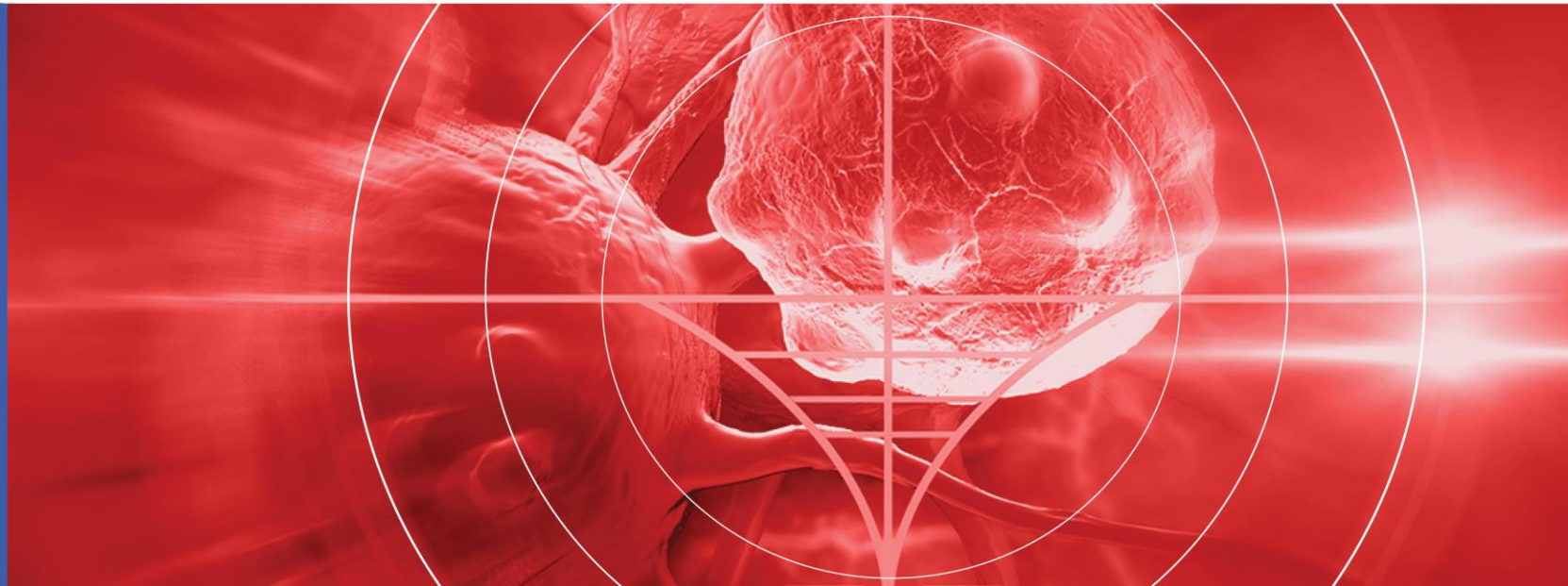
ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

APRIL 22, 2016

Adaptimmune

TRANSFORMING T CELL THERAPY



DISCLAIMER

This presentation contains "forward-looking statements," as that term is defined under the Private Securities Litigation Reform Act of 1995 (PSLRA), which statements may be identified by words such as "believe," "may", "will," "estimate," "continue," "anticipate," "intend," "expect" and other words of similar meaning. These forward-looking statements involve certain risks and uncertainties. Such risks and uncertainties could cause our actual results to differ materially from those indicated by such forward-looking statements, and include, without limitation: the success, cost and timing of our product development activities and clinical trials; our ability to submit an IND and successfully advance our technology platform to improve the safety and effectiveness of our existing TCR therapeutic candidates; the rate and degree of market acceptance of T-cell therapy generally and of our TCR therapeutic candidates; government regulation and approval, including, but not limited to, the expected regulatory approval timelines for TCR therapeutic candidates; and our ability to protect our proprietary technology and enforce our intellectual property rights; amongst others. For a further description of the risks and uncertainties that could cause our actual results to differ materially from those expressed in these forward-looking statements, as well as risks relating to our business in general, we refer you to our Annual Report on Form 20-F filed with the Securities and Exchange Commission (SEC) on October 13, 2015 and our other SEC filings.

We urge you to consider these factors carefully in evaluating the forward-looking statements herein and are cautioned not to place undue reliance on such forward-looking statements, which are qualified in their entirety by this cautionary statement. The forward-looking statements contained in this presentation speak only as of the date the statements were made and we do not undertake any obligation to update such forward-looking statements to reflect subsequent events or circumstances. We intend that all forward-looking statements be subject to the safe-harbor provisions of the PSLRA.

ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

APRIL 22, 2016

James Noble
Chief Executive Officer

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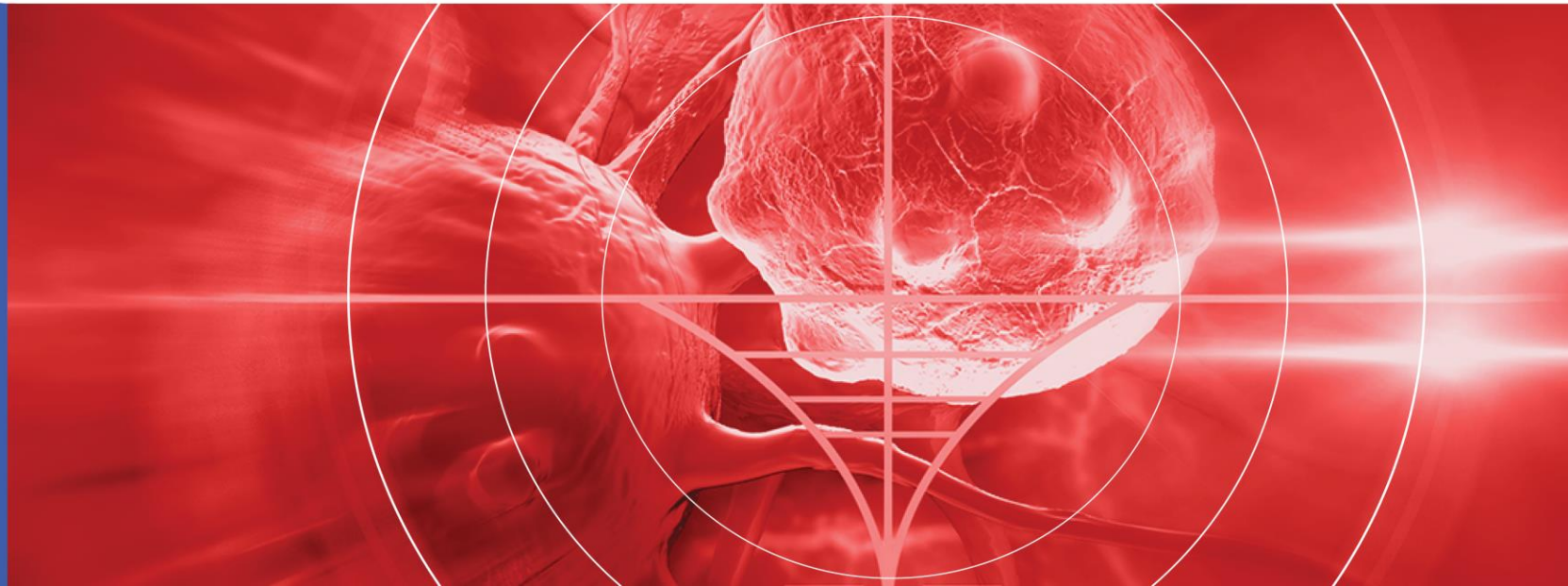
TRANSFORMING T CELL THERAPY



TODAY'S AGENDA

The Role of T Cells in the Immuno-Oncology Landscape
Helen Tayton-Martin, PhD, MBA; Chief Operating Officer, Adaptimmune

SPEAR T Cells™: Adaptimmune's Proprietary Technology Platform
Bent Jakobsen, PhD; Scientific Founder, Adaptimmune

Adoptive T Cell Therapy: Clinical Activity of NY-ESO-1 in a Solid Tumor
Stephan Grupp, MD, PhD; U.Penn Perelman School of Medicine

NY-ESO-1 T Cell therapy in Multiple Myeloma: Long Term Efficacy and Persistence
Aaron Rapoport, MD; U.Md Marlene & Stuart Greenebaum School of Medicine

Update on Progress with NY-ESO TCR Accelerating Adaptimmune's Wholly-Owned Clinical Pipeline
Rafael Amado, MD; Chief Medical Officer, Adaptimmune

The Adaptimmune Pipeline Engine Manufacturing Excellence and Commercial Delivery
Gwen Binder-Scholl, PhD; Chief Technology Officer, Adaptimmune

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

- Proprietary SPEAR T cell technology uniquely delivers:
  - Correctly identified targets
  - Specificity and optimal affinity
  - "Supra-natural" TCRs to accelerate programs
  - Enhanced effectiveness of TCRs
    - Generation 2 and 3 TCRs
- No other company can currently deliver all of these
- New data on the above are being presented today

Adaptimmune
TRANSFORMING T CELL THERAPY

ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

- Multiple clinical responses in synovial sarcoma, a solid tumor
  - Large solid lesions resolved
  - Breakthrough status
  - Pivotal trial planned for around year end 2016
- Over 90% response rate in multiple myeloma study in conjunction with ASCT
- No other company is as far advanced as Adaptimmune in the clinic with a TCR T cell
- New updates presented on both diseases today

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TRANSFORMING T CELL THERAPY

ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

- Company INDs open for NY-ESO, MAGE-A10 and AFP
- Next company INDs due 2017
- These TCRs all derive from Adaptimmune's proprietary technology
- No other company has routinely delivered INDs from an in-house TCR platform
- Today, we will disclose:
  - Our next IND target
  - The pipeline coverage of tumors

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TRANSFORMING T CELL THERAPY

ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

Strong financial position

- Current capital can fund the business through mid-2018

Adaptimmune
TRANSFORMING T CELL THERAPY

ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

Strong financial position

Proven ability to execute

- Three INDs open
- Manufacturing processes optimized
- Goal: first TCR T cell therapy to market

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TRANSFORMING T CELL THERAPY

BUILDING A LEADER

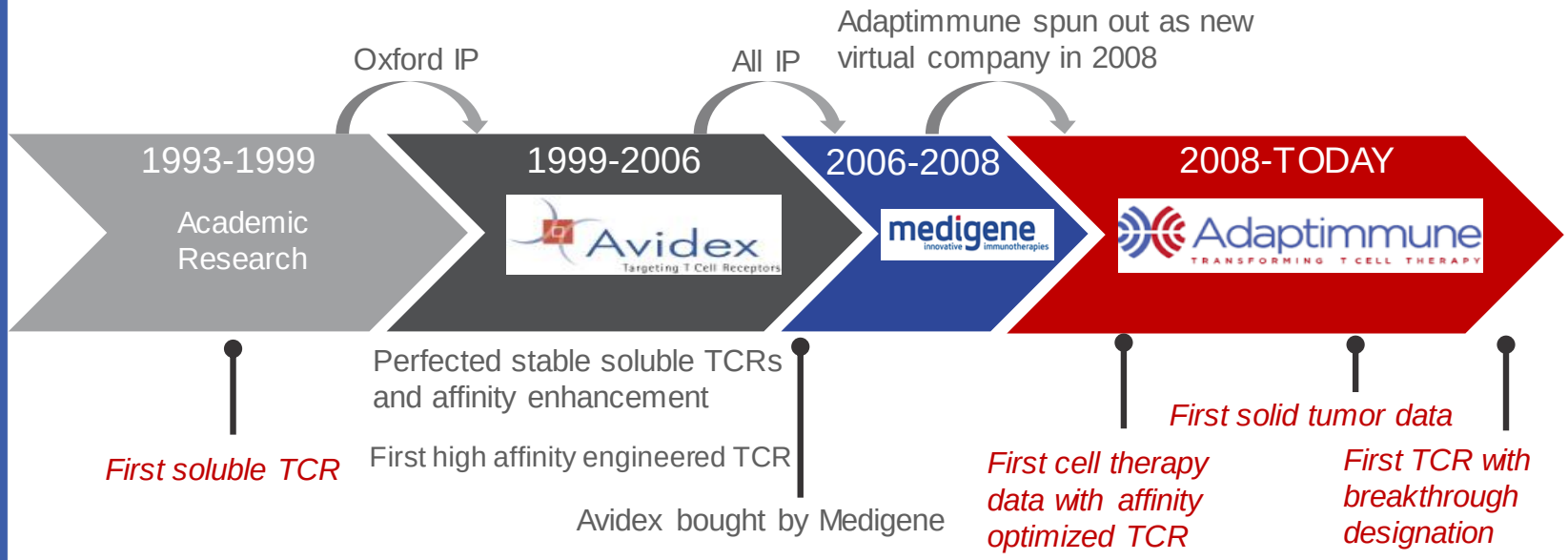
A HISTORY OF SCIENTIFIC PRE-EMINENCE

Origins of TCR technology

2005-2007 Collaboration with Steve Rosenberg, MD, Ph.D.

2008-2011 Collaboration with U. Penn

2016 + Adaptimmune SAB



Adaptimmune leadership position in:

- *Identifying targets*
- *Generating soluble TCRs used in R&D*
- *Engineering affinity optimized TCRs*
- *Cell Manufacturing*
- *TCR intellectual property*

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TRANSFORMING T CELL THERAPY

ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

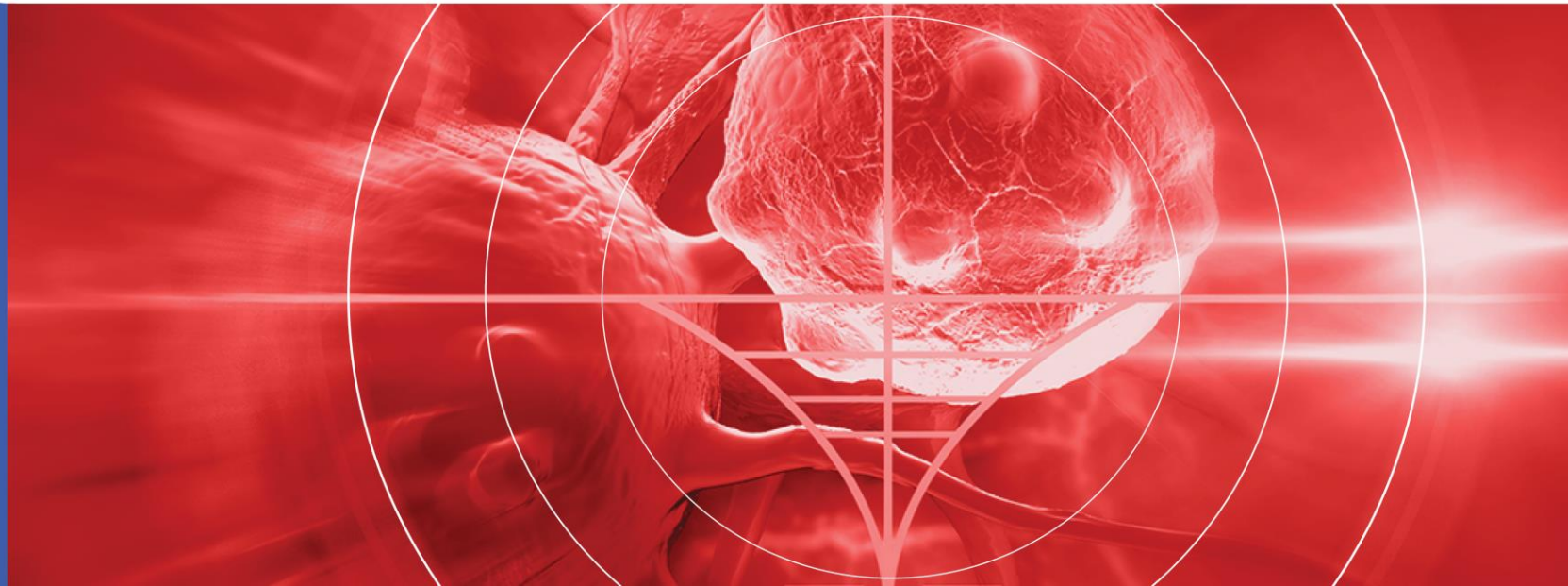
THE ROLE OF T CELLS IN THE IMMUNO-ONCOLOGY LANDSCAPE

APRIL 22, 2016

Helen Tayton-Martin, PhD, MBA
Chief Operating Officer

Adaptimmune

TRANSFORMING T CELL THERAPY



WHY IMMUNOTHERAPY?

THE KEY TO TACKLING CANCER EFFECTIVELY IS IMMUNE ENGAGEMENT

- Cancers
  - Primarily derived from changes to self-proteins
  - Contain many mutations
  - Are heterogeneous, even in the same patient
  - Are good at mutating to avoid selective pressure
  - Deploy a range of tactics to avoid immune system detection

Re-establishing T cell recognition and catalysing a polyclonal T cell response is key

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IMMUNOTHERAPY – EMERGING EVIDENCE

EARLY BEGINNINGS WITH TUMOR INFILTRATING LYMPHOCYTES

TIL Therapy

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IMMUNOTHERAPY – EMERGING EVIDENCE

EARLY BEGINNINGS WITH TUMOR INFILTRATING LYMPHOCYTES

TIL Therapy

- TIL therapy can mediate significant tumor regression in patients heavily pre-treated with IL-2 in refractory metastatic melanoma
- Significant toxicities

VOLUME 23 · NUMBER 10 · APRIL 1 2005

JOURNAL OF CLINICAL ONCOLOGY

Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma

Mark E. Dudley, John R. Wunderlich, James C. Yang, Richard M. Sherry, Suzanne L. Topalian, Nicholas P. Restifo, Richard E. Royal, Udai Kammula, Don E. White, Sharon A. Mavroukakis, Linda J. Rogers, Gerald J. Gracia, Stephanie A. Jones, David P. Mangiameli, Michelle M. Pelletier, Juan Gea-Banacloche, Michael R. Robinson, David M. Berman, Armando C. Filie, Andrea Abati, and Steven A. Rosenberg

2005

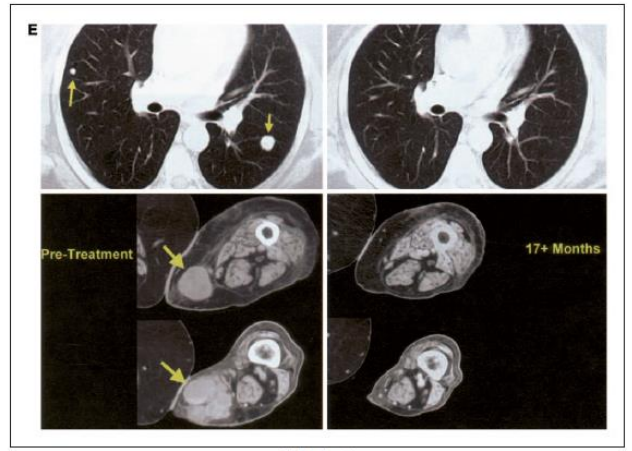

Fig 1. (continued)

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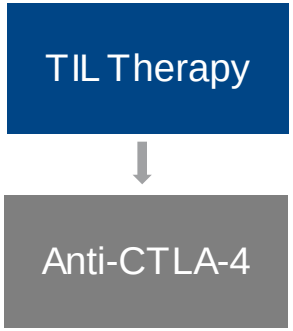
TRANSFORMING T CELL THERAPY

IMMUNOTHERAPY – EMERGING EVIDENCE

IMMUNE-MODULATION – CHECKPOINT BLOCKADE – ANTI-CTLA-4



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TRANSFORMING T CELL THERAPY

IMMUNOTHERAPY – EMERGING EVIDENCE

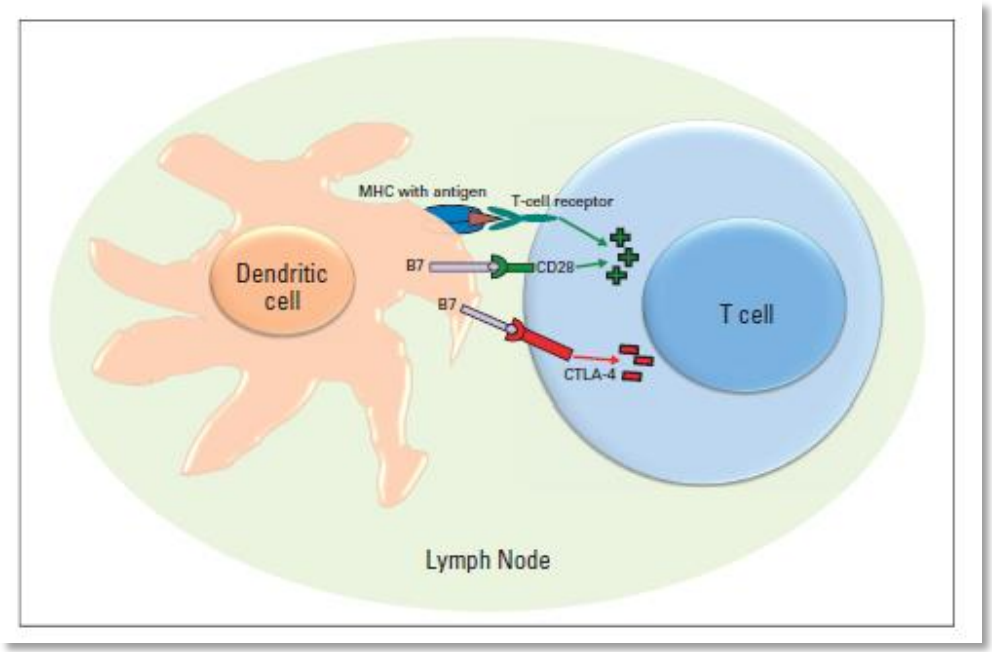
IMMUNE-MODULATION – CHECKPOINT BLOCKADE – ANTI-CTLA-4

TIL Therapy

↓

Anti-CTLA-4

- Anti-CTLA-4 antibodies block CTLA4 on T cells which disables their ‘brakes’



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TRANSFORMING T CELL THERAPY

Source: Postow, Callahan and Wolchok, J Clin Oncol 2015 33, 1974-1982

IMMUNOTHERAPY – EMERGING EVIDENCE

IMMUNE-MODULATION – CHECKPOINT BLOCKADE – ANTI-CTLA-4

TIL Therapy

↓

Anti-CTLA-4

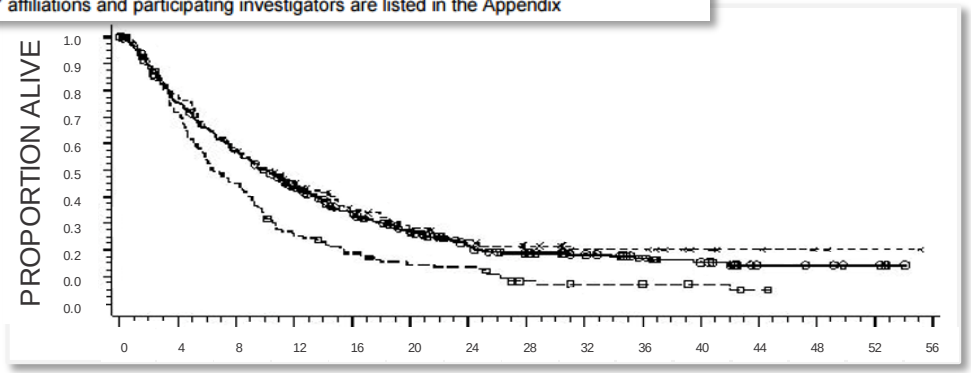
- Ipilimumab can cure patients, response rate is low but significant (1/5 get long term survival)
- Immune-mediated toxicity and adaptive resistance

2010

Published in final edited form as:
N Engl J Med. 2010 August 19; 363(8): 711–723. doi:10.1056/NEJMoa1003466.

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.
The authors' affiliations and participating investigators are listed in the Appendix



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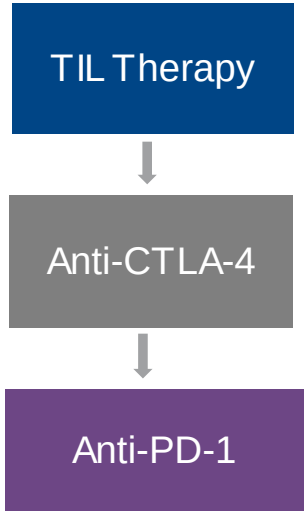
IMMUNOTHERAPY – EMERGING EVIDENCE

ANTI-PD-1 – NEXT STEP CHECKPOINT BLOCKADE



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TRANSFORMING T CELL THERAPY

IMMUNOTHERAPY – EMERGING EVIDENCE

ANTI-PD-1 – NEXT STEP CHECKPOINT BLOCKADE

TIL Therapy

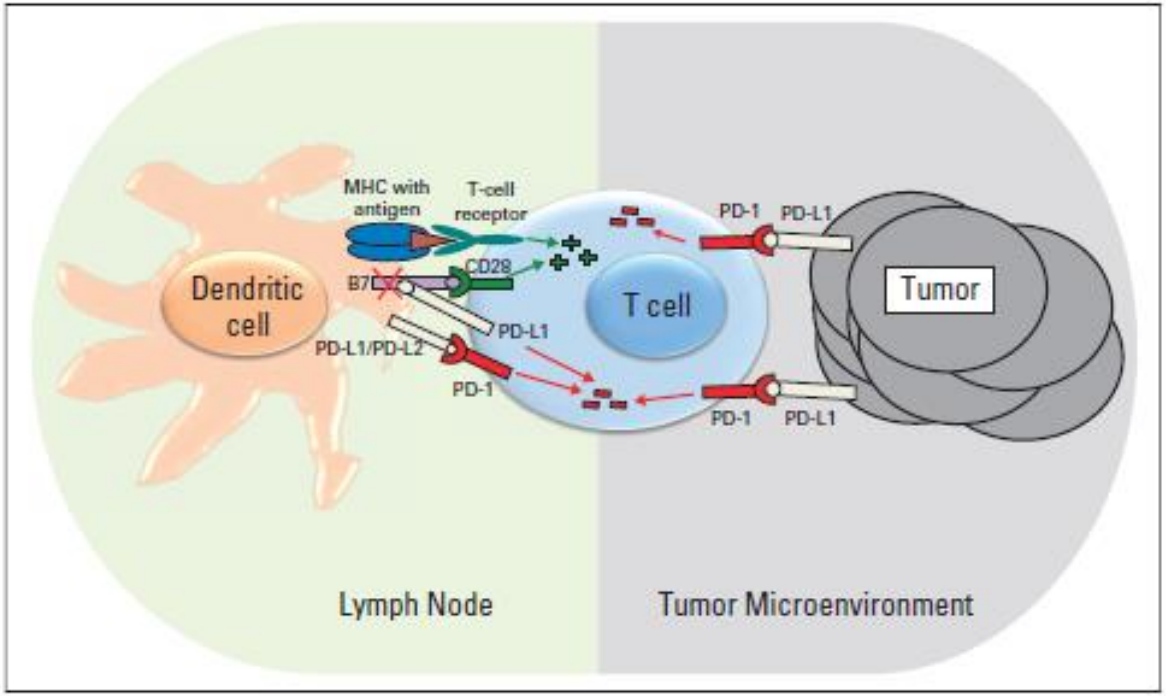
↓

Anti-CTLA-4

↓

Anti-PD-1

- Anti-PD-1 and anti-PDL-1 antibodies stop T cells from becoming fatigued, especially in the tumor



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TRANSFORMING T CELL THERAPY

Source: Postow, Callahan and Wolchok, J Clin Oncol 2015 33, 1974-1982

IMMUNOTHERAPY – EMERGING EVIDENCE

ANTI-PD-1 – NEXT STEP CHECKPOINT BLOCKADE

2015

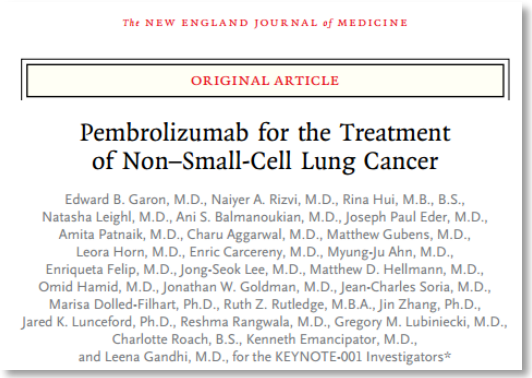
TIL Therapy

↓

Anti-CTLA-4

↓

Anti-PD-1

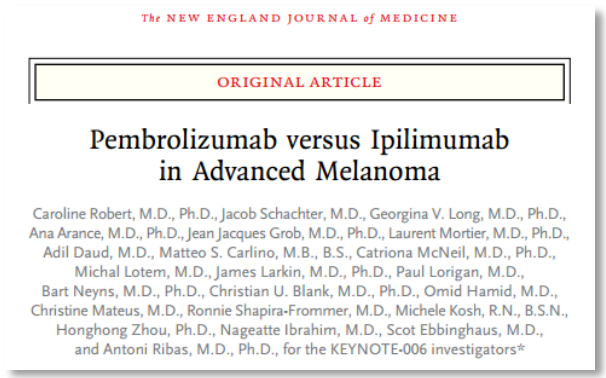


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

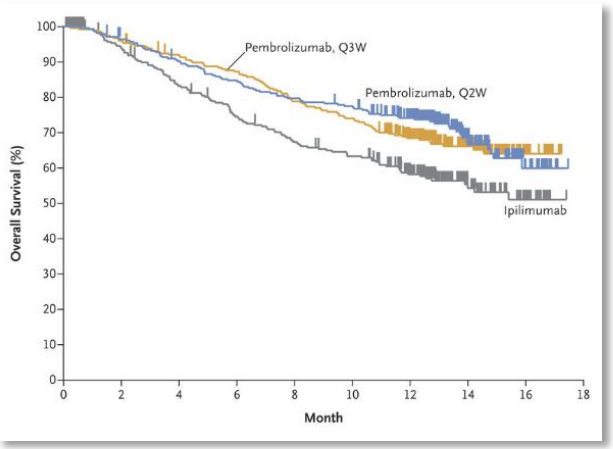
ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

- Clear effects on survival in multiple indications
- Durable responses, lower toxicity

Keytruda (anti PD-1 - Melanoma)



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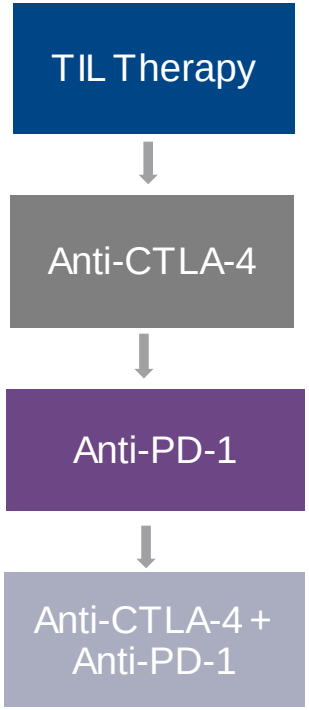
Source: www.Keytruda.com

IMMUNOTHERAPY – EMERGING EVIDENCE

CHECKPOINT COMBINATIONS



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IMMUNOTHERAPY – EMERGING EVIDENCE

CHECKPOINT COMBINATIONS

TIL Therapy

↓

Anti-CTLA-4

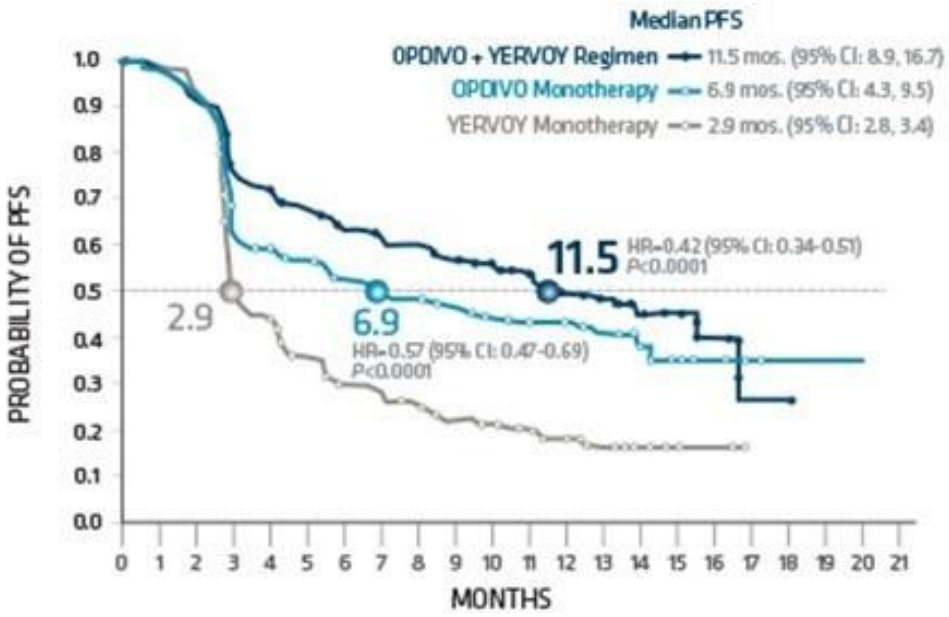
↓

Anti-PD-1

↓

Anti-CTLA-4 + Anti-PD-1

- Enhanced effects with multiple immune checkpoint blockade



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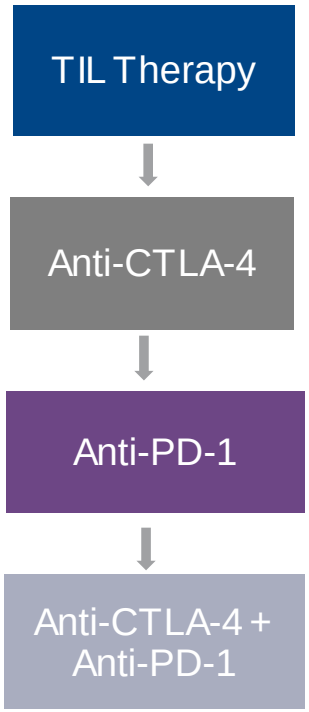
Source: www.Opdivo.com

IMMUNOTHERAPY CHALLENGES

STRONG EVIDENCE FOR T CELLS BUT…



Check-point blockade/TIL therapy requires effective pre-existing anti-tumor immunity

The endogenous immune response to self antigens is low affinity

Mutational burden is correlated with effectiveness of immunotherapy

Tumors are selected to avoid immune detection – a high affinity response is required

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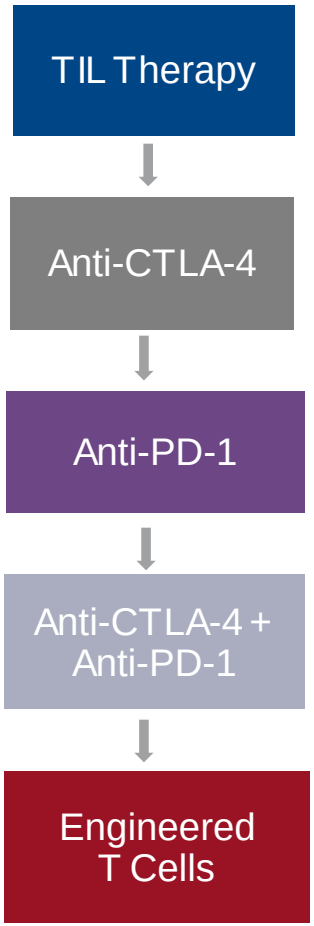
TRANSFORMING T CELL THERAPY

IMMUNOTHERAPY CHALLENGES

STRONG EVIDENCE FOR T CELLS BUT…



Check-point blockade/TIL therapy requires effective pre-existing anti-tumor immunity

The endogenous immune response to self antigens is low affinity

Mutational burden is correlated with effectiveness of immunotherapy

Tumors are selected to avoid immune detection – a high affinity response is required

Engineered T cells can overcome many of these challenges

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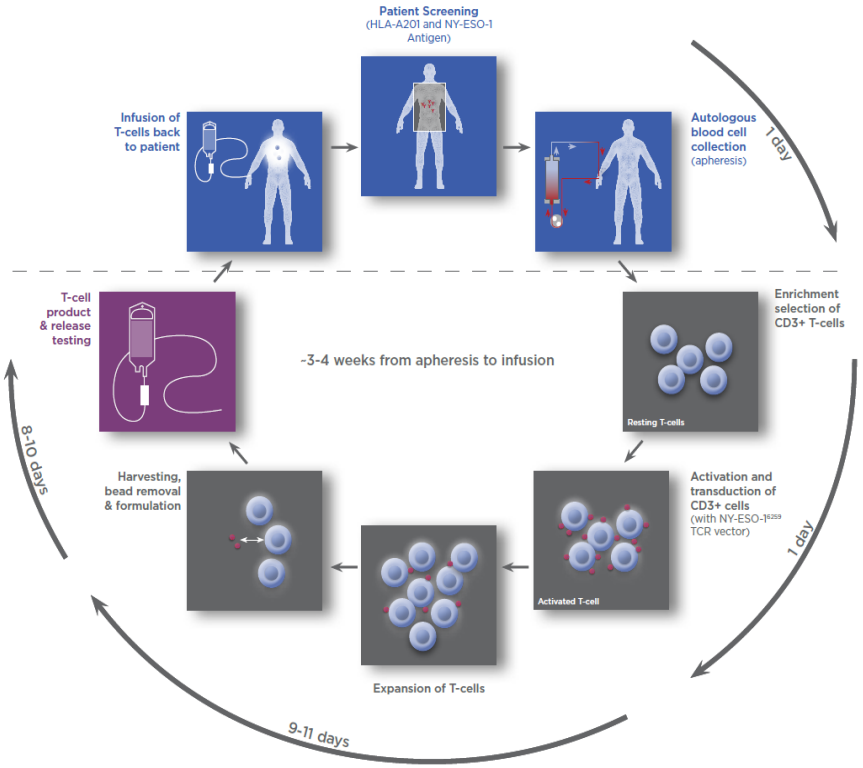
THE OPPORTUNITY FOR ENGINEERED T CELL THERAPY

A POWERFUL MODALITY



- Ability to engineer-in effective tumor antigen specificity to T cells
- Specific therapy: Engineered T cells migrate to antigen / tumor and provide localized responses
- Ability to engineer-in alterations to overcome the tumor microenvironment (next generation)

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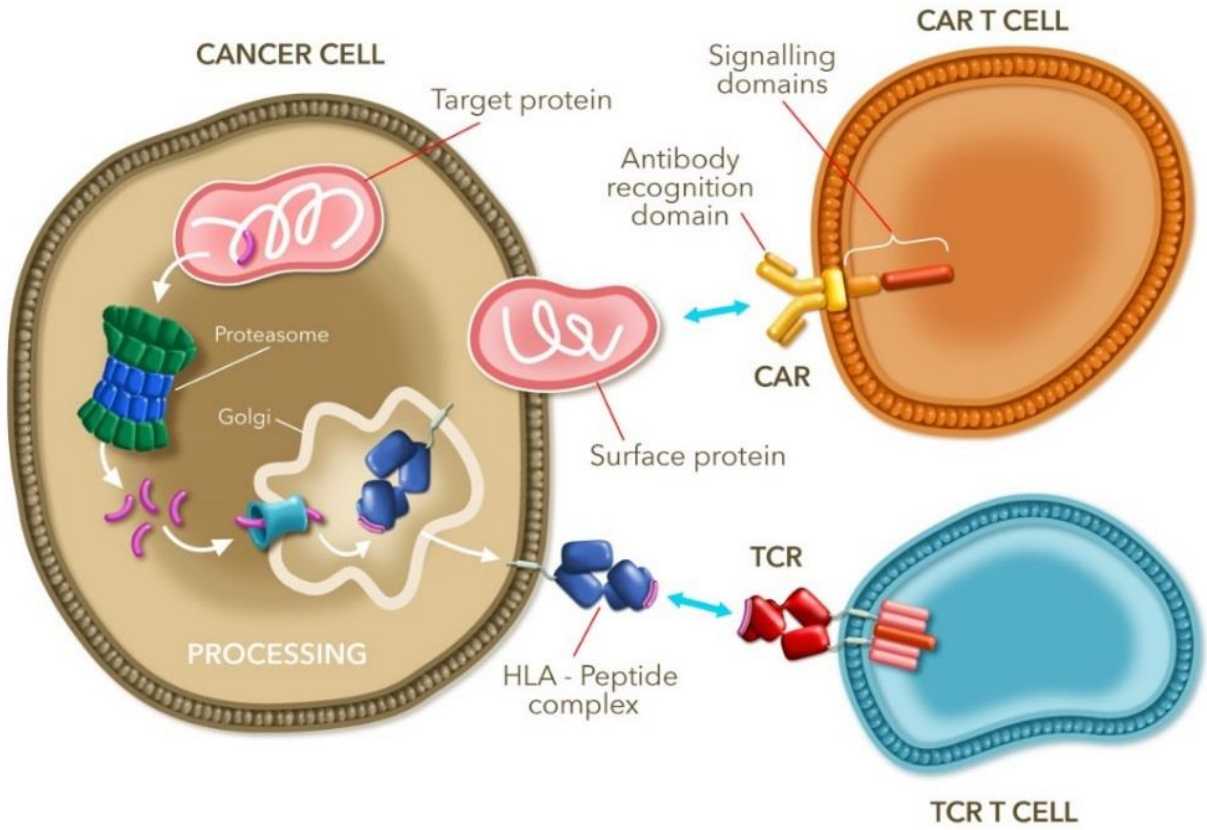
THERE ARE TWO MAIN WAYS TO REDIRECT A T CELL

SYNTHETIC RECEPTORS (CAR) AND T CELL RECEPTORS (TCR)



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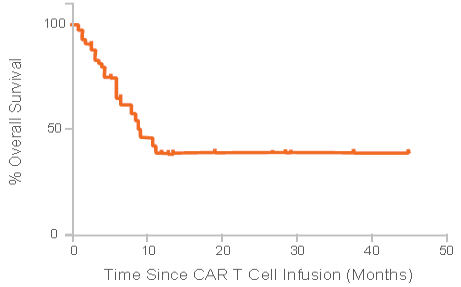
CAR T CELLS – EVIDENCE IN HEMATOLOGICAL CANCERS

NOT EASILY TRANSFERABLE TO SOLID TUMORS

- Anti-CD19 CAR-Ts have demonstrated evidence of high tumor shrinkage and remissions in B cell malignancies



Median overall survival 9.0 months
Median follow-up: 5.9 months (1-45+ months)

Historical SOC median survival ~3 months (O'Brien, et al, 2008)

Efficacy of CD19 CAR-Ts in **hematological** cancers

	NOVARTIS	KITE	JUNO	
CAR-T product	CTL019	KTE-C19	JCAR-015	JCAR-014
Pediatric ALL	94% CR, 73% CRM	70% CR, 60% CRM	64% CR, 45% CRM	-
Adult ALL	82% CR, 67% CRM	-	-	100% CR, 100% CRM
DLBCL	-	70% CR, 50% CRM	-	82% CR, 64% CRM

*CAR – Chimeric Antigen Receptor, ALL – Acute Lymphoblastic leukemia, DLBCL – Diffuse Large B-Cell Lymphoma, CR - Complete Response, CRM – Complete Molecular Remission

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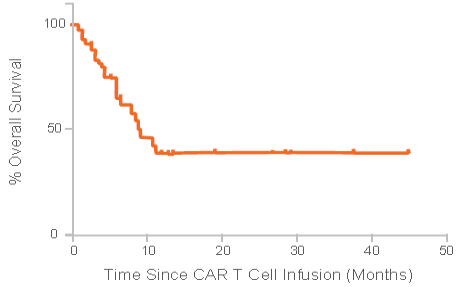
TRANSFORMING T CELL THERAPY

Source: Juno Therapeutics; CITI Car-T / TCR launch initiation report, 2016

CAR T CELLS – EVIDENCE IN HEMATOLOGICAL CANCERS

NOT EASILY TRANSFERABLE TO SOLID TUMORS

- Anti-CD19 CAR-Ts have demonstrated evidence of high tumor shrinkage and remissions in B cell malignancies



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DLBCL	-	70% CR, 50% CRM	-	82% CR, 64% CRM

Two issues: very few targets and little evidence of efficacy in solid tumors

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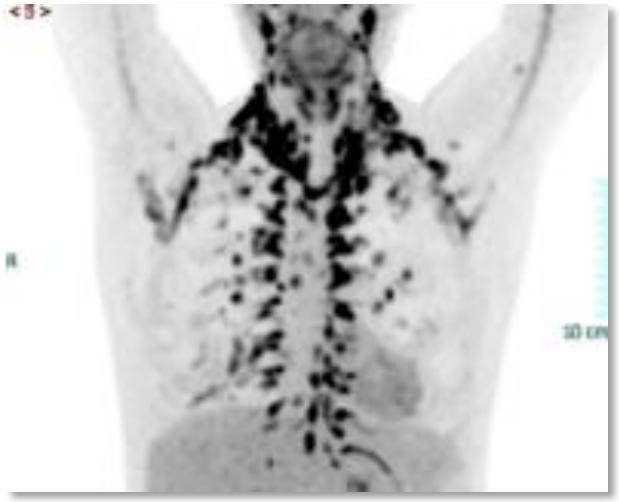
TRANSFORMING T CELL THERAPY

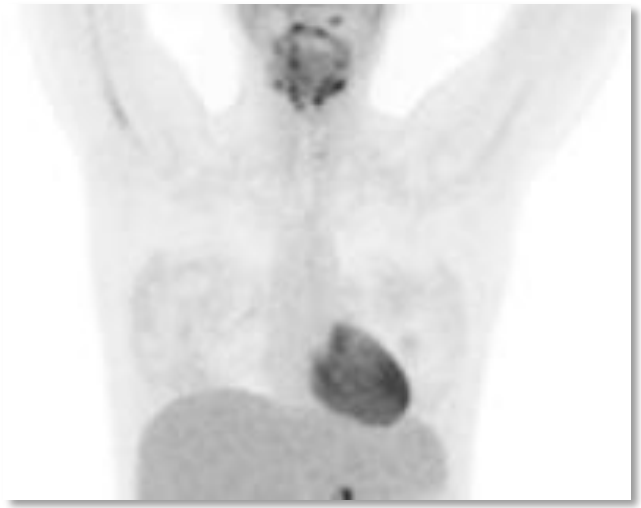
*CAR – Chimeric Antigen Receptor, ALL – Acute Lymphoblastic leukemia, DLBCL – Diffuse Large B-Cell Lymphoma, CR - Complete Response, CRM – Complete Molecular Remission

OPTIMIZED AFFINITY TCR T CELLS

ADDRESS SOLID TUMORS AND INTRACELLULAR TARGETS

- Optimized affinity TCR T cells demonstrate efficacy in **solid tumors**





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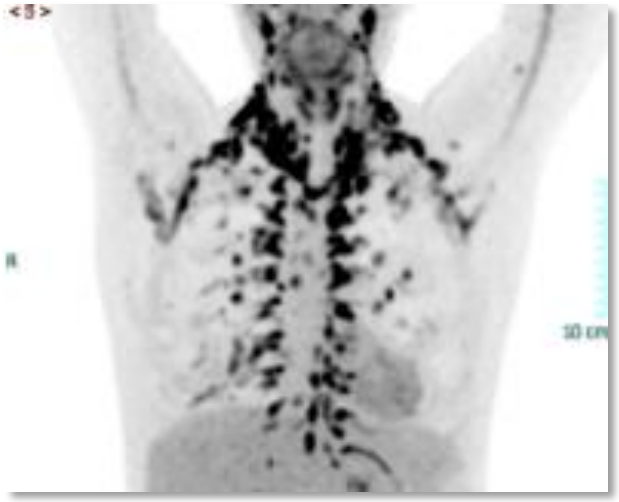
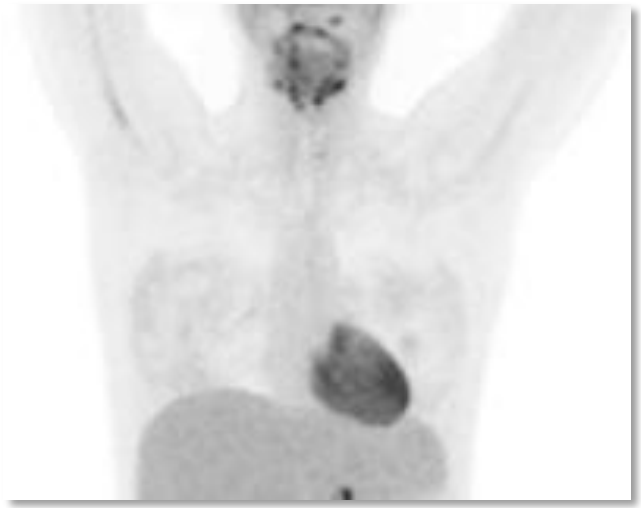
Sources: SITC, November 2015

OPTIMIZED AFFINITY TCR T CELLS

ADDRESS SOLID TUMORS AND INTRACELLULAR TARGETS

- Optimized affinity TCR T cells demonstrate efficacy in **solid tumors**





- Vast majority of cancer targets are intracellular and ONLY engaged by T cells via TCRs

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DEVELOPING EFFECTIVE AFFINITY OPTIMIZED TCR T CELLS

HIGH BARRIERS TO ENTRY

- Specialized data and expertise required to identify the correct peptide targets
- Challenging to identify TCRs
- Essential to optimize the affinity of the TCR
- Specialized expertise and assays required for establishing TCR specificity
- Manufacturing expertise for both cell and vector required
- Clinical expertise for safe administration and effective study design for cell therapy required

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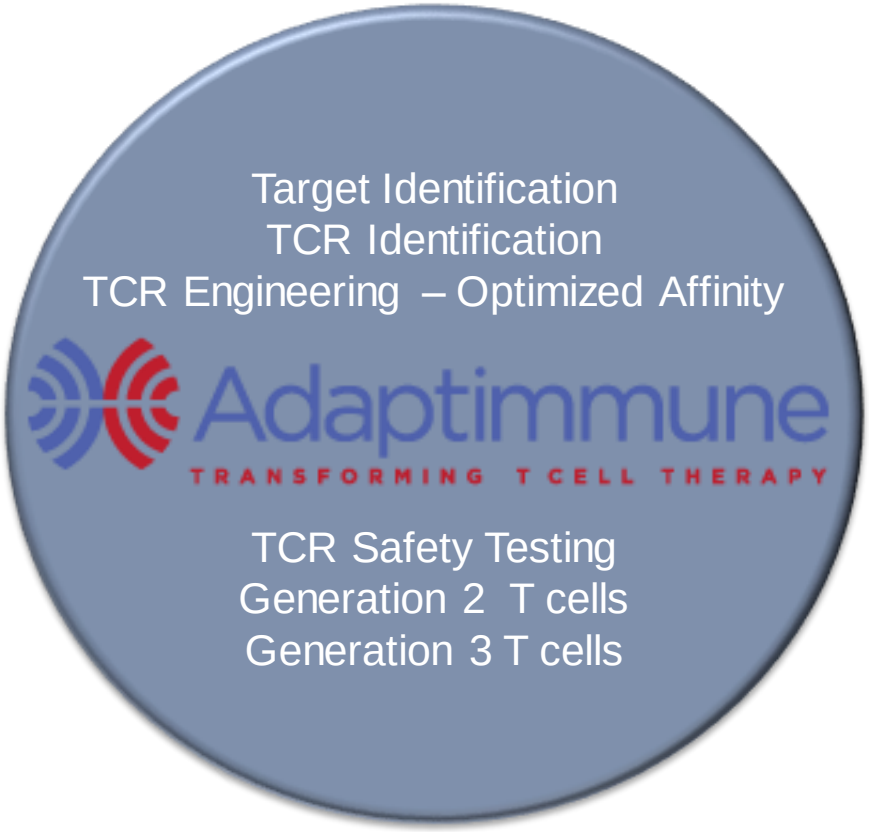
ADAPTIMMUNE SPEAR T CELL PLATFORM UNIQUELY OVERCOMES THESE HURDLES



SPEAR
T CELLS

Specific
Peptide
Enhanced
Affinity
Receptor

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TRANSFORMING T CELL THERAPY

ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

SPEAR T CELLS: ADAPTIMMUNE'S PROPRIETARY TECHNOLOGY PLATFORM
APRIL 22, 2016

Bent Jakobsen, Ph.D.
Chief Scientific Officer and Co-founder, Immunocore
Scientific Founder, Adaptimmune Therapeutics plc
Fellow of The Academy of Medical Sciences

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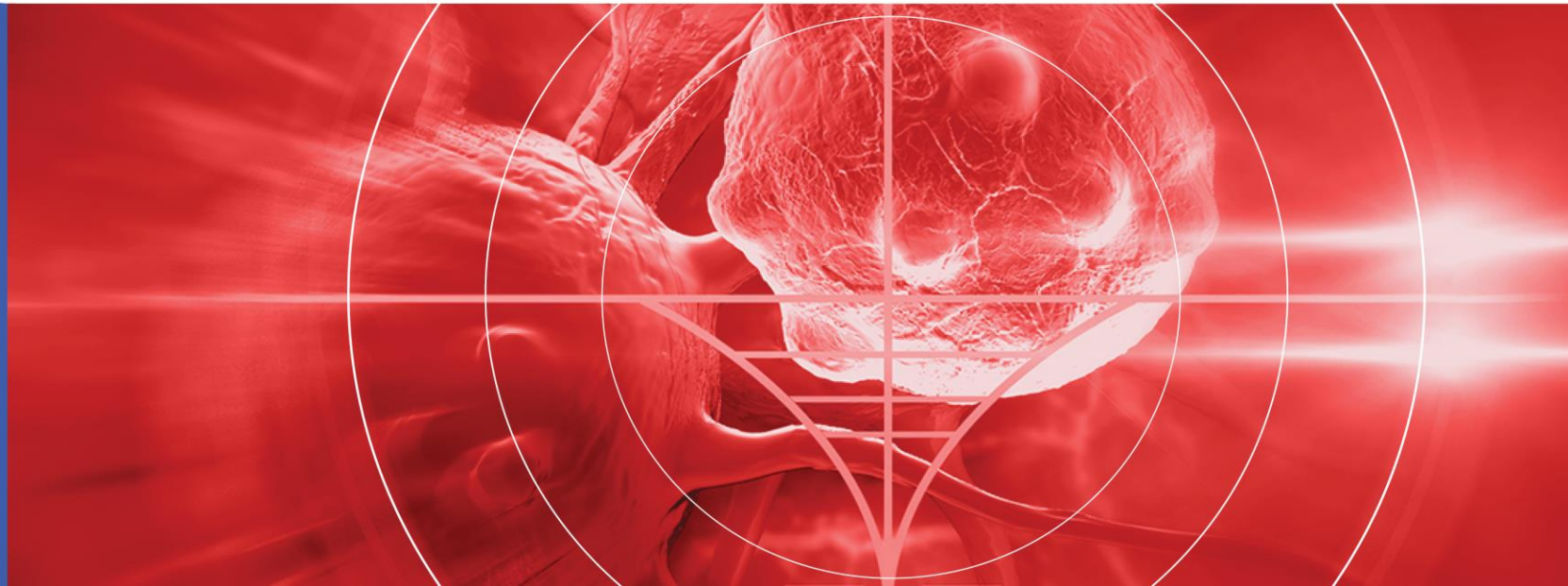
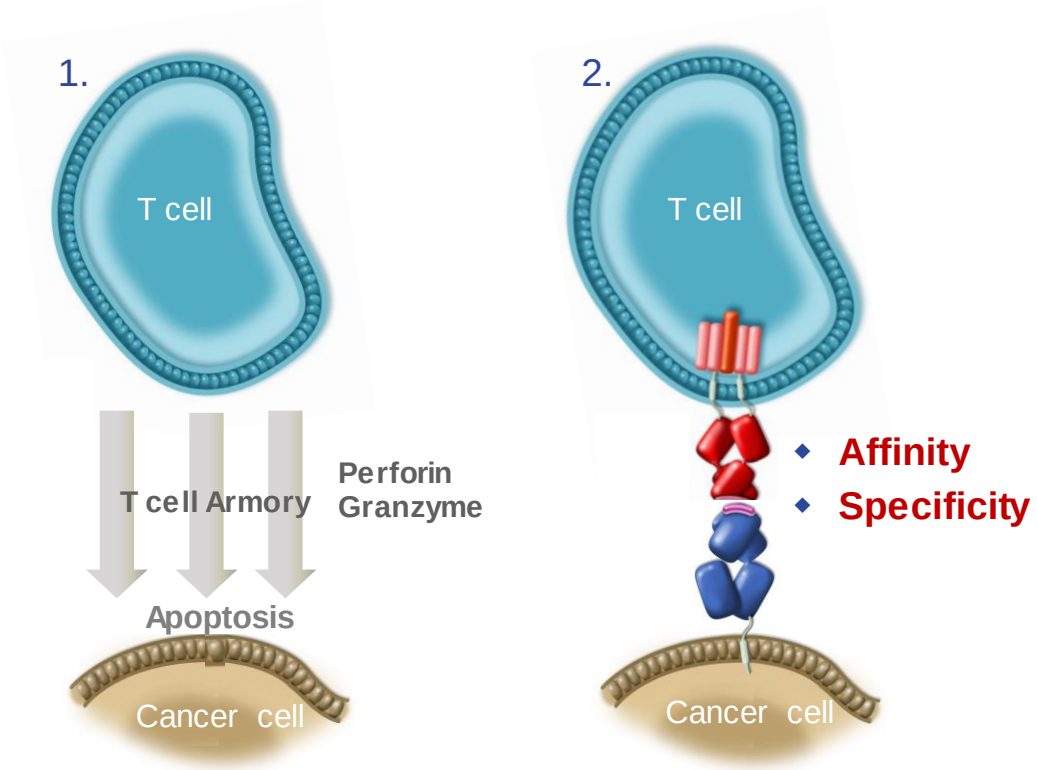


ADOPTIVE T CELL - MOST POWERFUL UNIT IN IMMUNOTHERAPY

Four components to an effective adoptive therapy:

1. T cell must recognize a cancer cell via a **guiding receptor**

2. The guiding receptor has two important aspects
   - **Affinity**
   - **Specificity**



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TRANSFORMING T CELL THERAPY

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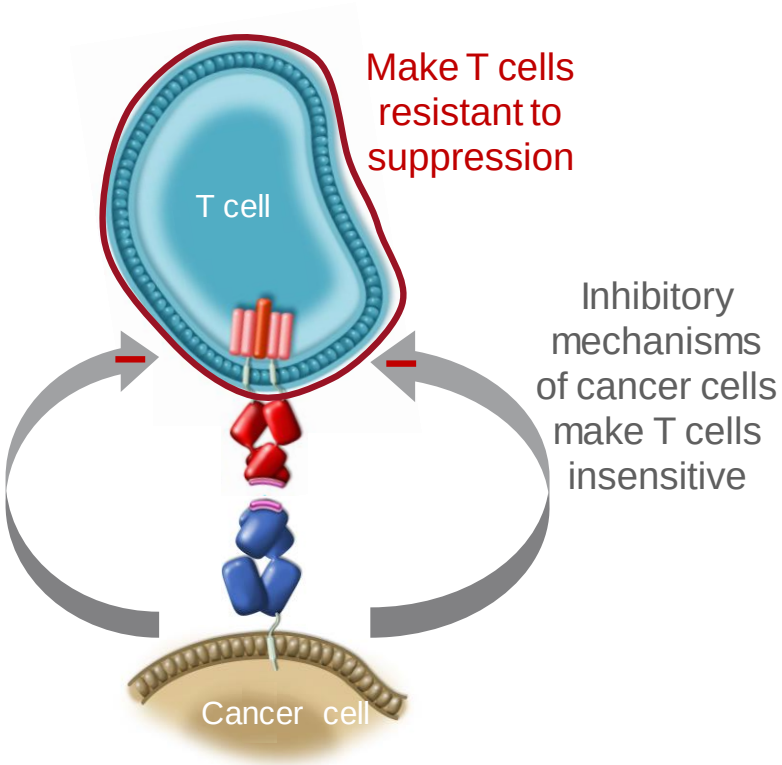

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TRANSFORMING T CELL THERAPY

ADOPTIVE T CELL - MOST POWERFUL UNIT IN IMMUNOTHERAPY

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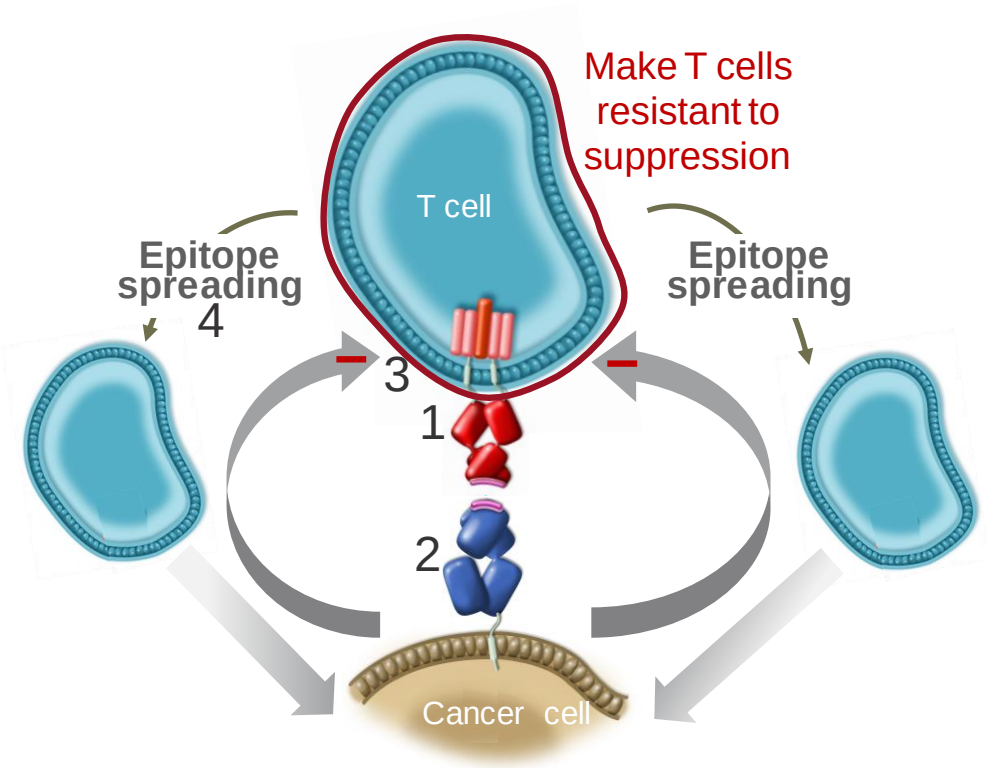
2. The guiding receptor must have two important aspects
   - **Affinity**
   - **Specificity**
3. The T cell needs to be **resistant to suppression**
4. The T cell (either alone or via other mechanisms) needs to **'break cancer immune tolerance'**



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AFFINITY & SPECIFICITY

ADOPTIVE T CELL - MOST POWERFUL UNIT IN IMMUNOTHERAPY

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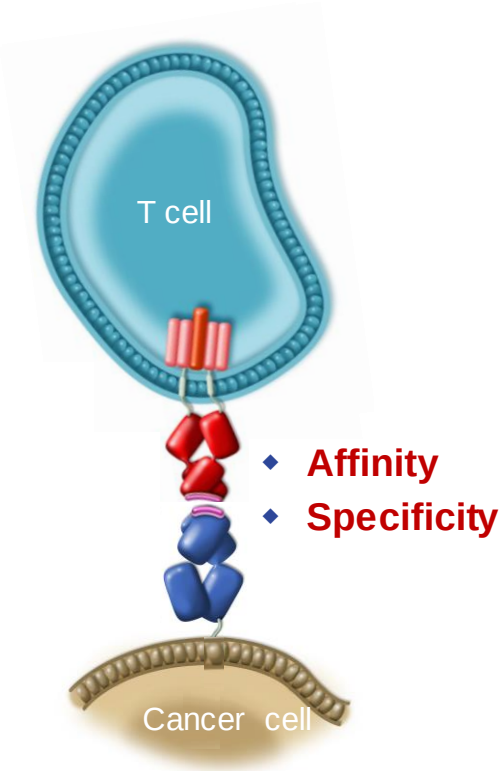

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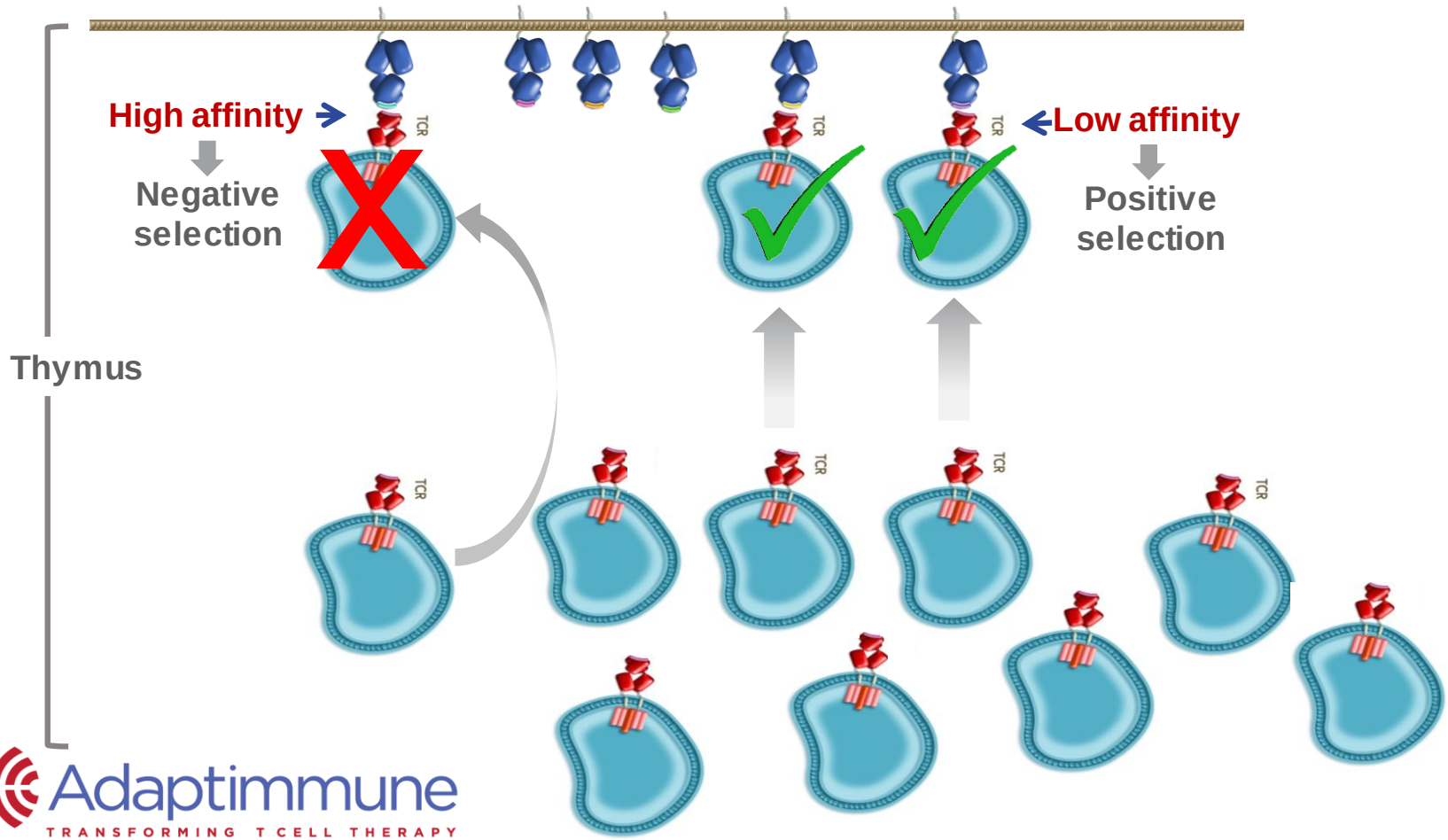
TCR AFFINITY - DETERMINED BY THYMIC SELECTION

- The entire peptidome (all peptides) is presented in the thymus
- T cells undergo **positive** and **negative** selection within the cortex and medulla of the thymus



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NATURAL T CELLS ARE ILL-EQUIPPED TO CLEAR CANCER

- Due to negative selection virtually all circulating T cells that have self peptide specificity will have low affinity TCRs
  - This mechanism guards the body against autoimmunity

- However all reasonably prevalent peptide antigens of cancer relevance are of self origin
  - Many of these peptide antigens are derived from proteins for which the encoding gene is silenced (or severely suppressed) in all (or almost all) adult tissues

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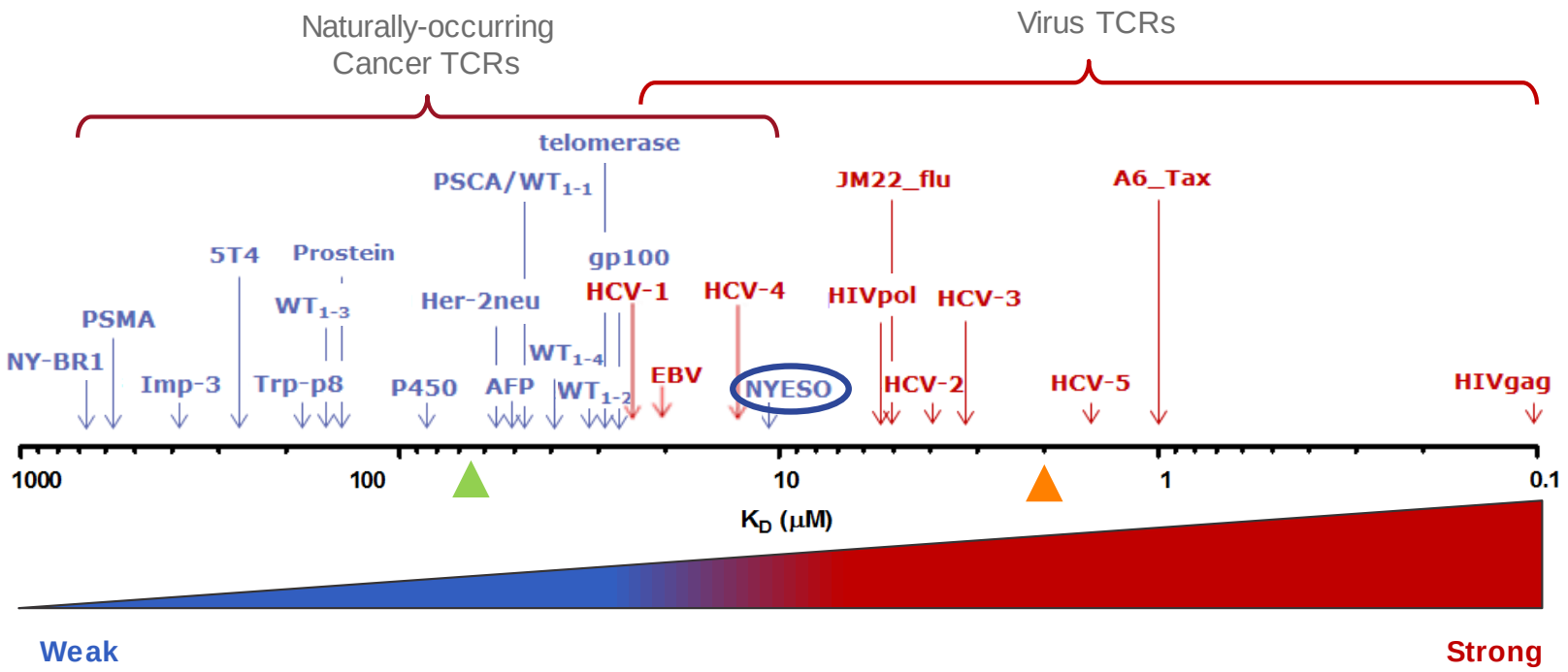
VIRAL TCRS HAVE HIGHER AFFINITY THAN NATURAL CANCER TCRS



MAGE-A4 K_D ~ 64 mM

MAGE-A10 K_D ~ 2 mM
- Not a natural TCR
- Identified from proprietary TCR display libraries

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Aleksic, M. et al. (2012). Eur J Immunol 10.1002/eji.201242606

AFFINITY OPTIMIZING CANCER TCRs IS PIVOTAL TO T CELL FUNCTION

- Some non-engineered TCRs will recognise antigen well
  - e.g. NY-ESO
  - Even so, engineering improves antigen recognition

- Some non-engineered TCRs fail to recognise antigen well
  - e.g. MAGE-A4
  - Engineering enables antigen recognition

Affinity engineering is a critical step in TCR optimization

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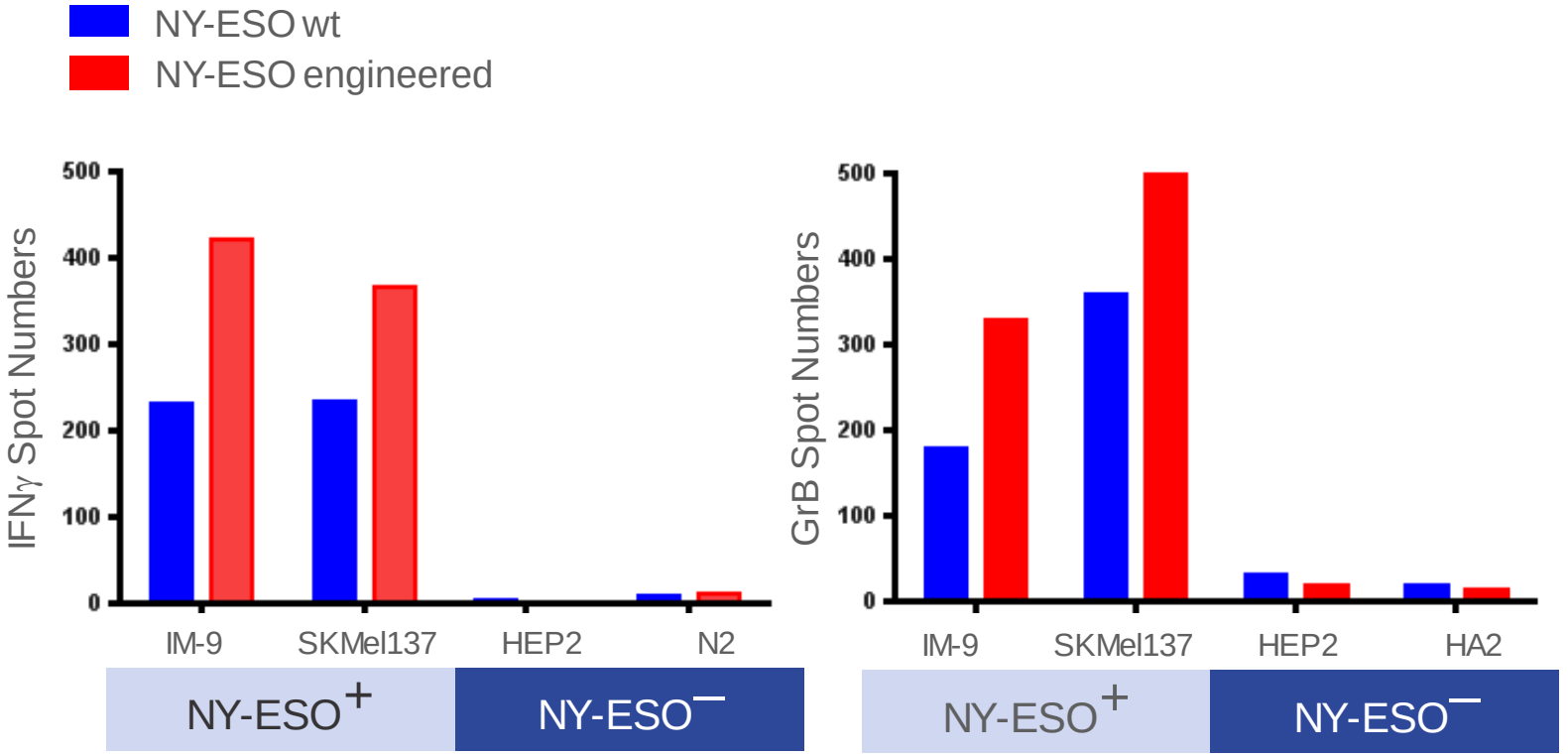
NY-ESO: NATURAL VERSUS ENGINEERED TCR FUNCTIONALITY



Even for NY-ESO affinity engineering improves T cell function

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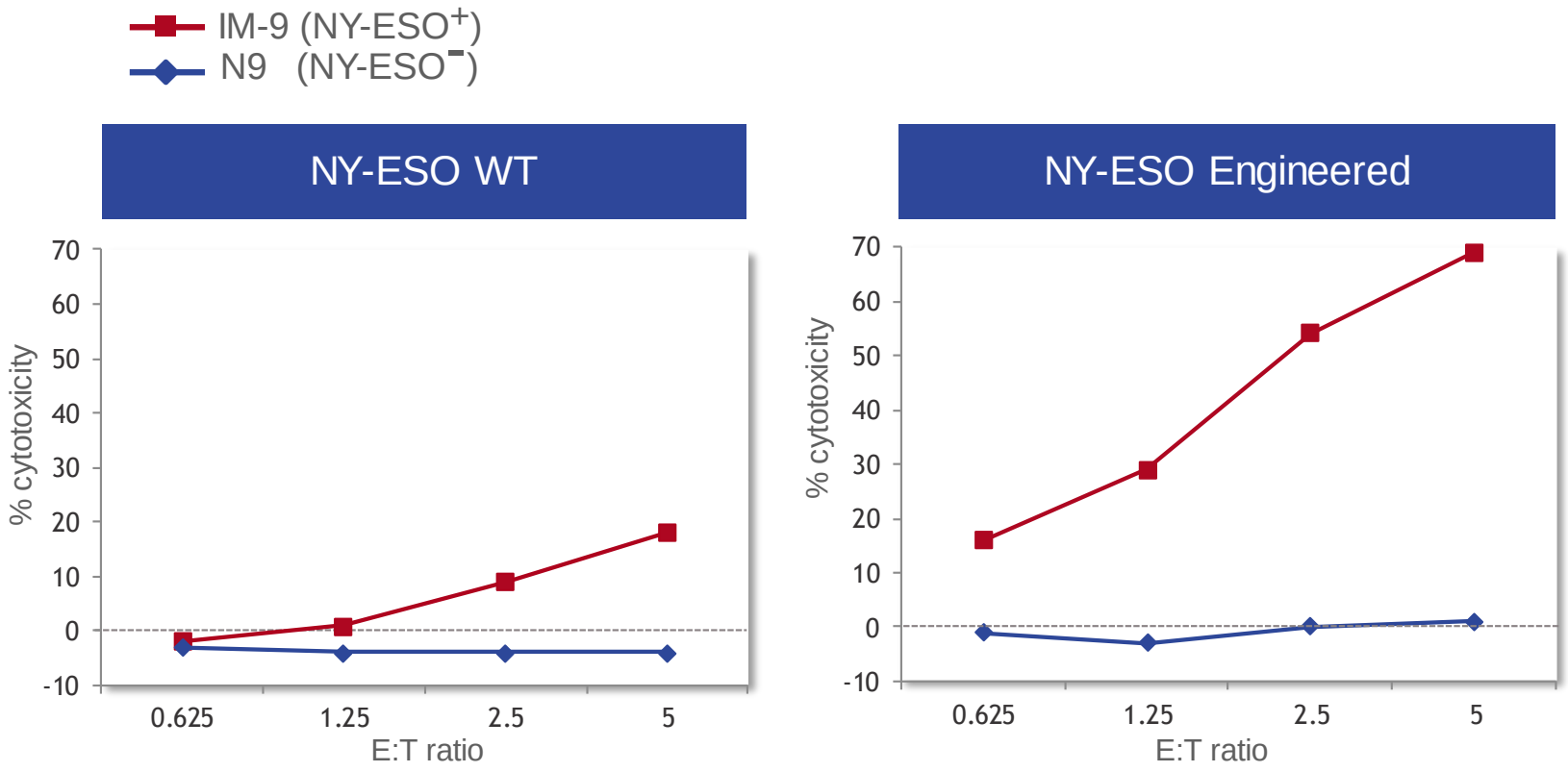
NY-ESO: NATURAL VERSUS ENGINEERED TCR FUNCTIONALITY



Even for NY-ESO affinity engineering improves cancer killing

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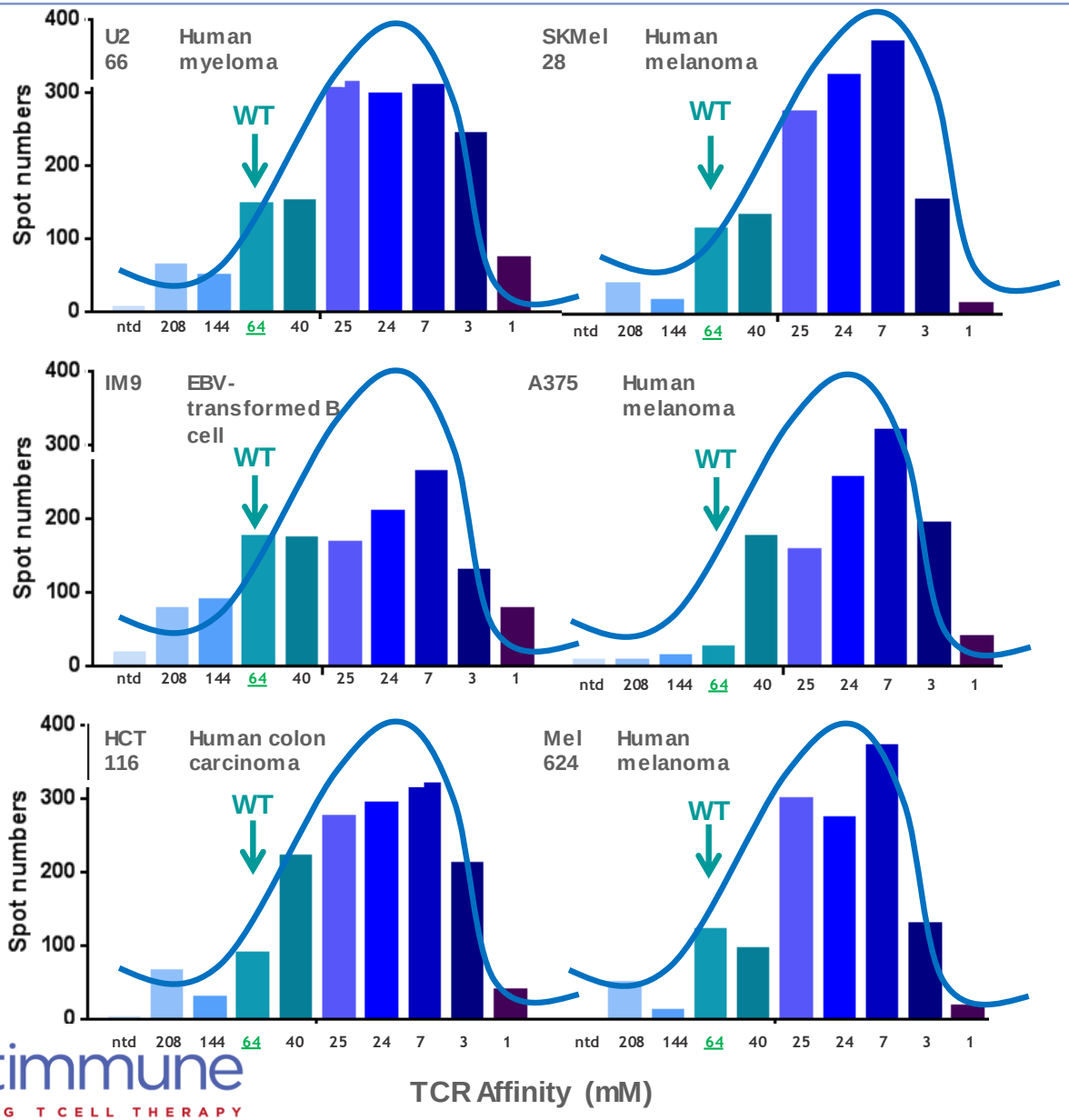
TRANSFORMING T CELL THERAPY

MAGE-A4: EFFECT OF OPTIMIZING TCR AFFINITY



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AFFINITY OPTIMIZING CANCER TCRs IS PIVOTAL TO T CELL FUNCTION

- Some non-engineered TCRs will recognise antigen well
  - e.g. NY-ESO
  - Even so, cancer cell killing is dramatically improved by affinity optimization
- Some non-engineered TCRs fail to recognise antigen well
  - e.g. MAGE-A4
  - The optimal affinity is crucial for T cell function and the same across all cancer cell lines

Affinity engineering is a critical step in TCR optimization

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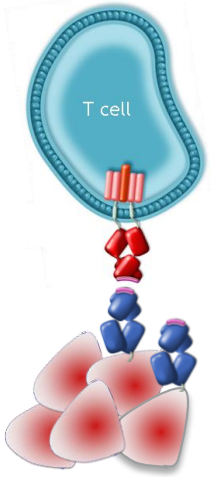
TRANSFORMING T CELL THERAPY

SPECIFICITY & TOXICITY

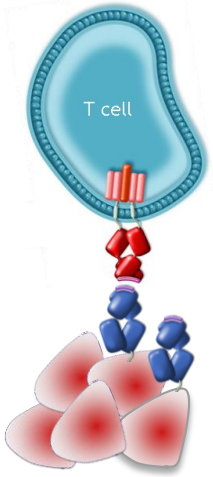
SPECIFICITY AND NON-SPECIFICITY

ON TARGET



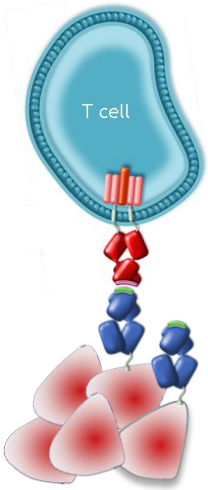
Target antigen on normal tissue

OFF TARGET (SPECIFIC)



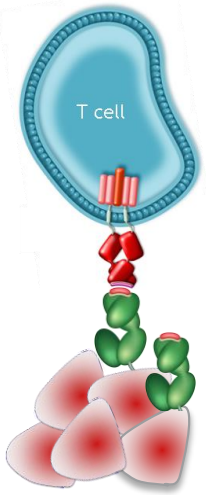
Closely related antigen on normal tissue

OFF TARGET (NON-SPECIFIC)



Promiscuous recognition (unrelated to target)

ALLOREACTIVITY



Alternate HLA restriction

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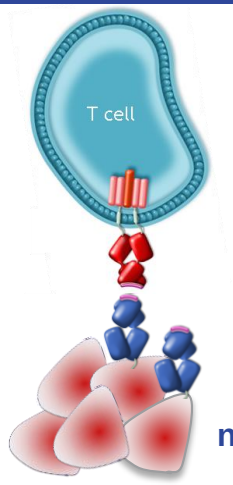
SPECIFICITY: TARGET EXPRESSION

ON TARGET



Optimized target selection process

1. Select targets expressed on cancer cell
   - Low expression (due to HLA downregulation) overcome by **high affinity TCRs**
2. No / extremely low expression in normal tissue*

*Expression tolerable in some normal tissues

(e.g. prostate, breast, pancreas, immuno-privileged tissues)

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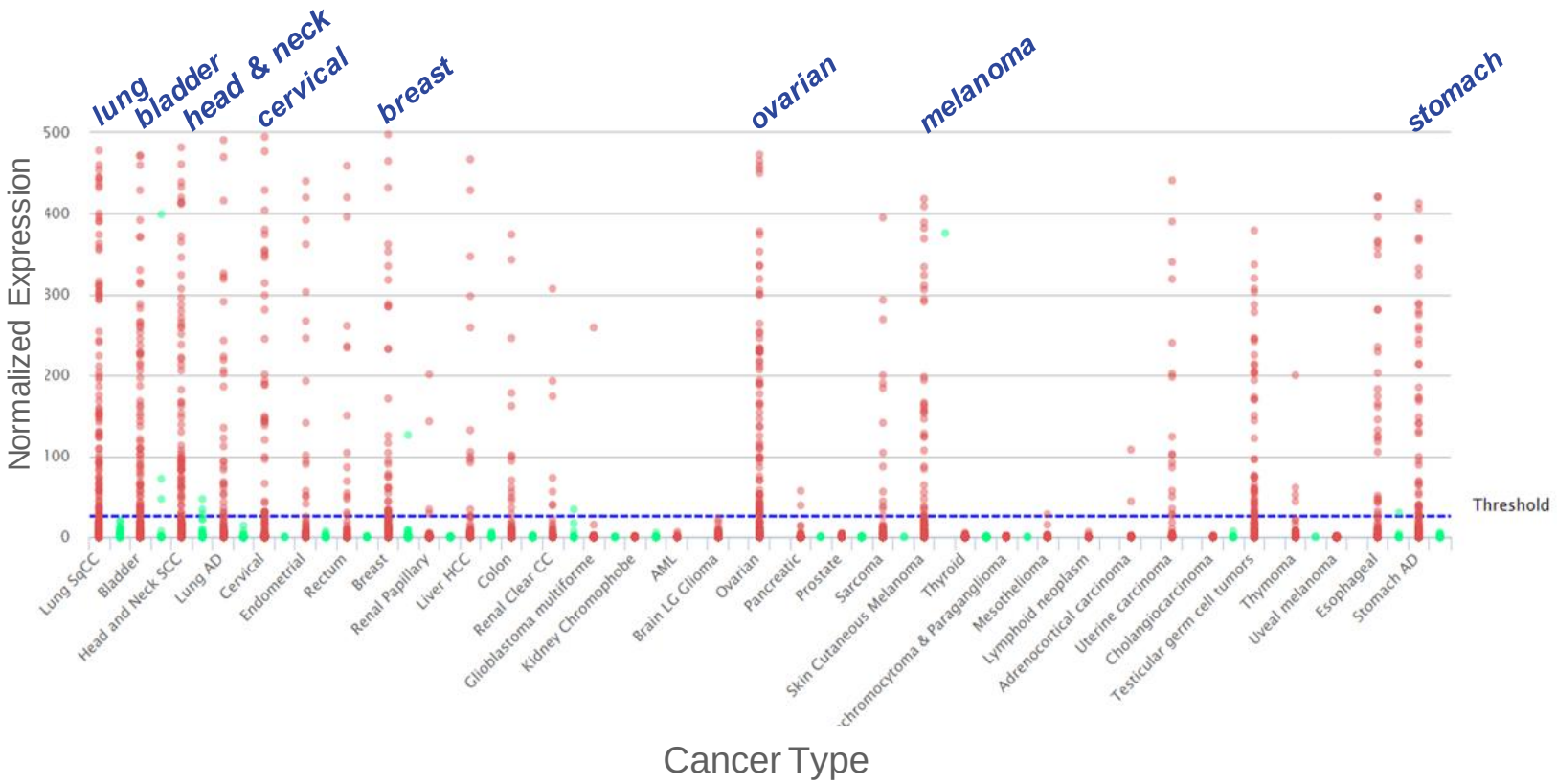
MAGE-A4 - EXPRESSION IN CANCER



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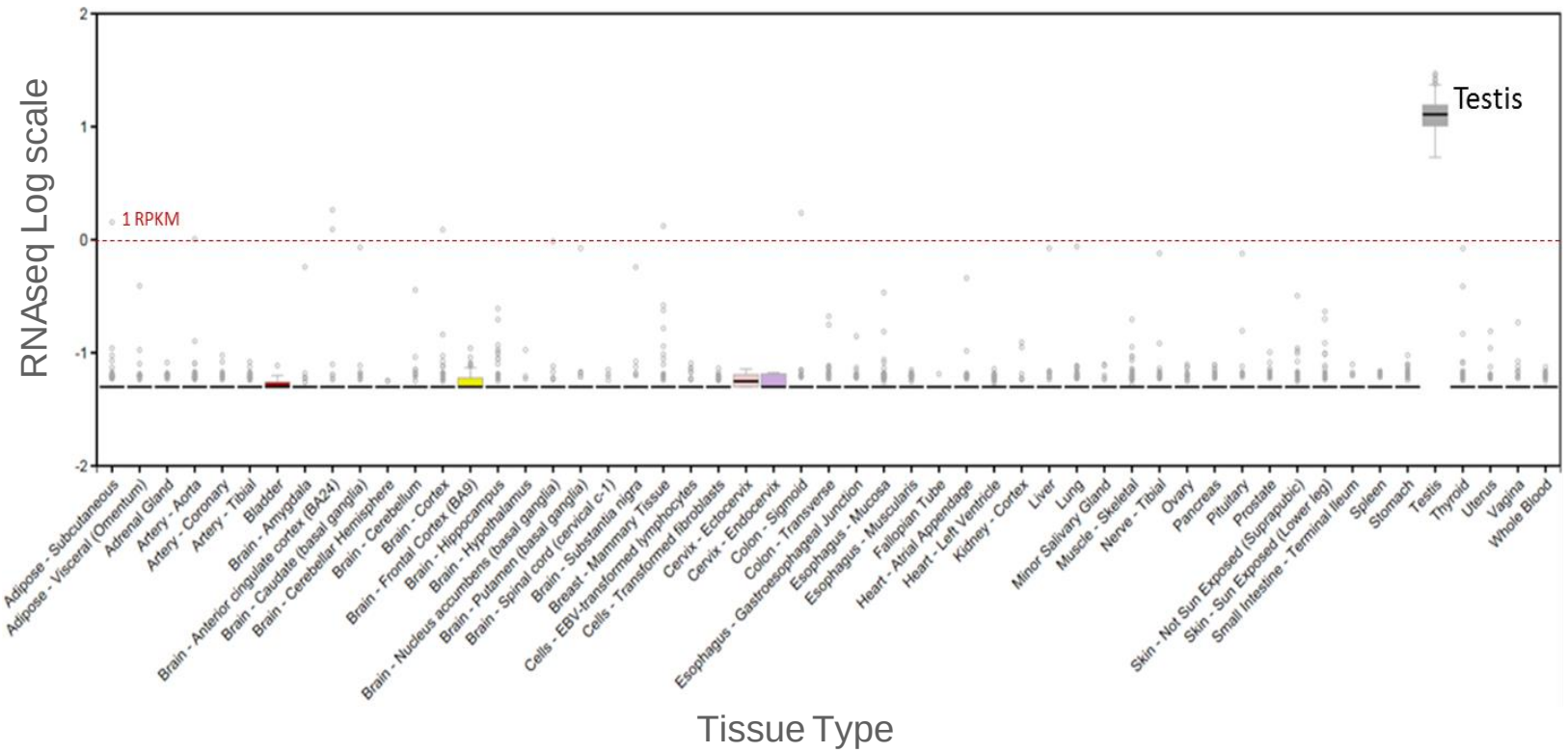
MAGE-A4 expression from cancer genome atlas (TCGA)

MAGE-A4 - EXPRESSION IN NORMAL TISSUE



Expression is absent / low in most adult non-reproductive tissues

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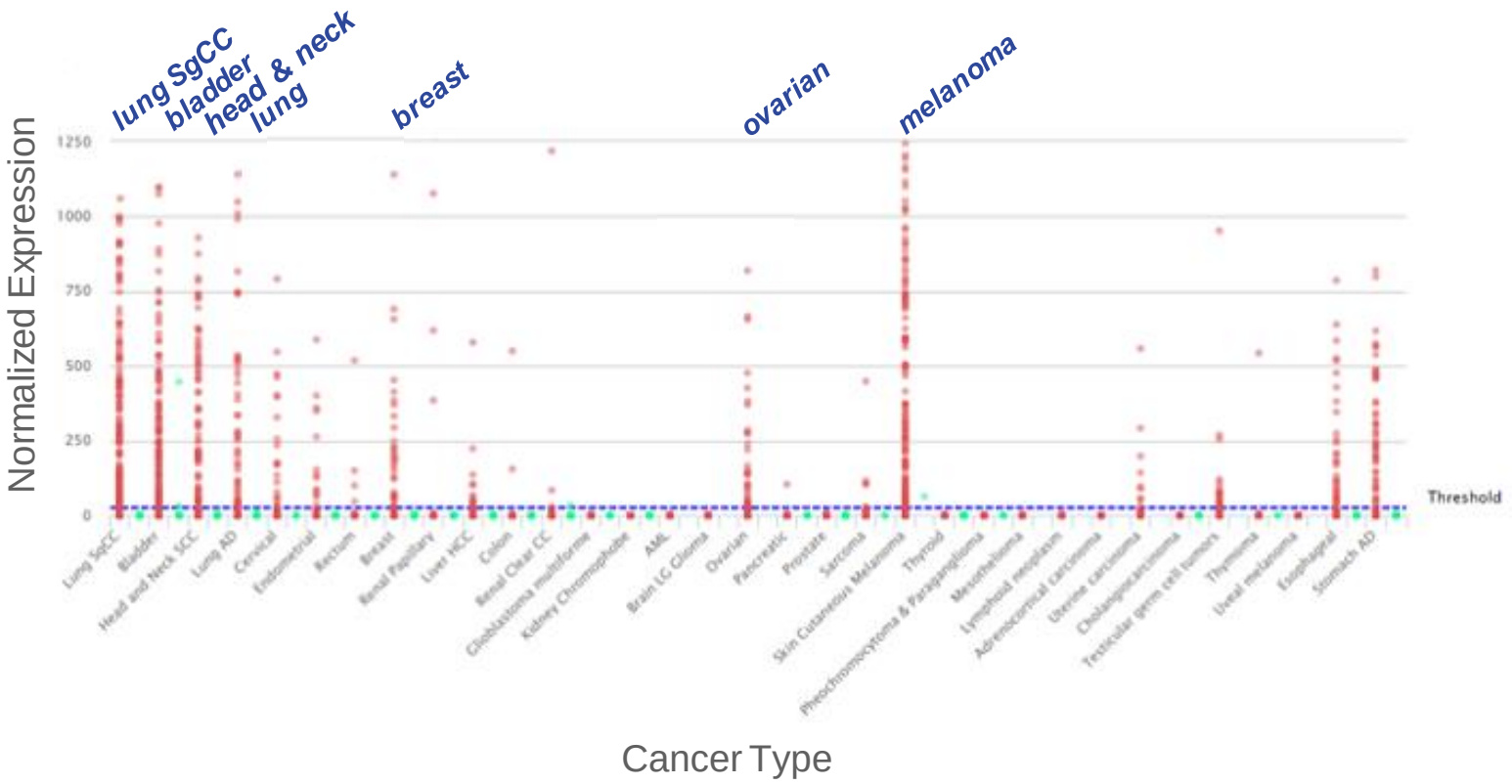
RNAseq (Log scale) GTEx Portal

MAGE-A10 - EXPRESSION IN CANCER



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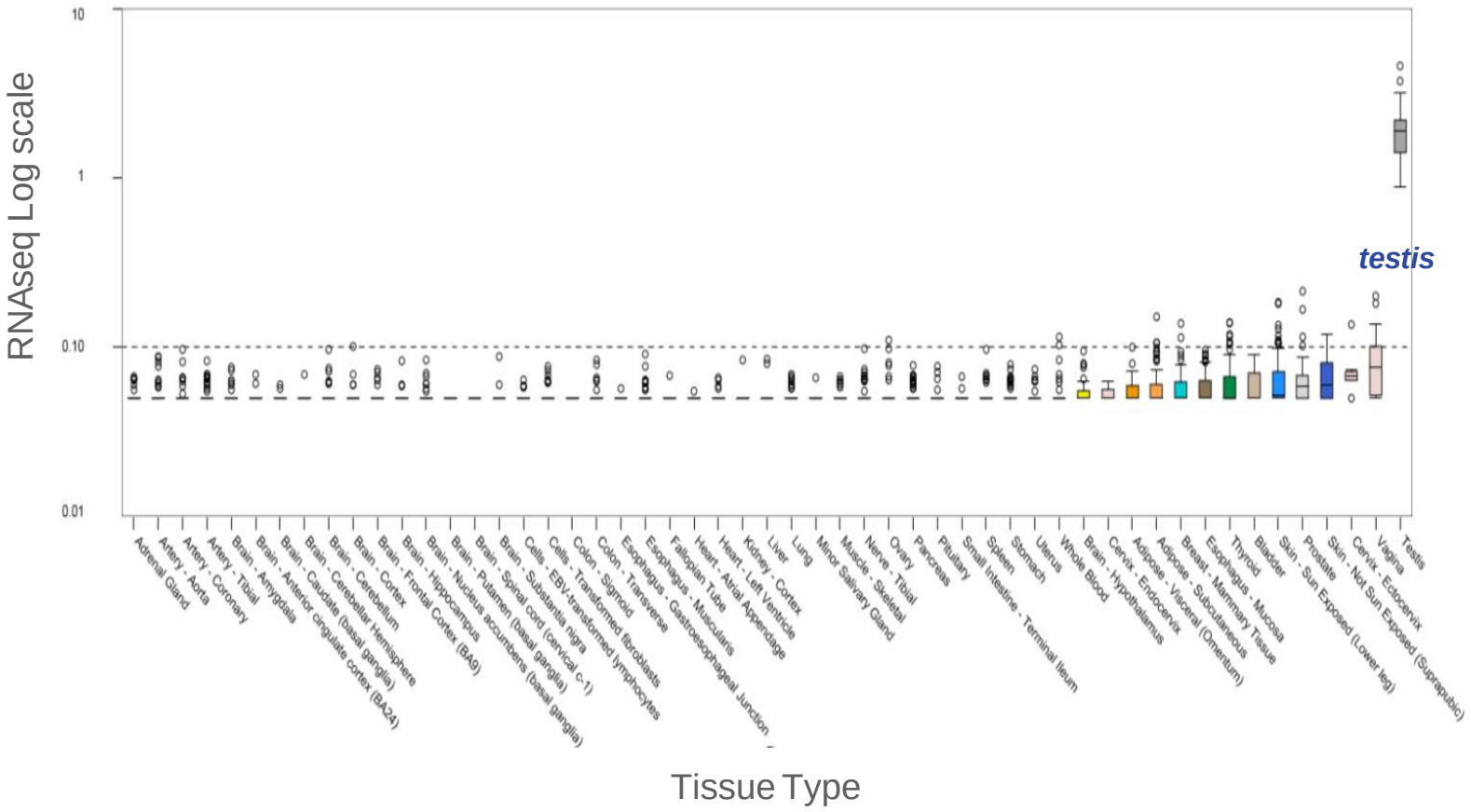
MAGE-A10 expression from cancer genome atlas (TCGA)

MAGE-A10 - EXPRESSION IN NORMAL TISSUE



Expression is absent / low in most adult non-reproductive tissues

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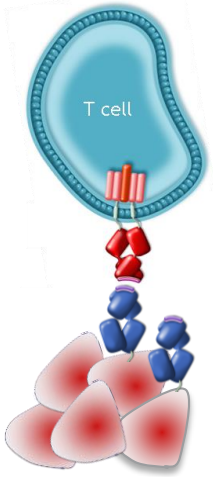
RNAseq (Log scale) GTEx Portal

SPECIFICITY AND NON-SPECIFICITY

OFF TARGET (SPECIFIC)



Closely related antigen on normal tissue

Potential for off-target specificity can be analyzed because the antigen is short and linear

- X-Scan
  1. Identify potential targets via genome search
  2. Test recognition by high affinity TCR

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X-SCAN: INDIVIDUAL PEPTIDE POSITION SPECIFICITY TESTING

Essential to determine which amino acids are critical

This is achieved by Single Amino Acid Substitution Mapping (X-scan)

T	A	R	G	E	T	H	E	R	E
A	A	R	G	E	T	H	E	R	E
C	A	R	G	E	T	H	E	R	E
D	A	R	G	E	T	H	E	R	E
E	A	R	G	E	T	H	E	R	E
F	A	R	G	E	T	H	E	R	E
G	A	R	G	E	T	H	E	R	E
H	A	R	G	E	T	H	E	R	E
I	A	R	G	E	T	H	E	R	E
K	A	R	G	E	T	H	E	R	E
L	A	R	G	E	T	H	E	R	E
M	A	R	G	E	T	H	E	R	E
N	A	R	G	E	T	H	E	R	E
P	A	R	G	E	T	H	E	R	E
Q	A	R	G	E	T	H	E	R	E
R	A	R	G	E	T	H	E	R	E
S	A	R	G	E	T	H	E	R	E
V	A	R	G	E	T	H	E	R	E
W	A	R	G	E	T	H	E	R	E
Y	A	R	G	E	T	H	E	R	E

T	A	R	G	E	T	H	E	R	E
A	I	K	-	-	M	-	-	E	D
C	L	H						K	G
D	V							N	K
E	S							Q	
F								S	
G								Y	
H									
I									
K									
L									
M									
N									
P									
Q									
R									
S									
V									
W									
Y									

TCR 'tolerance' motif

Search Human Genome for all possible peptide matches and investigate these via:

- *TCR recognition*
- *Peptide presentation*

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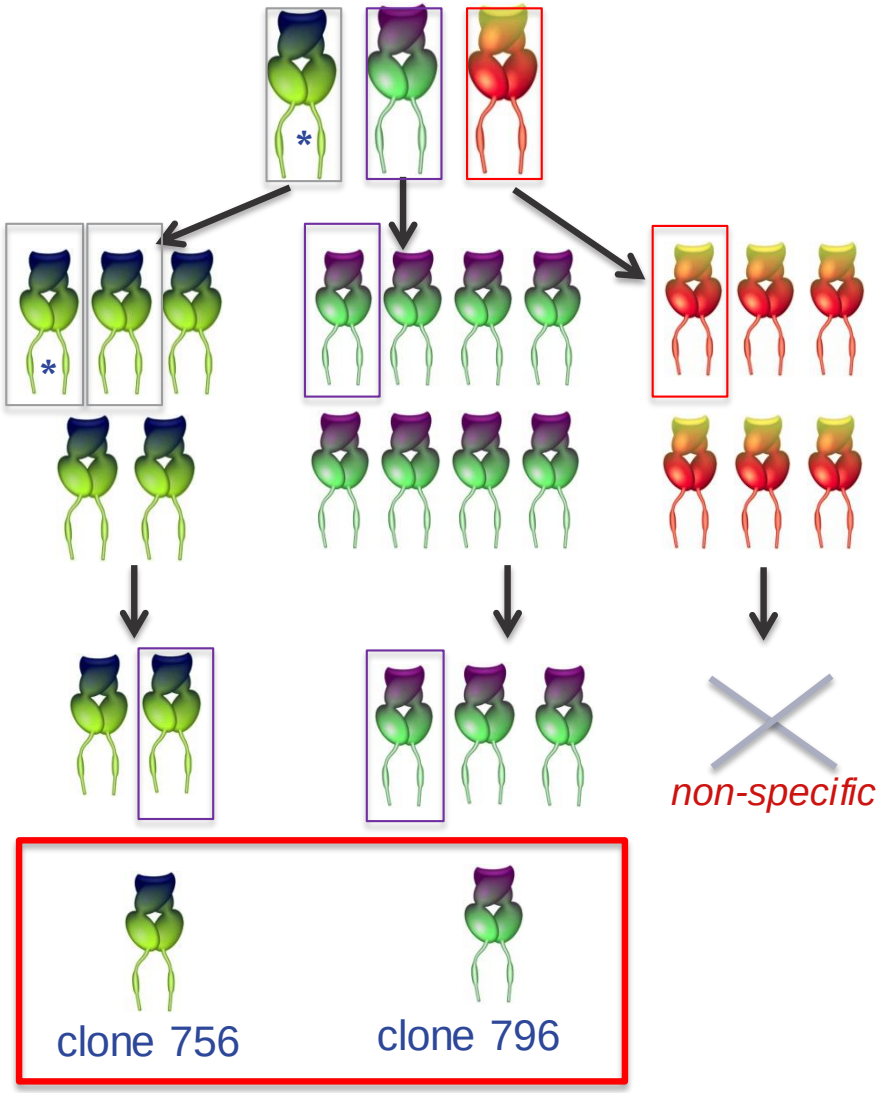
MAGE-A10 - TCR GENERATION AND SELECTION

1. Three TCRs selected by specificity testing from an original pool of 21 parentals
2. Affinity enhancement leads to 15 variants plus 3 parents and 1 reverted heavy chain parental for testing
3. Cell based potency and specificity testing to select five candidates from 2 parents
4. Additional efficacy testing resulted in two comparable leads for X scan evaluation



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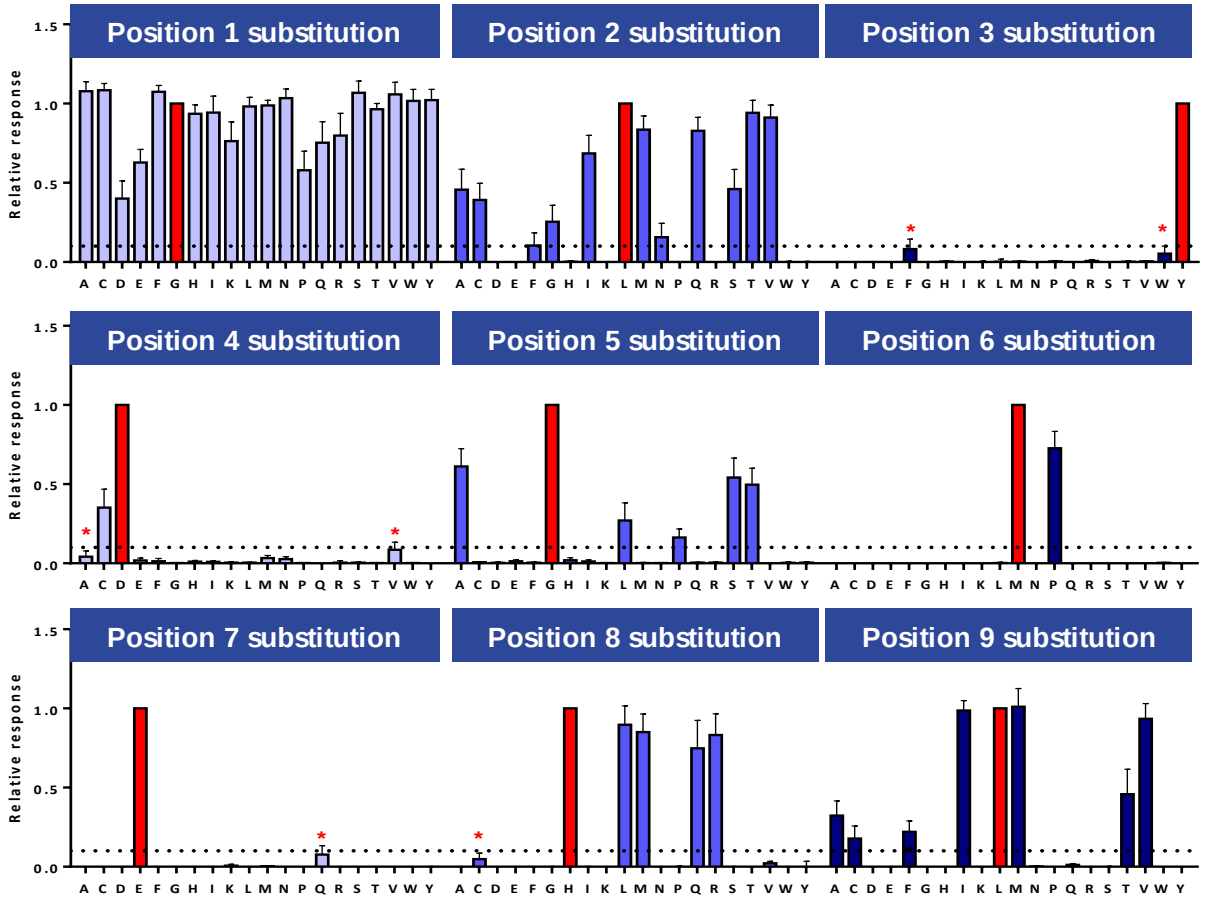
** Point mutation in heavy chain (corrected at level 2)*

MAGE-A10 TCR: 'X-SCAN' SPECIFICITY ANALYSIS

TCR PEPTIDE RECOGNITION MAPPING USING COMBINATORIAL AMINO ACID SUBSTITUTIONS

POSITION								
1	2	3	4	5	6	7	8	9
G	L	Y	D	G	M	E	H	L
X	L	Y	D	G	M	E	H	L
G	X	Y	D	G	M	E	H	L
G	L	X	D	G	M	E	H	L
G	L	Y	X	G	M	E	H	L
G	L	Y	D	X	M	E	H	L
G	L	Y	D	G	X	E	H	L
G	L	Y	D	G	M	X	H	L
G	L	Y	D	G	M	E	X	L
G	L	Y	D	G	M	E	H	X



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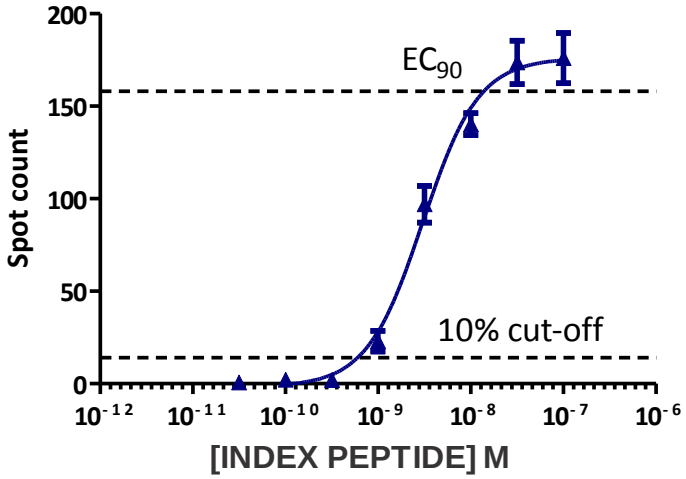
MAGE-A10 TCR: 'X-SCAN' SPECIFICITY ANALYSIS

TCR PEPTIDE RECOGNITION MAPPING USING COMBINATORIAL AMINO ACID SUBSTITUTIONS



Tolerated residues at each position cutoff:
>10% of native MAGE-A10 peptide response

G	T	Y	D	G	M	E	L	L
A	Q	F	C	A	P	Q	I	V
R	V	D	N	L	G	F	M	T
K	L	E	M	I	L	G	H	I
C	S	I	A	T	A	I	G	M
Q	A	K	Q	P	V	K	A	F
E	C	L	S	S	D	M	P	C
T	M	M	F	H	H	N	V	Q
P	I	V	H	C	I	P	C	A
W	G	A	K	E	K	T	F	S
M	N	T	P	F	N	V	S	W
L	F	W	G	M	S	S	T	D
H	Y	C	L	Q	C	R	Y	K
S	H	H	E	D	E	A	N	R
I	D	S	I	W	T	C	R	H
F	E	N	V	K	W	H	Q	N
D	P	P	W	R	F	L	D	E
N	K	Q	Y	N	R	W	K	G
Y	W	G	R	V	Y	Y	E	P
V	R	R	T	Y	Q	D	W	Y

>50%
>30%
>20%
>15%
>10%
NR

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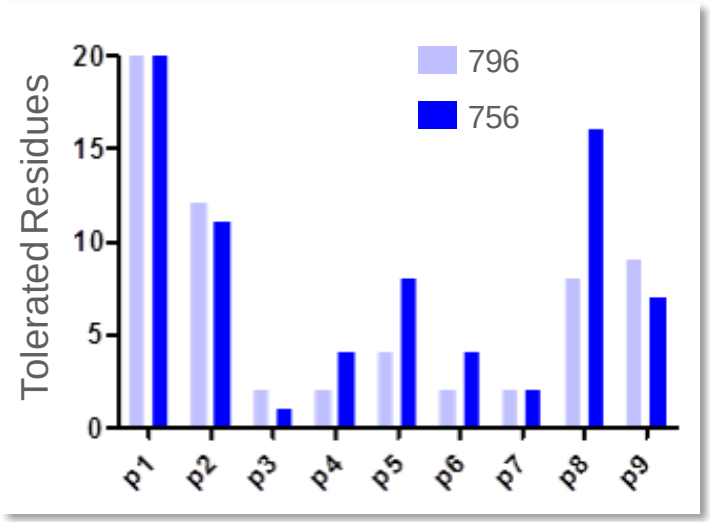
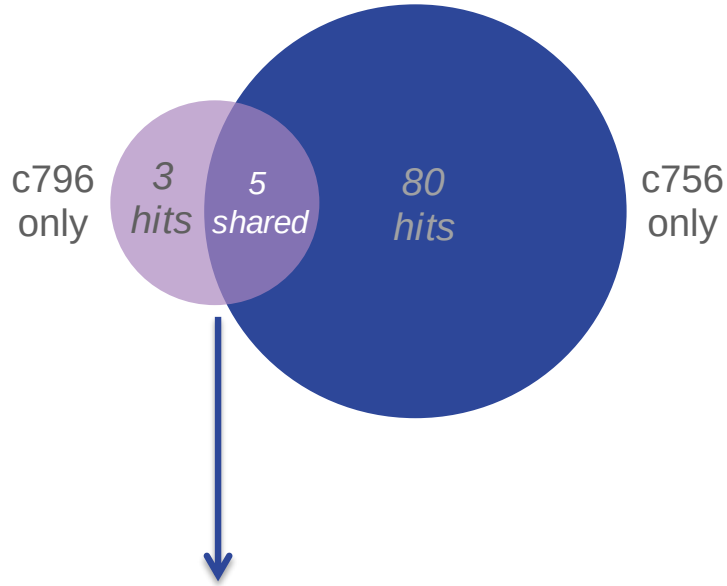
MAGE-A10 TCR SELECTION-MOTIF SEARCH AGAINST PROTEOME



Peptides contained within X-scan motif
(allowing any number of changes)



These 8 peptides were tested with c796 and no responses detected

TCR specificity is a key component

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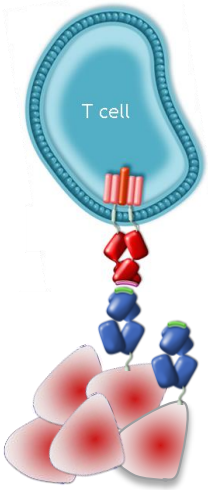
SPECIFICITY AND NON-SPECIFICITY

OFF TARGET (NON-SPECIFIC)



Promiscuous recognition (unrelated to target)

- Potential for off-target non-specific reactions are tested by examining the ability of high-affinity TCRs to react to a panel of normal cell-lines

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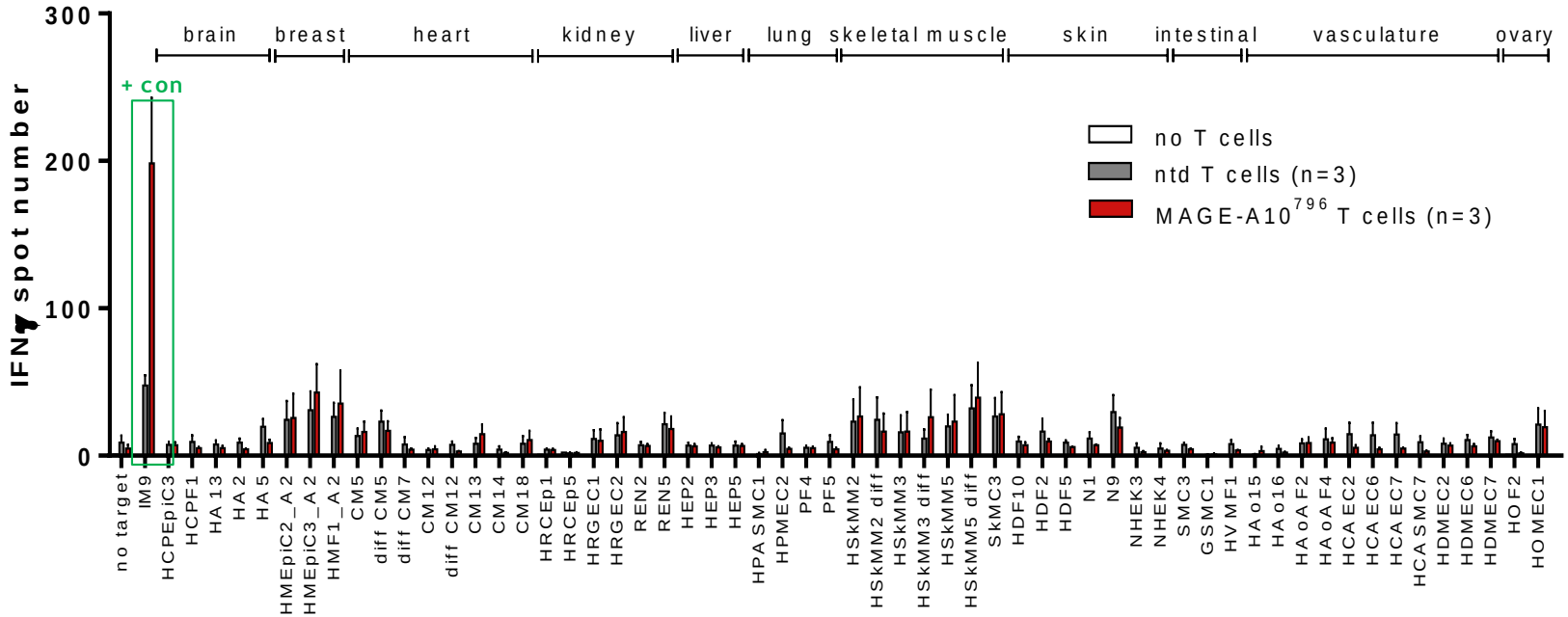
MAGE-A10 TCR - SCREENING AGAINST NORMAL PRIMARY CELLS

- MAGE-A10^{c796}T was evaluated in IFN-γ ELISpot assays against 59 normal primary cells expressing HLA-A2
- No increase above background levels with transduced T cells



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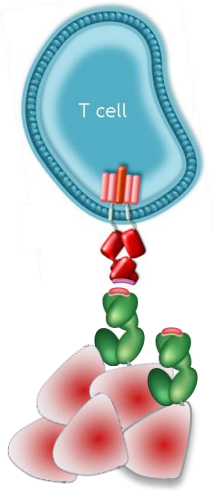
SPECIFICITY AND NON-SPECIFICITY

- Potential for alloreactivity are tested by examining the ability of high-affinity TCRs to react to a panel of normal cell-lines with alternate HLA restrictions

ALLOREACTIVITY



Alternate HLA restriction

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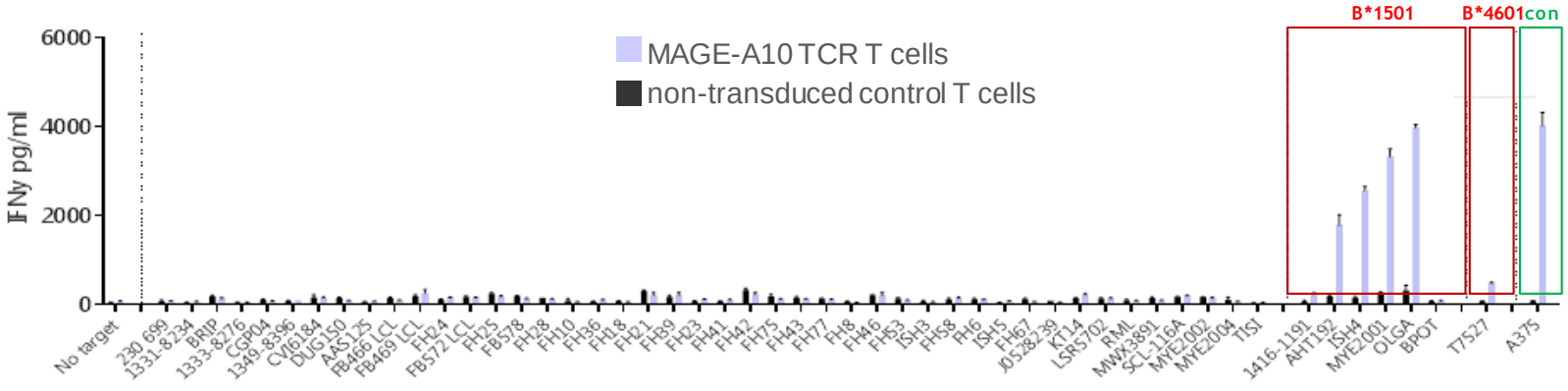
MAGE A10 TCR: ALLOREACTIVITY ASSAY

- Panel of EBV-transformed B cells expressing a range of HLA types
  - 67 cell lines expressing a total of 131 different HLA alleles
- Responses observed in cells expressing HLA-B*1501 and HLA-B*4601



HLA-B*1501 and HLA-B*4601 become exclusion criteria for clinical trial

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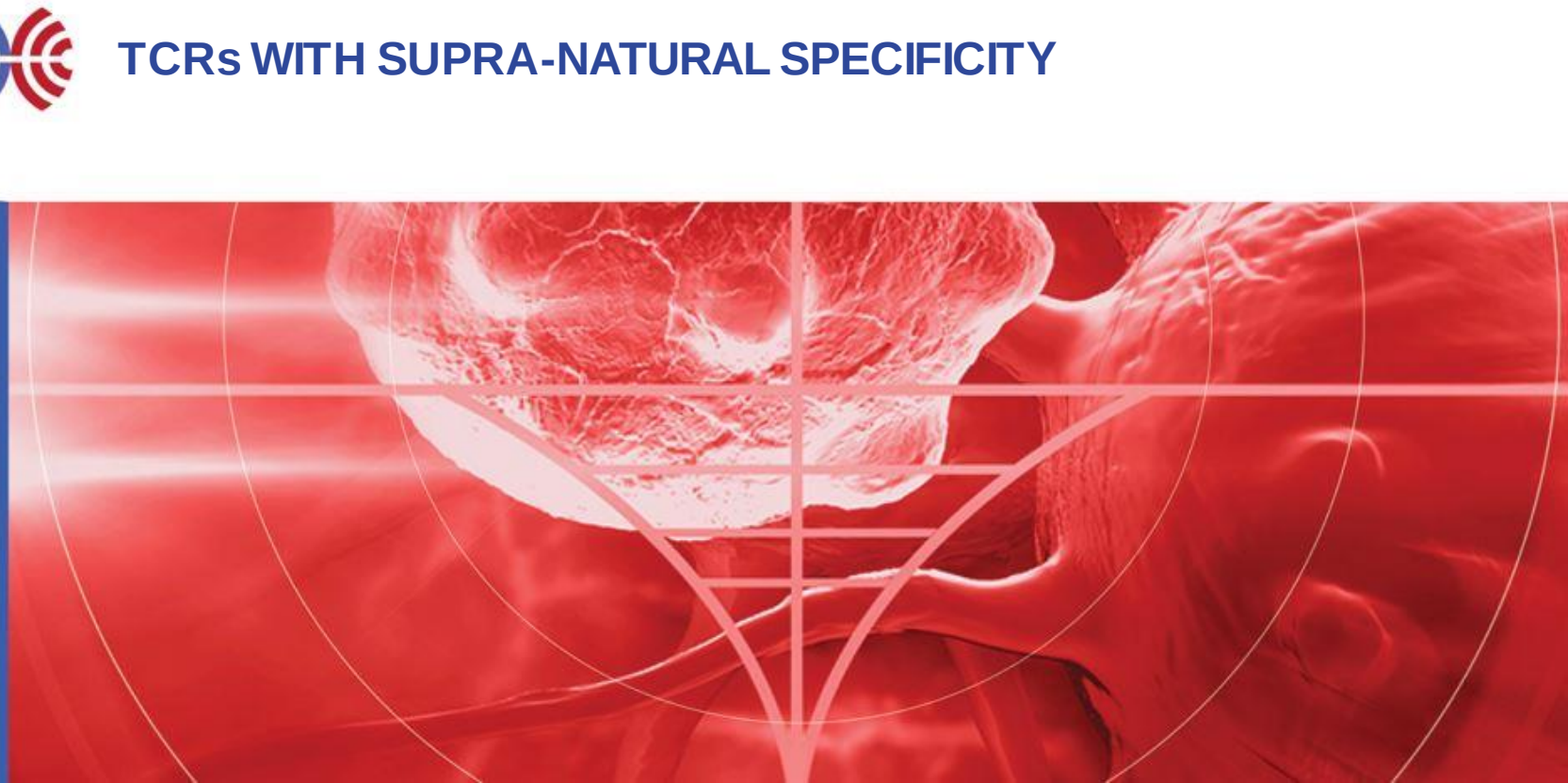
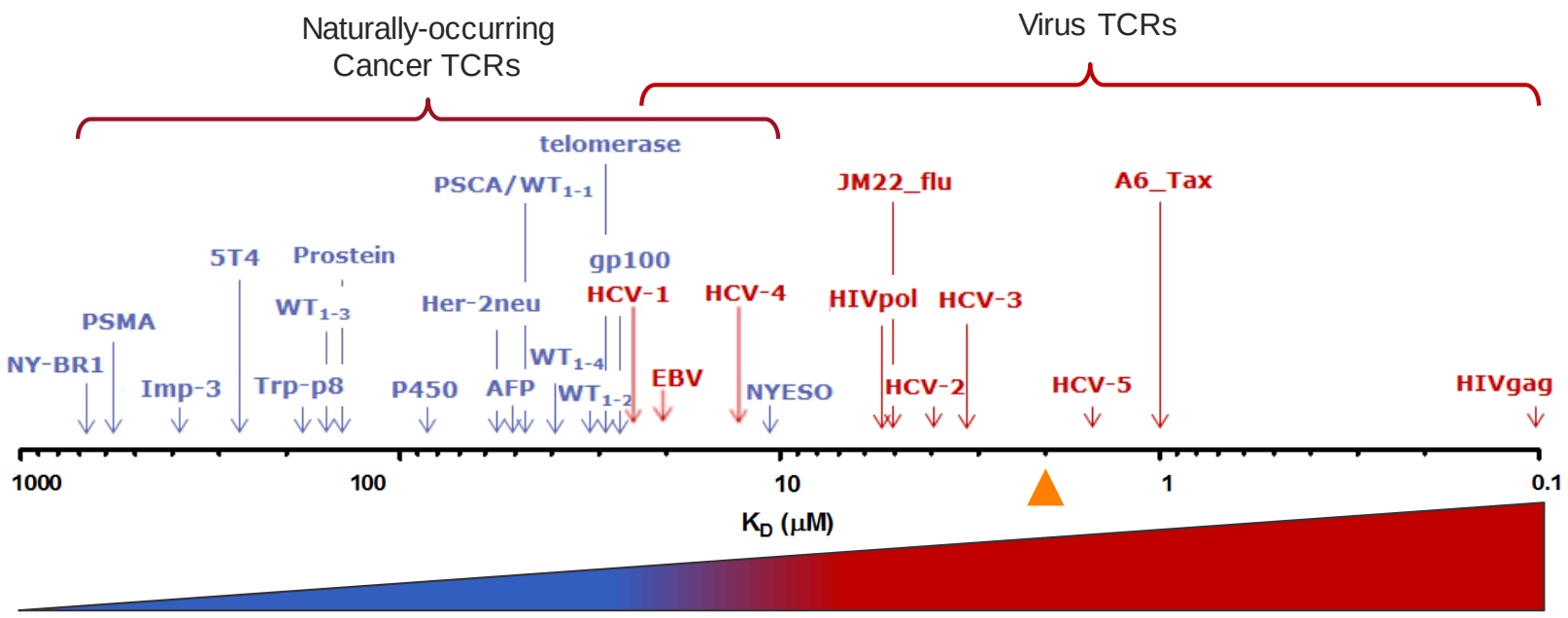
TCRs WITH SUPRA-NATURAL SPECIFICITY



TCR FROM DISPLAY LIBRARY HAS SUPRA-NATURAL AFFINITY



▲ MAGE-A10 K_D ~ 2 μM
- Not a natural TCR
- Identified from proprietary TCR display libraries

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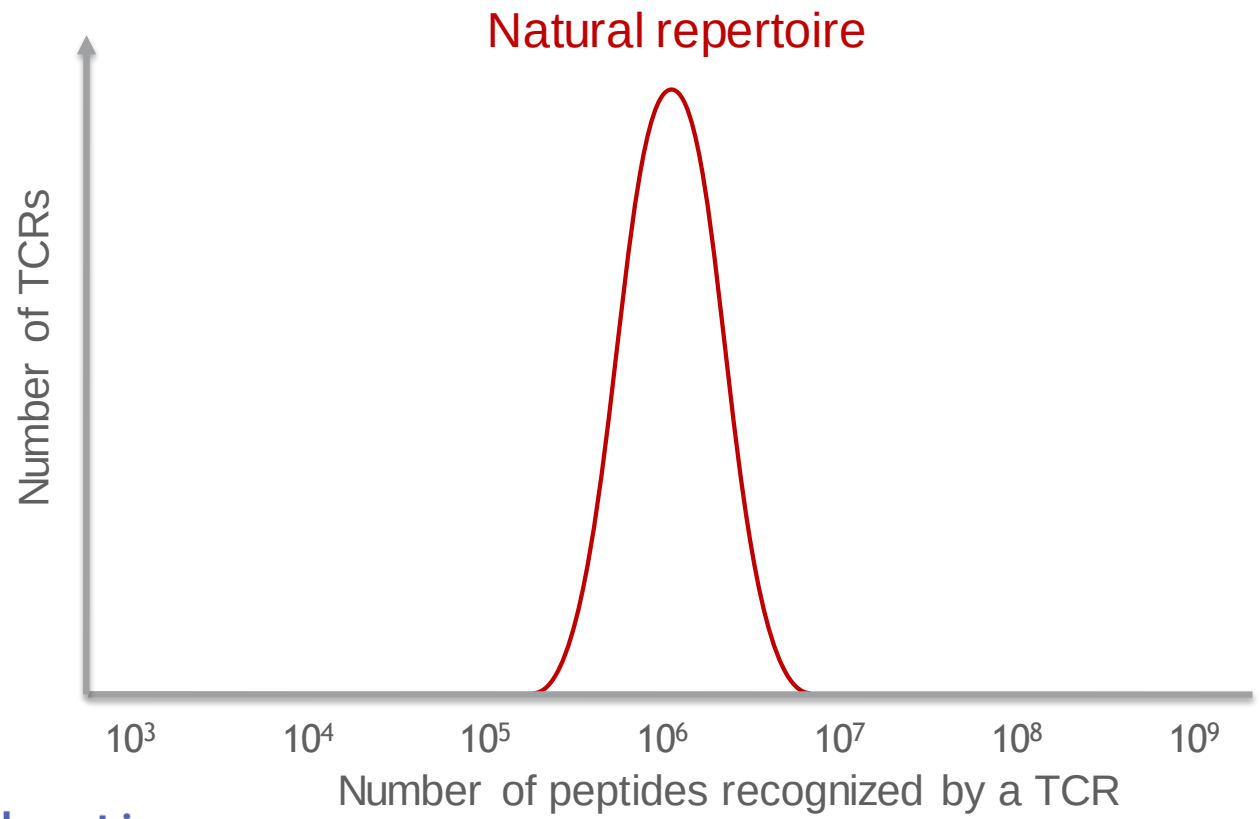
NATURAL TCRs TYPICALLY CAN RECOGNIZE ONE MILLION DIFFERENT PEPTIDES

- Thymic selection narrows TCR specificity / cross-reactivity spectrum
- TCR has to recognize approximately 1,000,000 peptides to be positively selected



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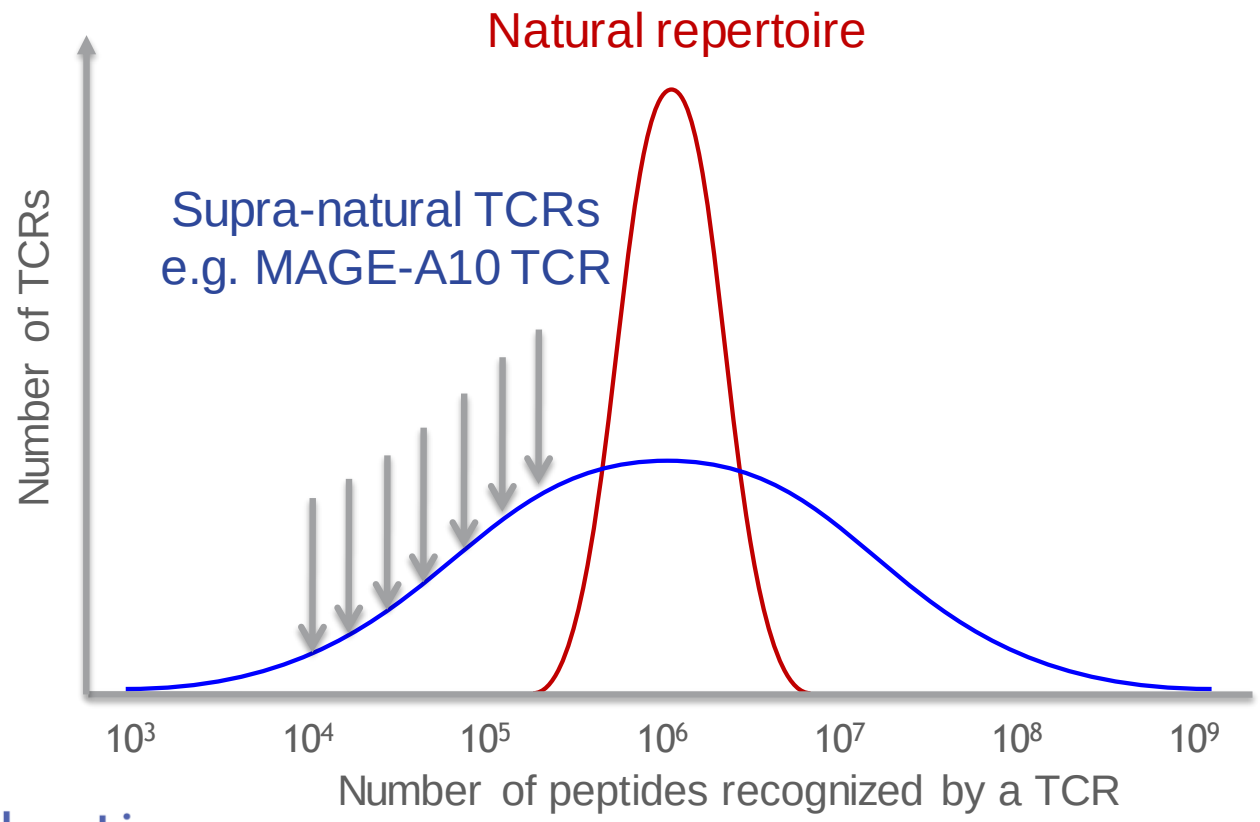
TCRs SELECTED FROM PHAGE LIBRARIES CAN HAVE SUPRA-NATURAL SPECIFICITY

- Thymic selection narrows TCR specificity / cross-reactivity spectrum
- TCR has to recognize approximately 1,000,000 peptides to be positively selected



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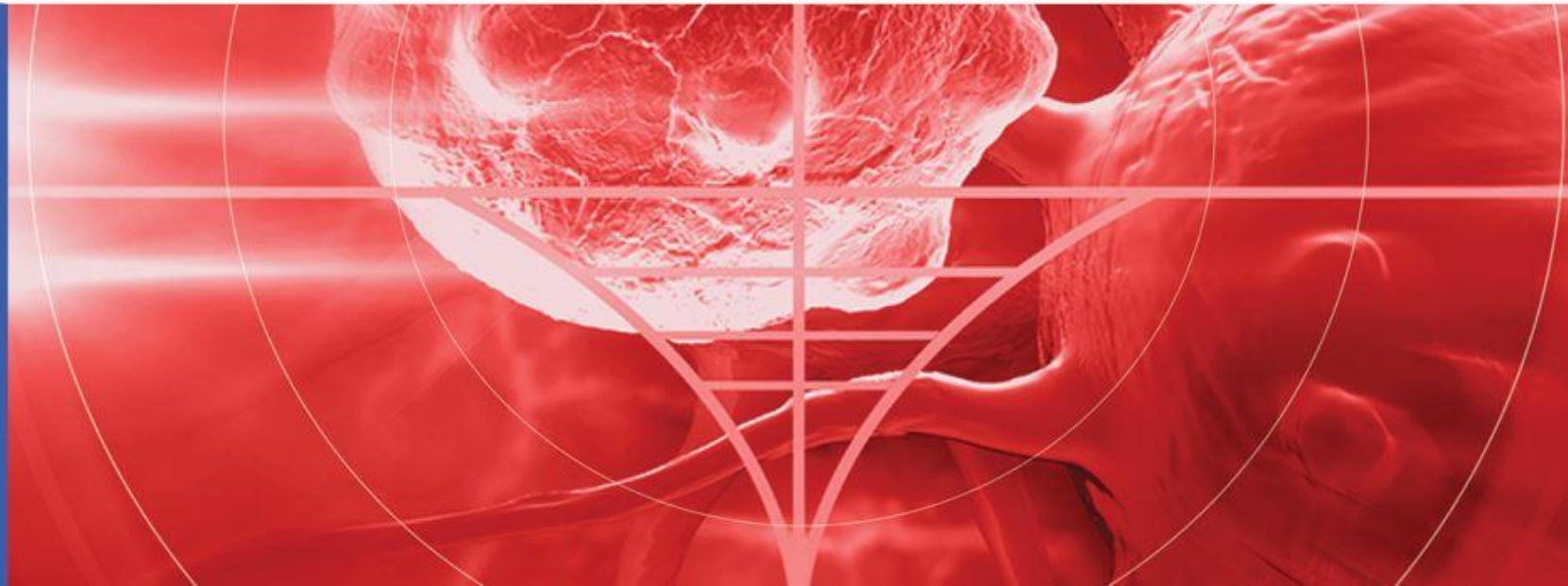
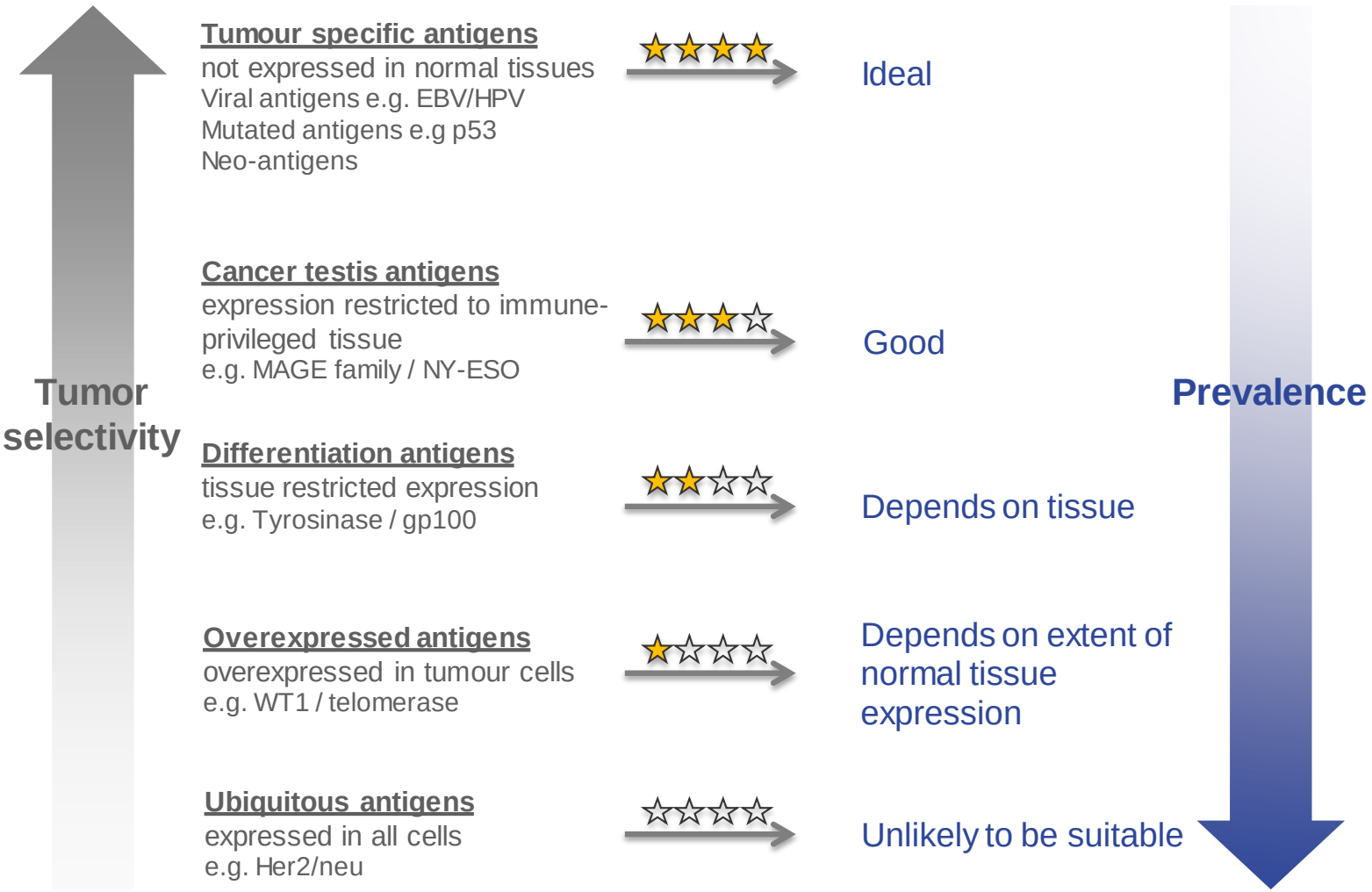
FINDING THE RIGHT TARGETS



THE SPECTRUM OF POTENTIAL CANCER TARGETS FOR IMMUNOTHERAPY



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see http://cancerimmunity.org/peptide/ for a list of tumor antigens reported in the literature

PEPTIDE TARGET VALIDATION VIA MASS SPECTROMETRY

- Many identified target peptides fail to be presented *in vivo*
  - PSCA 14-22 (ALQPGTALL)
  - WT1 126-134 (RMFPNAPYL)
  - Telomerase 540-548 (ILAKFLHWL)
    - Not found by Adaptimmune mass spectrometry
    - Not detected by potent TCRs / T cells

- Adaptimmune **ONLY** considers peptides to be validated if detected by mass spectrometry
  - Currently ~ 660,000 unique peptides within our databases

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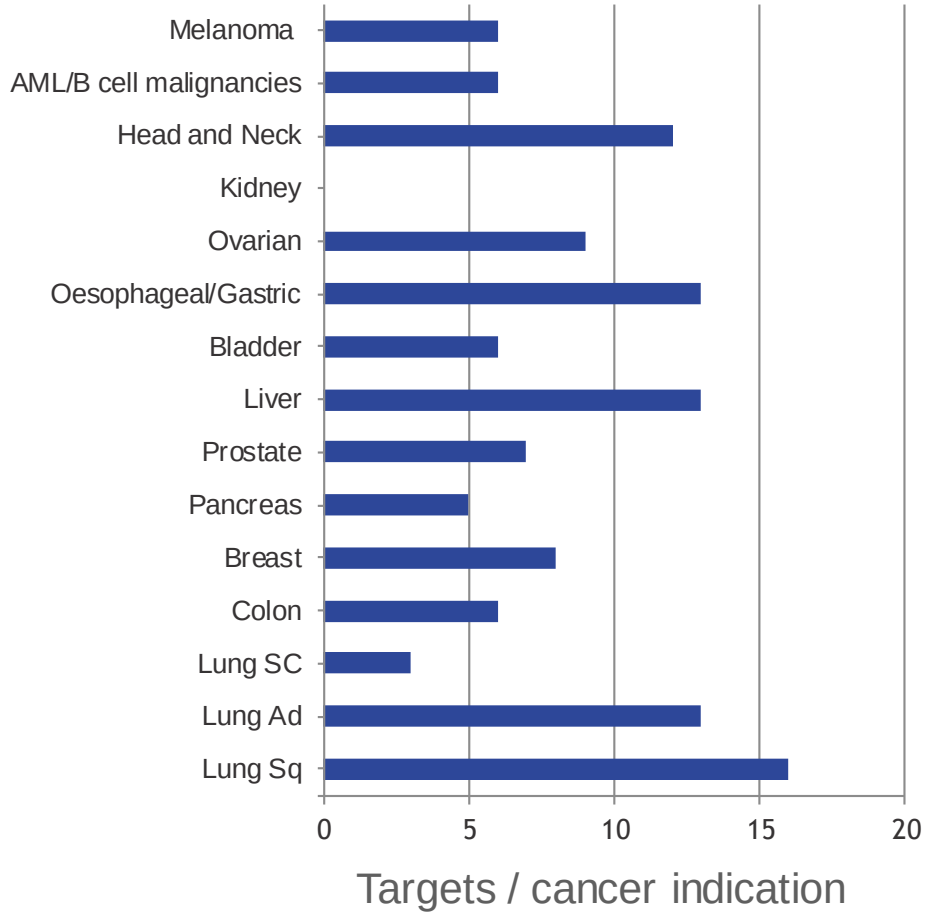
RECENTLY FILED PATENTS ON 63 TARGETS

873 PEPTIDES



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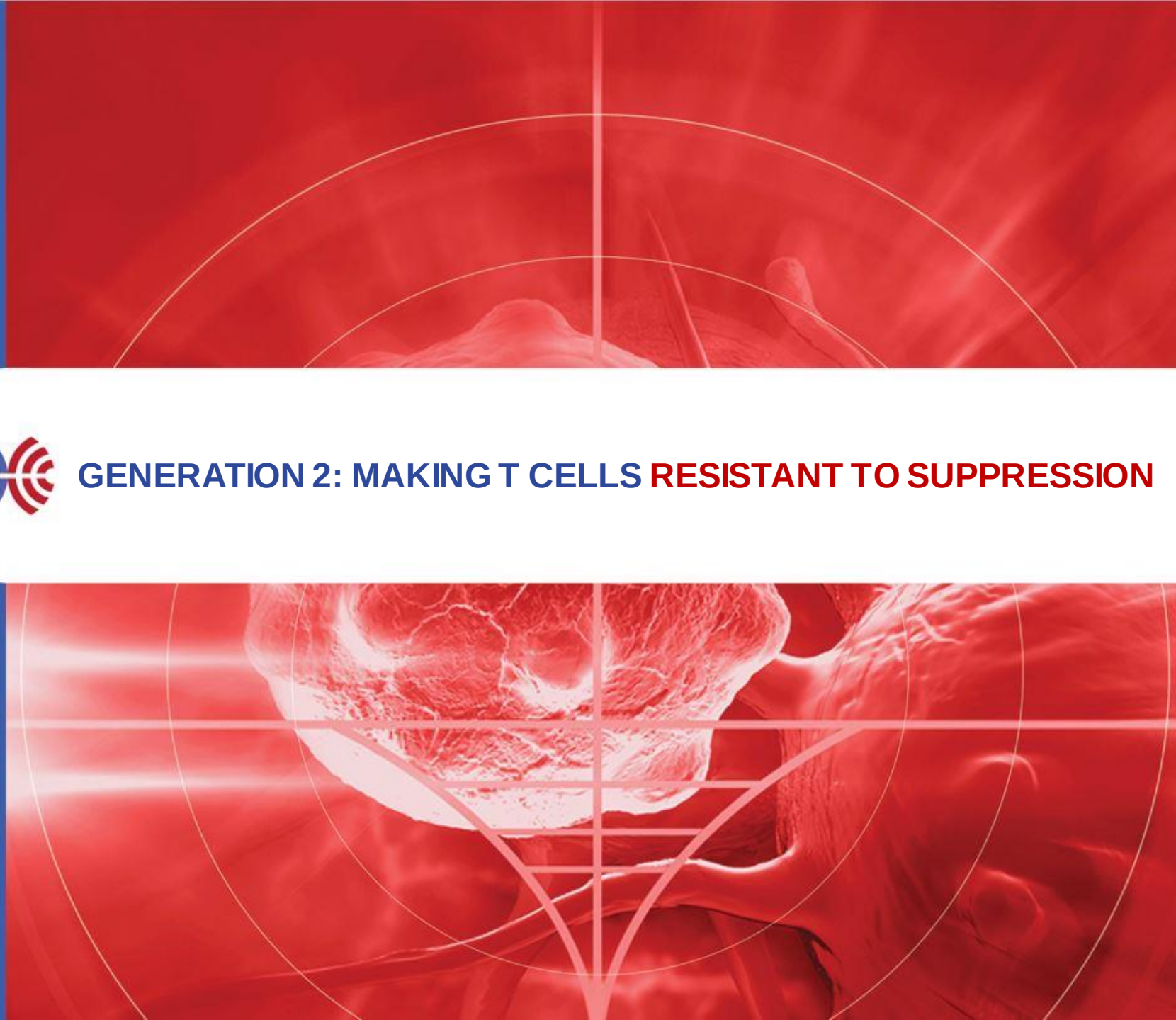
GENERATION 2: MAKING T CELLS RESISTANT TO SUPPRESSION



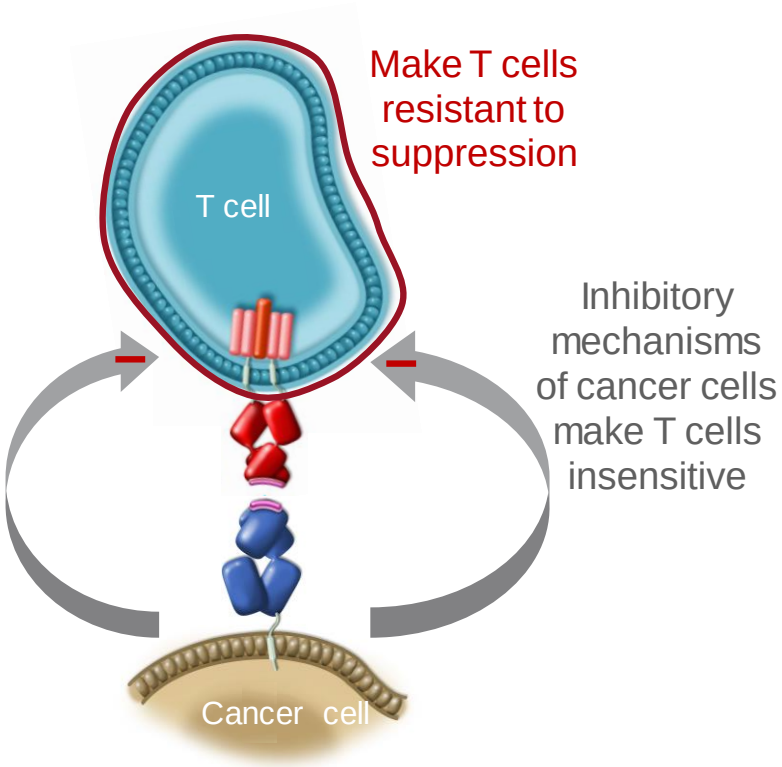
ADOPTIVE T CELL : GENERATION 2

Four components to an effective adoptive therapy:

1. T cell must recognize a cancer cell via a **guiding receptor**

2. The guiding receptor must have two important aspects
   - **Affinity**
   - **Specificity**

3. The T cell needs to be **resistant to suppression**



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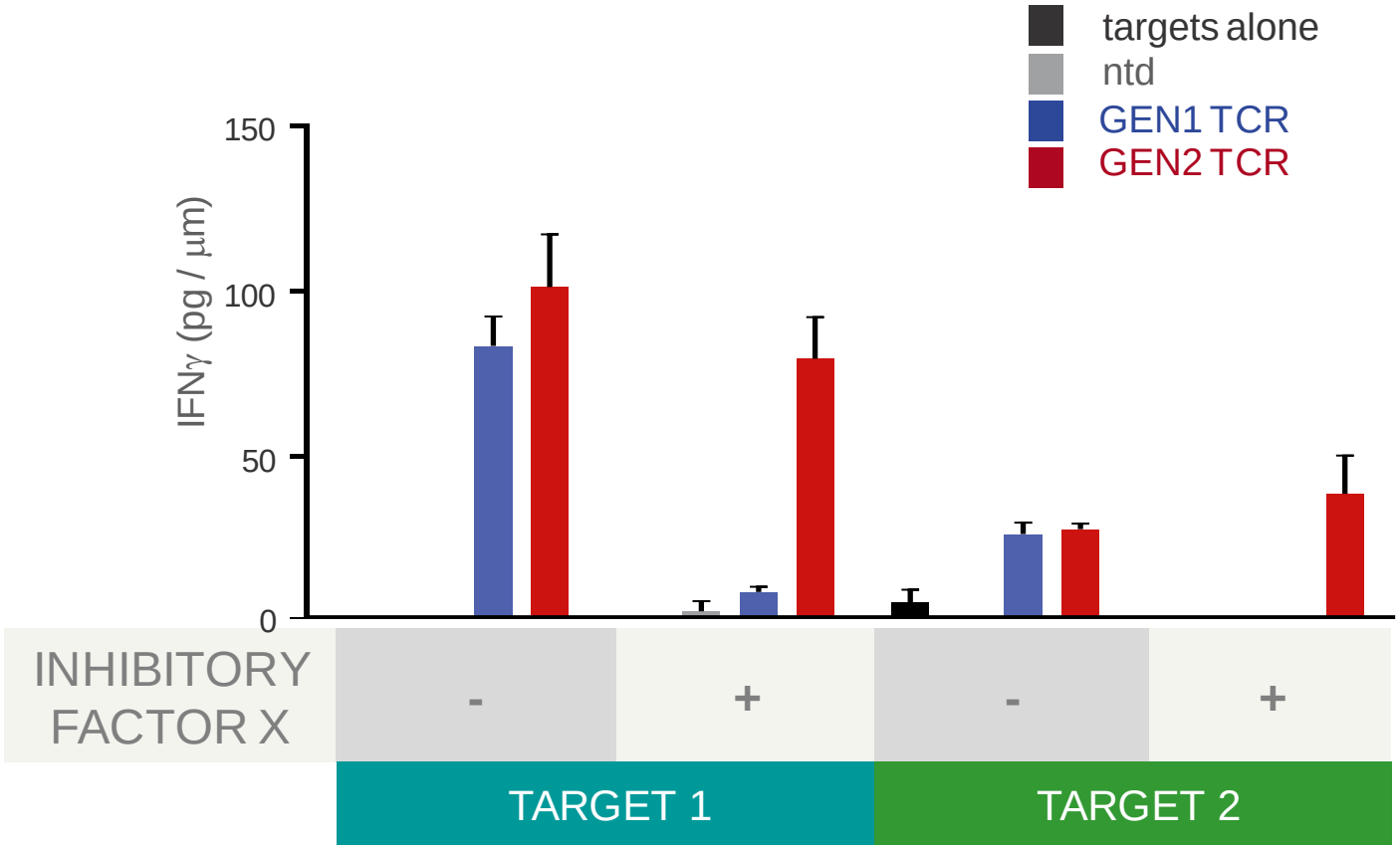
OVERCOMING INHIBITION IN THE TUMOUR MICROENVIRONMENT

GEN2(A) MAKES T CELLS INSENSITIVE TO INHIBITORY FACTOR X



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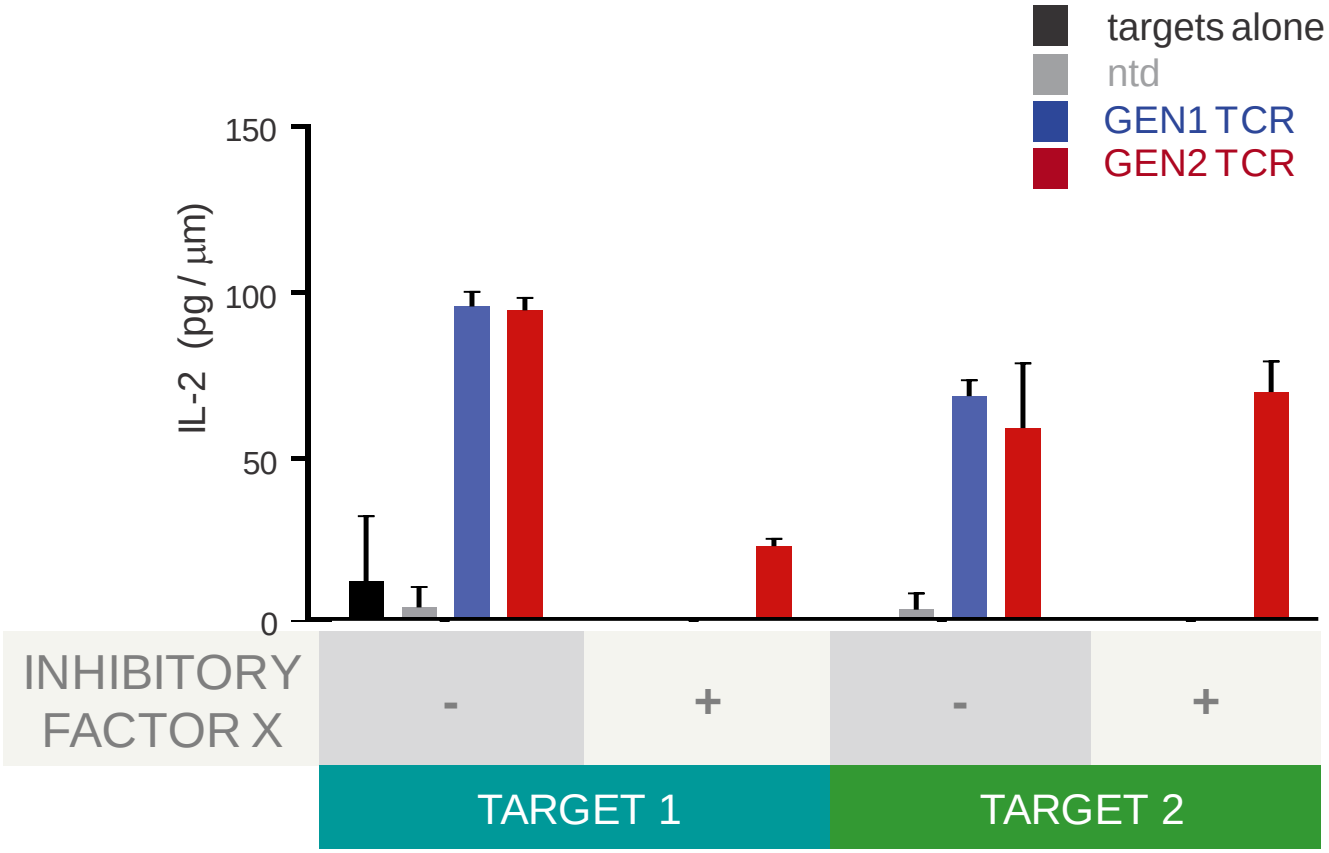
TRANSFORMING T CELL THERAPY

OVERCOMING INHIBITION IN THE TUMOUR MICROENVIRONMENT

GEN2(A) MAKES T CELLS INSENSITIVE TO INHIBITORY FACTOR X



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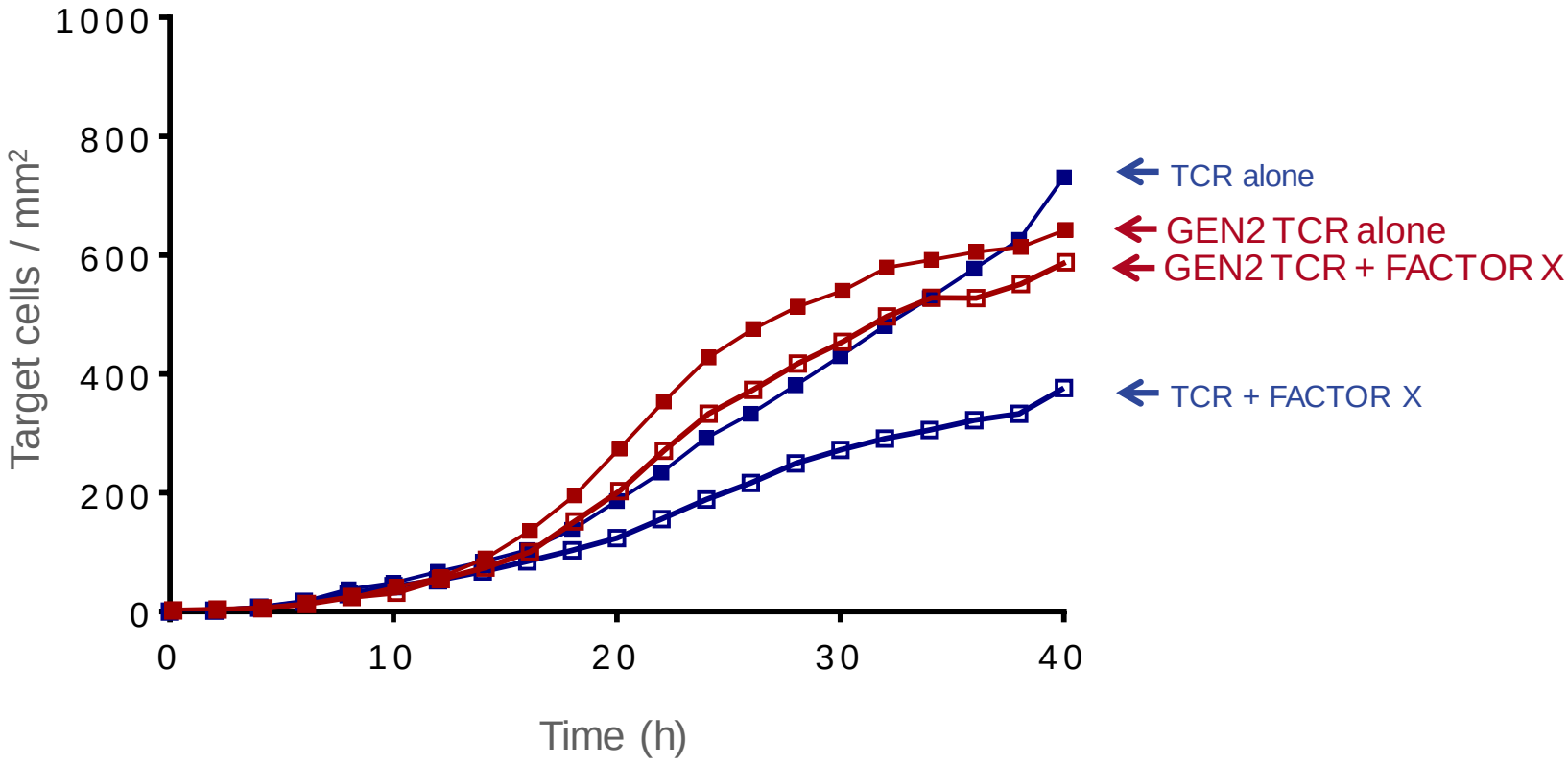
TRANSFORMING T CELL THERAPY

OVERCOMING INHIBITION IN THE TUMOUR MICROENVIRONMENT

GEN2(A) MAKES T CELLS INSENSITIVE TO INHIBITORY FACTOR X

- Gen2(A) TCR maintains enhanced killing in the presence of inhibitors



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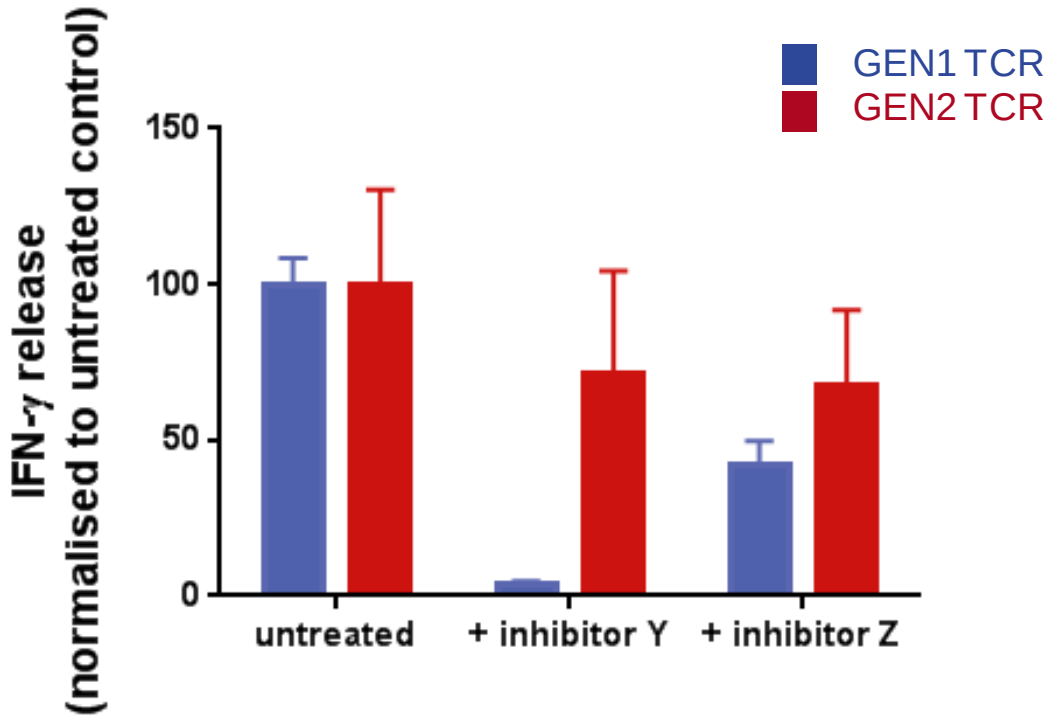
OVERCOMING INHIBITION IN THE TUMOUR MICROENVIRONMENT

GEN2(C) MAKES T CELLS INSENSITIVE TO INHIBITORY FACTORS Y & Z



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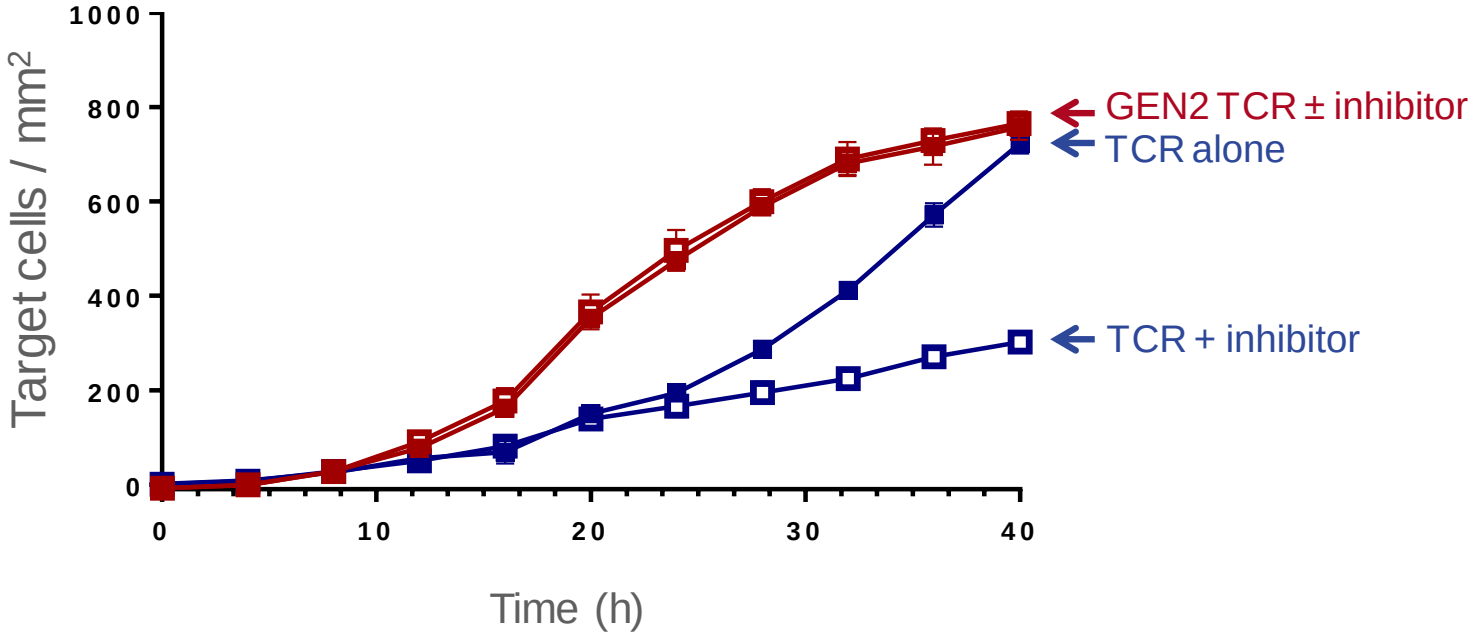
OVERCOMING INHIBITION IN THE TUMOUR MICROENVIRONMENT (II)

GEN2(C) MAKES T CELLS INSENSITIVE TO INHIBITORY FACTORS Y & Z

- Gen2(C) TCR maintains enhanced killing in the presence of inhibitors



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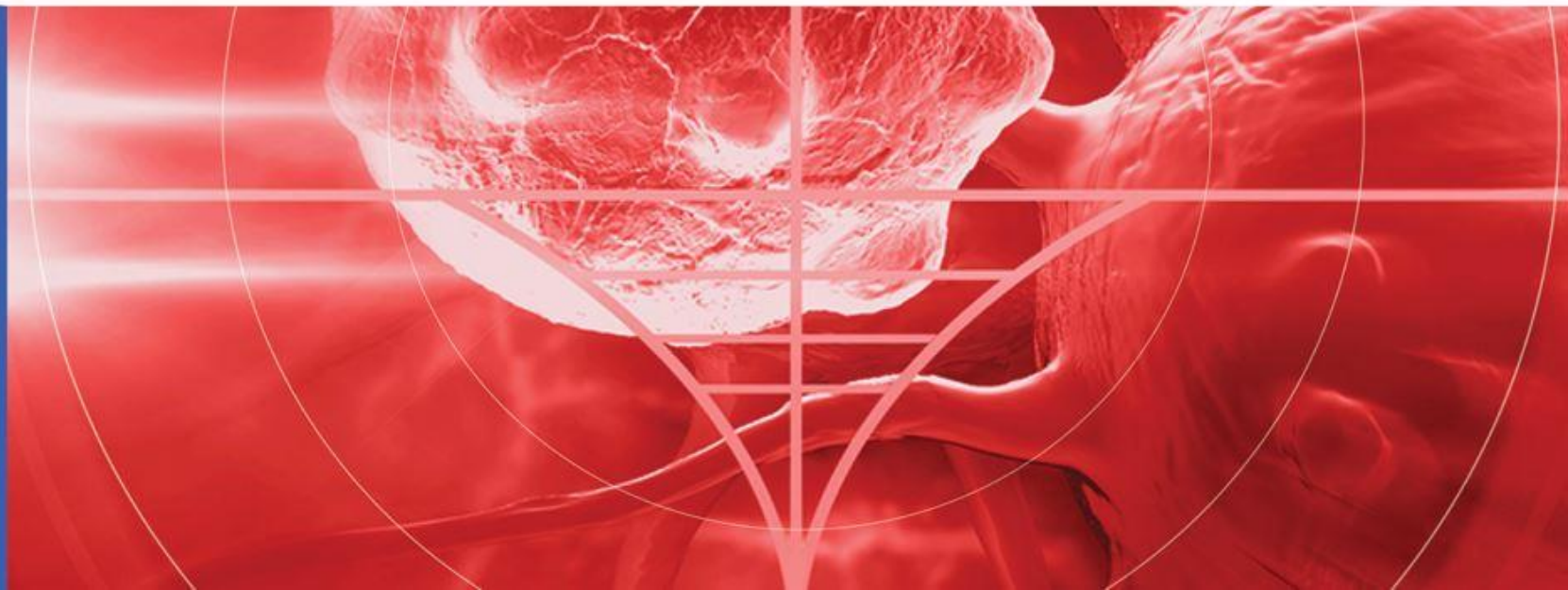
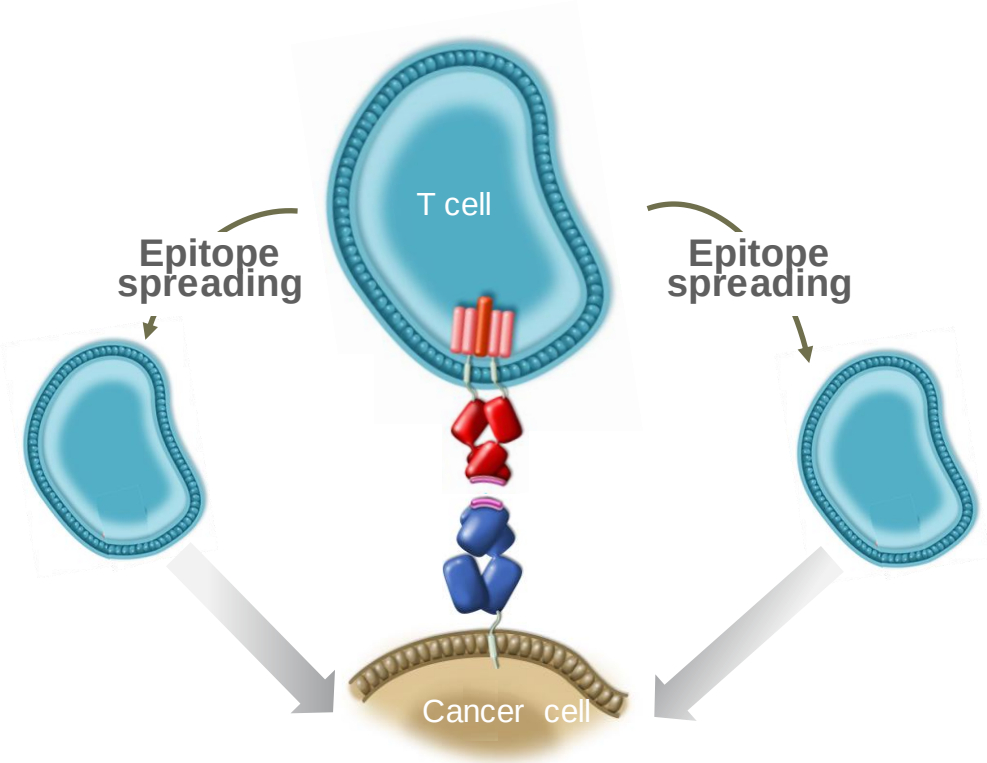
GENERATION 3: ENABLING T CELLS TO HELP ‘BREAK CANCER IMMUNE TOLERANCE’



ADOPTIVE T CELL : GENERATION 3

Four components to an effective adoptive therapy:

1. T cell must recognize a cancer cell via a **guiding receptor**
2. The guiding receptor must have two important aspects
   - **Affinity**
   - **Specificity**
3. The T cell needs to be **resistant to suppression**
4. The T cell (either alone or via other mechanisms) needs to **'break cancer immune tolerance'**



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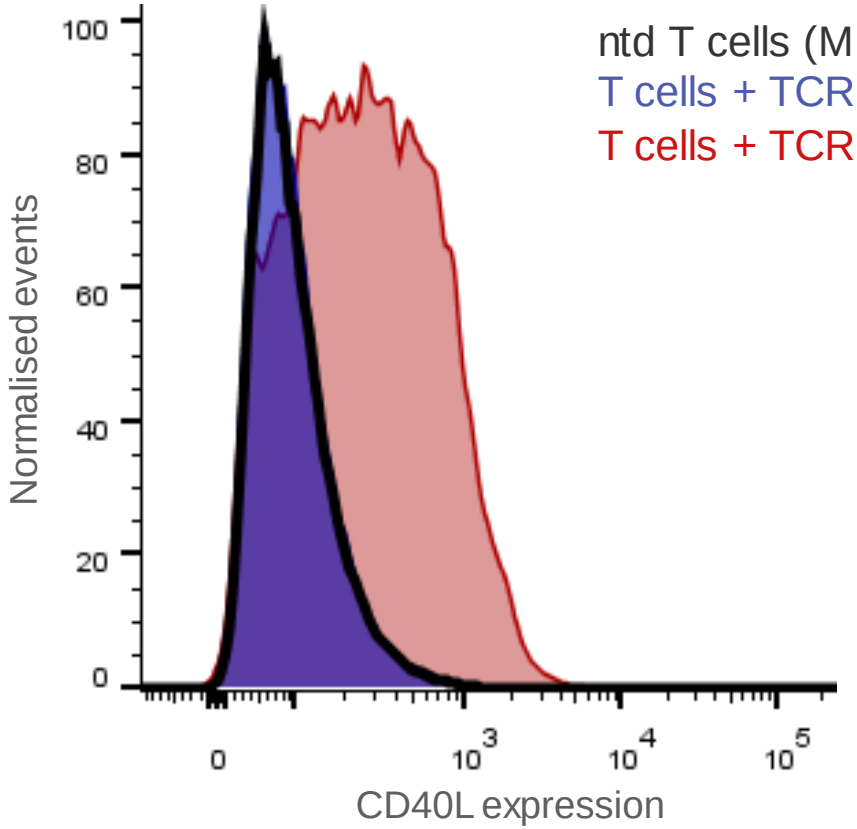
BROADENING THE IMMUNE RESPONSE

GEN3(B) ENHANCES CD40L EXPRESSION TO PROMOTE EPITOPE SPREADING

- Gen2(B) enhances TCR mediated CD40L upregulation on $CD4^+$ T cells in response to antigen positive targets



ntd T cells (MFI= 118)
T cells + TCR (MFI= 116)
T cells + TCR + Gen3(B) (MFI= 313)

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GENERATION 2 AND GENERATION 3 T CELLS

- Several Generation 2 projects that help T cells overcome sensitivity to inhibitory factors in the tumor microenvironment
- Several Generation 3 projects that enable T cells to promote epitope spreading and therefore have the potential to aid the breaking of tumor immune tolerance
- First Generation 2 / 3 IND anticipated in 2017

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ADAPTIMMUNE T CELL TECHNOLOGY

SUMMARY

- TCR affinity optimization crucial for best T cell response to cancer
- Specificity crucial for lowest toxicity – supra-naturally specific TCRs identified from proprietary display libraries
- Several Generation 2 technologies making T cells resistant to tumour microenvironment inhibitory factors
- Several Generation 3 technologies enabling T cells to facilitate breaking immune tolerance to tumor

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ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

ADOPTIVE T CELL THERAPY: CLINICAL ACTIVITY OF NY-ESO-1 IN A SOLID TUMOR

APRIL 22, 2016

Stephan Grupp, M.D., Ph. D.
Novotny Professor of Pediatrics
University of Pennsylvania
Perelman School of Medicine

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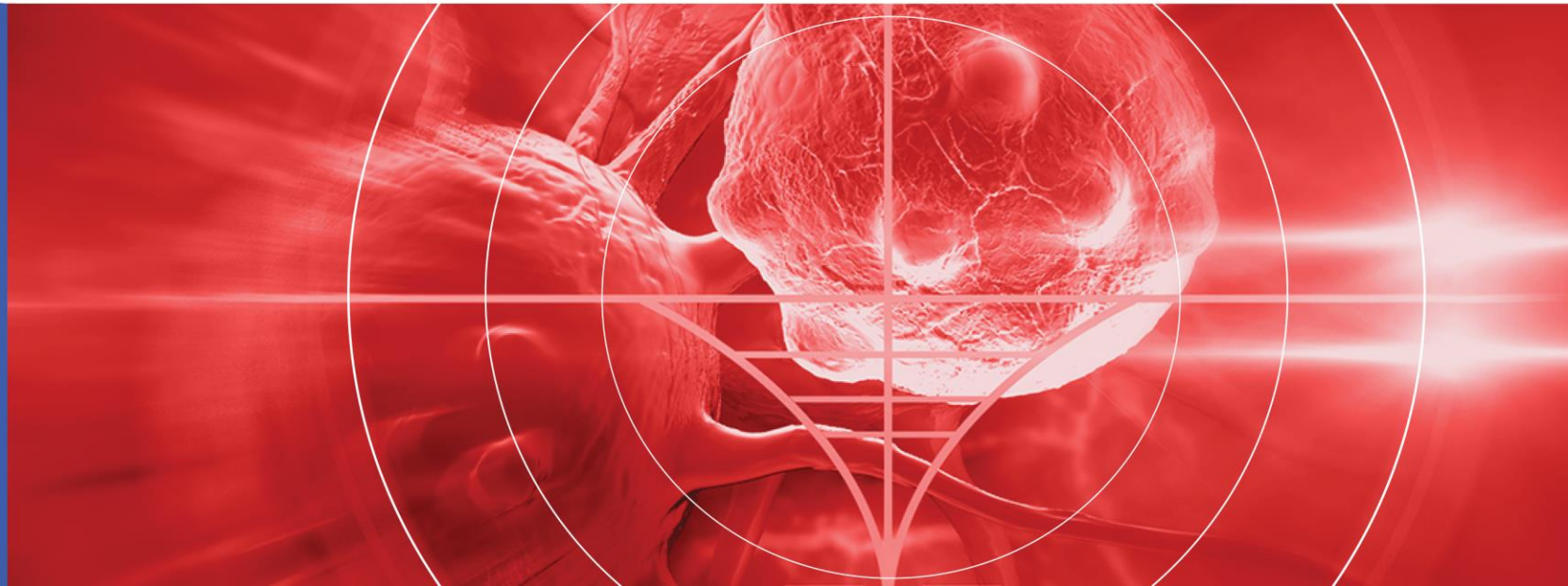
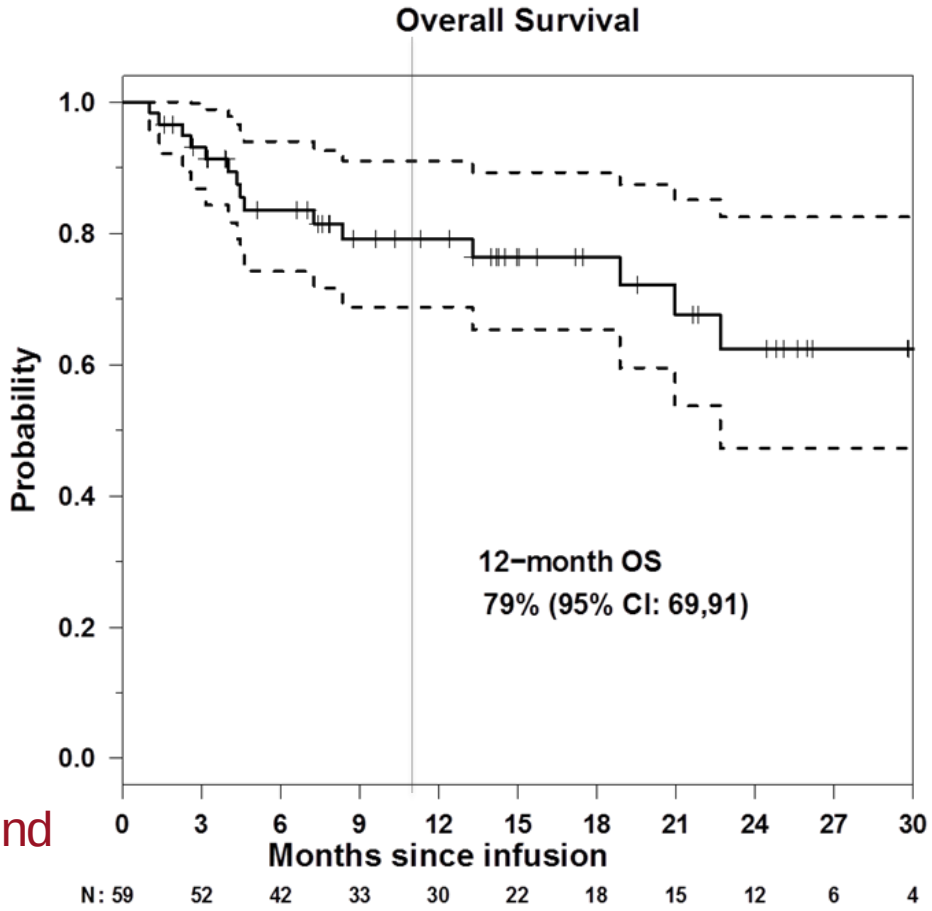


93% CR RATE FOR RELAPSED/REFRACTORY ALL AFTER CTL019

- 59 r/r pediatric ALL pts: 55 in CR at one mo (93%) median f/u 12 mo
- Six went to subsequent transplant, one to DLI
- Six mo RFS: 76% (95%CI:0.65,0.89)
- 12 mo RFS: 55% (95%CI: 0.42,0.73)
- No relapses past one year
- 18 patients in remission beyond one year, 13 without further therapy



The Children's Hospital of Philadelphia® CANCER CENTER

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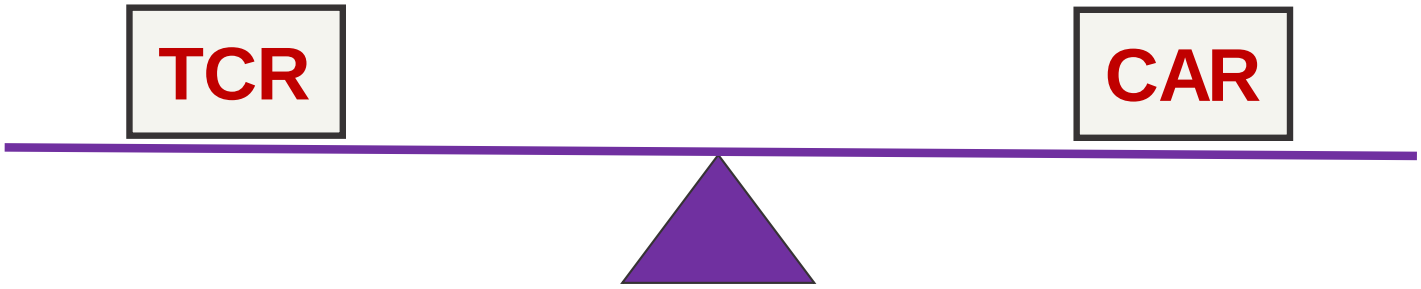
TWO APPROACHES TO GENETICALLY ENGINEERED T CELLS: CARs AND TCRs



- Sensitive signal amplification derived by evolution
- Hard to isolate and engineer
- Low avidity
- Can target intracellular proteome (3/4)
- Requires MHC-I expression and HLA matching on tumor

- Signal amplification from synthetic biology
- Easier to make
- Avidity controllable
- Targets only surface structures (1/4)
- MHC independent: "off the shelf"

Toxicity difficult to predict…

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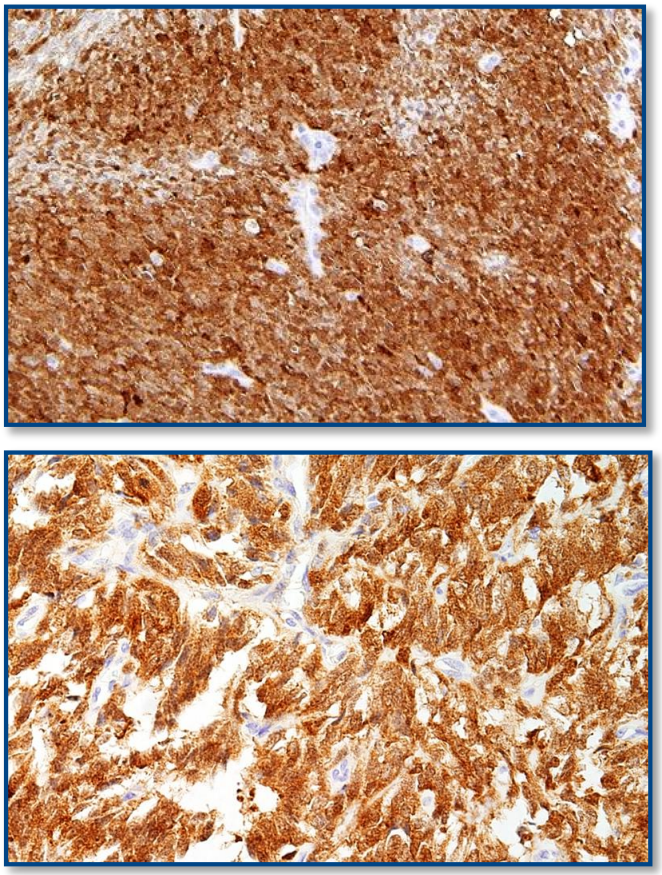
NY-ESO-1

A CANCER-TESTIS ANTIGEN HIGHLY EXPRESSED IN SYNOVIAL SARCOMA

- 76% of synovial sarcomas express strong staining, defined as 2-3+ in >50-70% *(Lai, Mod Pathol 2012)*
- A TCR recognizing NY-ESO-1 in the context of HLA:A0201 was cloned from a patient with cancer, then modified for higher affinity *(Zhao, J Immunol, 2007)*

NY-ESO IHC screening on Synovial Sarcomas



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TWO CLINICAL TRIALS OF ADAPTIMMUNE'S NY-ESO-1 TCR IN SYNOVIAL SARCOMA

- **Investigator Initiated Trial**: The Surgical Branch of the NCI did a study of Adaptimmune's NY-ESO-1-transduced lymphocytes in synovial sarcoma (Cy/Flu + HD IL-2)
  - Partial response in 4 of 6 synovial sarcomas *(Robbins et al, JCO 2011)*
  - Follow-up report: Objective responses in 11 of 18 synovial cell sarcomas (61%) *(Robbins, Clin Can Res 2015)*
  - Estimated 3-year OS: 38%; 5-yr OS 14%
- **Adaptimmune Trial**: Included changes to improve safety and treatment feasibility
  - Determine response rate without HD IL-2
  - Use of lentiviral vector
  - Central manufacturing site (GMP) and cryopreserved final product
  - Recent new cohort with cyclophosphamide alone (no fludarabine)
  - Recent additional cohort of NY-ESO-1 low expressors (<2+ in 50%)

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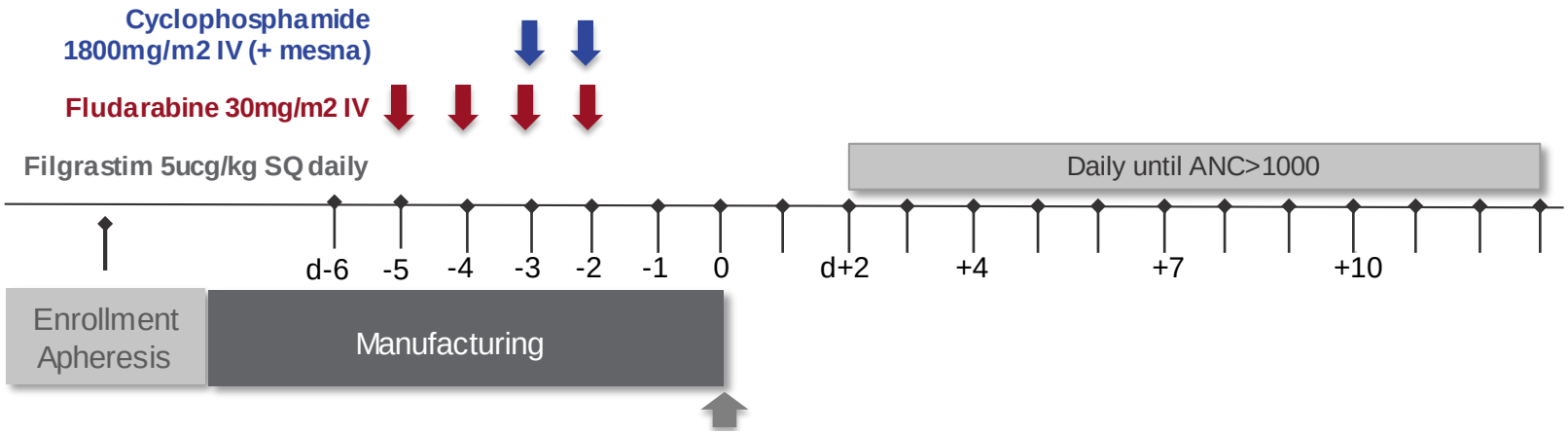
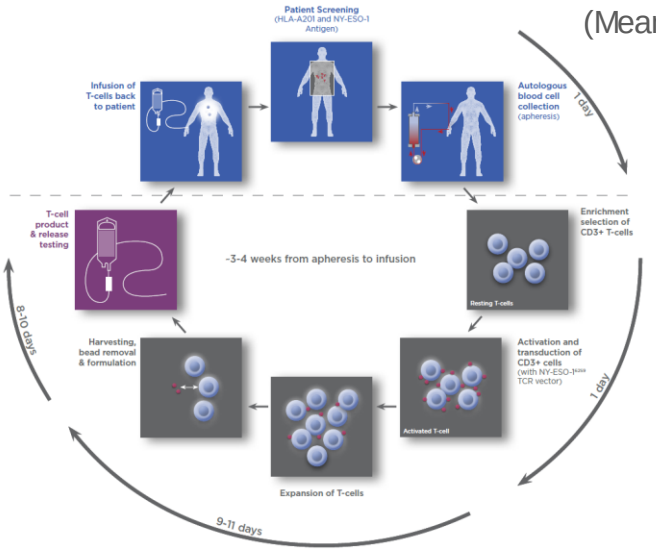
ADAPTIMMUNE'S NY-ESO-1 SARCOMA TRIAL SCHEMA



T cell infusion:
(Mean=5x10^9 cells*)

No IL-2



Supportive care:
Infection prophylaxis, observation for CRS, GvHD, f/u safety and efficacy

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* 1 x 10^9/kg (min 1 x 10^7/kg; max 40x10^9 total)

NY-ESO-1 SARCOMA STUDY: COHORT 1

60% OBJECTIVE RESPONSE RATE IN PATIENTS TREATED AT TARGET DOSE

Patient	NY-ESO Staining (archival tissue)	Total Transduced T cells ($x10^9$)	NY-ESO TCR+ T cells / kg ($x10^6$)	Best Overall Response
200	2-3+ in >50%	14.4	91.3	SD
201	3+ in 100%	8.3	165.01	CR
202*	3+ in 30%	6.6	69.99	PR
204	2-3+ in 50%	3.8	60.32	PR
205	3+ in ~100%	3.4	62.50	PR
261	3+ >99%	0.72	9.11	SD
206	2+ >50%	0.45	5.51	SD
207	3+ >80%	2.67	25.36	SD
208	3+ >95%	4.84	47.97	PR
209	3+ in ~100%	2.51	27.9	PR
263	3+ >50%	2.51	45.39	PD
230	2-3+ in 100%	7.86	143	PD
Mean		4.17	57.4	

*Treated in cohort 1 under a protocol exception

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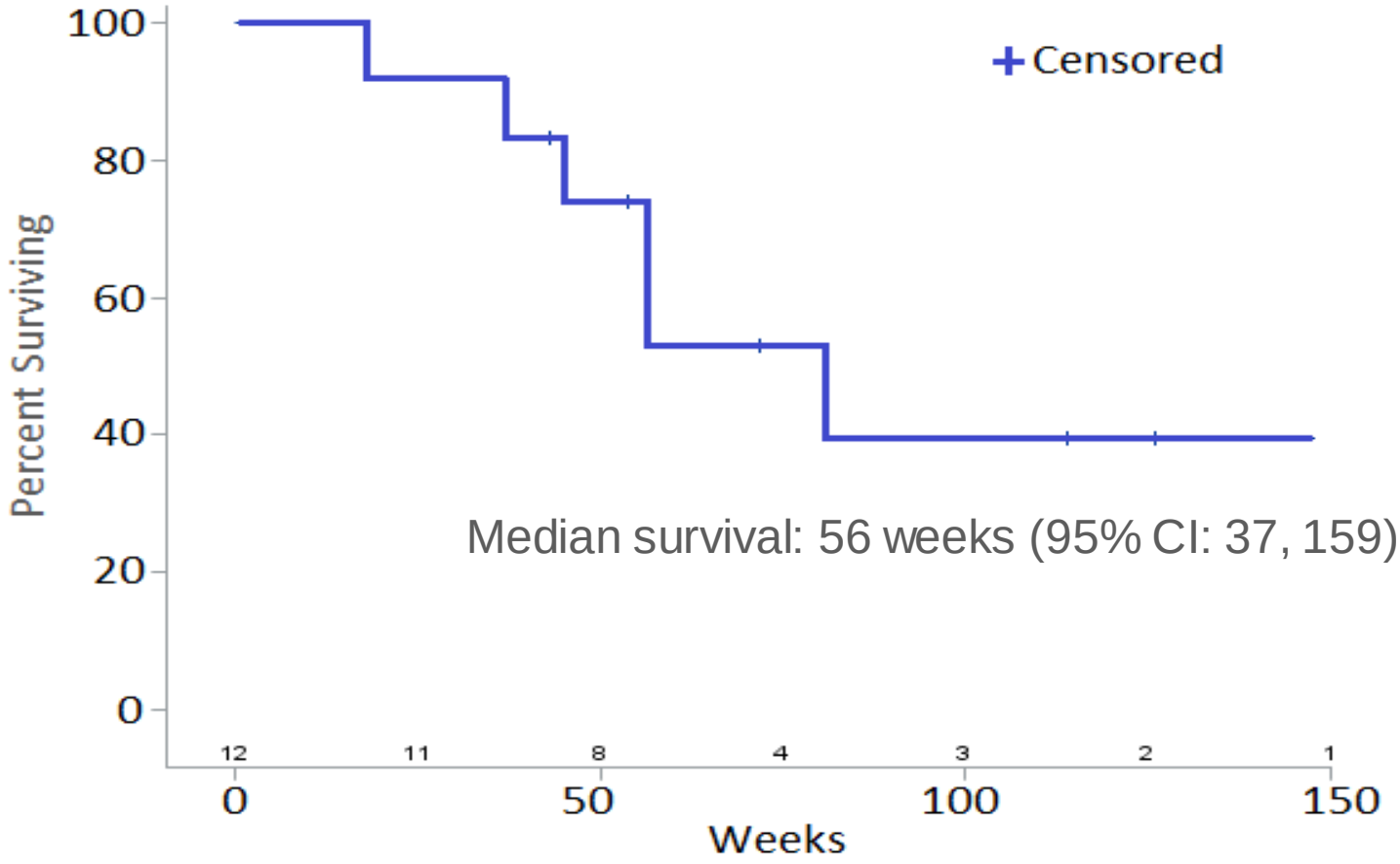
SYNOVIAL SARCOMA OVERALL SURVIVAL COHORT 1



Source: Adaptimmune
April 2016 cutoff

- 5/12 patients alive 4/2016
  - 1 year survival: 75%
  - 2 year survival: 25%

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SYNOVIAL SARCOMA STUDY: ALL COHORTS INCIDENCE (N,%) OF SAEs (>1 OCCURRENCE)

Preferred Term	Number of Subjects by Maximum Grade (N=16)		
	All SAEs	Related*	Fatal
Pyrexia	4 (25)	2 (12.5)	0
Cytokine release syndrome	2 (12.5)	2 (12.5)	0
Lymphopenia/Lymphocyte count decreased	2 (12.5)	2 (12.5)	0
Neutropenia	2 (12.5)	2 (12.5)	0
Febrile neutropenia	2 (12.5)	1 (6.3)	0
Thrombocytopenia	2 (12.5)	2 (12.5)	0
Dyspnea	2 (12.5)	1 (6.3)	0

January 2016 cutoff

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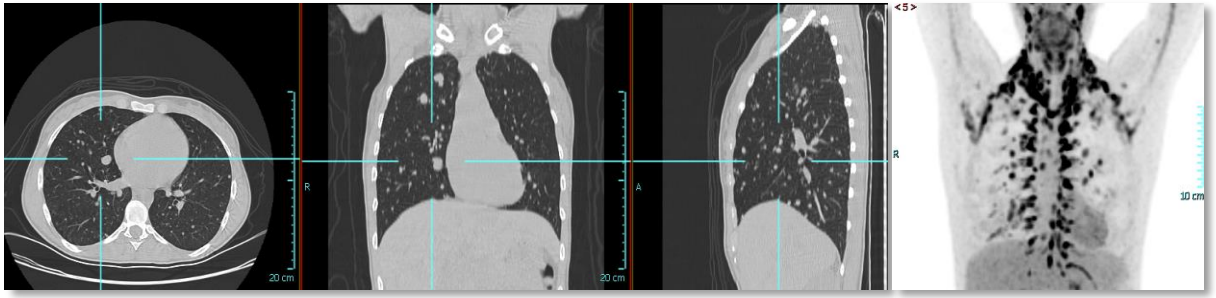
Source: Adaptimmune

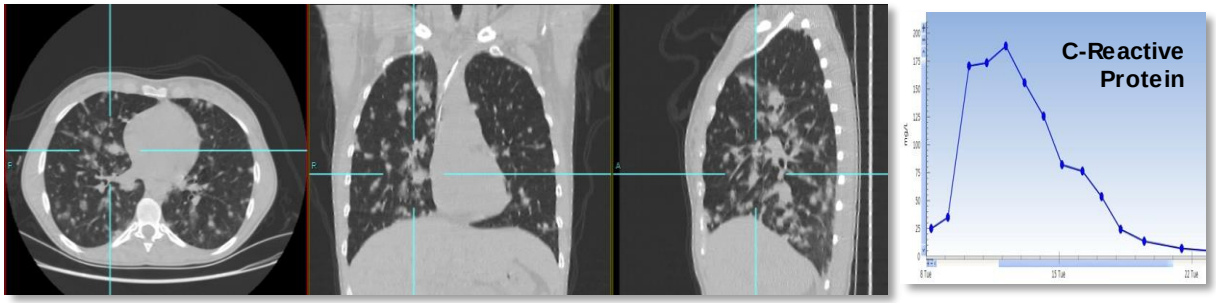
PHASE I/II STUDY IN SYNOVIAL SARCOMA

RADIOGRAPHIC PSEUDOPROGRESSION AND RESPONSE OF LUNG METASTASES LEADING TO COMPLETE RESPONSE

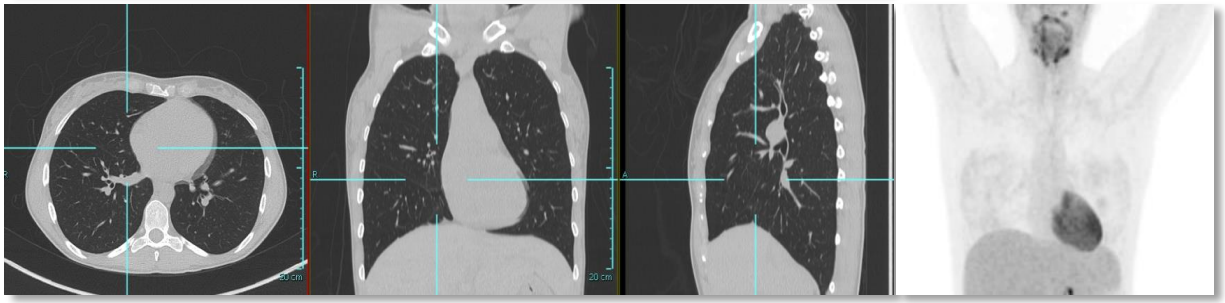
Baseline:
Bilateral miliary metastatic disease



Day +2:
Pseudoprogression due to immune infiltration



Day +101:
Complete Response



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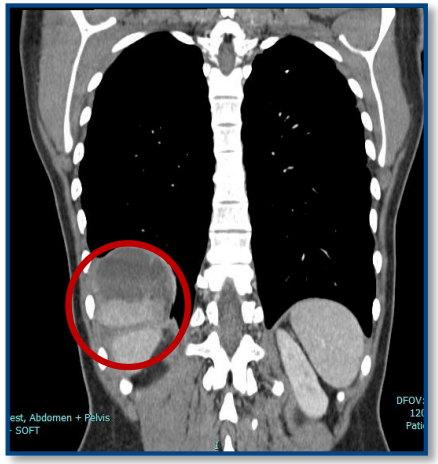
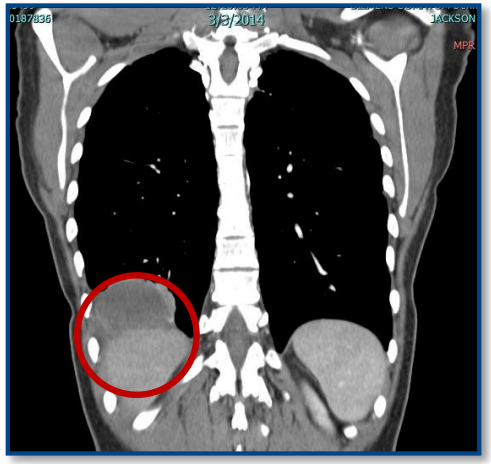
Source: AACR April 2015

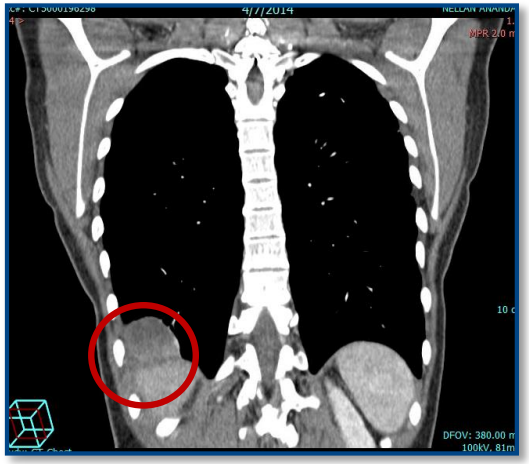
CLINICAL RESPONSE FOLLOWED BY RESECTION AT PROGRESSION



1/22/14



3/3/14



4/7/14

- Mass began to show regrowth ~6 months
- Surgically resected at 7 months
  - No NY-ESO-1 TCR cells found in tumor
  - Substantial CD4+ T cells

No evidence of disease 27 months post NY-ESO-1 T cell infusion;
20 months from surgical resection of metastasis

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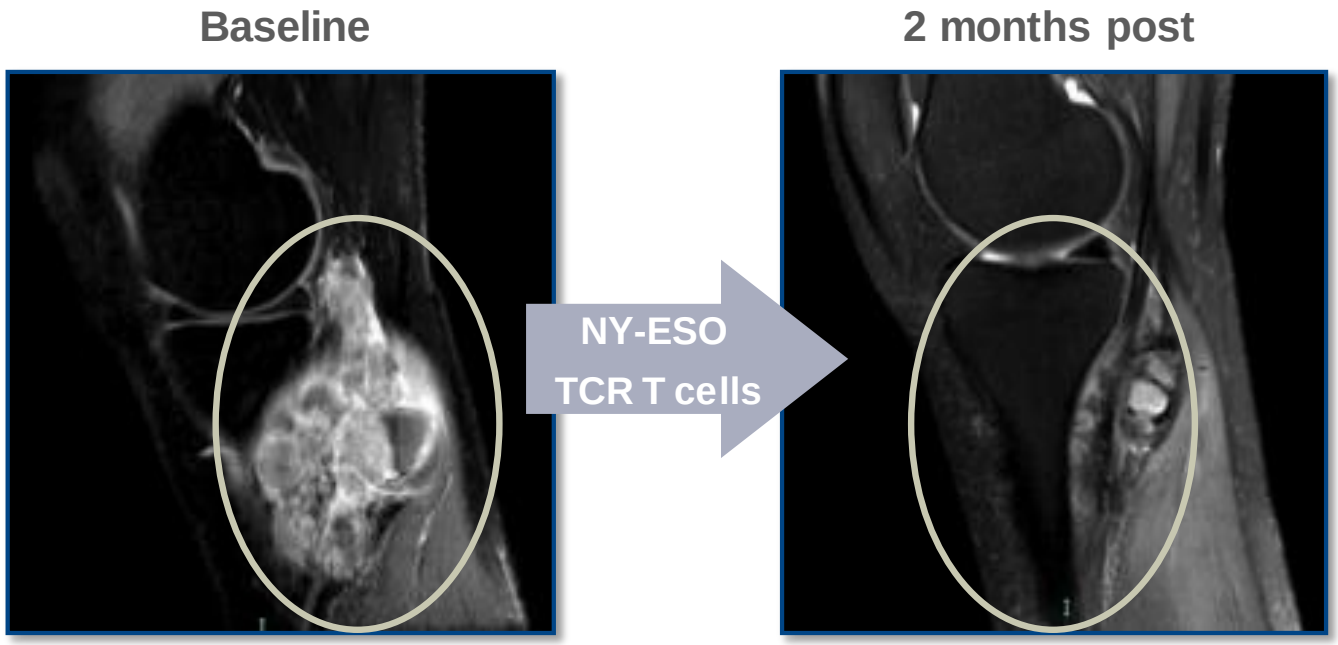
NEAR COMPLETE RESPONSE TO NY-ESO-1 T CELLS OF UNRESECTABLE PRIMARY TUMOR IN THE KNEE



- Complete surgical resection accomplished, no irradiation
- Local disease remained controlled; patient developed lung metastasis with loss of NY-ESO-1

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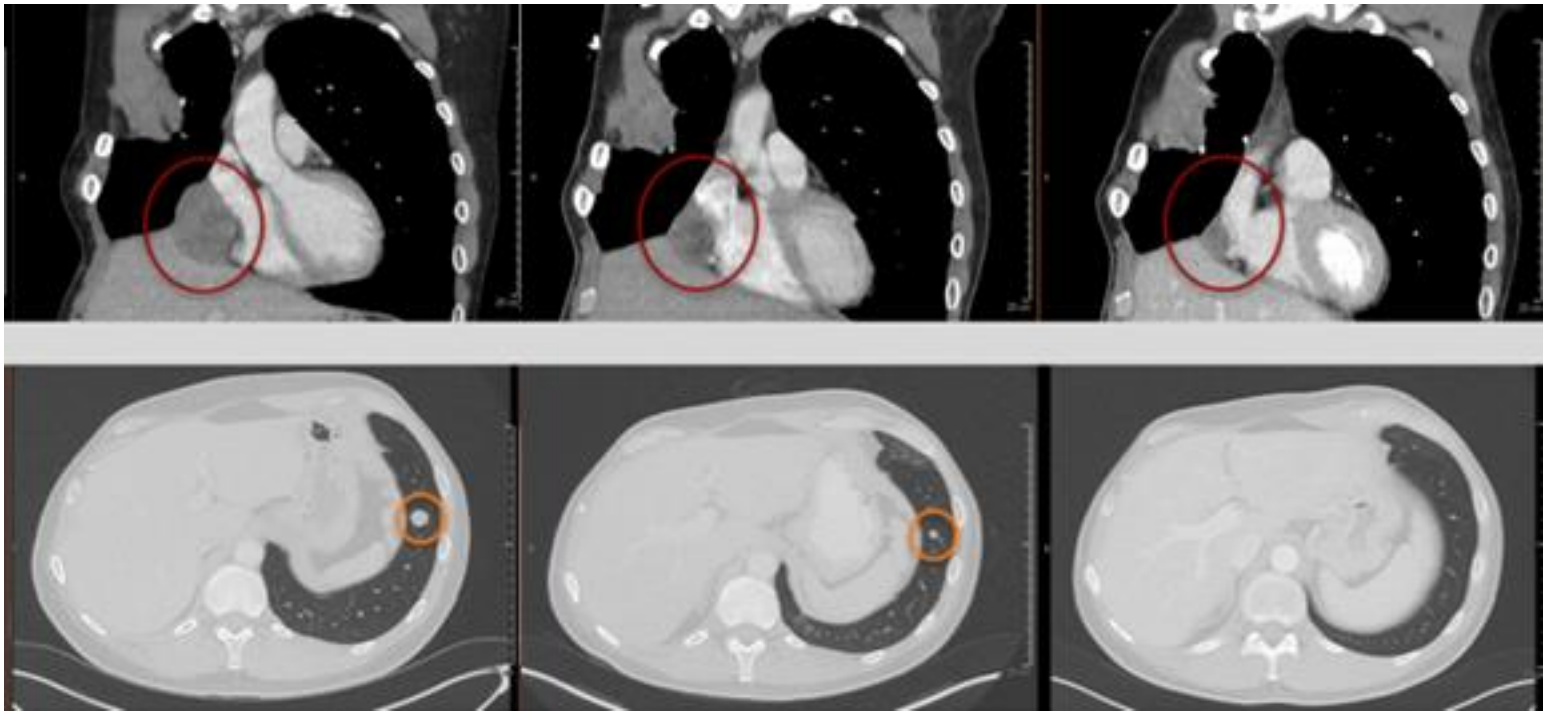
TRANSFORMING T CELL THERAPY

Source: SITC, November 2015

TUMOR SHRINKAGE OVER THE COURSE OF SEVERAL MONTHS FOLLOWING NY-ESO-1 TCR FOR SYNOVIAL SARCOMA

MULTIPLY RECURRENT, UNRESECTABLE PULMONARY MASSES

Baseline | 2 months | 12 months



Ongoing PR 400+ days post T cell infusion

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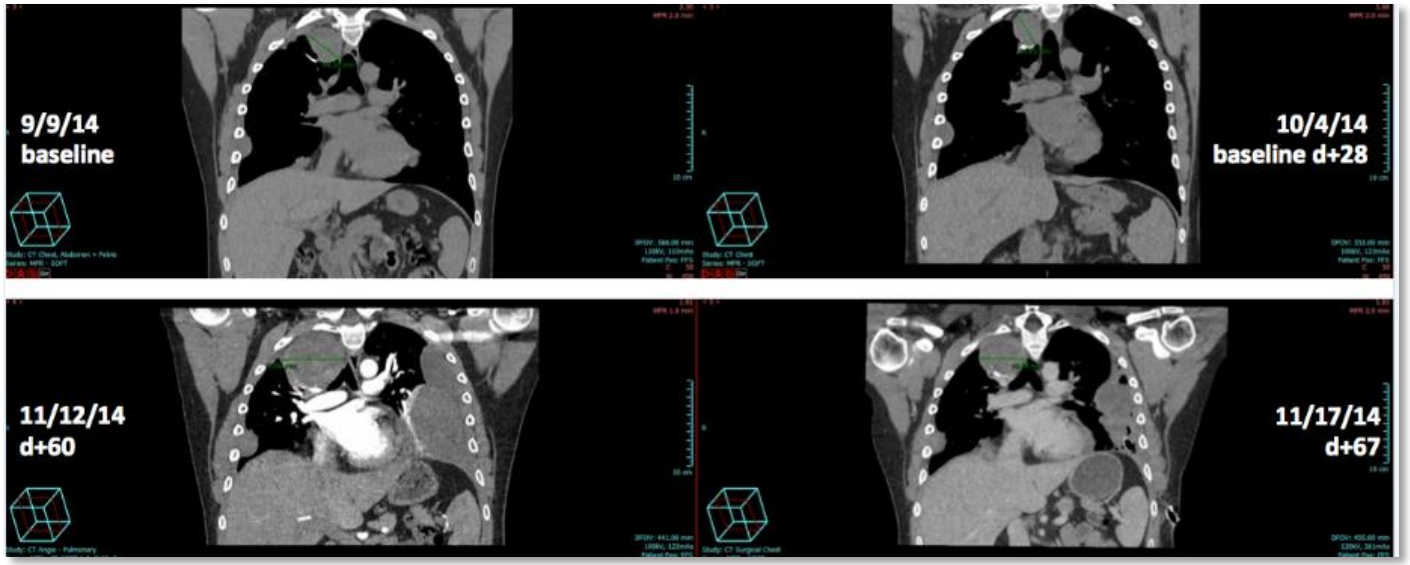
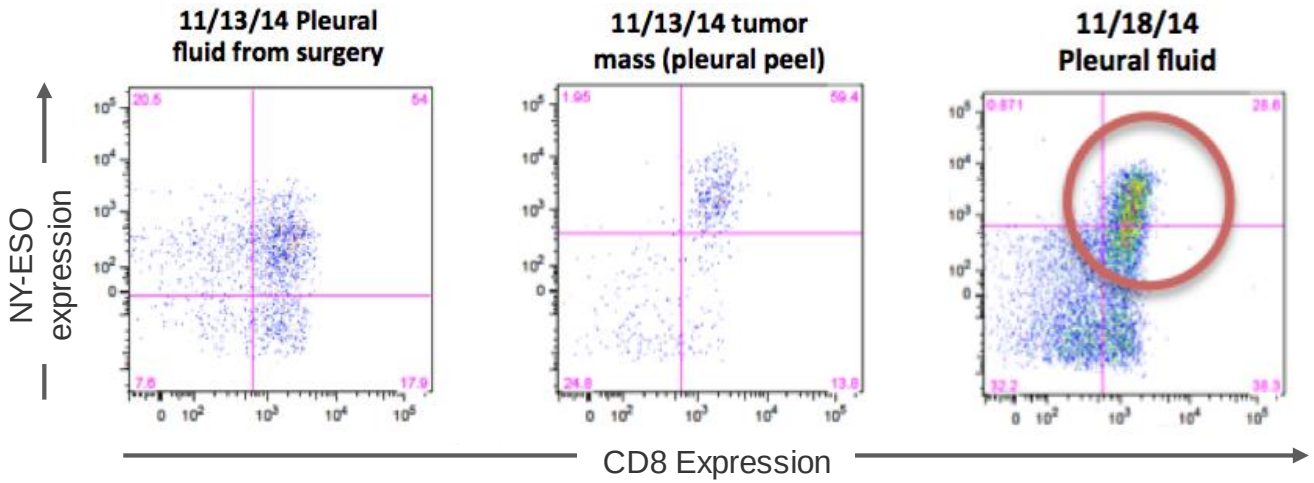
Source: Adaptimmune

T CELLS TRAFFIC TO THE SITE OF TUMOR

AT RESECTION REMAINING TUMOR WAS NY-ESO NEGATIVE





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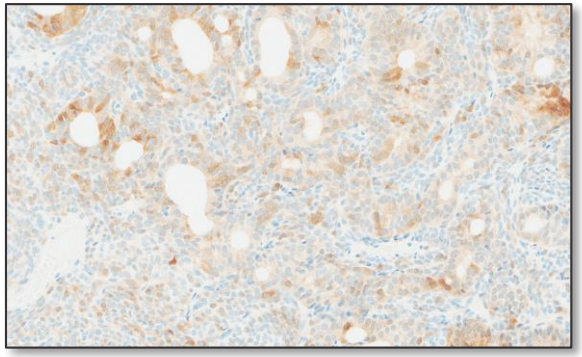
Source: Adaptimmune

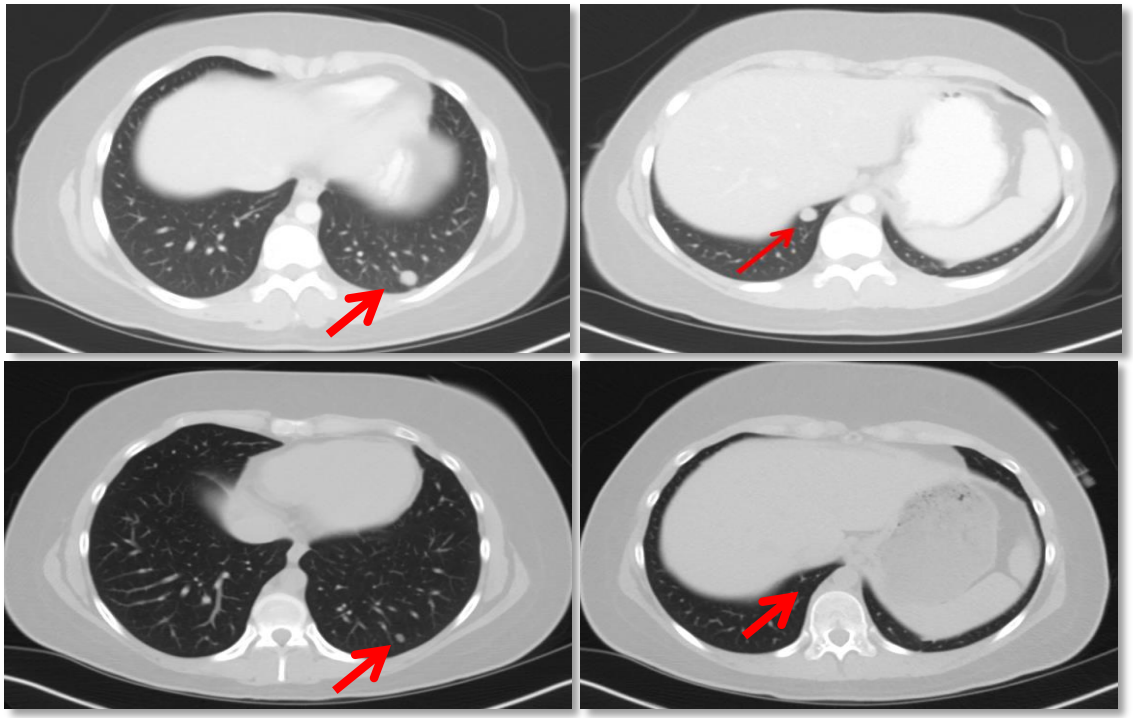
CLINICAL RESPONSES OBSERVED ACROSS A SPECTRUM OF NY-ESO-1 EXPRESSION

RESPONSE IN A PATIENT WITH LOW NY-ESO-1 EXPRESSION



Baseline
11-05-13

Month 3
02-18-14



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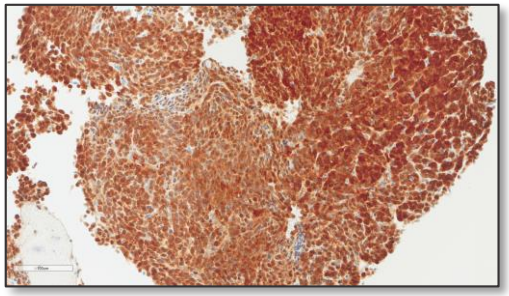
Source: Adaptimmune

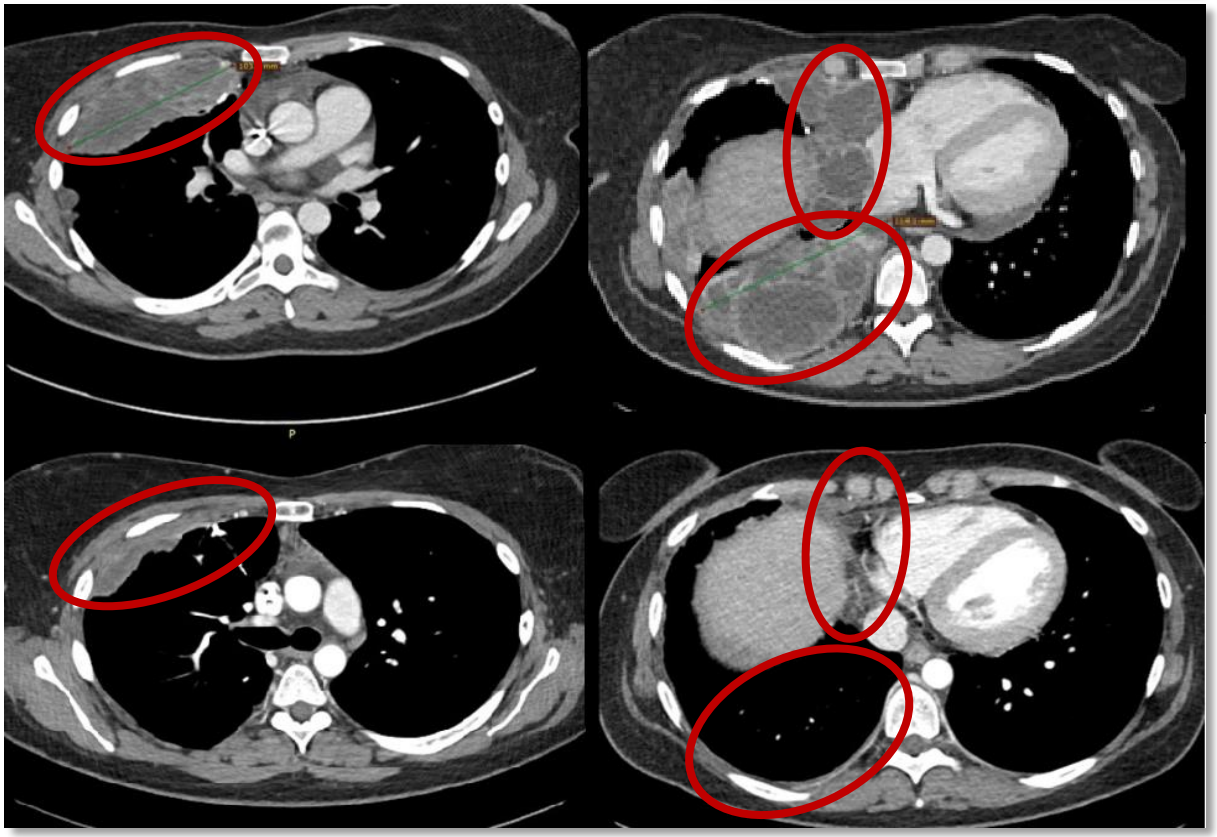
CLINICAL RESPONSES OBSERVED ACROSS A SPECTRUM OF NY-ESO-1 EXPRESSION

RESPONSE IN A PATIENT WITH VERY HIGH NY-ESO-1 EXPRESSION



Baseline

Month 6



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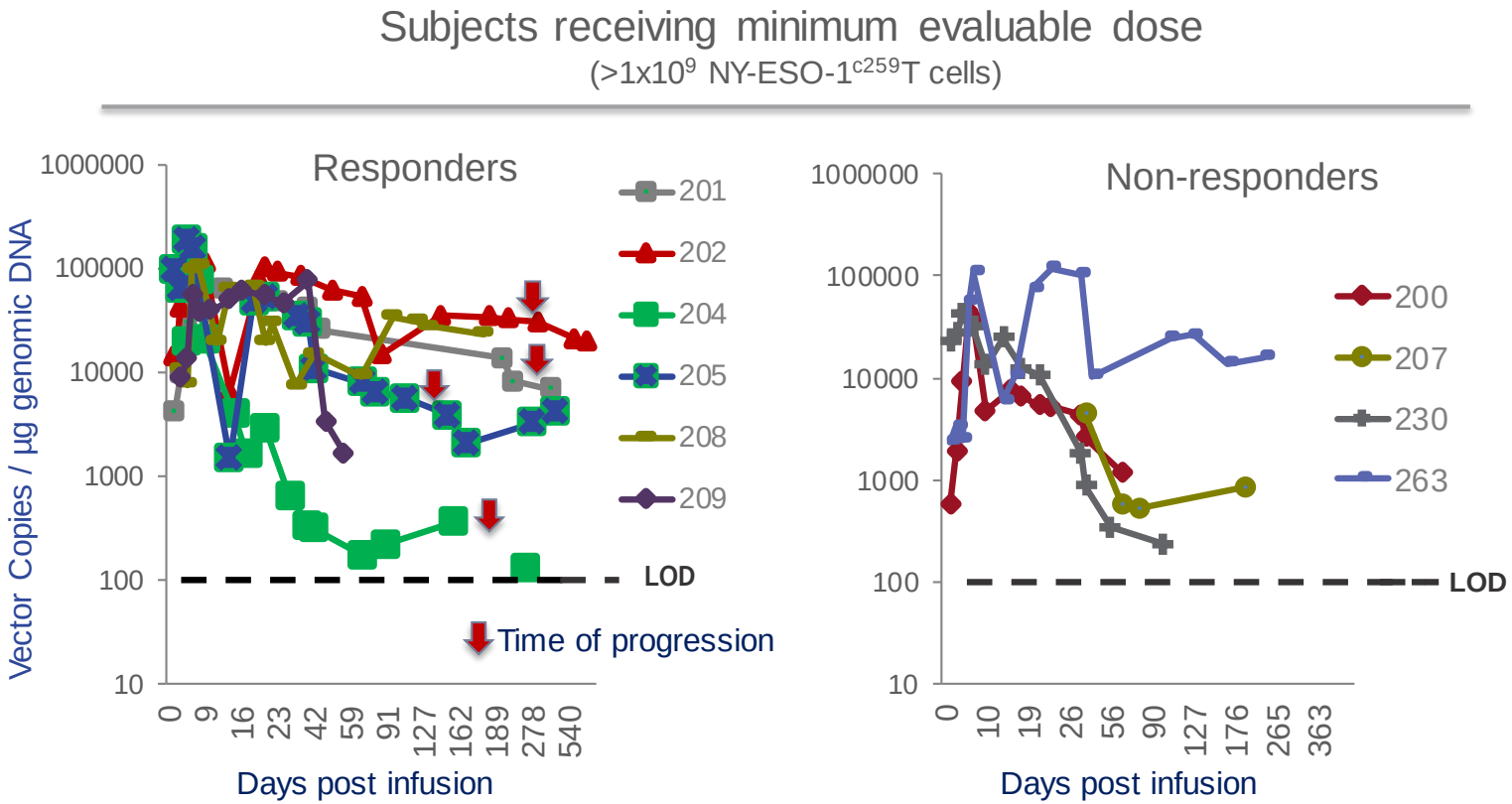
Source: Adaptimmune

NY-ESO-1 SARCOMA STUDY

DURABLE PERSISTENCE OF NY-ESO-T



- Among evaluable subjects, higher peak persistence was observed among responders compared to non responders
- To date, among responders, NYESO-1 T cells have been detected up to 21 months.

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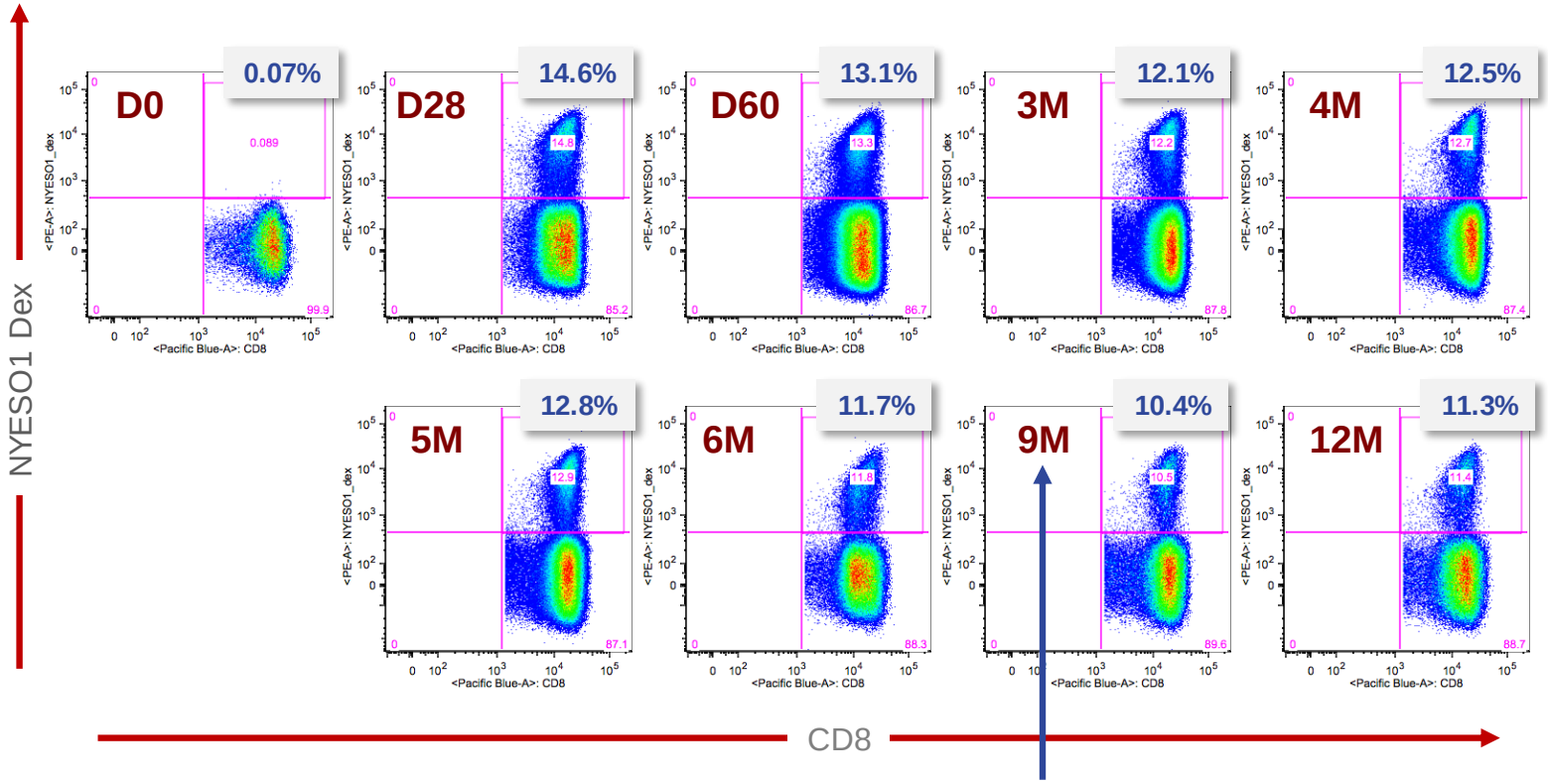
Source: November SITC, 2015

NY-ESO-1 SARCOMA STUDY

REMARKABLE PERSISTENCE OF NY-ESO TCR+ T CELLS IN SARCOMA PATIENT EXPERIENCING A COMPLETE RESPONSE



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CLINICAL SUMMARY

- NY-ESO-1 TCR T cells has manageable toxicity
  - Fever, low grade cytokine release common in the week following cell infusion
- Anti-tumor activity confirmed in the absence of HD IL-2:
  - 60% response without HD IL-2
- Pseudo-progression, gradual reductions in tumor burden and NY-ESO TCR+ T cells in resected tumor indicate immunologic basis for response
- NY-ESO-1 TCR T cells are highly persistent
  - Longest persistence observed with a TCR to date
- Mechanisms of resistance:
  - Elucidating mechanisms of immune escape through analysis of pre- and post-treatment tissue

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ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

NY-ESO-1 T CELL THERAPY IN MULTIPLE MYELOMA: LONG TERM EFFICACY AND PERSISTENCE

APRIL 22, 2016

Aaron P. Rapoport, MD
Professor of Medicine
Gary Jobson Professor in Medical Oncology
University of Maryland Marlene and Stewart Greenebaum Cancer Center

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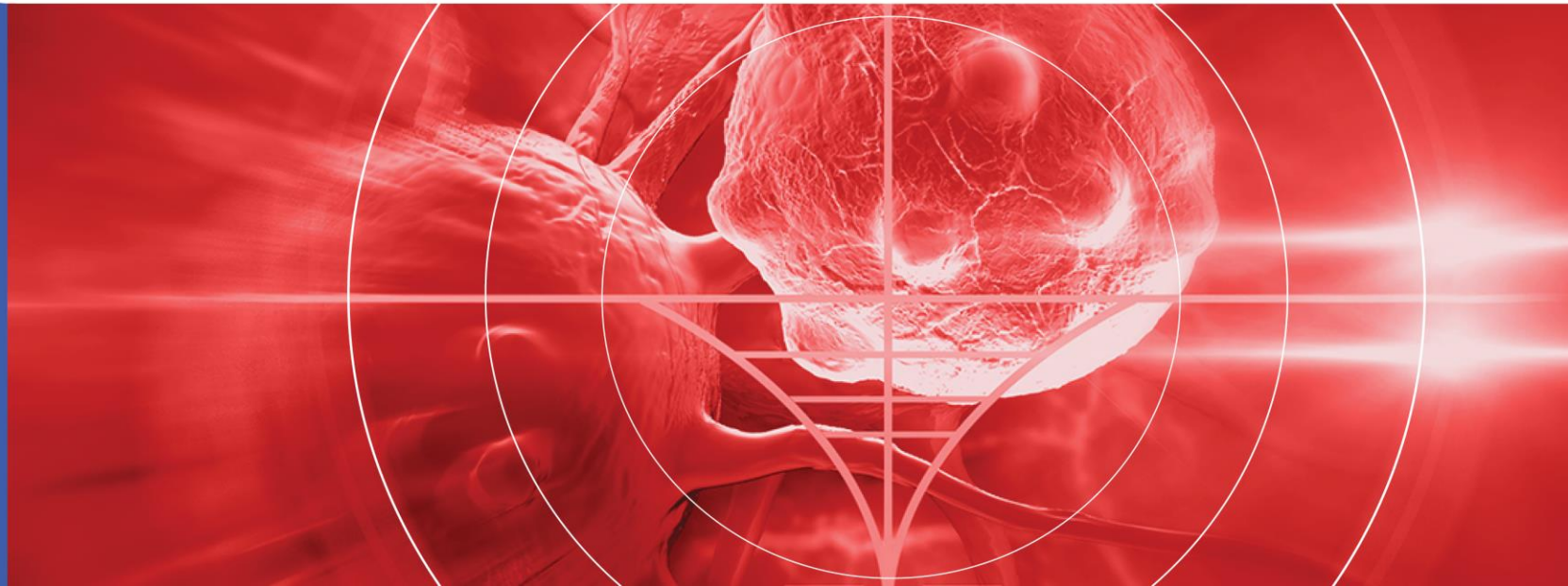
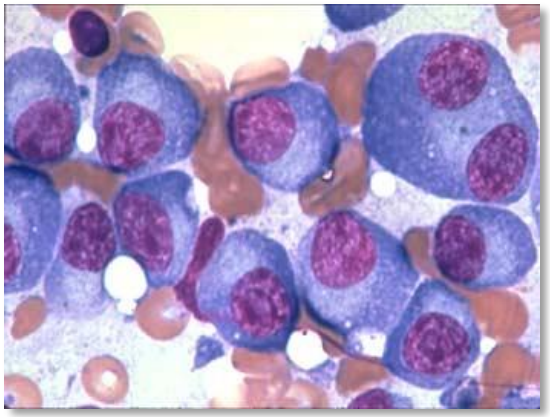
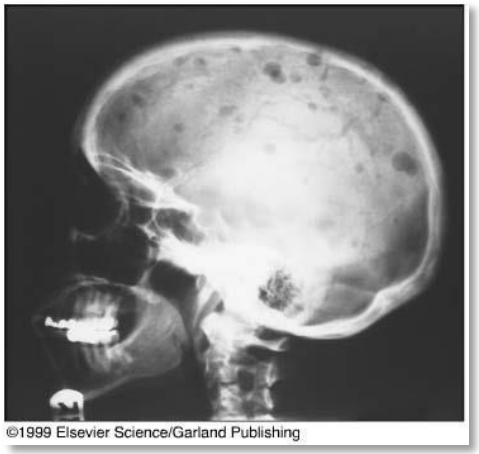
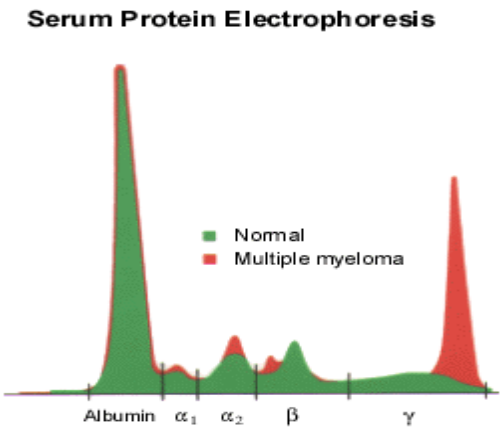


MULTIPLE MYELOMA

MODEL BLOOD CANCER







- The American Cancer Society estimates that in 2016*
  - ~30,330 new cases will be diagnosed
  - ~12,650 deaths will occur
  - 1/143 lifetime risk
- Slightly more common in men than women
- Incidence in African-Americans about twice that in Caucasians
- Mean age is approximately 60 years

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*https://cancerstatisticscenter.cancer.org/?_ga=1.104040064.1641643651.1460834859#/cancer-site/Myeloma

ADVANTAGES OF CELLULAR IMMUNOTHERAPY

- Kills “resistant” tumors (e.g. 17p – P53 del)
- Penetrates “sanctuary” sites (e.g. CNS)
- Through expansion and serial killing can eradicate “large” tumors
- Can generate long-lived “memory” responses to protect against recurrence
- High degree of specificity, avoids second malignancies and immunodepletion

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WHY TARGET CANCER TESTIS ANTIGENS IN MM

- Advanced MM frequently expresses the Cancer Testis antigens NY-ESO-1 or LAGE-1
  - Expression of Cancer Testis antigens is associated with poor prognosis in myeloma[1]
- Adaptimmune's NY-ESO-1 TCR was tested in multiple myeloma
  - Same epitope present on both antigens[2]

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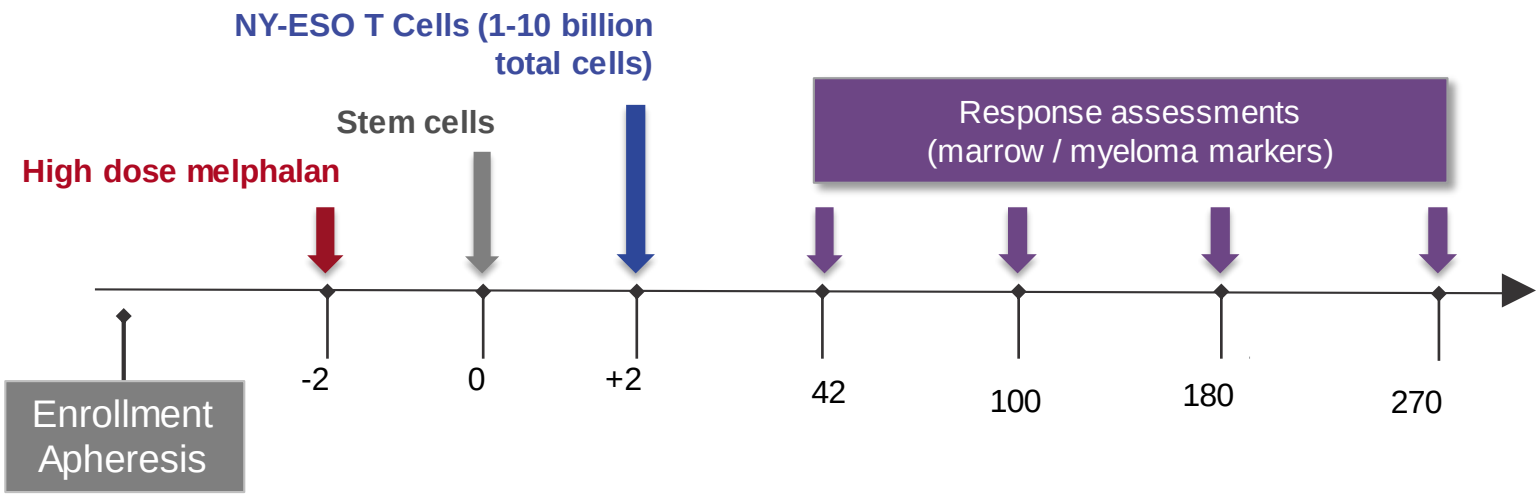
1. Dhodapkar et al, Cancer Immun, 2003
Atanackovic et al, Clin Cancer Res, 2009; and others
2. Li et al, Nat Bio, 2005; Robbins et al, JCO 2011 and CCR 2014

PHASE I/II STUDY IN MULTIPLE MYELOMA



- All enrolled patients (n=25): Symptomatic myeloma with active disease
- High risk population
  - Average of 3 prior Rx; range 1-5
    - 7 patients had prior autologous stem cell transplant (ASCT)
  - Twelve with cytogenetic abnormalities (7 categorized as high-risk)
- Conditioned with high-dose melphalan followed 2 days later by ASCT

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PHASE I/II STUDY IN MULTIPLE MYELOMA

STUDY PATIENT POPULATION

- Medically eligible for transplant
- High risk or relapsed disease
- ECOG performance status: Grade 0-2
- HLA-0201
- Myeloma cells express NY-ESO-1 and/or LAGE-1 by RT-PCR

STUDY ENDPOINTS

- Safety and Tolerability
- Secondary:
  - Clinical Responses
  - Proof of Mechanism

RESPONSE ASSESSMENTS

- International Uniform Response Criteria
  - Additional category of nCR: -ve M spike but +ve by immunofixation

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PHASE I/II STUDY IN MULTIPLE MYELOMA

RESPONSE ASSESSMENT

Best Response by day 100	Number of Patients	% Total
CR	3	14%
nCR	10	45%
VGPR	2	9%
PR	5	23%
SD	1	5%
PD	1	5%
Not assessable*	**3**	**NA**
Total evaluable	22	100%

* Patients with VGPR or better going into transplant

- RR= 91%
- CR+nCR+VGPR = 68%

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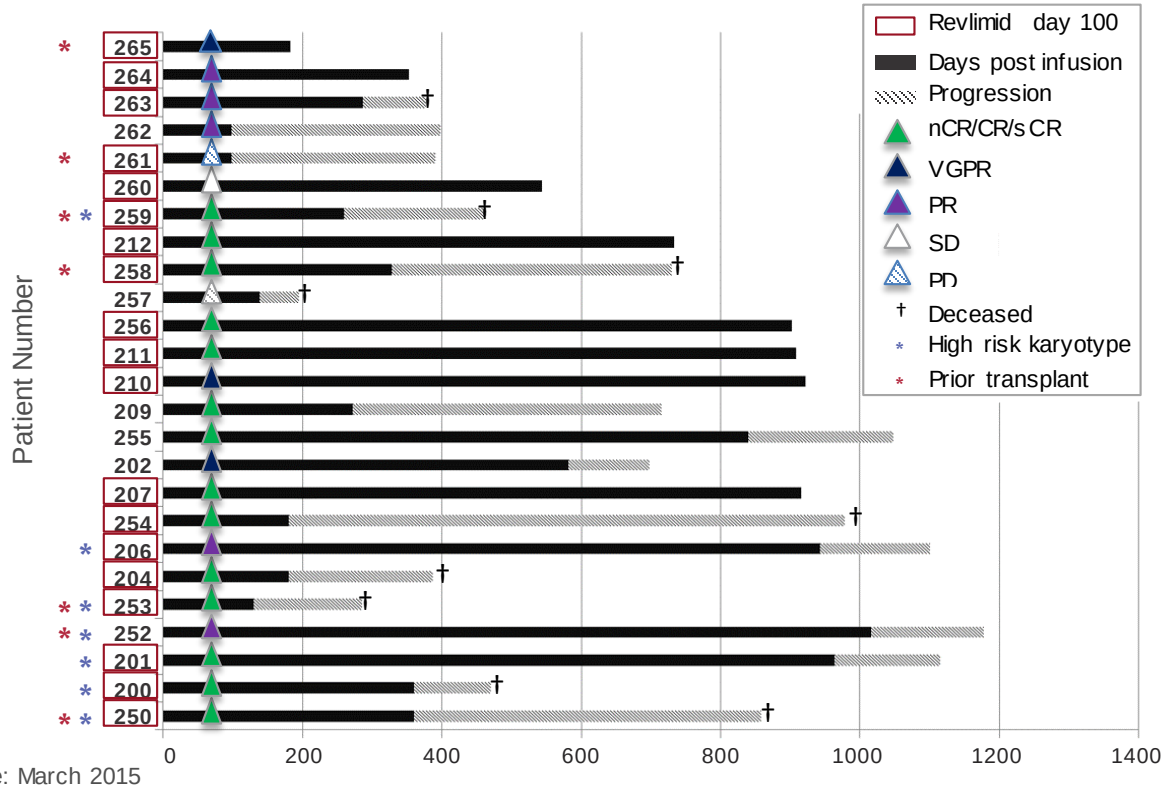
Rapoport et al. Nat Med 21(8):914-21

PHASE I/II STUDY IN MULTIPLE MYELOMA

DURATION OF RESPONSE



Cut-off date: March 2015

- Overall survival as of January 2016:
  - Median OS ~3 years (Cut-off date: January 2016)
- Progression free survival (PFS) as of November 2015
  - Median PFS = 19.1 months (Cut-off date: November 2015)

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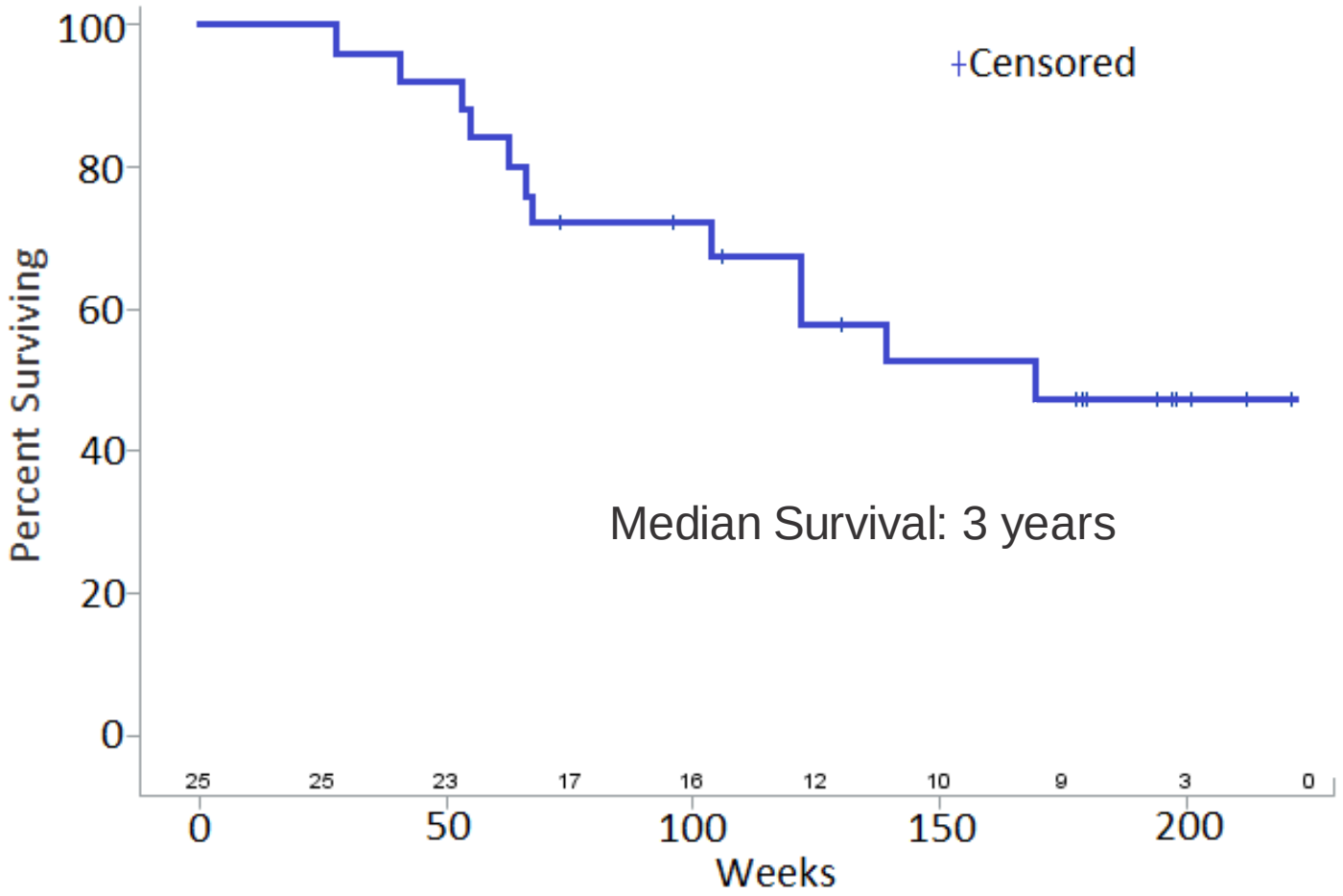
Rapoport et al. Nat Med 21(8):914-21

MULTIPLE MYELOMA OVERALL SURVIVAL

MEDIAN SURVIVAL: ~3 YEARS (RANGE: 28 WEEKS TO 4.25+ YEARS)



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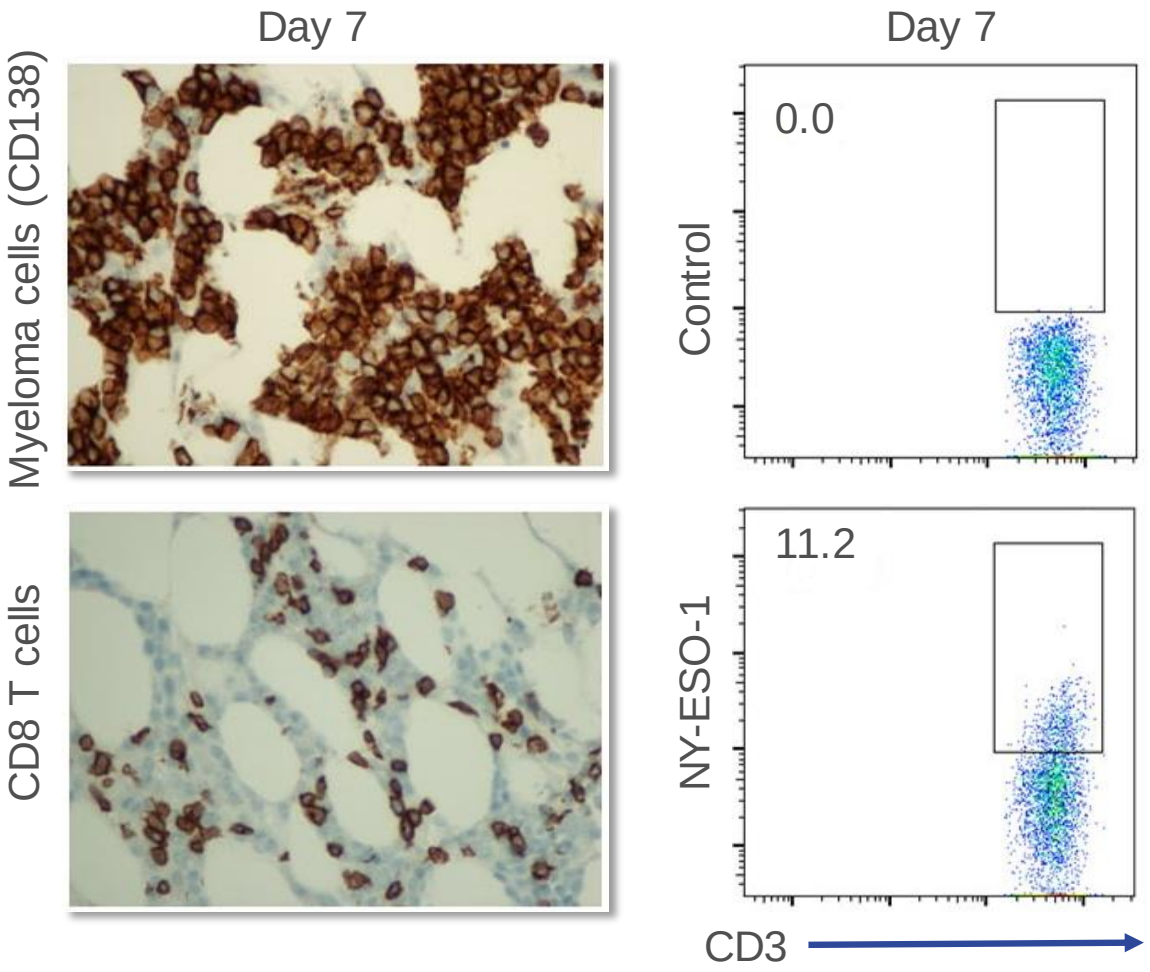
Source: Adaptimmune
January 2016 Cutoff

PHASE I/II STUDY IN MULTIPLE MYELOMA

NY-ESO-1 T CELLS TRAFFIC TO SITES OF TUMOR (BONE MARROW)



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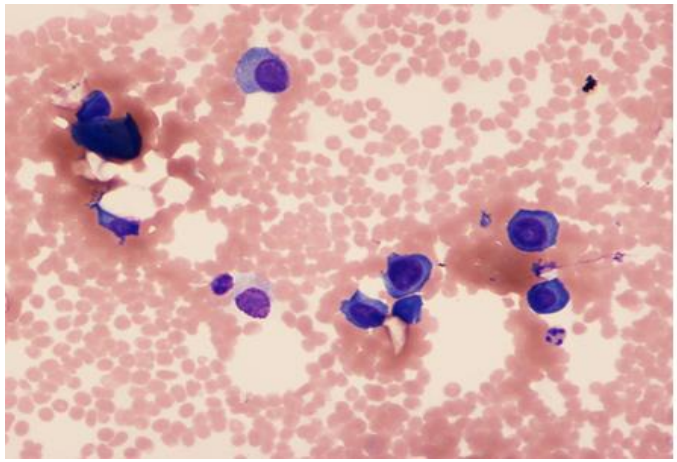
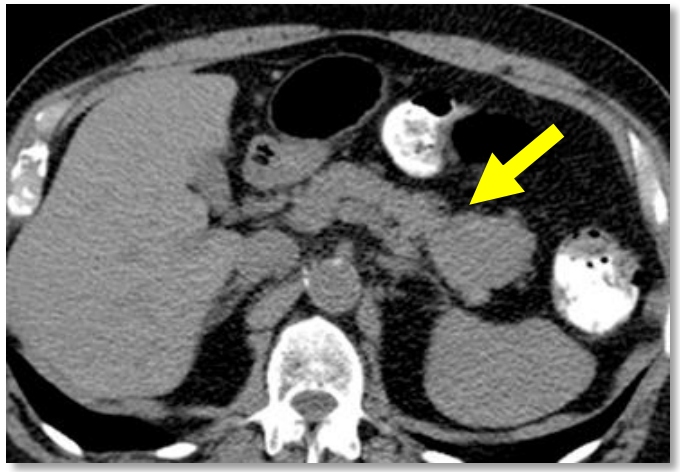
PHASE I/II STUDY IN MULTIPLE MYELOMA

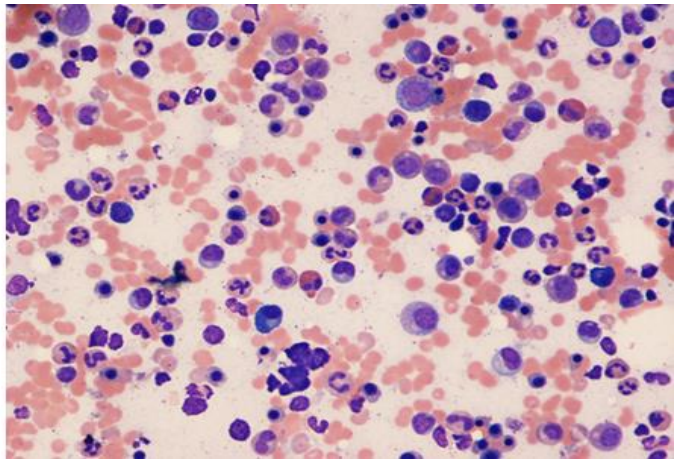
RESOLUTION OF DISEASE IN BONE MARROW AND PLASMACYTOMA BY DAY 56 POST-THERAPY WITH NY-ESO-1 TCR TRANSDUCED T CELLS

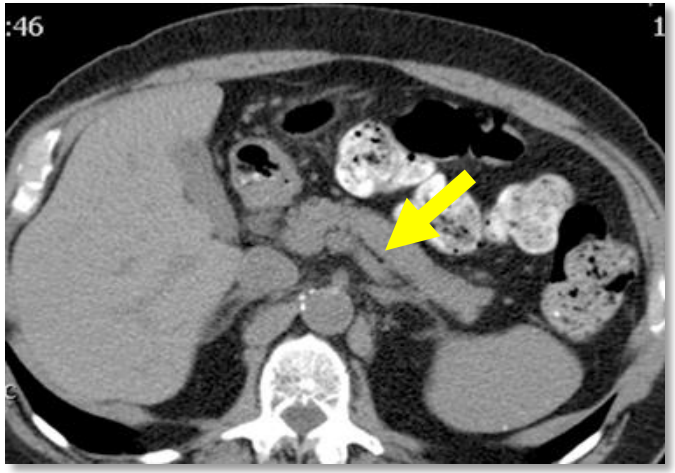
Pre-treatment





Day 56





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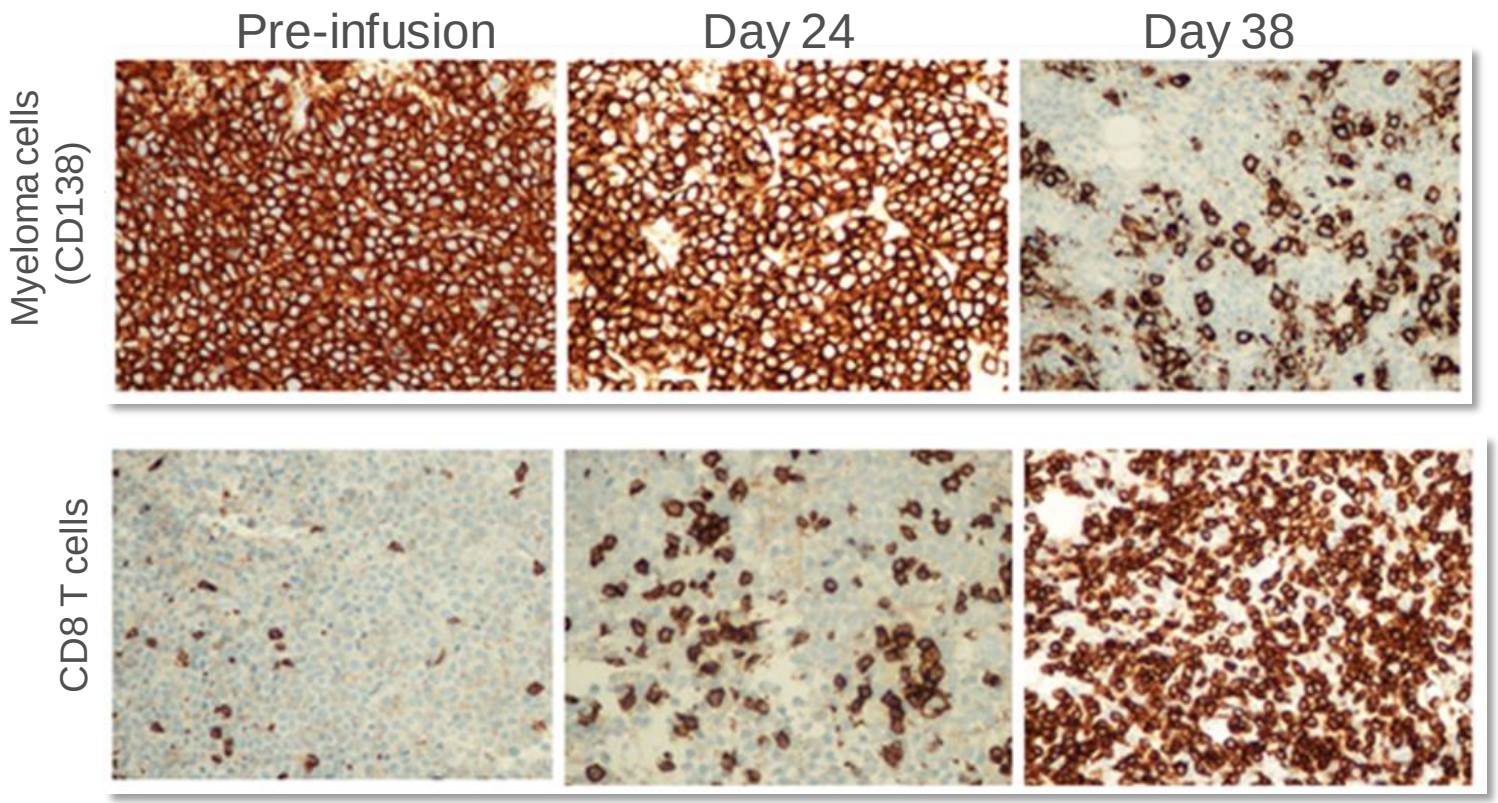
PHASE I/II STUDY IN MULTIPLE MYELOMA

MASSIVE INFILTRATION OF T CELLS INTO MARROW CORRELATE WITH RESPONSE FOLLOWING SECOND INFUSION



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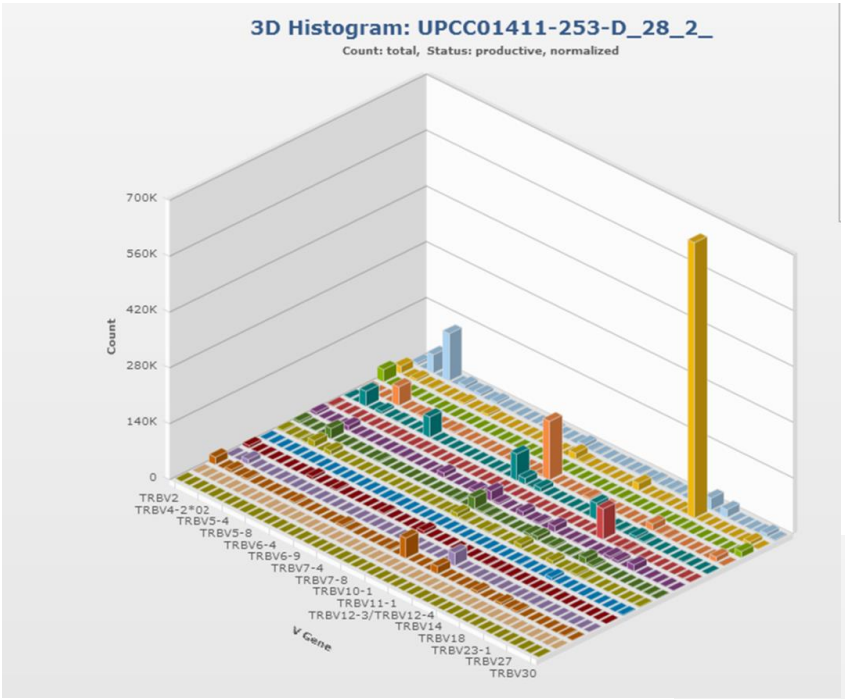
PHASE I/II STUDY IN MULTIPLE MYELOMA

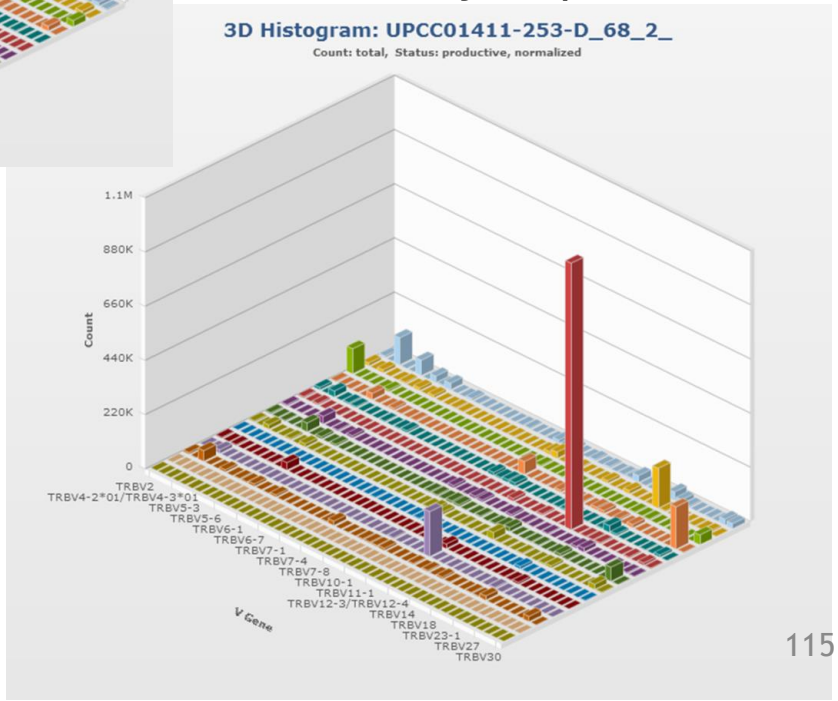
ANTIGEN SPREADING: CLONAL EXPANSION OF TWO TCR CLONOTYPES

Patient 253



Day 28 post infusion

Day 68 post infusion



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PHASE I/II STUDY IN MULTIPLE MYELOMA

INCIDENCE (N,%) OF ALL SAEs (>1 OCCURRENCE)

Preferred Term	Number of Subjects by Maximum Grade (N=25)*		
	All SAEs**	Related	Fatal
Neutropenia	4 (16.0)	2 (8.0)	0
Pyrexia	3 (12.0)	1 (4.0)	0
Atrial fibrillation	3 (12.0)	0 (0.0)	0
Graft versus host disease	2 (8.0)	2 (8.0)	0
Diarrhoea	2 (8.0)	2 (8.0)	0
Hypoxia	2 (8.0)	1 (4.0)	0
Staphylococcal infection	2 (8.0)	0 (0.0)	0

*No episodes of CRS SAEs were reported

**Includes all events reported as of 27Jan2016 excluding disease progression and laboratory abnormalities with the investigations and nutritional disorders SOCs except for combined haematologic terms above

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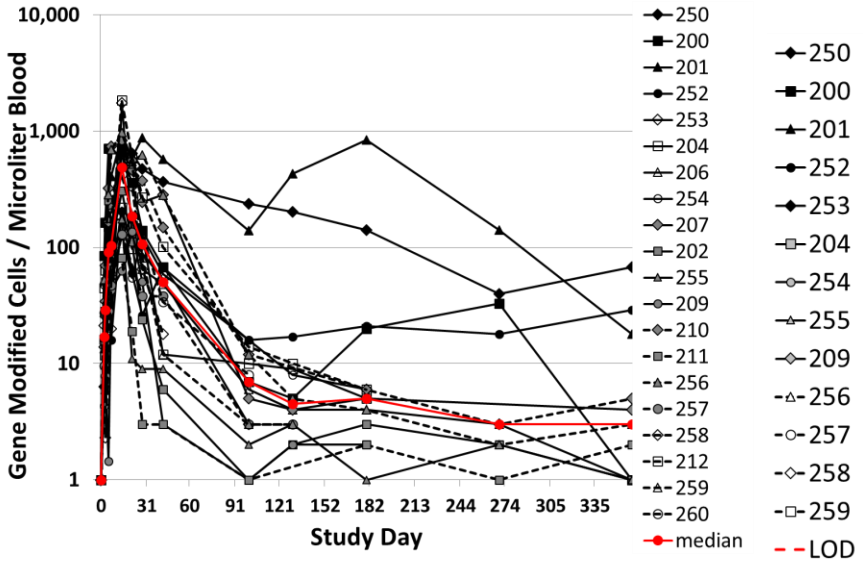
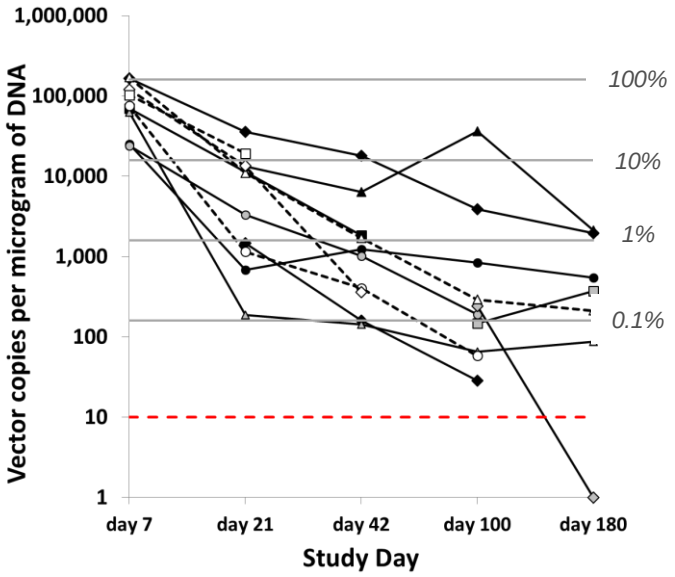
PHASE I/II STUDY IN MULTIPLE MYELOMA

NY-ESO-1 T CELL PERSISTENCE IN PERIPHERAL BLOOD

Blood persistence



Marrow (site of tumor) persistence



IN FURTHER FOLLOW UP, NY-ESO-1 T CELLS ARE DETECTED BEYOND THREE YEARS IN PERIPHERAL BLOOD

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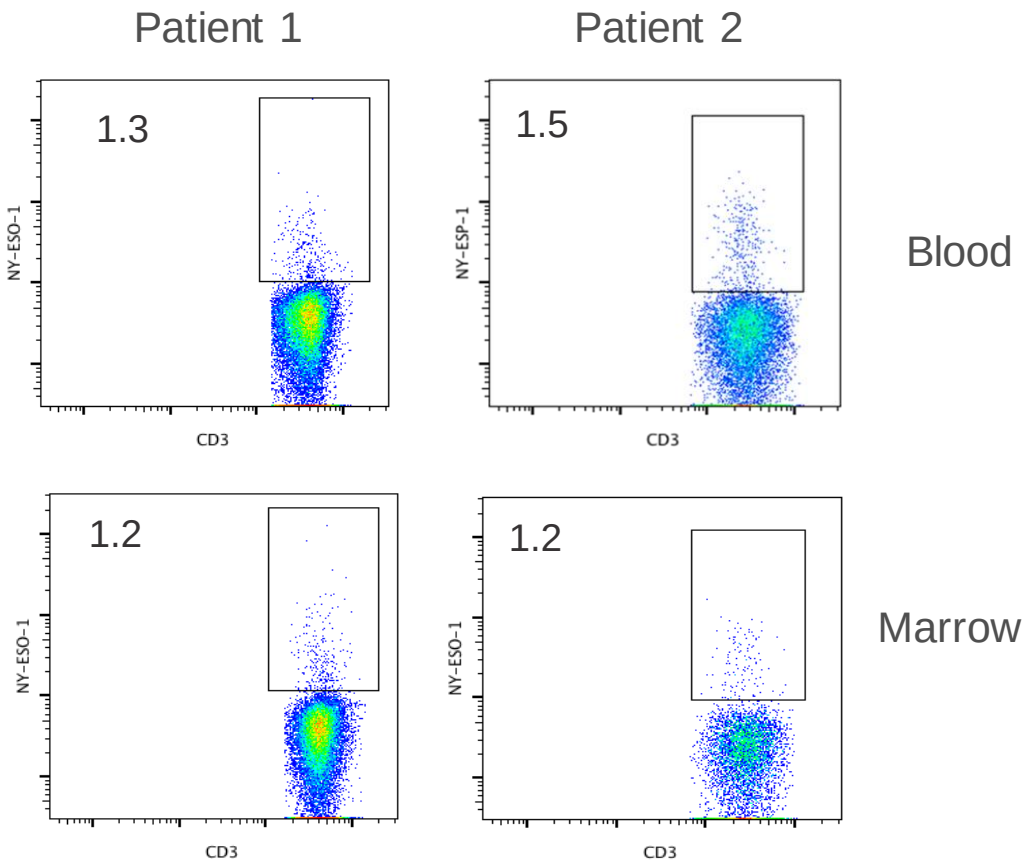
PHASE I/II STUDY IN MULTIPLE MYELOMA

CONTINUED EXPRESSION OF NY-ESO-1 TCR IN BLOOD AND AT SITE OF TUMOR: DAY 360



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PHASE I/II STUDY IN MULTIPLE MYELOMA

PERSISTENCE AND RELAPSE CORRELATION

Patient ID	Timepoint at relapse	Best response	Persistence of NY-ESO T at relapse	Antigen expression on tumor at relapse?
250	1 year	sCR	Y	N
200	1 year	nCR	Y	N
252	2.75 year	PR	N	Y
253	4 months	nCR	N	Y
204	6 months	nCR	N	Y
254	6 months	PR	Y	N
255	1.75 years	nCR	N	Y
209	8 months	nCR	N	Y
257	4 months	nCR	N	Y
258	9 months	nCR	N	Y
259	9 months	sCR	N	Y
261	3 months	PR	N	Y
262	5 months	PR	N	Y
263	9 months	PR	N	Y

- At the time of relapse, blood and tumor were evaluated for NY-ESO-1 persistence and antigen, respectively
- Relapse corresponds to loss of persistence or loss of antigen

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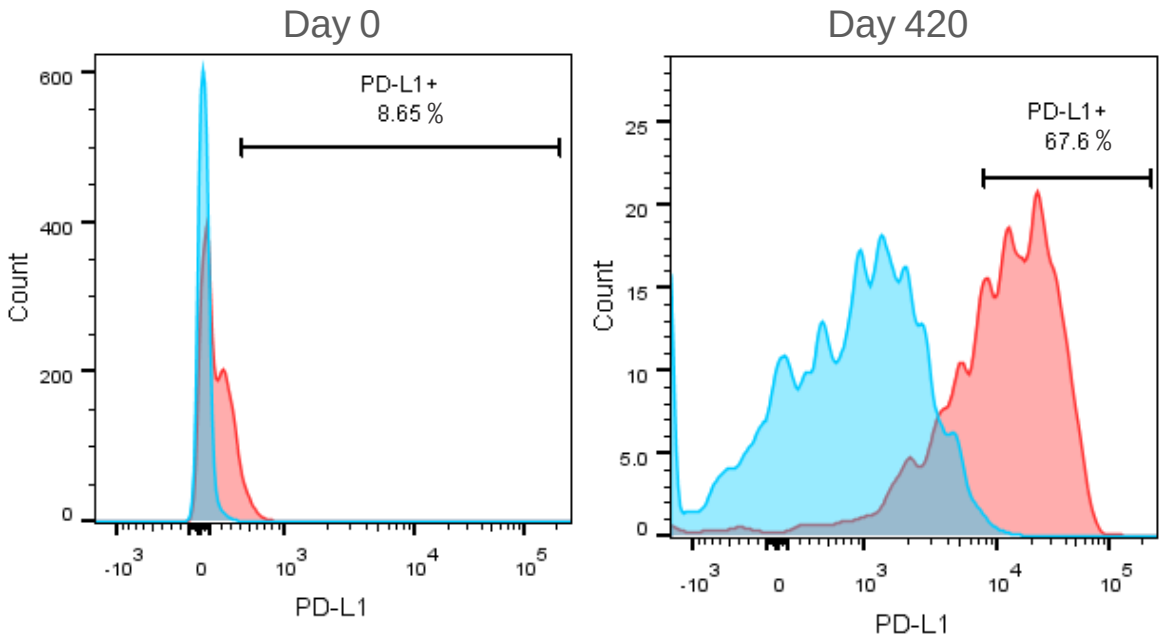
PD-L1 EXPRESSION UPREGULATED IN MYELOMA CELLS AT PROGRESSION

PLANNED COMBINATION STUDY NY-ESO-1 T CELLS + PD-1 INHIBITOR



Planned Study

- Patients with Relapsed/refractory myeloma
- Cyclophosphamide/Fludarabine conditioning

Randomization 1:1

→ NY-ESO-1

→ NY-ESO-1 + anti-PD1

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SUMMARY

- Infusion of autologous T cells engineered with Adaptimmune's affinity enhanced TCR specific for NY-ESO-1 and LAGE-1 antigens is well tolerated
- The duration of response is better than would be expected with transplant alone
- Toxicity related to cytokine release syndrome has not been observed
- Prolonged persistence (without IL-2) and trafficking of cells to bone marrow were detected
- Initial data suggest infused cells remain functional, without exhaustion, and include a diversity of phenotypes
- Upregulation of PDL-1 in relapsed patients supports combination studies

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TRANSFORMING T CELL THERAPY

ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

UPDATE ON PROGRESS WITH NY-ESO TCR
APRIL 22, 2016

Rafael Amado, M.D.
Chief Medical Officer

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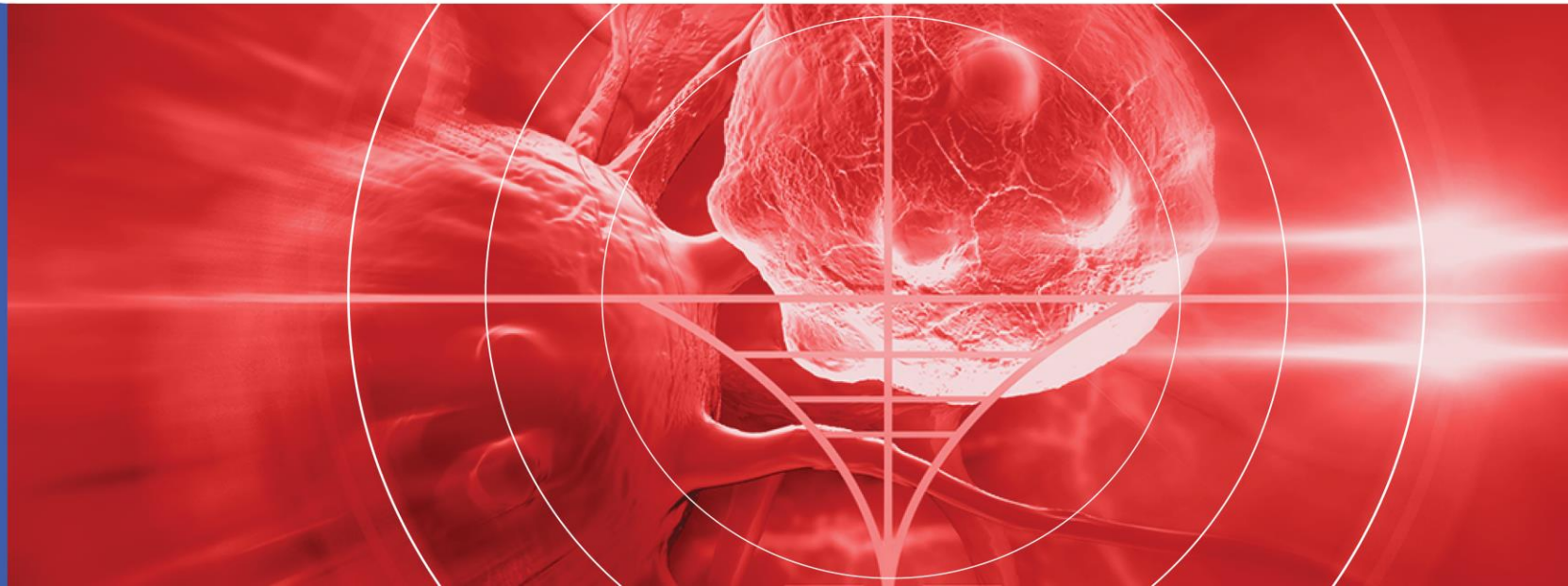

INDUSTRY-LEADING TCR PIPELINE IN SOLID AND HEMATOLOGIC CANCERS

ONGOING PROGRAMS FOR NY-ESO

INDICATION	RESEARCH / PRE-IND / PHASE I/II	STATUS
Synovial Sarcoma	Cohort 1: High NY-ESO expression, 12 patients	Complete
	Cohort 2: Low NY-ESO expression, 10 patients	Enrolling
	Cohort 3: Removal of fludarabine, 10 patients	Enrolling
	Cohort 4*: Modified CTX / fludarabine, 10 patients	Opening 2016
Multiple Myeloma	Autologous SCT, 25 patients (Rapoport Nat Med, 2015)	Complete
	Combination study, no auto SCT; 2 cohorts	In planning
Ovarian	10 patients	Enrolling
Melanoma	6 patients	Enrolling; potential for combination study
Non-small cell lung cancer	10 patients, Stage IIIb / IV NSCLC	Initiated Q4 2015
Investigator Initiated studies	NCI: synovial sarcoma (16 patients) and melanoma (13 patients)	Complete
	ATTACK: Esophageal: 12 patients	Active; recruitment to resume

*Pending analysis of cohort 3

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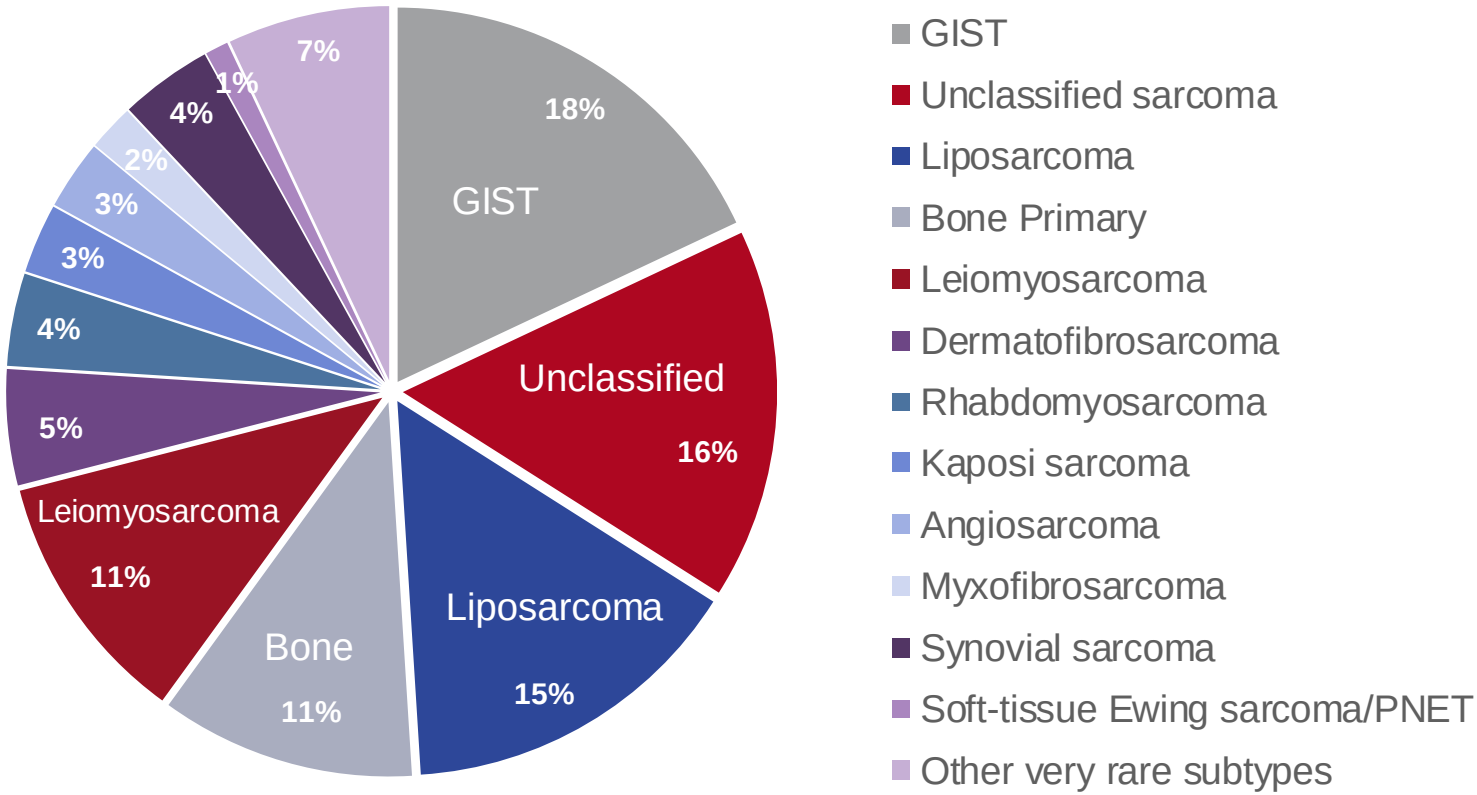
SARCOMAS

A DIVERSE COLLECTION OF UNCOMMON MESENCHYMAL TUMORS



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Ducimetiere et al. PLoS ONE 6(8): e20294.
doi:10.1371/journal.pone.0020294. epub AUG 2011

SARCOMA DEMOGRAPHICS AND MORTALITY

RELAPSED METASTATIC SOFT TISSUE SARCOMA REPRESENTS AN UNMET MEDICAL NEED

Disease	Incidence US/EU	Annual Mortality US/EU
Synovial Sarcoma & Myxoid Round Cell Liposarcoma	2,400-3,000	840-1,050

Breakthrough Designation: Granted in the U.S. on February 4, 2016

*"for the treatment of HLA-A*0201, HLA-A*0205, HLA-A*0206 allele-positive patients with inoperable or metastatic synovial sarcoma who have received prior chemotherapy and whose tumor expresses the NY-ESO-1 tumor antigen"*

Orphan Designation: Granted in the U.S. on March 29, 2016

"autologous CD4+/CD8+ NY-ESO-1^{c259}-T cells for the treatment of soft tissue sarcoma"

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MYXOID ROUND CELL LIPOSARCOMA

NEXT SOFT TISSUE SARCOMA TO BE STUDIED WITH ADAPTIMMUNE'S NY-ESO-1 TCR

- Represent 30-35% of all liposarcomas; 10% of all soft tissue sarcomas
- 80-90% express NY-ESO at high levels
- Characterized by chromosomal translocation (t(12;16)(q13;p11); as in the case of synovial sarcomas, it allows for accurate diagnosis)
- Present primarily in the extremities, particularly the thigh, and in the trunk and retroperitoneum
- Localized disease is managed with surgery, radiation and chemotherapy
- One third of patients develop metastatic disease with multifocal spread, commonly to the bone and lungs.
- Chemotherapy has a limited, non-curative role in metastatic disease

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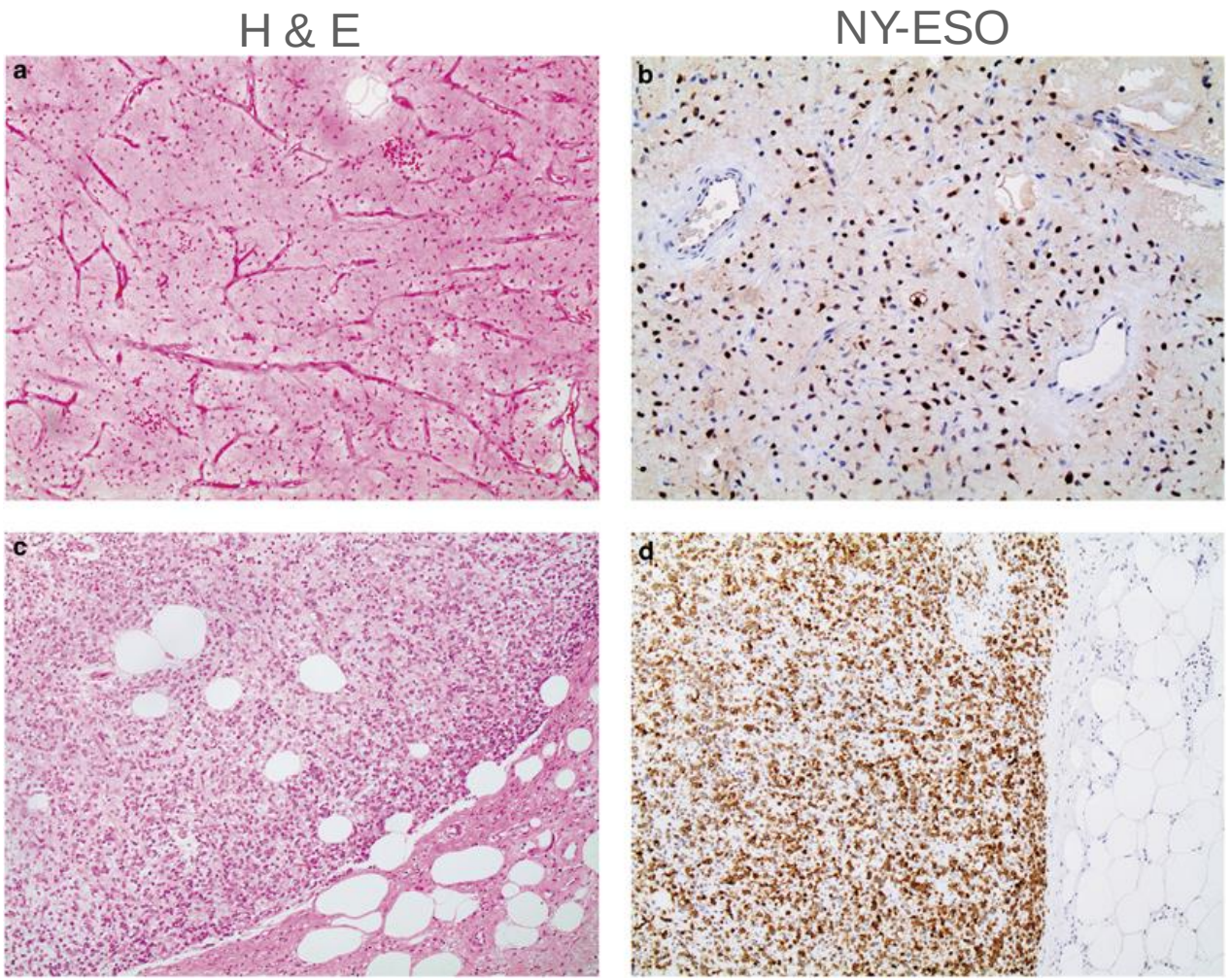
WHO Classification: https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb5/bb5-classifsofttissue.pdf

MYXOID ROUND CELL LIPOSARCOMA

NY-ESO IS HIGHLY EXPRESSED IN THE MAJORITY OF MRCLS



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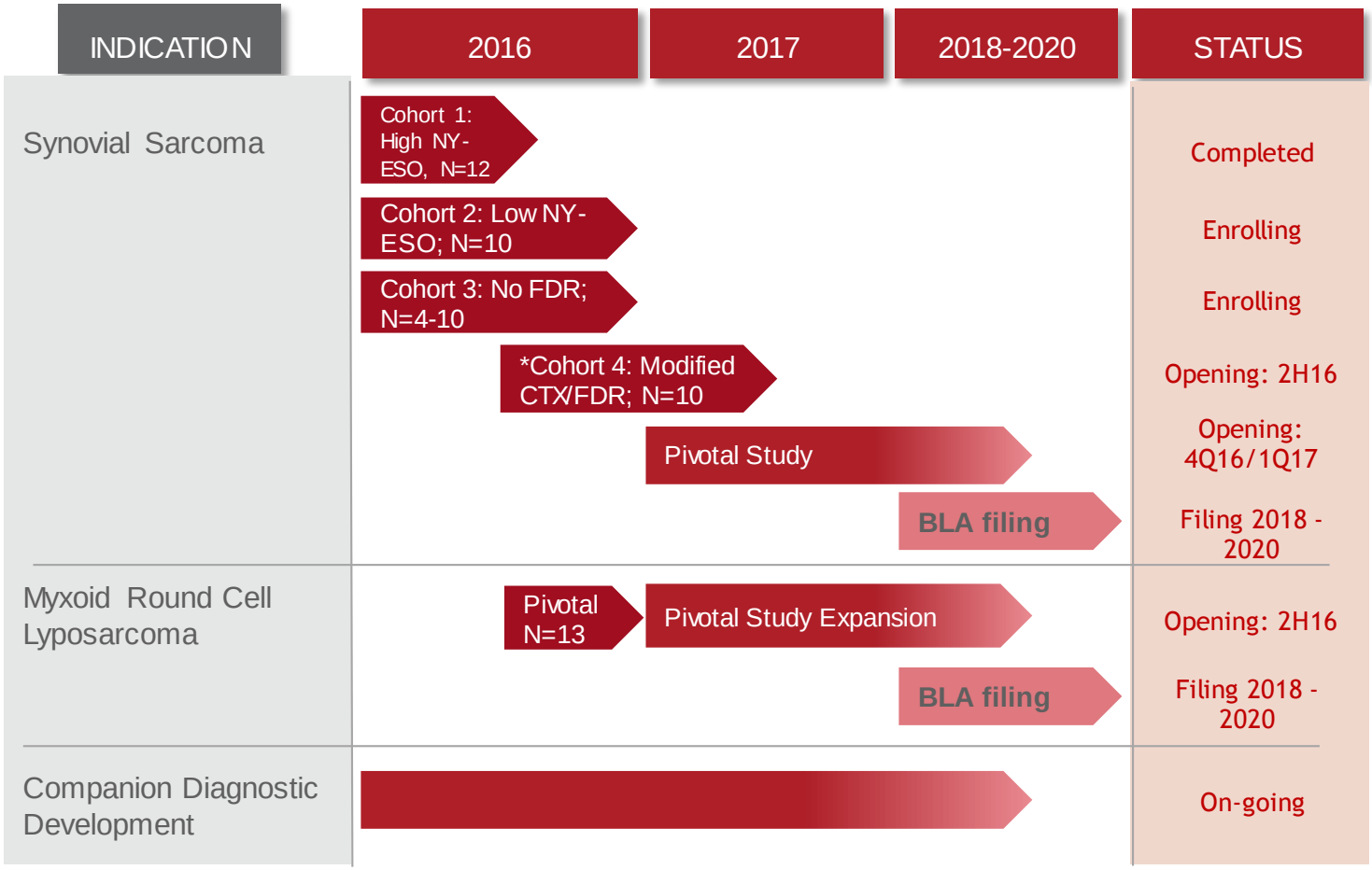
Hemminger J, Modern Pathology 26, 2013

NY-ESO CLINICAL PROGRAM UPDATE

REGISTRATION IN SOFT TISSUE SARCOMA



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*Pending analysis of cohort 3

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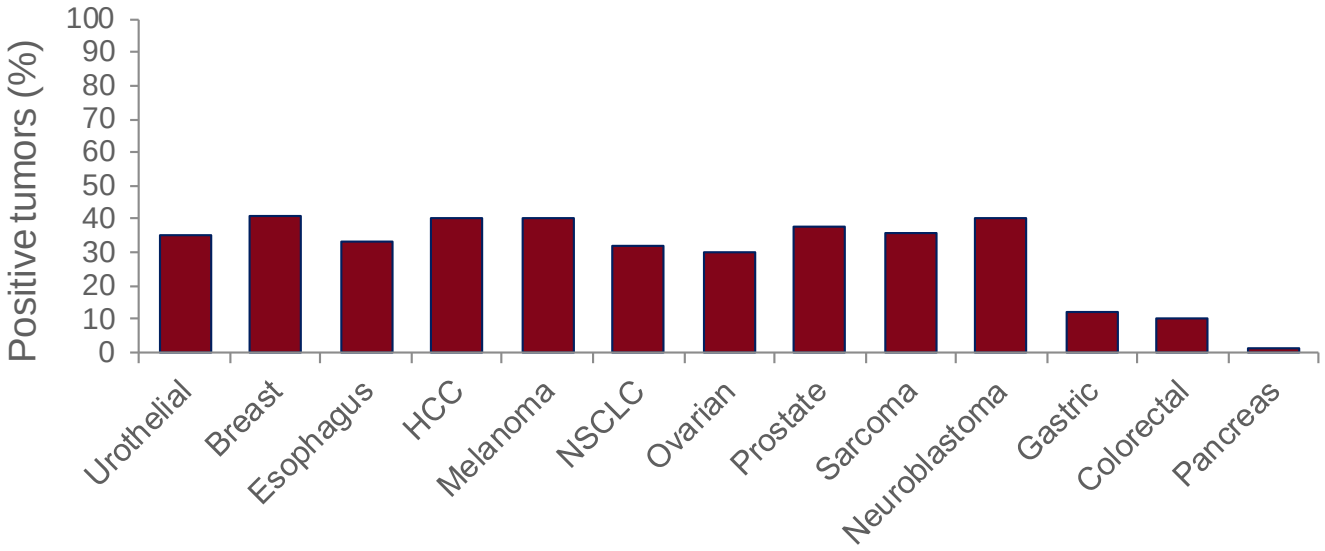
NY-ESO EXPRESSION ACROSS TUMOR TYPES

NY-ESO-1 IS EXPRESSED AT LOW TO MEDIUM LEVELS ACROSS A WIDE RANGE OF TUMORS



Estimated Annual Deaths*

	Melanoma	Ovarian	NSCLC	Myeloma
US[1]	9,940	14,180	158,040	11,240
EU[2]	12,051	42,716	254,532	12,213

* HLA02 represents approx. 40-50% of these patients

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1. Source: seer.cancer.gov
2. Source: eco.iarc.fr/eucan

NY-ESO PROGRAM

2016 DEVELOPMENT MILESTONES AND DATA FLOW

COMPLETED	TARGET DATE	MILESTONE
√	1H 2016	Breakthrough designation for NY-ESO in synovial sarcoma
√	2H 2016	Orphan drug designation for NY-ESO in soft tissue sarcoma
	4Q 2016	Additional phase I/II data from clinical studies in: •Sarcoma •Myeloma •Lung •Ovarian •Melanoma
	2H 2016	Initiation of first combination study
	2H 2016	Initiation of Myxoid Round Cell Liposarcoma Study
	4Q16/1Q17	Initiation of pivotal synovial sarcoma study

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ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

ACCELERATING ADAPTIMMUNE'S WHOLLY-OWNED CLINICAL PIPELINE

APRIL 22, 2016

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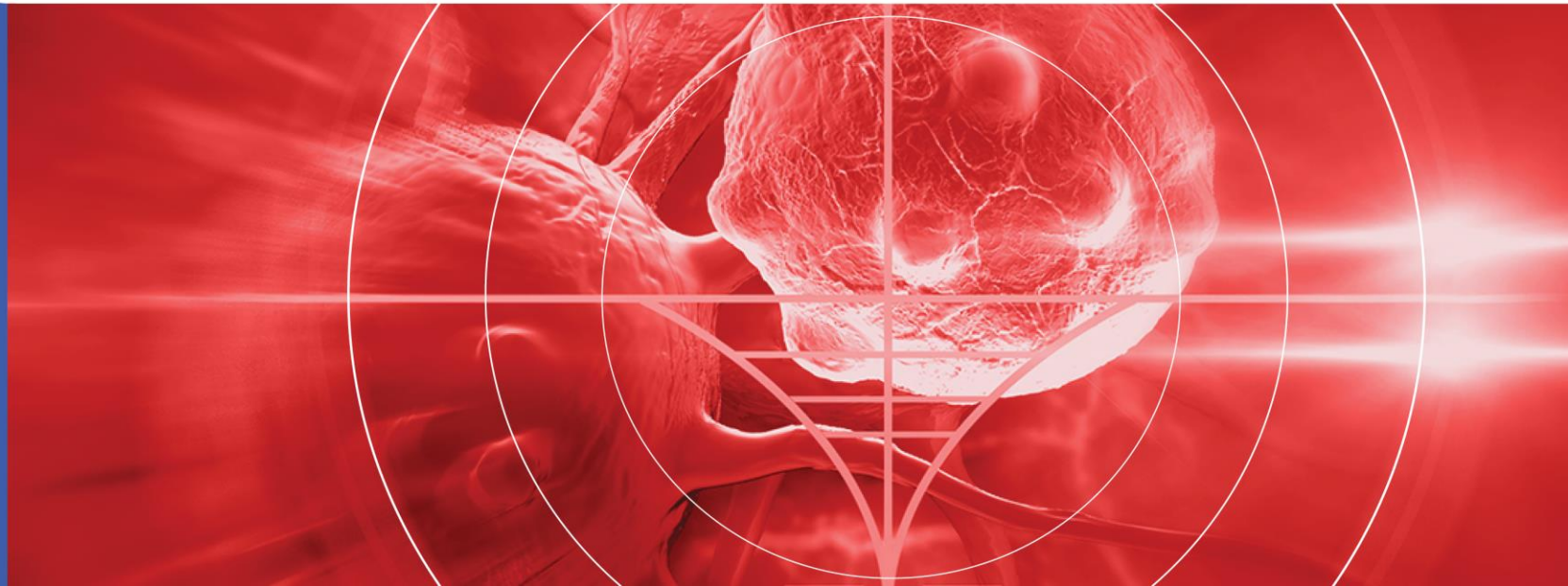

NY-ESO CLINICAL PROGRAM UPDATE

DEEP PIPELINE OF WHOLLY-OWNED TCRs

INDICATION	RESEARCH	PRE-IND	PHASE I/II	STATUS
Non-Small Cell Lung Cancer (NSCLC)	MAGE-A10 TCR dose escalation			Initiated Q4 2015
Urothelial Melanoma Head and neck	MAGE-A10 TCR			Initiate in 2016
Hepatocellular cancer	AFP TCR			IND open; enrollment in 2016
Multiple cancer types	MAGE-A4 TCR			RAC and IND submission in 2017
Multiple cancer types	Generation 2 and 3 TCRs			INDs in 2017+
Multiple cancer types	Undisclosed			INDs from 2017+

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CANCER TESTIS EXPRESSION

BROAD COVERAGE OF MANY CANCERS WITH ADAPTIMMUNE'S EXISTING TCR PIPELINE

Indication	Frequency (%)	
	NY-ESO-1	MAGE-A10
Lung Squamous Cell	26	33
Bladder Cancer	26	31
Cutaneous Melanoma	32	29
Head and Neck	11	14
Ovarian Cancer	13	12
TN breast cancer	19	10
Endometrial Cancer	7	7
Esophageal Cancer	11	18
Gastric and Esophageal Cancer	11	17
Lung Adenocarcinoma	12	10
Cervical Cancer	4	7
Breast Cancer (all)	5	3

Source: TGCA RNAseq datasets

≥30%

20-30%

≥ 45%

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CANCER TESTIS EXPRESSION

BROAD COVERAGE OF MANY CANCERS WITH ADAPTIMMUNE'S EXISTING TCR PIPELINE

Indication	Frequency (%)		
	NY-ESO-1	MAGE-A10	MAGE-A4
Lung Squamous Cell	26	33	64
Bladder Cancer	26	31	38
Cutaneous Melanoma	32	29	23
Head and Neck	11	14	44
Ovarian Cancer	13	12	38
TN breast cancer	19	10	26
Endometrial Cancer	7	7	17
Esophageal Cancer	11	18	36
Gastric and Esophageal Cancer	11	17	32
Lung Adenocarcinoma	12	10	12
Cervical Cancer	4	7	23
Breast Cancer (all)	5	3	7

Source: TGCA RNAseq datasets

≥30%

20-30%

≥ 45%

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TRANSFORMING T CELL THERAPY

CANCER TESTIS EXPRESSION

BROAD COVERAGE OF MANY CANCERS WITH ADAPTIMMUNE'S EXISTING TCR PIPELINE

Indication	Frequency (%)			
	NY-ESO-1	MAGE-A10	MAGE-A4	Expression by 1 or more
Lung Squamous Cell	26	33	64	69
Bladder Cancer	26	31	38	50
Cutaneous Melanoma	32	29	23	48
Head and Neck	11	14	44	46
Ovarian Cancer	13	12	38	44
TN breast cancer	19	10	26	35
Endometrial Cancer	7	7	17	21
Esophageal Cancer	11	18	36	40
Gastric and Esophageal Cancer	11	17	32	35
Lung Adenocarcinoma	12	10	12	19
Cervical Cancer	4	7	23	26
Breast Cancer (all)	5	3	7	11

Source: TGCA RNAseq datasets

≥30%

20-30%

≥ 45%

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WHOLLY-OWNED PIPELINE

2016 DEVELOPMENT MILESTONES AND DATA FLOW

COMPLETED	TARGET DATE	MILESTONE
√	1H 2016	File and open IND for AFP TCR
	2H 2016	Complete enrollment in NSCLC dose-escalation study for MAGE-A10
	2H 2016	Initiate AFP clinical study
	2H 2016	Initiate MAGE-A10 multi-tumor study
	2017	File IND for MAGE-A4

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SUMMARY

- Rapid progress with NY-ESO-1 in sarcoma, anticipate initiating pivotal trials around year end 2016
- Multiple studies examining efficacy of NY-ESO-1 in additional indications
- Expect to initiate combination trials with NY-ESO-1 and check-point inhibitor in 2016
- Broad tumor coverage across Adaptimmune's clinical pipeline
- Delivering on internal pipeline; 2 active INDs in the past 8 months
  - MAGE-A10 study in bladder cancer, head and neck cancer and melanoma, in addition to the ongoing NSCLC study
  - Open IND with AFP TCR; enrollment to start in 2016
- Next IND in 2017: MAGE-A4
  - High level of expression in multiple tumor types

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ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

ADAPTIMMUNE PIPELINE ENGINE:
AN ABUNDANCE OF POTENTIAL TARGETS AND PRECLINICAL CANDIDATES
APRIL 22, 2016

Gwen Binder-Scholl, Ph.D.
Chief Technology Officer

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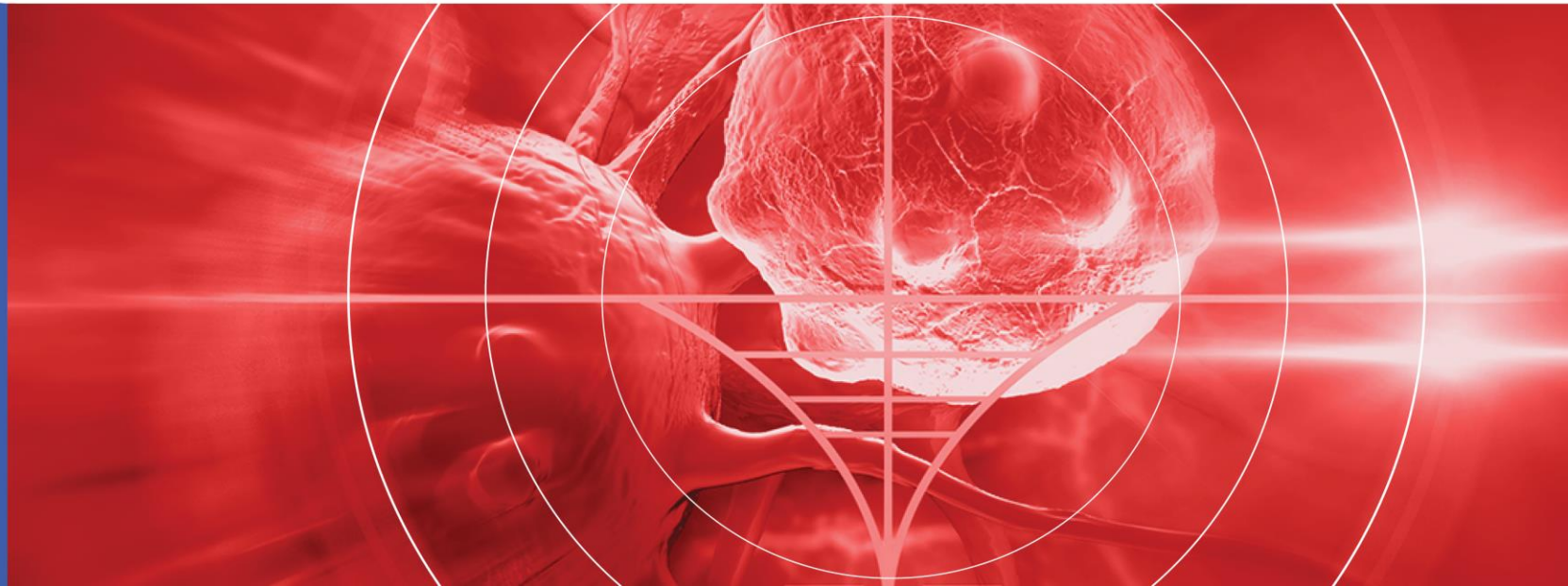
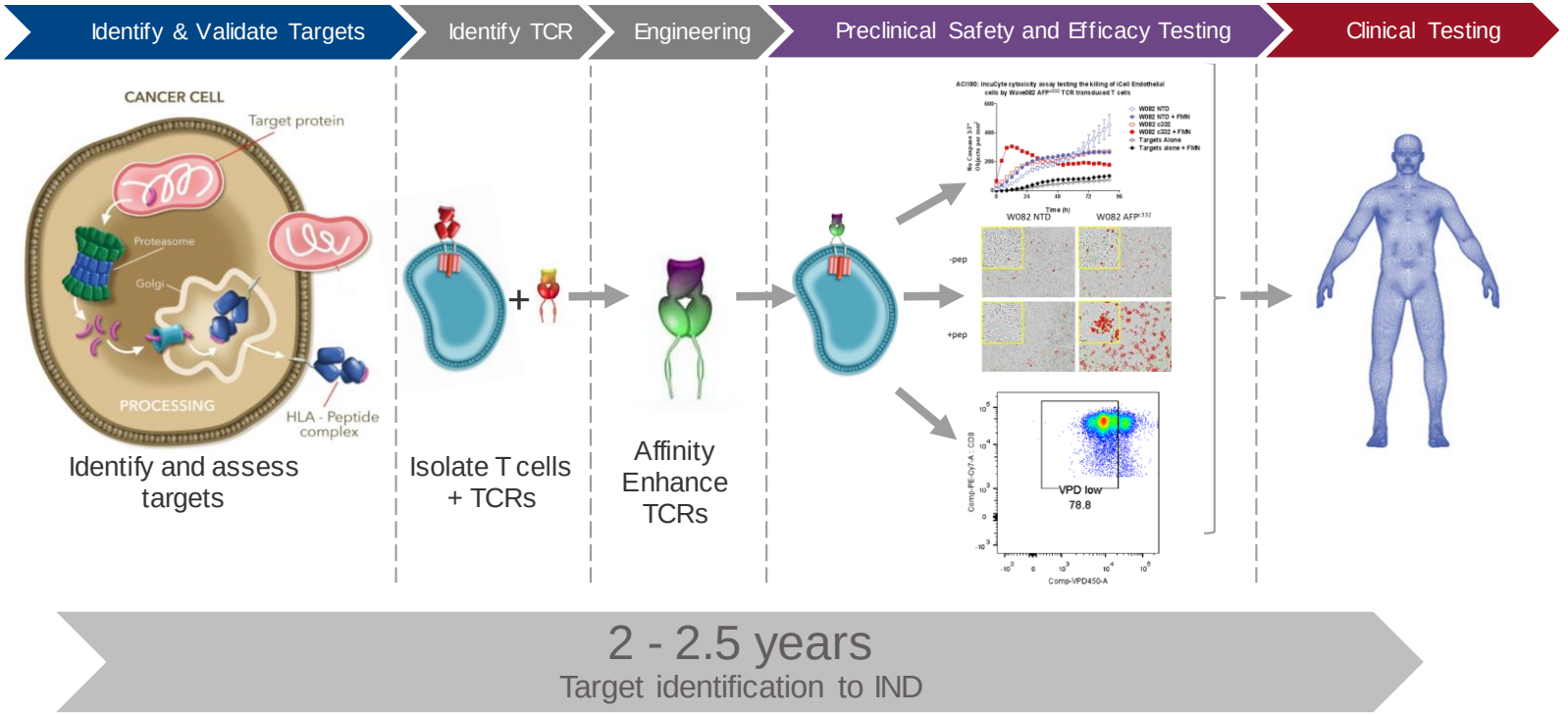


TCR IDENTIFICATION AND TESTING – THE PIPELINE ENGINE



- SPEAR T cell platform supports development across different HLA types
- 3 HLA types cover ~70% of the world population*

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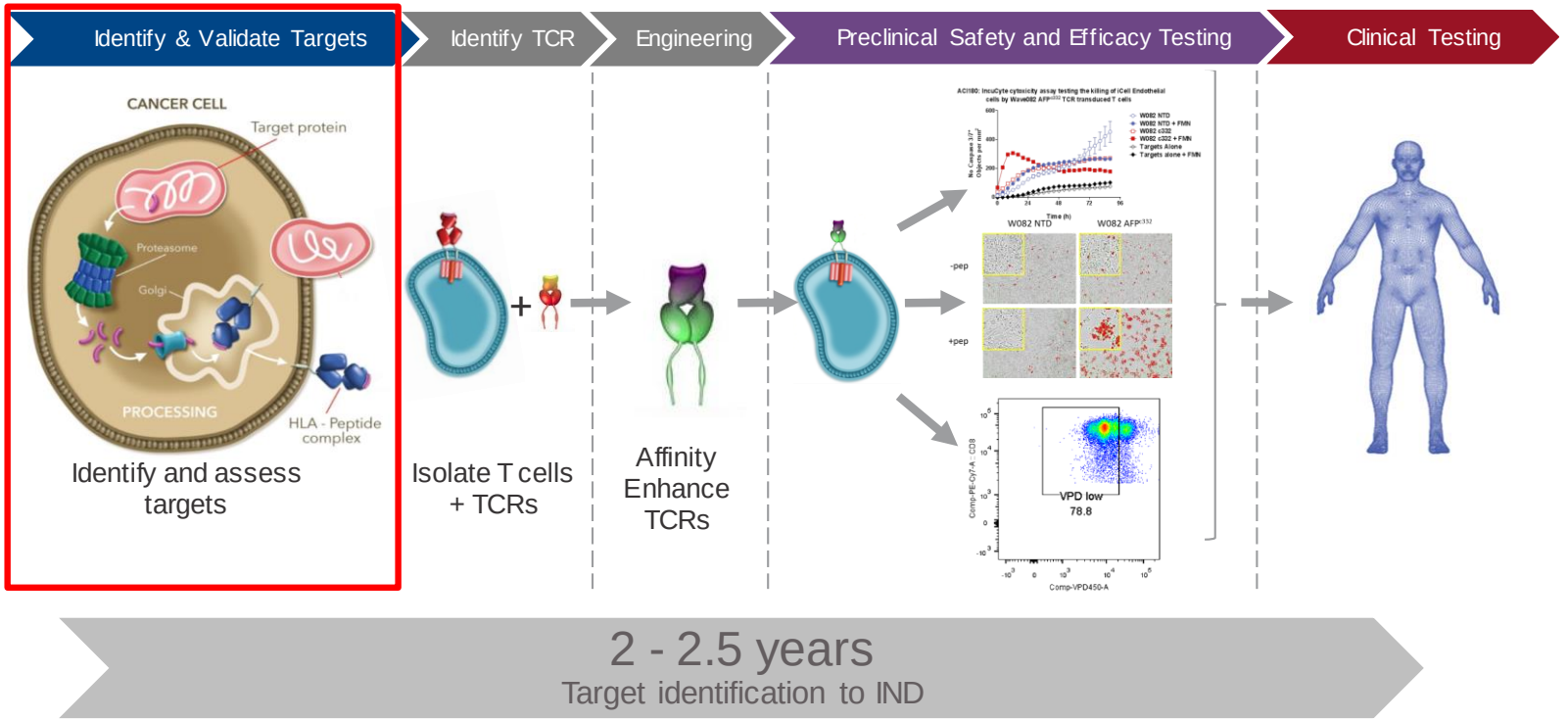
* www.allelefrequencies.net; internal model

TCR IDENTIFICATION AND TESTING – THE PIPELINE ENGINE



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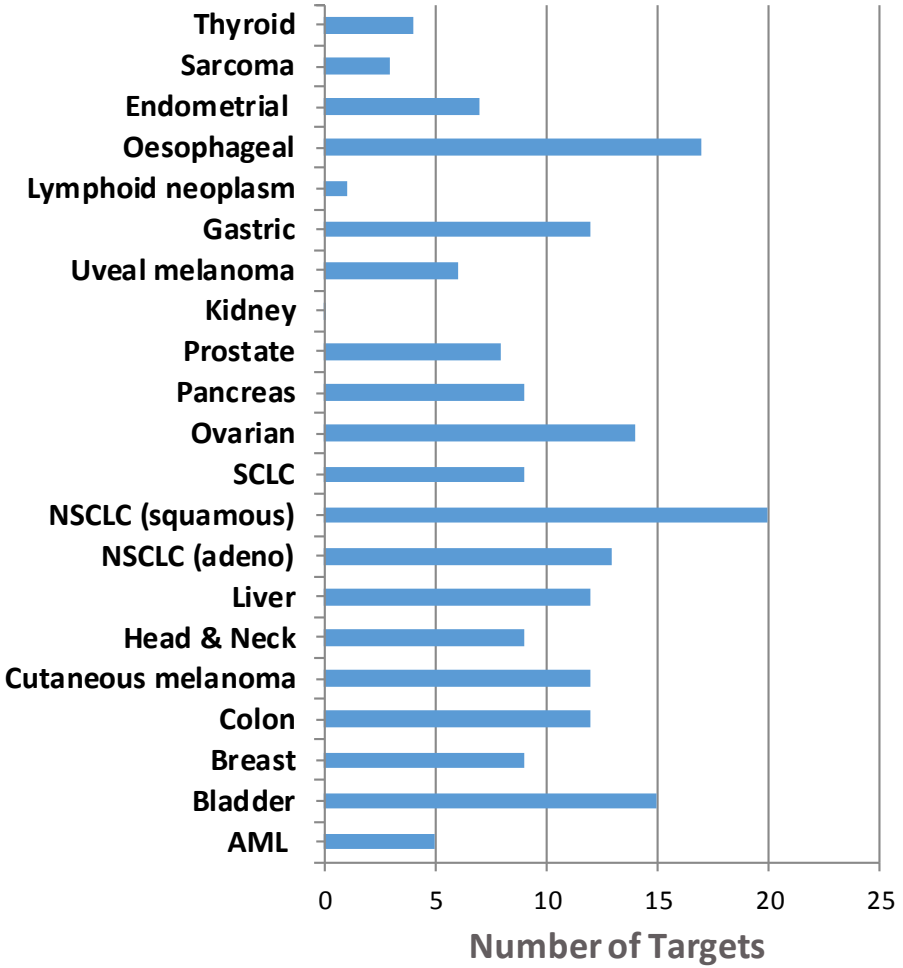
TECHNOLOGY ALLOWS ADAPTIMMUNE TO FIND TUMOR-ASSOCIATED TARGETS

NEW TARGET SELECTION DRIVEN BY CLINICAL PRIORITIES

Multiple new targets identified across indications*



* Examples to demonstrate the breadth of targets; actual indications selected for development are not disclosed

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WHOLLY OWNED TARGET PIPELINE (APRIL 2016)

Cancer indication	Top 3 Targets Identified for Each Indication (%) TCGA		
	Target 1	Target 2	Target 3
Sarcoma	(30%)	(21%)	
Endometrial		(23%)	
Esophageal	(72%)		(38%)
Lymphoid neoplasm	(29%)	(25%)	(25%)
Gastric	(51%)		(45%)
Uveal melanoma	(100%)	(100%)	(100%)
Prostate			
Pancreatic			
Ovarian			
Lung AD		(34%)	(34%)
Lung SqCC		(47%)	
Liver HCC		(36%)	(34%)
Head and Neck SCC		(40%)	(38%)
Skin Cutaneous Melanoma	(88%)	(87%)	
Colon			
Breast			
Bladder			(40%)
AML			

Key:

Target – New targets due assessment (peptides identified)

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Uveal melanoma	(100%)	(100%)	(100%)
Prostate	(100%)		(90-95%)
Pancreatic	(54%)		(37%)
Ovarian	(54%)		
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Colon	(55%)	(32%)	
Breast	(63%)	(41%)	(25%)
Bladder			(40%)
AML	(73%)	(50%)	

Key:

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Target – Targets in assessment

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Uveal melanoma	(100%)	(100%)	(100%)
Prostate	(100%)	(99%)	(90-95%)
Pancreatic	(54%)	(49%)	(37%)
Ovarian	(54%)		
Lung AD	(43%)	(34%)	(34%)
Lung SqCC	(58%)	(47%)	(46%)
Liver HCC	(44%)	(36%)	(34%)
Head and Neck SCC	(44%)	(40%)	(38%)
Skin Cutaneous Melanoma	(88%)	(87%)	
Colon	(55%)	(32%)	
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Key:

Target – New targets due assessment (peptides identified)

Target – Targets in assessment

Target – Targets with TCRs in the discovery/optimisation programme

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Blue – Cancer Testis Antigens

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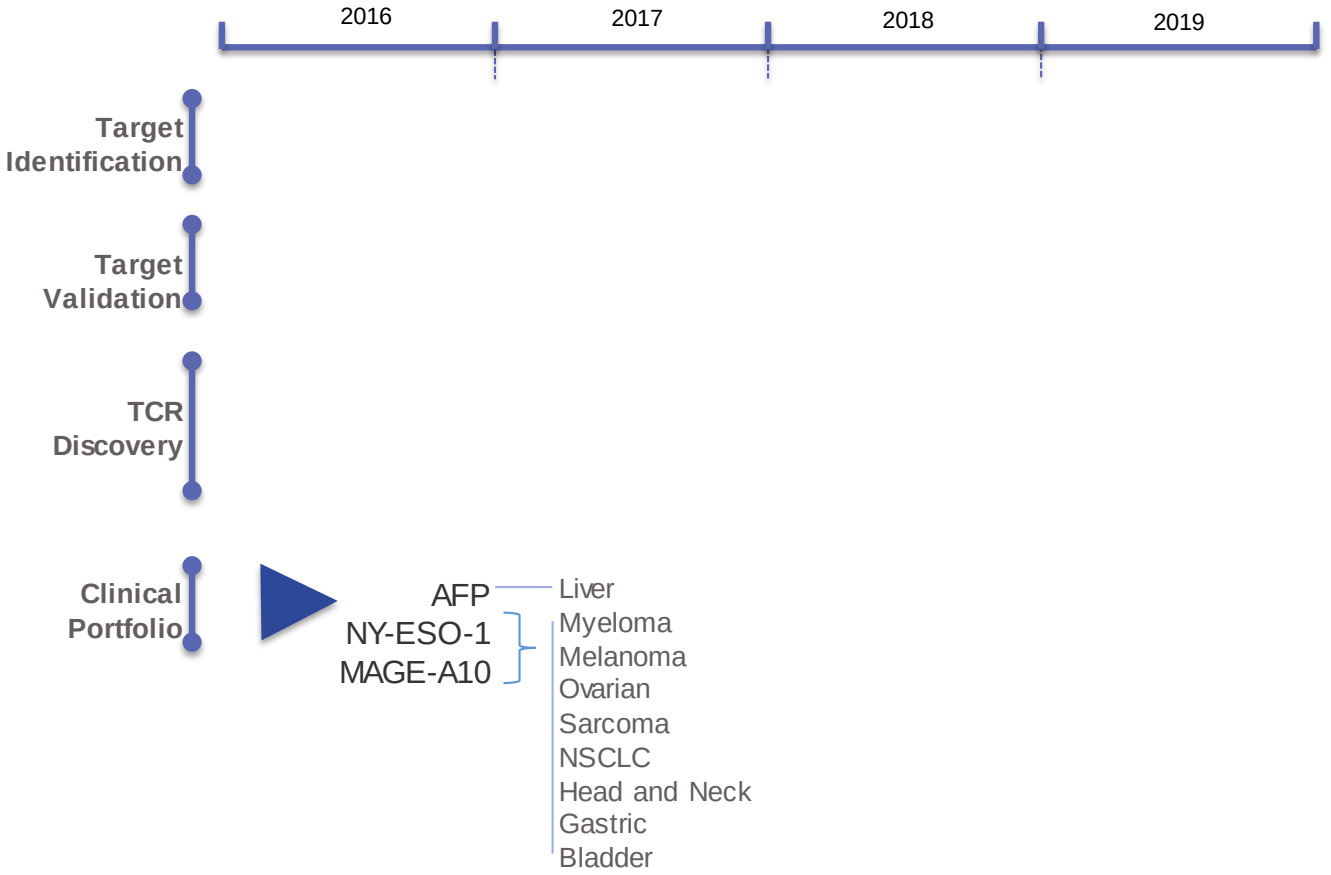
MULTIPLE TARGETS TO ENTER CLINIC IN NEXT 3 YEARS

MULTIPLE INDs FROM 2017 ONWARDS (TARGETS AND NEXT GENERATION)



- All programs are run under Adaptimmune-owned INDs.
- Next generation programs not represented on this chart.

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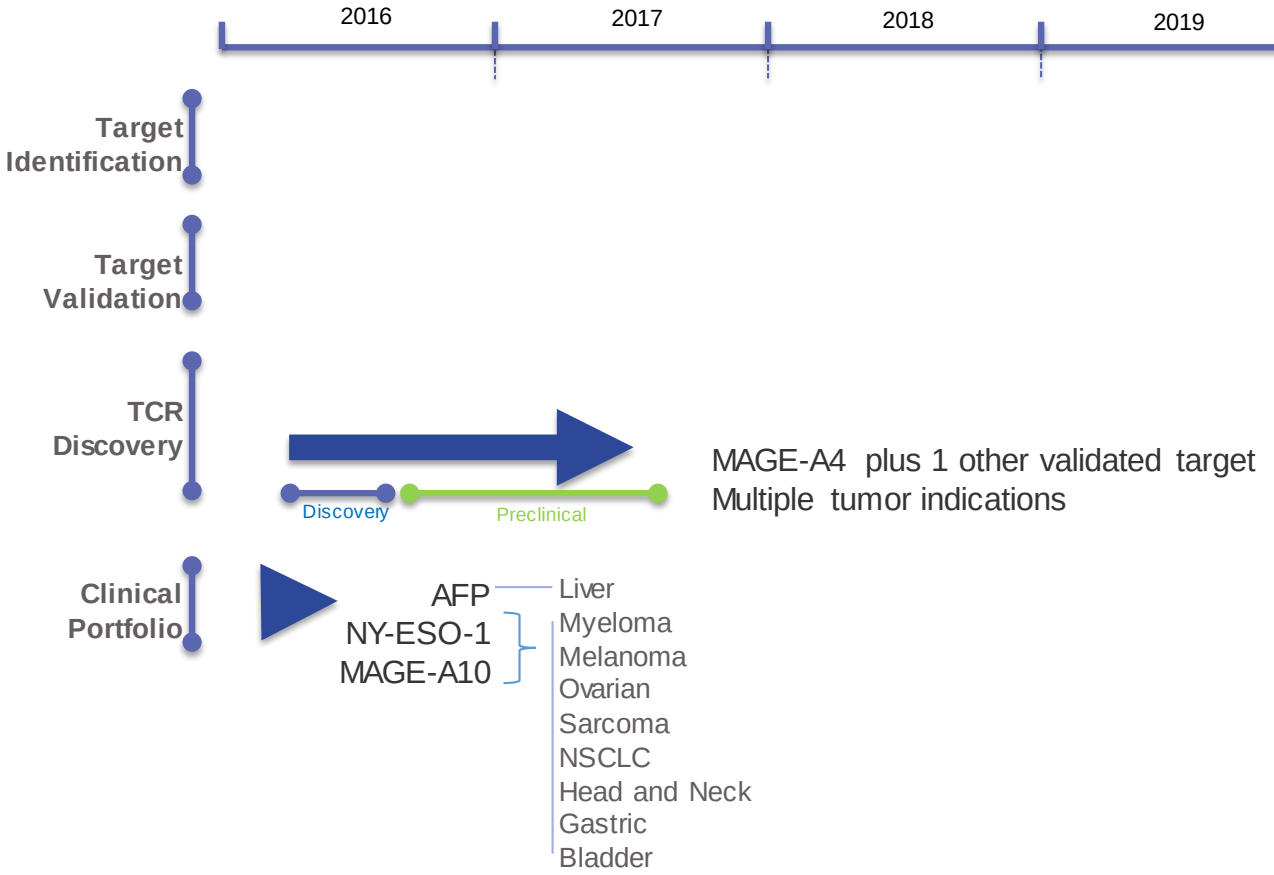

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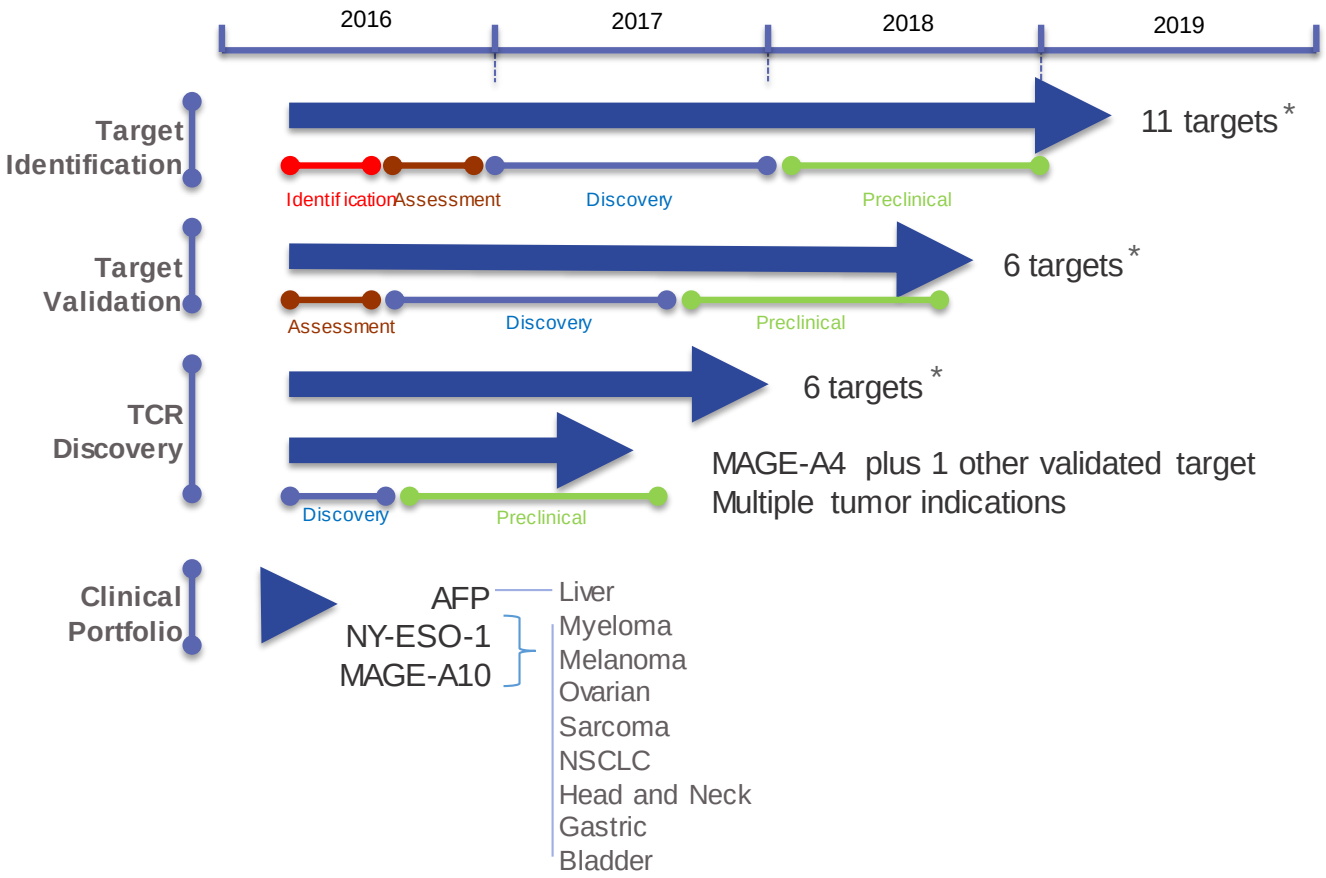

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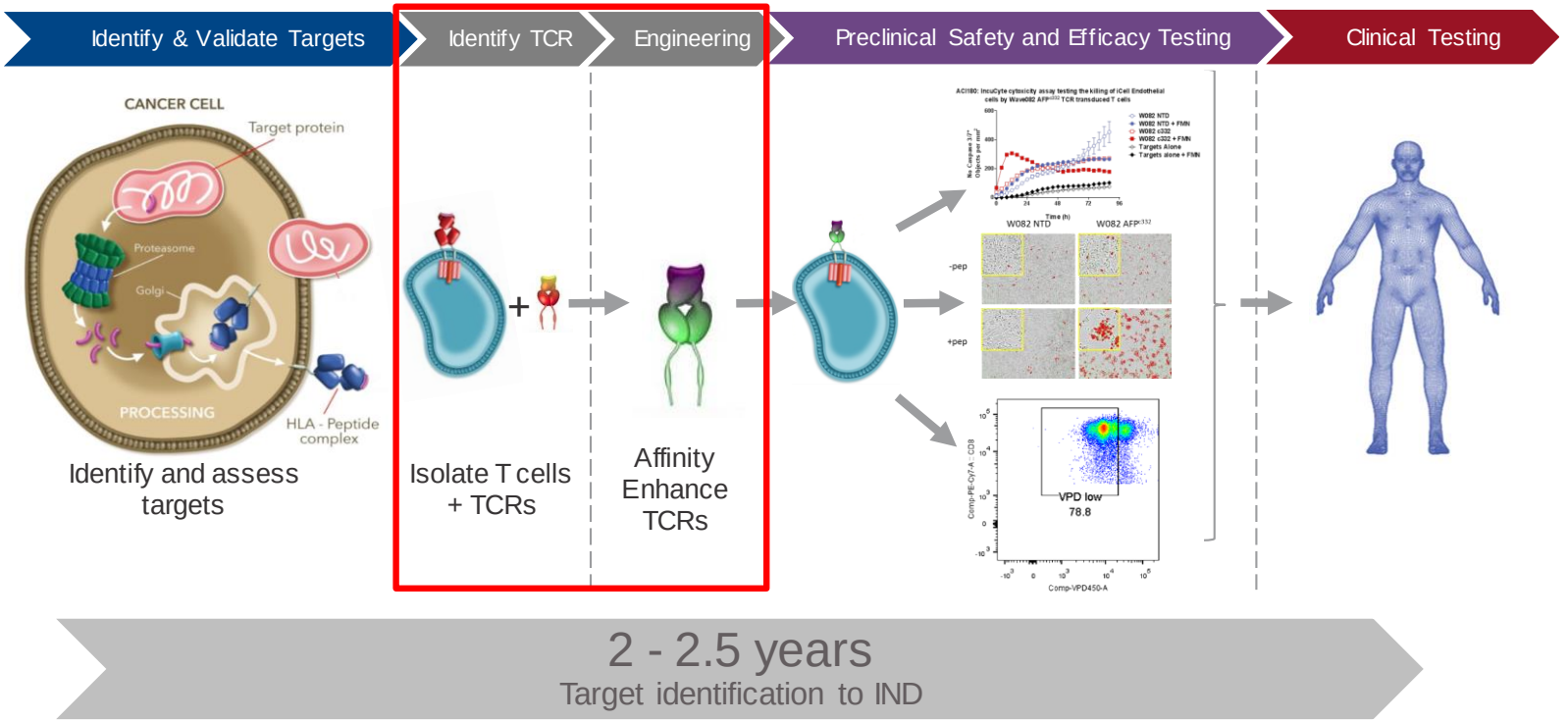
* Early targets – attrition expected

TCR IDENTIFICATION AND TESTING – THE PIPELINE ENGINE



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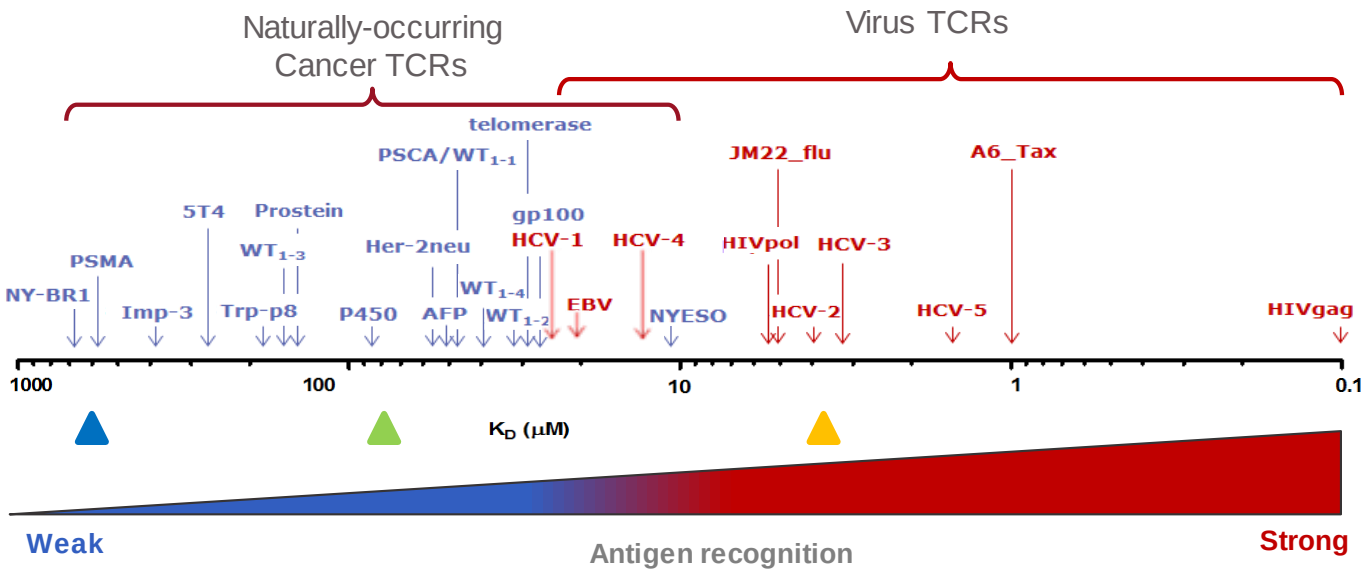
CANCER ANTIGEN SPECIFIC TCRs FROM CLONES AND LIBRARIES

ORIGINAL ISOLATES DISPLAY A WIDE RANGE OF AFFINITIES



AFP

Single clone

MAGE-A4

Selected from a pool of 69 parental TCRs

MAGE-A10

Selected from a pool of 21 parental TCRs
supra-natural TCR

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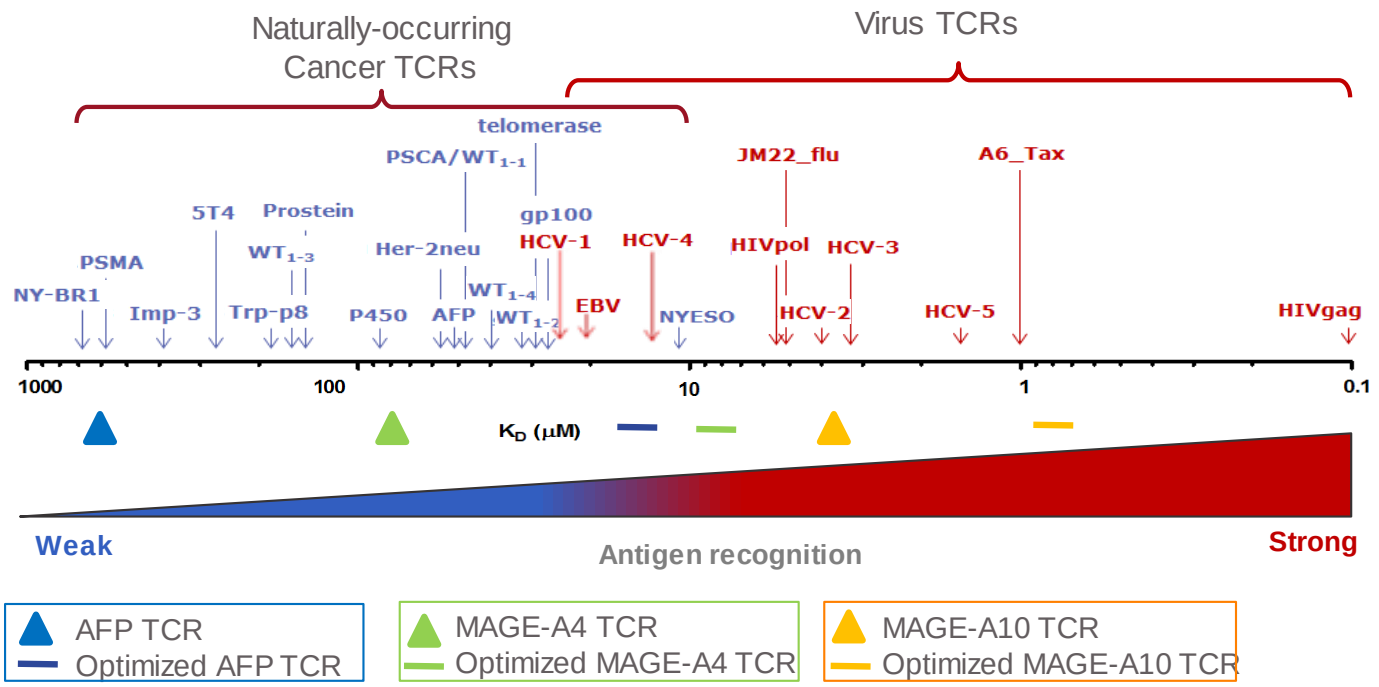
Aleksic, M. et al. (2012). Eur J Immunol 10.1002/eji.201242606

AFFINITY OPTIMIZATION IS IMPORTANT IN ALL CASES SO FAR

INDEPENDENT OF STARTING AFFINITY, OPTIMIZATION IS RELEVANT



- Having multiple parental TCRs to start from allows selection of the most specific TCR
- The ideal affinity is different for each TCR and not possible to predict

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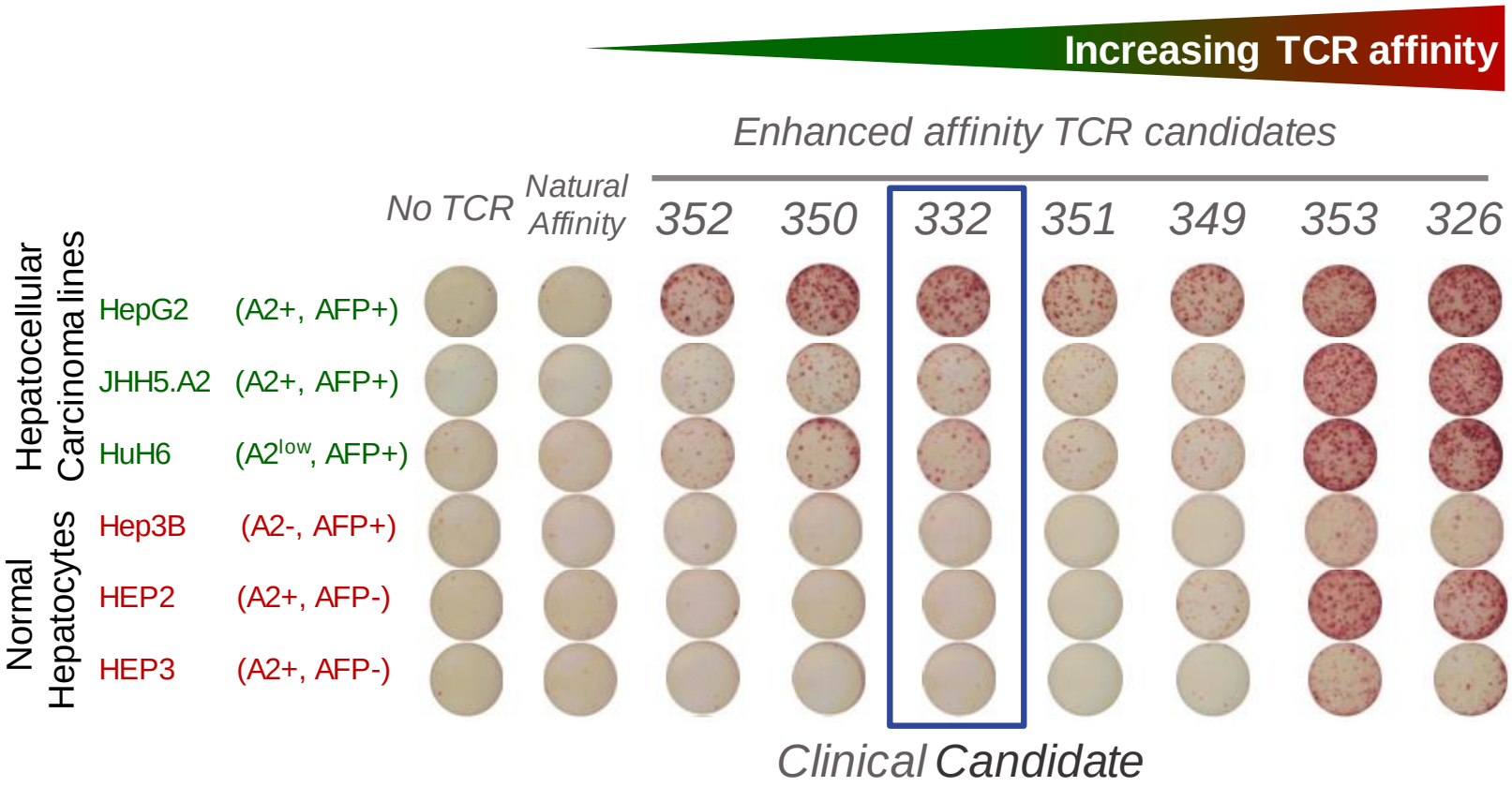
Aleksic, M. et al. (2012). Eur J Immunol 10.1002/eji.201242606

EACH TCR HAS A WINDOW OF ENHANCED POTENCY

IT IS POSSIBLE TO OVER-ENGINEER – THIS IS CAREFULLY MONITORED



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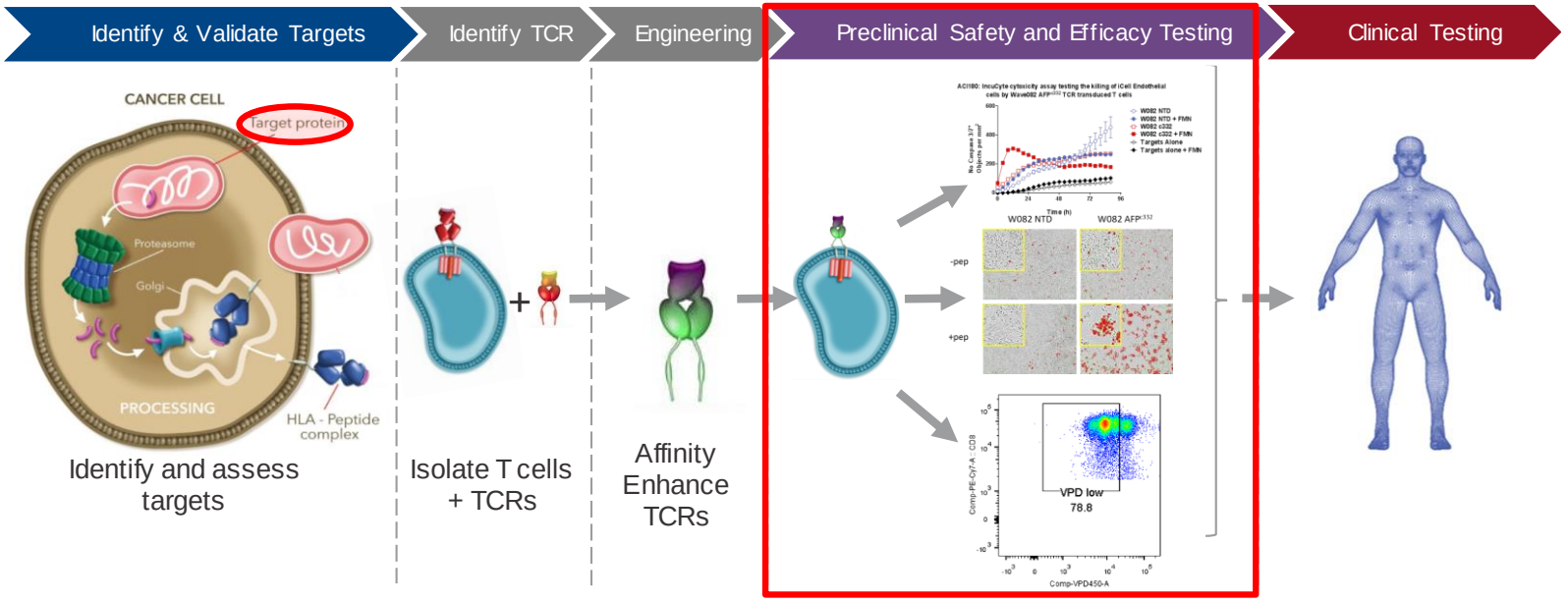
TCR IDENTIFICATION AND TESTING – THE PIPELINE ENGINE



- TCR specificity is mapped by X-scanning
- Alloreactivity and further TCR specificity tested in cell-based assays
- Potency tested in primary tumor and tumor cell lines

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SUMMARY

ADAPTIMMUNE HAS A PIPELINE FOR AN INDUSTRY

- Multiple tumor associated targets across oncology indications – nearly every indication can be addressed
- Affinity optimization is important for optimal efficacy, but…
  - The ideal affinity must be empirically determined
  - Adaptimmune has a unique set of tools to ensure specificity of engineered TCRs
- The SPEAR T cell platform supports development across multiple HLA types
- Multiple company-owned INDs from 2017 onwards
  - Includes new targets, and next generation cells

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ADAPTIMMUNE SCIENTIFIC ADVISORY BOARD

Crystal Mackall, M.D., *Chair, Adaptimmune Scientific Advisory Board*; Professor of Pediatrics and Medicine; Associate Director of the Stanford Cancer Institute

Nabil Ahmed, M.D., Associate Professor, Department of Pediatrics, Texas Children's Hospital, Texas Children's Cancer Center; Center for Cell and Gene Therapy, Houston Methodist Hospital, Baylor College of Medicine

Michael Dustin, Ph.D., Professor of Immunology and Wellcome Principal Research Fellow, Director of Research of the Kennedy Institute, Oxford, UK

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Mario Sznol, M.D., Professor, Internal Medicine; Leader, Disease-Related Research Team, Melanoma and Renal cell Carcinoma; Vice-Chief, Medical Oncology; Co-Director, Yale Skin SPORE, Yale Cancer Center

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ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

MANUFACTURING EXCELLENCE AND COMMERCIAL DELIVERY

APRIL 22, 2016

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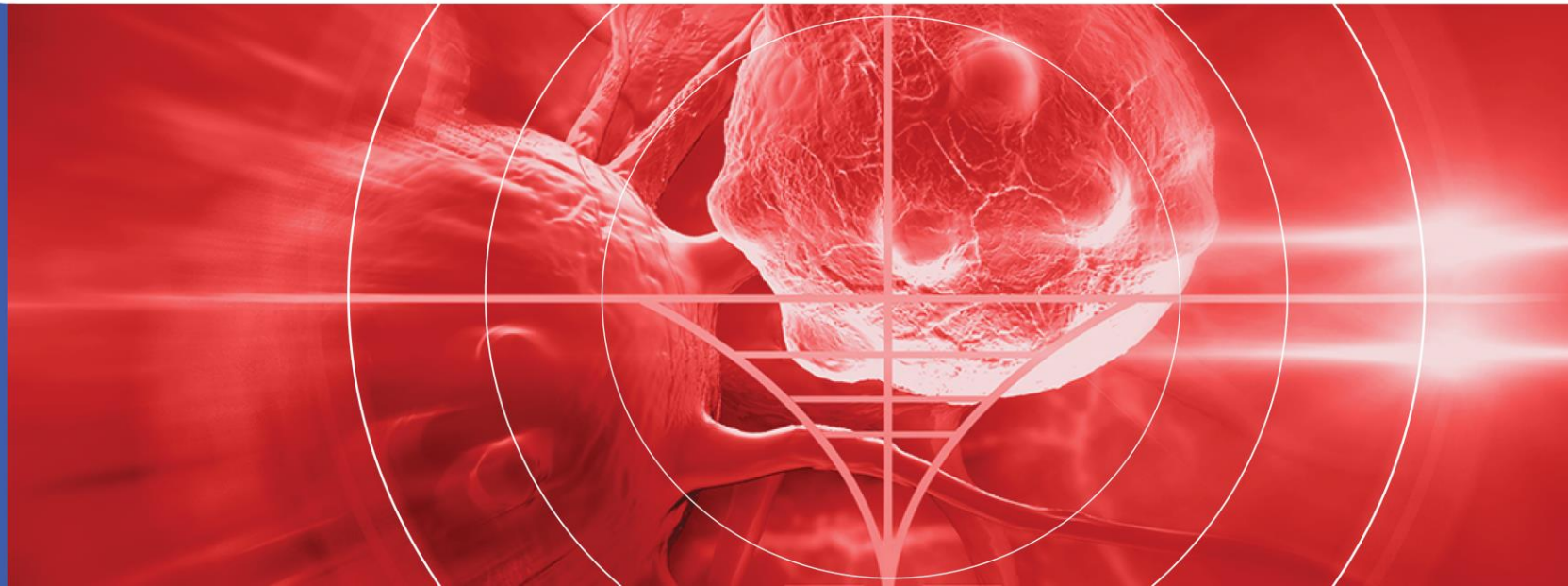
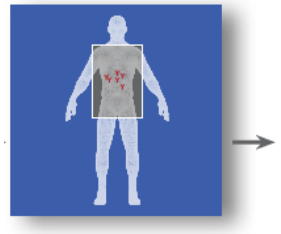


MANUFACTURING PROCESS OVERVIEW

Patient Screening
(HLA-A201 and NY-ESO-1 Antigen)



Clinical sites across the globe
Fully closed system
8-10 day release testing

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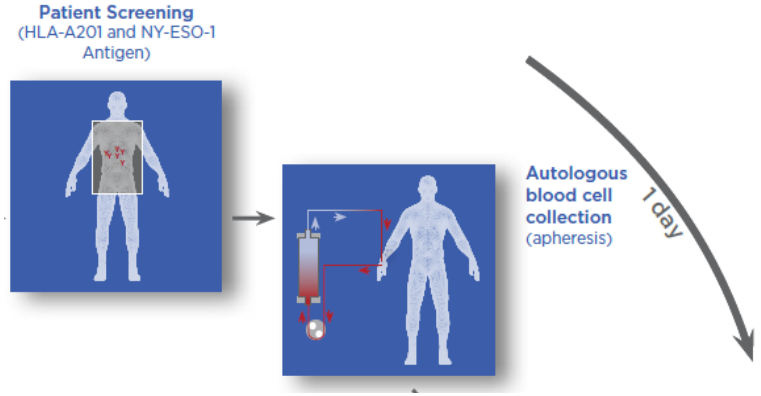
MANUFACTURING PROCESS OVERVIEW



Clinical sites across the globe
Fully closed system
8-10 day release testing

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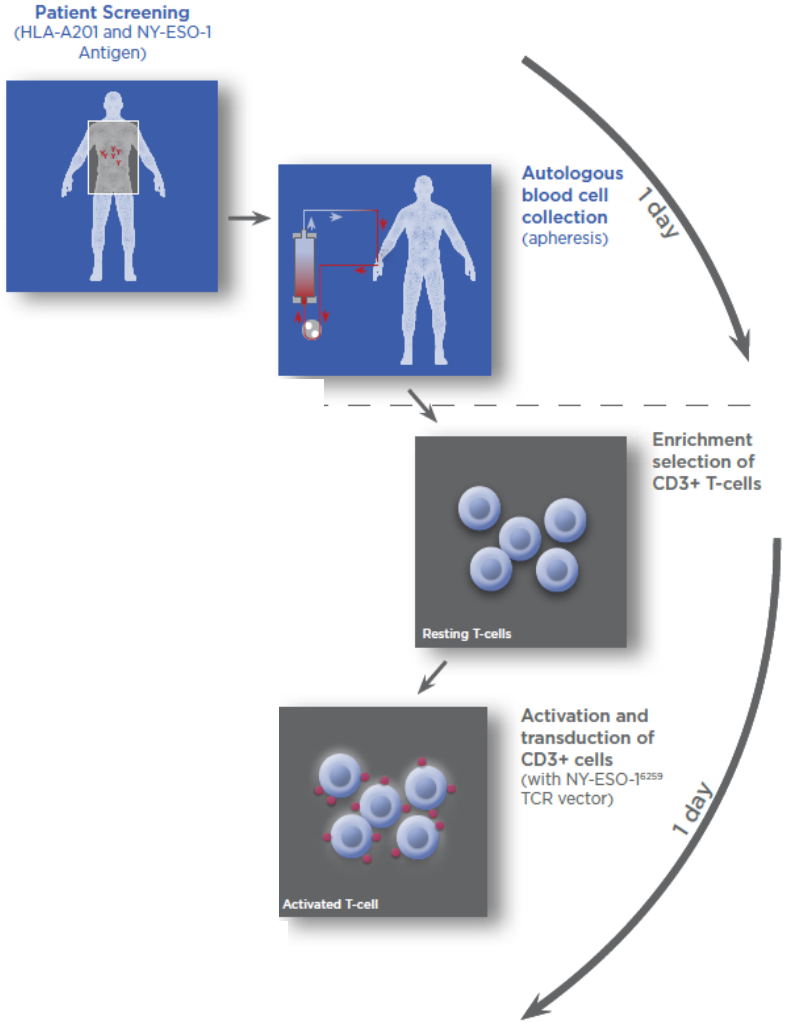
MANUFACTURING PROCESS OVERVIEW



Clinical sites across the globe
Fully closed system
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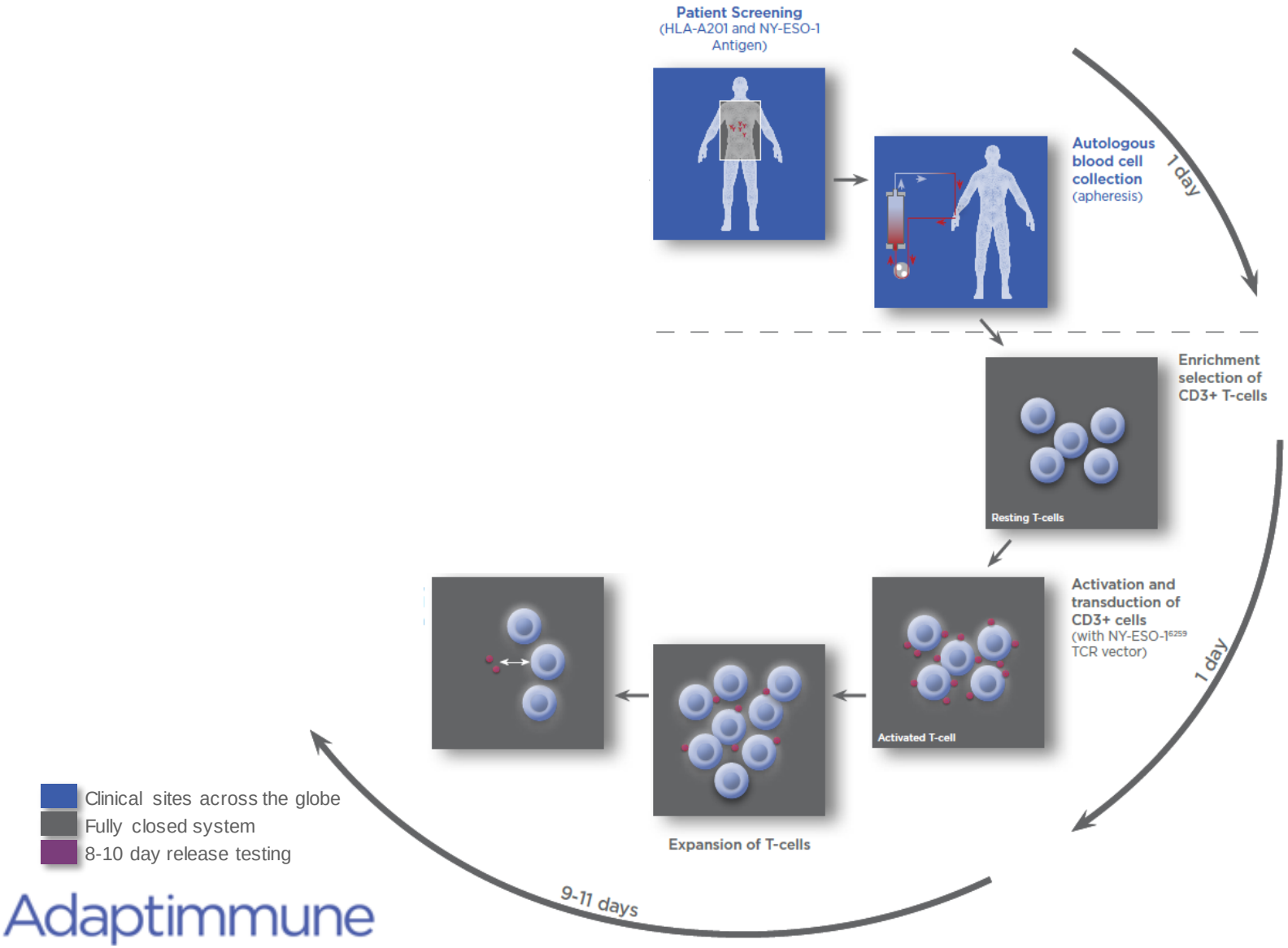
MANUFACTURING PROCESS OVERVIEW



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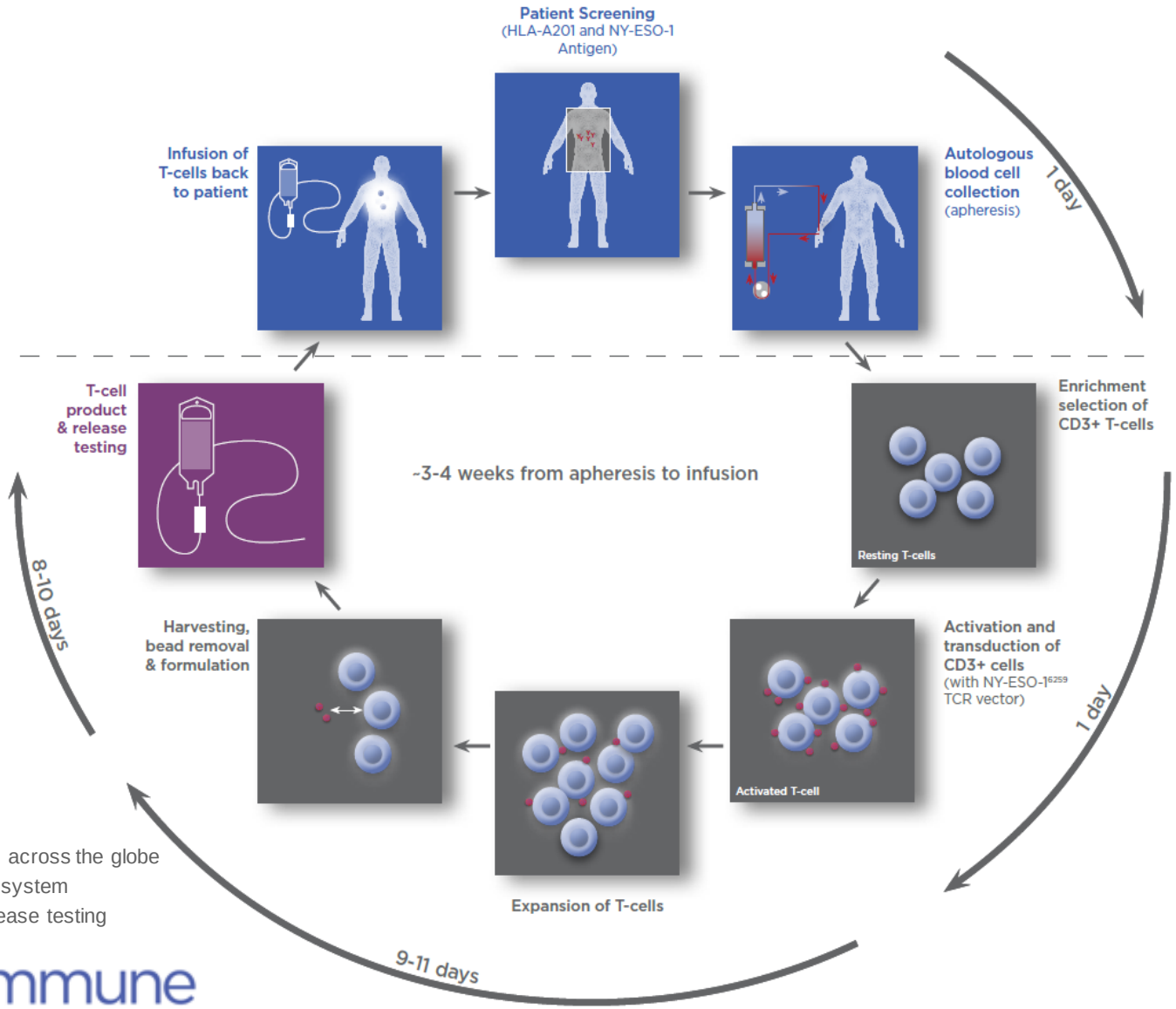
MANUFACTURING PROCESS OVERVIEW



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TRANSFORMING T CELL THERAPY

CONTINUUM OF MANUFACTURING PROCESS DEVELOPMENT

INITIALLY DEVELOPED AT UNIVERSITY OF PENNSYLVANIA*

		Academic process
Cell	Commercial expansion method	√
	Fully closed system	
	Industry standard Good Manufacturing Practices	
	Contract manufacturer – fully controlled and owned process	
	Freeze both ends	
	Wholly owned facility	
	Automation of some process steps	
	Automation of most / all process steps	
Vector	Academic vector backbone	√
	Academic vector production – fixed scale	√
	Proprietary vector backbone	
	Proprietary vector production - fixed scale	
	Fully scalable vector production	

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2006

*Levine et al, J Immunol, 1997

CONTINUUM OF MANUFACTURING PROCESS DEVELOPMENT

BROUGHT IN HOUSE IN 2013 – MINIMAL CHANGES WITH GREATER CONTROL

		Academic process	Adaptimmune process
Cell	Commercial expansion method	√	√
	Fully closed system		√
	Industry standard Good Manufacturing Practices		√
	Contract manufacturer – fully controlled and owned process		√
	Freeze both ends		
	Wholly owned facility		
	Automation of some process steps		
	Automation of most / all process steps		
Vector	Academic vector backbone	√	√
	Academic vector production – fixed scale	√	√
	Proprietary vector backbone		
	Proprietary vector production - fixed scale		
	Fully scalable vector production		
		2006	***2013***

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TRANSFORMING T CELL THERAPY

CONTINUUM OF MANUFACTURING PROCESS DEVELOPMENT

OPTIMIZED FOR COMMERCIAL USE AND OPENING A COMMERCIAL FACILITY

		Academic process	Adaptimmune process	Commercial ready process
Cell	Commercial expansion method	√	√	√
	Fully closed system		√	√
	Industry standard Good Manufacturing Practices		√	√
	Contract manufacturer – fully controlled and owned process		√	√
	Freeze both ends			√
	Wholly owned facility			√
	Automation of some process steps			√
	Automation of most / all process steps			
Vector	Academic vector backbone	√	√	
	Academic vector production – fixed scale	√	√	
	Proprietary vector backbone			√
	Proprietary vector production - fixed scale			√
	Fully scalable vector production			
		2006	***2013***	***2016 - 2017***

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TRANSFORMING T CELL THERAPY

CONTINUUM OF MANUFACTURING PROCESS DEVELOPMENT

NEXT GENERATION IMPROVEMENTS UNDERWAY

		Academic process	Adaptimmune process	Commercial ready process	Next generation process
Cell	Commercial expansion method	√	√	√	√
	Fully closed system		√	√	√
	Industry standard Good Manufacturing Practices		√	√	√
	Contract manufacturer – fully controlled and owned process		√	√	√
	Freeze both ends			√	√
	Wholly owned facility			√	√
	Automation of some process steps			√	√
	Automation of most / all process steps				√
Vector	Academic vector backbone	√	√		
	Academic vector production – fixed scale	√	√		
	Proprietary vector backbone			√	√
	Proprietary vector production - fixed scale			√	
	Fully scalable vector production				√
		2006	***2013***	***2016 - 2017***	***2018***

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TRANSFORMING T CELL THERAPY

KEY OBJECTIVES OF *EX VIVO* T CELL MANUFACTURING

- Select the right T cells for anti-tumor efficacy
- Gene modify and activate / rejuvenate these T cells to generate potency
- Expand these T cells to meet the target dose for patients
- Build in manufacturing flexibility – freeze the product at both ends

Adaptimmune's manufacturing meets these objectives

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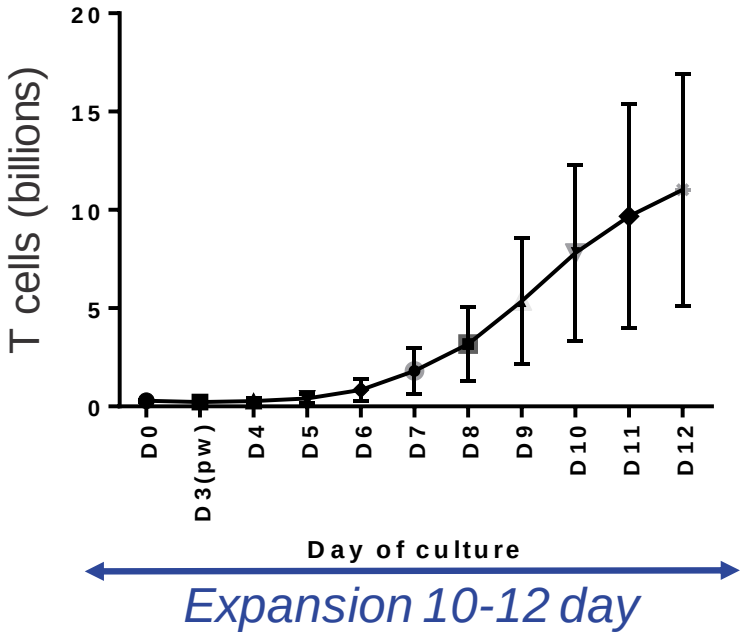
TRANSFORMING T CELL THERAPY

ABILITY TO EXPAND THE T CELLS TO DELIVER REQUIRED DOSE

T CELLS EXPANDED ON AVERAGE 40-FOLD IN EX VIVO CULTURE



- Minimizes vector usage at culture start (cost of goods reduction)
- Apheresis always yields sufficient cells for manufacture
- Target patient dose routinely achieved

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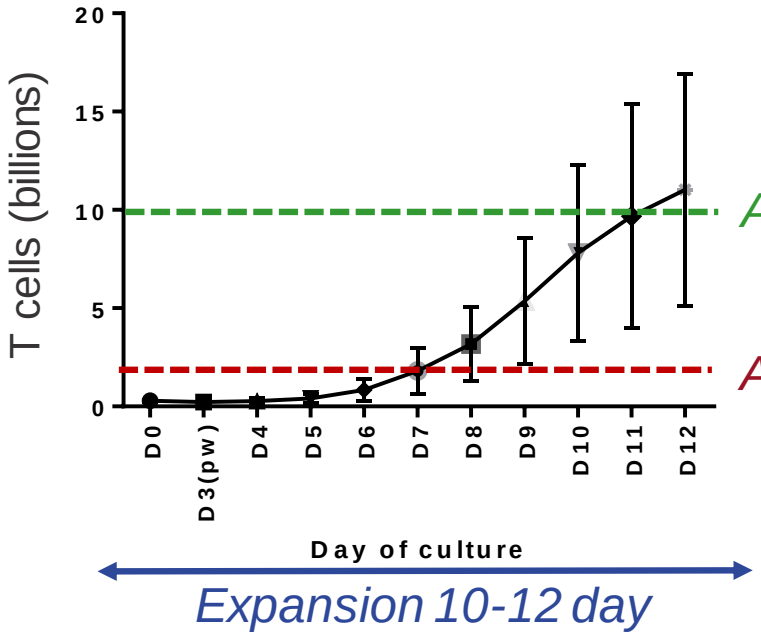
TRANSFORMING T CELL THERAPY

ABILITY TO EXPAND THE T CELLS TO DELIVER REQUIRED DOSE

ROUTINELY MEETS REQUIRED PATIENT DOSE



*Approximate target dose**

*Approximate minimum dose**

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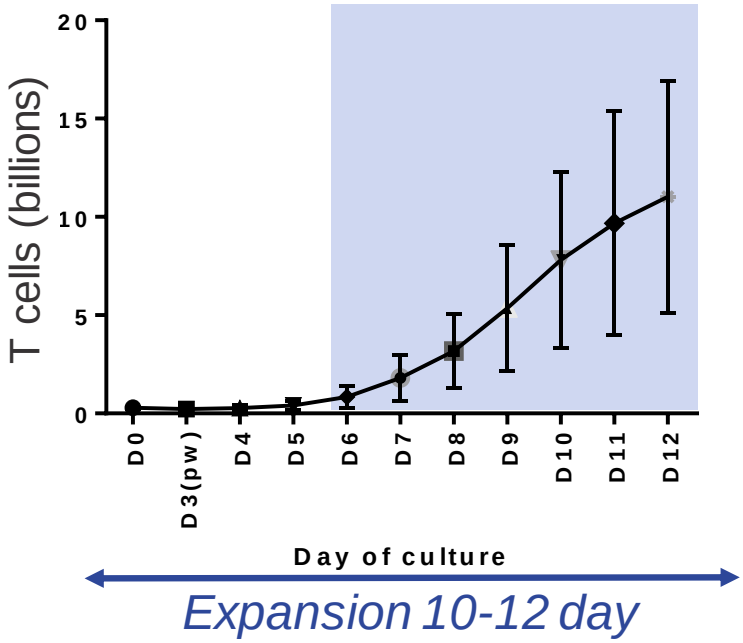
** dependent on frequency of gene transduction – typically ~50%*

ABILITY TO EXPAND THE T CELLS TO DELIVER REQUIRED DOSE

CULTURE BEYOND 6 DAYS REQUIRED TO ACHIEVE ADEQUATE PRODUCT



The majority of expansion occurs day 6-12

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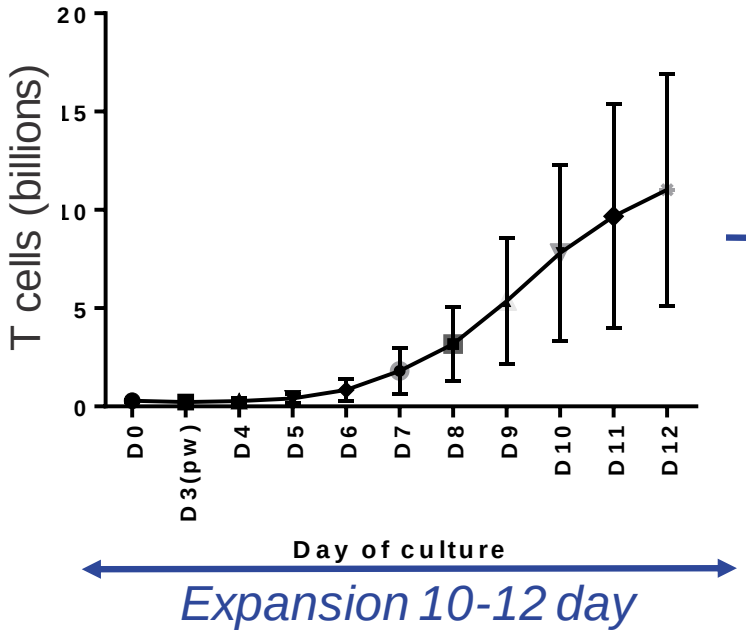
ABILITY TO EXPAND THE T CELLS TO DELIVER REQUIRED DOSE

RELEASE TESTING – AN IMPORTANT SAFETY REQUIREMENT



\+ ⟷ *Release testing (10 day)* = 20-22 days vein to vein

All engineered T cell therapy products are required to undergo post production release testing

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TRANSFORMING T CELL THERAPY

THE METHOD OF T CELL MANUFACTURING IS IMPORTANT

NOT ALL METHODS ARE EQUAL

- T cells are expanded through triggering of the TCR and provision of a second signal (to overcome peripheral tolerance mechanisms)

- Original manufacturing method – used in academic studies
  - Anti-CD3 (TCR signal) antibody (OKT-3) with IL-2*
  - Exogenous feeder cells often added to improve expansion (co-stimulation)**

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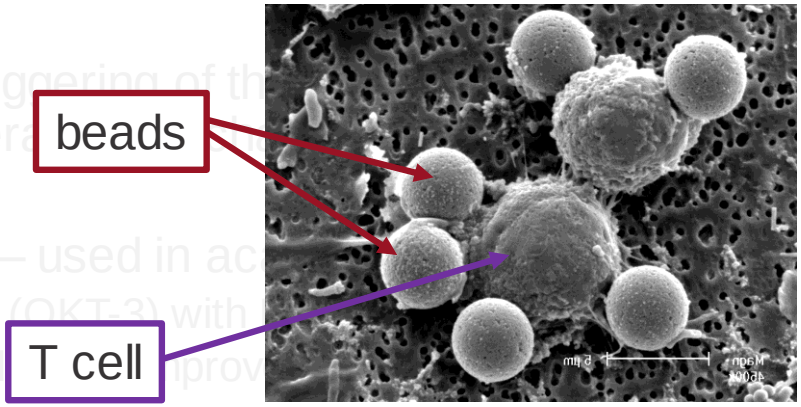
TRANSFORMING T CELL THERAPY

* Better et al, 2014 ASCO abstract #3079 (Kite)
** Morgan et al, Science, 2006; Riddell and Greenberg, J Immunol Meth (1990)

MANUFACTURING THE BEST T CELLS

METHODS OF MANUFACTURING



Dynabeads® CD3/CD28 reagent**

- Commercial method:
  - Co-ordinated activation and co-stimulation through CD3 and CD28 ligation*
  - Magnetic beads bound to anti-CD3 and CD28 antibodies - easy to add and remove
  - Good safety record to date – hundreds of patients treated**
  - Used by Novartis under exclusive license for CAR-T***

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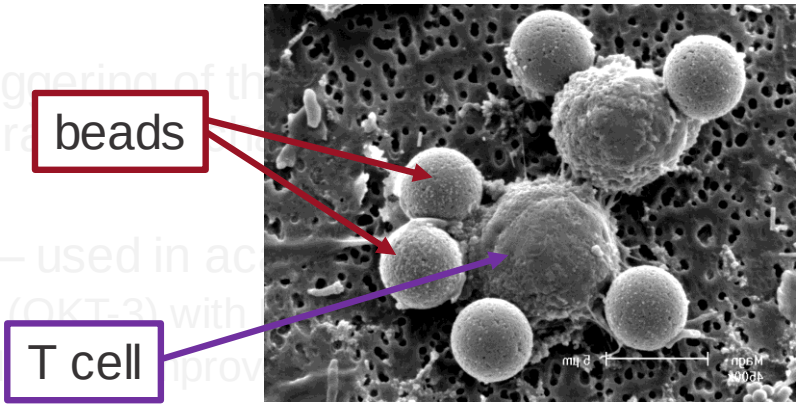
TRANSFORMING T CELL THERAPY

* Levine et al, J Immunol, 1997
** source: internal
*** source: Thermo Fisher website

MANUFACTURING THE BEST T CELLS

METHODS OF MANUFACTURING



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  - Magnetic beads bound to anti-CD3 and CD28 antibodies - easy to add and remove
  - Good safety record to date – hundreds of patients treated**
  - Used by Novartis under exclusive license for CAR-T***
  - Patented IP exclusively licensed to Adaptimmune for TCR engineered T cell therapy
  - De-risks regulatory path to licensure - all of our clinical data has been generated using this process
  - Supports positive selection for CD4 and CD8 T cells

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TRANSFORMING T CELL THERAPY

* Levine et al, J Immunol, 1997
** source: internal
*** source: Thermo Fisher website

MANUFACTURING THE BEST T CELLS

THE IMPORTANCE OF T CELL ACTIVATION WITH CO-STIMULATION

Benefits of the CD3/28 method (compared to anti-CD3 with IL-2)

- Have a higher telomerase activity
- Are younger (cells express the CD27+ and CD28+ markers)
- Have longer telomeres and greater replicative potential
- Have more of a central memory profile
- Have lower levels of senescence

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Source: Better et al, 2014 ASCO abstract #3079 (Kite); Weng et al, JExpMed (1996)); Hamann et al, J Exp Med (1997); and Azuma, Phillips and Lanier, J Immunol (1993); Barrett et al, Cytotherapy (2014)

MANUFACTURING THE BEST T CELLS

THE BENEFITS OF SIMULTANEOUS STIMULATION AND CO-STIMULATION

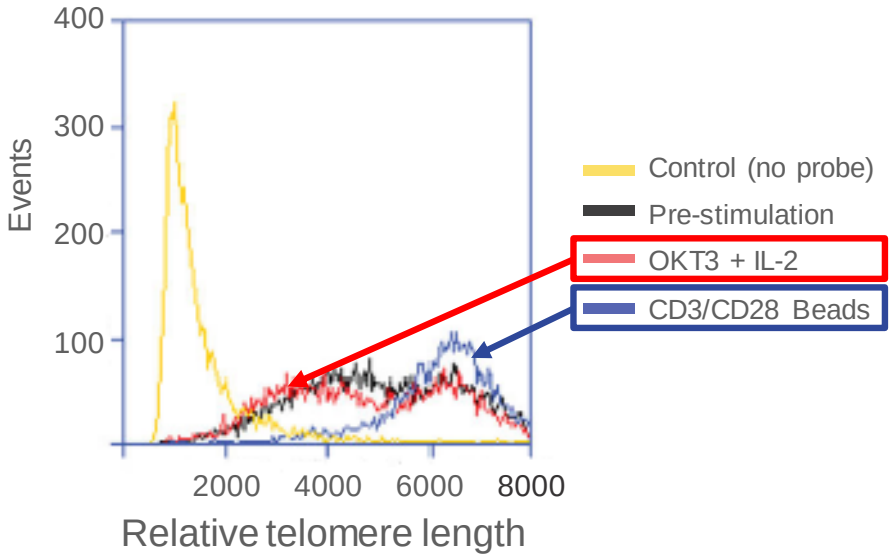
	CD45RO+/CD62L+	CD27+/CD28+
OKT3+IL-2*	30% +/- 2	31% +/- 1
CD3/CD28	76% +/- 4 *	81% +/- 6 *

Markers of central memory

Markers of T cell youth

Adaptimmune process

Adaptimmune process (CD3/CD28 beads) significantly increases telomere length vs OKT3+IL-2



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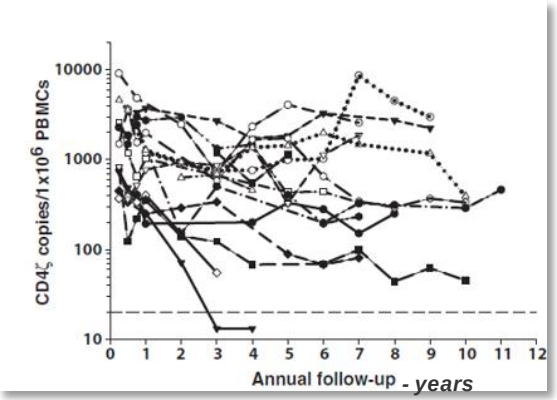
Data from: Barrett et al, Cytotherapy 2014
*method reported in Better et al, 2014 ASCO abstract #3079

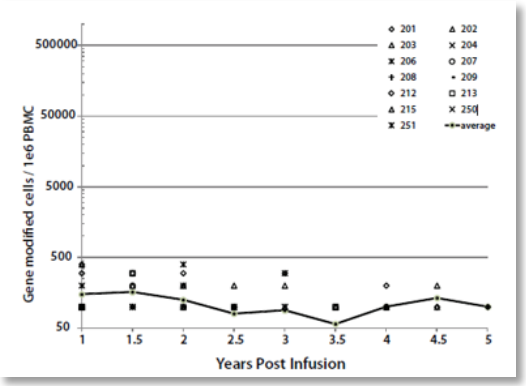
MANUFACTURING THE BEST T CELLS

CD3/CD28 BEAD METHOD PRODUCES LONG TERM PERSISTING T CELLS

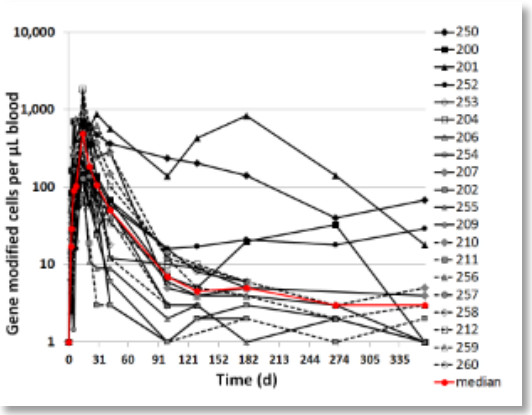
CAR and TCR products associated with long term persistence use this technology; some examples…



Scholler



Tebas



Rapoport
(Adaptimmune data)

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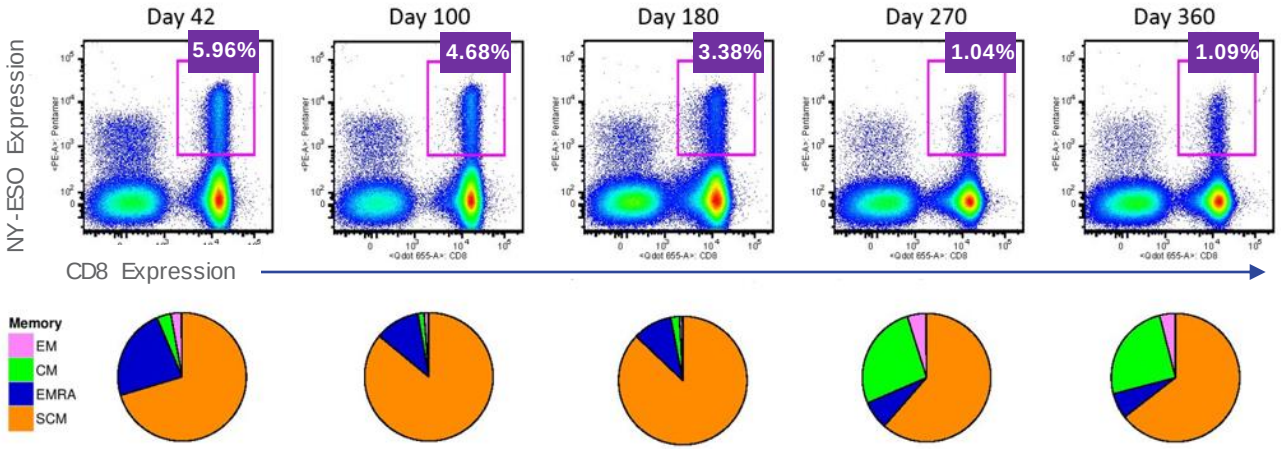
TRANSFORMING T CELL THERAPY

Source: Scholler et al, Mol Ther (2013); Tebas et al, Blood (2013); Rapoport et al, Nat Med (2015); Porter et al, STM (2015)

MANUFACTURING THE BEST T CELLS

CDC3/CD28 METHOD PRODUCES LONG TERM PERSISTING T CELLS



- Long term expression of the TCR – no gene silencing
- Programming of central memory and stem central memory cells which are associated with enhanced antitumor responses

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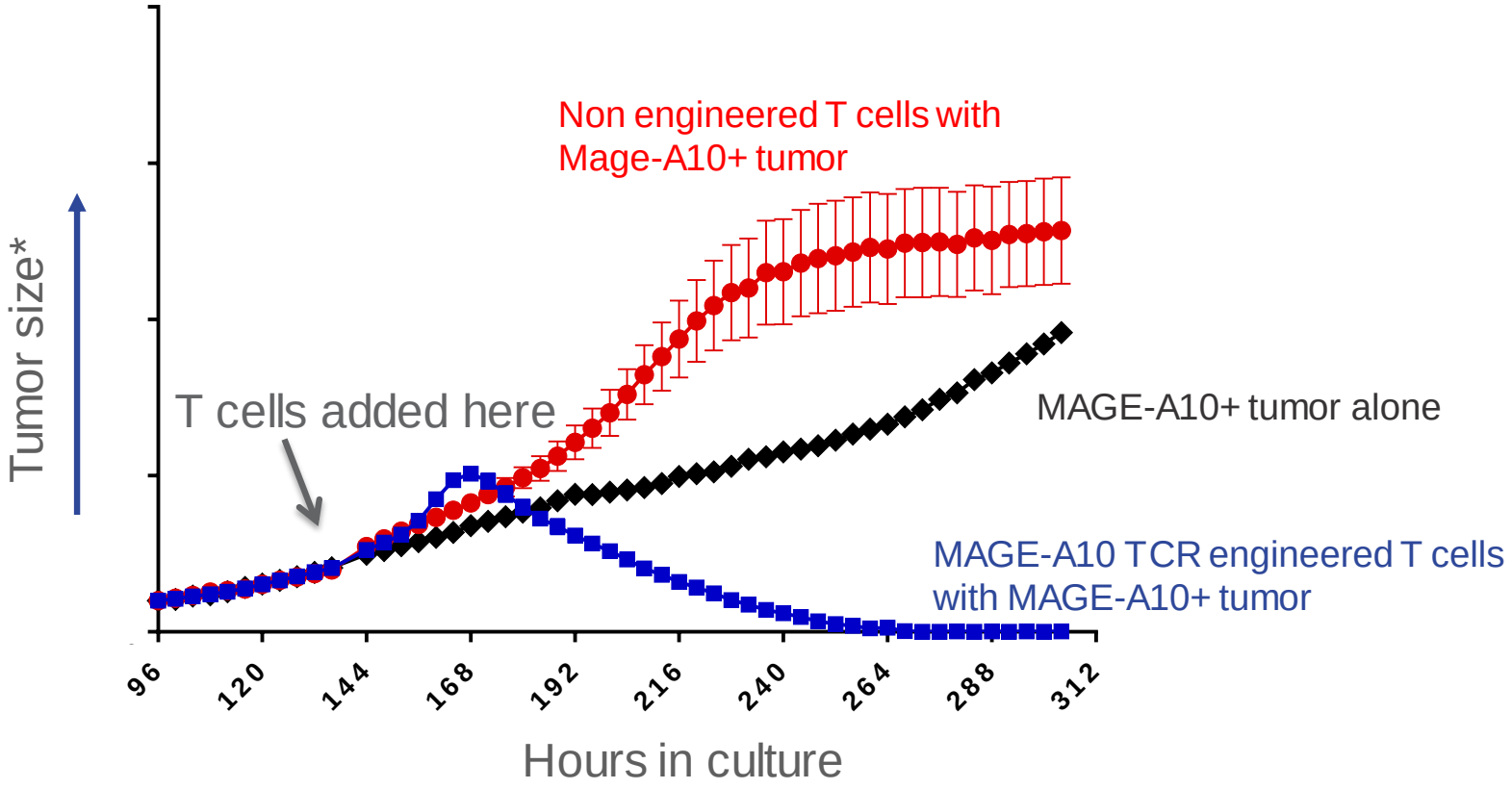
Source: Gattinoni et al, Nat Med, 2011

MANUFACTURED T CELLS ARE HIGHLY POTENT

ANTIGEN-SPECIFIC KILLING IN A THREE DIMENSIONAL TUMOR MODEL



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*GFP positive tumor – tumor size is measured by taking the average GFP fluorescence in the whole well; addition of T cells increases tumor size because they infiltrate the tumor

MEETING CLINICAL SUPPLY

EXPERIENCED, INDUSTRY-LEADING CONTRACT MANUFACTURERS

PCT (Allendale, NJ)

- >20,000 products made treating >6,000 patients
- 16 years of operation
- US and EU supply possible
- Dedicated space allocated for Adaptimmune

MaSTherCell (Gosselies, BE)

- Authorized by AFMPS in 2013
- Acquired by Orgenesis in 2015
- EU supply

PCT
A Caladrius Company

MaSTherCell

Working with professional non-academic CMOs; well-controlled processes, GMP trained staff, commercial quality systems

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TRANSFORMING T CELL THERAPY

Source: www.pctcaladrius.com; www.masthercell.com

MEETING COMMERCIAL SUPPLY

DEDICATED MANUFACTURING PLANT – OPENING EARLY 2017

- Located in the Philadelphia Navy Yard Biotechnology Park
- 10 minutes from the Philadelphia Airport; ideal for product logistics

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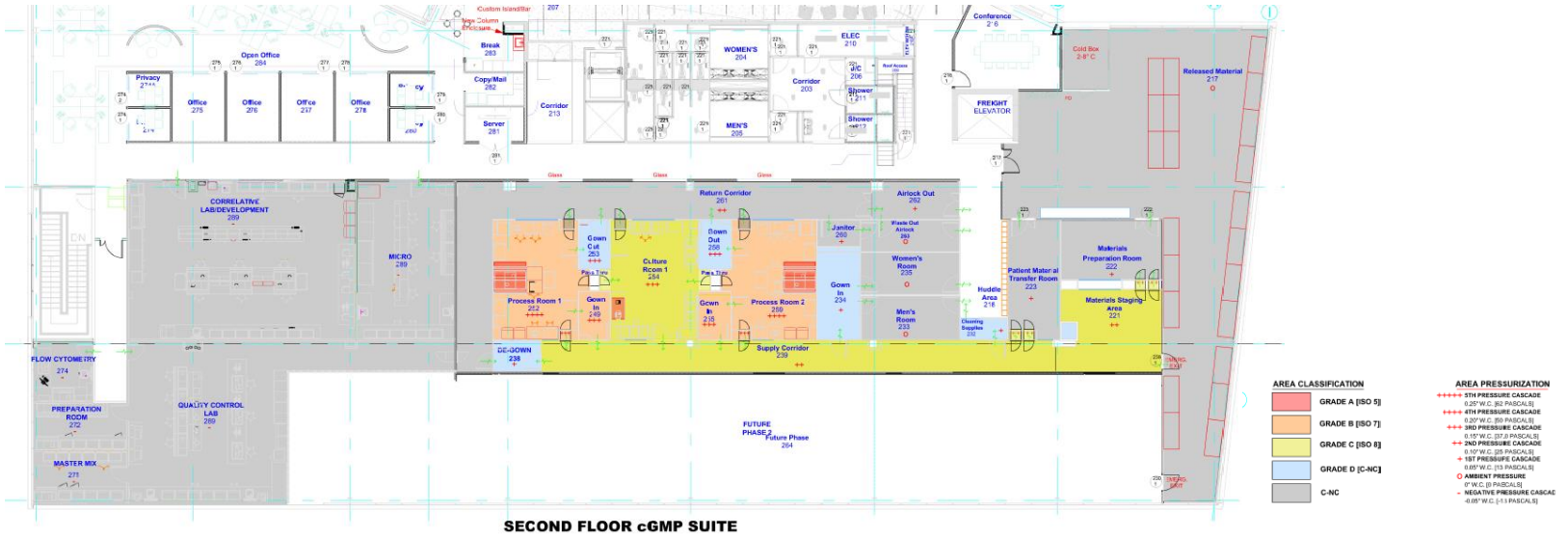
MEETING COMMERCIAL SUPPLY

DEDICATED MANUFACTURING PLANT



SECOND FLOOR cGMP SUITE

- Potential for up to 1,200 patients per year
- Build in a module fashion (3 planned, one shown here)
- Option to bring vector manufacture in-house

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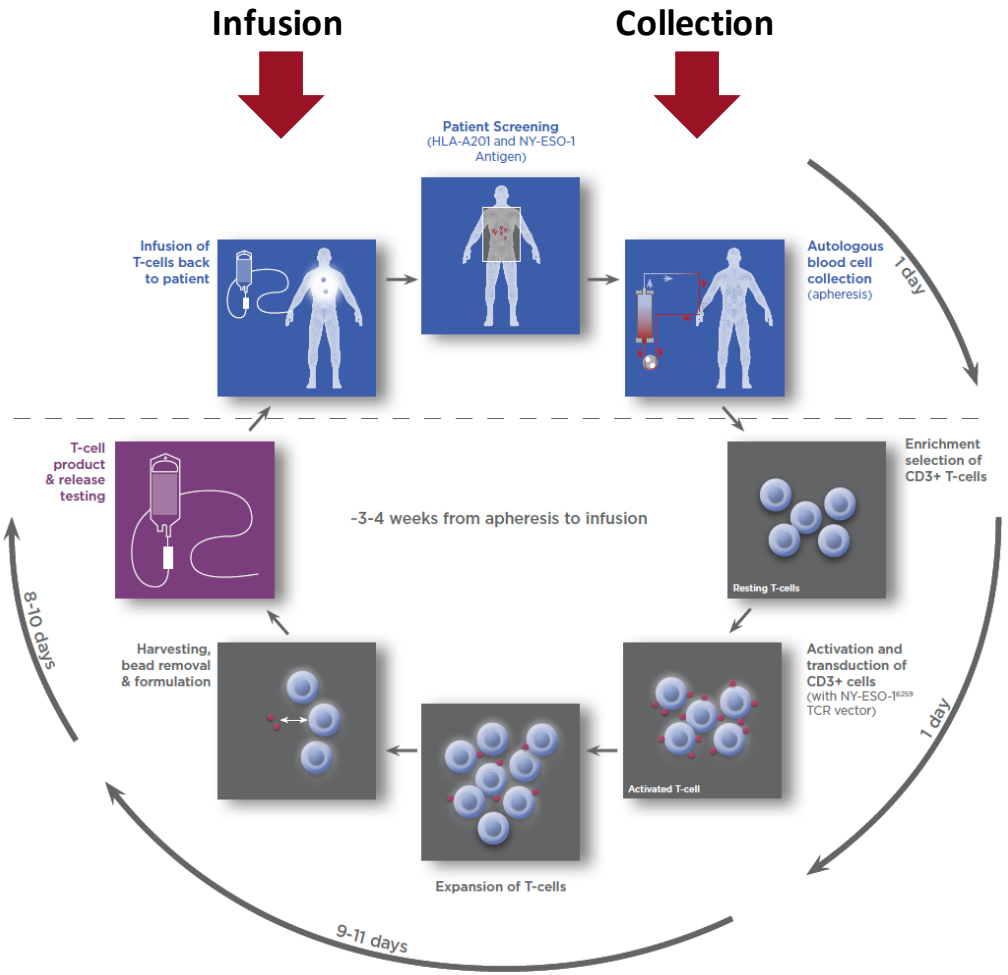
TRANSFORMING T CELL THERAPY

PROCESS OVERVIEW

KEY PROCESS ELEMENTS TO SUPPORT COMMERCIAL DELIVERY

Freeze at both ends enables flexible manufacturing scheduling



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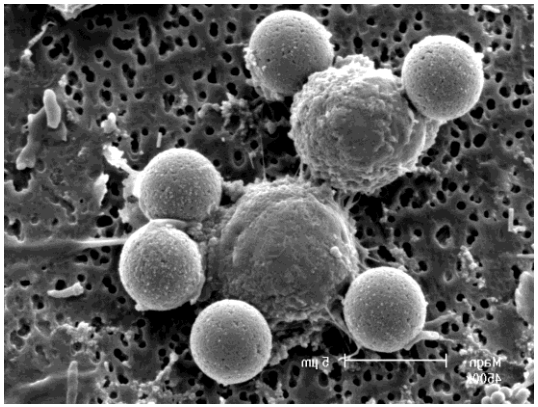
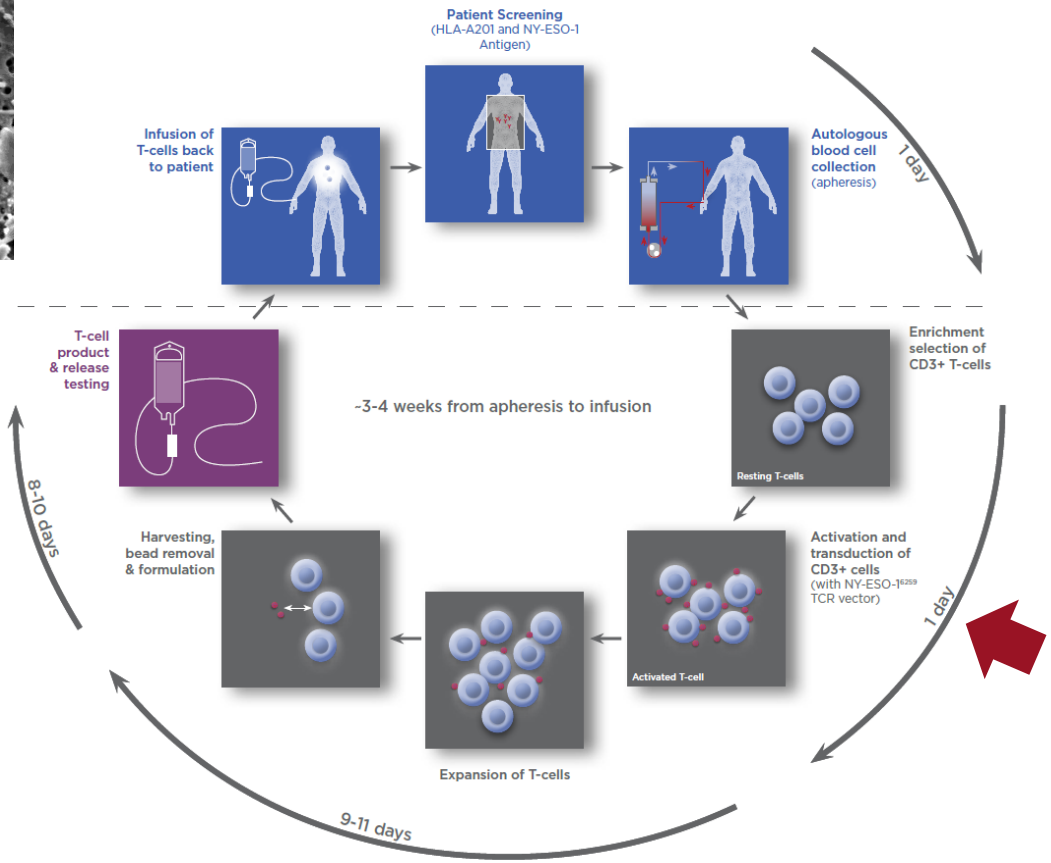
PROCESS OVERVIEW

KEY PROCESS ELEMENTS TO SUPPORT COMMERCIAL DELIVERY

Positive selection of T cells





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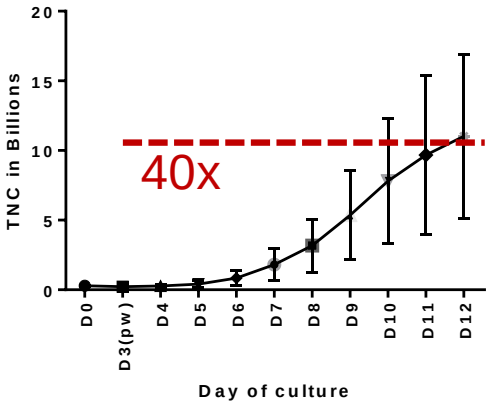
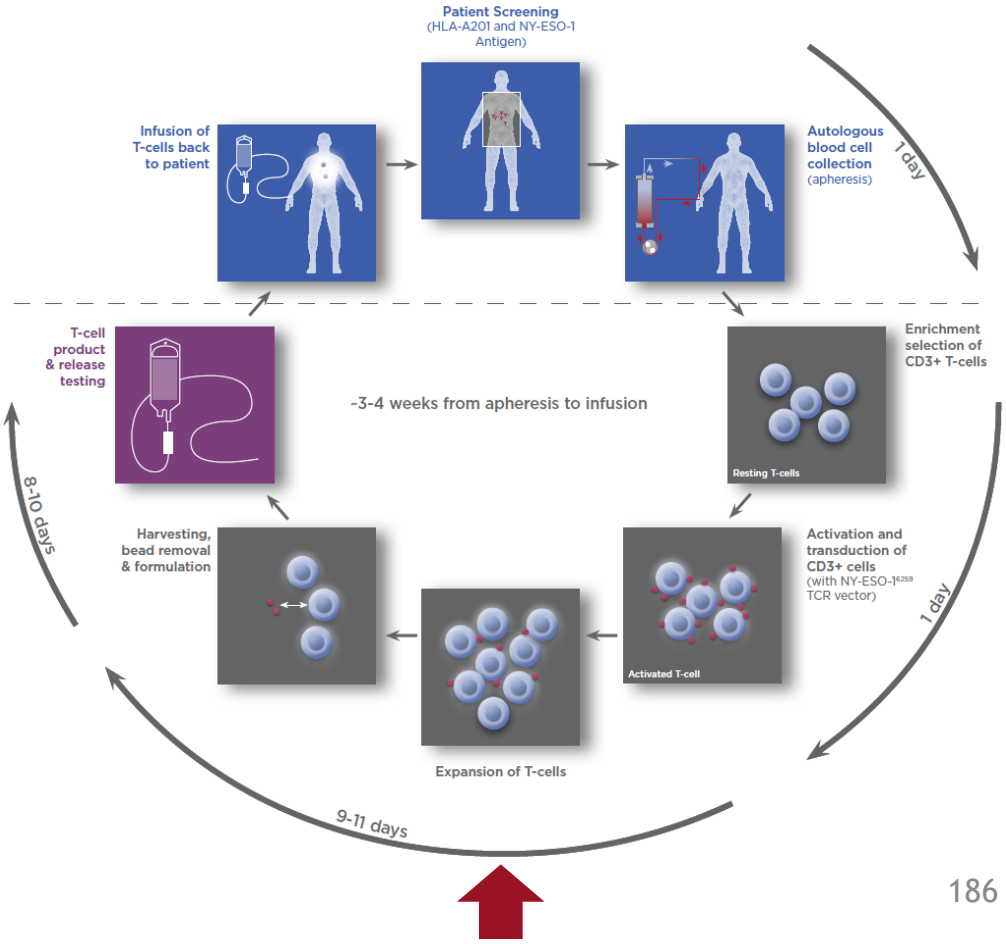
PROCESS OVERVIEW

KEY PROCESS ELEMENTS TO SUPPORT COMMERCIAL DELIVERY

Robust Expansion





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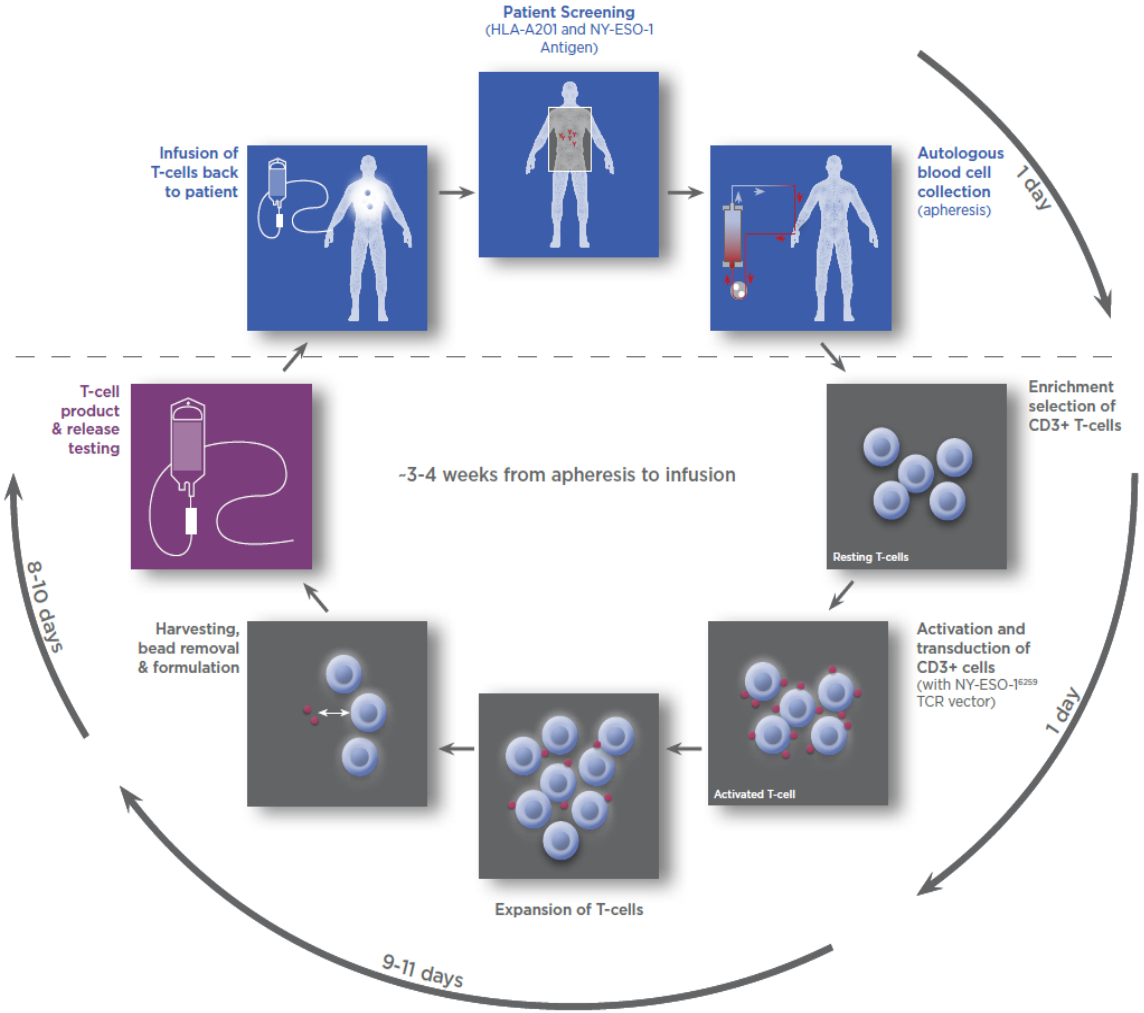
PROCESS OVERVIEW

KEY PROCESS ELEMENTS TO SUPPORT COMMERCIAL DELIVERY



FULLY CLOSED CELL MANUFACTURING PROCESS

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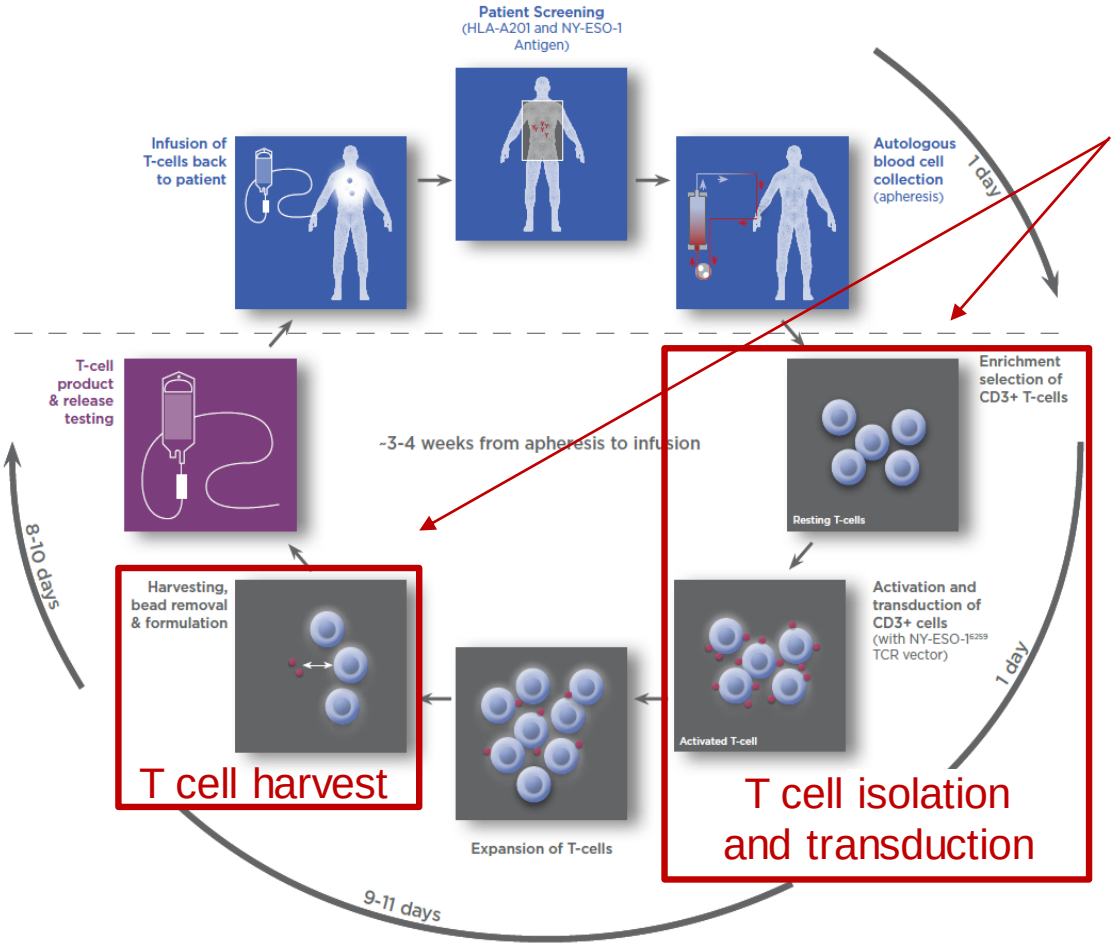
INCORPORATING AUTOMATION IN THE CELL PROCESS

REDUCES COST AND PROMOTES CONSISTENCY



- Automate most complex steps
- Retain flexibility in any automation plan, as the process will evolve with emerging scientific findings

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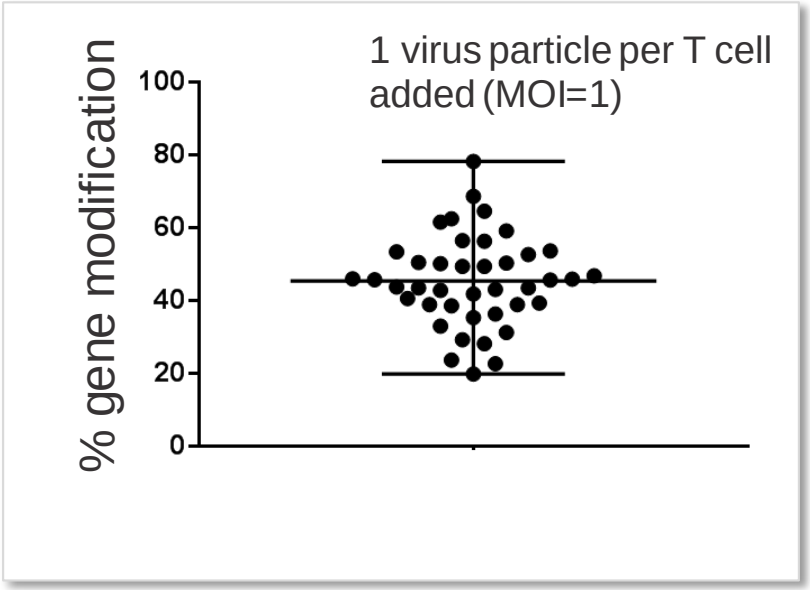
OPTIMIZING TRANSFER OF TCR TO THE CELLS

LENTIVIRAL VECTOR EFFICIENTLY DELIVERS TCR TO T CELLS

- Well established safety profile in T cells – no cases of insertional oncogenesis
- Efficient transduction at low vector input per cell (multiplicity of infection of 1 unit per cell)
- Optimized backbone for safety – WPRE removed to reduce perceived safety risks



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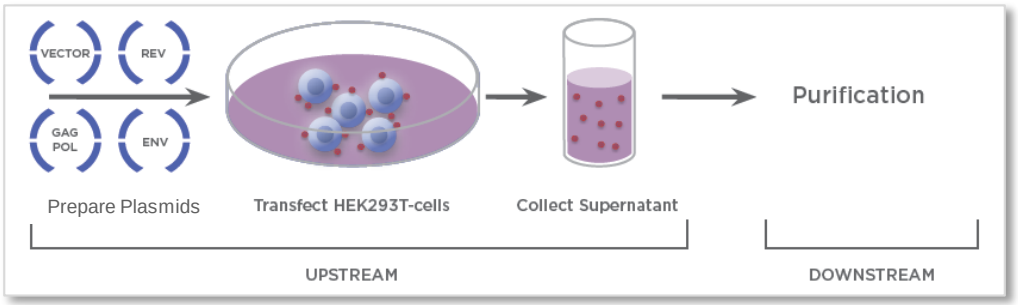
Source: Kingsman, Mitrophanous, Olsen, Gene Therapy 2005

MEETING LENTIVIRAL VECTOR COMMERCIAL SUPPLY

CURRENT PROCESS IS COMMERCIAL READY; OPTIMIZATION ONGOING

- Development of proprietary process for initial commercial supply
  - Optimized backbones for transfer vector and packaging plasmids
  - Developed upstream and downstream production methods



- Dedicated process development group to maximize production yield
  - Adapt this process to scalable bioreactors
  - Establish a packaging cell line to enable continuous production in bioreactors

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BRINGING IT ALL TOGETHER FOR COMMERCIAL DELIVERY

		2006 Academic process	2013 Adaptimmune process	2016 Commercial ready process
Cell	Commercial expansion method	√	√	√
	Fully closed system		√	√
	Industry standard Good Manufacturing Practices		√	√
	Contract manufacturer – fully controlled and owned process		√	√
	Freeze both ends			√
	Wholly owned facility			√
	Automation of some process steps			√
	Automation of most / all process steps			
Vector	Academic vector backbone	√	√	
	Academic vector production – fixed scale	√	√	
	Proprietary vector backbone			√
	Proprietary vector production - fixed scale			√
	Fully scalable vector production			

√

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ADAPTIMMUNE MANUFACTURING SUMMARY

NOT ALL T CELL MANUFACTURING METHODS ARE EQUAL

- Proprietary T cell expansion method
  - Produces young, potent, persistent cells
  - Routinely meets required patient doses
- Commercial ready process in place
  - Fully closed
  - No significant changes since initial trials – de-risks regulatory path
- Supply in place
  - US and EU contract manufacturers in place
  - Dedicated manufacturing plant opening in 2017

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ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

CONCLUSION

James Noble
Chief Executive Officer, Adaptimmune

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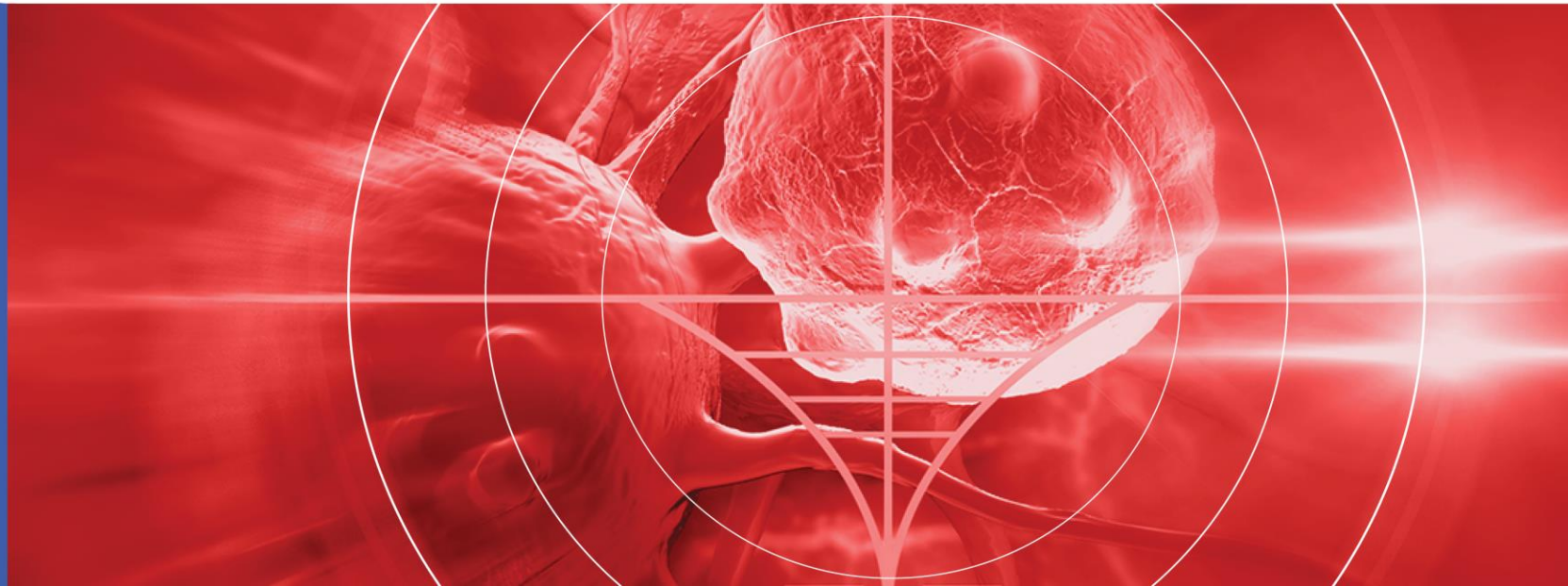

ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

- Proprietary SPEAR T cell technology uniquely delivers:
  - Correctly identified targets
  - Specificity and optimal affinity
  - "Supra-natural" TCRs to accelerate programs
  - Enhanced effectiveness of TCRs: Generation 2 and 3
- No other company can currently deliver all of these

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TRANSFORMING T CELL THERAPY

ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

- Proprietary SPEAR T cell technology uniquely delivers:
  - Correctly identified targets
    - Mass spectrometry critical
  - Specificity and optimal affinity
    - Adaptimmune platform finds window of safety and cross reactivity for each TCR
  - "Supra-natural" TCRs to accelerate programs
    - Numerous parental TCRs derived from libraries lead to multiple INDs
  - Enhanced effectiveness of TCRs: Generation 2 and 3
    - Generation 2: Designed to overcome tumor microenvironment
    - Generation 3: Designed to induce epitope spreading and break tumor immune tolerance
- No other company can currently deliver all of these
  - New data on above presented today

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

- Multiple clinical responses in synovial sarcoma, a solid tumor
- Over 90% response rate in multiple myeloma study in conjunction with ASCT
- No other company is as far advanced as Adaptimmune in the clinic with a TCR T cell

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

- Multiple clinical responses in synovial sarcoma, a solid tumor
  - New images showing resolution of large solid lesions
  - Cohort 2 suggests responses in low expressers
  - Cohort 3 suggests importance of fludarabine
  - Cohort 4 starting shortly
- Over 90% response rate in multiple myeloma study in conjunction with ASCT
  - Median overall survival of ~3 years
- No other company is as far advanced as Adaptimmune in the clinic with a TCR T cell
  - New updates presented on both diseases today
  - Pivotal studies to start in 4Q16/1Q17

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

- Company INDs open for NY-ESO, MAGE-A10 and AFP
- These TCRs all derive from Adaptimmune's proprietary technology
- No other company has routinely delivered INDs from in-house TCR platform

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

- Company INDs open for NY-ESO, MAGE-A10 and AFP
  - MAGE-A4 next IND 2017
  - Generation 2 INDs from 2017
- These TCRs all derive from Adaptimmune's proprietary technology
  - Active programs give broad coverage of tumors
- No other company has routinely delivered INDs from in-house TCR platform

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

Strong financial position

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

Strong financial position

- Total liquidity position of $248 million*
- Current capital can fund the business through mid-2018

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*As of December 31, 2015

ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

- Clear scientific leadership in the field of T cell engineering
- Most compelling clinical data in the field
- Deep pipeline across major cancers
- Strong financial position
- Proven ability to execute

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

Strong financial position

Proven ability to execute (1)

- Milestones met through April 2016
  - Expanded into autoimmune
  - Expanded strategic immunotherapy collaboration with GSK
  - Secured NY-ESO breakthrough therapy designation in synovial sarcoma
  - Secured NY-ESO orphan drug designation
  - IND opened for AFP in hepatocellular cancer

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

Strong financial position

Proven ability to execute (2)

- Manufacturing processes optimized
  - Proprietary T cell expansion method
  - Commercial-ready process in place
  - EU and US contract manufacturers in place

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ADAPTIMMUNE: LEADING THE TCR T CELL SPACE

Clear scientific leadership in the field of T cell engineering

Most compelling clinical data in the field

Deep pipeline across major cancers

Strong financial position

Proven ability to execute

Goal: first TCR T cell therapy to market

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ADAPTIMMUNE INVESTOR AND ANALYST DAY 2016

APRIL 22, 2016

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