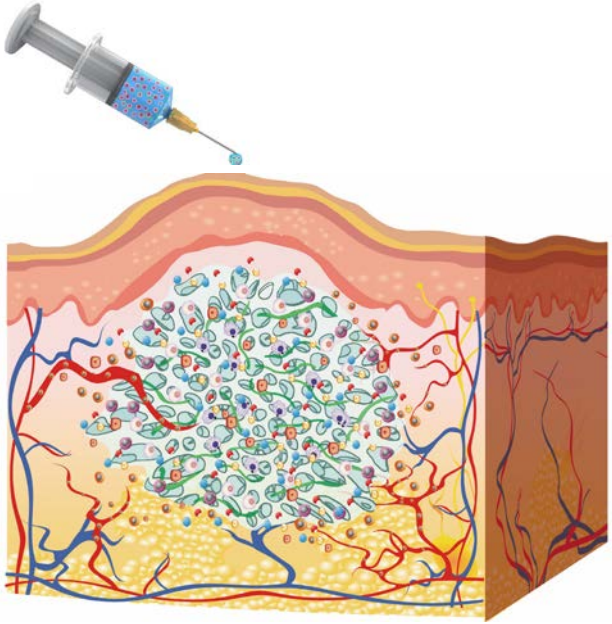
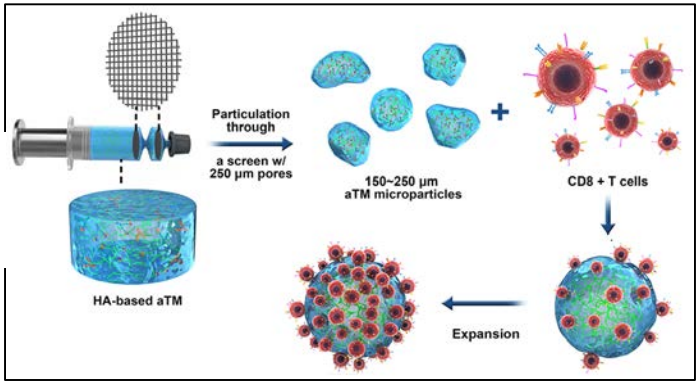


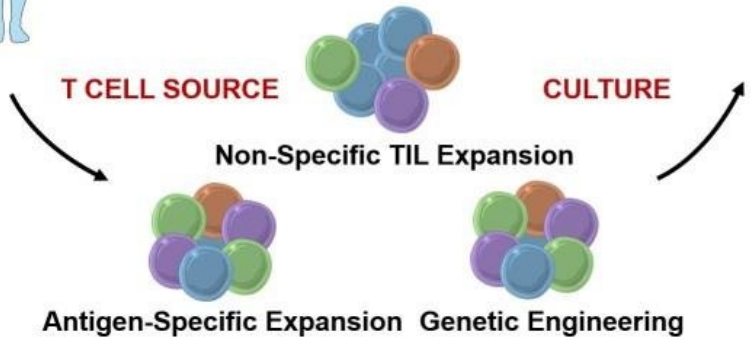


Goal: *in vivo* T cell activation

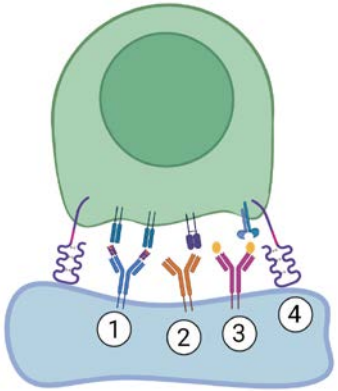


Subcutaneous injection





Artificial Lymph Node (aLN)



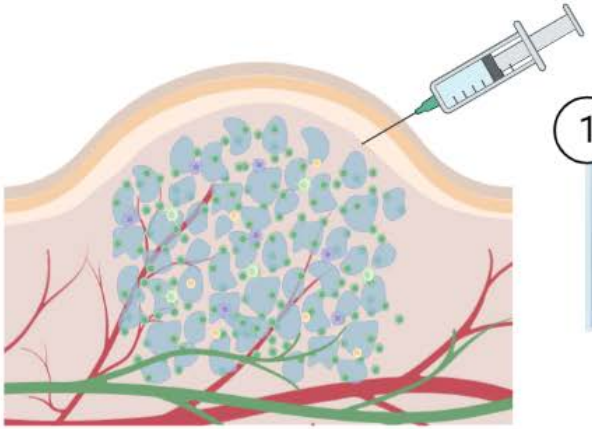
① pMHC

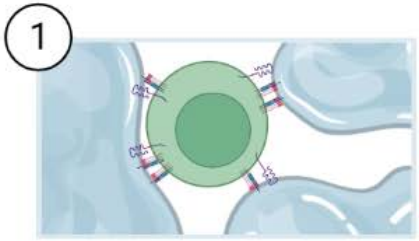
② αCD28

③ IL-2+Ab

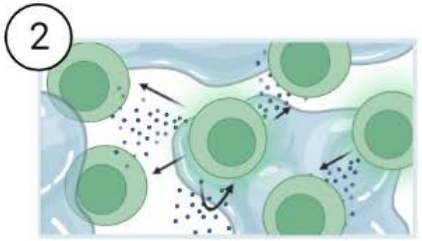
④ ECM

Co-inject aLN and naïve B6 CD8+ T cells





Increased cell-matrix contact



Increased cell-cell contact

Host cell infiltration

Potential Collaboration

David Avigan: R01CA262629 - Personalized Adoptive T-cell Therapy for AML
07/2021 – 06/2026

1) Developed a personalized cancer vaccine in which patient derived tumor cells are fused with autologous dendritic cells (DCs), 2) Completed a phase II clinical trial in which patients that achieve remission following chemotherapy undergo serial vaccination with DC/AML fusions.
2) The DC/AML vaccine can be used as a platform to generate activated leukemia-specific T cells ex- vivo for adoptive immunotherapy. In this way, effector cells may be generated that are leukemia-specific, capture tumor heterogeneity, and are activated ex vivo
3) In the third aim, we will conduct a Phase I study in which patients with AML who achieve complete remission will undergo adoptive therapy with vaccine stimulated T cells.

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2) The DC/AML vaccine can be used as a platform to generate activated leukemia-specific T cells ex- vivo for adoptive immunotherapy. In this way, effector cells may be generated that are leukemia-specific, capture tumor heterogeneity, and are activated ex vivo
    1) An aAPC or hydrogel-based expansion approach
    2) HLA Class I, A201, or Class II, DR4 or DP4
3) In the third aim, we will conduct a Phase I study in which patients with AML who achieve complete remission will undergo adoptive therapy with vaccine stimulated T cells.

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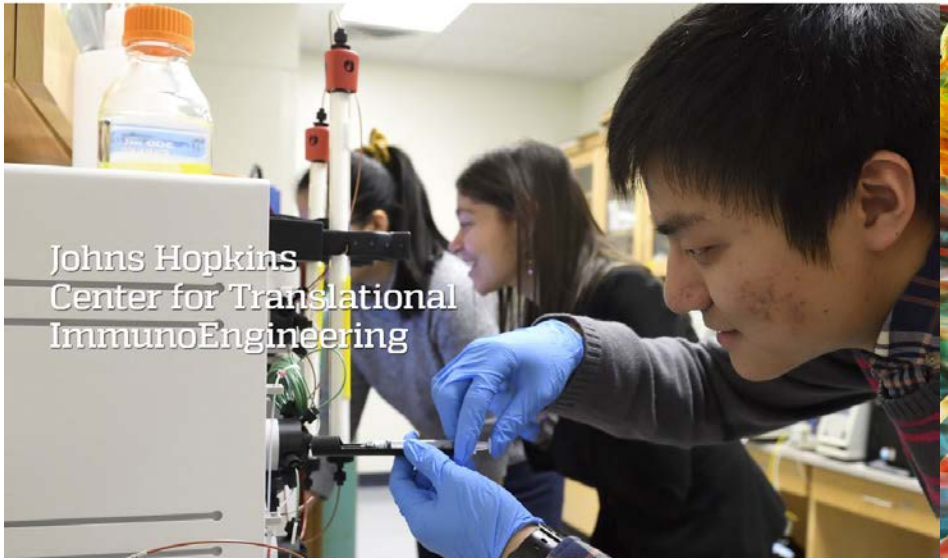
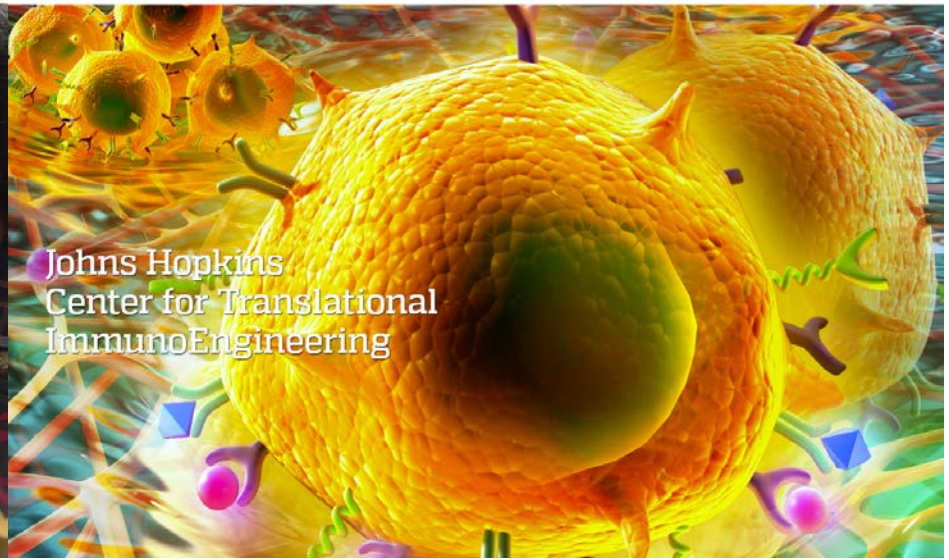
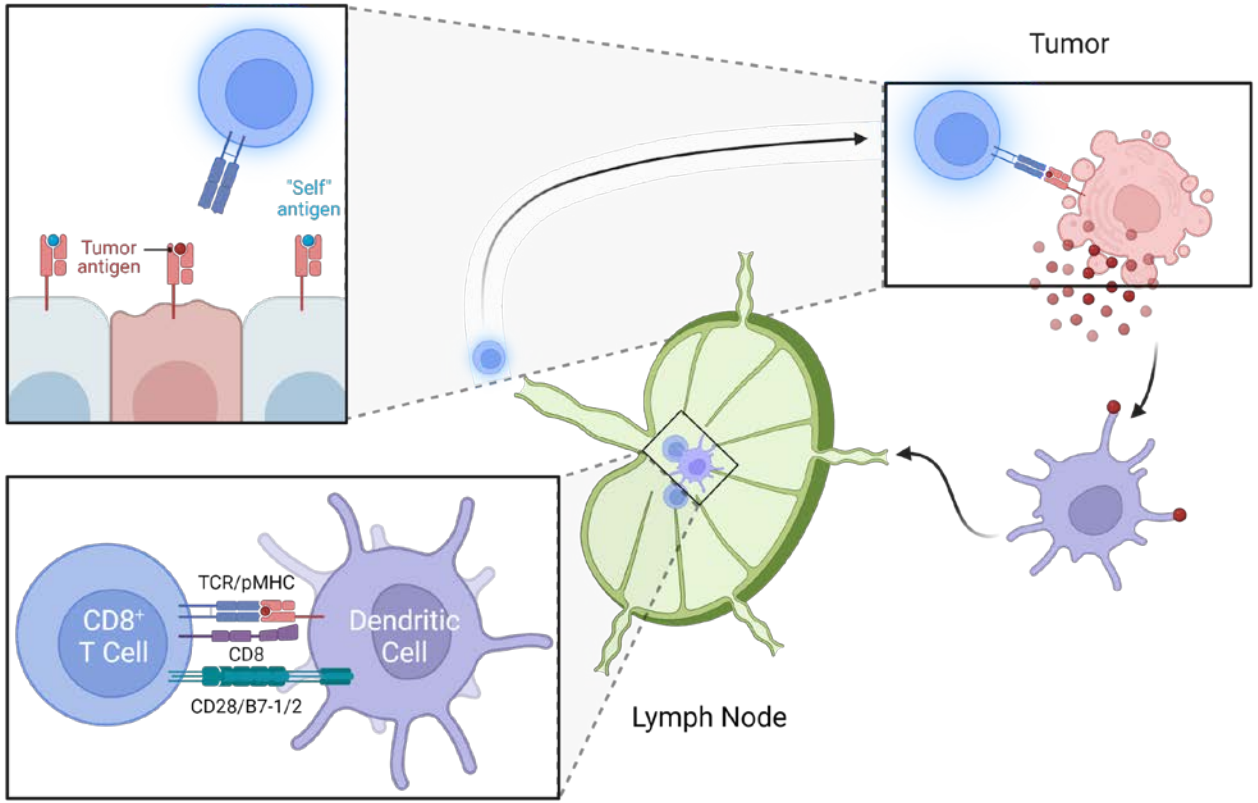




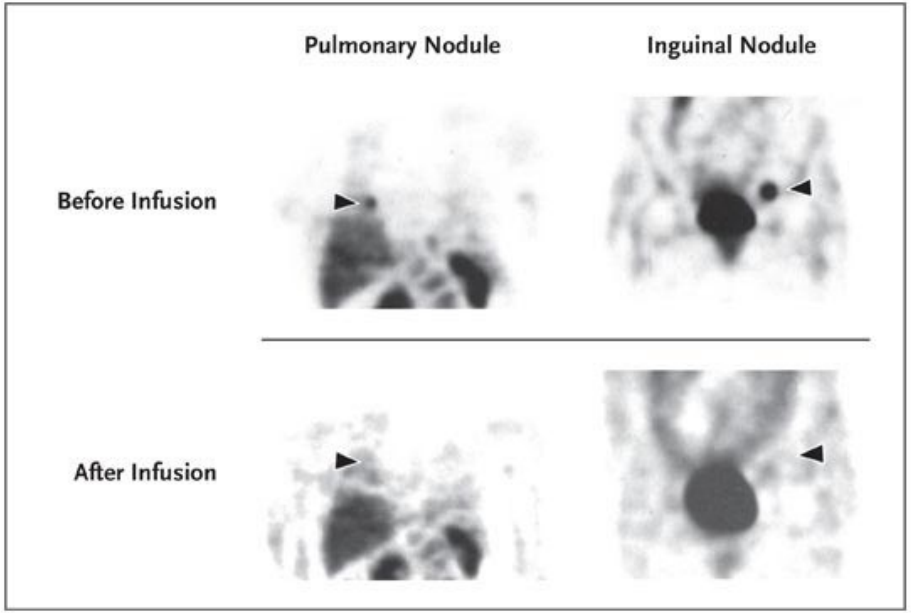
Magic Bullets of the Immune System: Tapping CD4+ Cells for ACT



Created in BioRender.com

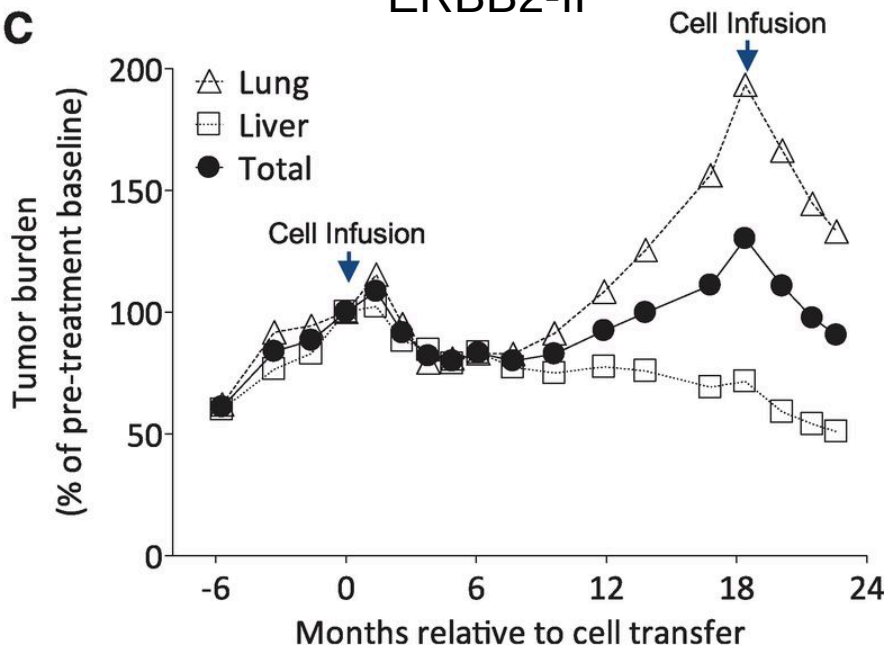
$CD4^+$ T cell-based ACT has demonstrated clinical efficacy

NY-ESO-1



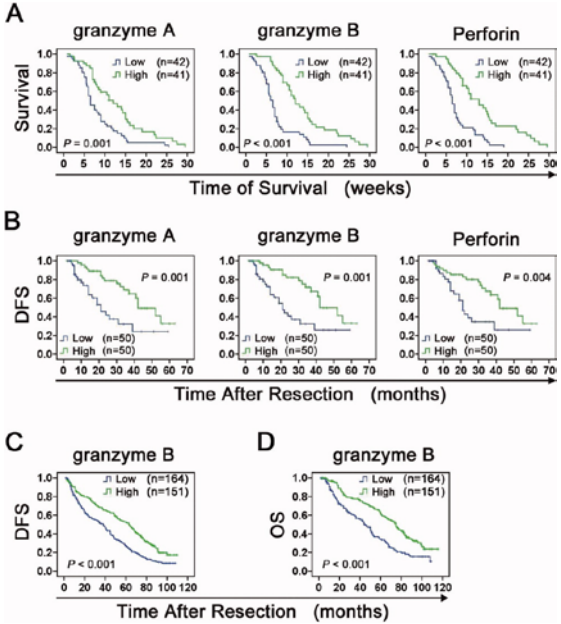
Hunder et. al., *NEJM*, 2008

ERBB2-IP

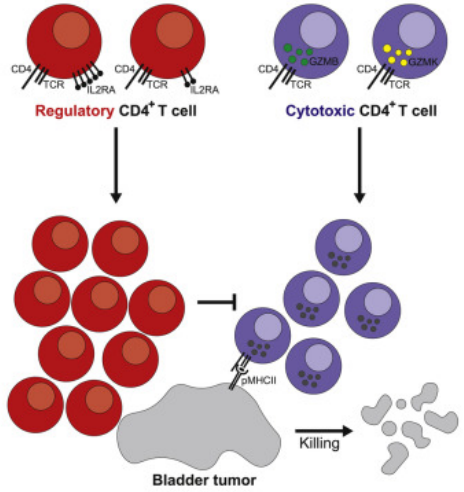


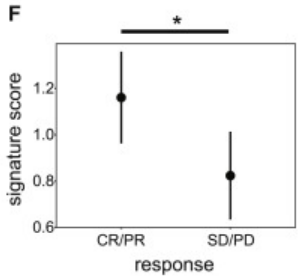
Tran et. al., *Science*, 2014

Cytotoxic CD4⁺ T cells are therapeutically relevant in cancer

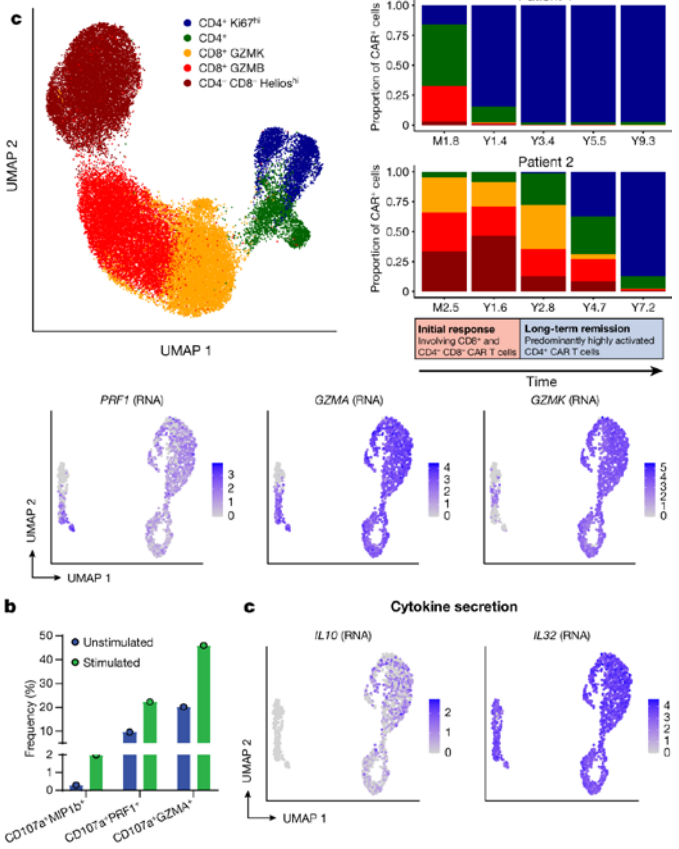


Fu et. al., *Hepatology*, 2012





Oh et. al., *Cell*, 2020



Melenhorst et. al., *Nature*, 2022

CD4+ T cells play a wide array of helper and effector roles in the cancer immune response

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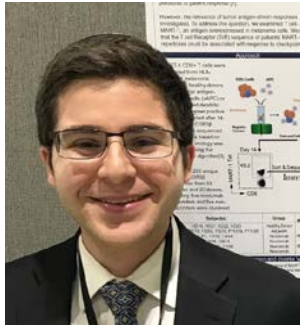
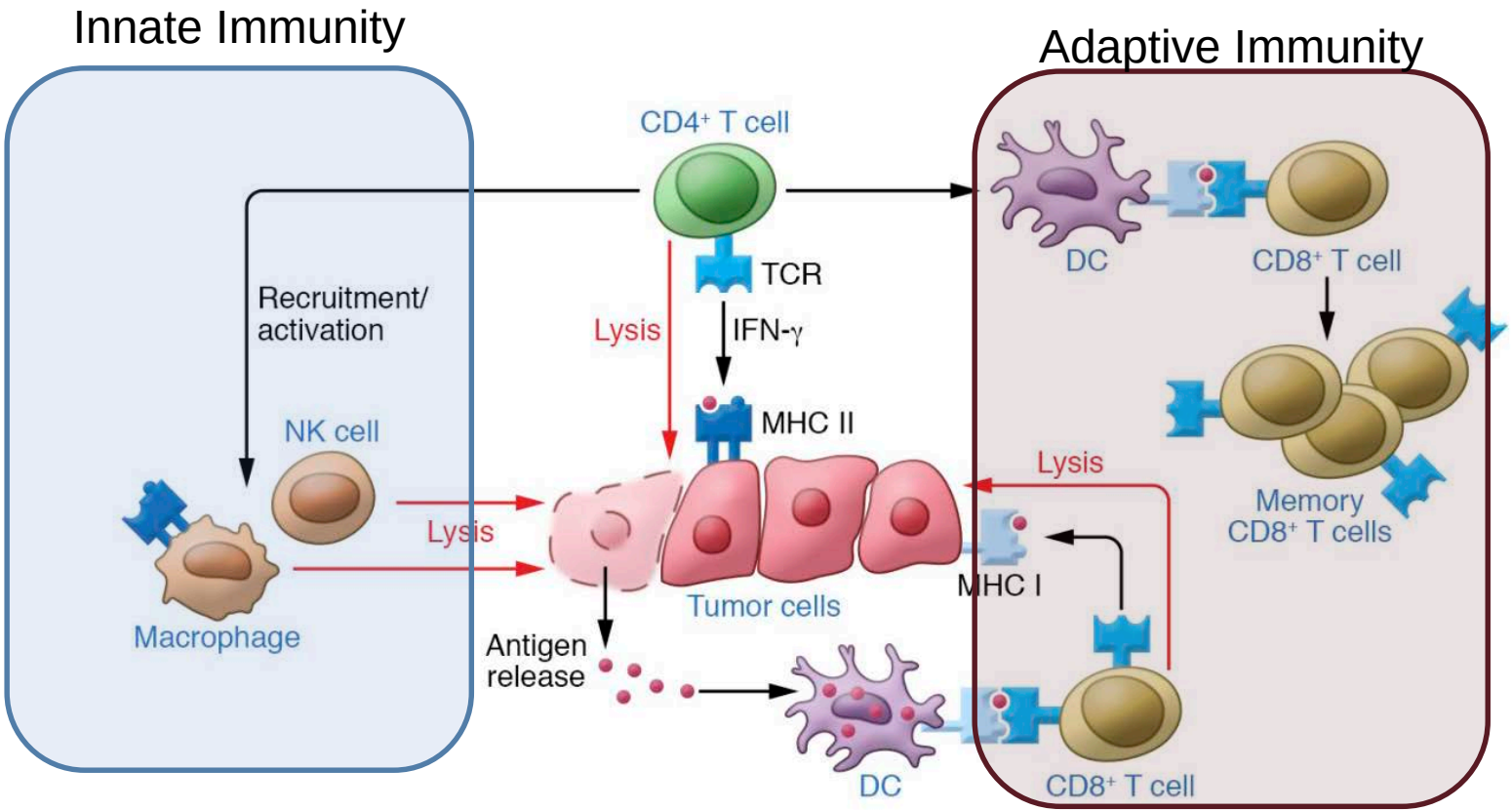
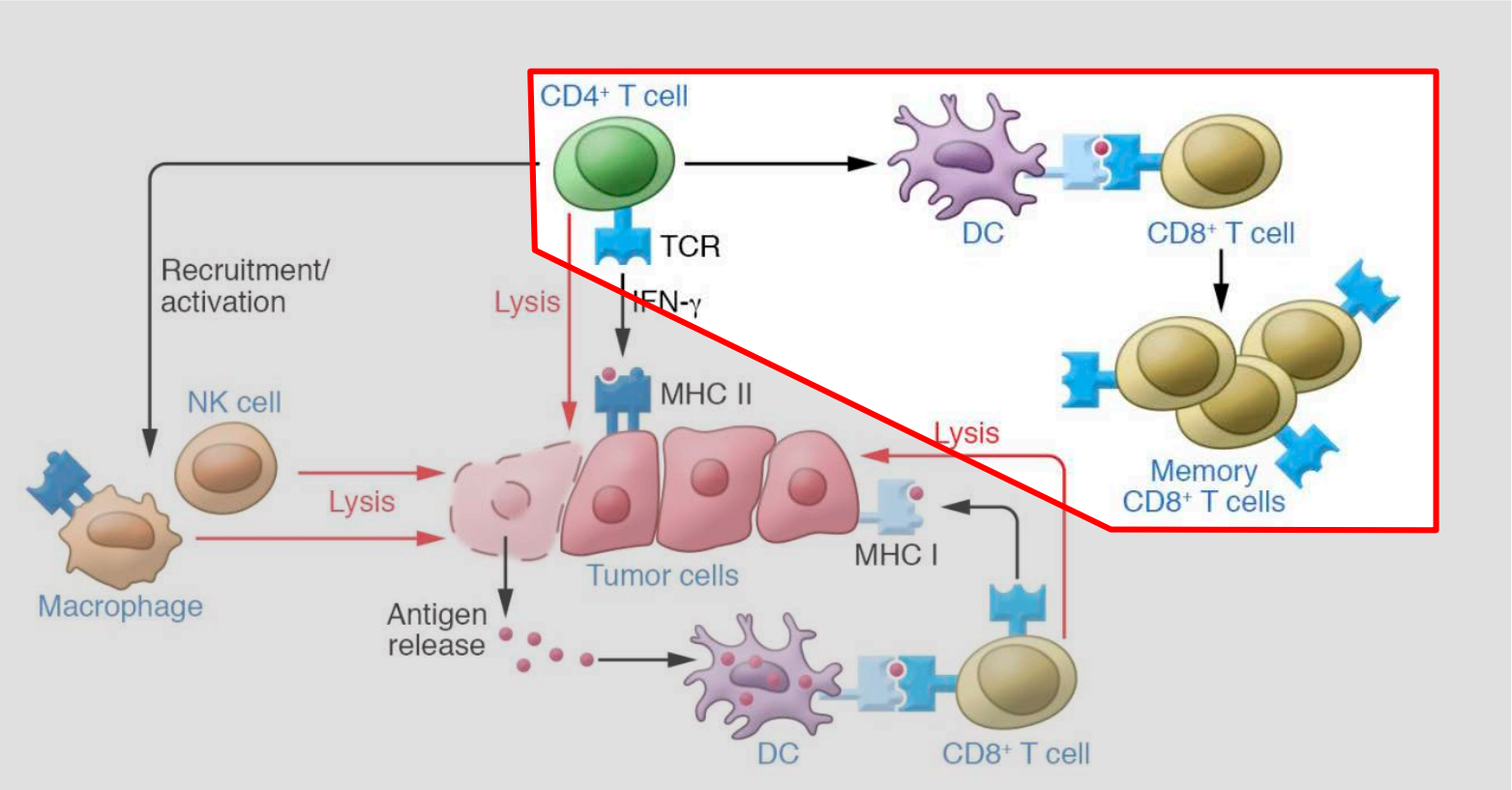




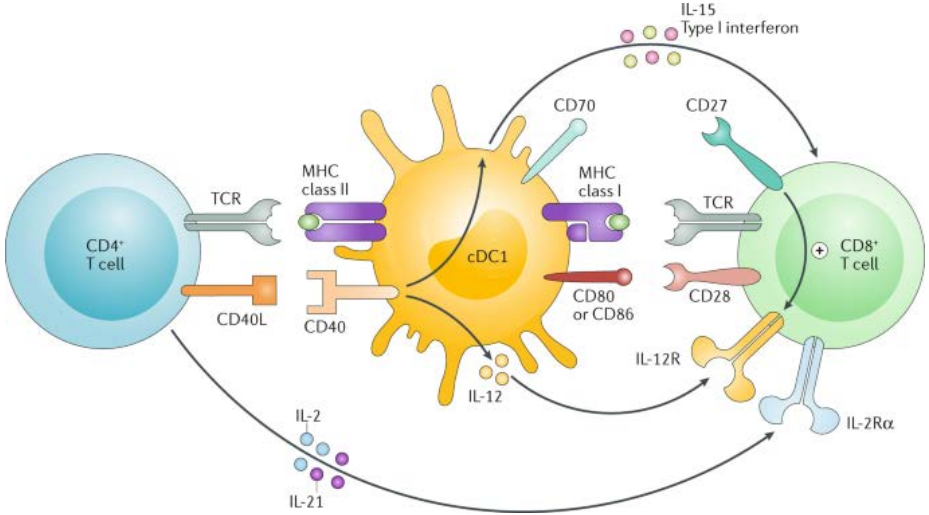
Isser, *J. Clin. Invest.*, 2019

CD4+ T cells provide "help" to CD8+ T cells



Isser, *J. Clin. Invest.*, 2019

Combined MHC I/II aAPCs mimic dendritic cell-mediated CD4+/CD8+ T cell cross-talk



Isser et al https://www.nature.com/articles/s41467-022-33597-y

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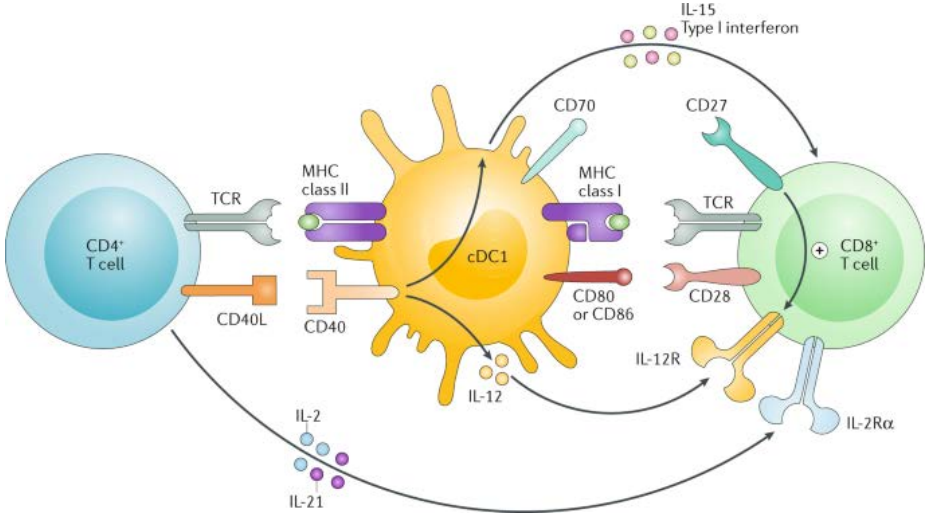

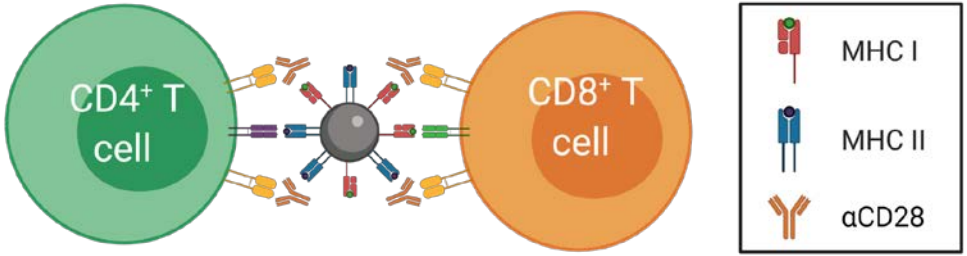

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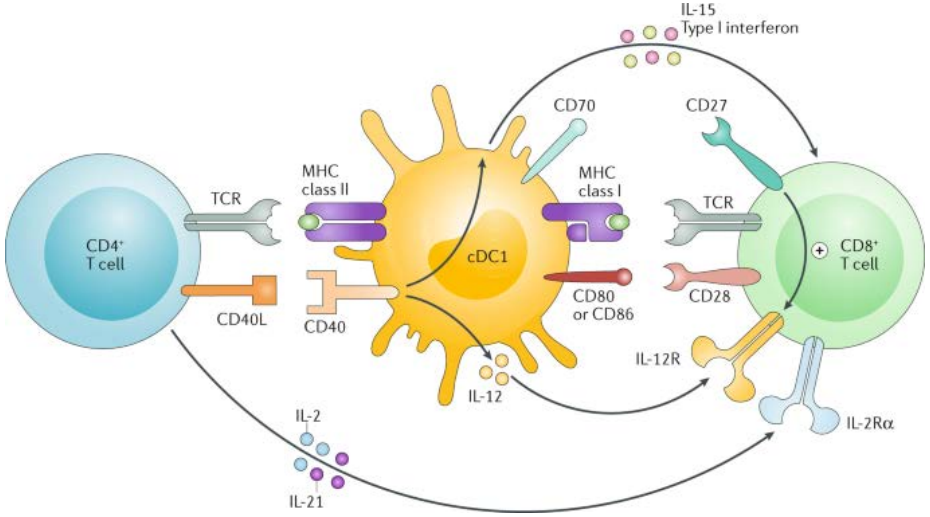
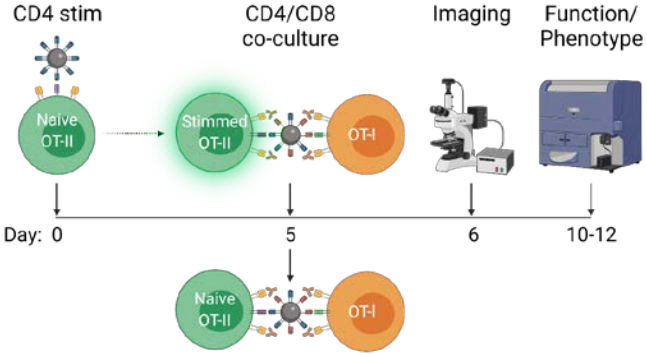
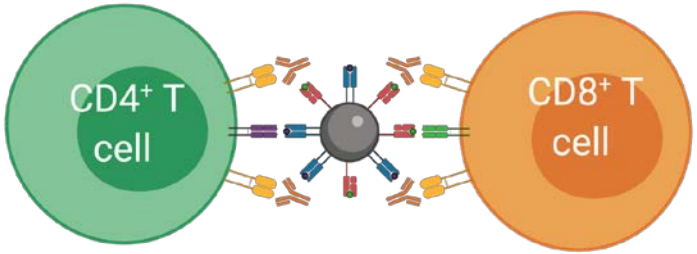
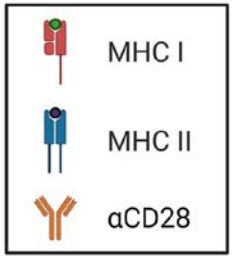
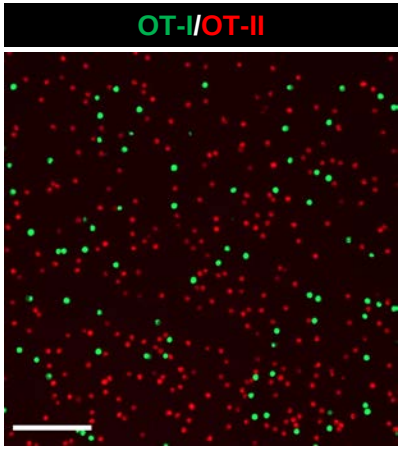




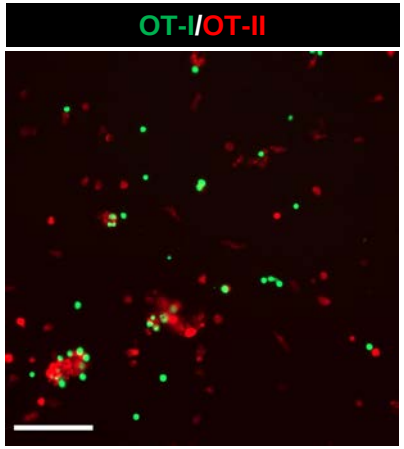




OT-I+naive OT-II



OT-I+Th1 OT-II



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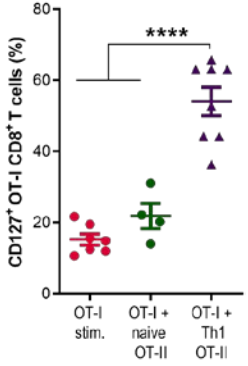
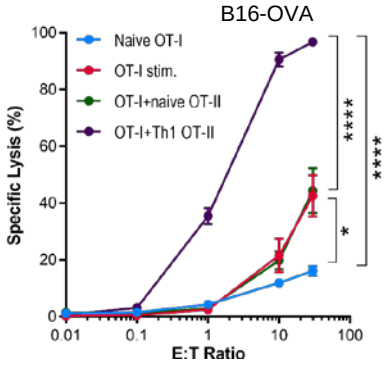
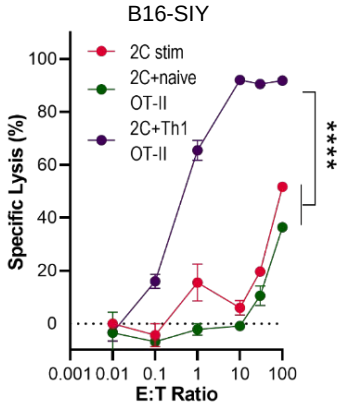
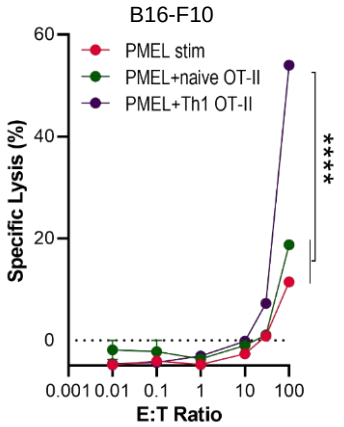
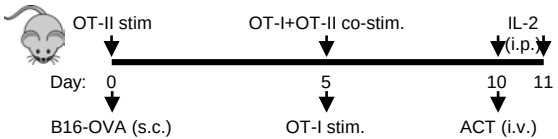
Combined MHC I/II aAPCs boost the memory phenotype, function, and antitumor activity of transgenic CD8+ T cells

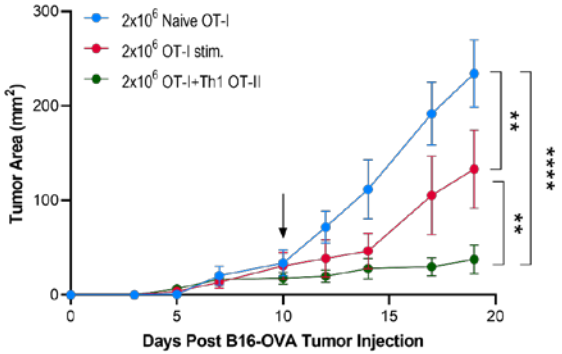


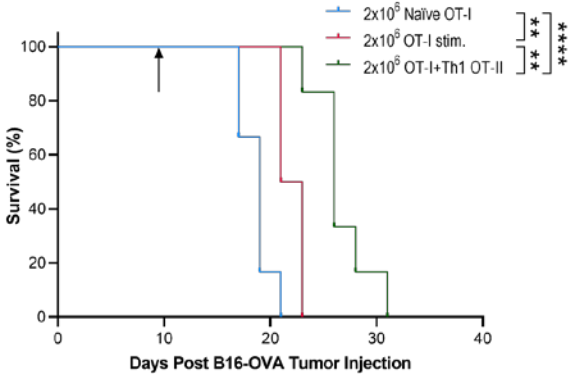












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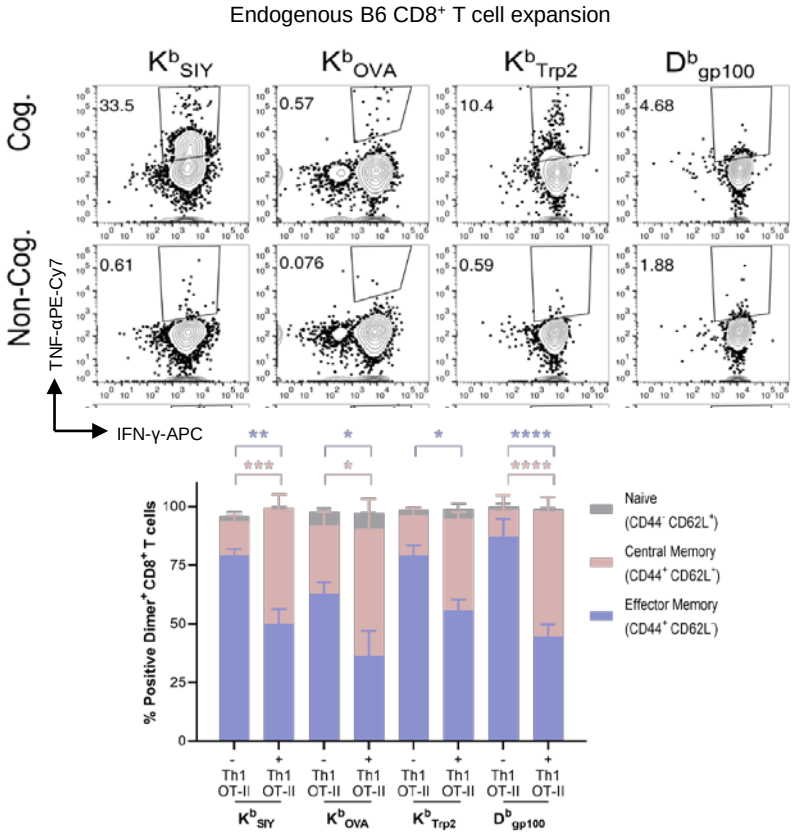
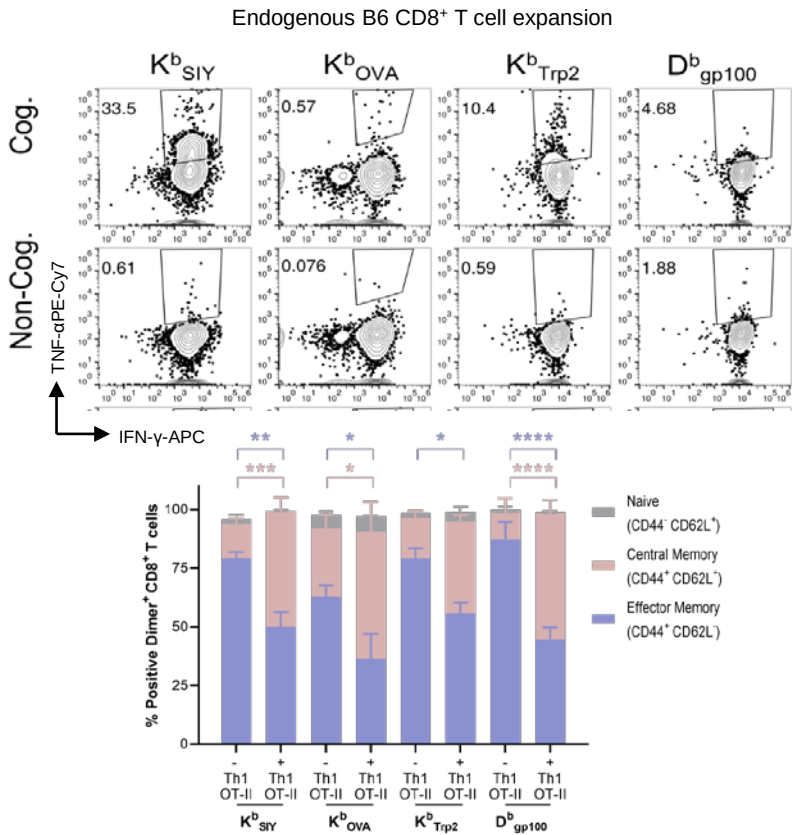
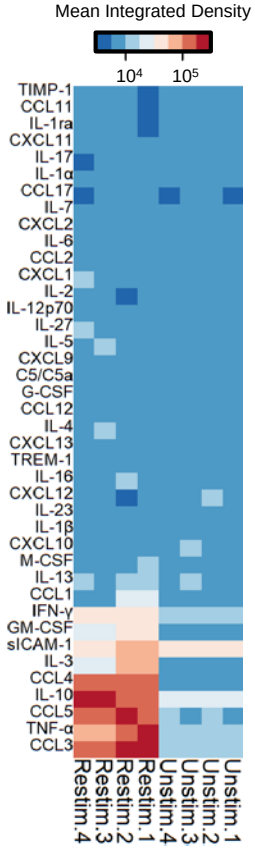
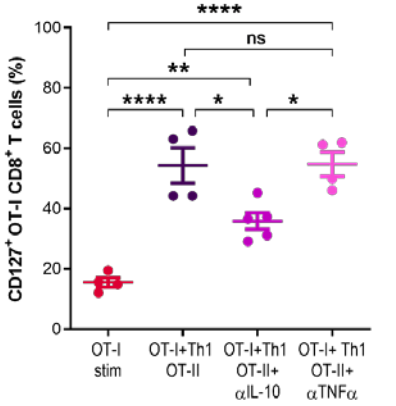
aAPC mediated help can be redirected to a wide range of endogenous CD8+ T cells

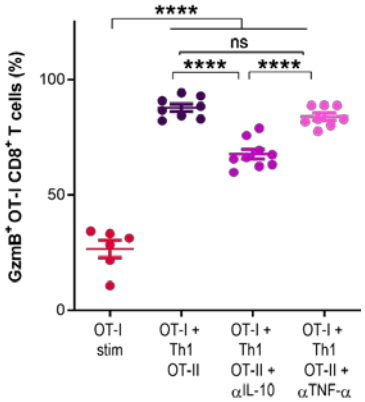


And OT-II help requires re-stimulation, is delivered solubly, and partially depends on IL-10

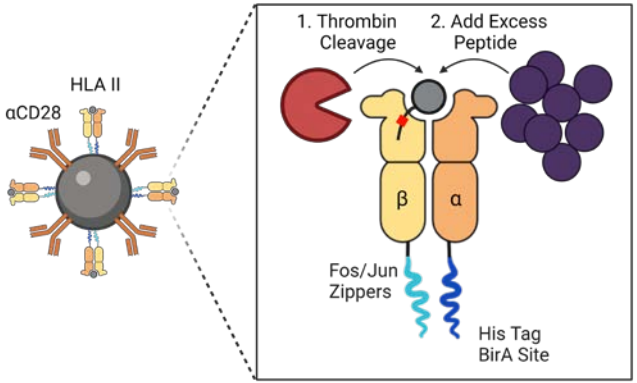


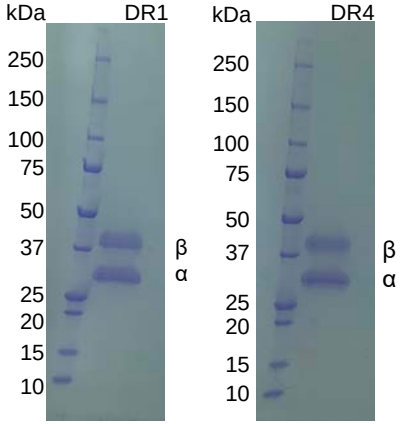


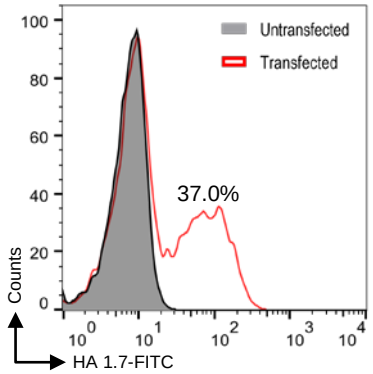


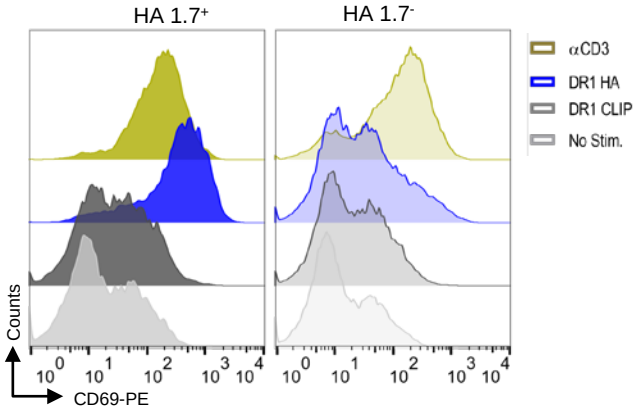


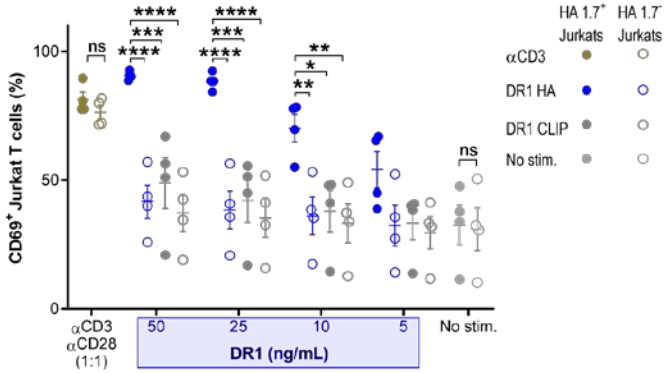
HLA II aAPCs stimulate cognate Jurkat T cells











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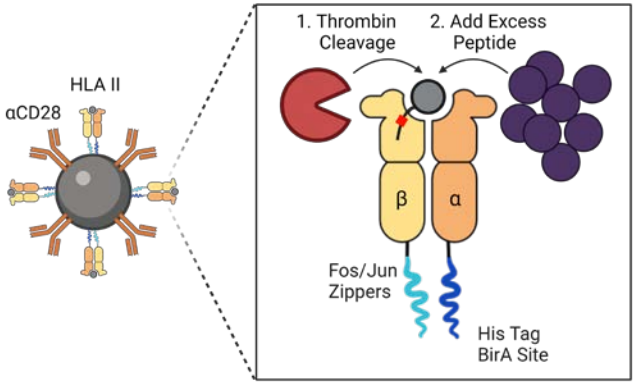
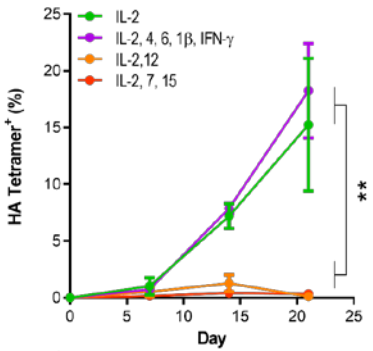
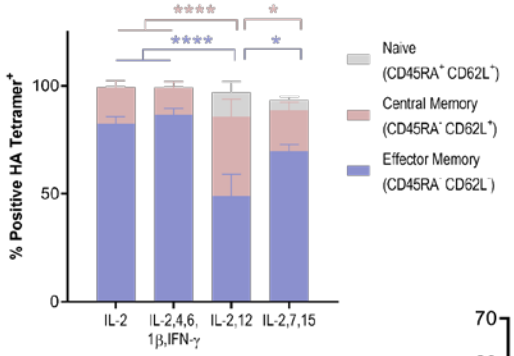
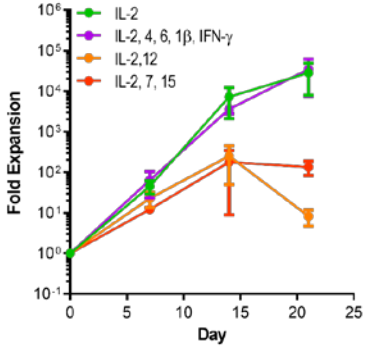
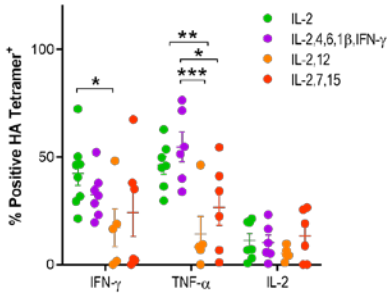
HLA II aAPCs expand flu-specific CD4+ T cells from HLA DR4+ donors

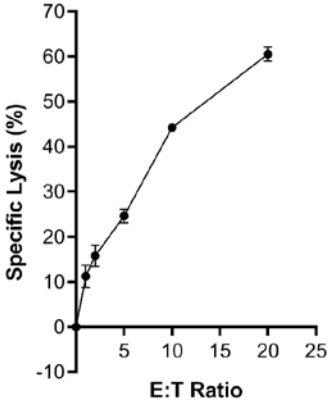












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