
THE POWER OF tomorrow
Engaging the TCR to Transform
the Treatment of Solid Tumors
R&D Day
October 2021
TCR2
THERAPEUTICS

Forward Looking Statements

This presentation has been prepared by TCR2 Therapeutics Inc. (“we,” “us,” or “our”) and contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our clinical results and other future conditions. All statements, other than statements of historical facts, contained in this presentation, including express or implied statements regarding our expectations for the Phase 1/2 clinical trials of gavo-cel and TC-110, our expectations for the safety and efficacy of our product candidates and enhancements, including gavo-cel and TC-110, compared to current T-cell therapy approaches, our expectations regarding the estimated patient populations and related market opportunities in gavo-cel’s and TC-110’s targeted indications, and our expectations regarding manufacturing of our product candidates are forward-looking statements. These statements are based on management’s current expectations and beliefs and are forward-looking statements which involve risks and uncertainties that could cause actual results to differ materially from those discussed in such forward-looking statements.

Such risks and uncertainties include, among others: uncertainties inherent in clinical studies and in the availability and timing of data from ongoing clinical studies; whether interim results from a clinical trial will be predictive of the final results of a trial; the possibility that positive results from preclinical studies and correlative studies may not necessarily be predictive of the results of our planned clinical trials, including the Phase 1/2 clinical trials of gavo-cel and TC-110; the risk that the results from the Phase 1/2 clinical trials of gavo-cel and TC-110 will not support further development and marketing approval; the risk that we may be unable to gain approval of gavo-cel, TC-110 and our other product candidates on a timely basis, if at all; the risk that we have over-estimated the potential patient population for our product candidates, if approved; the risk that the current COVID-19 pandemic will impact our clinical trials and other operations; and the other risks set forth under the caption “Risk Factors” in our most recent Annual Report on Form 10-K for the year ended December 31, 2020, as filed with the SEC on March 16, 2021, as updated in our most recent Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, as filed with the SEC on August 5, 2021, and in our future filings with the SEC available at the SEC’s website at www.sec.gov. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. You should not place undue reliance on any forward-looking statements, which speak only as of the date they are made.

While we may elect to update these forward-looking statements at some point in the future, we assume no obligation to update or revise any forward-looking statements except to the extent required by applicable law. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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Agenda

Leading the Way in Solid Tumors	**Garry Menzel**, President and CEO
Utilizing the Full Power of the TCR	**Robert Hofmeister**, CSO
Beginning with gavo-cel and Mesothelin • History of Anti-Mesothelin Clinical Therapies • Phase 1 Clinical Trial & Next Steps	**Raffit Hassan**, National Cancer Institute **Alfonso Quintás-Cardama**, CMO
Boosting TRuC-T Cells with Enhancements • TC-510: PD-1:CD28 Switch • IL-15 Enhancements	**Robert Hofmeister**, CSO **Robert Tighe**, VP of Research
Novel Targets: CD70	
Advancing our Allogeneic Program	**Robert Hofmeister**, CSO
Beyond Oncology with TRuC T-Regs	
Closing Remarks	**Garry Menzel**, President and CEO
Q&A	

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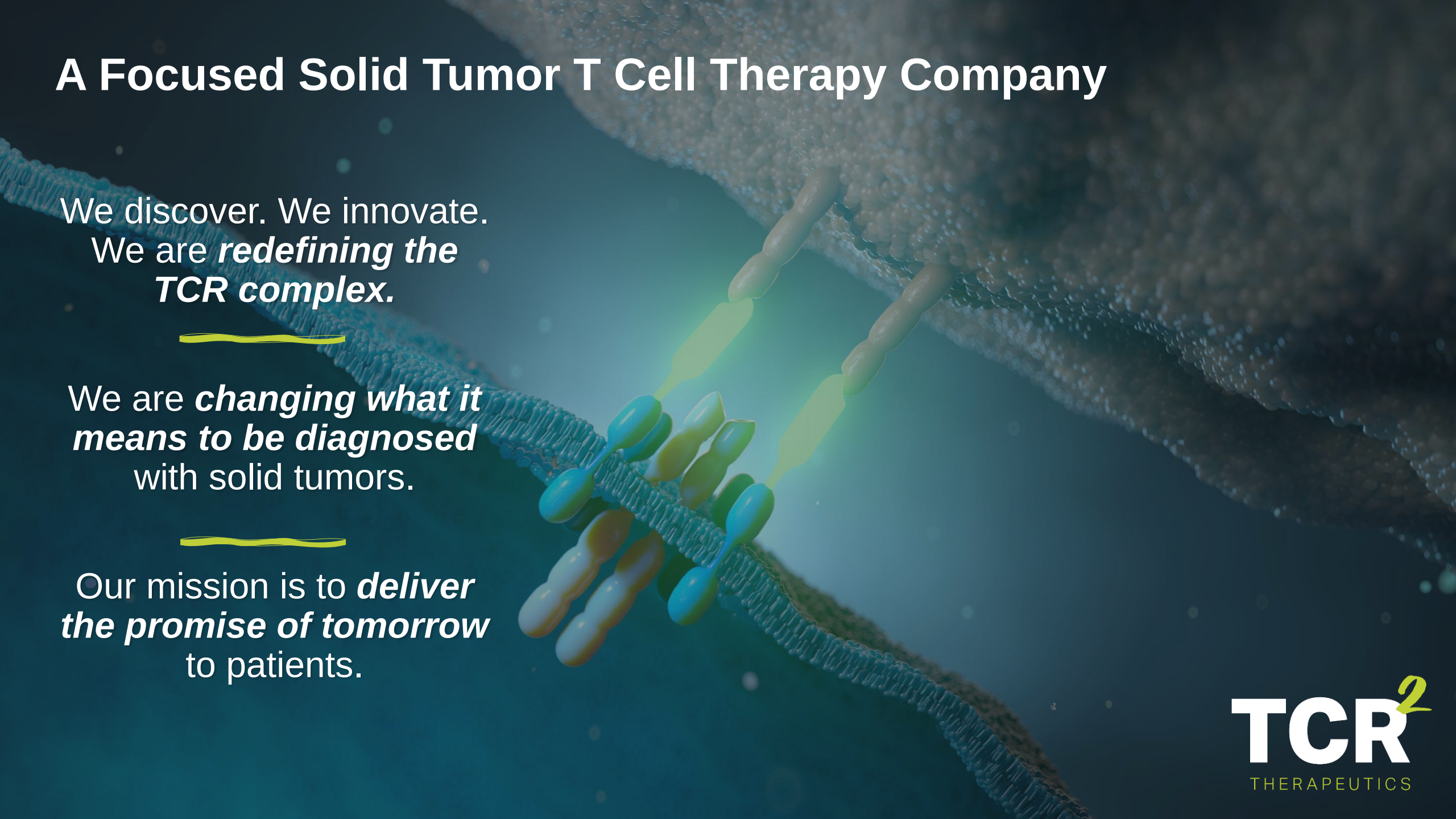
Leading the Way in Solid Tumors

Garry Menzel, Ph.D.
President and Chief Executive Officer

TCR2 THERAPEUTICS

A Focused Solid Tumor T Cell Therapy Company



We discover. We innovate.
We are ***redefining the TCR complex.***

We are ***changing what it means to be diagnosed*** with solid tumors.

Our mission is to ***deliver the promise of tomorrow*** to patients.

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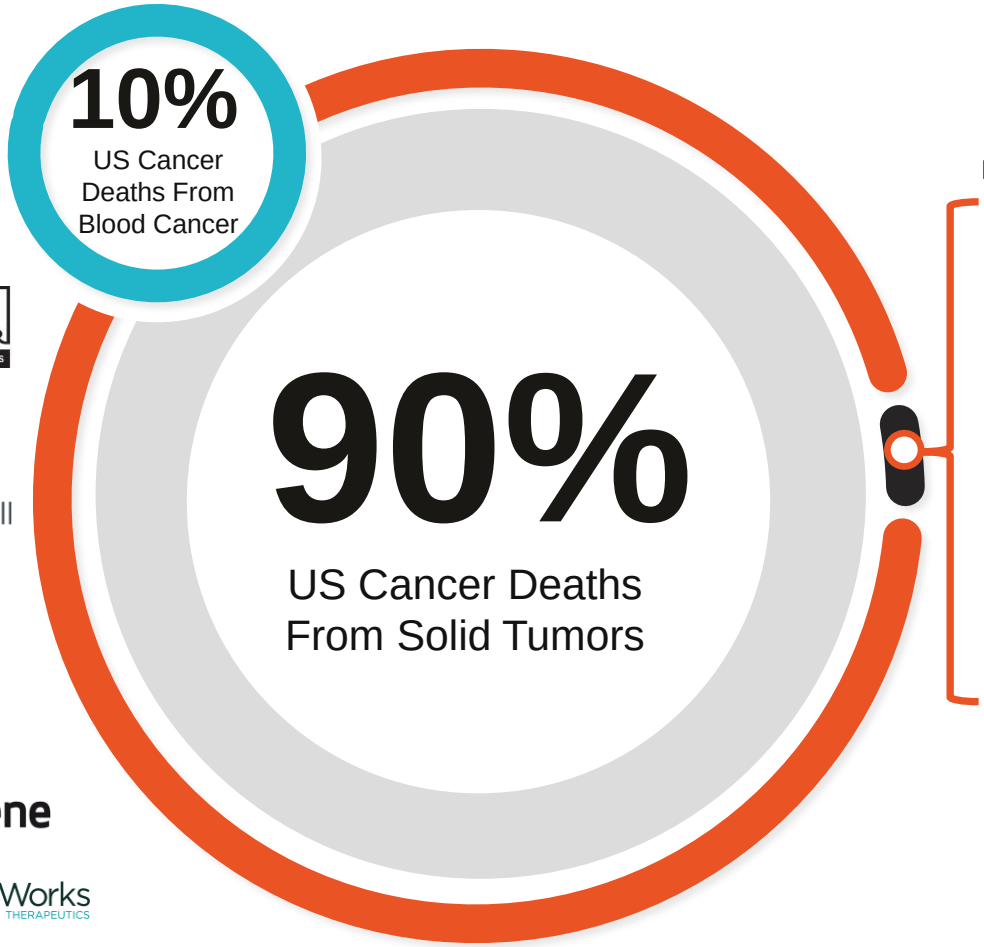
The Solid Tumor Market Is a Significant and Open Opportunity

Clinically Validated Cell Therapies in Solid Tumors All Utilize the Full TCR Complex



4 **Clinical Validation in Solid Tumors**

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IOVANCE BIOTHERAPEUTICS

Adaptimmune

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Ref: ACS Cancer Statistics 2020

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Advancing a Diverse Pipeline of Solid Tumor Programs

Target	Indication(s)	Program	Enhancement / Combo	Discovery	Lead Optimization	IND Enabling	Phase 1/2	Phase 2/3
Oncology								
Autologous								
MSLN	Ovarian cancer, NSCLC, MPM, Cholangiocarcinoma	gavo-cel						
MSLN	Ovarian cancer, NSCLC, MPM, Cholangiocarcinoma	gavo-cel	Checkpoint inhibitor					
MSLN	Solid tumors	TC-510	PD-1 switch					
CD70	Renal cell carcinoma	TC-520	IL-15					
GPC3	Solid tumors							
Nectin-4	Solid tumors							
Allogeneic								
MSLN	Solid tumors	gavo-cel	IL-15 / PD-1 switch					
CD70	Renal cell carcinoma	TC-520	IL-15 / PD-1 switch					
Autoimmune								
HLA-A*02	Solid organ transplant / GvHD							

MSLN, mesothelin; NSCLC, non-small cell lung cancer; MPM, mesothelioma; GvHD, Graft versus Host Disease

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Executing Pipeline Value Strategy

Pick the Best Target → **Design the Core TRuC** → **Integrate Enhancements** → **Tailor to Indications**

Target Selection

Core TRuC

Enhancements

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Utilizing the Full Power of the TCR

Advancing a Differentiated Approach in Cell Therapy

Robert Hofmeister, Ph.D.
Chief Scientific Officer

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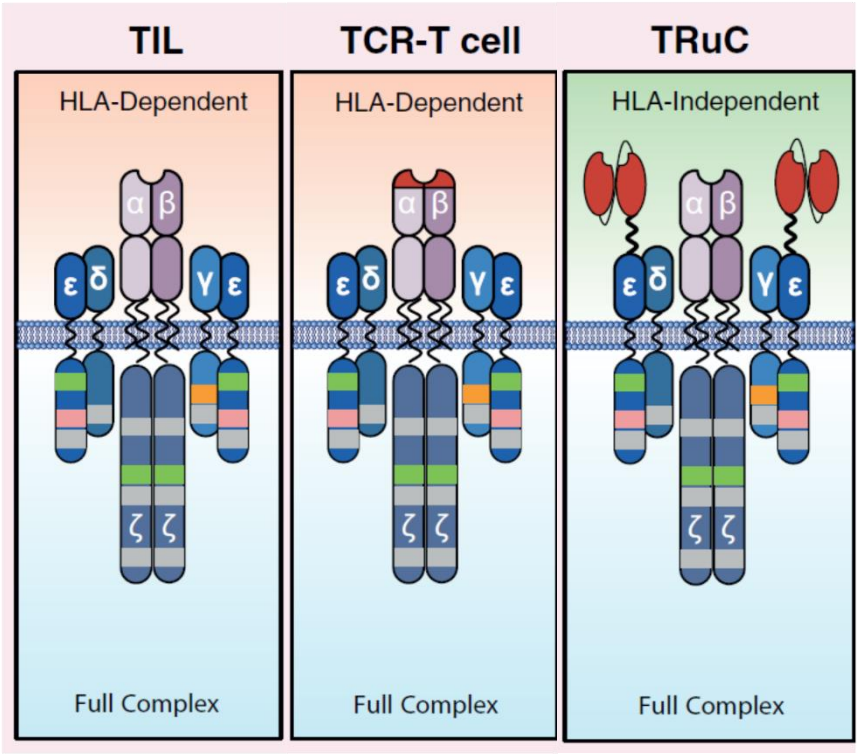
TCR-Based Therapies: An Innovative Approach in Solid Tumors

- **A Superior Starting Point**: utilization of the full TCR retains auxiliary molecules of TCR signal transduction pathway
  - Critical element limiting CAR activity in solid tumors
- **Success in Solid Tumors with Full TCR Complex**: encouraging clinical responses (CRs, PRs) in patients with solid tumors, even with refractory disease, emerging with TCR-based therapy studies (i.e. TILs, TCR-Ts and TRuCs)



Hardy et al., Immunotherapy 2020

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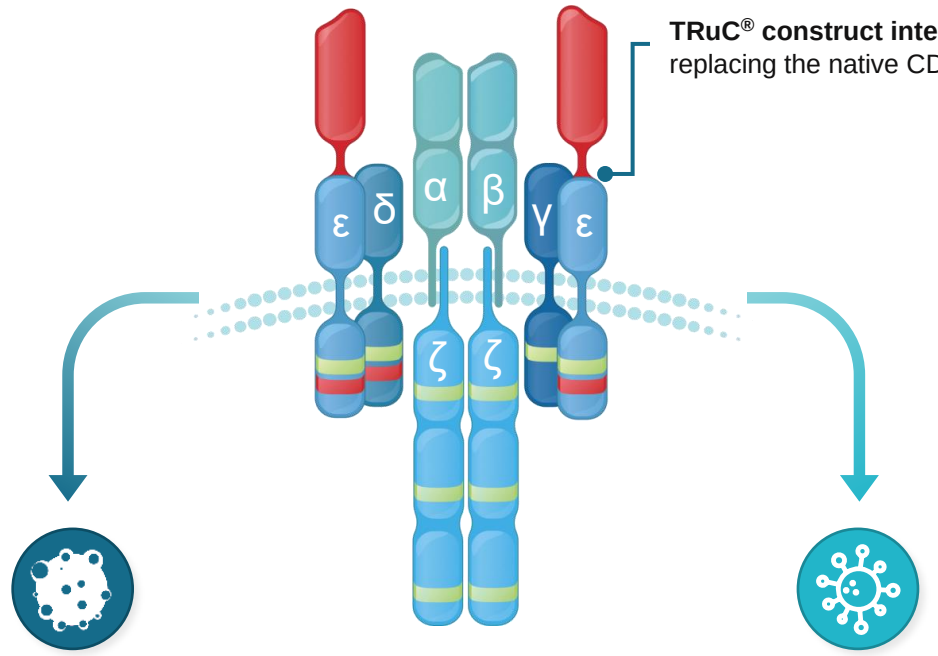
Evolving the Natural Power of the TCR

Advancing a New Cell Therapy Modality to Create Life-Transforming Medicines

Harnessing the TCR Complex

- Comprehensive T cell activation to **tackle solid tumors**
- **No HLA restriction** supports broad patient access
- **Versatile platform** with flexibility to add enhancements
- **Potential across oncology and autoimmune** in multiple high-value indications

TRuC® Platform
(T Cell Receptor Fusion Constructs)



TRuC® construct integrates into the TCR replacing the native CD3ε subunit

Cytotoxic TRuC-T Cells

Solid Tumors

Hematological Malignancies

TRuC Treg Cells

Autoimmune Diseases

Transplant Rejection

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Mesothelin Targeted Therapies

Raffit Hassan, M.D.

Chief of Thoracic and GI Malignancies Branch at the National Cancer Institute

Disclosures

Some of the clinical trials are supported by a Cooperative Research and Development Agreement between National Cancer Institute and:
Bayer AG
TCR^2 Therapeutics

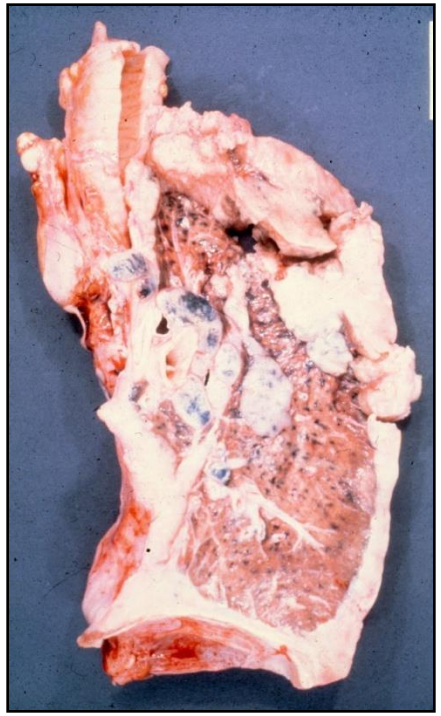
Malignant mesothelioma

Mesothelin as a target for cancer therapy

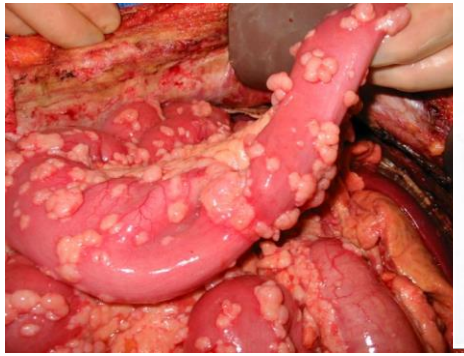
Anti-mesothelin agents in clinical trials

Adoptive cell therapies targeting mesothelin

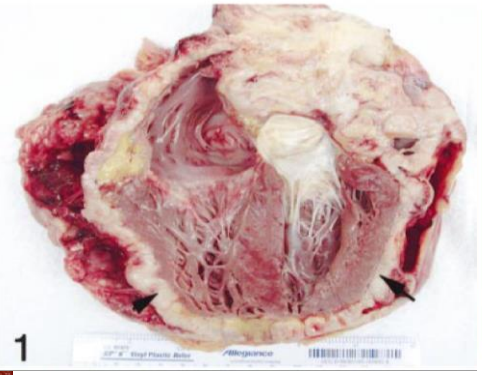
Malignant mesothelioma arises at sites that are lined by mesothelial cells



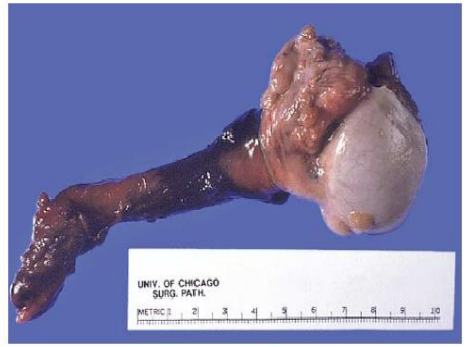
Pleural



Peritoneal

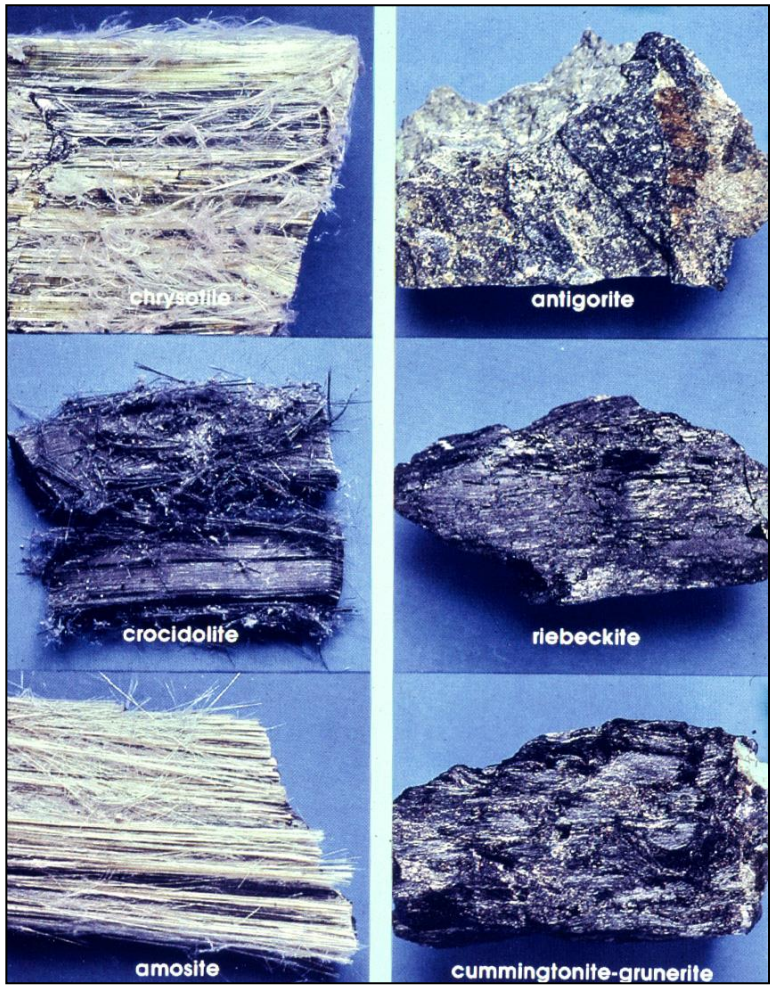


Pericardial



Tunica vaginalis

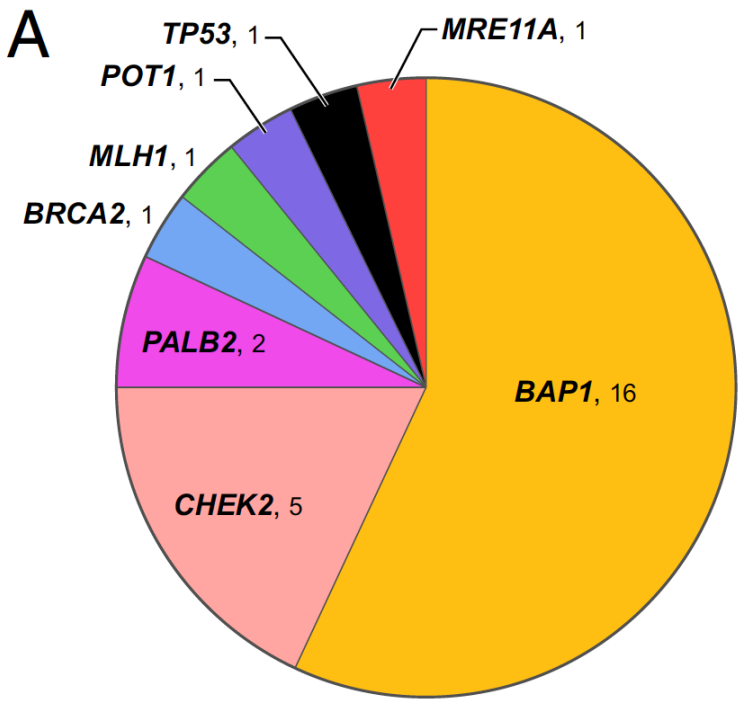
Malignant mesothelioma



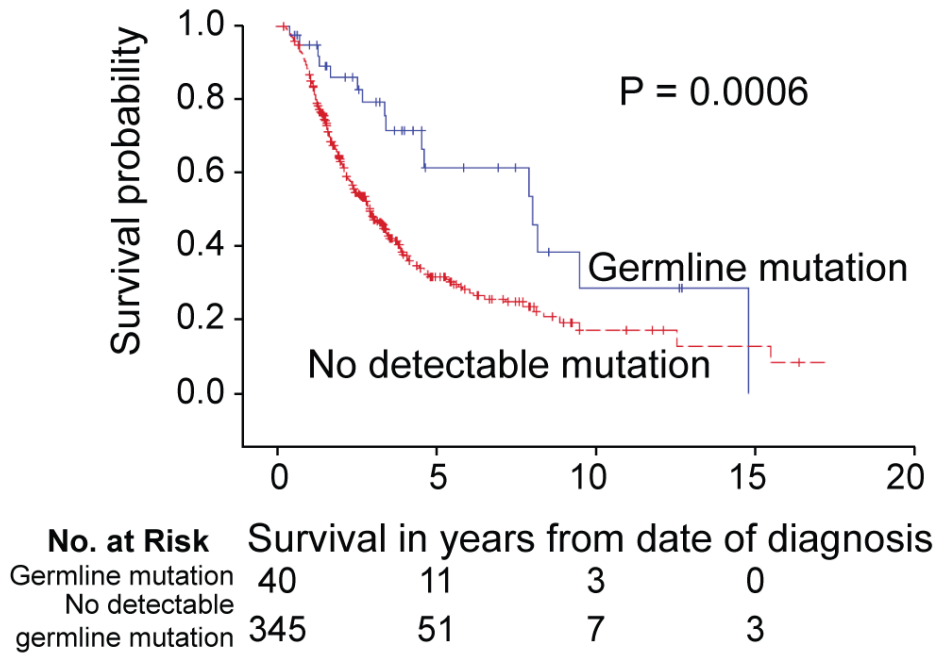
Asbestos fibers

- Asbestos is the primary cause of mesothelioma
- Patients with Hodgkin's disease and NHL that have received XRT have an increased risk of developing mesothelioma
- Mesothelioma risk also increased in patients with germline mutations in the *BAP1* gene

Germline mutations in DNA repair genes present in 12% of mesothelioma patients and associated with improved survival



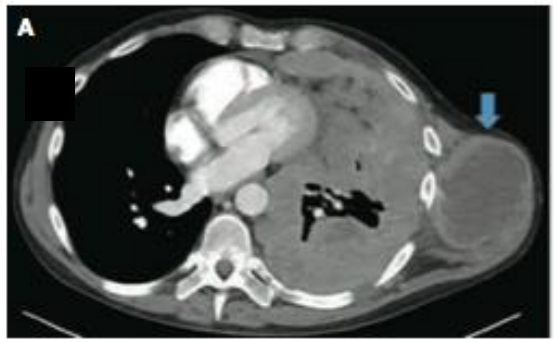
28 of 241 unselected patients

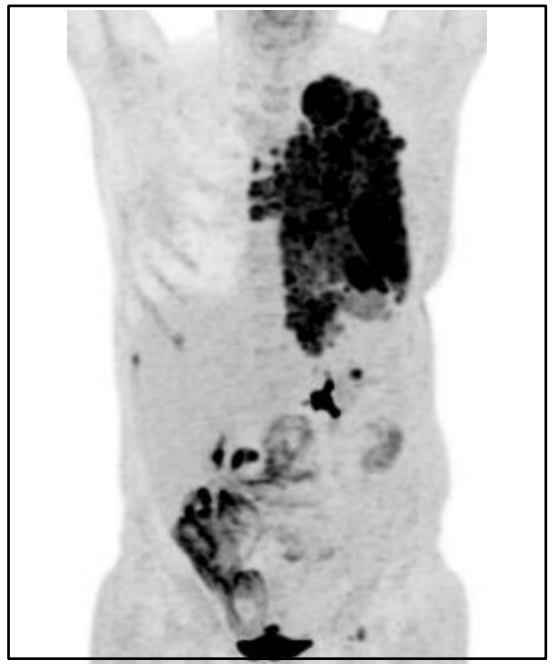


Hassan R et. al. *PNAS*, 2019

Pastorino S et. al., *J Clin Oncol*., 2018
Panou V et. al., *J Clin Oncol*., 2018
Zauderer MG et. al., *J Thorac Oncol*., 2019

Malignant pleural mesothelioma is an aggressive disease with poor prognosis

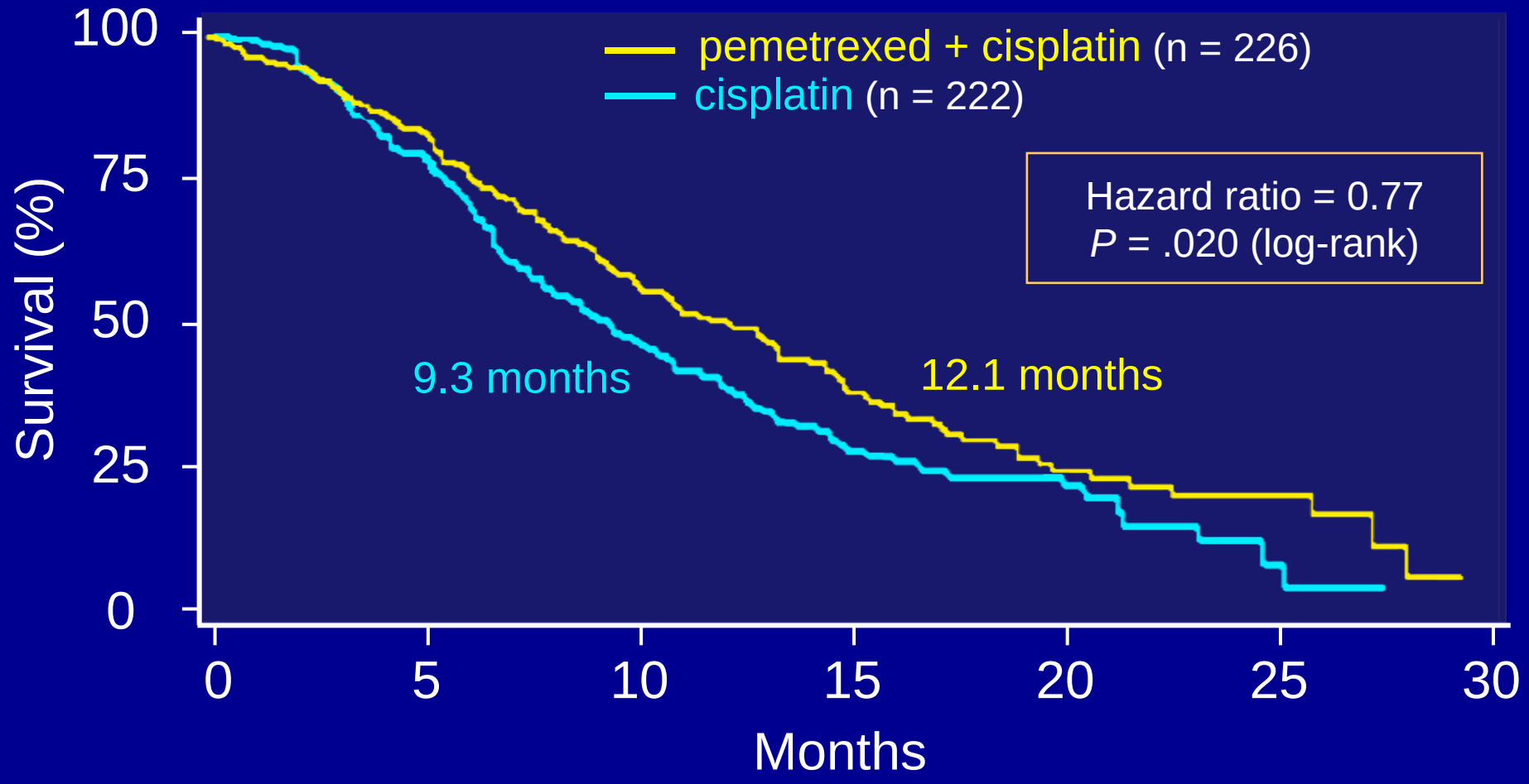




- About 3,000 cases in US each year
- Most patients present with advanced disease and not candidates for surgical resection
- Only FDA approved therapy for a long time was pemetrexed with cisplatin (2004)

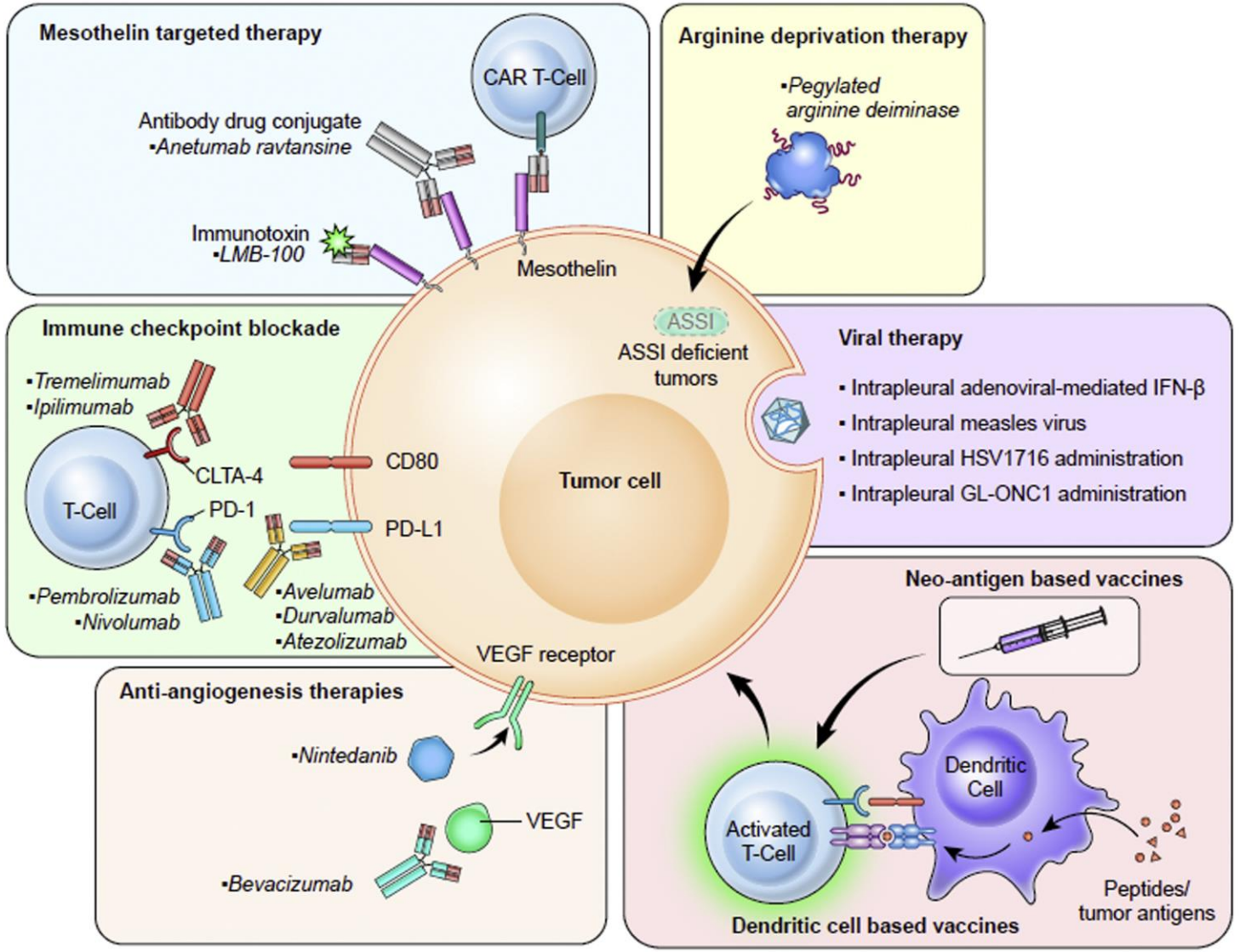
Kindler H,…Hassan R, *J Clin Oncol*., 2018
Vogelzang NJ et. al., *J Clin Oncol*., 2003

Phase III Study of Pemetrexed plus Cisplatin in MPM



Vogelzang NJ et al. *J Clin Oncol* 2003

Selected examples of different strategies currently in clinical trials for therapy of malignant mesothelioma



Luciano M,…Hassan, R. JTO, 2018

Efficacy of immune checkpoints in mesothelioma

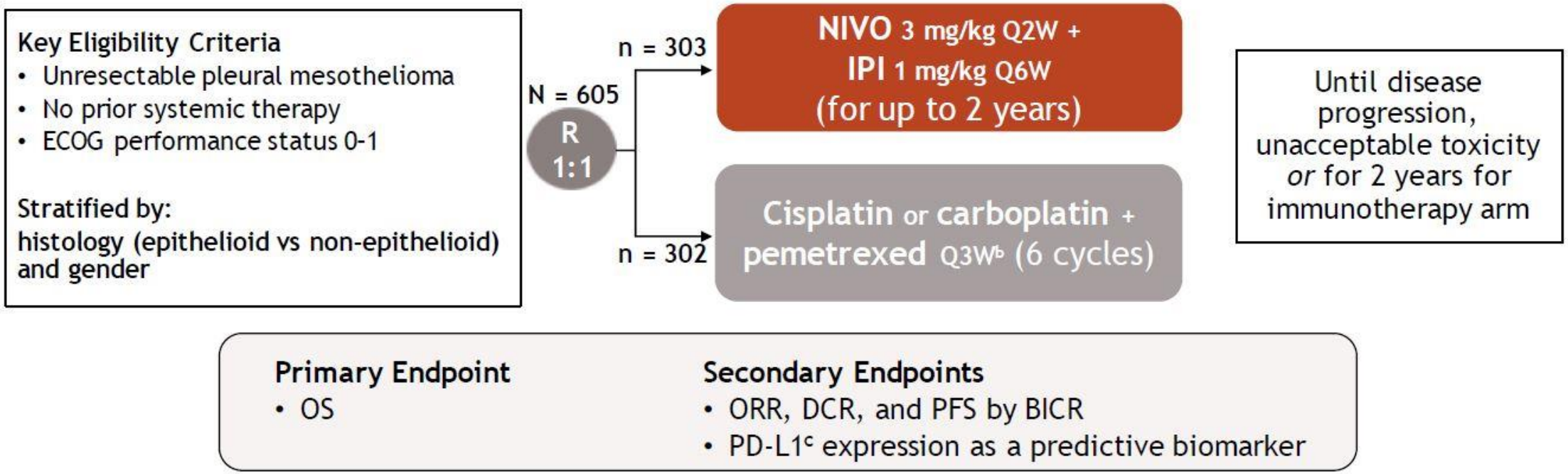
Checkpoint Inhibitor (Target)	Clinical Trials	Objective Response Rate (No. of Responders/ Total No. Enrolled)	References
Pembrolizumab (Anti-PD-1)	KEYNOTE-028: Ph 1b, 10 mg/kg every 2 wk up to 2 y	PR: **20%** (5/25)	Alley et al., 2017, Lancet Oncol
	Ph 2, 200 mg every 21 d	PR: **19%** (12/65)	Desai et al., 2018, J of Clin Oncol
Nivolumab (Anti-PD-1)	Ph 2, 3mg/kg every 2 wk	PR: **24%** (8/34)	Quispel-Janssen et al., 2018, J Thorac Oncol
	MERIT: Ph 2, 240 mg every 2 wk	ORR: **29%** (10/34)	Okada et al., 2019, Clin Cancer Res
Avelumab (Anti-PD-L1)	JAVELIN: Ph 1b, 10 mg/kg every 2 wks	1CR, 4PR: **9%** (5/53)	Hassan et al., 2019, JAMA Oncol
Tremelimumab (Anti-CTLA-4)	Ph 2, 15 mg/kg every 90 d	PR: **7%** (2/29)	Calabro et al., 2013, Lancet Oncol
	Ph 2, 10 mg/kg every 4 wk for 6 doses then every 12 wk	PR: **3%** (1/29)	Calabro et al., 2015, Lancet Respir Med
	DETERMINE: Ph 2b, same dose and schedule as above, treated (n=382) vs placebo (n=189)	**No benefit in OS**	Maio et al., 2017, Lancet Oncol

First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial

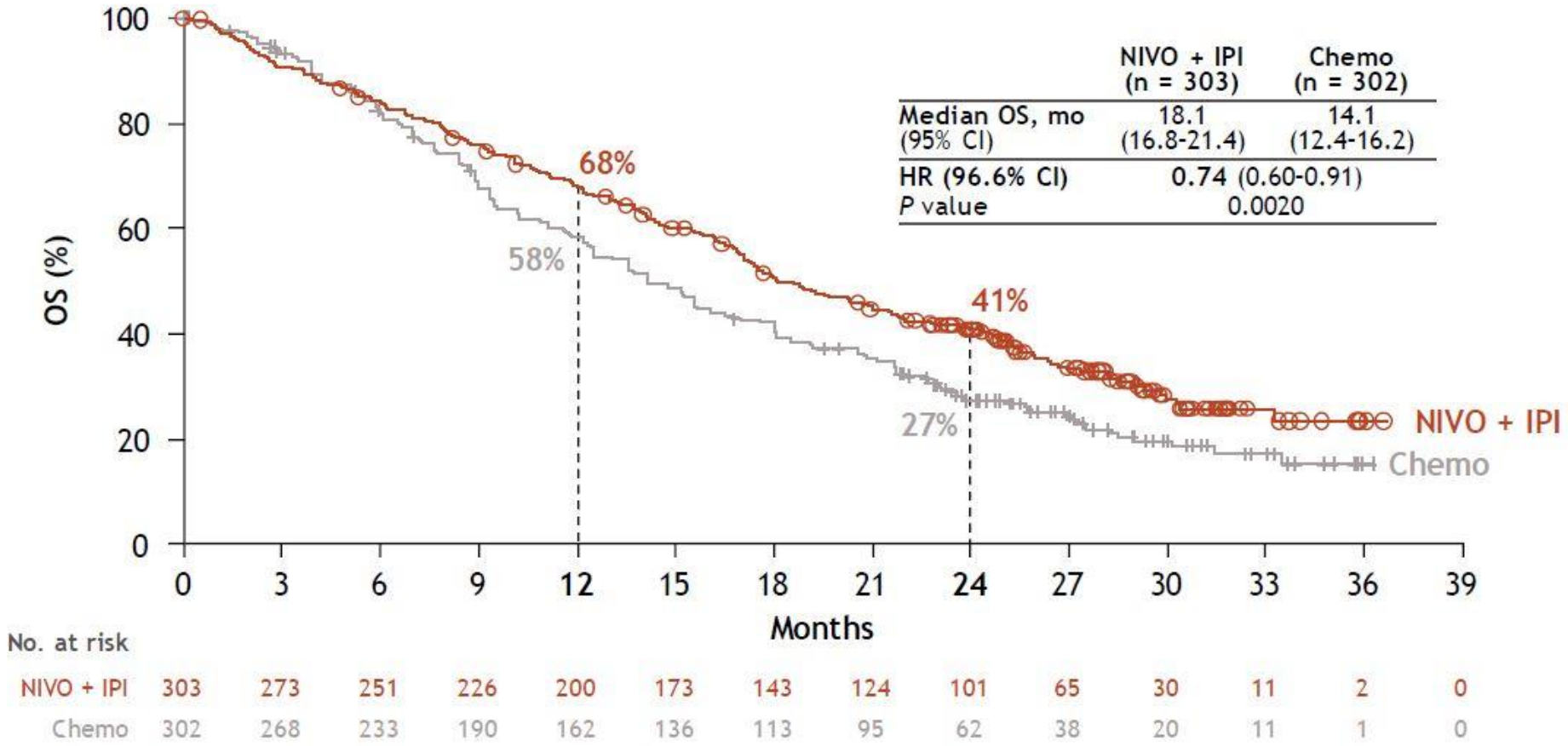
Paul Baas, Arnaud Scherpereel, Anna K Nowak, Nobukazu Fujimoto, Solange Peters, Anne S Tsao, Aaron S Mansfield, Sanjay Popat, Thierry Jahan, Scott Antonia, Youssef Oulkhouir, Yolanda Bautista, Robin Cornelissen, Laurent Greillier, Francesco Grossi, Dariusz Kowalski, Jerónimo Rodríguez-Cid, Praveen Aanur, Abderrahim Oukessou, Christine Baudelet, Gérard Zalcman

***Lancet*, 2021**

Trial Design (CheckMate 743)



Overall survival



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS, mo (95% CI)	18.1 (16.8-21.4)	14.1 (12.4-16.2)
HR (96.6% CI)	0.74 (0.60-0.91)	
P value	0.0020	

Summary (CheckMate 743)

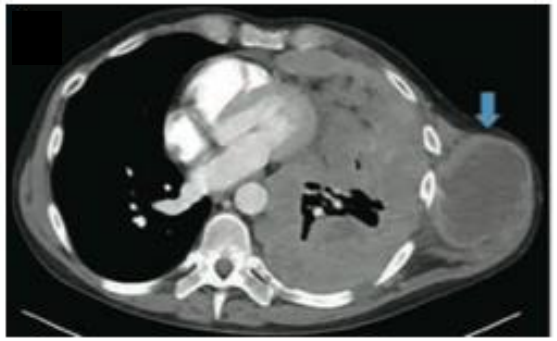
- **Frontline therapy with ipilimumab plus nivolumab increased overall survival in patients with mesothelioma**
- **This regimen significantly increase OS in sarcomatoid mesothelioma**
- **Effect on OS less profound in epithelioid mesothelioma**
- **FDA approved in US in 2020**

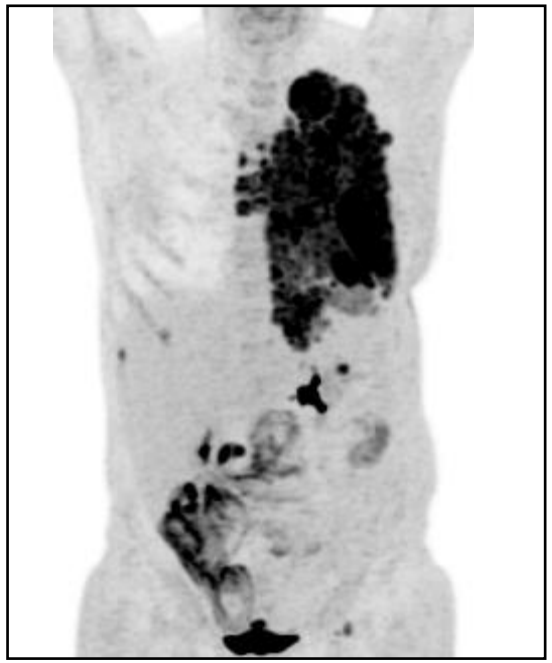
Other chemotherapy agents for mesothelioma have limited efficacy

Author, Date	Regimen	Setting	Number of Patients	ORR	PFS (months)	OS (months)
Stebbing, 2008	Vinorelbine	Phase 2 open-label non-comparative study; relapsed MPM	63	16%		9.6
Zauderer, 2014	Vinorelbine	Retrospective study; second- or third-line treatment in MPM	45	0%	1.7	5.4
Zauderer, 2014	Gemcitabine	Retrospective study; second- or third-line treatment in MPM	27	4%	1.6	4.9

MPM = malignant pleural mesothelioma; ORR = overall response rate (complete response + partial response); PFS = progression-free survival; OS = overall survival

Treatment options for patients with malignant mesothelioma in 2021





- **FDA approved therapies:**

  Pemetrexed plus cisplatin, 2004

  Nivolumab plus Ipilimumab, 2020

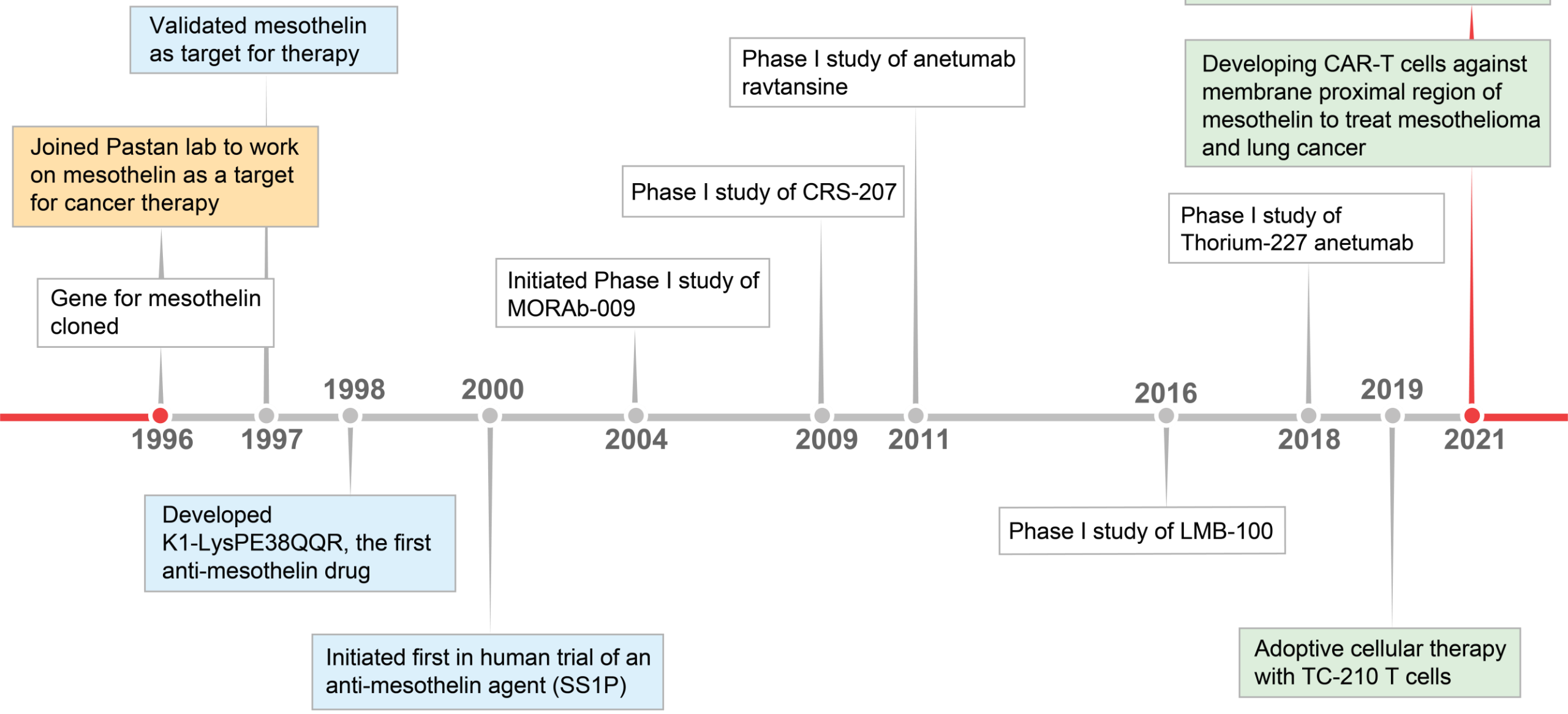
- **Third line agents: gemcitabine, vinorelbine**
- **Participation in clinical trials**

Median overall survival ~18 months

Kindler H,…Hassan R, *J Clin Oncol*., 2018
Vogelzang NJ et. al., *J Clin Oncol*., 2003
Baas P et. al., *Lancet*, 2021

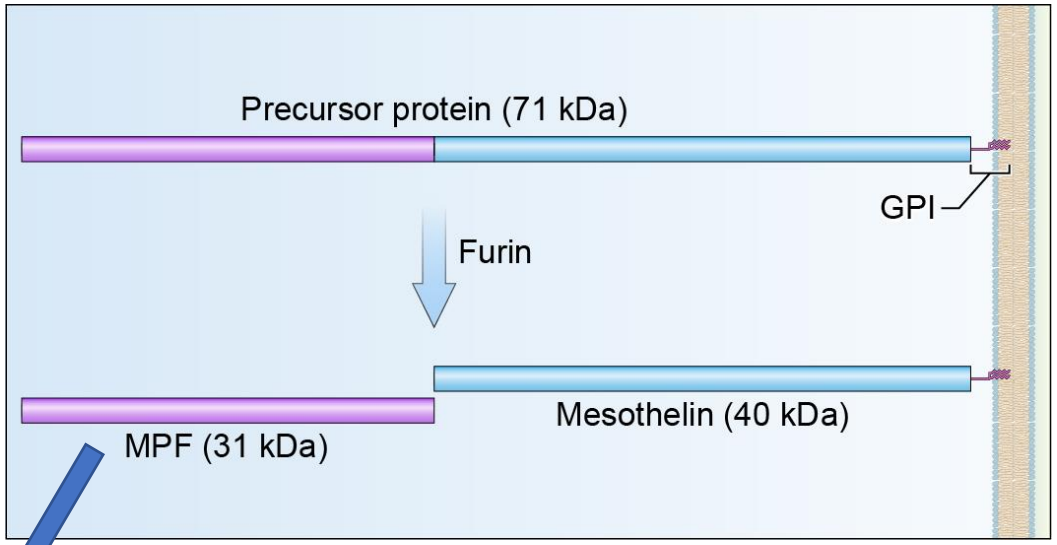
Mesothelin Targeted Immunotherapy for Malignant Mesothelioma

Developing therapies to target mesothelin has been the main focus of my lab over last 25 years



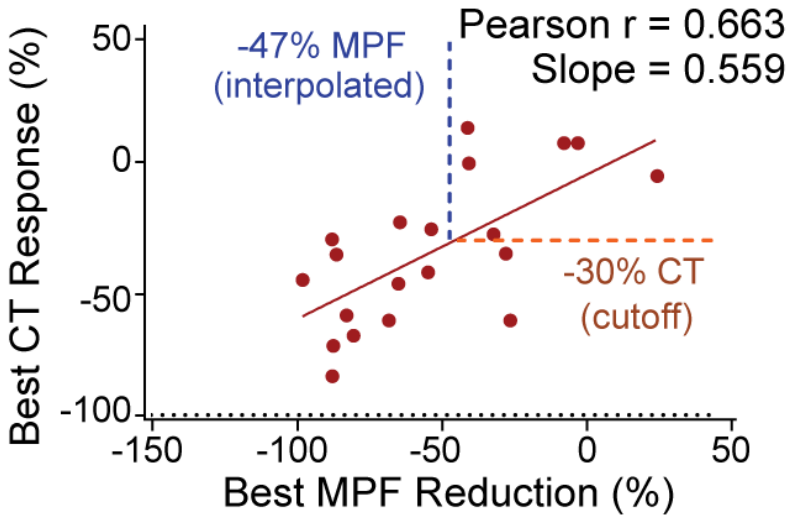
Mesothelin

- Cell surface glycoprotein
- Expression in normal human tissues limited to mesothelial cells lining pleura, peritoneum and pericardium
- Mesothelin binds MUC16 and may play a role in tumor metastases



Chang K, Pastan I., PNAS 1996
Pastan I, Hassan R., Cancer Res. 2014

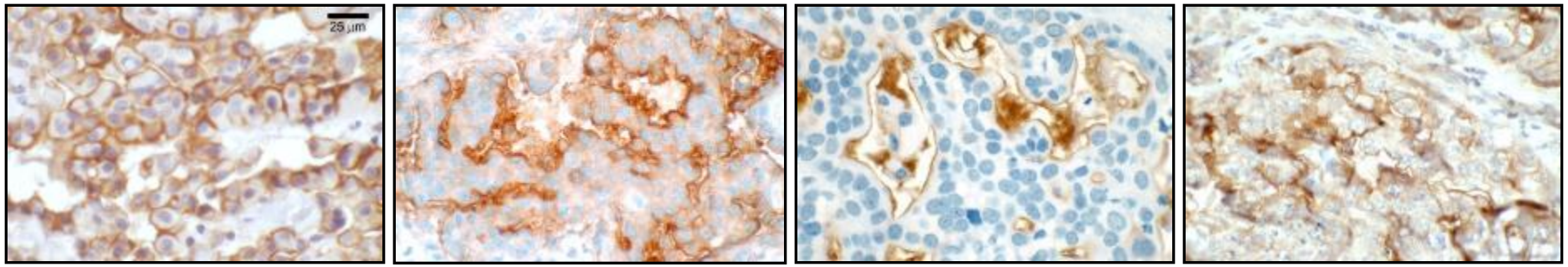
Serum MPF a biomarker of tumor response



Yu Y et. al., *J Appl Lab Med*., 2018
Cao L et. al., *JCO Precis Oncol*., 2018

Mesothelin is highly expressed in most solid tumors

- Mesothelioma (epithelial) ~ 100%
- Pancreatic Cancer ~ 80%
- Ovarian Cancer 67-71%
- Lung adenocarcinoma 41-53%
- Gastric cancer, synovial sarcomas, TNBC, biliary cancers, thymic



Mesothelioma Ovarian Cancer Pancreatic Cancer Lung Cancer

Hassan et al. Clin. Cancer Res., 2004
Ordonez NG. Am J Surg Pathol, 2003.
Ho M et al. Clin Cancer Res, 2007

European Journal of Haematology ISSN 0902-4441

ORIGINAL ARTICLE

Mesothelin, a possible target for immunotherapy, is expressed in primary AML cells

Daniel Steinbach[1,2], Masanori Onda[3], Astrid Voigt[1], Kristin Dawczynski[1], Susan Wittig[1], Raffit Hassan[3], Bernd Gruhn[1], Ira Pastan[3]

[1]University Children's Hospital Jena, Germany; [2]University Children's Hospital Ulm, Germany; [3]Laboratory of Molecular Biology, National Cancer Institute, Bethesda, MD, USA

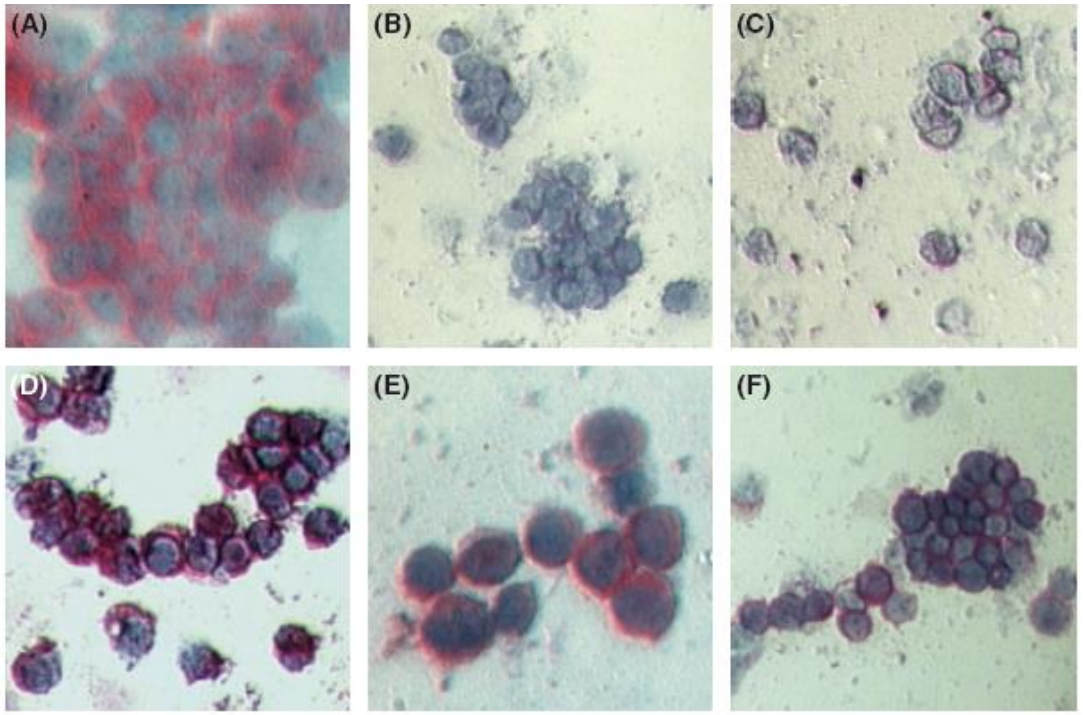
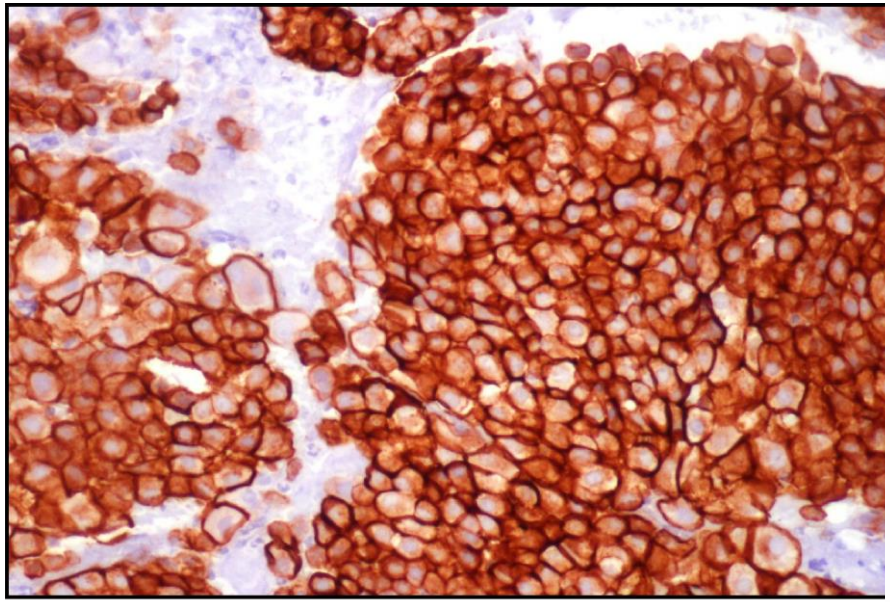


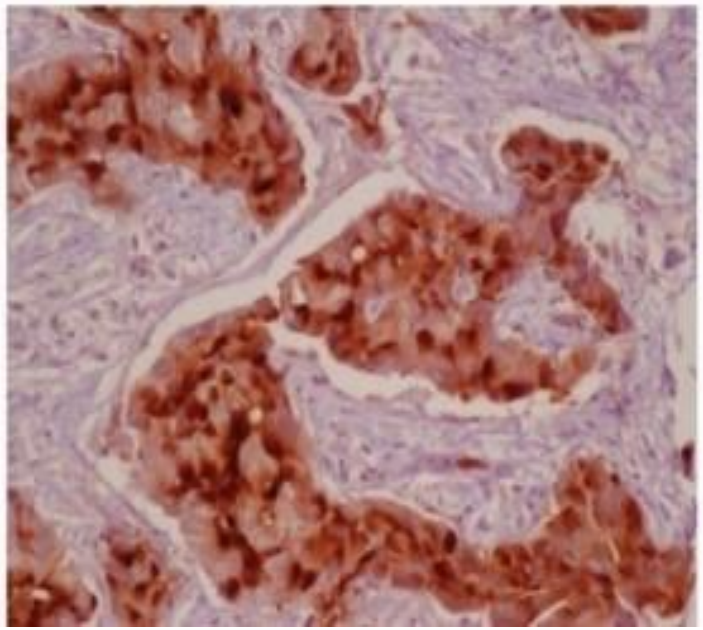
Figure 2 Immunocytochemistry using the anti-mesothelin antibody K1. (A) cell line OVCAR3; (B) cell line SK-N-MC; (C) patient 1; (D) patient 13; (E) patient 7; (F) patient 8.

Cell surface mesothelin expression in AML blasts

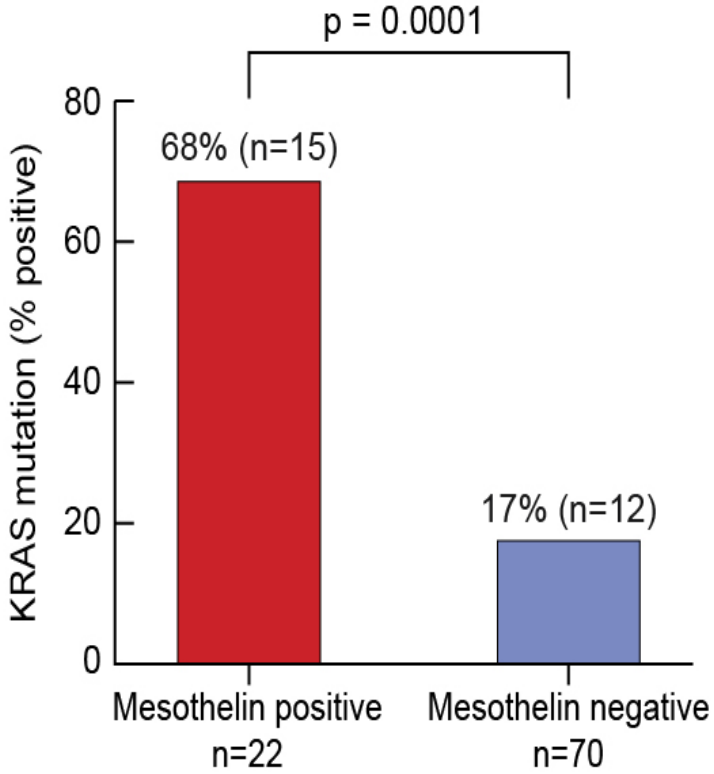
My research has mostly focused on mesothelioma (and lung cancer)



Epithelial mesothelioma



Lung adenocarcinoma



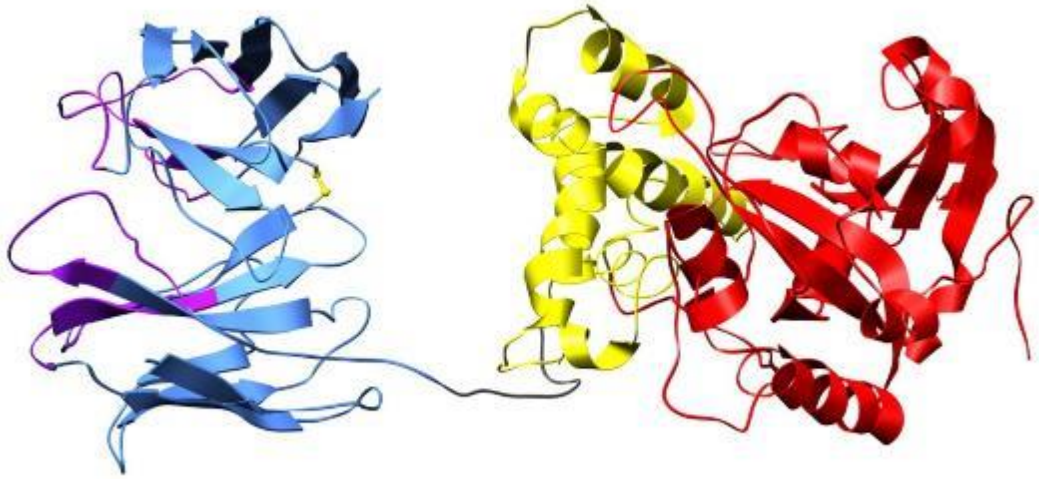
Correlation of tumor mesothelin expression with KRAS mutations

Ho M et. al., *Clin Cancer Res.*, 2007
Zhang J et. al., *PLoS One*, 2014
Thomas A et. al., *Oncotarget*, 2015

Targeting mesothelin for cancer therapy

- **High cell surface expression in many solid tumors makes it a good target for antibody based therapies**
- **Expression on pleura, pericardium and peritoneum was a concern when we decided to exploit it as a target for cancer therapy in 1996**

SS1P: The first anti-mesothelin drug in clinic



Anti-Mesothelin Fv PE38

First patient treated 2001

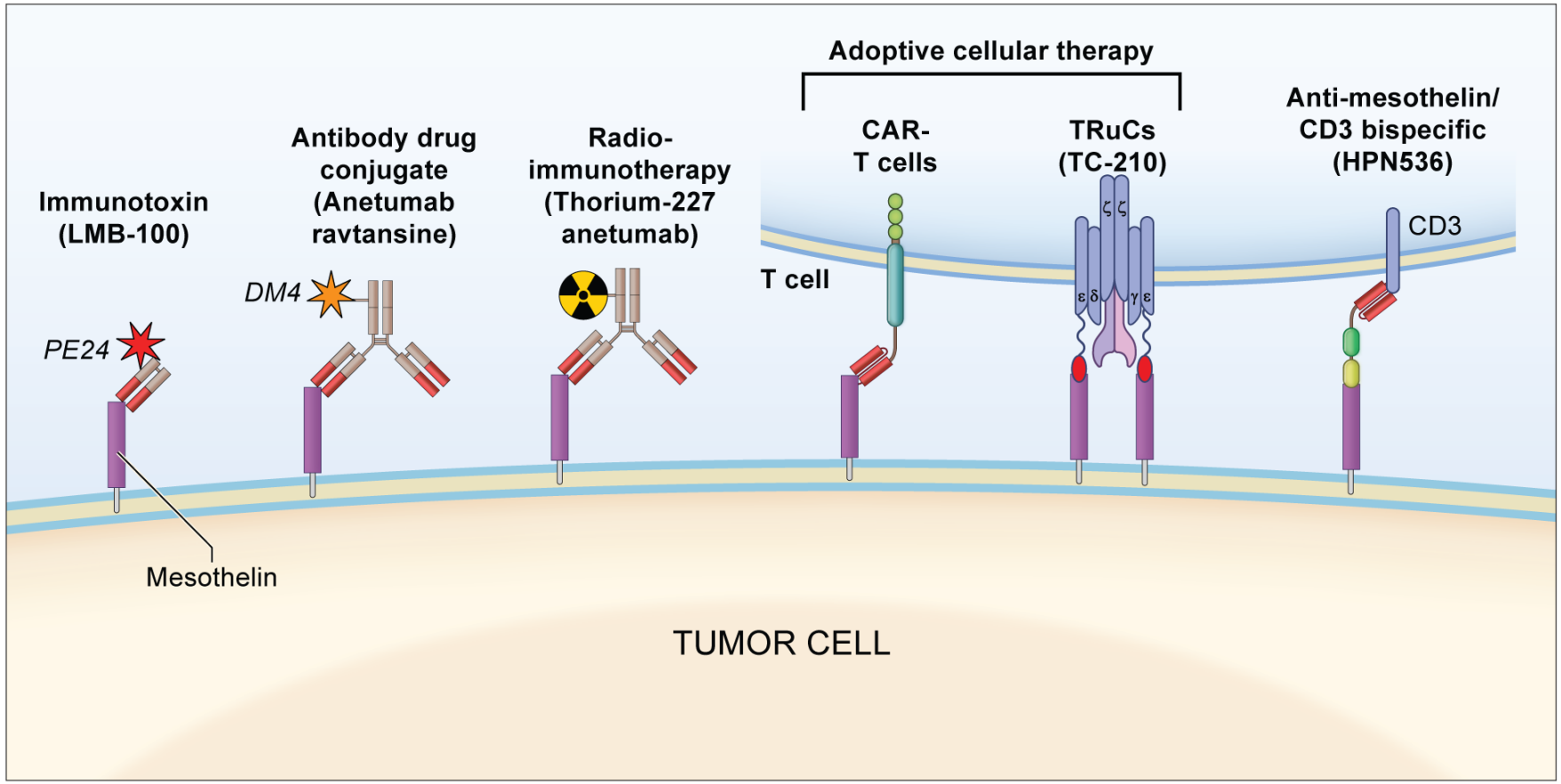
- **Cytotoxic to tumor cells of patients with mesothelioma and ovarian cancer**
- **Safety shown in phase I clinical trial, DLT -pleuritis**
- **Immunogenic, 30/34 (88%) pts. developed neutralizing antibodies after cycle 1**

Chowdhury P, Pastan I., PNAS 1998
Hassan R et al., Clin. Cancer Res. 2002
Hassan R et al., Clin. Cancer Res. 2007

Lessons learned form SS1P Phase I Study

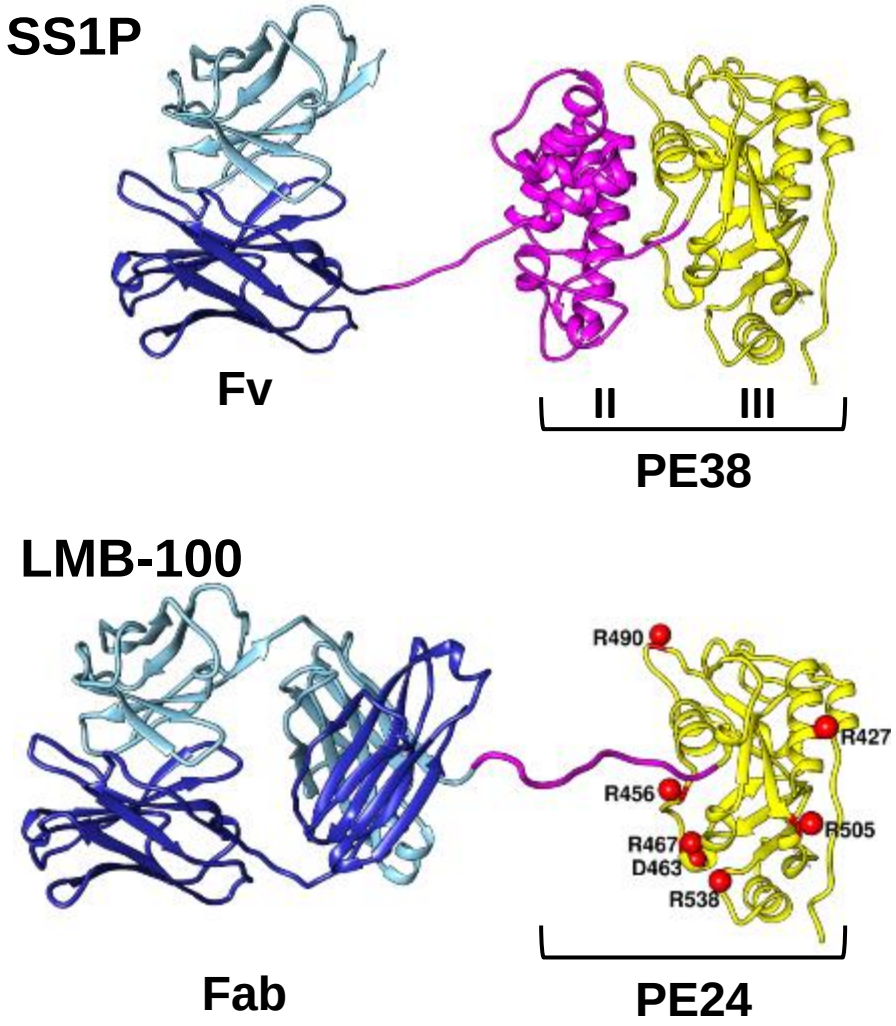
- **Mesothelin is a good target for cancer therapy**
- **No off-target toxicity or pericarditis**
- **Led to interest in developing other anti-mesothelin therapies**

Mesothelin targeted therapies currently in clinical trials



Hassan R et. al. *Journal of Clinical Oncology*, 2016
Hassan R et. al. *Cancer, 2020*
Hassan R et. al. *Journal of Clinical Oncology*, 2020
Hassan R et. al. *Clin Cancer Res*., 2019
Jiang Q…Hassan R. *Science Transl. Medicine,* 2020

LMB-100: an improved immunotoxin targeting mesothelin



- All known human B cell epitopes and many T cell epitopes of PE have been removed or mutated
- It has reduced antigenicity

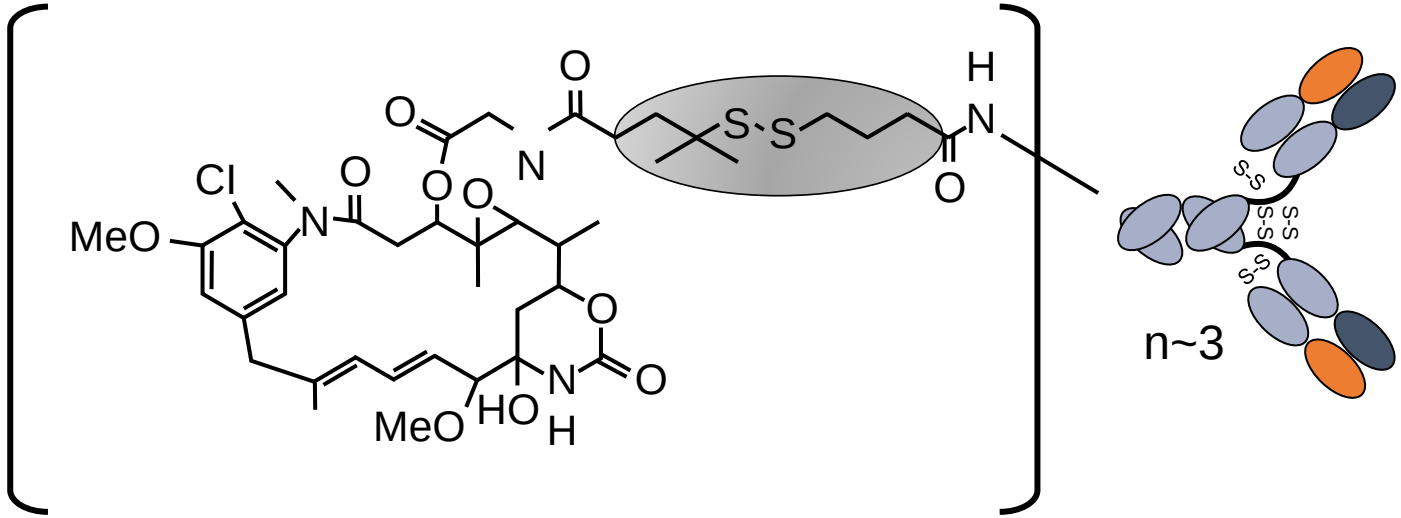
Liu et al., PNAS, 2012
Mazor R et al., PNAS,2014
Weldon JE et al., Mol Cancer Ther, 2013
Hollevoet K et al., Mol Cancer Ther, 2014
Onda M et. al. PNAS, 2008

LMB-100 Phase I Clinical Trial: Summary

- **25 patients enrolled**
- **MTD: 140 mcg/kg on days 1, 3, 5 q 3 weeks**
- **DLT: vascular leak syndrome**
- **All patients had good blood levels in cycles 1 and half in cycle 2**
- **Out of 10 evaluable mesothelioma patients 8 stable disease; 2 had PD**

Hassan R et. al. *Cancer, 2020*

Anetumab ravtansine : Anti-mesothelin ADC

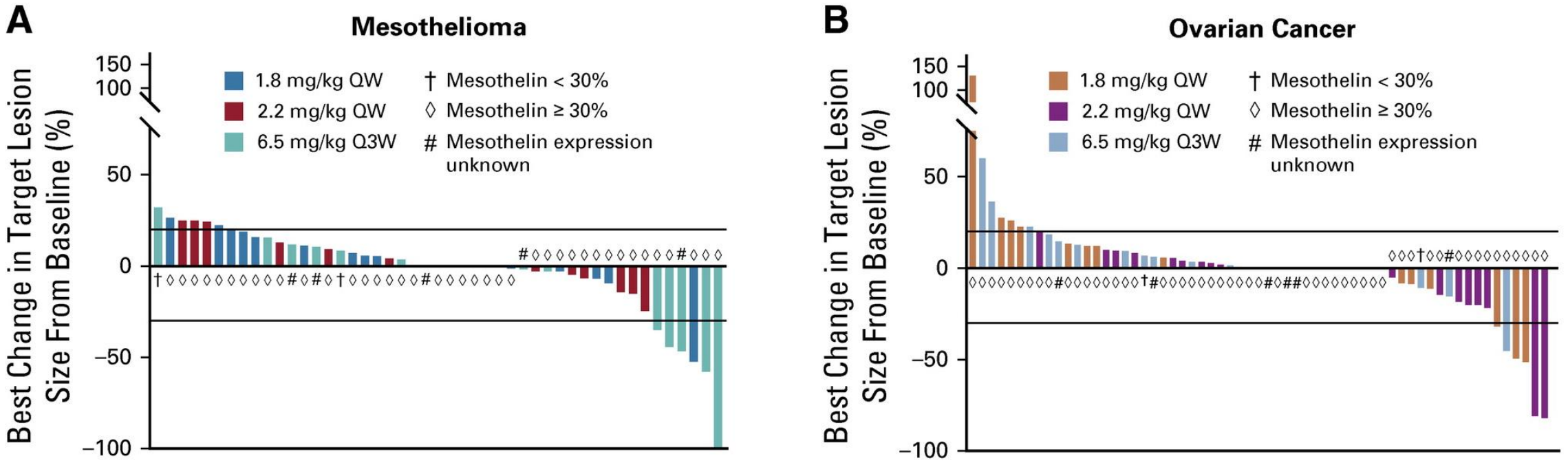


- **Fully human anti-mesothelin antibody conjugated to DM4**
- **Targeted delivery of the potent anti-proliferative toxophore DM4 (tublin inhibitor) to tumor cells expressing mesothelin**
- **Anti-tumor activity against mesothelin expressing xenografts including mesothelioma PDX models**

Golfier S et al. Mol. Cancer Ther. 2014

original reports

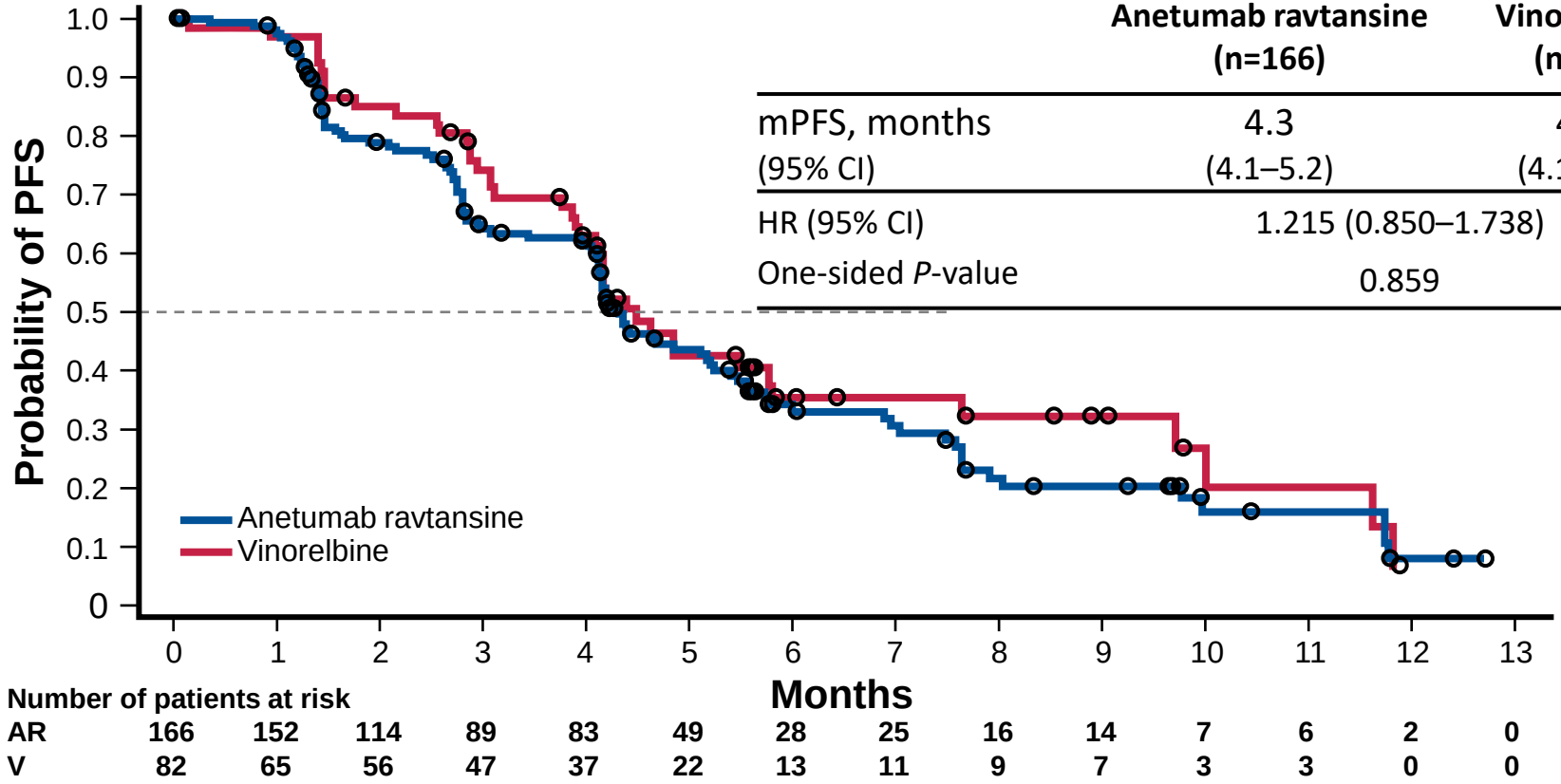
First-in-Human, Multicenter, Phase I Dose-Escalation and Expansion Study of Anti-Mesothelin Antibody–Drug Conjugate Anetumab Ravtansine in Advanced or Metastatic Solid Tumors



Hassan et al., J Clin Oncol, 2020

Phase II Study of Anetumab Ravtansine versus Vinorelbine in Patients with Malignant Pleural Mesothelioma

Primary Endpoint: PFS

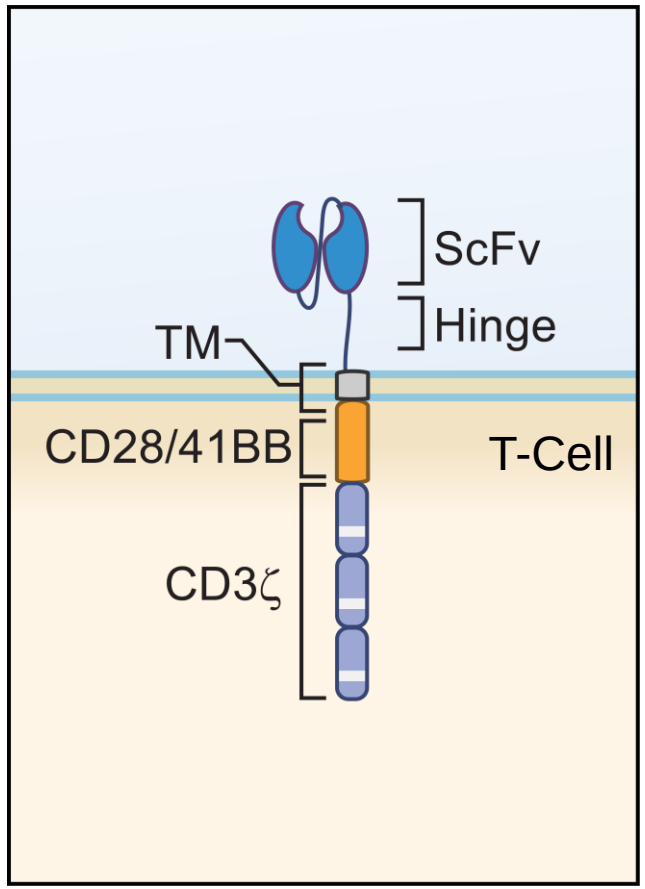


	Anetumab ravtansine (n=166)	Vinorelbine (n=82)
mPFS, months (95% CI)	4.3 (4.1–5.2)	4.5 (4.1–5.8)
HR (95% CI)	1.215 (0.850–1.738)	
One-sided *P*-value	0.859	

IASLC Annual Meeting, 2017

Mesothelin as a target for adoptive T cell therapy

Developing effective CAR-T cell therapy for solid tumors



CAR-T cell

- **This is a major challenge in the field**
- **Limited efficacy in epithelial cancers**

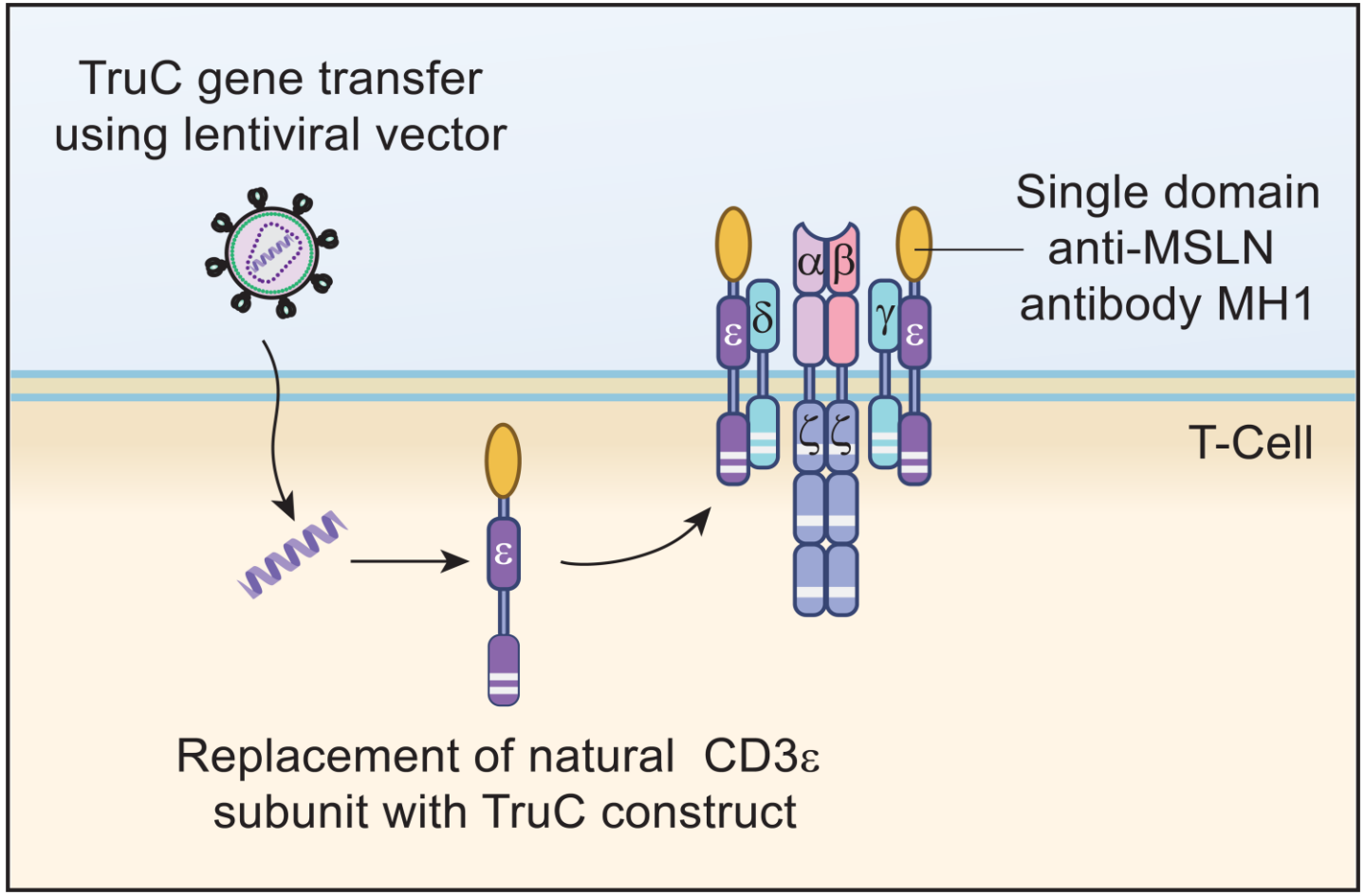
Rafiq S et. al. *Nature Reviews Clinical Oncology*, 2020
Fuca G et. al. *Clin Cancer Res.*, 2020
Schmidts A et. al. *Frontiers in Immunology*, 2018
Morello A,..Adusumilli P. *Cancer Discovery*, 2016

Anti-mesothelin CAR-T cells have not been effective

NCT number	CAR-T cell product	Delivery Route	Malignancies	No. of Patients	Response to CAR-T	References
NCT01355965	mRNA transduced mouse ScFv	Intravenous	MPM and PDAC	4	**1PR**	Maus et al., 2013, Cancer Immunol Res Beatty et al., 2014, Cancer Immunol Res
NCT02159716	CAR-T meso, Lentiviral transduced mouse ScFv	Intravenous	MPM, Ovarian Carcinoma and PDAC	15	**No PR/CR**	Hass et al., 2019, Mol Therapy
NCT02414269	iCasp9M28z	Intrapleural	MPM, Breast Cancer, Lung Cancer	27 (25 MPM)	**No PR/CR***	Adusumilli et al., 2021, Cancer Discovery
NCT03608618	mRNA transduced PBMC	Intra-peritoneal	Peritoneal mesothelioma and Ovarian cancer	11	**No PR/CR**	Annunziata et al., ASCO 2020
NCT03545815	MPTK-CAR-T (PD-1/TCR deficient)	Intravenous	Mesothelin expressing solid tumors	15	**No PR/CR**	Wang et al., 2021 Cell Mol Immunology
NCT03054298	huCART-meso, Lentiviral transduced human scFv	Intravenous/ intrapleural	Mesothelin expressing solid tumor	Recruiting	Not available	
NCT04577326	M28z-1XXPD1DNR	Intrapleural	MPM	Recruiting	Not Available	

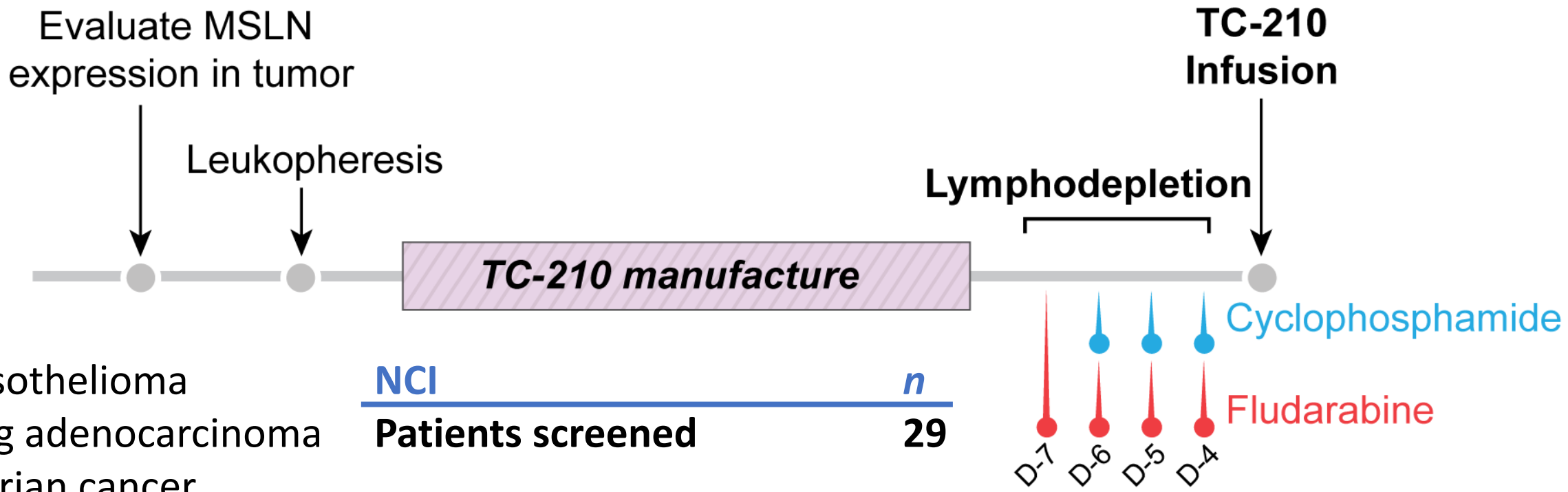
* 2 out of 18 patients who received off protocol pembrolizumab had PR

Gavocabtagene autocel (Gavo-cel; TC-210): anti-mesothelin T cell receptor fusion construct (TRuC)



- **Anti-tumor efficacy in pre-clinical mesothelin positive tumor models**
- **Long-term functional persistence of TC-210 cells**
- **Better efficacy than CAR-T cells using same anti-mesothelin antibody**

Phase I study of gavo-cel



Mesothelioma
Lung adenocarcinoma
Ovarian cancer
Cholangiocarcinoma

NCI	*n*
Patients screened	**29**
High mesothelin expression	**18**
Leukapheresis performed	**13**
TC-210 cells infused	**5**

Grade ≥3 adverse events of special interest

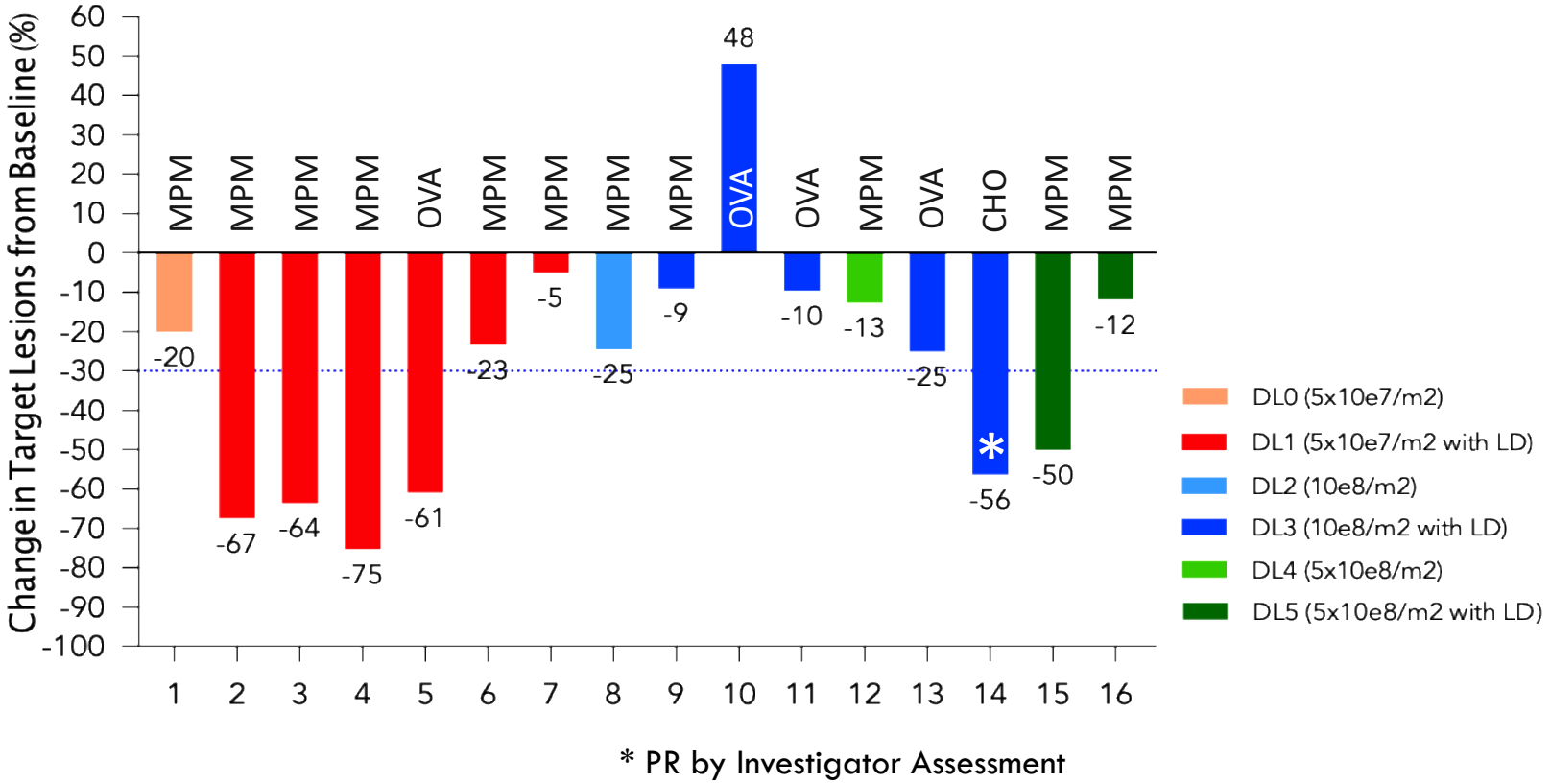
Adverse Event	DL 0 (no LD) $5x10^7/m^2$ n=1 (%)	DL 1 $5x10^7/m^2$ n=6 (%)	DL 2 (no LD) $1x10^8/m^2$ n=1 (%)	DL 3 $1x10^8/m^2$ n=5 (%)	DL 4 (no LD) $5x10^8/m^2$ n=1 (%)	DL 5 $5x10^8/m^2$ n=3 (%)	Overall n=17 (%)
On target/On tumor							
CRS	0	2 (33)	0	1 (20)	0	3 (100)	6 (35)
Neurotoxicity	0	0	0	0	0	0	0
On target/Off tumor							
Pericarditis / Pericardial effusion	0	0	0	0	0	0	0
Pleuritis / Pleural effusion	0	0	0	0	0	0	0
Peritonitis/Ascites	0	0	0	0	0	0	0
Other							
Pneumonitis	0	1 (17)*	0	0	0	0	1 (6)
Sepsis	0	1 (17)	0	0	0	0	1 (6)
Hemorrhage	0	0	0	0	0	1 (33)*	1 (6)

* Dose Limiting Toxicity

Data cut-off date: June 30th, 2021

Tumor Regression and Response Assessment

Evaluable patients, N=16



* PR by Investigator Assessment

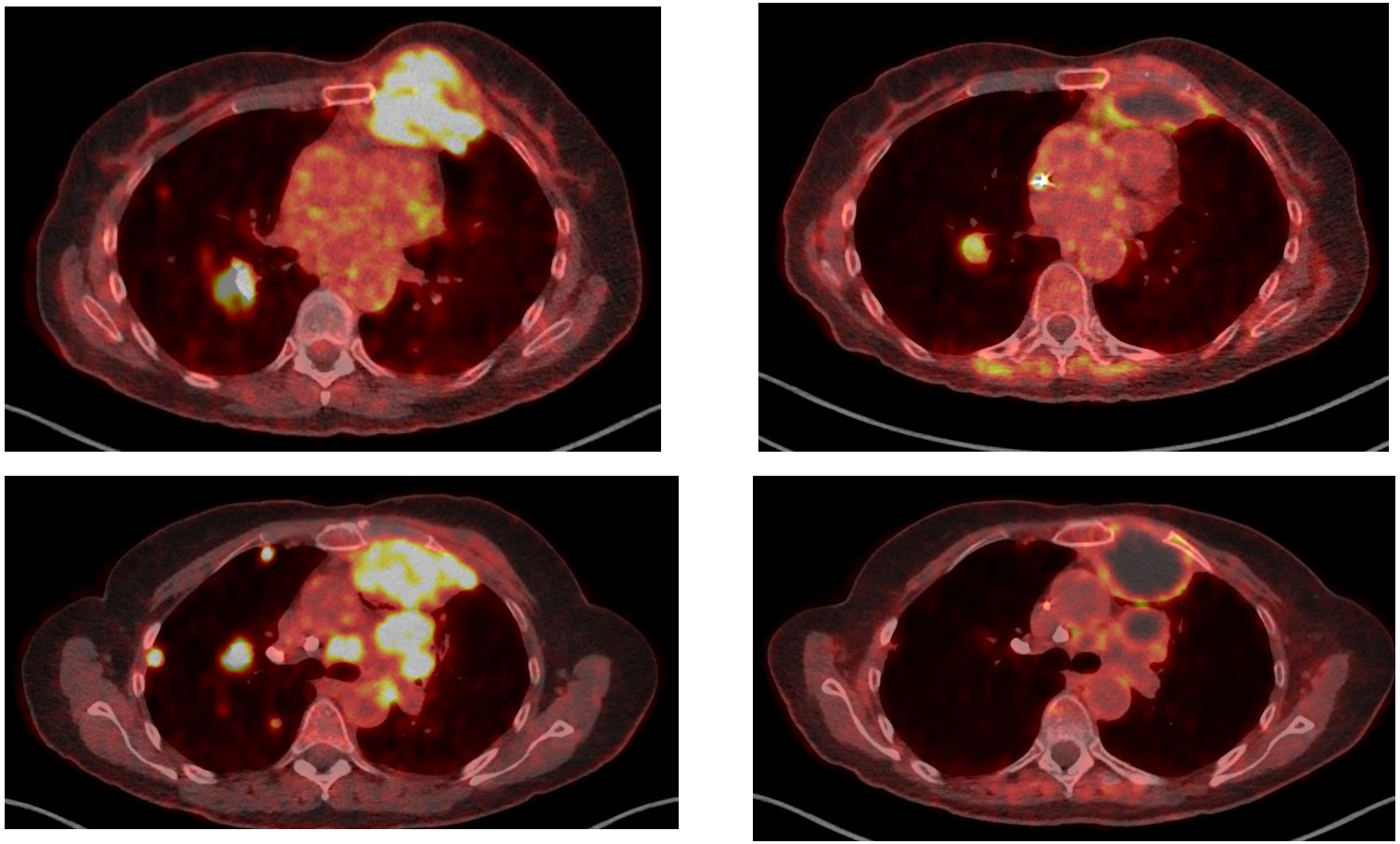
	Overall	LD Group
DCR	81%	77%
ORR (independent)	25%	31%
ORR (investigator)	31%	38%

DCR = PR or SD lasting at least 3 months

2021 ESMO congress

MPM: malignant pleural/peritoneal mesothelioma; OVA: ovarian cancer; CHO: cholangiocarcinoma; DL: dose level; LD: lymphodepletion; DCR: disease control rate; ORR: overall response rate

Treatment response in a patient with extensive treatment refractory mesothelioma with single infusion of gavo-cel



Baseline

Day 28

Gavo-cel: summary

- Phase I dose-escalation ongoing
- Cytokine release syndrome is common but manageable
- Radiologic and biomarker response in some patients
- Efficacy in mesothelioma patients is encouraging and warrant phase II studies

Acknowledgements

Hassan Lab

Qun Jiang

Jingli Zhang

Betsy Morrow

Manjistha Sengupta

Sakshi Tomar

Chaido Stathopoulou

Abhilash Venugopalan

Vikram Misra

Keval Yerigeri

Clinical Team

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Jeevan Puthiamadathil

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Yvonne Mallory

Maria Gracia Agra

Cathy Wagner

Susan Sansone

NCI-NIH collaborators

Ira Pastan

Mitchell Ho

Christine Alewine

David Schrump

Markku Miettinen

Mark Raffield

Javed Khan

Seth Steinberg

Eytan Ruppin

Alexandra Lebensohn

gavo-cel Clinical Update

Identification of RP2D within Reach

Alfonso Quintás-Cardama, M.D.
Chief Medical Officer

TCR2 THERAPEUTICS

Patients Treated post ESMO

Dose Level	DL3 ($1x10^8/m^2$)	DL3.5A ($3x10^8/m^2$ fractionated)		
Patients	18	19	20	21
Age/Sex	59/F	66/F	50/M	43/F
Diagnosis	MPM	MPM	MPM	MPM
MSLN 2+/3+	60	92	75	70
No. Prior Rx	5	9	7	10
ICI	No	Yes	Yes	Yes
Anti-MSLN Rx	No	No	Yes	No
Bridging Therapy	Yes	Yes	Yes	Yes
LD Chemo	Yes	Yes	Yes	Yes
Highest CRS	Gr 1	Gr 1	Gr 2	None yet

Data Cutoff – October 13, 2021

ICI, immune checkpoint inhibitor; MSLN, mesothelin; LD, lymphodepletion; CRS, cytokine release syndrome; Gr, grade; MPM, malignant pleural/peritoneal mesothelioma

TCR2 THERAPEUTICS

gavo-cel Phase 1 Summary and Next Steps

- MTD identified at DL5 ($5x10^8/m^2$ following LD)
  - Currently testing lower doses with fractionation
    - DL3.5A: 3/3 split patients treated
- Identification of RP2D before year-end

- Next steps:
  - *Proposed Phase 2 design to FDA, including:*
    - New mesothelin expression cutoff
    - gavo-cel redosing
    - Checkpoint combinations
  - *Initiation of Phase 2 study*

TCR2 THERAPEUTICS

gavo-cel + Checkpoint Inhibitor Combination Rationale

- Cancer limits antitumor responses by expressing immune checkpoints such as PD-L1[1,2,3]
- PD-L1 expression is induced by T cell–secreted IFN-γ and TNF-α[2]
- The addition of PD-(L)1 blockade therapy[1,2,3]:
  - Rescues the function of exhausted T cells
  - Enhances persistence and function of CAR T cells
  - Induces epitope spreading and neoantigen response through promotion of endogenous immunity
- Clinical synergism between anti-MSLN CAR T and pembrolizumab shown in mesothelioma[4]

[1]Cherkassky et al. J Clin Invest 2016; [2]Grosser et al. Cancer Cell 2019; [3]Adusumilli et al. Sci Transl Med 2014; [4]Adusumilli et al. Cancer Discov 2021

Boosting TRuC-T Cells with Enhancements

Matching Enhancements with Indication Specific Biology

Robert Hofmeister, Ph.D.
Chief Scientific Officer

TCR2 THERAPEUTICS

The TRuC Platform Has Exponential Options

Solid Tumor Franchise

MSLN, CD70, GPC3, NECTIN4

Enhancements

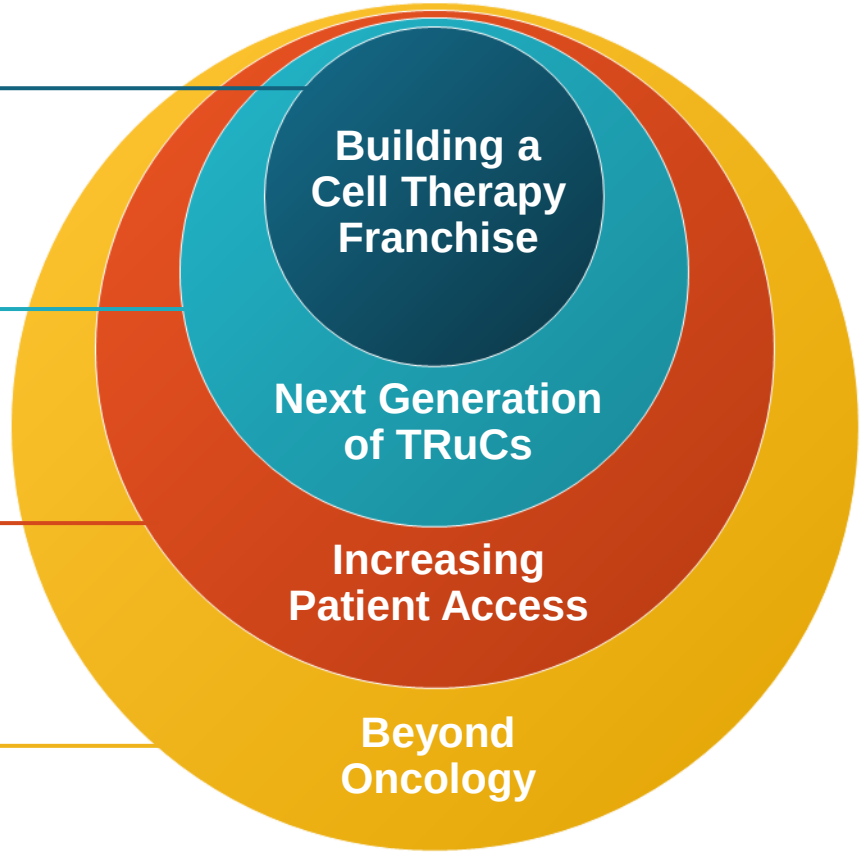
PD-1 Switch, IL-15 and Many More

Allogeneic Platform

POC for Lead Candidate, αβ and γδ chain TRuCs

TRuC-Tregs

Multiple High-Value Indications – GvHD, T1D, ALS, MS



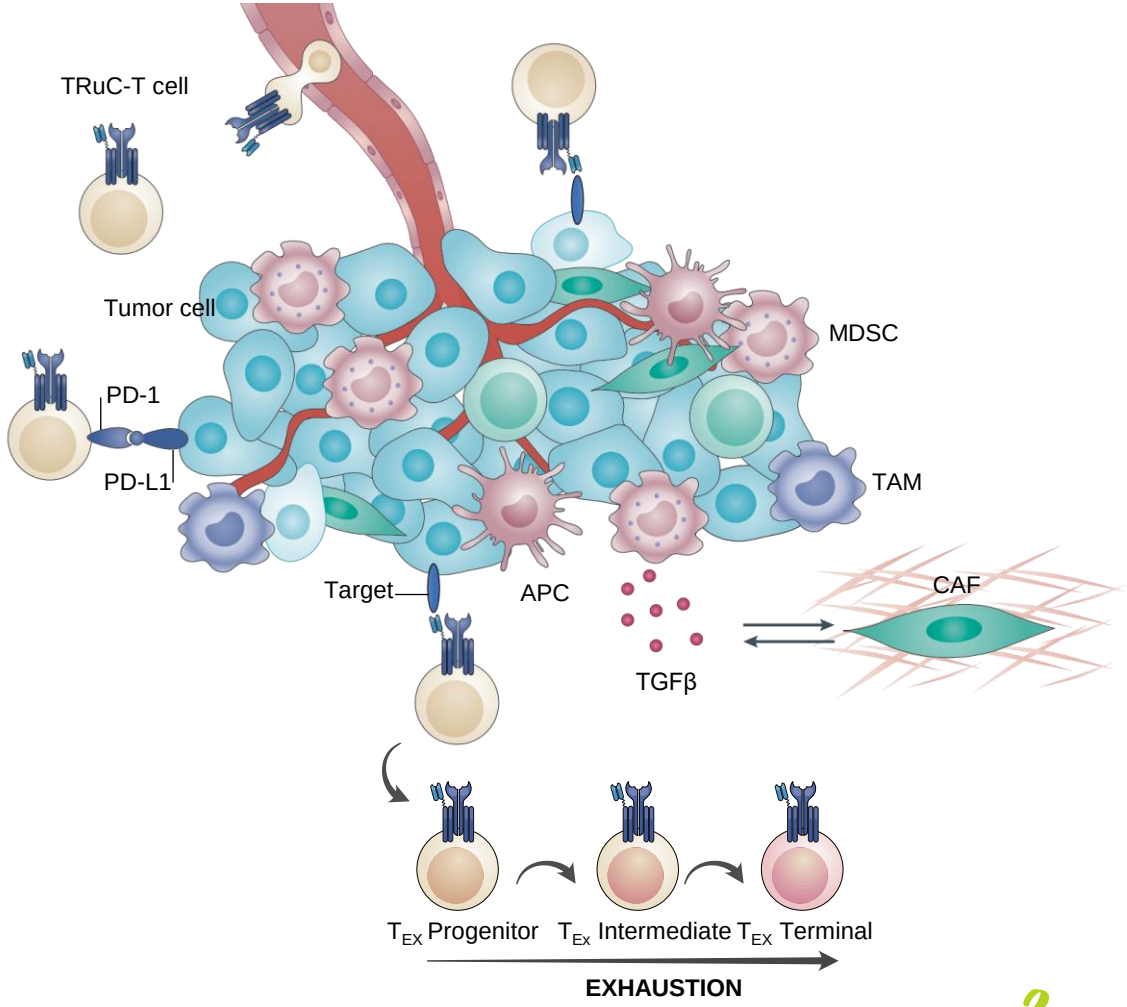
MSLN, mesothelin; POC, proof-of-concept; GvHD, Graft versus Host Disease; T1D, Type 1 Diabetes; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis

TCR2 THERAPEUTICS

Immunosuppressive Mechanisms in Solid Tumors Drive T Cells into a Dysfunctional State

With our enhancements we want to solve for the major hurdles of cell therapy

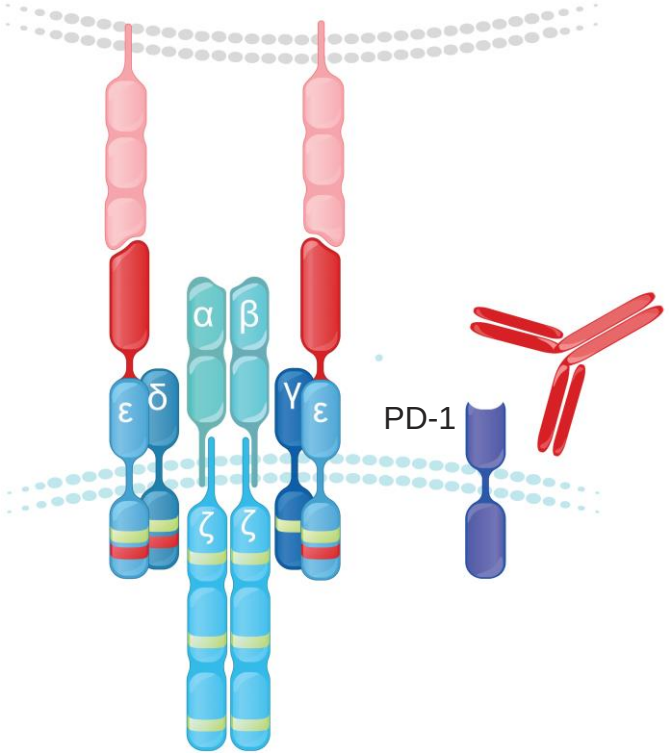
- Inhibition of T cell activity by immunosuppressive factors (PD-1, TGFβ)
- Chronic T cell stimulation resulting in T cell exhaustion
- Lack of stemness limiting durability of response



Enhancements Endow TRuC-T Cells with Characteristics to Improve Efficacy in Solid Tumors

gavo-cel + anti-PD1

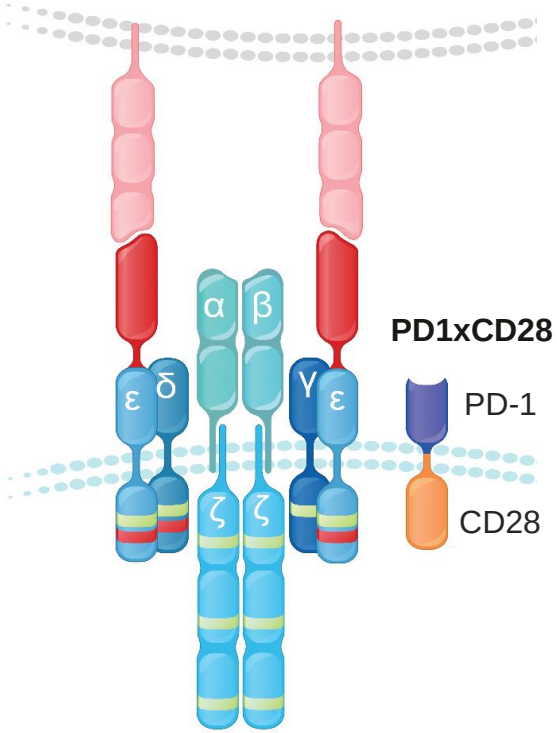
Re-invigorate TRuC-T cells



- Enhances gavo-cel and TILs in the tumor microenvironment
- Reverts T cell exhaustion

PD1xCD28 Switch

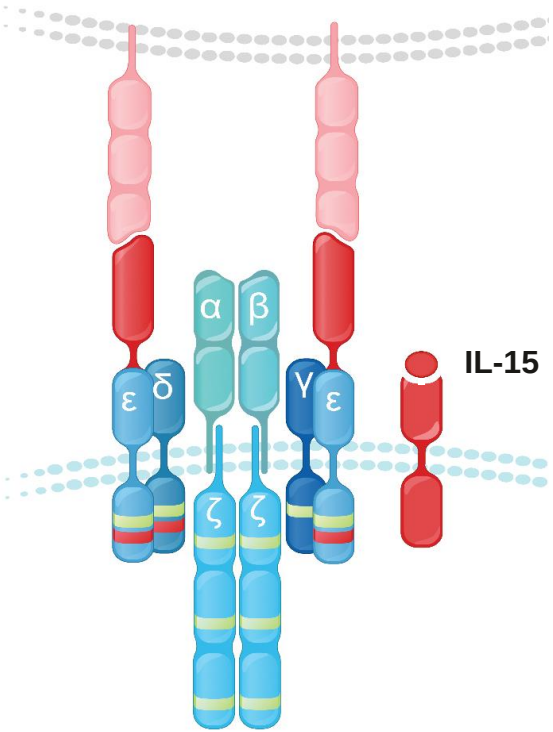
Maintenance of T cell potency



- Enhances T cell activity in tumor microenvironment (TME)
- Delays T cell exhaustion

IL-15

Stem-like properties for persistence



- Maintains naïve and memory T cell phenotype
- Enhanced survival, proliferation and T cell fitness

PD1xCD28 & IL-15 Are Suited for Different Tumor Environments

PD1xCD28 Switch

- Provides an extra boost (PD-L1 dependent co-stimulation) by increasing effector function
- Longer persistence of TRuC-T cells leads to tumor regression in rechallenge model
- Co-stimulation may protect TRuC-T cells from activation induced cell death (AICD) tumors with low antigen expression

Tumors with high PD-L1 expression and established role of the PD-1 pathway

IL-15

- Provides an autonomous survival signal in the absence of TCR signal
- Endows TRuC-T cells with stem-like properties (upregulation of TCF1)
- Very strong proliferation upon TCR activation, preferential effect on CD8+ T cells
- Long persistence of cells post tumor clearance

Tumors with low antigen expression and less relevance of PD-1 pathway

TCR2 THERAPEUTICS

TC-510: gavo-cel + PD1xCD28 Switch

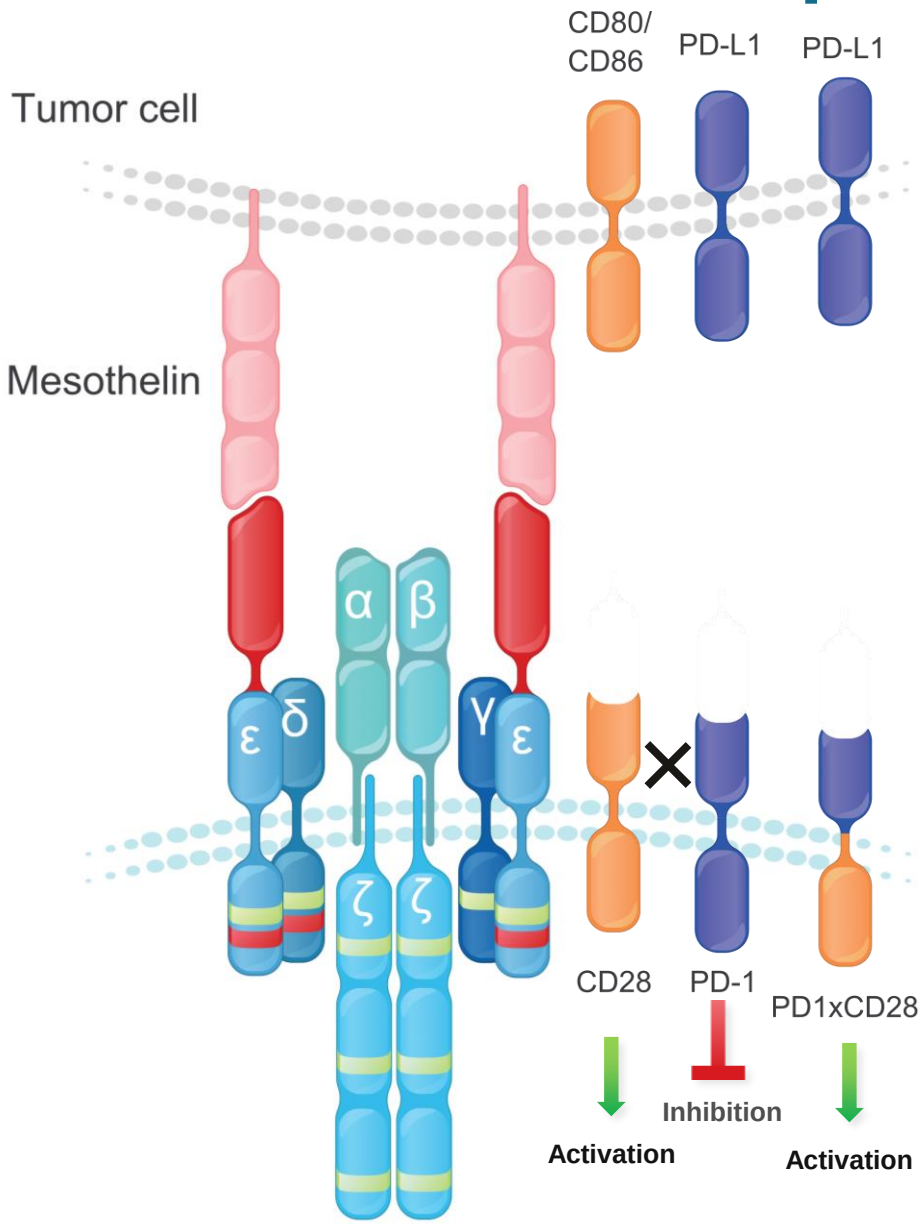
Expanding our Reach into Mesothelin-Expressing Tumors

Robert Tighe
Vice President of Research

TCR2 THERAPEUTICS

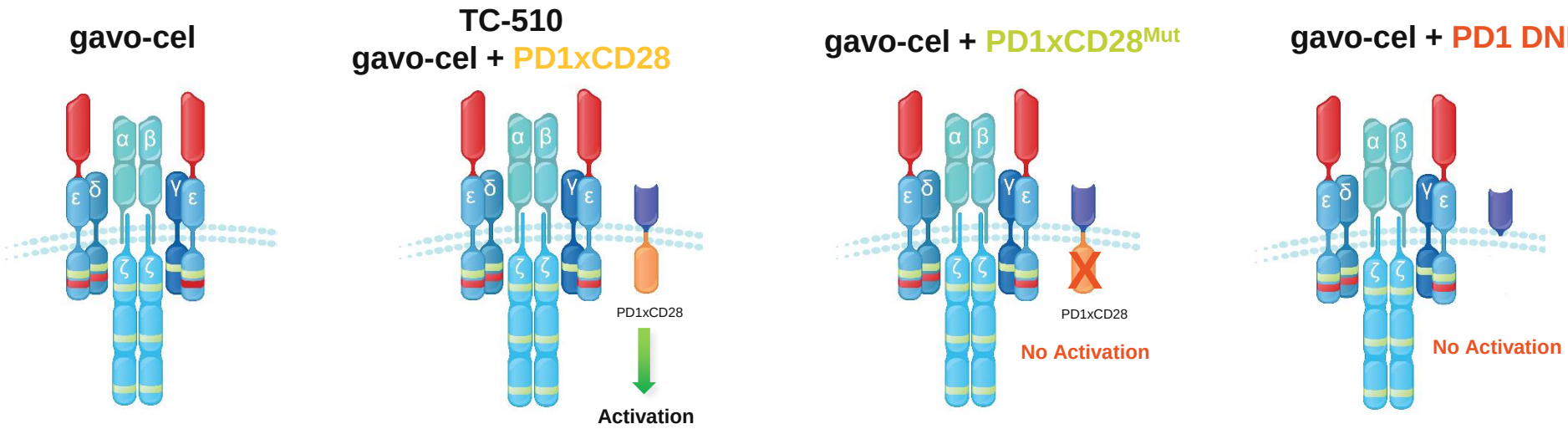
Enhancing gavo-cel with a PD1xCD28 Switch Receptor

- TC-510 is designed to improve upon the already promising clinical activity observed with gavo-cel
- PD1xCD28 switch is designed to hijack the PD-1/PD-L1 inhibitory pathway, transforming it into a potent costimulatory signal
- Preclinically, TC-510 shows enhanced T cell function and anti-tumor activity compared to gavo-cel



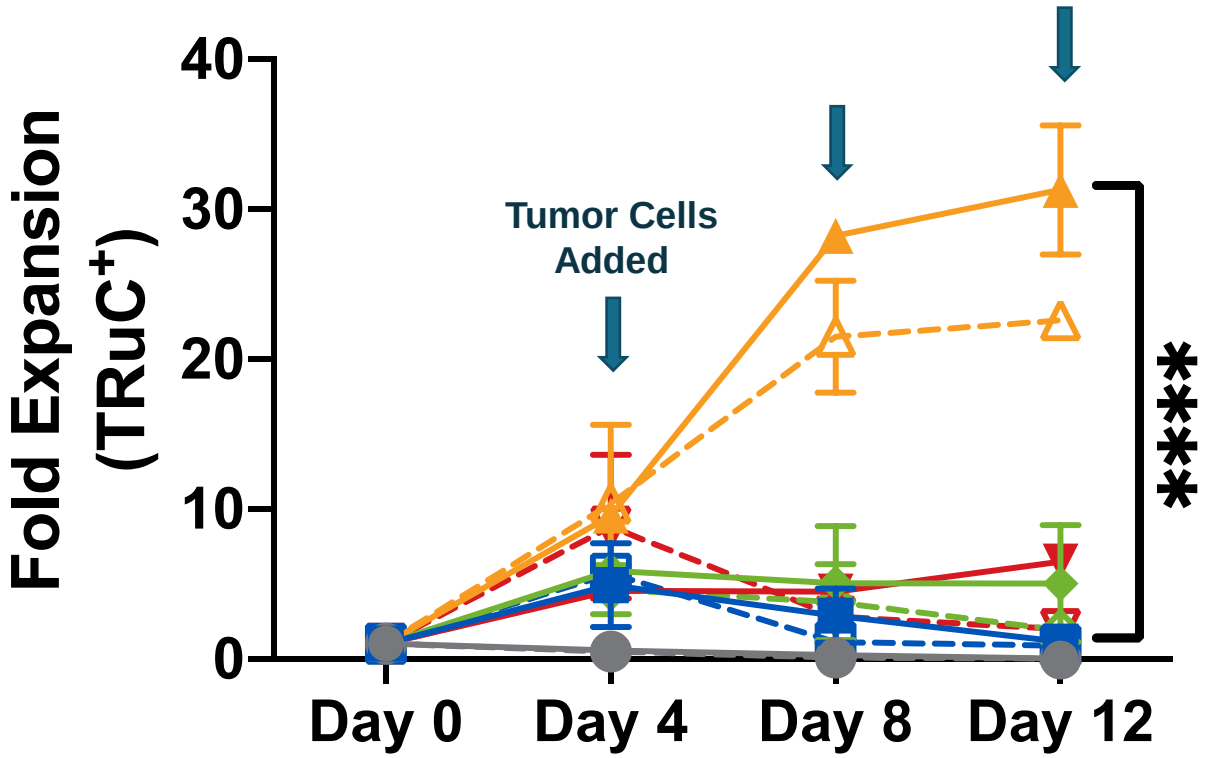
Elucidating TC-510's Mechanism of Action

Costimulatory Signaling vs. PD-1 Dominant Negative Receptor (DNR)

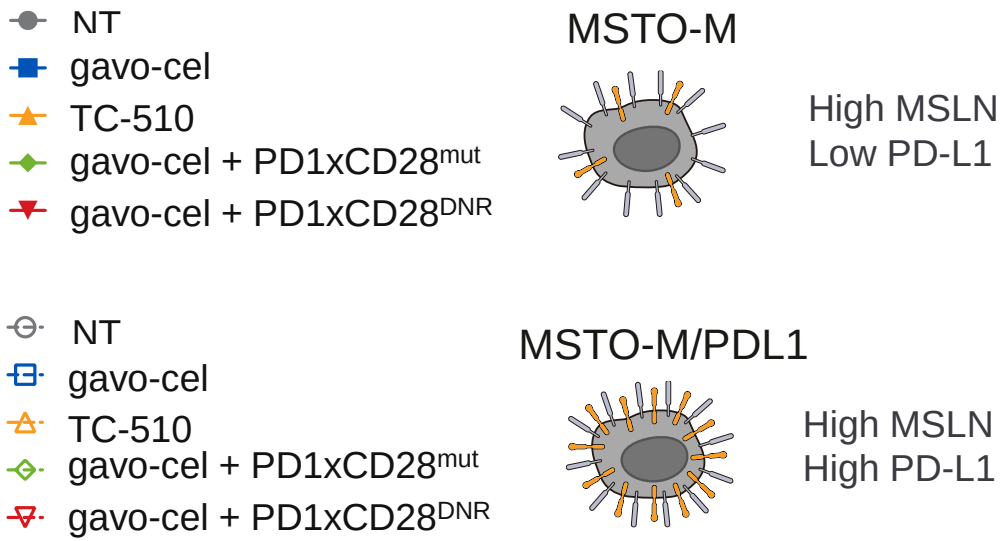


TRuC Signaling	**Yes**	**Yes**	**Yes**	**Yes**
Co-Receptor	**No**	**Active Signaling and Decoy Function**	**Decoy Function**	**Decoy Function**

TC-510 Demonstrates Improved *In Vitro* Expansion and Persistence vs gavo-cel

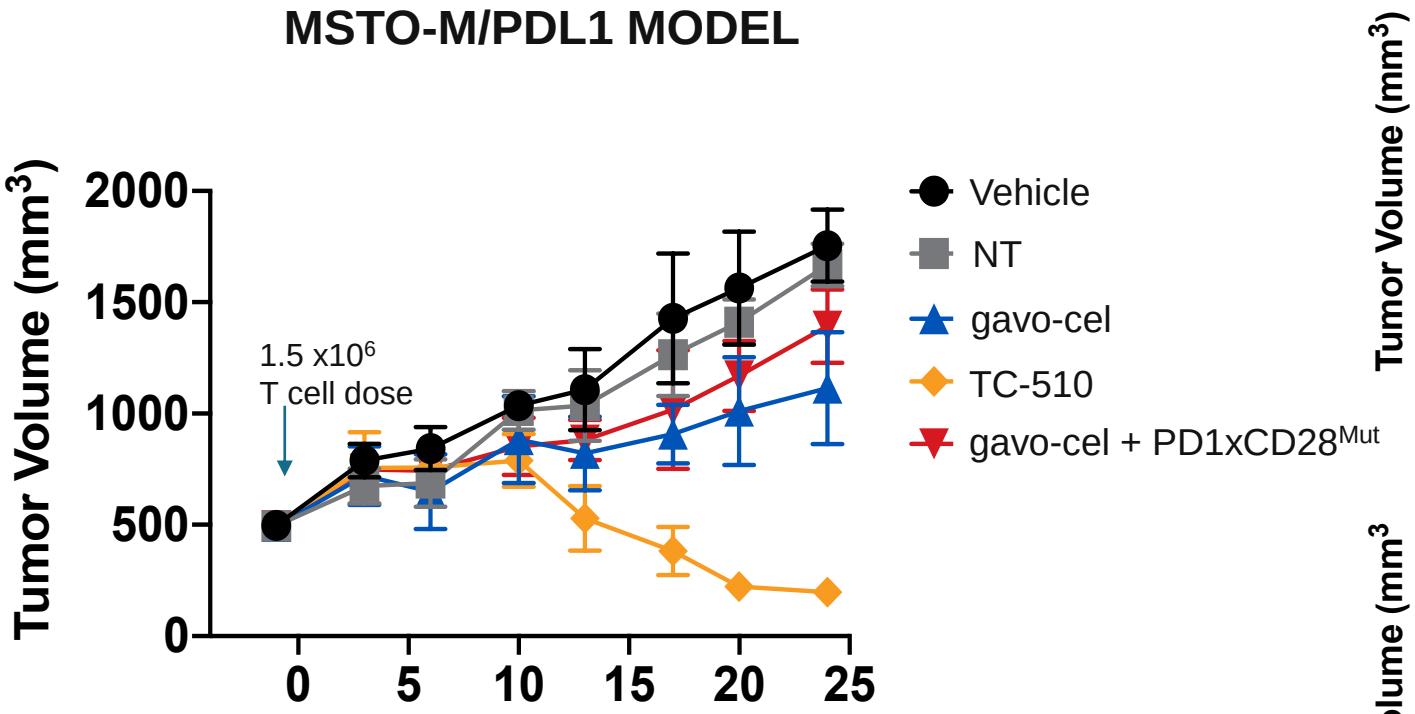


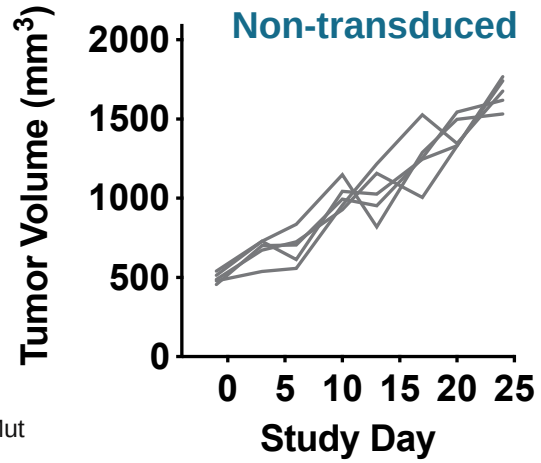
TRuC-T cells in co-culture with MSTO-M or MSTO-M/PDL1 cells at 1:20 ratio

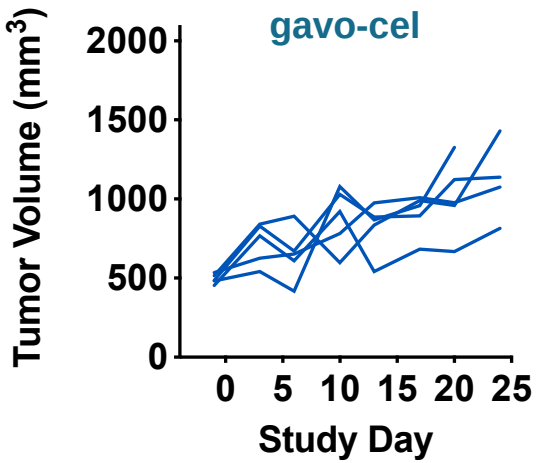


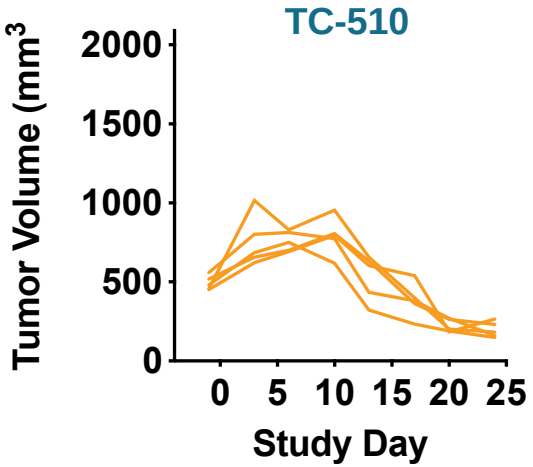
- Increased expansion and persistence was observed against both high and low PD-L1 tumor targets
- Enhancement of expansion is primarily driven by signaling activity rather than decoy function

Against Tumors with High PD-L1 Expression, TC-510 Shows Superior Efficacy to gavo-cel *In Vivo*









TC-510: Opportunities for an Enhanced gavo-cel

- Preclinical data demonstrated:
  - Enhances efficacy of gavo-cel against PD-L1 overexpressing tumors
  - Prevented exhaustion upon repeated antigen stimulation
- Further expand the TRuC platform into additional solid tumor indications
- Promising strategy to improve the clinical efficacy of TRuC-T cells
- IND-enabling studies ongoing with filing expected in 1Q 2022

TCR2 THERAPEUTICS

IL-15 Enhancements

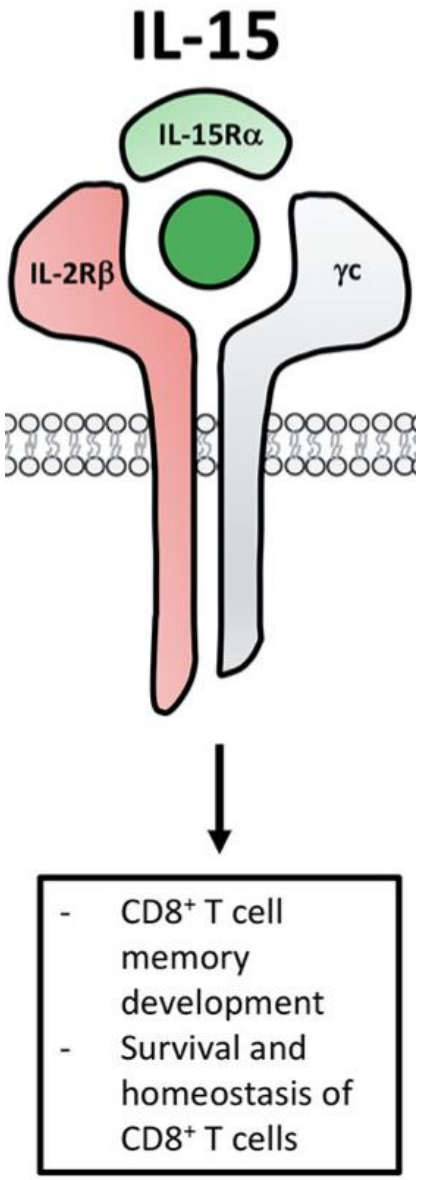
Evolving TRuC-T Cell Persistence and Phenotype with IL-15

Robert Tighe
Vice President of Research

TCR2 THERAPEUTICS

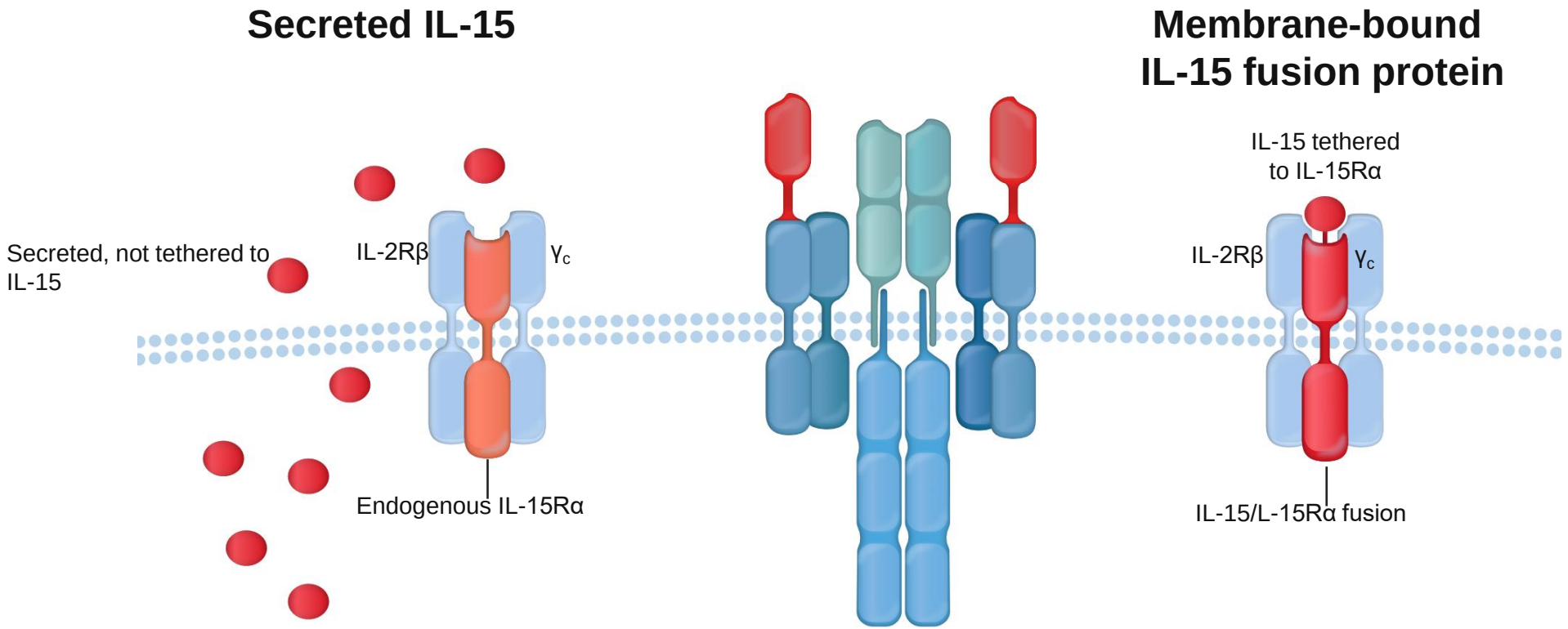
IL-15 as an Enhancement for T Cell Function

- γ chain cytokine important for the development and homeostasis of NK cells and CD8+ T cells
- IL-15 has a crucial role in the maintenance and survival of naïve and central memory T cells with high proliferative capacity
  - Promotes the survival and proliferation of naïve and central memory CD8+ T cells
  - Promotes survival of T cells in the absence of TCR stimulation
- Inhibits IL-2 activation induced cell death (AICD)
- Based on these properties, IL-15 signaling is expected to enhance TRuC-T cell persistence and improve efficacy against solid tumors



Dwyer et. al. *Frontiers in Immunology* 2019.

Head-to-Head Testing of Two IL-15 Concepts that Primarily Differ in Modes of Signaling



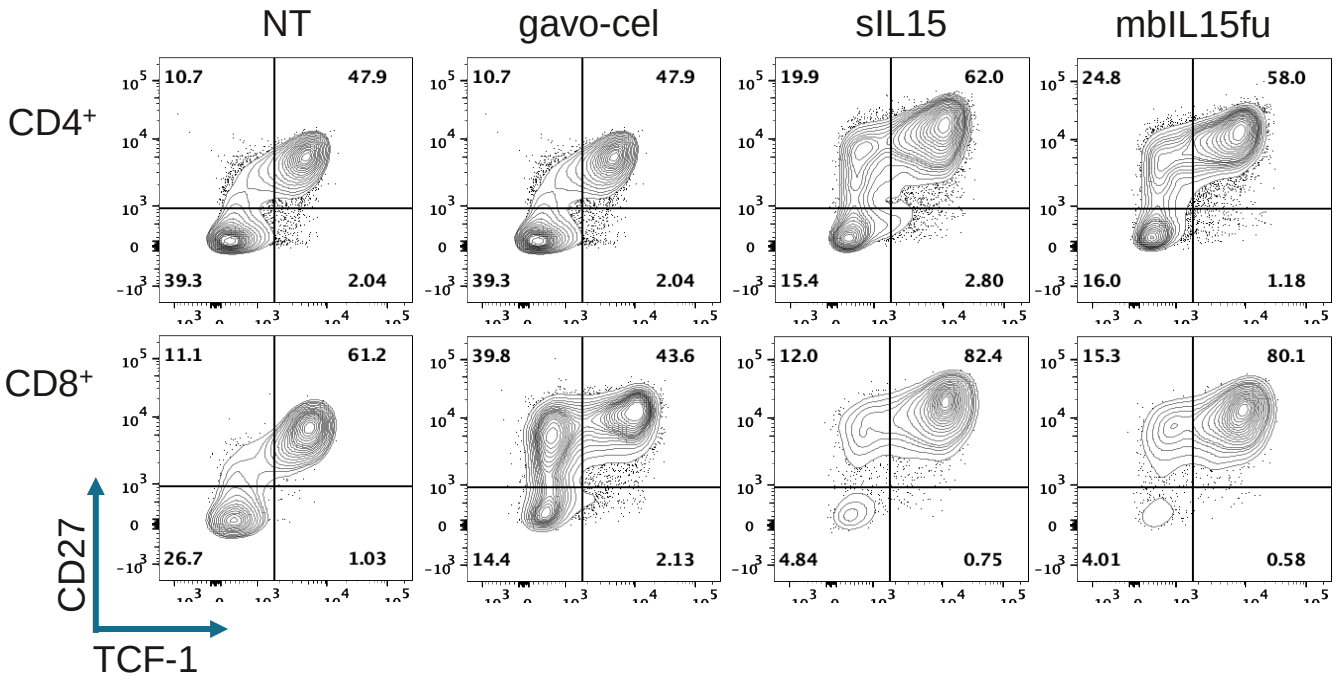
- Constitutively secreted, soluble form that binds to endogenous IL-15Rα
- IL-15 presentation to IL2Rβ/γc in *cis* and *trans*

- Constitutively overexpressed IL-15/IL-15Ra fusion
- IL-15 presentation to IL2Rβ/γc in *cis* and *trans*

TCR2 THERAPEUTICS

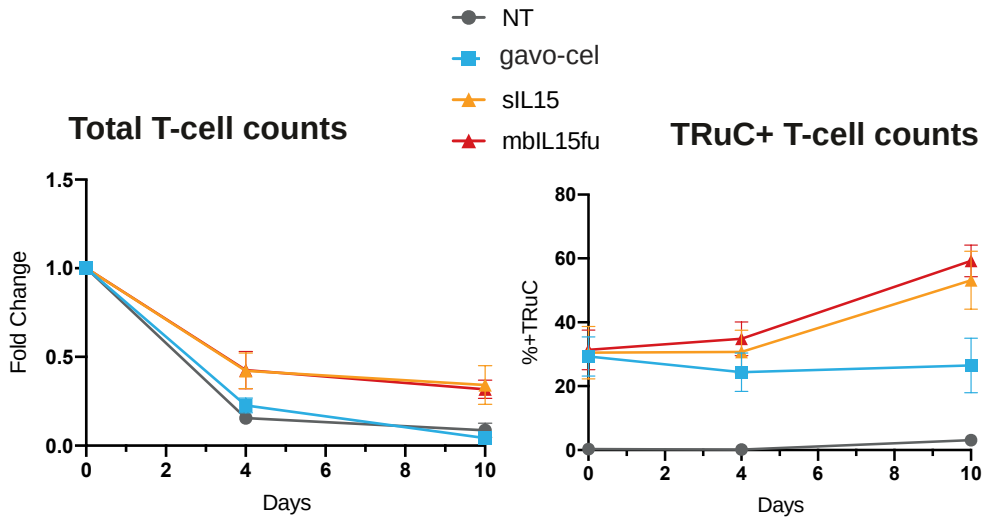
IL-15 Expressing TRuC-T Cells Upregulate Stemness Markers and Show Autonomous Persistence *In Vitro*

Upregulation of Stemness Markers Following T Cell Activation



T-cells were cocultured with MSTO-MSLN cells for 96 hours and then stained for TCF-1 and CD27 and analyzed by flow cytometry.

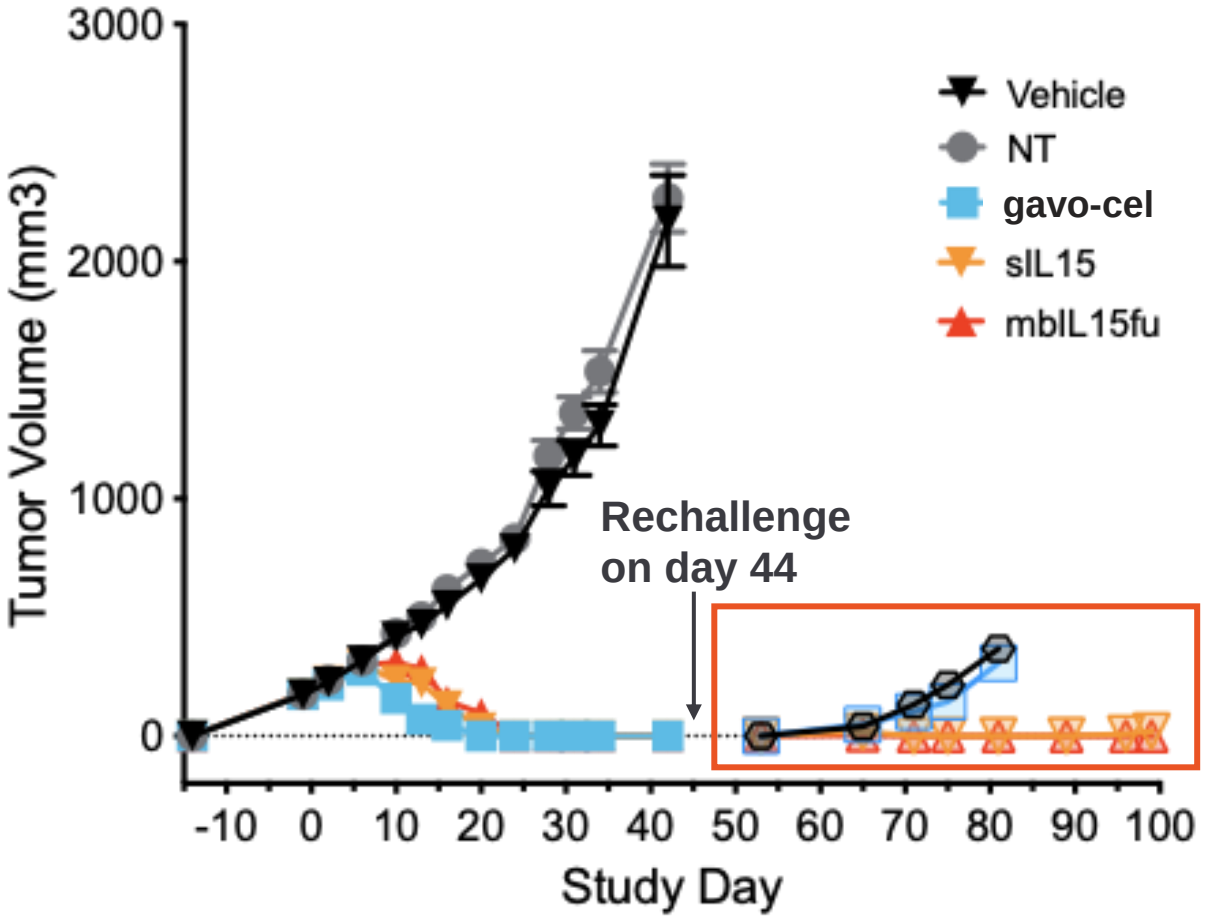
Enhanced Persistence in Absence of Stimulation

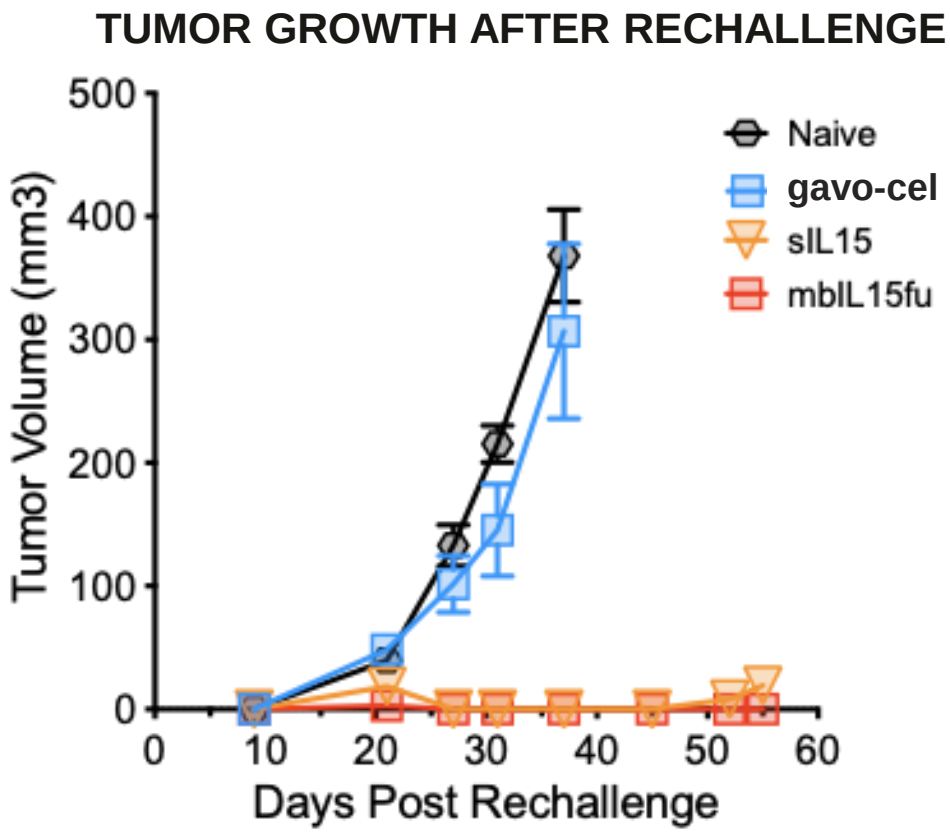


T-cells were cultured in vitro for 10 days in cytokine-free media and cell numbers were quantified on indicated days

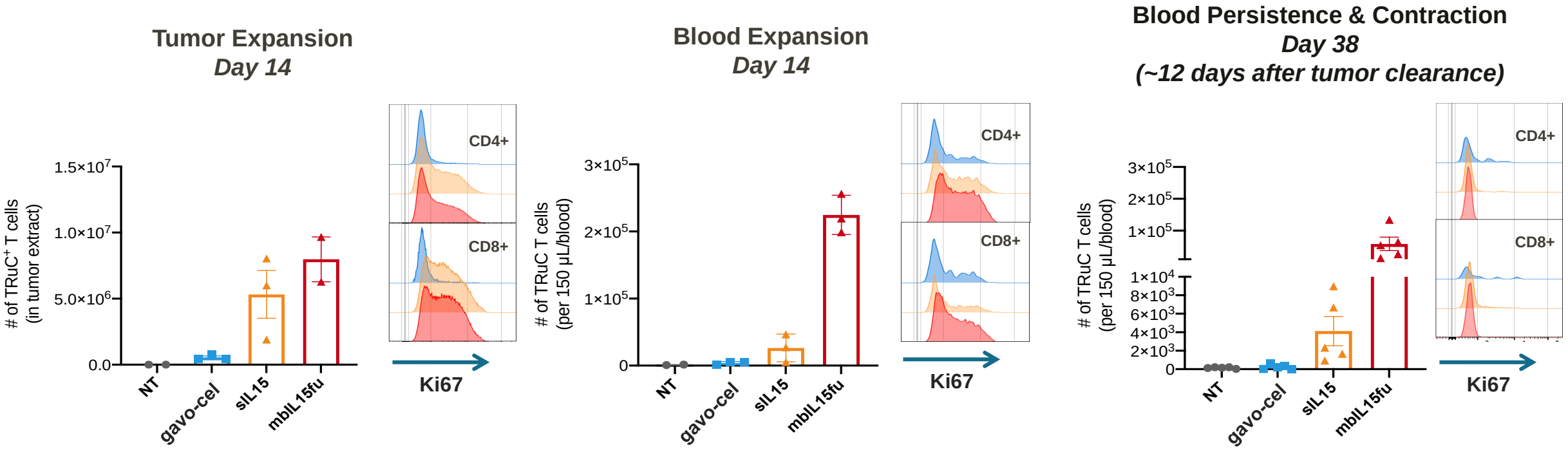
TCR2 THERAPEUTICS

IL-15 Enhanced TRuCs Show Durable Functional Persistence *In Vivo* that Protects from Tumor Rechallenge





IL-15 Enhanced TRuC-T Cells Increased Proliferation & Persistence with Contraction after Tumor Clearance



- IL-15 enhanced TRuC-T cells show significantly increased expansion in tumor and blood
- Higher expansion and proliferation of mbIL-15fu vs. sIL-15
- After tumor clearance, IL-15 enhanced T cells stop proliferating and start to contract

TCR2 THERAPEUTICS

Early Data Supports Role of IL-15 in Phenotype and Persistence

- Preclinical data demonstrated:
  - Favorable phenotype with CD8+ naïve/T cell central memory cells
  - Enhanced stemness markers associated with long-term proliferative capacity
  - Increased persistence in the absence of external, activating stimuli
  - Increased expansion and persistence to fully protect from tumor rechallenge

- Enabled to potentially increase TRuC-T cell persistence in cancer patients for improved efficacy against solid tumors

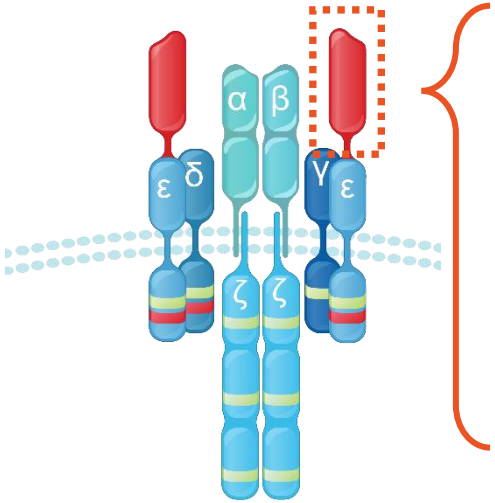
Identification of Novel Targets

CD70, GPC3, NECTIN4

Robert Tighe
Vice President of Research

TCR2 THERAPEUTICS

Novel Target Selection Process



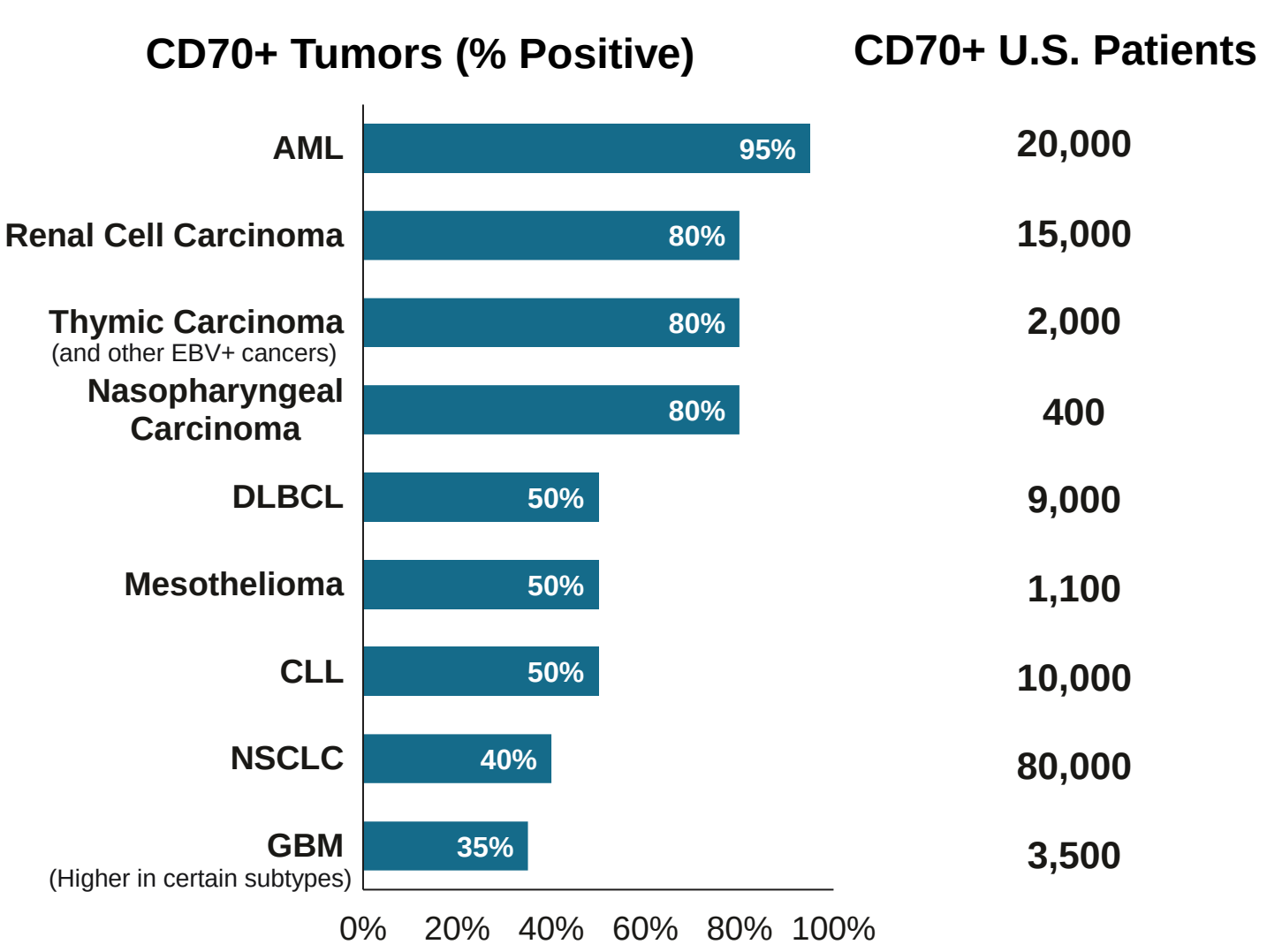
1. **Expression profile** of the tumor antigen
2. **Scientific evidence and validation** of the tumor antigen
3. **Evaluation of target indication** patient population, market landscape and competition
4. **Clinical path forward**

Target	Characteristics	Indications
CD70	• Increases frequency and activation of Tregs in TME • Limited expression to highly activated T cells and B cells, epithelial cells of the thymic medulla	• Wide range of solid tumors, hematological malignancies
GPC3	• Linked to proliferation and oncogenic pathways, Wnt, Yap and hedgehog • Proteolytically shed domain is detected in serum • Little expression in adult healthy tissue, associated with poor prognosis	• Liver cancer
NECTIN4	• Role as stimulatory co-receptor for prolactin receptor • Soluble form detected in serum, prognostic risk factor • Abundant in fetal tissue but declines in adult life, overexpressed in many cancers (~97% of urothelial cancers)	• Urothelial cancer

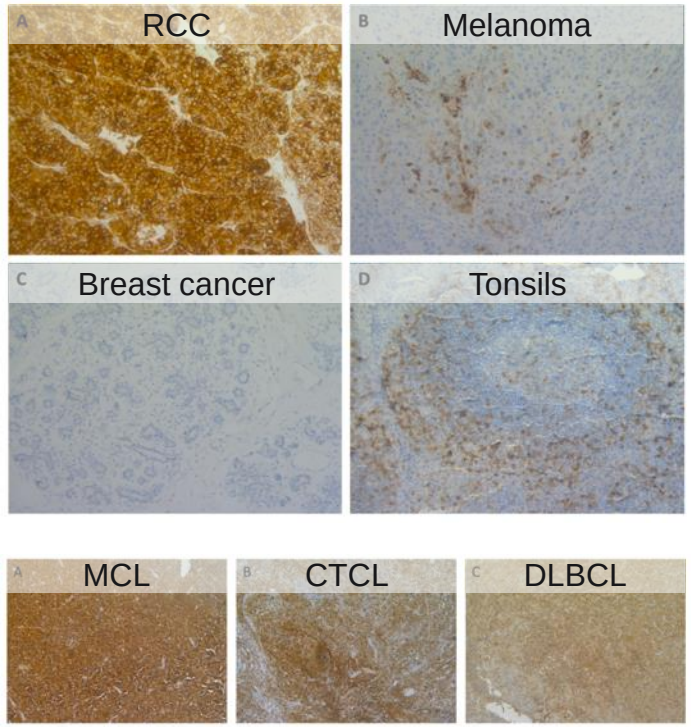
TCR2 THERAPEUTICS

CD70 Population is Large and Spans a Diverse Set of Tumors

Up to 141,000 CD70+ patients in the US alone



Examples of Tissue Staining



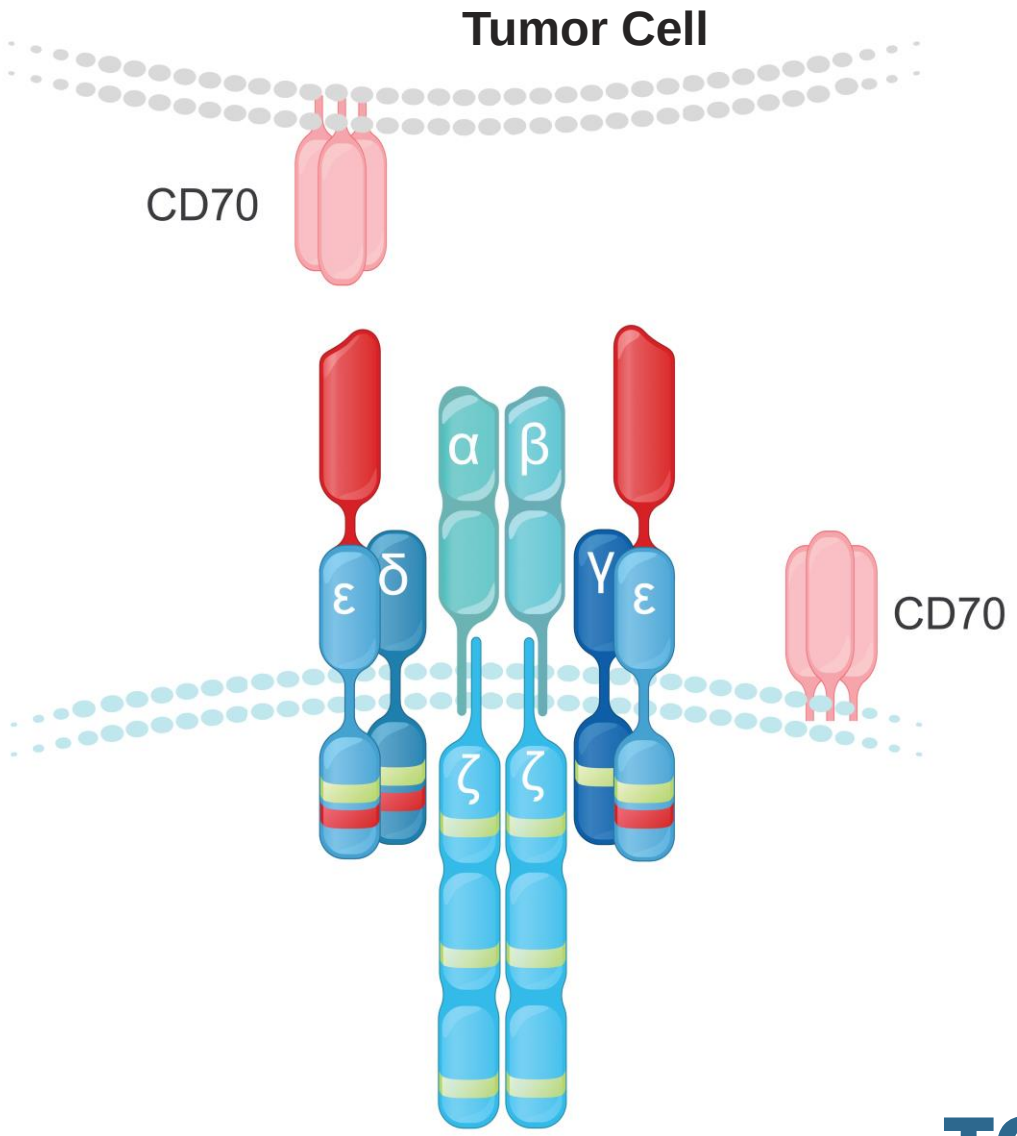
Flieswasser et al., Cancers 2019

Sources: SEER, Flieswasser et al., Cancers 2019, Agathanggelou et al., Am J Pathol. 1995, Riether J Exp Med 2017

TCR2 THERAPEUTICS

CD70: Highly Attractive Target with an Innate Fratricide Challenge

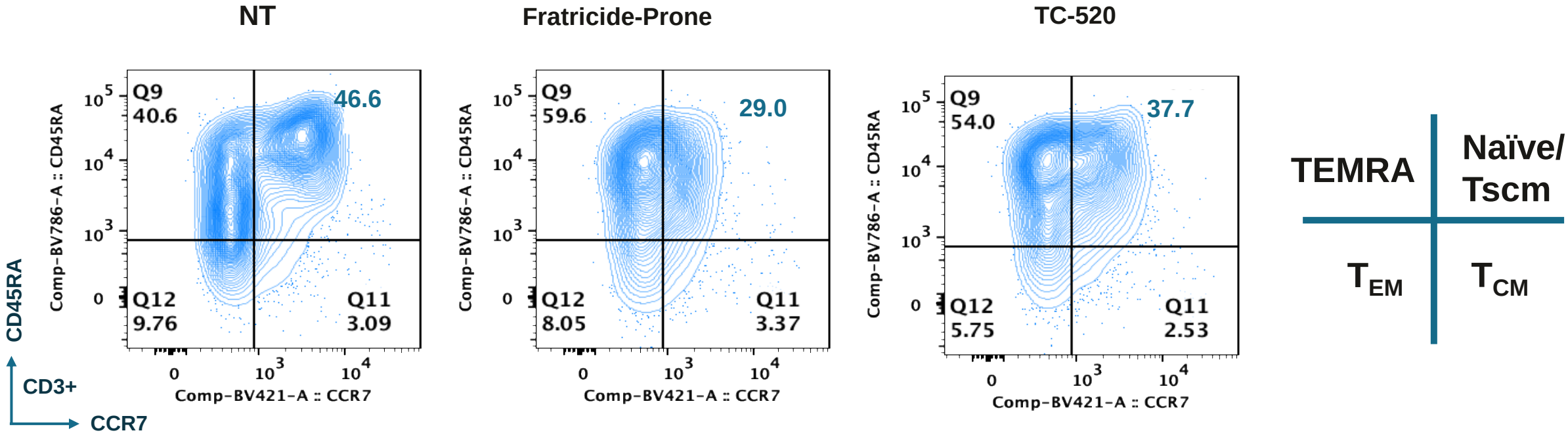
- Expressed in a broad range of solid and hematological malignancies
- Expression in normal, healthy cells limited to activated lymphocytes (i.e., subset of T cells, B cells, and dendritic cells)
- Expression in activated T cells renders CD70-directed T cell therapies susceptible to fratricide



Discovery of Fratricide-Resistant CD70 Lead (TC-520)

Characterization at end of 10-day manufacturing process

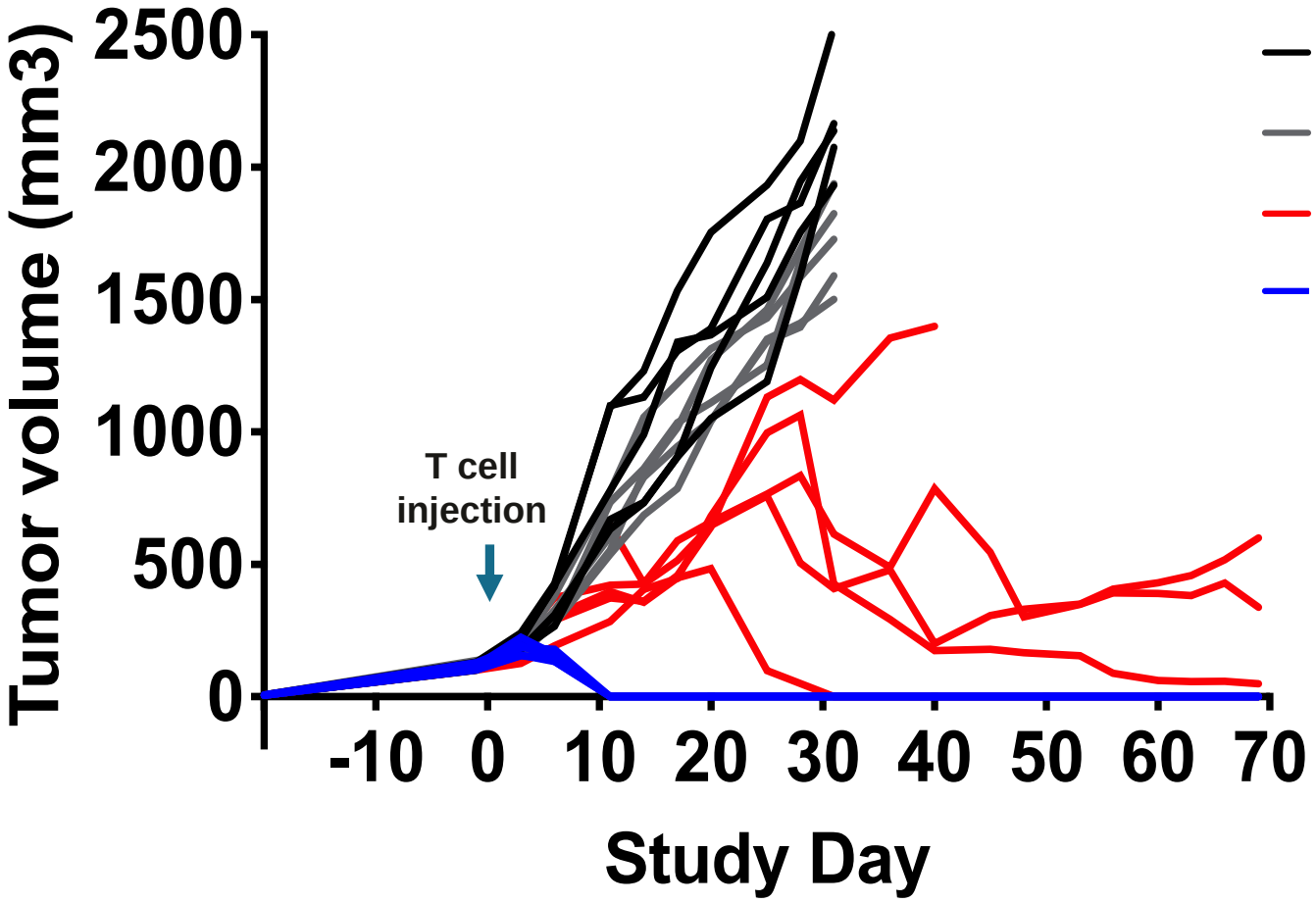
Differentiation



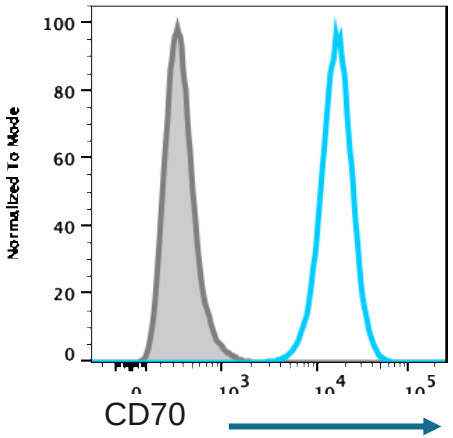
- Fratricide-resistant TC-520 shows a more robust naïve/T_{SCM} phenotype important for *in vivo* efficacy/persistence
- TC-520 further shows normal expansion and lower basal activation
- TC-520 shows high *in vitro* potency against tumor targets with low levels of CD70 expression

TCR2 THERAPEUTICS

TC-520 Exhibits Potent and Persistent *In Vivo* Efficacy

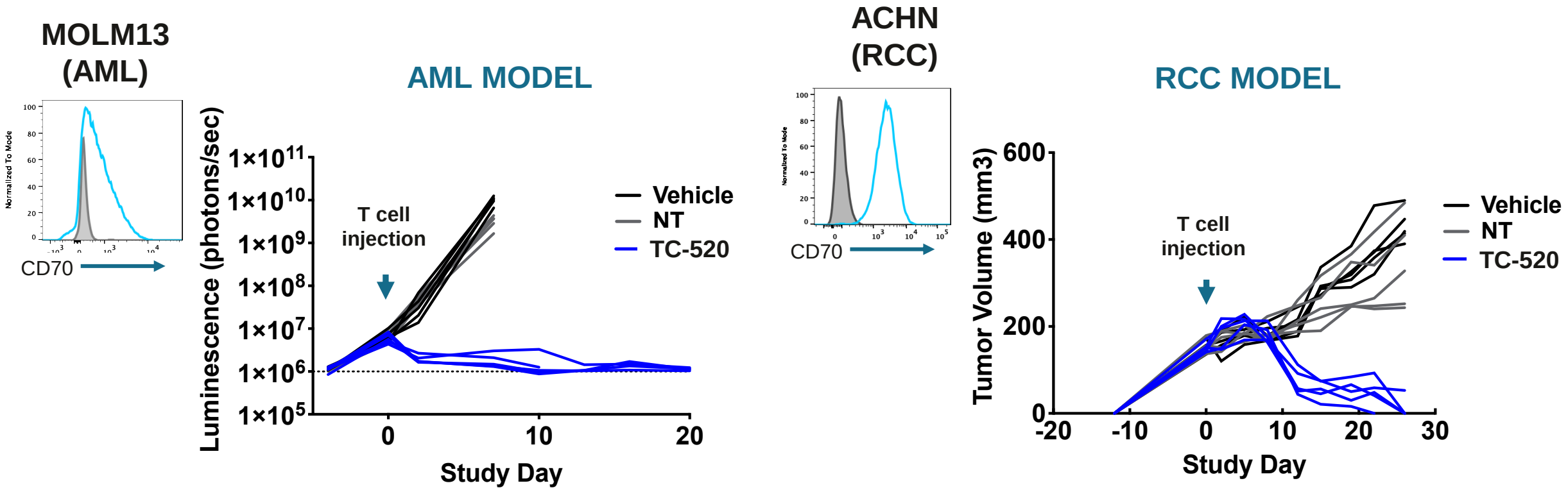


786-O (RCC)



RCC, renal cell carcinoma

TC-520 Exhibits Potent Efficacy in Tumor Models with Low and Moderate Expression

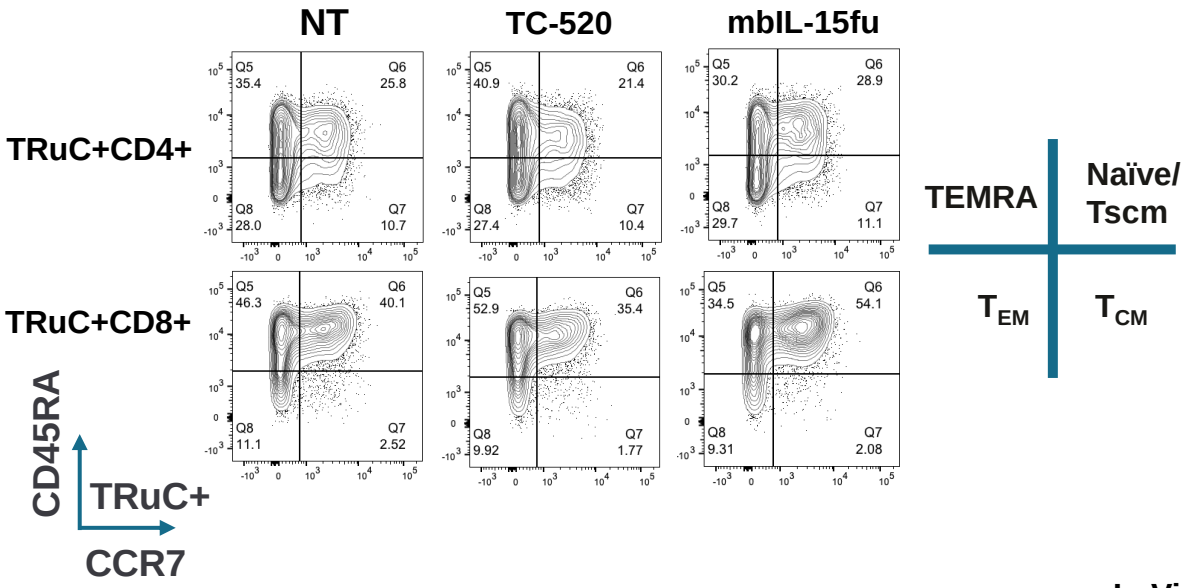


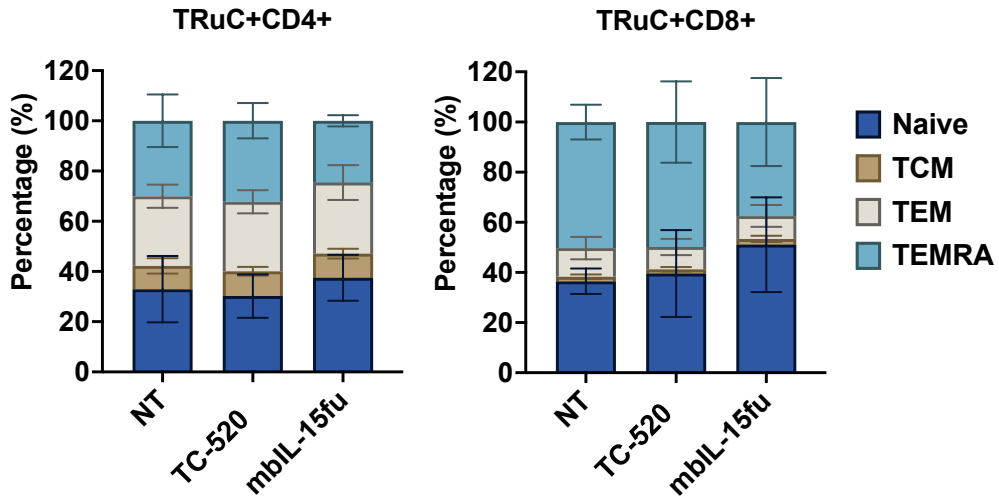
- A single dose of TC-520 induced tumor regression in a disseminated AML model with low CD70 expression and a RCC model with moderate CD70 expression.

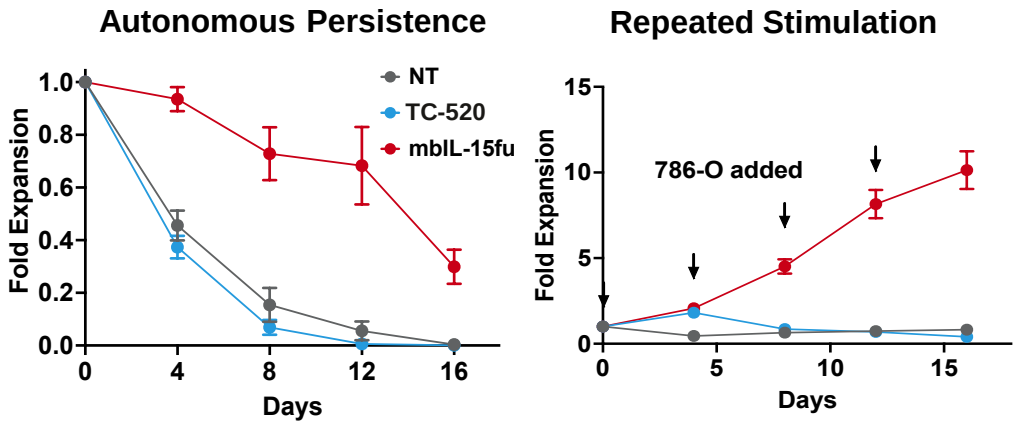
AML, acute myeloid leukemia; RCC, renal cell carcinoma

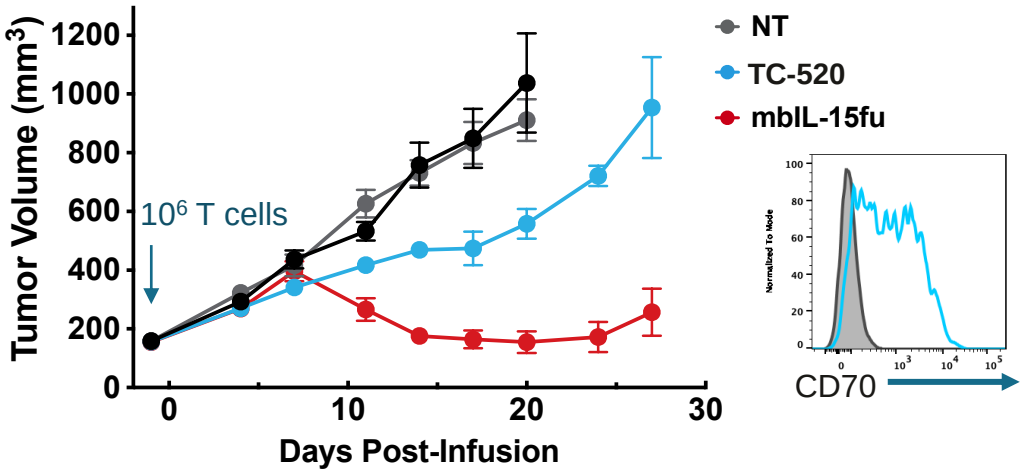
TCR2 THERAPEUTICS

IL-15 Enhancement Improves TC-520 Phenotype and Function









TC-520: Pursuing Path Forward with Enhancements

- Preclinical data demonstrated:
  - Successfully identified fratricide-resistant anti-CD70 TRuC that displays a favorable phenotype
  - Potent *in vivo* efficacy against tumors with low, moderate and high CD70 expression
- Potential to target new indications (both solid tumors and hematological malignancies), broadening the market opportunity of TRuC-T cells
- IL-15 enhancement further improves the phenotype and preclinical efficacy of TC-520
- IND-enabling studies for TC-520, our TRuC-T cell targeting CD70 co-expressing an IL-15 enhancement, targeted in 2022 with an indication focus on renal cell carcinoma

TCR2 THERAPEUTICS

Allogeneic TRuCs

Broadening Platform, Increasing Patient Access

Robert Hofmeister, Ph.D.
Chief Scientific Officer

TCR2 THERAPEUTICS

Expanding TRuC-T Cell Reach with Allogeneic Capabilities

Potency

- Use of healthy donor apheresis product
- Engineering of primary T cells to maintain functional and phenotypical properties of T cells
- Restoration of the full TCR for optimal T cell activation

Safety

- Removal of TCR variable domains to avoid GvHD
- Introduction of fully human TCRγ/δ constant domains to reduce risk of immunogenicity

Persistence

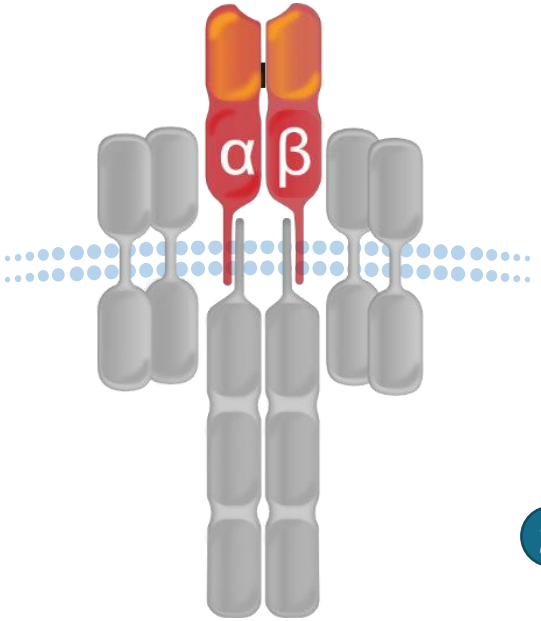
- Knock-out of B2M to avoid host rejections
- Co-expression of IL-15 to increase T cell fitness and persistence

TCR2 THERAPEUTICS

Allo TRuC-T Cells are Generated in a Two-Step Process

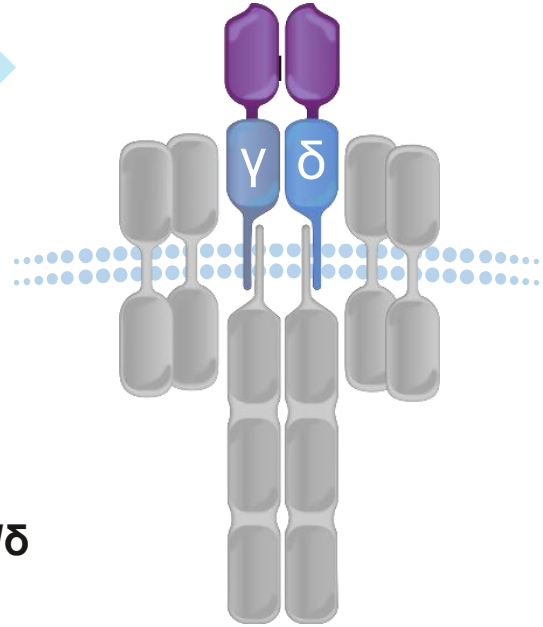
Natural TCR (Alloreactive)

Natural TCRα_v and β_v domains

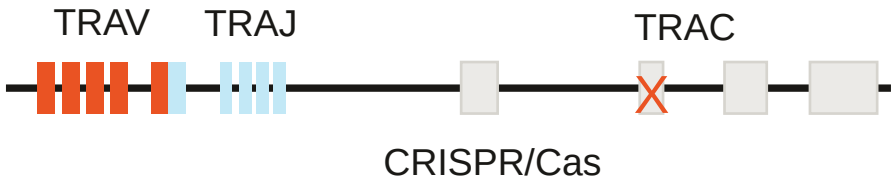


TRuC TCR (Not alloreactive)

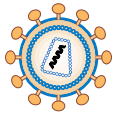
sdAb binder



1 **Knocking-out TRAC locus to delete TCR**

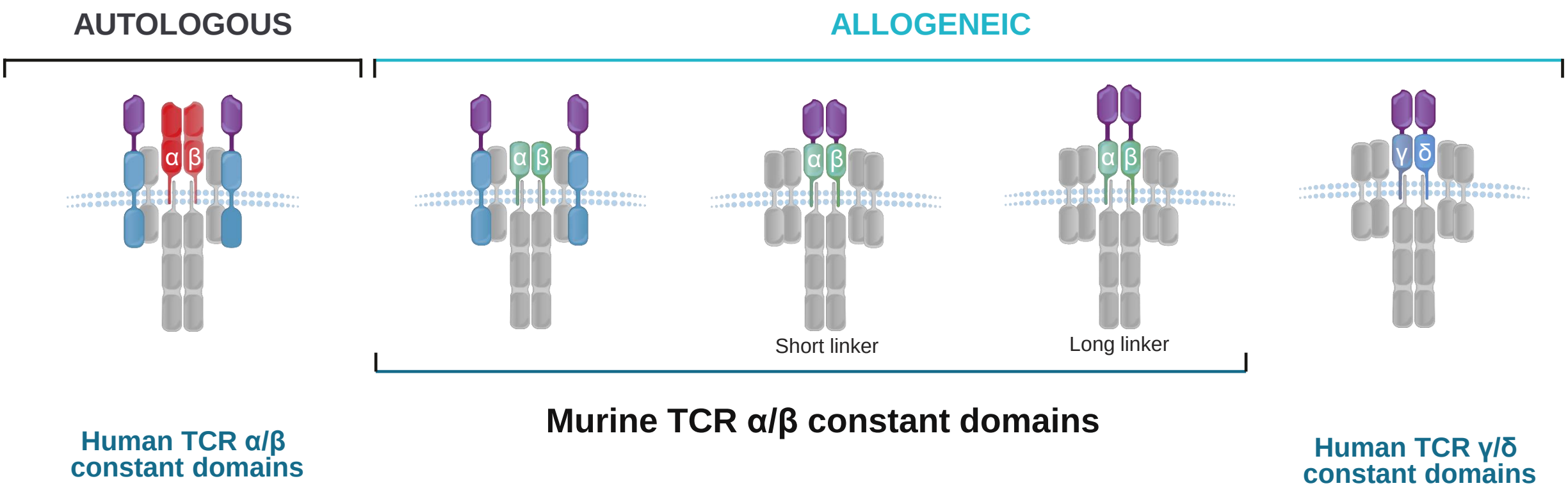


2 **Introduction of mouse TCRα/β or human TCRγ/δ constant regions to enable TCR assembly**



TCR2 THERAPEUTICS

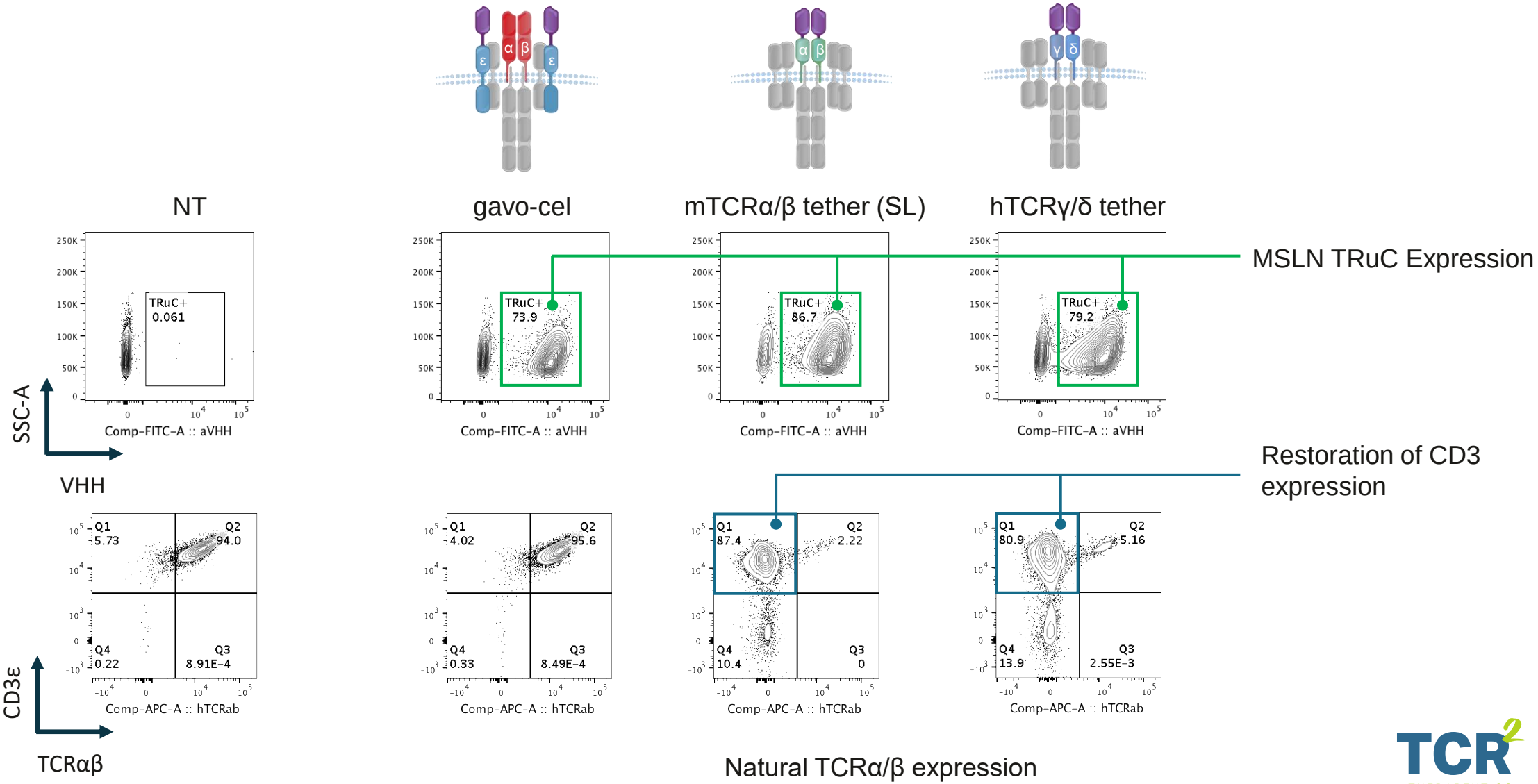
Optimization and Selection of Allo TRuC Designs



- The re-expression of murine TCR α/β or γ/δ constant domains avoids mis-pairing with the endogenous human TCRβ subunit thereby enhancing the restoration of the TCR

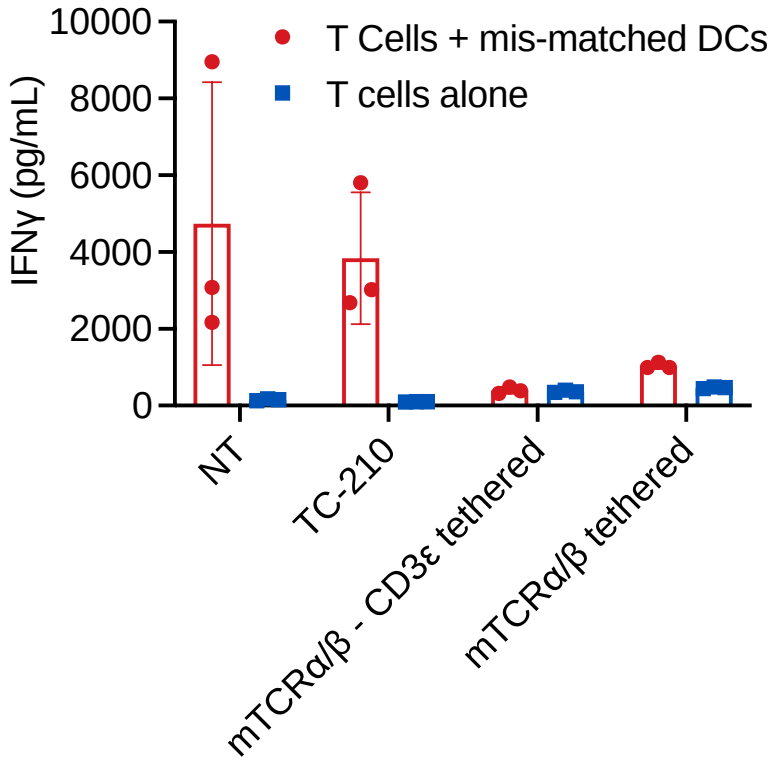
TCR2 THERAPEUTICS

Re-Introduction of TCR Constant Domains Restores TCR Expression on Allo TRuC-T Cells

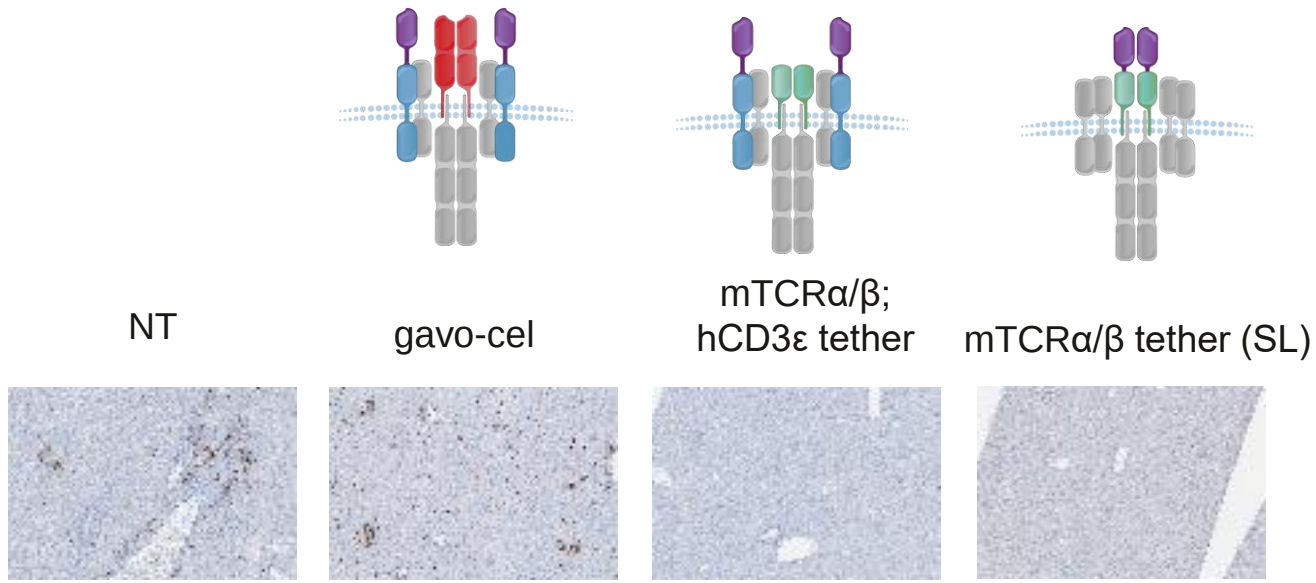


Mesothelin-Specific Allo TRuC-T Cells Do Not Cause GvHD

Mixed Lymphocyte Reaction



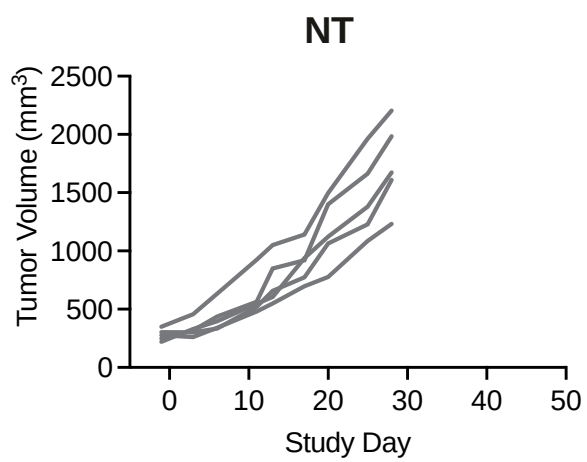
Immunohistochemistry

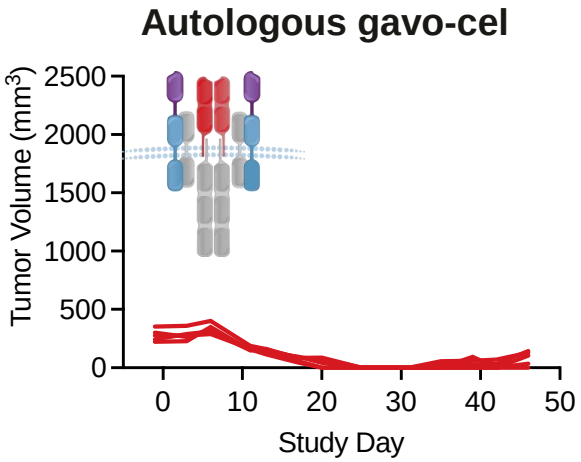


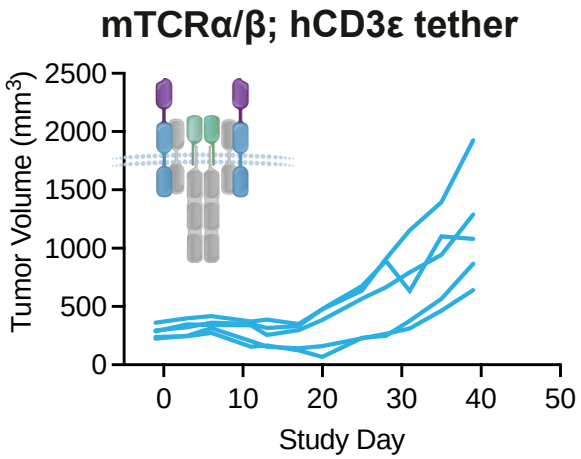
No infiltration of CD7⁺ human T in the livers 50 days post non-transduced (NT) or TRuC-T cell administration

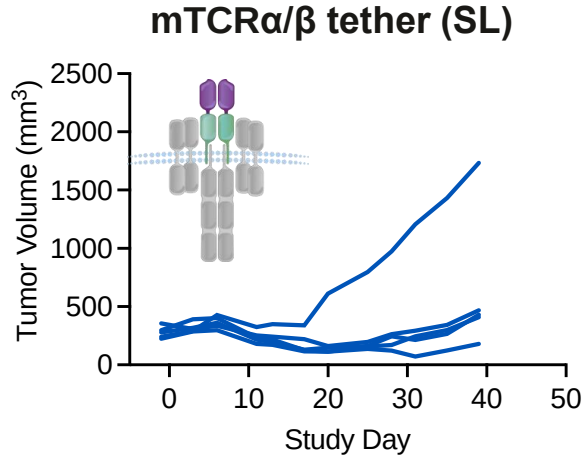
TCR2 THERAPEUTICS

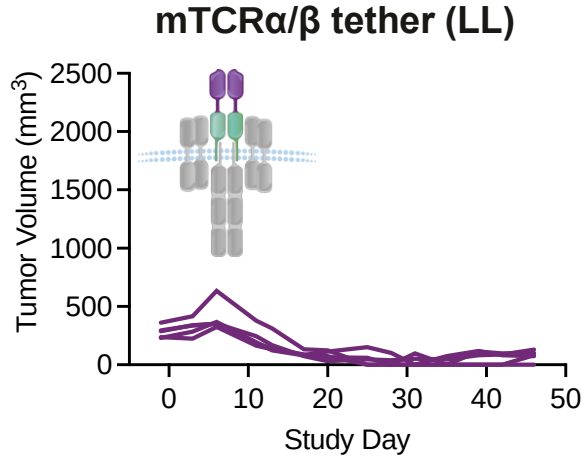
Equivalent Anti-Tumor Activity of gavo-cel with Allogeneic TRuC-T Cells

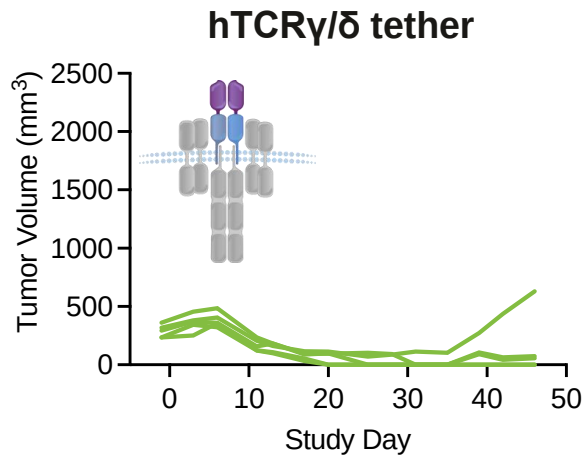












Allogeneic Platform Further Expands Patient Reach

- Preclinical data demonstrated:
  - TCR complex can be restored in TRAC-deficient T cells and efficiently integrated enabling full TCR signaling
  - Allogeneic TRuCs show equivalent efficacy to autologous TRuCs
  - Allogeneic TRuCs are not alloreactive and do not cause GvHD in mice
- Currently evaluating the combination of enhancements with allogeneic TRuC-T cells to improve persistence and stemness
- Identification of lead candidate in 2022
  - Lead based on fully human TCR γδ fusion constructs to reduce the risk of immunogenicity
  - Knock-out B2M in addition to TRAC to mitigate host rejection

TCR2 THERAPEUTICS

TRuC Tregs

Diversification Opportunity in Autoimmune Diseases

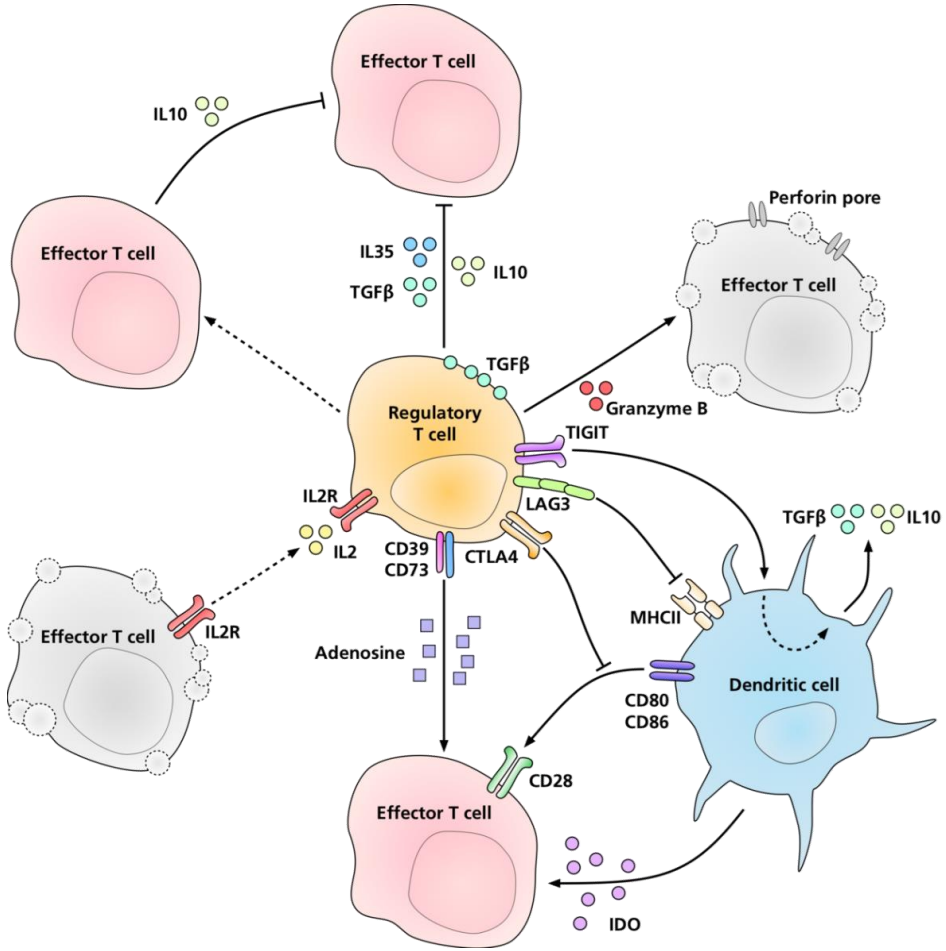
Robert Hofmeister, Ph.D.
Chief Scientific Officer

TCR2 THERAPEUTICS

Innovative T Cell Engineering for the Treatment of Autoimmune Diseases

Regulatory T Cells are the Master Controllers of Self-Tolerance

- Secretion of immunosuppressive cytokines
- Direct killing of effector T cells and APCs
- Delivery of co-inhibitory signals
- Secretion of immunosuppressive metabolites
- Deprivation of growth factors by acting as an IL-2 sink



Adapted from Vignali DAA. et al., (2008) Nature Immunology 8(7)525-532

TCR2 THERAPEUTICS

TRuC Tregs at Forefront of Autoimmune Cell Therapy

Adoptive Treg Therapy has Evolved and Gained Significant Momentum

Increasing specificity and potency

Polyclonal Tregs

- >100 patients worth of feasibility and safety data with no GVHD or "class-switching" to T_{eff} cells
- Early signs of efficacy in GVHD[1,2] and transplant[3]
- Tregs detected up to 1-year post-infusion[4]

Antigen Specific Tregs

- Antigen reactive Tregs selected and expanded
- Efficacy seen in preclinical models where polyclonal Tregs fail[5]
- Early signs of efficacy demonstrated in liver transplant[6] and Crohn's[7]

Engineered Tregs

- Engineered to stabilize phenotype and enhance homing
- First CAR-Treg clinical trial in 2021, targeting HLA-A*02 in organ transplant[8]
- Preclinical data suggest tissue-specific antigen is sufficient for Treg function[9]

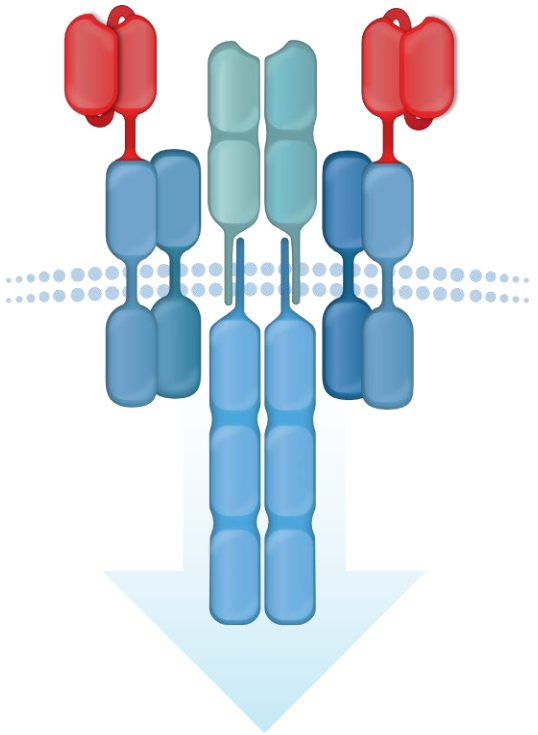
~$670M Raised by <10 Early-Stage Private Treg-focused Biotechs in 2021

1. Tronkowski, 2009, 2. Brunstein 2010, 3. Sawitzki, 2020, 4. Bluestone, 2015, 5. Stephens, 2009, 6. Todo, 2016, 7. Desreumaux, 2012, 8.Sangamo, 2021 9. Eshhar, 2014

TCR2 THERAPEUTICS

TRuC Treg Function Predicated on the Natural TCR Signal

- **TCR Signal**
  - All TCR subunits (not just CD3ζ) have been shown to be important for Treg development and stability (Rudensky, 2016)
  - Residual inflammatory cytokine production reported when a CAR-Treg is activated via its CAR but not its TCR (Boroughs, 2019)
  - Certain costimulatory domains and contexts can drive CAR-Tregs to effector function (Dawson 2020)
- **Tissue Homing**
  - Like TRuCs targeting solid tumors, Treg efficacy is dependent on controlled and faster trafficking to tissues
- **T Cell Persistence**
  - CAR tonic signaling can cause a hyporesponsive, exhausted phenotype and decreased persistence (Lemarche, 2020)



Entire TCR Signaling

TRuC Tregs Can Address Multiple Therapeutic Markets

Neuroinflammatory Disorders

ALS, Myasthenia Gravis, Progressive Multiple Sclerosis

- Decreased Treg levels and Treg dysfunction are associated with several neurological diseases
- Opportunity to slow disease progression and delay disability in diseases with high need

Severe Autoimmune Disorders

Aplastic Anemia, Systemic Sclerosis

- Tregs can reduce pathogenic inflammation and restore homeostasis
- Opportunity to provide disease modifying therapies in high need indications

Transplant

Solid organ transplant, GVHD

- Tregs can drive tolerance to alloantigen rejection
- Opportunity to reduce or eliminate need for long-term immune suppression (and associated side effects)

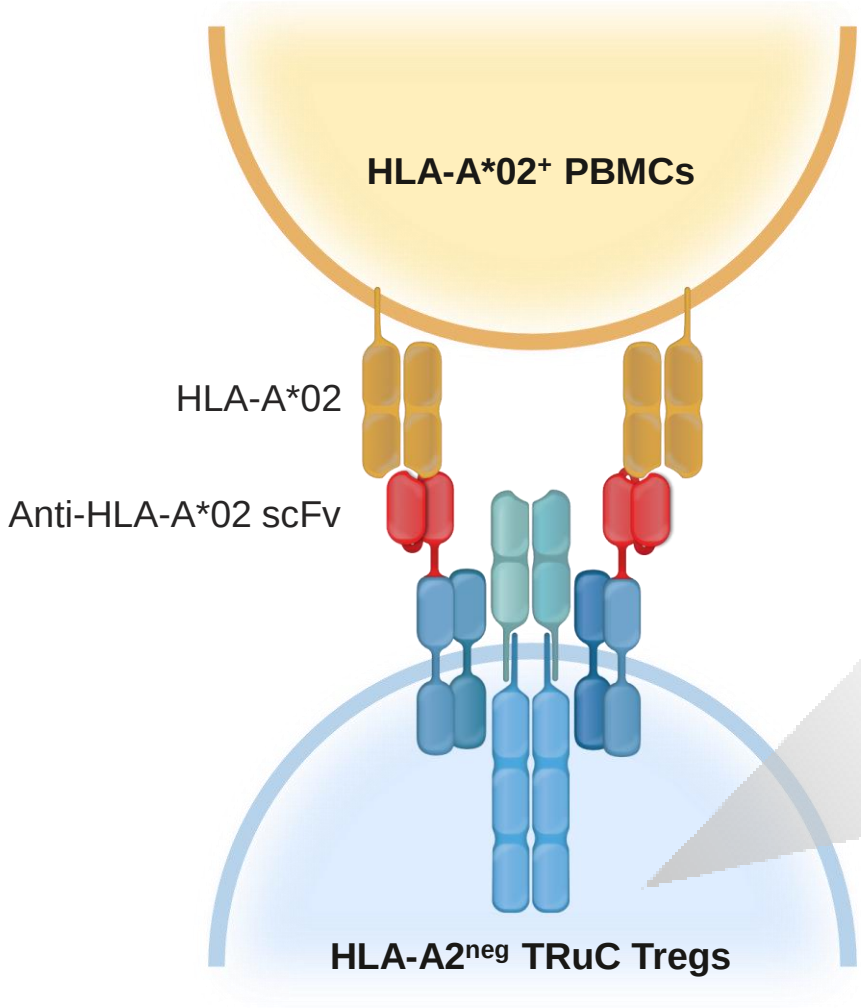
Large Autoimmune Markets

Type 1 Diabetes, Crohn's, Lupus Nephritis

- Large markets where even a small share of patients would be meaningful
- Opportunity to target refractory/ severe niches, possibility to drive long-term remissions or cures with single dose

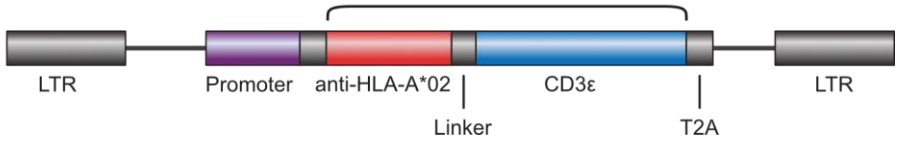
TCR2 THERAPEUTICS

We Chose a GvHD Model to Demonstrate Proof-of-Concept

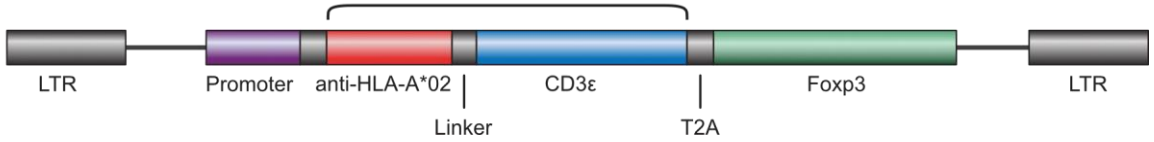


We tested the effect of Foxp3 overexpression on the TRuC Treg phenotype and functional activity

↳ Construct 1: anti-HLA-A*02 TRuC



↳ Construct 2: anti-HLA-A*02 TRuC + FOXP3

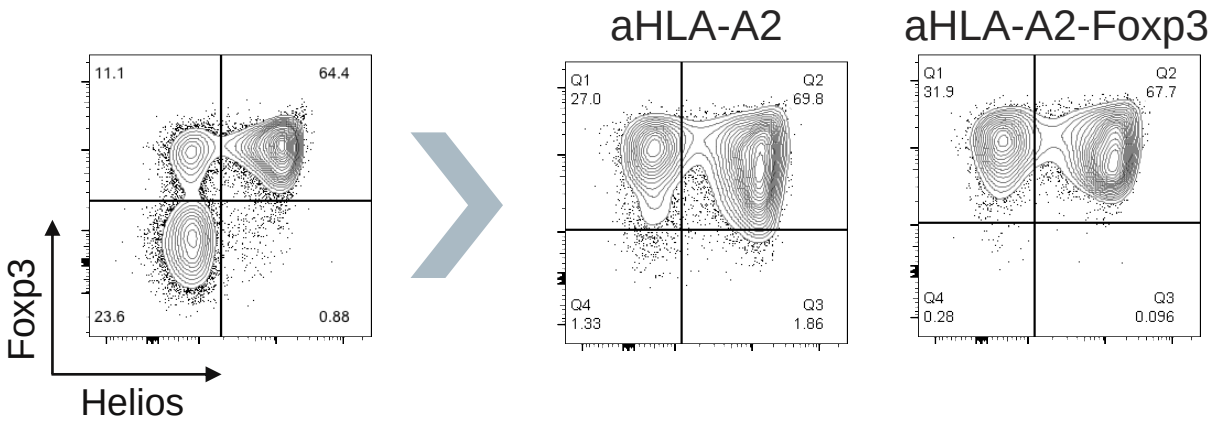


TCR2 THERAPEUTICS

TRuC Treg Cell Product Maintains Treg Hallmarks: Foxp3 and Helios Expression and Hypomethylated TSDR/CNS

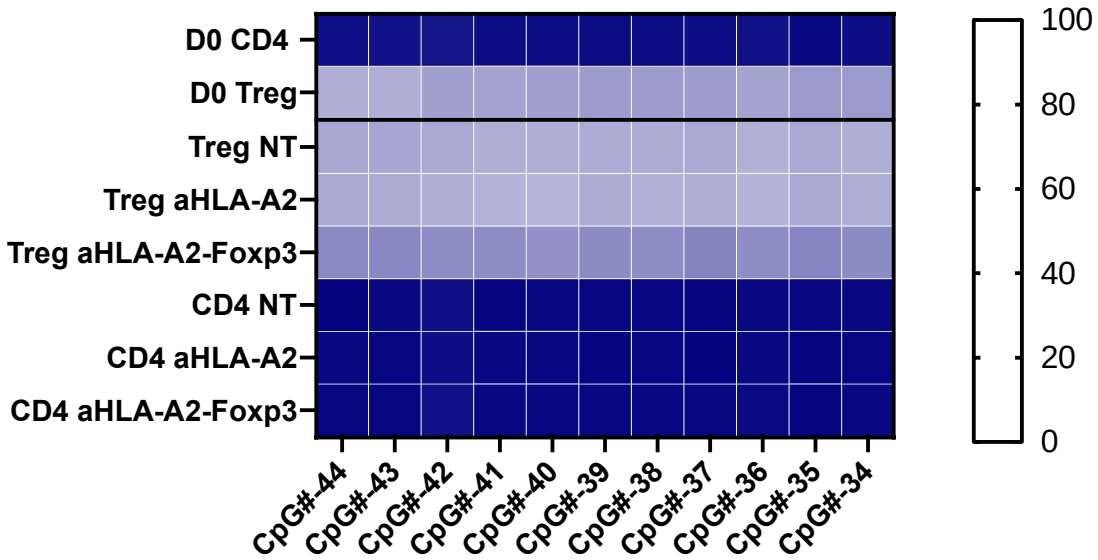
T_{REG} STARTING MATERIAL

TRuC T_{REG} PRODUCT



Anti-HLA-A*02 TRuC Treg cells maintain high expression of Foxp3 and Helios.

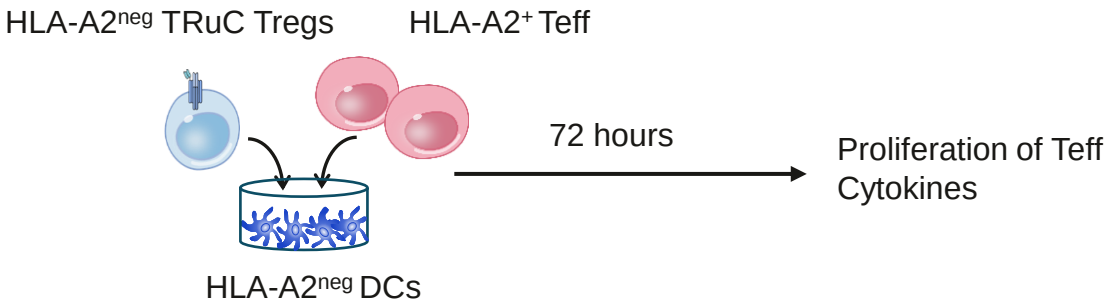
TSDR/CNS2 METHYLATION PHENOTYPE

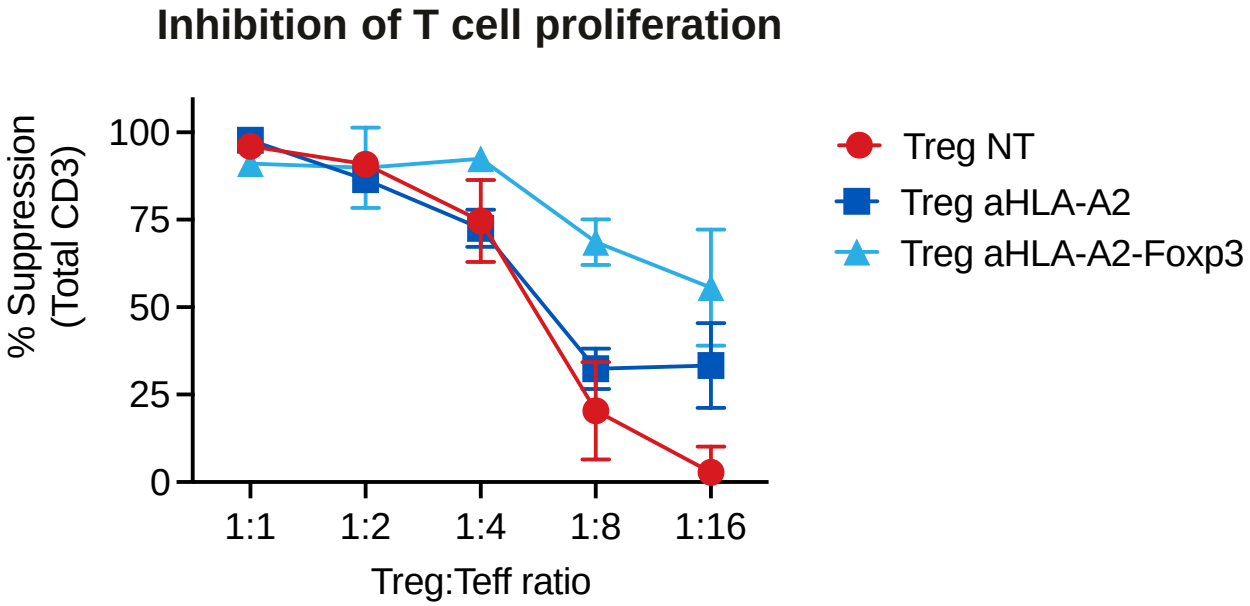


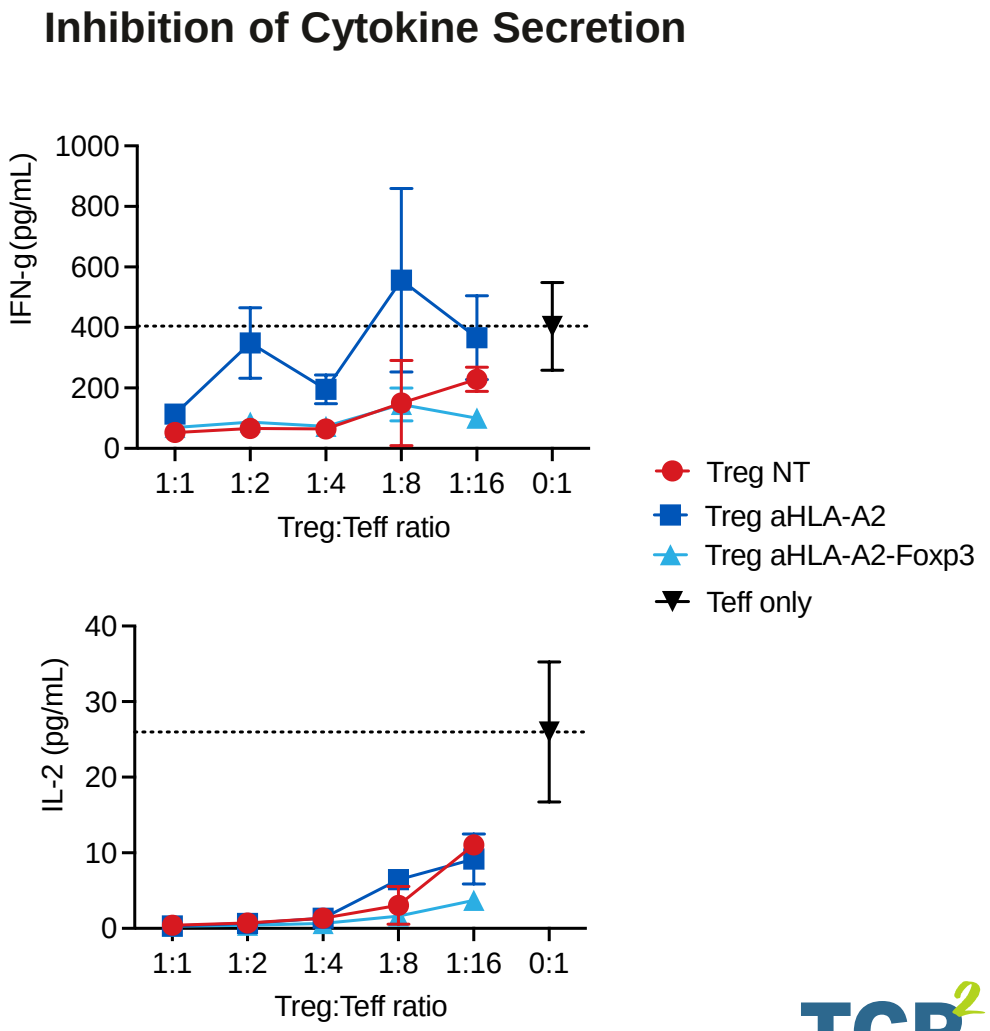
TRuC Treg cells maintain hypomethylated TSDR/CNS regions

TCR2 THERAPEUTICS

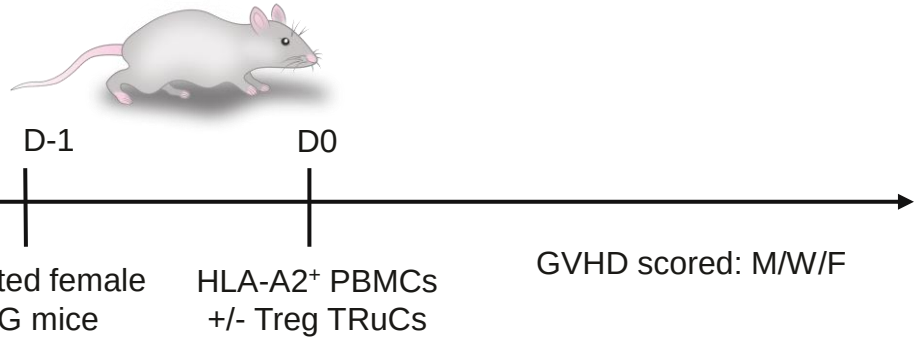
TRuC Treg Cells Suppress Effector T Cell Proliferation and Cytokine Secretion in an *In Vitro* MLR Assay

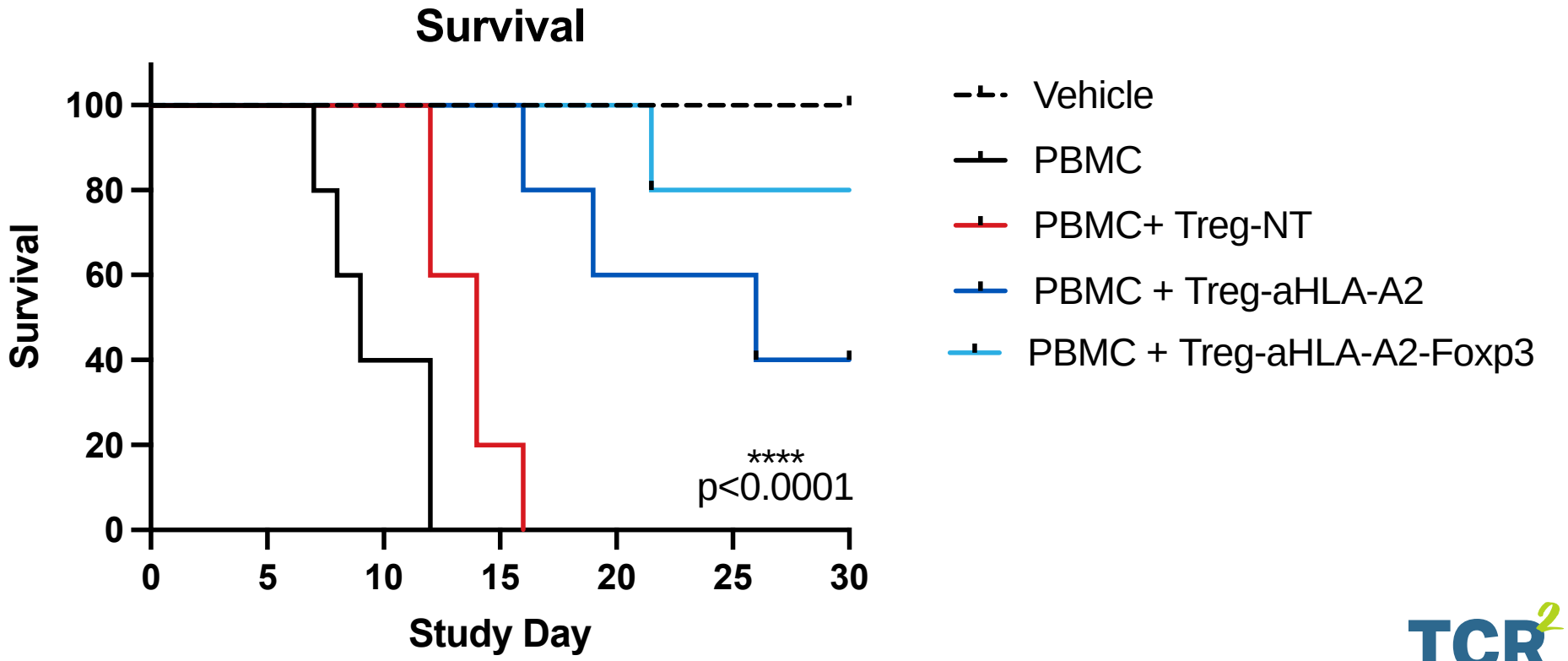






HLA-A*02-specific TRuC Treg Cells Provide Better Protection From GvHD than Polyclonal Treg Cells





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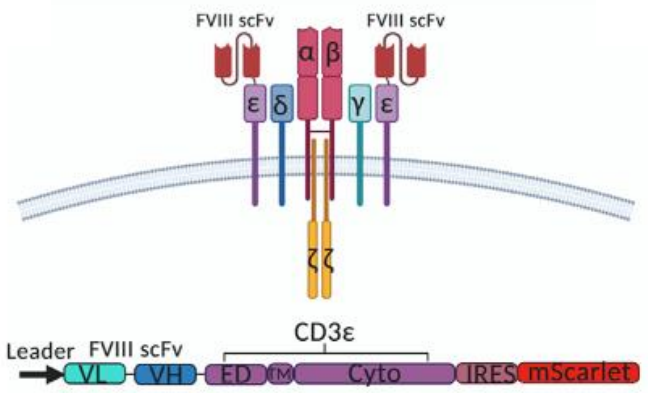
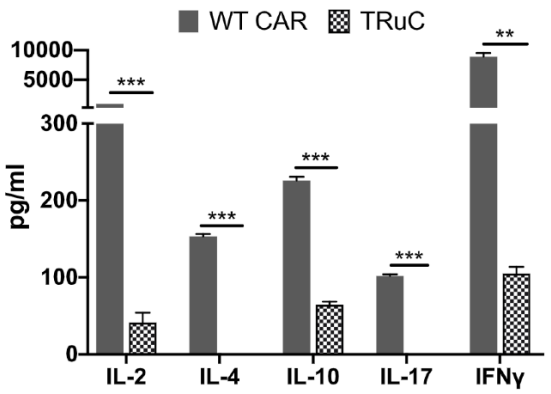
Potential of TRuC Treg Cells Independently Observed in a Mouse Hemophilia A Model

- CAR- or TRuC Tregs were generated against Factor VIII to prevent anti-Factor VIII formation
- CAR-Tregs secrete high levels of effector cytokines when stimulated *in vitro*
- TRuC Tregs suppressed the production of FVIII antibodies better than polyclonal Tregs at 4 and 8 weeks

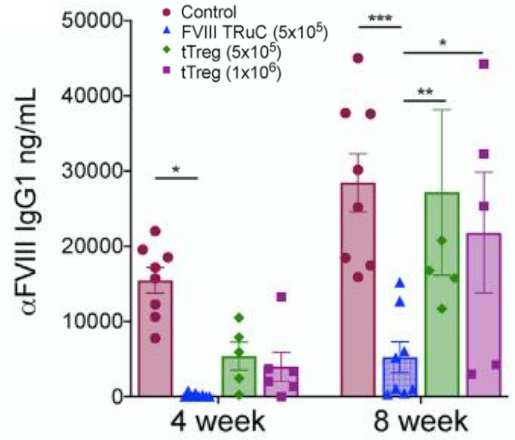
Construct Design



48-hr stimulation with recombinant FVIII



In vivo efficacy



Rana et al., Mol Therapy, 2021

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A Significant BD Opportunity to Unlock TRuC Treg Platform Value

Represents Opportunity Outside of Oncology Focus

- TRuC Tregs build on our clinically validated TRuC-T cell cancer platform
  - Full TCR signaling important for Treg function
  - Natural signaling complex in Tregs to avoid overactivation and effector-like function
  - Established TRuC Treg IP with T cell engineering, PD and manufacturing in place
- Proof of Concept achieved
  - Robust process leading to 70-80-fold Treg expansion while sustaining Treg stability
  - TRuC Tregs targeting HLA-A*02 suppress effector T cells in MLR reaction
  - *In vivo* proof-of-principle for prevention of GvHD by HLA-A*02 PBMCs in a NSG model
- With investment in emerging Treg cell therapies increasing, the TRuC Treg platform is well positioned for leadership in autoimmune disorders
  - Differentiated TRuC Tregs could fill substantial unmet need, including larger indications

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Closing Remarks

Garry Menzel, Ph.D.

President and Chief Executive Officer

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Advancing a Diverse Pipeline of Solid Tumor Programs

Target	Indication(s)	Program	Enhancement / Combo	Discovery	Lead Optimization	IND Enabling	Phase 1/2	Phase 2/3
Oncology								
Autologous								
MSLN	Ovarian cancer, NSCLC, MPM, Cholangiocarcinoma	gavo-cel						
MSLN	Ovarian cancer, NSCLC, MPM, Cholangiocarcinoma	gavo-cel	Checkpoint inhibitor					
MSLN	Solid tumors	TC-510	PD-1 switch					
CD70	Renal cell carcinoma	TC-520	IL-15					
GPC3	Solid tumors							
Nectin-4	Solid tumors							
Allogeneic								
MSLN	Solid tumors	gavo-cel	IL-15 / PD-1 switch					
CD70	Renal cell carcinoma	TC-520	IL-15 / PD-1 switch					
Autoimmune								
HLA-A*02	Solid organ transplant / GvHD							

MSLN, mesothelin; NSCLC, non-small cell lung cancer; MPM, mesothelioma; GvHD, Graft versus Host Disease

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Q&A

TCR² Management and Dr. Hassan