TCR-T Therapies Using Novel Solid Cancer Targets

CAR-TCR Digital Week, Sept 14, 2020

Dr. Steffen Walter, Chief Technology Officer, Immatics

Disclaimer

This presentation ("Presentation") is provided by Immatics N.V. ("Immatics" or the "Company") for informational purposes only. The information contained herein does not purport to be all-inclusive and Immatics nor any of its affiliates nor any of its or their control persons, officers, directors, employees or representatives makes any representation or warranty, express or implied, as to the accuracy, completeness or reliability of the information contained in this Presentation. You should consult your own counsel and tax and financial advisors as to legal and related matters concerning the matters described herein, and, by accepting this presentation, you confirm that you are not relying upon the information contained herein to make any decision.

Forward-Looking Statements. Certain statements in this presentation may be considered forward-looking statements. Forward-looking statements generally relate to future events or the Company's future financial or operating performance. For example, statements concerning timing of data read-outs for product candidates, the IND filing for IMA204, IMA301, IMA401, the Company's focus on partnerships to advance its strategy, projections of future cash on hand and other metrics are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "may", "should", "expect", "intend", "will", "estimate", "anticipate", "believe", "predict", "potential" or "continue", or the negatives of these terms or variations of them or similar terminology. Such forward-looking statements are subject to risks, uncertainties, and other factors which could cause actual results to differ materially from those expressed or implied by such forward looking statements. These forward-looking statements are based upon estimates and assumptions that, while considered reasonable Immatics and its management, are inherently uncertain. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Factors that may cause actual results to differ materially from current expectations include, but are not limited to, various factors beyond management's control including general economic conditions and other risks, uncertainties and factors set forth in the Company's filings with the Securities and Exchange Commission (SEC). Nothing in this presentation should be regarded as a representation by any person that the forward-looking statements set forth herein will be achieved or that any of the contemplated results of such forward-looking statements will be achieved. You should not place undue reliance on forward-looking statements, which speak only as of the date they are made. Company undertakes no duty to update these forward-looking statements.

No Offer or Solicitation. This communication is for informational purposes only and does not constitute, or form a part of, an offer to sell or the solicitation of an offer to sell or an offer to buy or the solicitation of an offer to buy any securities, and there shall be no sale of securities, in any jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such jurisdiction. No offer of securities shall be made except by means of a prospectus meeting the requirements of Section 10 of the Securities Act of 1933, as amended, and otherwise in accordance with applicable law.

Certain information contained in this Presentation relates to or is based on studies, publications, surveys and the Company's own internal estimates and research. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while the Company believes its internal research is reliable, such research has not been verified by any independent source. This meeting and any information communicated at this meeting are strictly confidential and should not be discussed outside your organization.

Agenda

Introduction

Case study: Novel TCRs targeting COL6A3 exon 6

Summary

Agenda

Introduction

Case study: Novel TCRs targeting COL6A3 exon 6

Summary

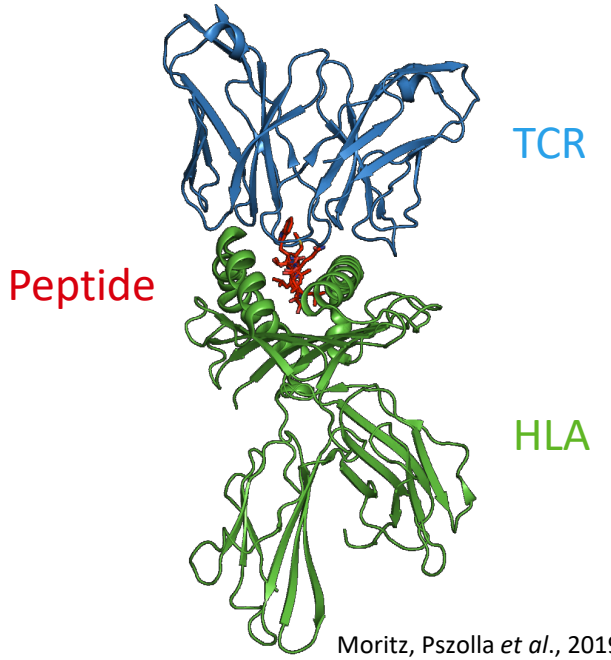
Cancer Therapy Against Peptide-HLA (pHLA) Targets

Discovering Targets beyond the Cancer Cell Surface to Unlock Immunotherapies for Solid Cancers

- mAb and CAR-T approaches target membrane-associated proteins (e.g. HER-2, EGFR, CD19/20/30, BCMA)
  - ➢ Number of surface targets is limited
- Intracellular targets are accessible via peptide-HLA
  - ➢ pHLA targets represent the entire proteome
- TCR-based approaches (TCR-T, TCR Bispecifics) address both intra- and extracellular pHLA targets
  - ➢ **TCR-based therapies exhibit an approx. 300% increased cancer target space**

Membrane-associated proteins
Potential targets for mAb, CAR-T, TCR-T and TCR Bispecifics

Intracellular proteins
Targets for TCR-T and TCR Bispecifics

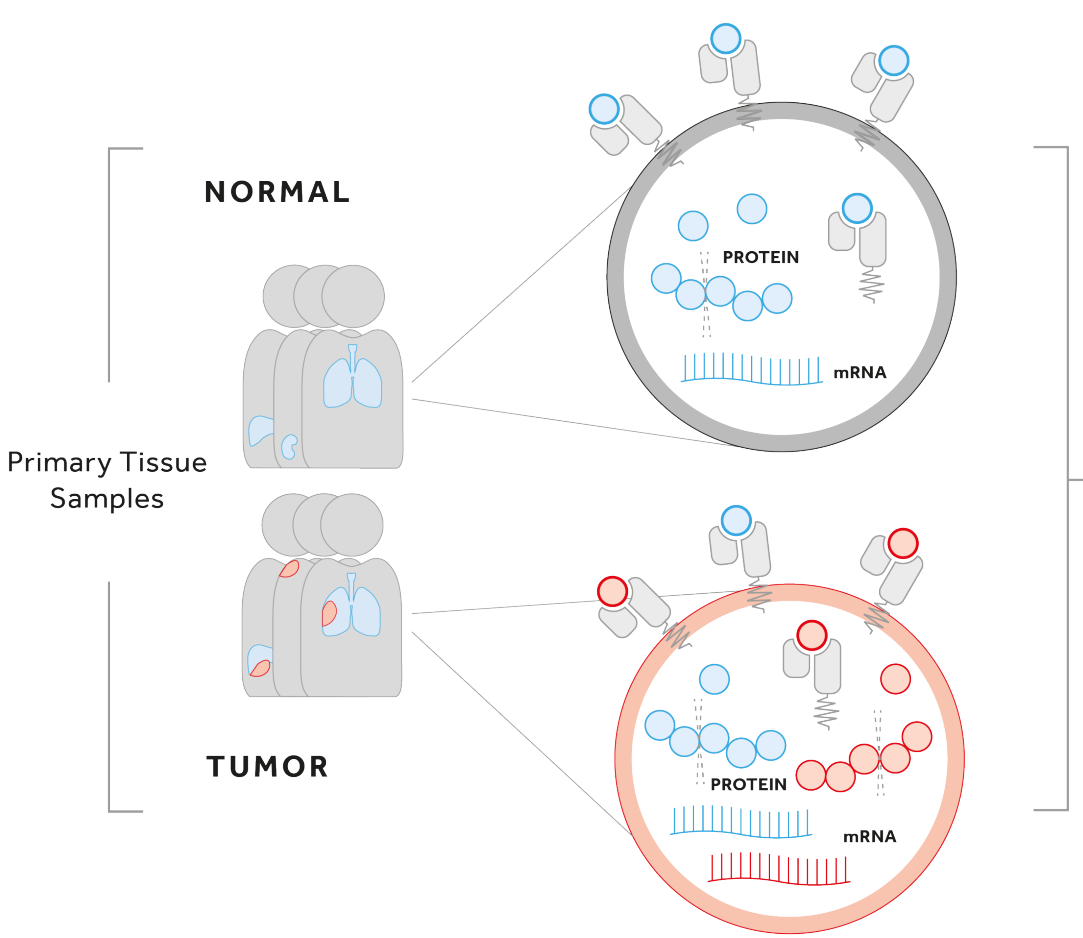


Moritz, Pszolla *et al.*, 2019

Adapted from Chandran *et al.*, 2019

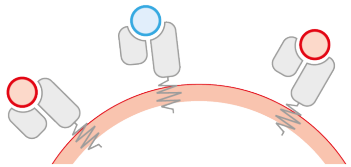
Discovery of True Cancer Targets – XPRESIDENT® Technology Platform

Highly Sensitive and Accurate High-throughput Technology



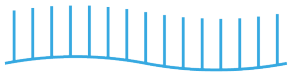
ANALYSIS

QUANTITATIVE HLA PEPTIDOMICS



LC-MS/MS
>1200 tumors
>900 normals
in-house samples

QUANTITATIVE TRANSCRIPTOMICS



RNAseq
>13000 tumors
>8000 normals
in-house samples & public databases

Large-scale HLA target Database

Target Discovery
Sensitive detection of pHLA targets at attomolar amounts

Target Validation
Absolute quantification of presented peptides (AbsQuant™)

Target Specificity
On- and off-target toxicity screening for right TCRs

Target Biomarker
qPCR-based patient and target selection for treatment personalization (IMADetect™)

Target Prediction
Artificial intelligence for highly personalized immunotherapy

Immatics publications on XPRESIDENT®
Weinschenk *et al.*, Cancer Research 2002; Walter *et al.*, Nature Medicine 2012; Yadav *et al.*, Nature 2014; Fritsche *et al.*, Proteomics 2018; Zhang *et al.*, Nature Communications, 2018; Hilf *et al.*, Nature, 2018

Discovery of True Cancer Targets – XPRESIDENT® Technology Platform

Prioritization of >200 pHLA Targets Covering All Target Classes

TARGET CLASSES

Well known and characterized parent protein e.g. MAGE family of cancer testis antigens

- Immatics' expertise: Identification of relevant target peptides → Patents and unique know-how

Unknown or poorly characterized parent protein e.g. COL6A3

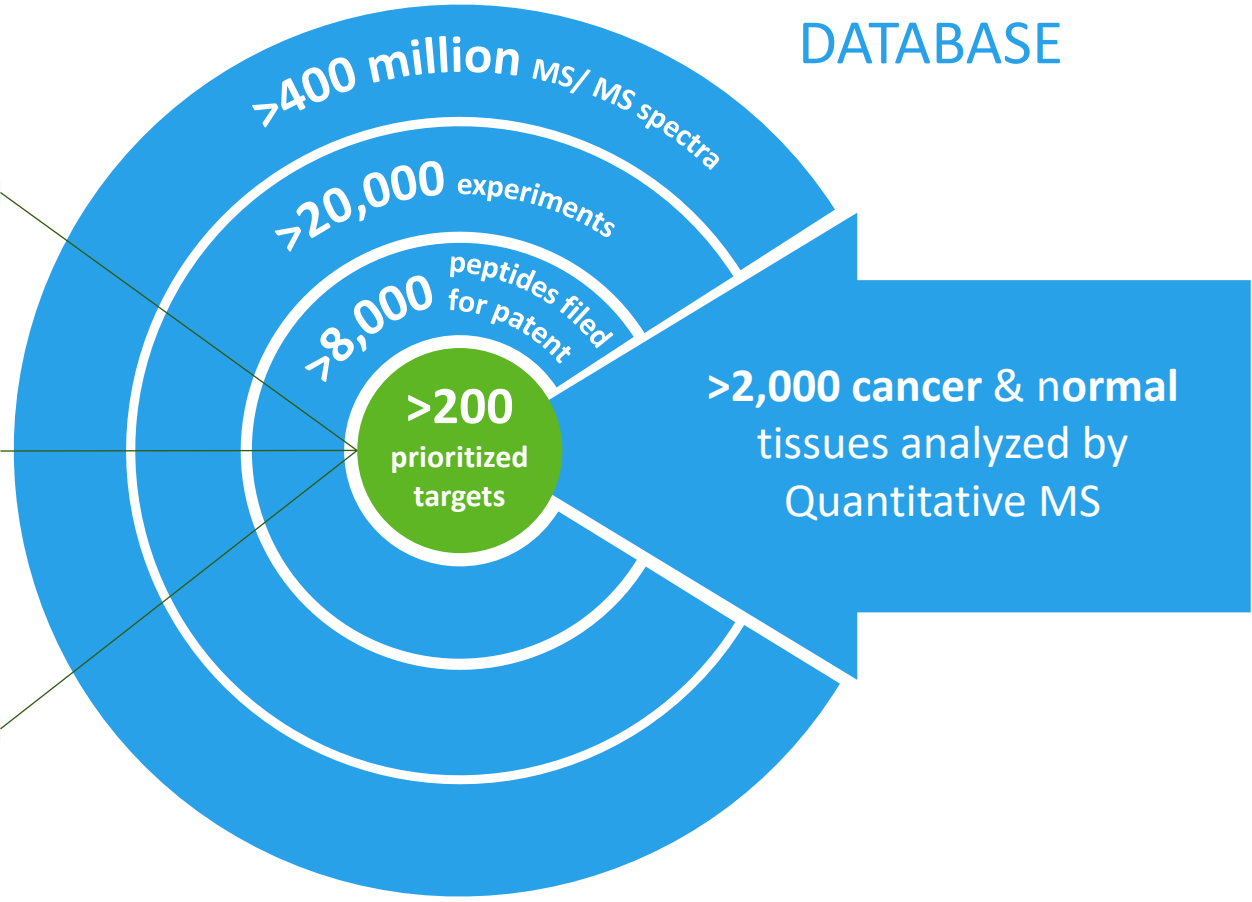
- Immatics' expertise: Identification of a new target family
- Patent protection of the actually presented peptide

Crypto-targets/ Neoantigens: Novel target class which includes RNA-edited peptides and non-classical neoantigens

- Immatics' expertise: Identification of a new target space → only accessible by Mass Spec

See: Zhang, Fritsche et al., *Nature Communications*, 2018

PRIMARY TISSUE DATABASE



Proprietary Pipeline of Adoptive Cell Therapy (ACT) & TCR Bispecifics

Developing Novel Treatments Across Two Distinct Therapeutic Modalities

Product Class	Product Candidate	Indications	Preclinical	Phase 1	Phase 2	Phase 3	Next expected Milestones
ACTengine® TCR-T	IMA201 (MAGEA4/8)	Solid cancers					Combined initial data read-out 1Q 2021
	IMA202 (MAGEA1)	Solid cancers					
	IMA203 (PRAME)	Hematological & solid cancers					
	IMA204 (COL6A3)	Solid cancers					IND filing 2021
ACTallo® γδ T cells	IMA301 (Cancer testis antigen)	Hematological & solid cancers					IND filing 2022
ACTolog®	IMA101 (Multi-target pilot trial)	Solid cancers					Topline data YE 2020
TCER™ TCR Bispecifics	IMA401 (Cancer testis antigen)	Solid cancers					IND filing YE 2021
	IMA402 (Cancer testis antigen)	Hematological & solid cancers					Lead Candidate YE 2020

Agenda

Introduction

Case study: Novel TCRs targeting COL6A3 exon 6

Summary

pHLA Target Characteristics of Immatics' ACTengine® Lead Programs

Comparison of our Frontrunner Targets to Clinically Validated NY-ESO-1

		Ongoing clinical ACTengine® trials			IND expected 2021
	NY-ESO-1[5]	**MAGEA4/A8** IMA201	**MAGEA1** IMA202	**PRAME** IMA203	**COL6A3 exon 6** IMA204
Naturally presented	Yes[1]	Yes[2]	Yes[2]	Yes[2]	Yes[2]
Specificity class[3]	1	1	1	1	2
Copy number	10-50[4]	100-1,000[2]	50-900[2]	100-1,000[2]	100-700[2]
Tumor types with significant prevalence	Synovial sarcoma (80%) Melanoma (40%) HCC (40%) …	Sq NSCLC (50%) HNSCC (35%) Bladder carcinoma (30%) Uterine carcinosarcoma (25%) Esophageal carcinoma (25%) Ovarian carcinoma (20%) Melanoma (20%) Sarcoma Subtypes (up to 80%) …	HCC (40%) Sq NSCLC (35%) Melanoma (30%) Bladder carcinoma (20%) Esophageal carcinoma (20%) HNSCC (15%) Sarcoma Subtypes (up to 30%) …	Uterine carcinoma (100%) Melanoma (95%) Ovarian carcinoma (80%) Sq NSCLC (65%) Uveal melanoma (50%) Cholangiocarcinoma (35%) Diffuse large B-cell lymphoma (30%) Breast carcinoma (25%) HNSCC (25%) Sarcoma Subtypes (up to 100%) …	Pancreatic carcinoma (80%) Breast carcinoma (75%) Stomach carcinoma (65%) Sarcoma (65%) Esophageal carcinoma (60%) NSCLC (55%) HNSCC (55%) Uterine carcinosarcoma (55%) Colorectal carcinoma (45%) Mesothelioma (45%) Ovarian carcinoma (40%) Cholangiocarcinoma (40%) Melanoma (35%) Bladder carcinoma (35%) …

Immatics' clinical frontrunner targets show specificity profiles similar to NY-ESO-1 while having significantly higher peptide copy numbers

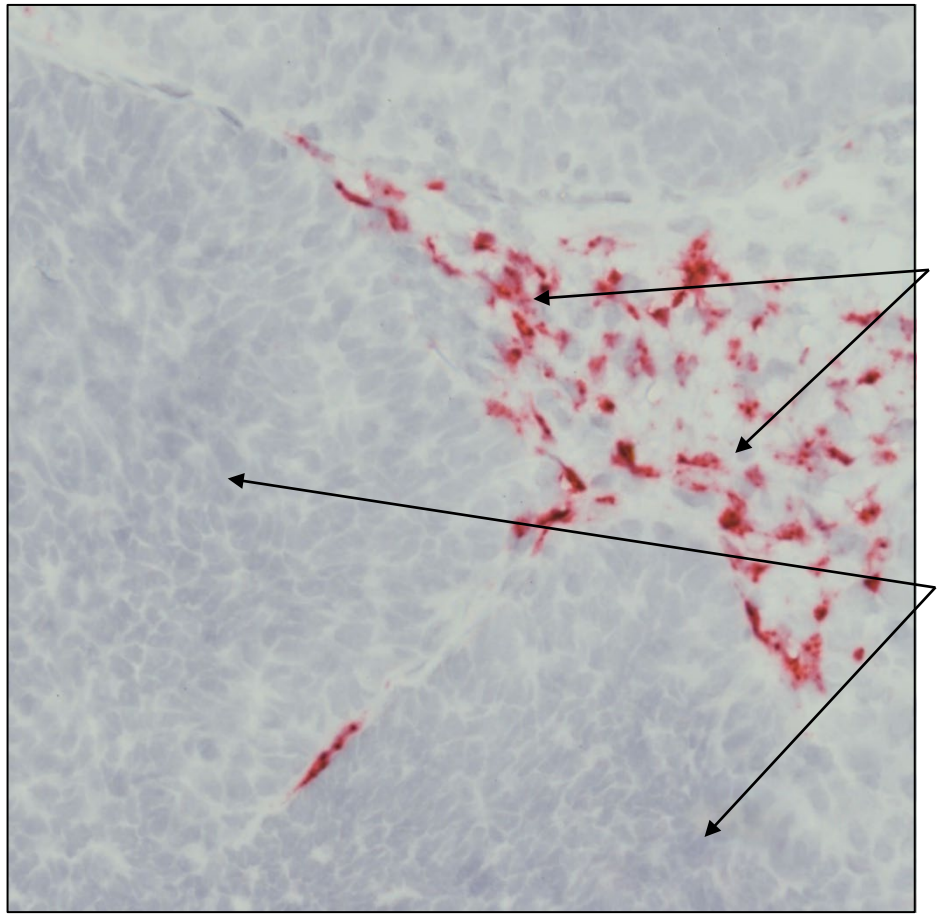
IMA204 target COL6A3 shows broader target prevalence and higher copy numbers than NY-ESO-1

1 Natural presentation of this peptide has been validated by clinical data, **2** Validated by XPRESIDENT® mass spectrometry. Target peptide copy numbers per cell were determined by AbsQuant™ technology, **3** Internal specificity categorization used at Immatics. Specificity class 1: peptide not routinely found on any normal tissue; no relevant RNA expression detected on critical organs, Specificity class 2: peptide showing a therapeutic window with rare detections on normal tissue and low RNA expression on critical organs. **4** Purbhoo *et al.*, J Immunol 176:7308-7316 (2006), **5** Robbins *et al.*, J Clin Onco 29(7): 917-924 (2011). Target prevalences for ACTengine® targets are based on TCGA data combined with a XPRESIDENT®-determined target individual MS-based mRNA expression threshold.

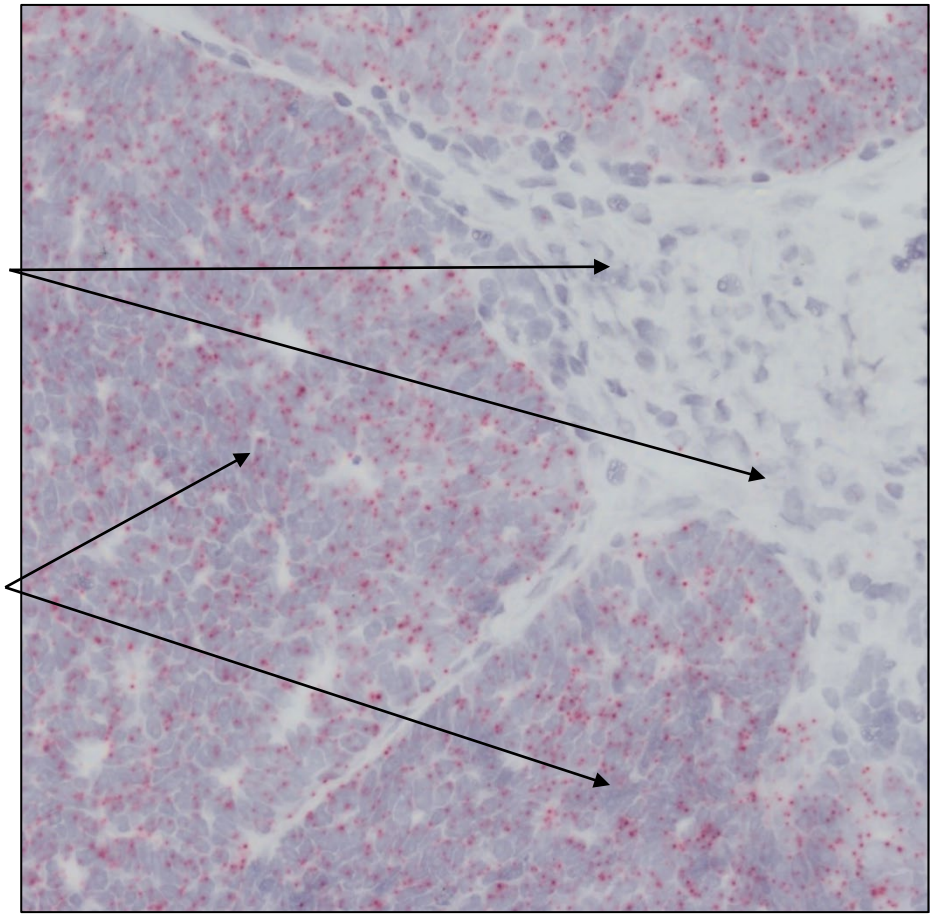
Pioneering Novel Targets

IMA204 Tumor Stroma Target COL6A3 Exon 6

Example of a Stroma Target (COL6A3 exon 6) in an Ovarian Cancer sample



Example of a Tumor Target in the same Ovarian Cancer sample

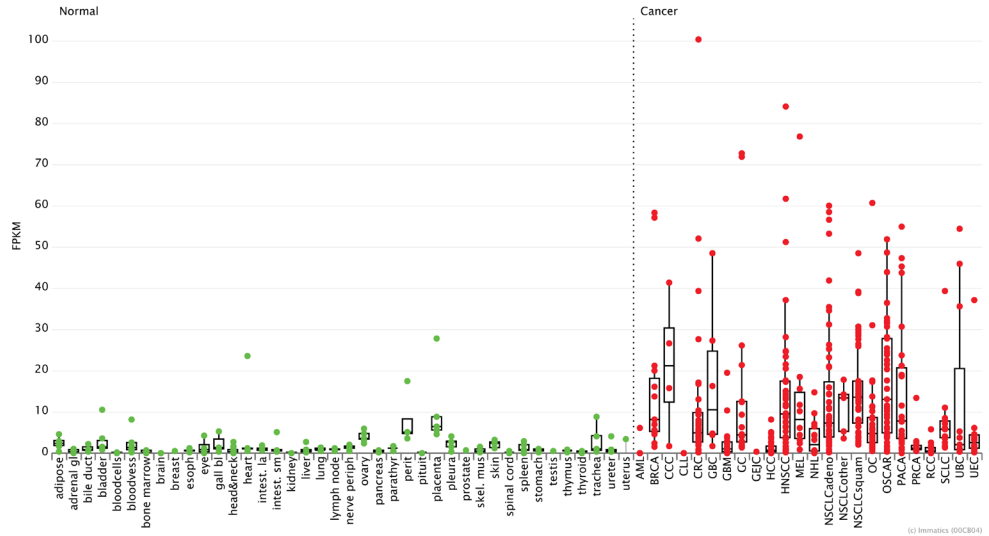


Pioneering Novel Targets

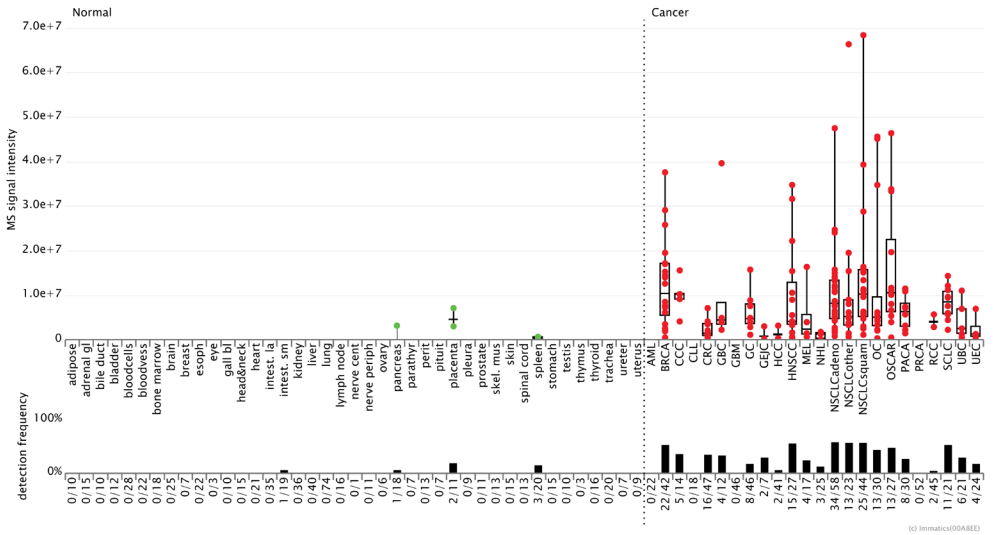
IMA204 Tumor Stroma Target COL6A3 Exon 6

- **Novel HLA-A*02-restricted cancer stroma target identified by XPRESIDENT®**
- Extracellular matrix component found in most connective tissues
- **Collagen, type VI, alpha 3 exon 6:**
  Cancer-specific splicing of exon 6 encoding COL6A3
- Expressed predominantly by tumor stromal cells
- Relevant in a broad range of tumors including lung, pancreas, esophagus, breast, ovary, colon, stomach cancer and others

Target Profile – RNAseq

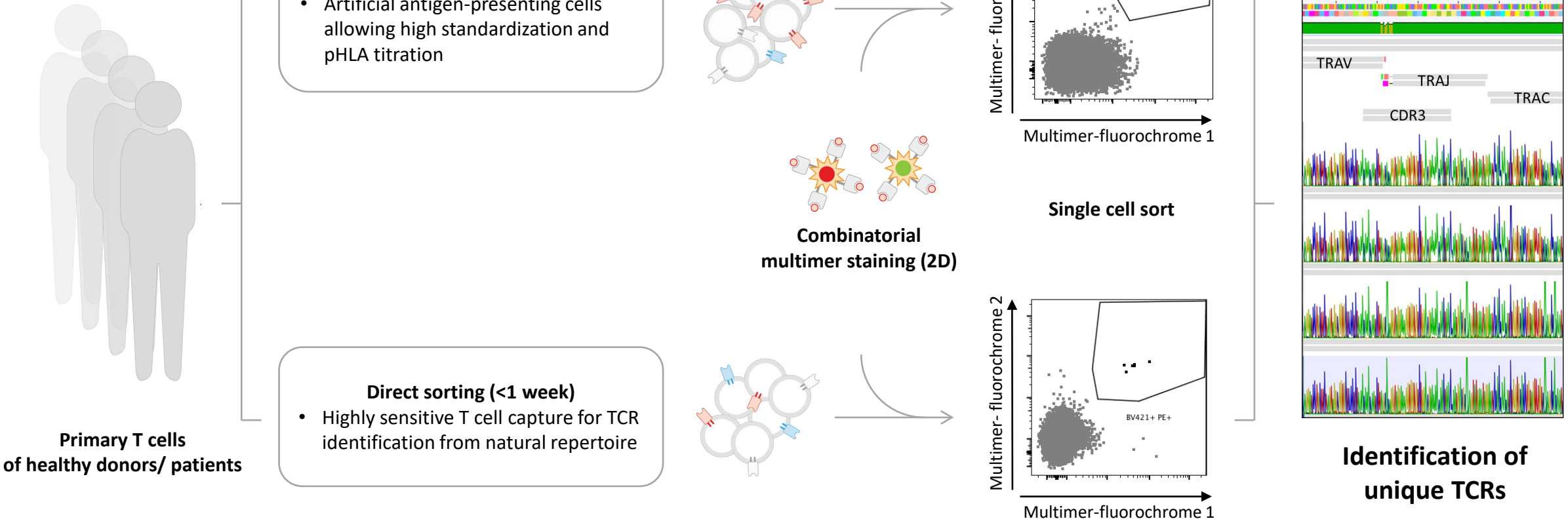


Target Profile – Quantitative Mass Spectrometry



XCEPTOR™ – TCR Discovery, Engineering and Validation Platform

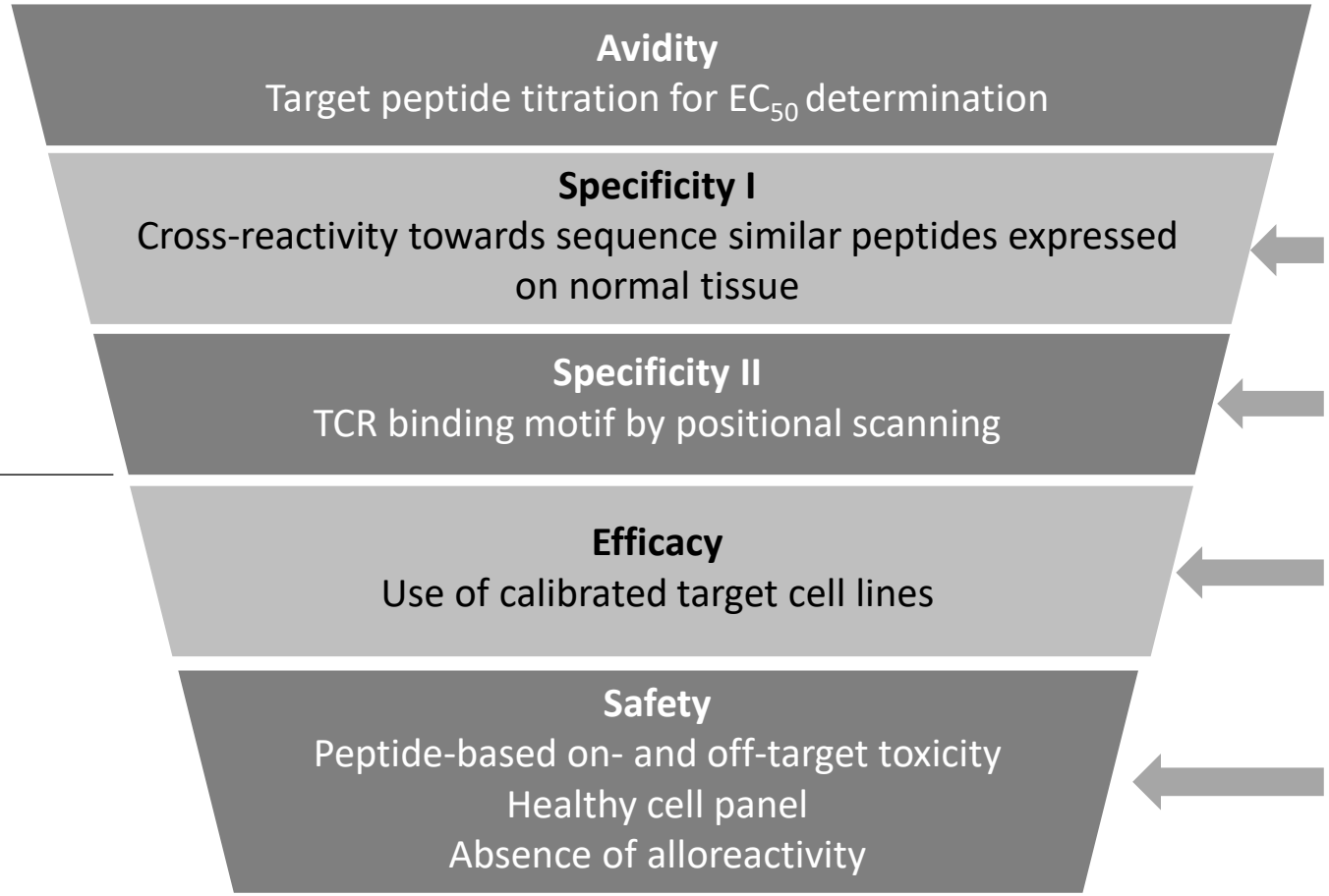
Mode of Action – Isolation of Target-specific T cells and TCR Gene Retrieval



Discovery of the Right TCR

XCEPTOR™

Multiple TCRs candidates per target



Assessment of Specificity

Assessment of Efficacy & Safety

XPRESIDENT® guidance:

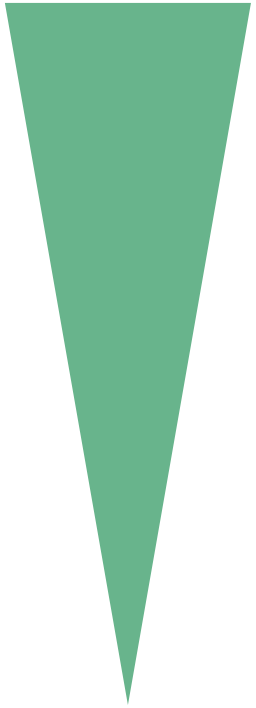
- Similar peptide expression on normal tissue
- Motif similar peptide expression on normal tissue
- Absolute target-HLA copy number
- Abundance and surface expression of target/ off-targets on normal tissue

Optional:
TCR optimization by engineering at various steps

<5 frontrunner TCRs

Developing the Right TCR

Overview of COL6A3 Exon 6 TCR Discovery and Characterization

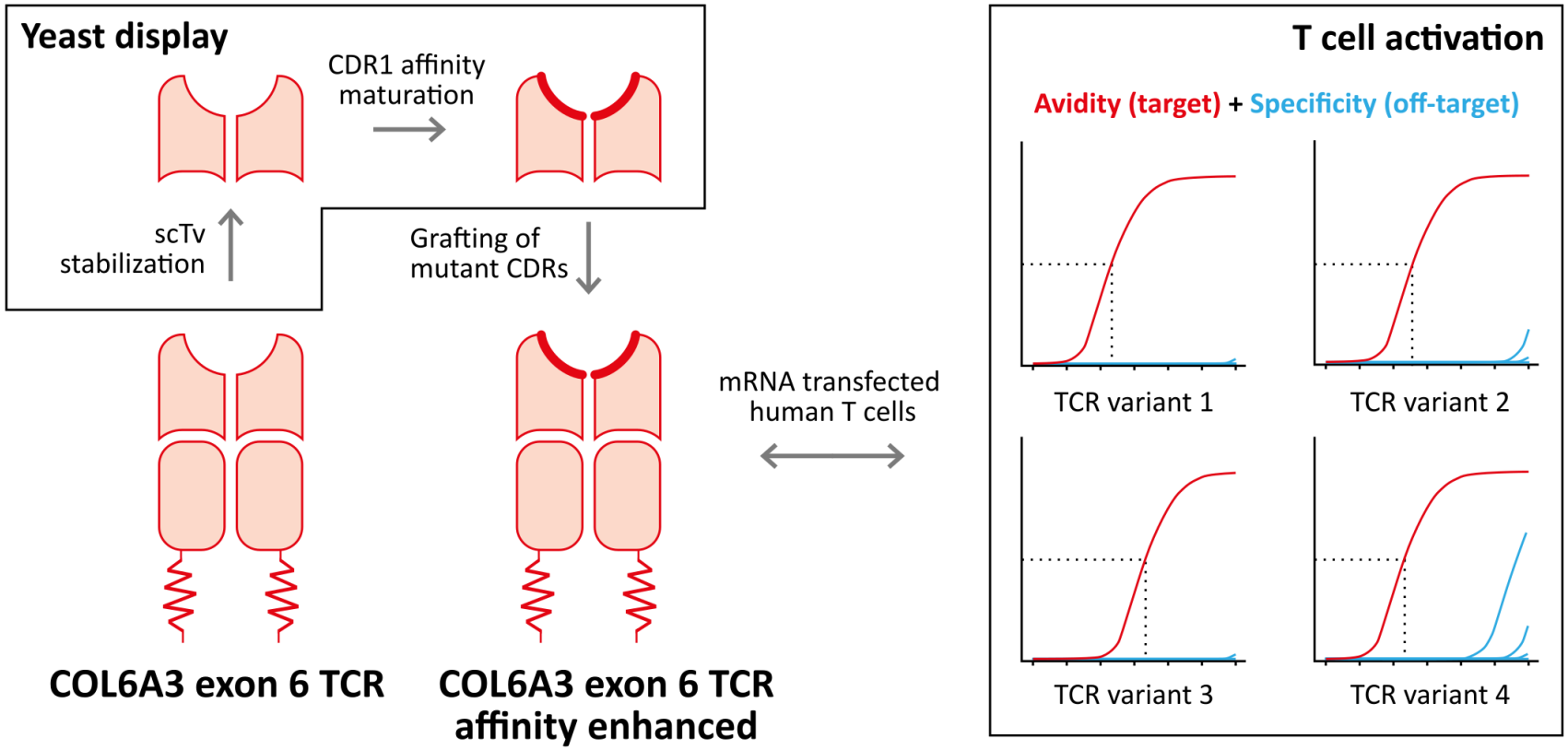


- **91 TCRs identified from >20 healthy donors**
- **91 TCRs entered characterization**
- **10 TCRs completed characterization stage I**

  (specificity against similar peptides, TET binding, functional avidity/ EC_{50} and TCR motif determination)
- **10 TCRs selected for refolding and affinity determination**
- **1 TCR (high specificity, but low affinity) underwent affinity maturation**
- **2 affinity maturated TCRs showed increased functional avidity and are available for further development**

TCR Affinity Maturation and Validation for ACT

Schematic Overview

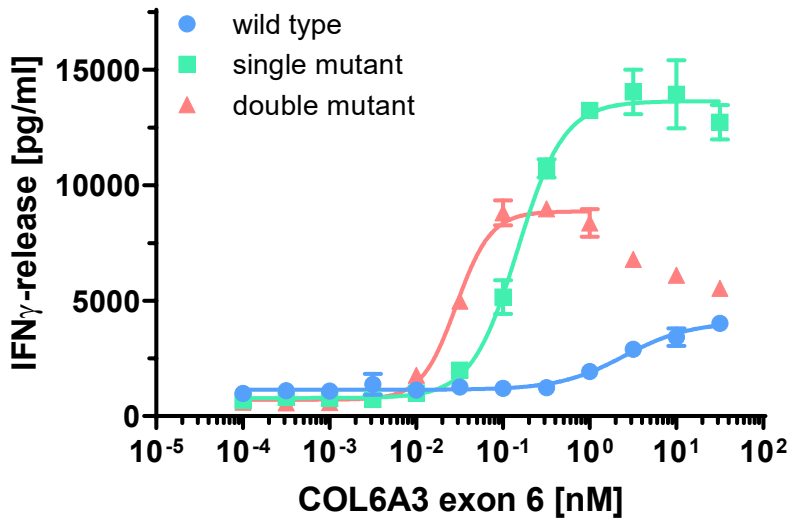


Naturally occurring TCRs are converted into single-chain TCR fragments (scTv) and affinity maturated via yeast display.
Resulting CDR mutations are then grafted onto the parental TCR.
Mutant TCR variants were assessed for improved target recognition and absence of off-target recognition.

Affinity Maturated COL6A3 Exon 6 TCRs

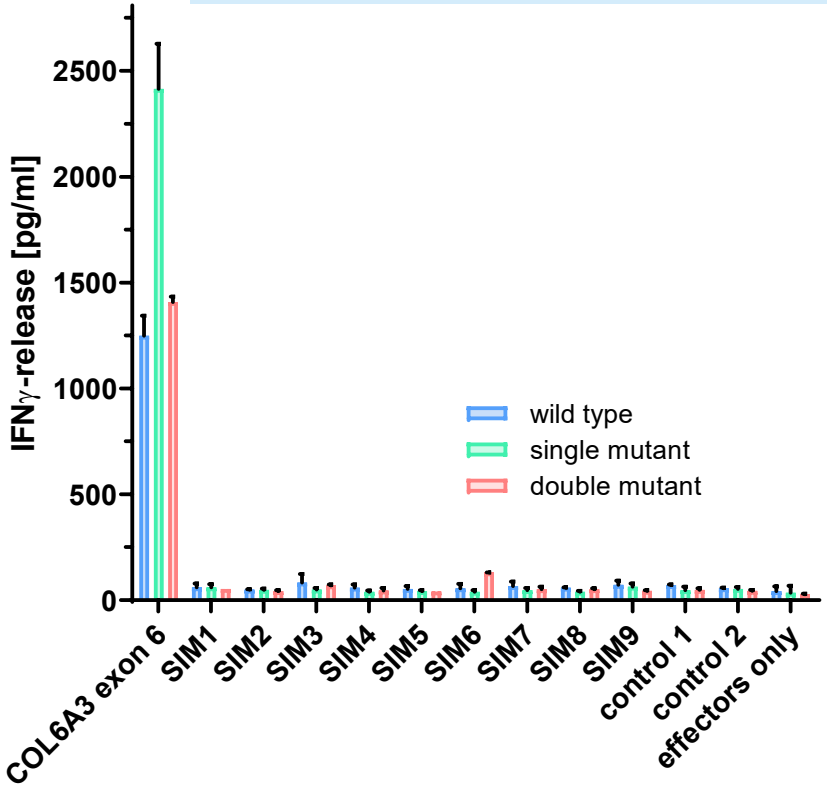
Functional Avidity and Specificity of mRNA Transfected CD8 T cells

Functional avidity



TCR variant	wild type	single mutant	double mutant
EC50 [nM]	2.5	0.15	0.03

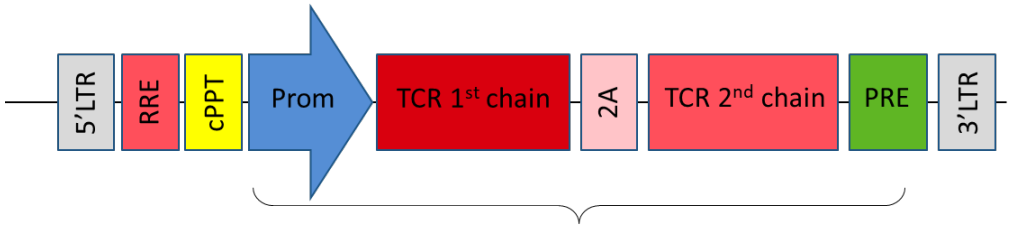
Target sequence-based similar peptide screen (specificity)



Maturated COL6A3 exon 6 TCR variants show pronounced increase in functional avidity and a retained specificity profile.

Affinity Enhanced Double Mutant Yields Higher TCR Expression

Wild Type < Single Mutant < Double Mutant

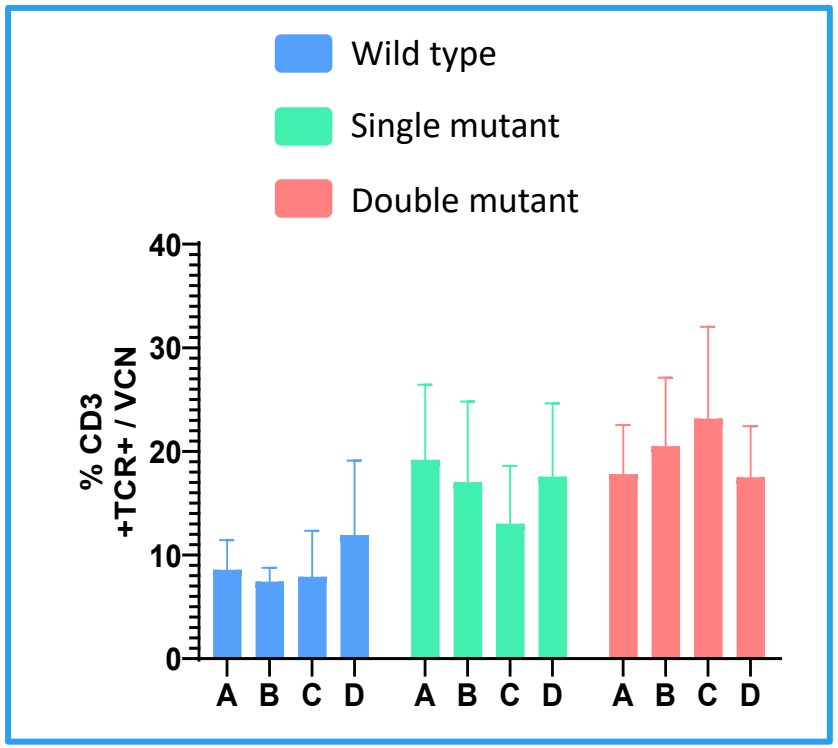


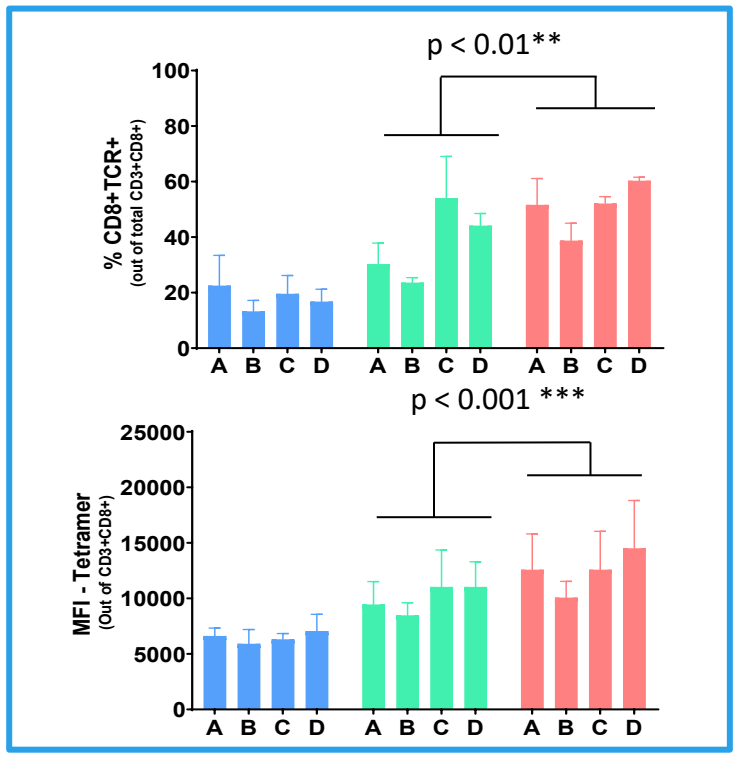
IMA204 construct selection

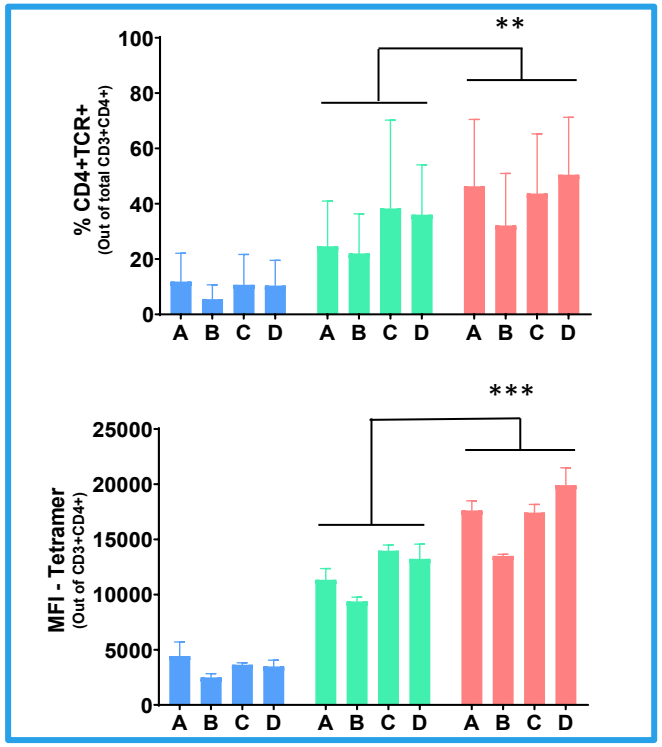
(2) selected affinity enhanced candidates from natural TCR

(4) LV construct variants of each mutant to enhance expression and safety

(12) total LV construct candidates



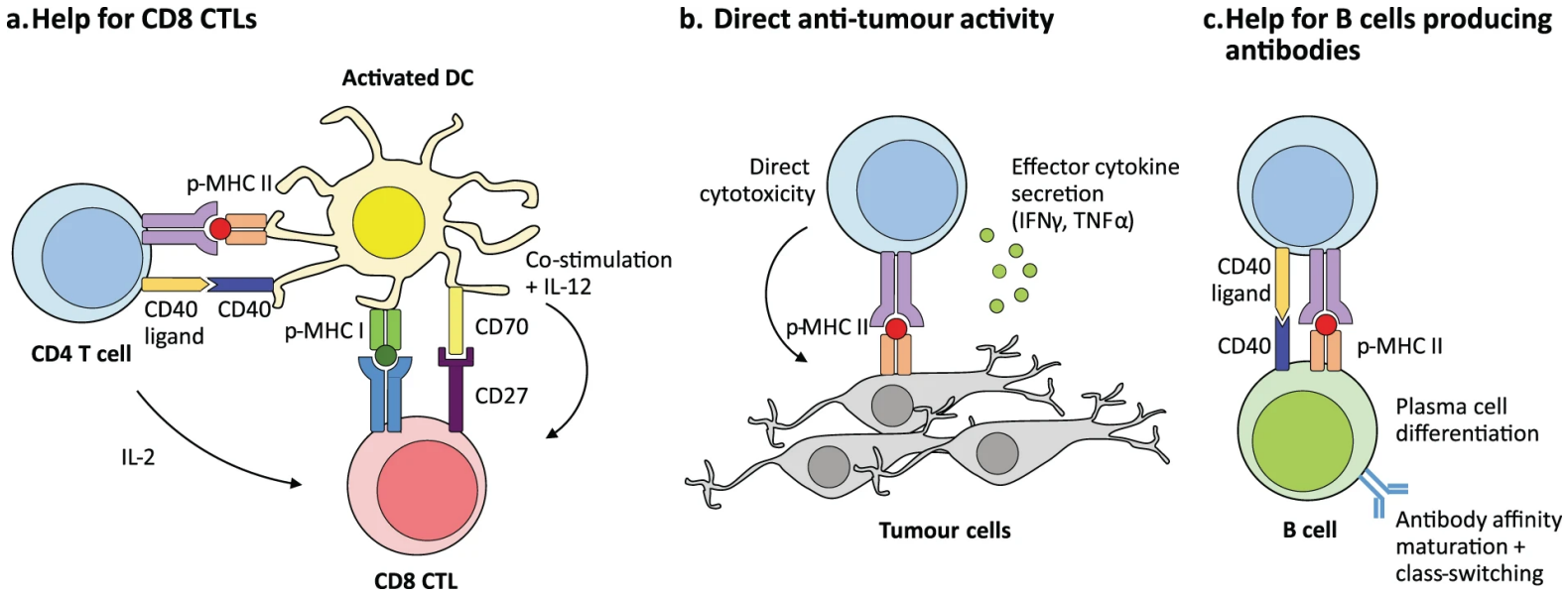




Engaging CD4 T cells for Enhancing the Potential of TCR-T Therapies

CD4 T cells Play Multifaceted Roles in Anti-Tumor Immunity

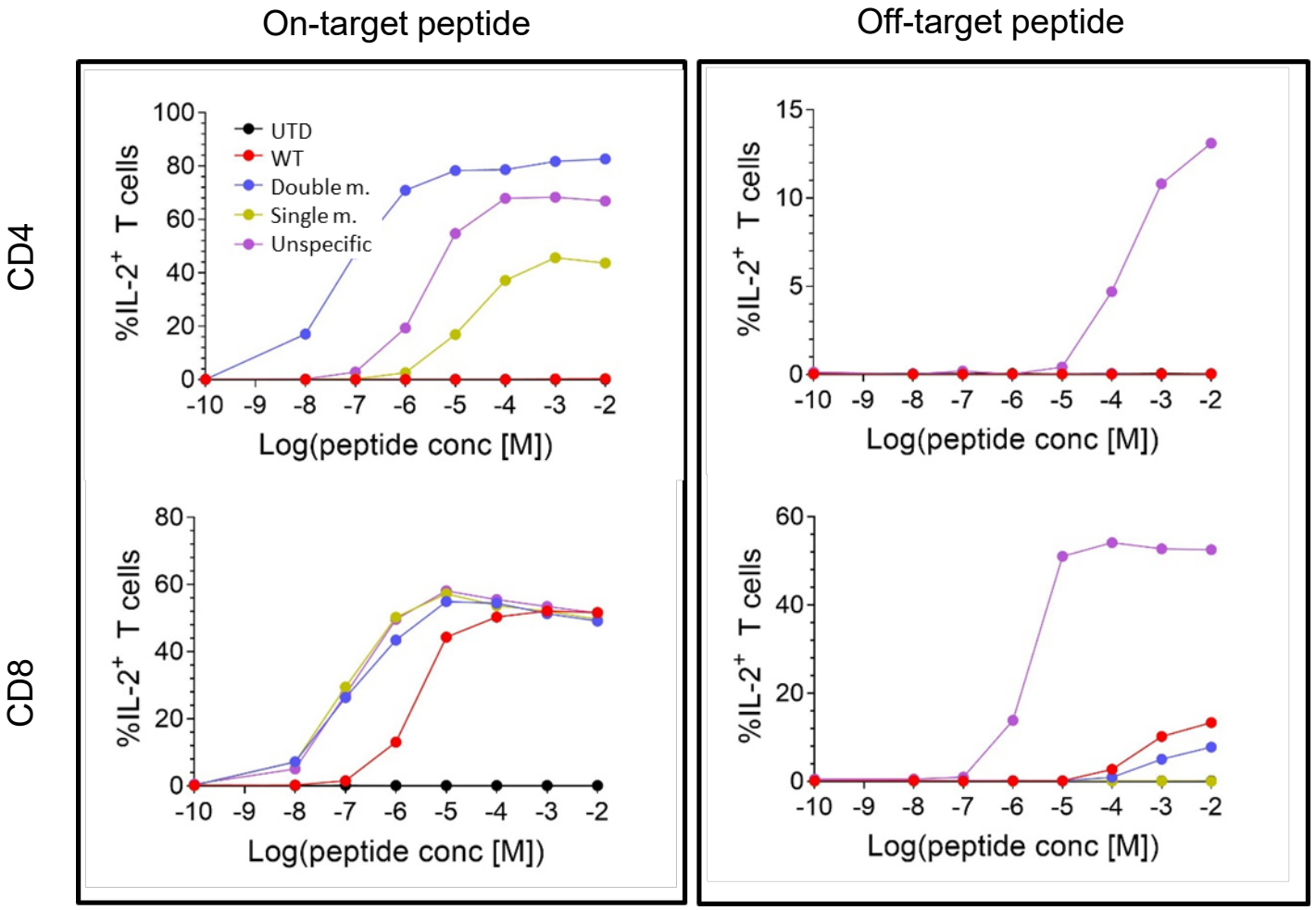
- **A vast body of pre-clinical and emerging clinical data from ACT field highlights the significance of CD4 T cells in achieving sustained and durable anti-tumor responses**



- **Potential strategies for implementation in current genetically modified TCR-T therapies**
  - Targeting Class II antigens
  - Engineering with CD8 independent TCRs
  - Introduction of CD8 co-receptor into CD4 T cells along with transgenic TCRs

Tay *et al.*, Cancer Gene Therapy; May 2020

Double Mutant TCR Shows Fully CD8 Independent Recognition

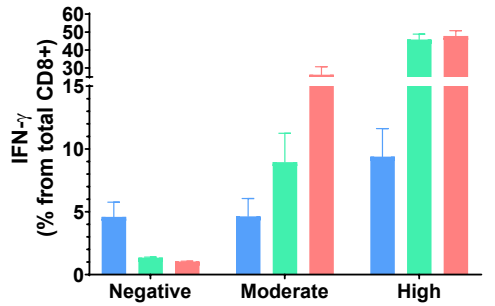


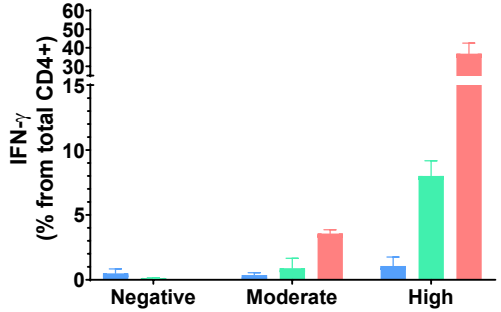
Jim Riley, University of Pennsylvania

Anti-Tumor Cytokine Response Demonstrates CD8 Independence of Affinity Enhanced Double Mutant

O/N Co-Culture with Target Positive Cell Lines at a 1:1 E:T Ratio.

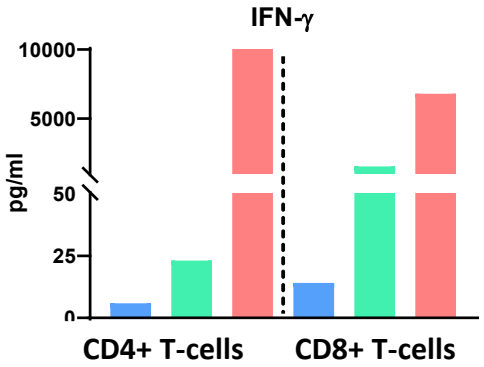
Intracellular Cytokine Staining

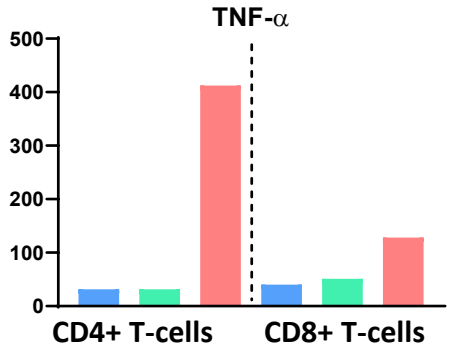


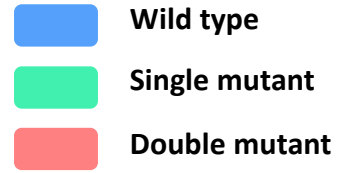


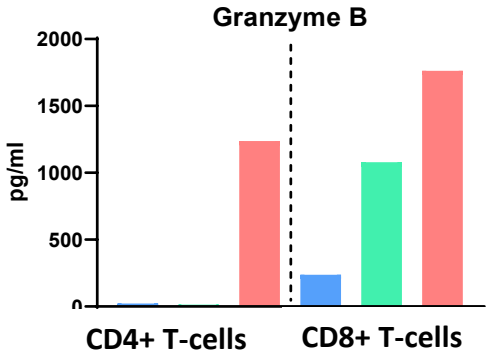
Target cell antigen intensity

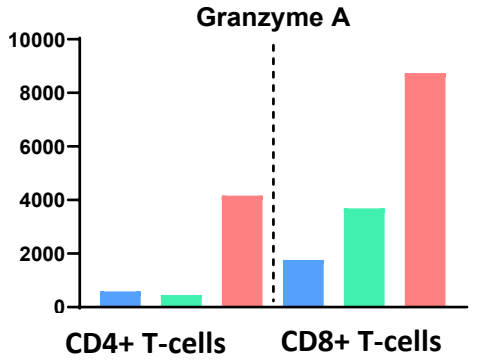
Multiplex Cytokine Assay

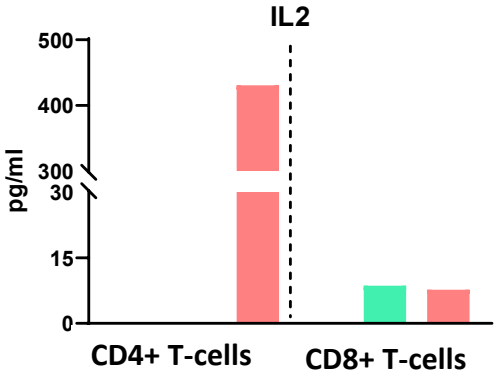










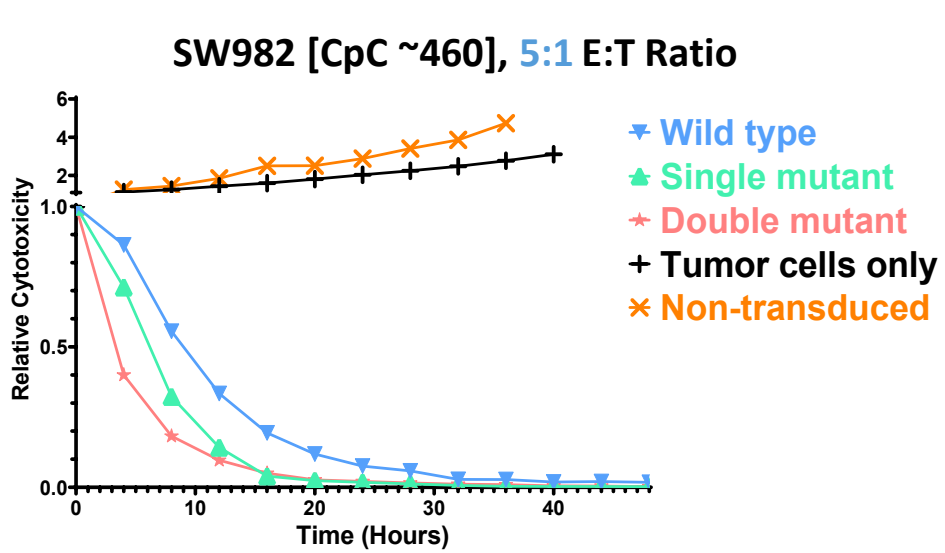


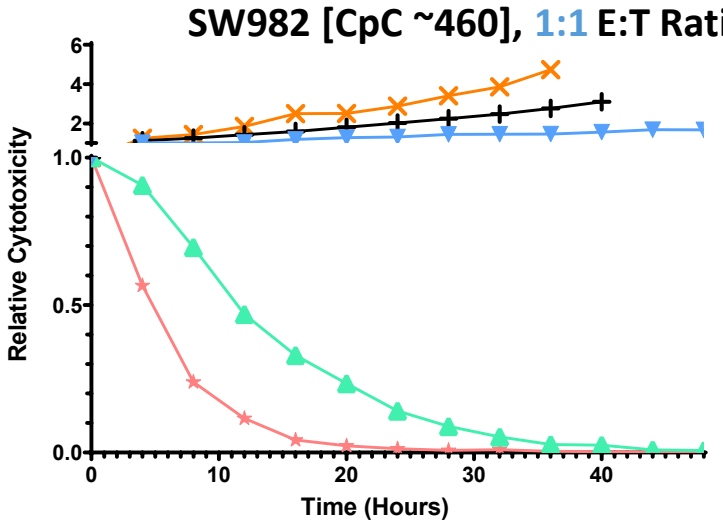
Unselected or CD4/CD8 selected PBMC-derived products were stimulated by co-culturing with a target positive cell line and cytokines assessed in culture supernatants

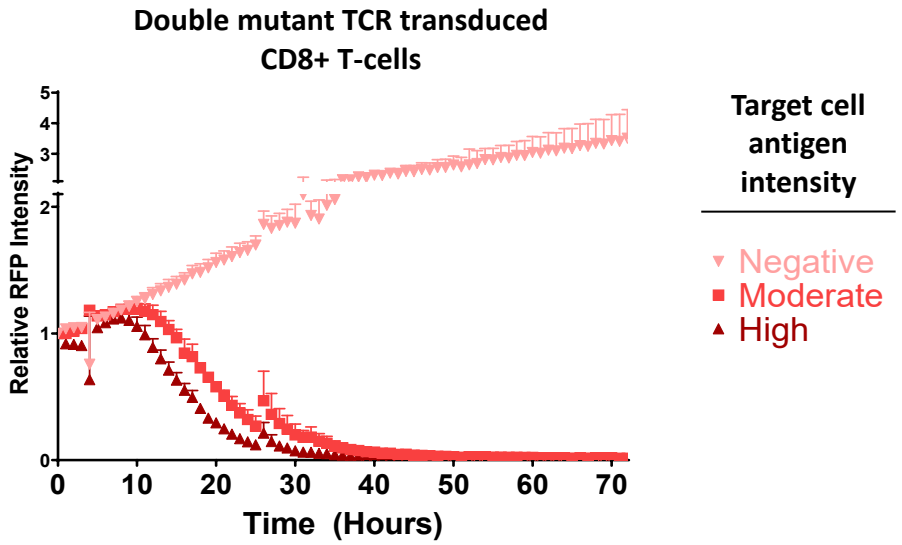
One Donor Shown with (3) Biological Replicate Wells

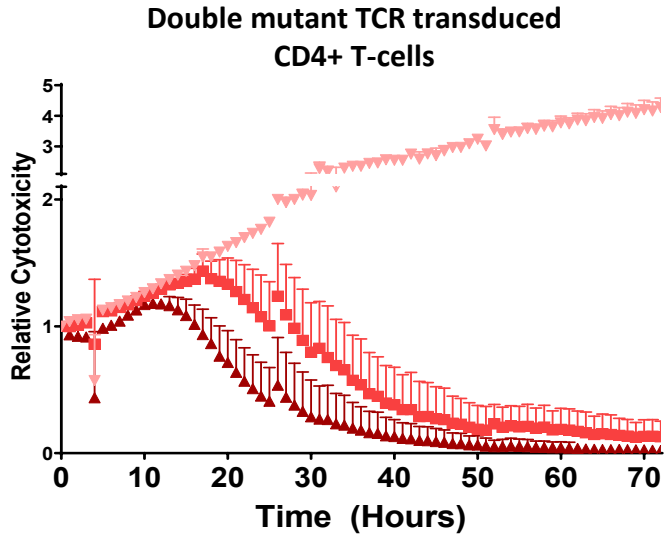
Affinity-enhanced TCR Leads to Rapid Tumor Elimination *in vitro*

Immune Cell-mediated Killing Assay









TCR Motif Based Similar Peptide Screen Shows No Significant Safety Signal

30 TCR-Motif Based Similar Peptides Were Tested Using CD4+ and CD4- T cells

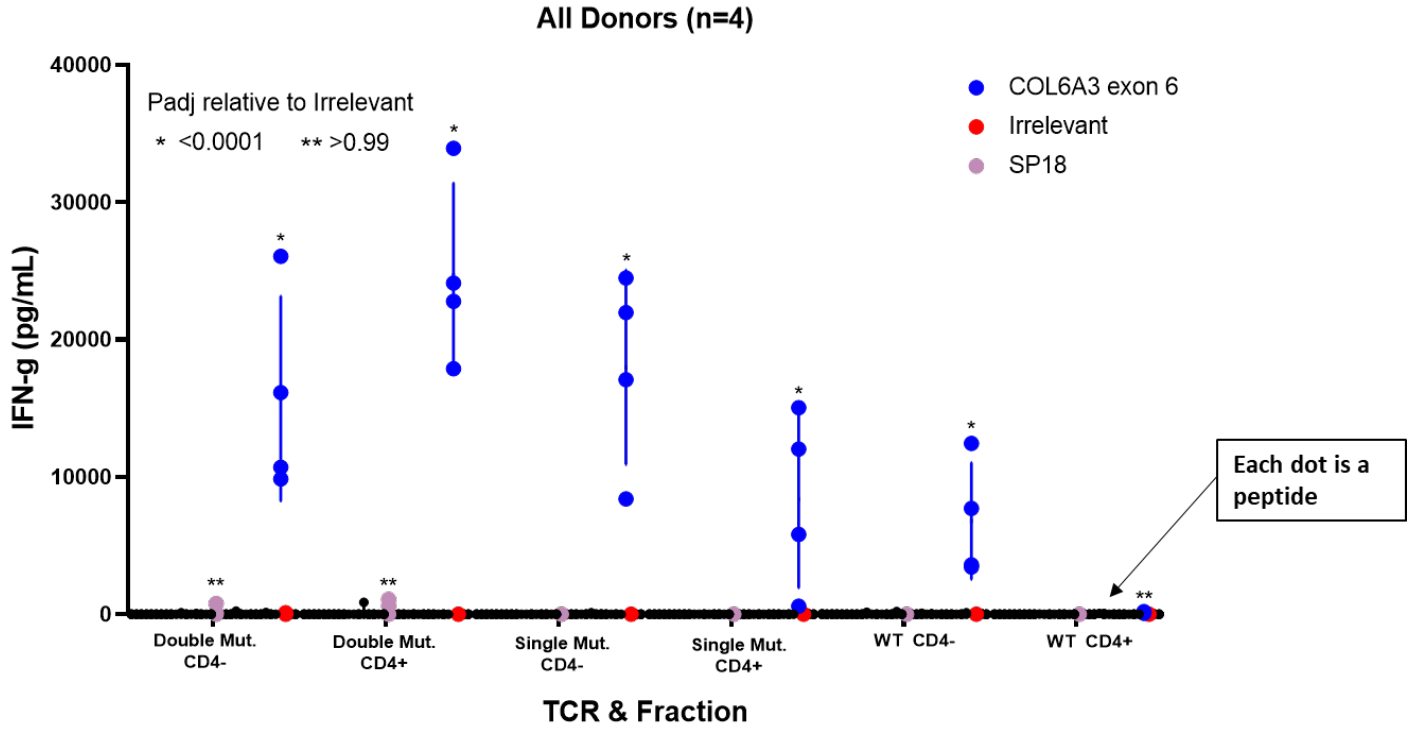
	CD4+								
Position	1	2	3	4	5	6	7	8	9
WT Motif	X	X	X	X	X	X	X	X	X
Single Mutant Motif	X	X	X	O	X	X	X	X	X
Double Mutant Motif	X	X	X	O	X	X	X	X	O

	CD4-								
	1	2	3	4	5	6	7	8	9
WT Motif	X	X	X	X	X	X	X	O	O
Single Mutant Motif	X	X	X	O	X	X	X	X	O
Double Mutant Motif	O	O	X	O	X	X	O	X	O

Motif Position Calling

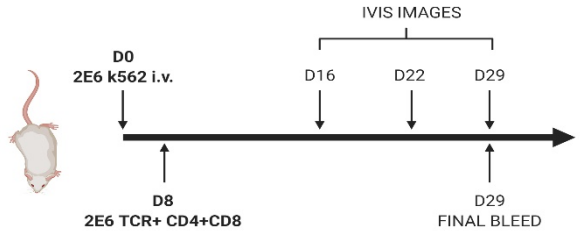
X = stringent position | 3/4 donors < 30% WT signal w/ substitution

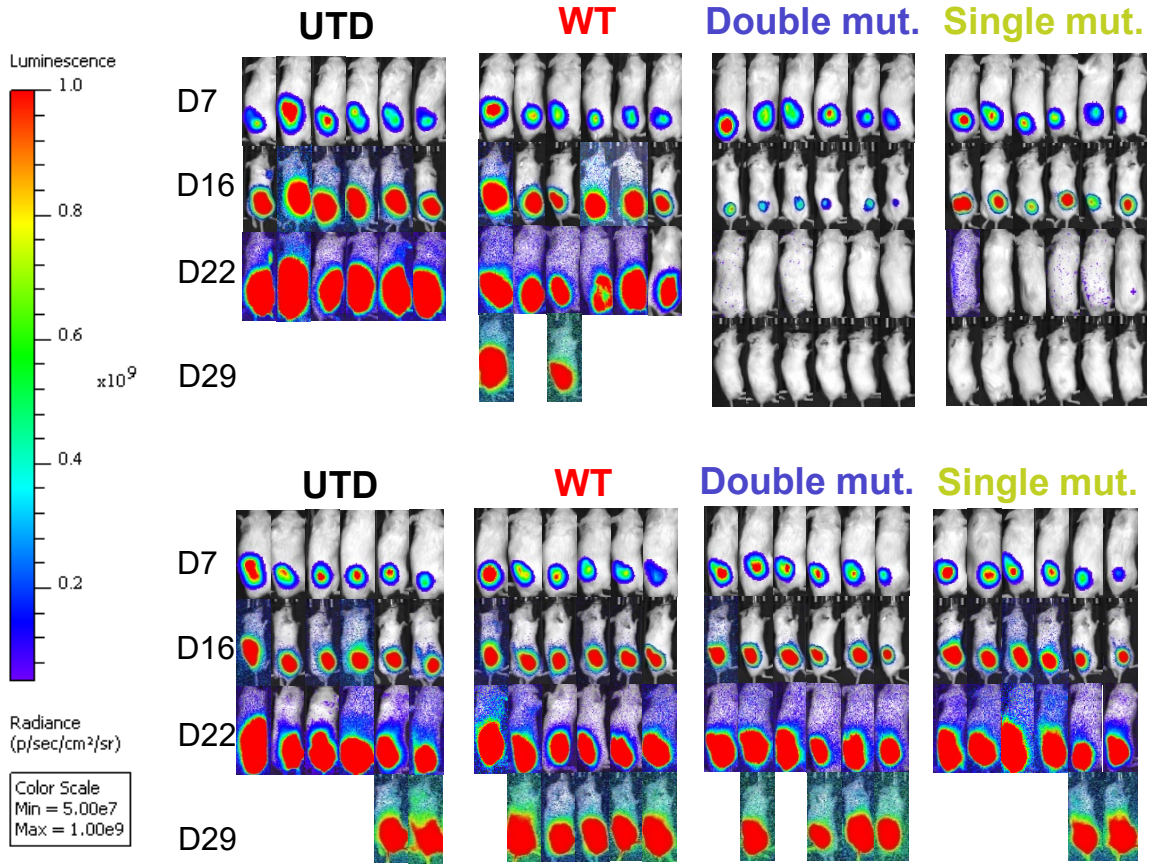
O = mutable position | 3/4 donors > 30% WT signal w/ substitution



Affinity-enhanced COL6A3 Exon 6 Specific TCR Is Able to Eradicate Tumors from All Mice with High Disease Burden

NSG Model with Implanted K562-A2-COL6A3 or K562-A2-COL6A1 Tumors





K562-A2-COL6A3

K562-A2-COL6A1

Jim Riley, University of Pennsylvania

Agenda

Introduction

Case study: Novel TCRs targeting COL6A3 exon 6

Summary

Summary

- **ACTengine® IMA204 target COL6A3 exon 6 is broadly expressed in the stroma of many solid tumors**
- **This target shows low levels of expression and presentation in healthy tissues**
- **A high-copy number peptide binding to HLA-A*02:01 was identified by XPRESIDENT®**
- **Two affinity-enhanced TCRs were designed against COL6A3 exon 6 using the XCEPTOR™ technology platform**
- **Both affinity-enhanced TCRs demonstrate excellent properties**
  - High avidity (sub-nM EC50)
  - Ability to recognize cell lines with physiological levels of target presentation
  - High specificity (no recognition of sequence-based or motif-based similar peptides)
- **One affinity-enhanced TCR shows fully CD8 independent target recognition**
  - This TCR engages both CD4+ and CD8+ T cells without the need of CD8 co-transduction
- **Final preclinical safety evaluation of the target and the two candidate TCRs is currently ongoing**
- **Immatics is planning to submit an IND for ACTengine® IMA204 in 2021 followed by careful introduction into the clinic**

Thank you

www.immatics.com

Please contact us via partnering@immatics.com to learn more about partnering and licensing opportunities utilizing our platform technologies XPRESIDENT®, XCEPTOR™, IMADetect™ and AbsQuant™.