City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

NOVEL THERAPEUTIC AGENTS FOR PLEURA & PERITONEAL CANCERS

Translational Intraperitoneal Immunotherapeutic Strategies Targeting Tumor-Associated Antigens

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Sidney Kimmel Medical College
Chief, Section of Surgical Oncology
Director, Peritoneal Surface Malignancy Program
Thomas Jefferson University Hospital

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- Research Funding
  - NORD – AC /PMP Research Foundation
  - Saligman Family
  - Commonwealth Universal Research Enhancement Program (CURE)
  - Clinical Translational Research Institute (CTRI-Drexel)
  - Oncolyze

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Surgeons and Immunotherapy

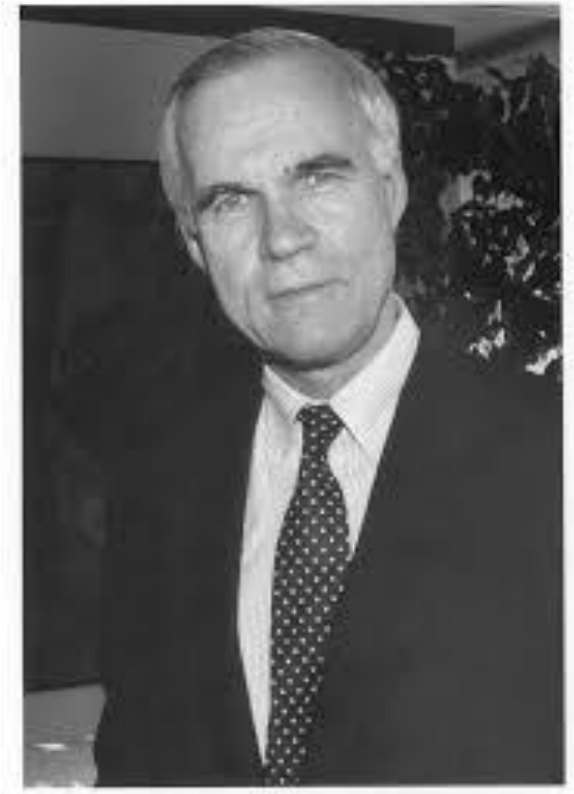
Dr. William Bradley Coley

Signor Zola

Infectious Pathogens = Coley's Toxins

Hall SS. A Commotion in the Blood (Book). 1977 "Laudable Pus"
Morano WF et al. Cancer Gene Therapy, 2016

Milestones in Cancer Immunotherapy

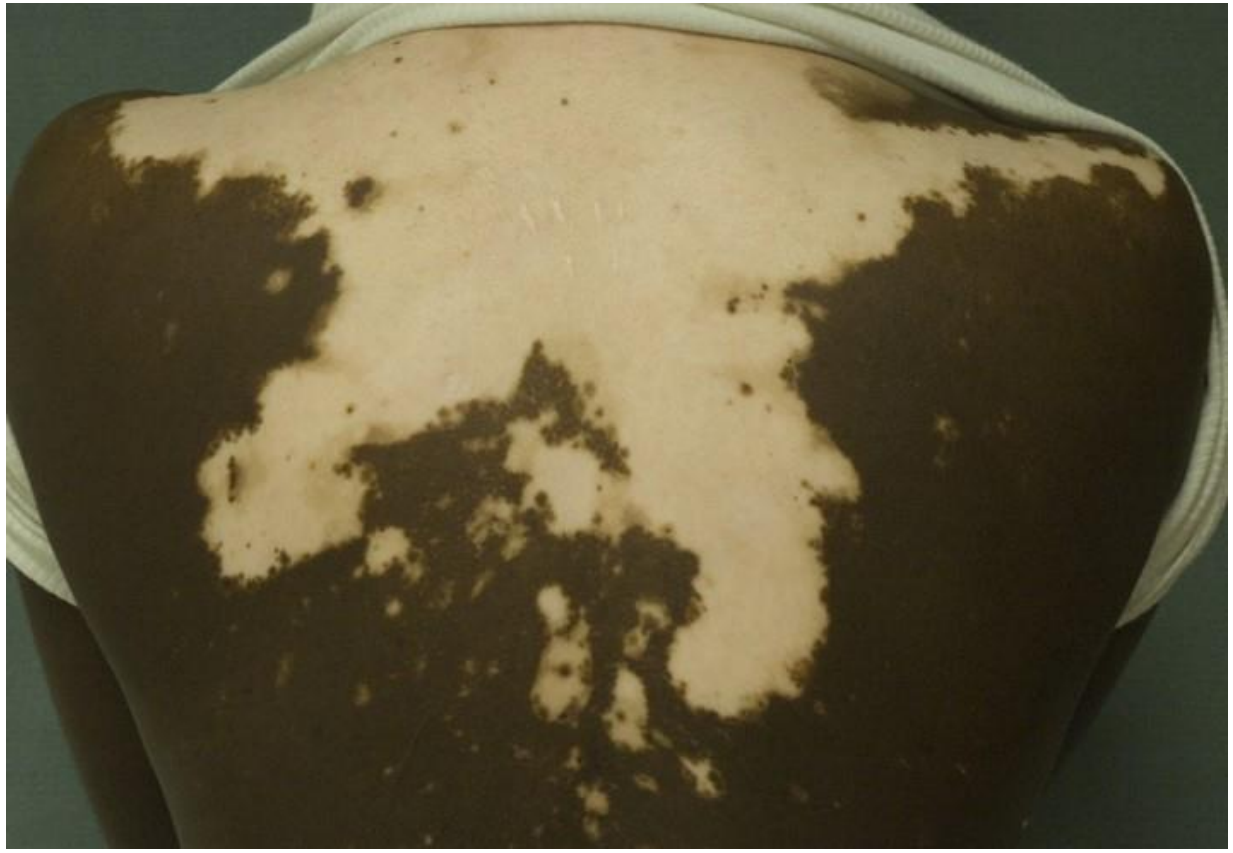


Lloyd J. Old

Alan N. Houghton

Hall SS. A Commotion in the Blood. 1977 “Laudable Pus”
Morano WF et al. Cancer Gene Therapy, 2016

Breaking Immune Tolerance

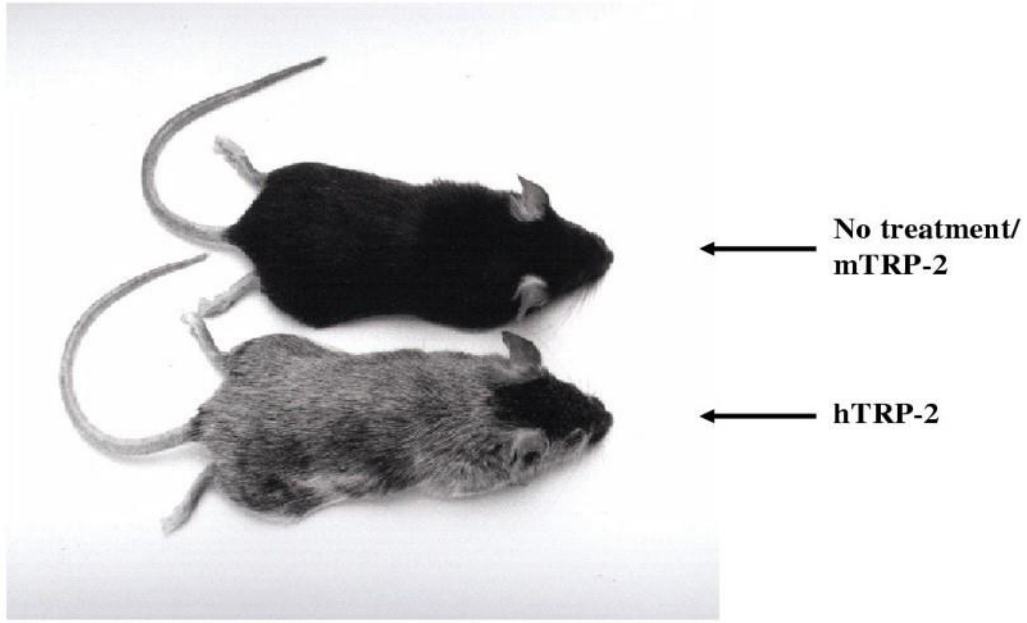


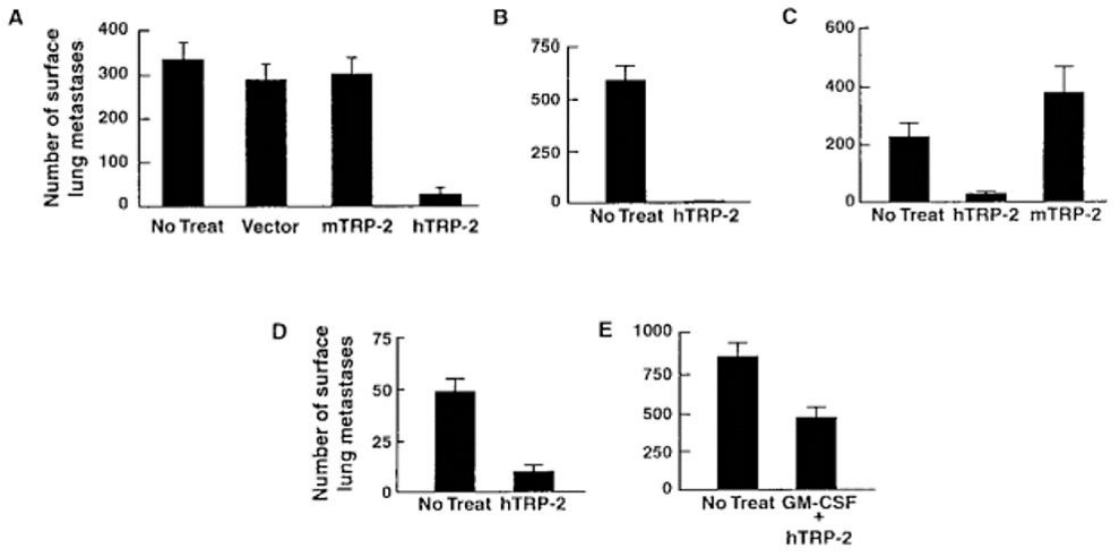
Patient V. F. – Memorial Hospital 1972

Albino AP and Houghton AN. Cancer Surveys 1985

Strategies Targeting Tumor-Associated Antigens

- Recognition of 'Altered Self'



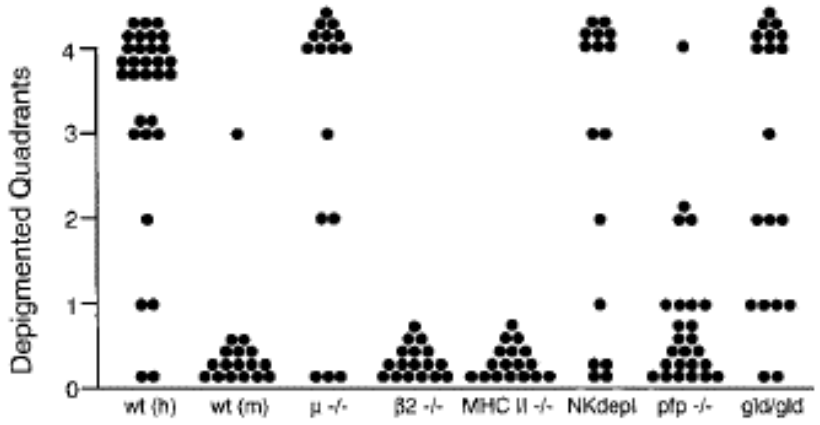


Bowne WB, Srinivasan R, Wolchok JD et al,. J Exp Med 1999

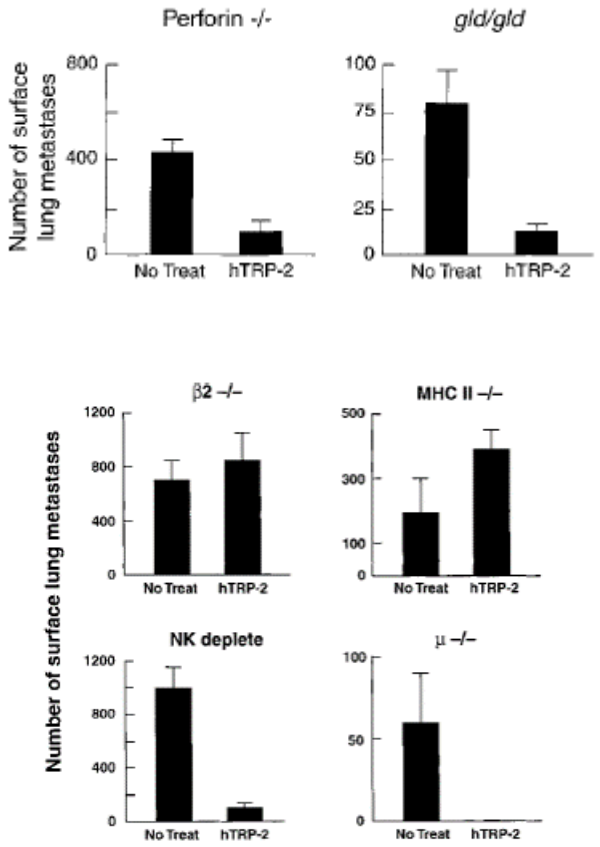
Tumor Immunity & Autoimmunity

- Effector Cells and Mechanisms

Depigmentation / Vitiligo



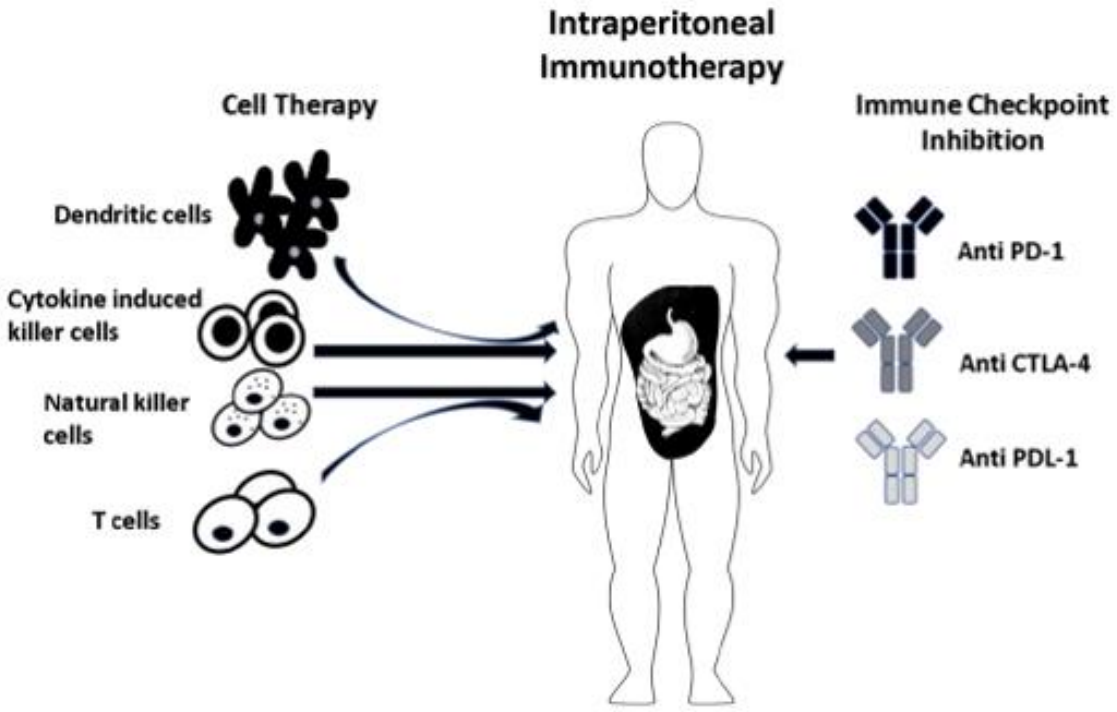
Depletion Tumor Rejection Studies



Bowne WB, Srinivasan R, Wolchok JD et al,. J Exp Med 1999

Intraperitoneal Immunotherapy

- Adoptive Cell Therapy



Thadi A, Morano WF, Katz SC et al., Vaccines 2018; 6 (3): 54

Rationale for IP immunotherapy

- Better therapeutic index with regional delivery
- HIPEC results
- Peritoneal leukocytes contain active immune cells
  - 45% macrophages (CD68+)
  - 45% T cells (CD3+)
  - >70% of T cells are memory/effector subsets
- Sparing of mesothelial cells when targeting epithelial antigens

Strohlein M, Heiss M J Surg Onc. 2009
Kubicka U et al. Scand J Immunol. 1996

Vaccine studies for peritoneal malignancies

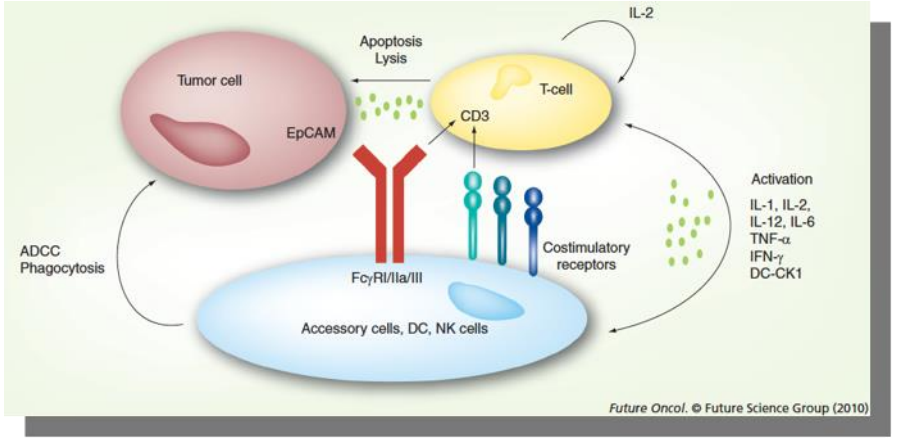
Cancer Type	Treatment	Target	Model	Author (Year)
Ovarian cancer, peritoneal carcinomatosis	GL-ONC1	Malignant ascites	Human	Lauer et al. [69] (2018)
Colon cancer	MG1-IL12-ICV	CD69 and IP10	Murine	Alkayyal et al. [70] (2017)
Colon cancer	FRα targeted lipoplex delivering IL-15 gene.	FRα	Murine	Liang et al. [71] (2016)
Colon and breast	Anti PD-L1 and CTLA-4 in combination with IL-18	PD-L1 and CTLA-4	Murine	Ma et al. [72] (2016)
Chronic myelogenous leukemia	NK cells stimulated by IL-21	NKs	Murine	Oyer et al. [68] (2016)
Ovarian cancer, peritoneal metastasis	Survivac vaccine	Survivin	Human	Berinstein et al. [73] (2015)
Colon, ovarian, gastric, pancreatic cancer	Dendritic cell vaccine+CIKs	Tumor inducing cytokines, CD4+CD25+Tregs	Human	Ai et al. [65] (2014)
Ovarian cancer	Reovirus based anti-cancer therapy	Gr 1.1+, CD11b+MDSCs, FOXP3+Tregs, CD3+cells.	Human, Murine	Gujar et al. [74] (2013)
Ovarian cancer	IP delivered human NKs		Murine	Geller et al. [66] (2013)
Ovarian cancer	Anti MUC1 T cells	MUC1	Human	Dobrzanski et al. [75] (2009)
Ovarian cancer	Multipeptide vaccine	MAGE-A1, FBP, Her-2/neu	Human	Chianene-Bullock et al. [76] (2008)

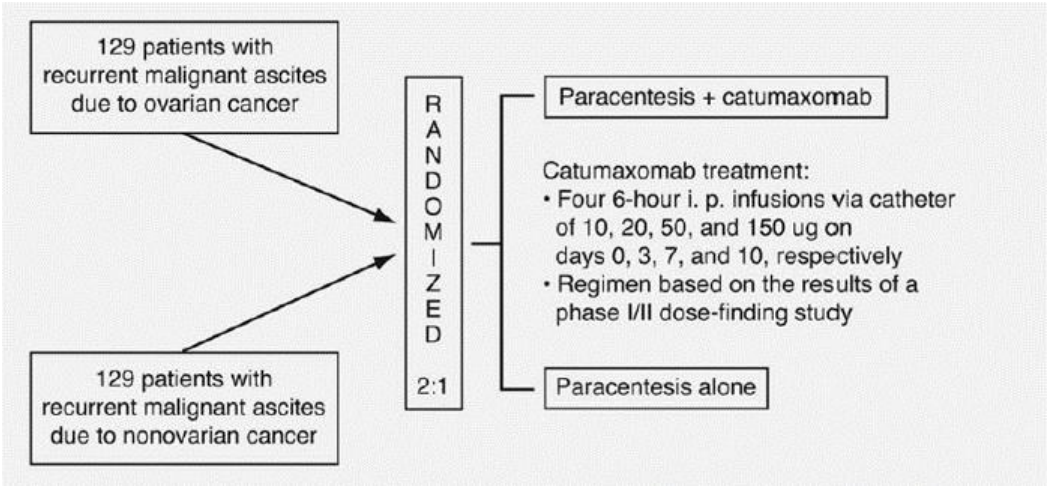
DREXEL UNIVERSITY College of Medicine

A. Thadi, M. Khalili Vaccines 2018

Catumaxomab phase 2/3 data

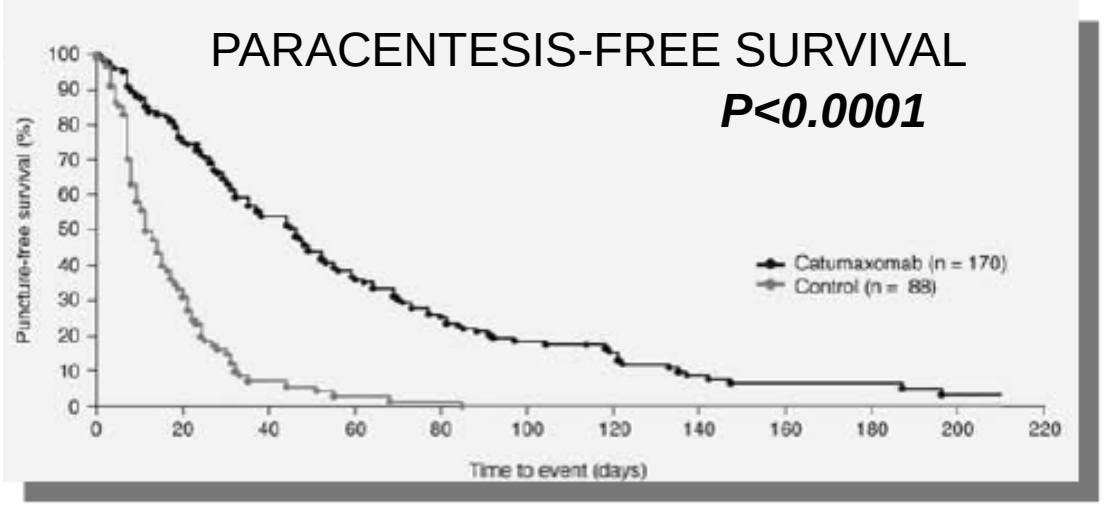
- 258 patients randomized to paracentesis with or without catumaxomab
  - 50% ovarian and 50% non-ovarian
- Improves paracentesis-free time (46 v 11 days, P<0.0001)
- Fewer ascites-related symptoms
- Improved OS in gastric cancer patients
  - 71 v 44 days (p=0.03)

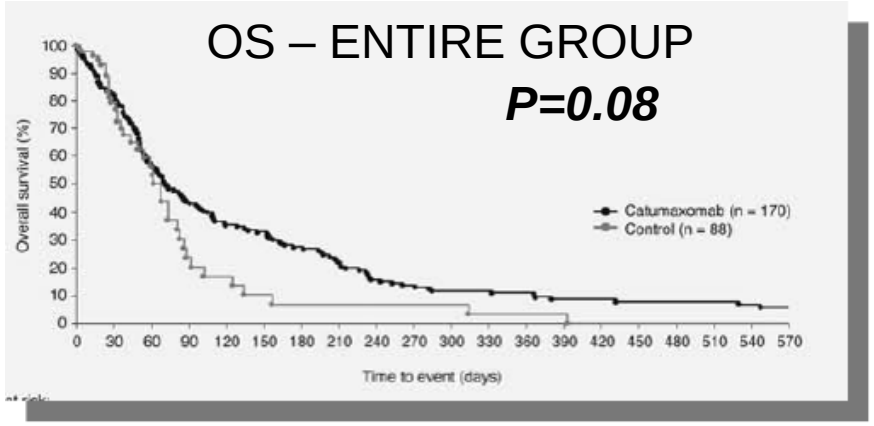


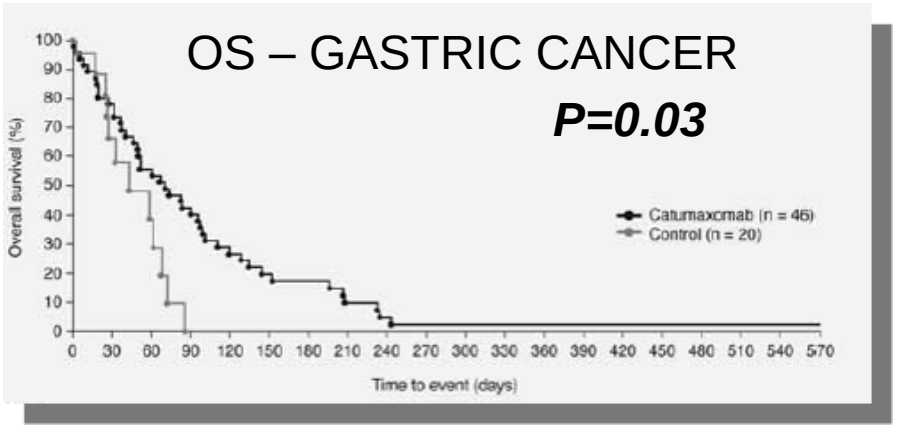


Heiss M et al. Int J Can. 2010

Catumaxomab phase 2/3 data







Heiss M et al. Int J Can. 2010

Surgical Perspective

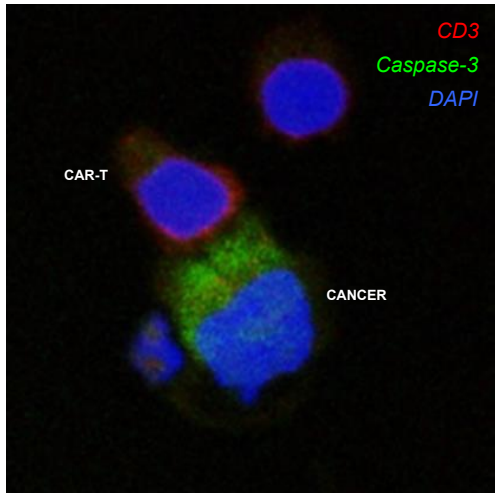
- **Peritonectomy procedures and visceral resections are performed to remove all visible evidence of disease.**
- **HIPEC is to preserve the surgical complete response.**

- Paul H. Sugarbaker

PH Sugarbaker. Annals of Surgery (1995) 1, 29-42

CAR-T Immunotherapy

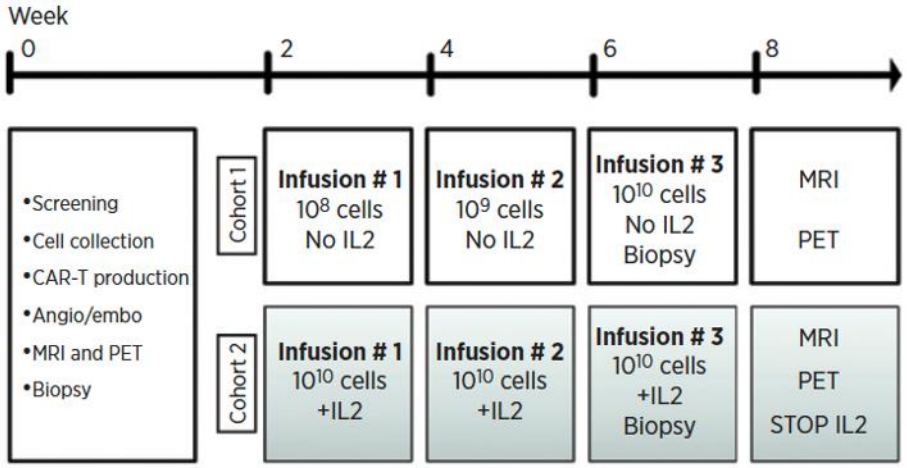
- Pros
  - Manufacturing possible for any patient with target
  - Highly specific
  - Potential for modification to enhance function
  - Not MHC dependent
- Cons
  - Not all tumors and patients have targets
  - Manufacturing time and logistics
  - Cytokine release and neurotoxicity

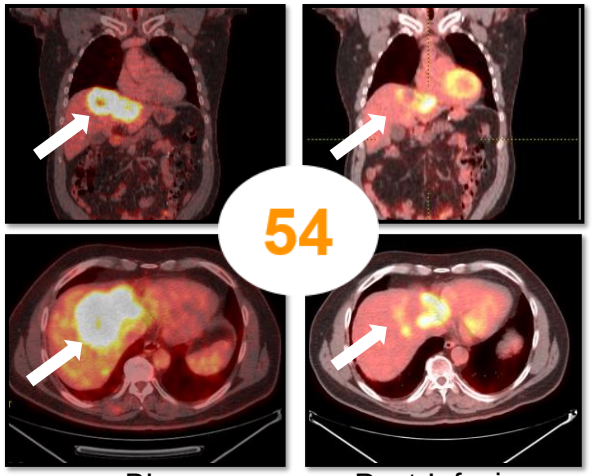


Steven C. Katz

Intrahepatic CAR-T infusions

HITM®
HEPATIC IMMUNOTHERAPY FOR METASTASES
NCT01373047





BL Post-Infusion

- Phase I trial: CAR-T HAI, CEA$^+$ liver metastases
- 8 patients anti-CEA CAR-T regional infusion
- Outpatient IR procedure
- No life-threatening events or death due to treatment
- Encouraging response data to support phase 2


Cancer Therapy: Clinical

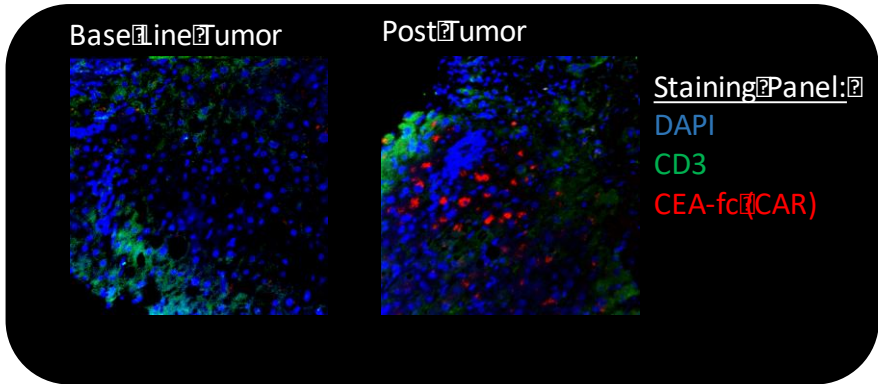
Clinical Cancer Research

Phase I Hepatic Immunotherapy for Metastases Study of Intra-Arterial Chimeric Antigen Receptor–Modified T-cell Therapy for CEA$^+$ Liver Metastases

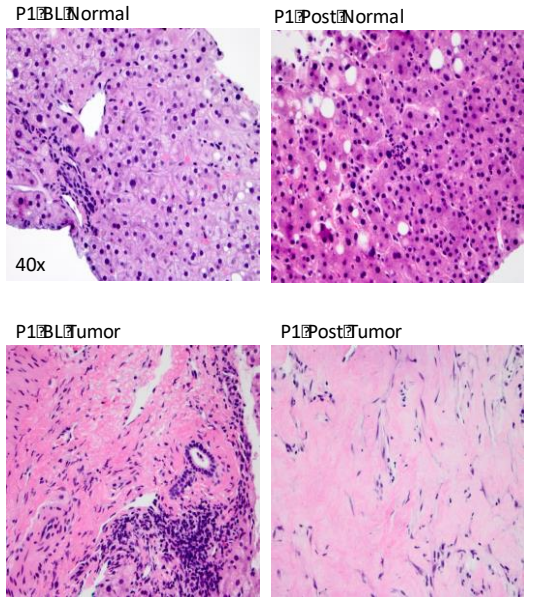
Steven C. Katz[1], Rachel A. Burga[1], Elise McCormack[2], Li Juan Wang[3], Wesley Mooring[3], Gary R. Point[1], Pranay D. Khare[4], Mitchell Thorn[1], Qiangzhong Ma[2], Brian F. Stainken[5], Earle O. Assanah[5], Robin Davies[4], N. Joseph Espat[1], and Richard P. Junghans[2]

Intrahepatic CAR-T Delivery & Clinical Activity

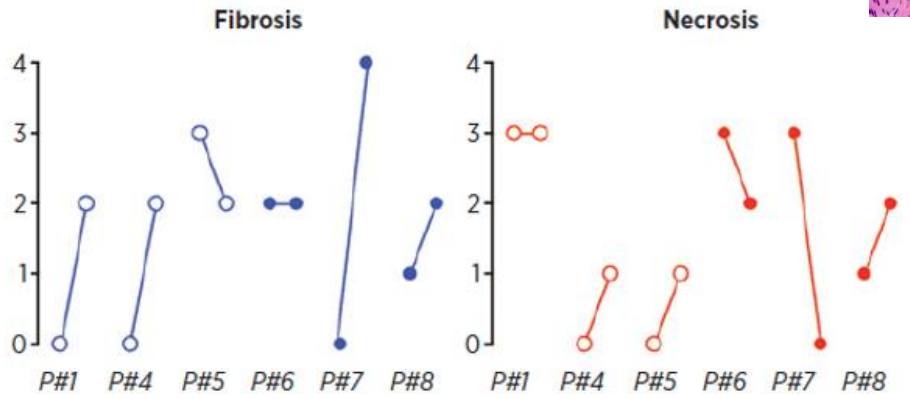
A



B



C



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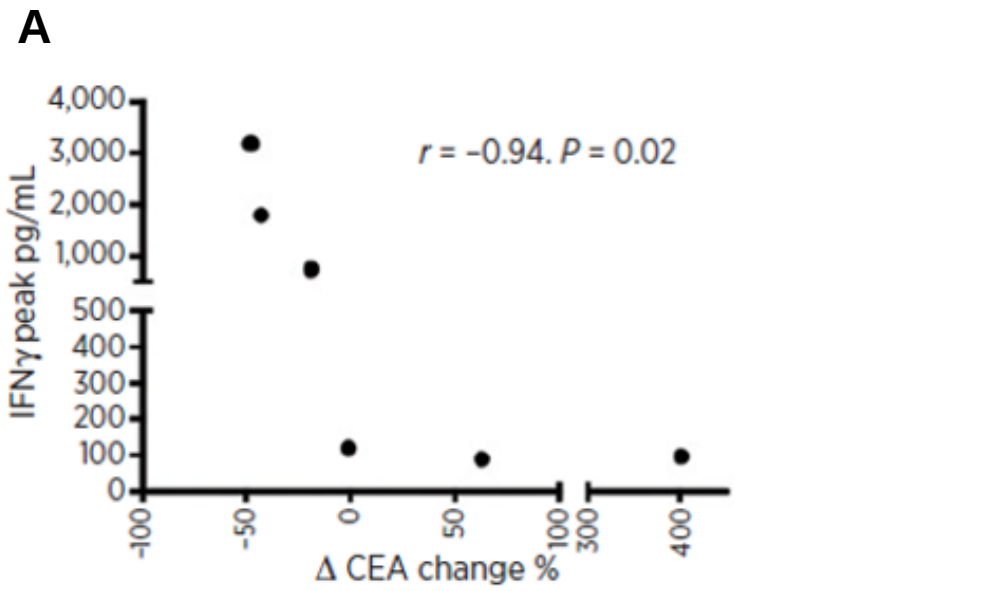
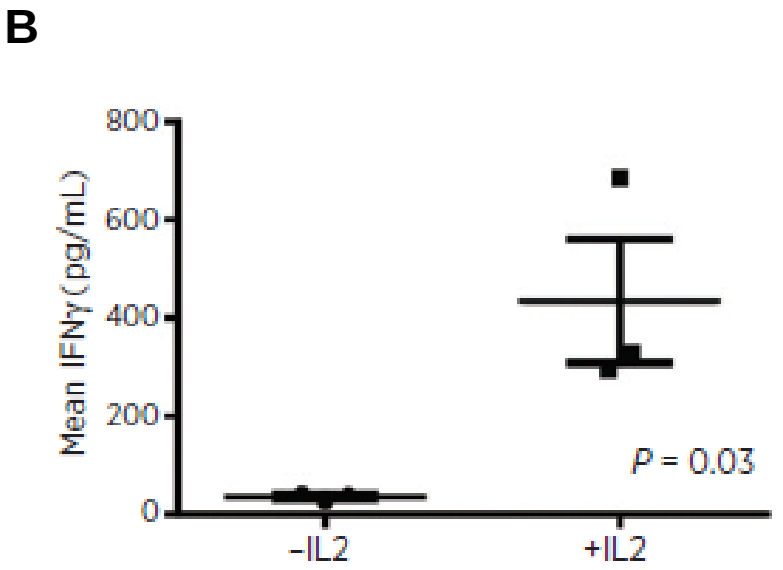
Surrogates for CAR-T activity in liver tumors





Clinical Cancer Research

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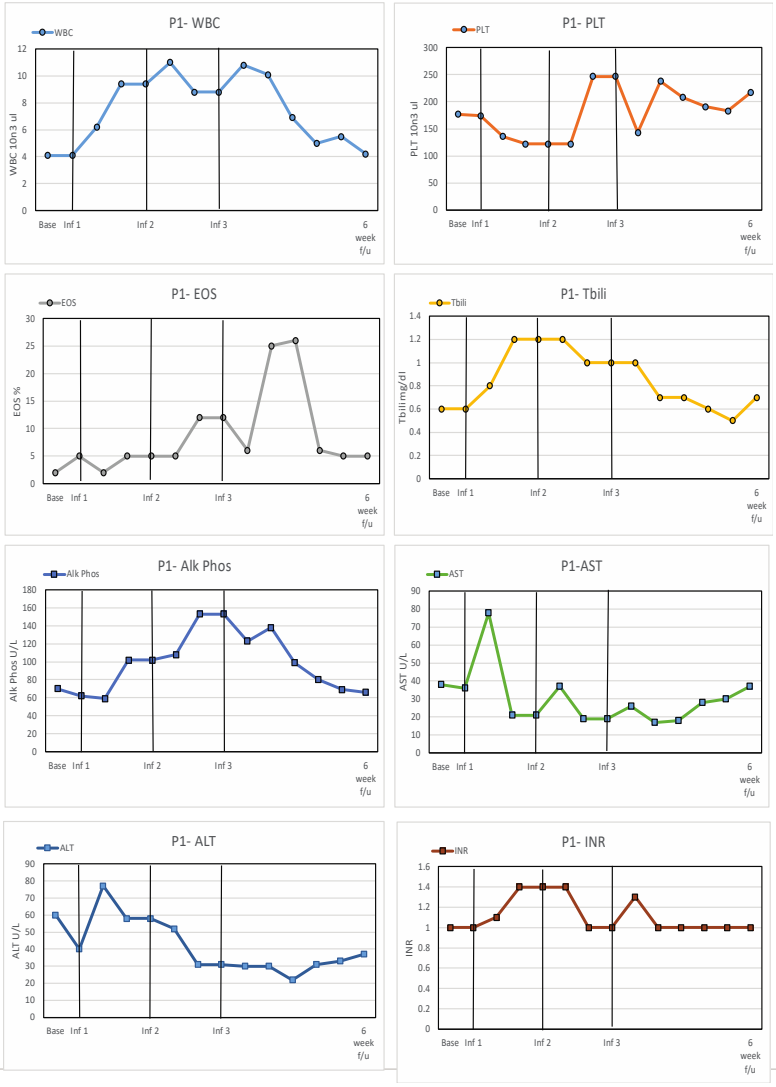
Safety Profile of CAR-T HAI



No severe liver or biliary adverse events

No severe CRS or neurotoxicity

No severe on-target/off-tumor

1e10 cells via HAI is safe

Cancer Therapy: Clinical

Clinical Cancer Research

Phase I Hepatic Immunotherapy for Metastases Study of Intra-Arterial Chimeric Antigen Receptor–Modified T-cell Therapy for CEA$^+$ Liver Metastases

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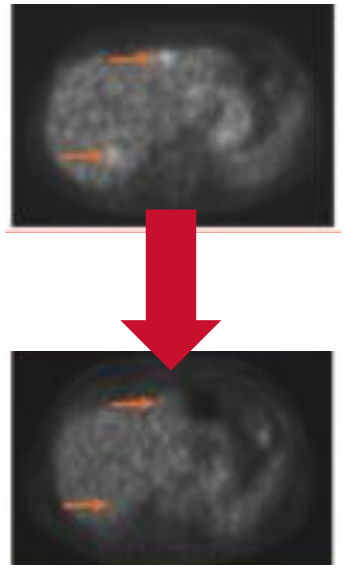
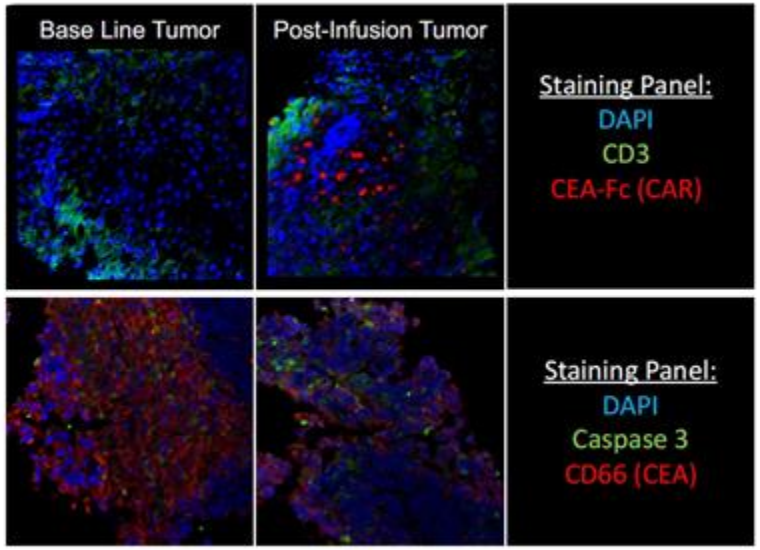
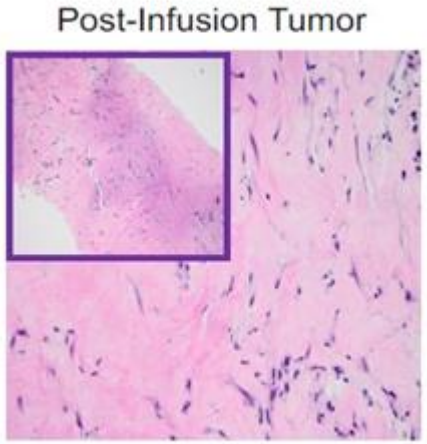
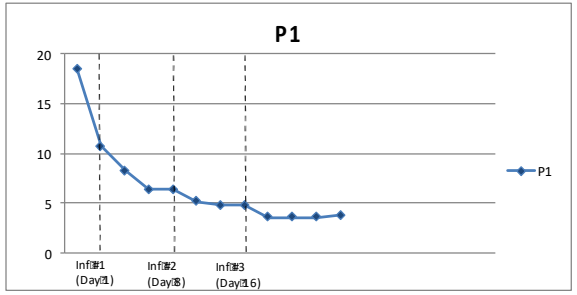
Stage IV pancreas cancer – durable PET CR



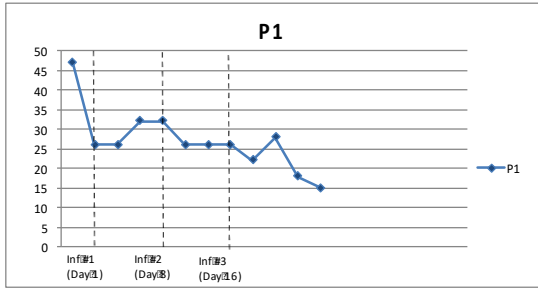




CEA



CA19-9

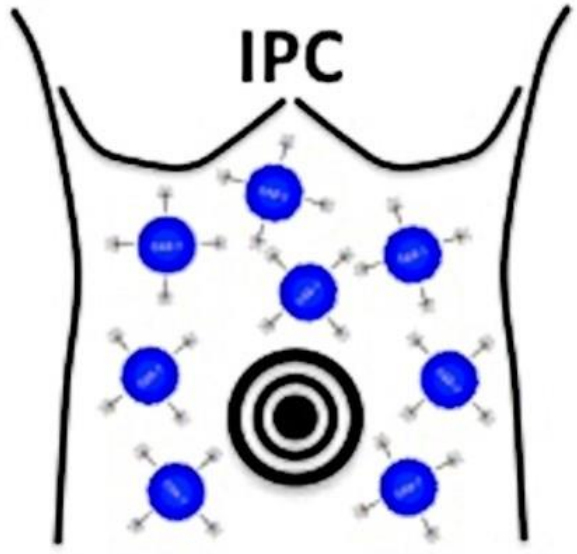


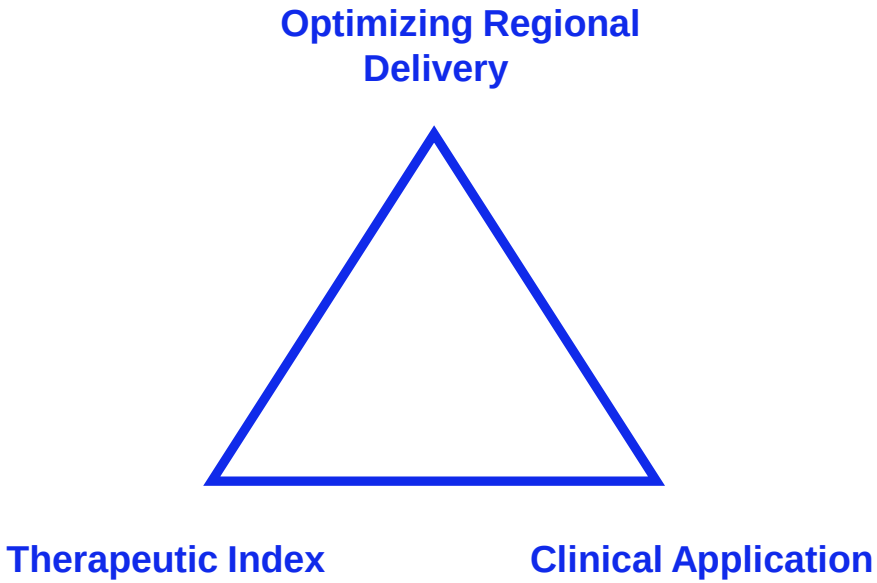
HITM-SURE: Hepatic immunotherapy for metastases phase Ib anti-CEA CAR-T study utilizing pressure enabled drug delivery

Steven C Katz,[1,2,3] Ashley E Moody,[1] Prajna Guha,[1] John C Hardaway ,[1] Ethan Prince,[4] Jason LaPorte,[1] Mirela Stancu,[5] Jill E Slansky,[6] Kimberly R Jordan,[6] Richard D Schulick,[6] Robert Knight,[7] Abdul Saied,[1] Vincent Armenio,[2] Richard P Junghans[8]

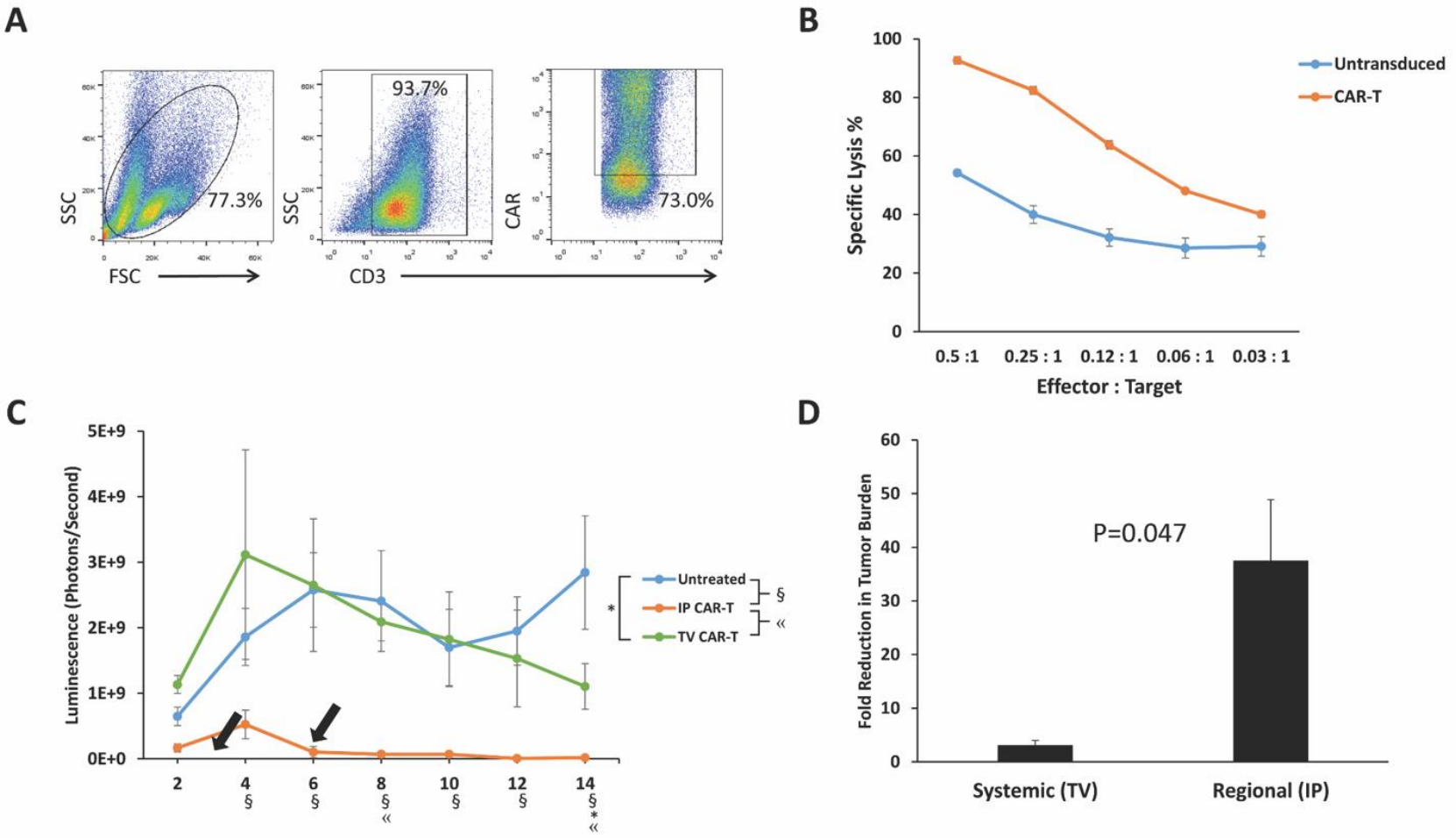
Immunotherapy for **P**eritoneal **C**arcinomatosis

- Translational / Proof of Concept Studies



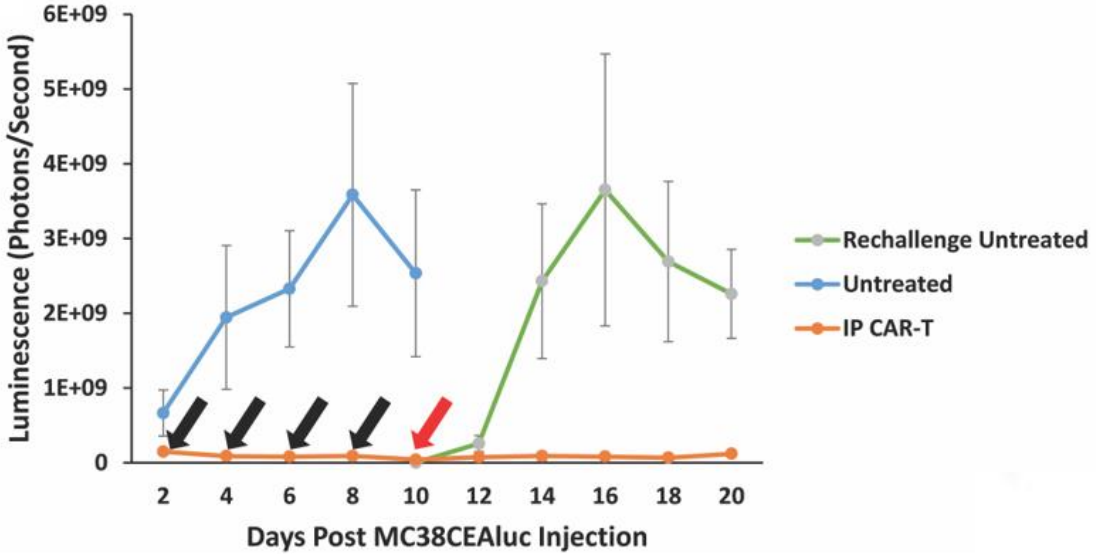


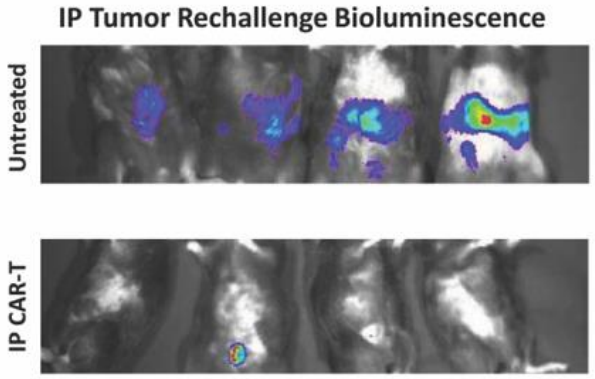
Intraperitoneal delivery of CAR-T

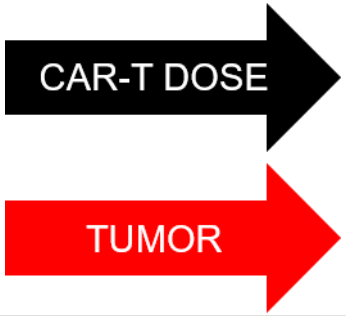


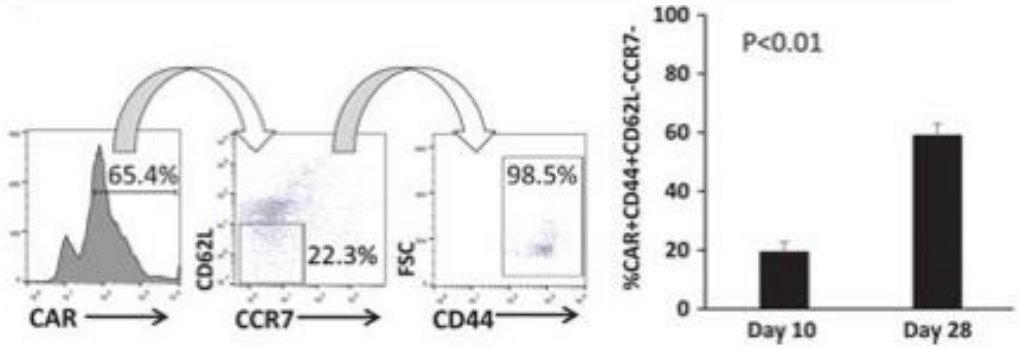
SC Katz et al. Cancer Gene Therapy (2016) 23, 142–148

Durable response from IP CAR-T





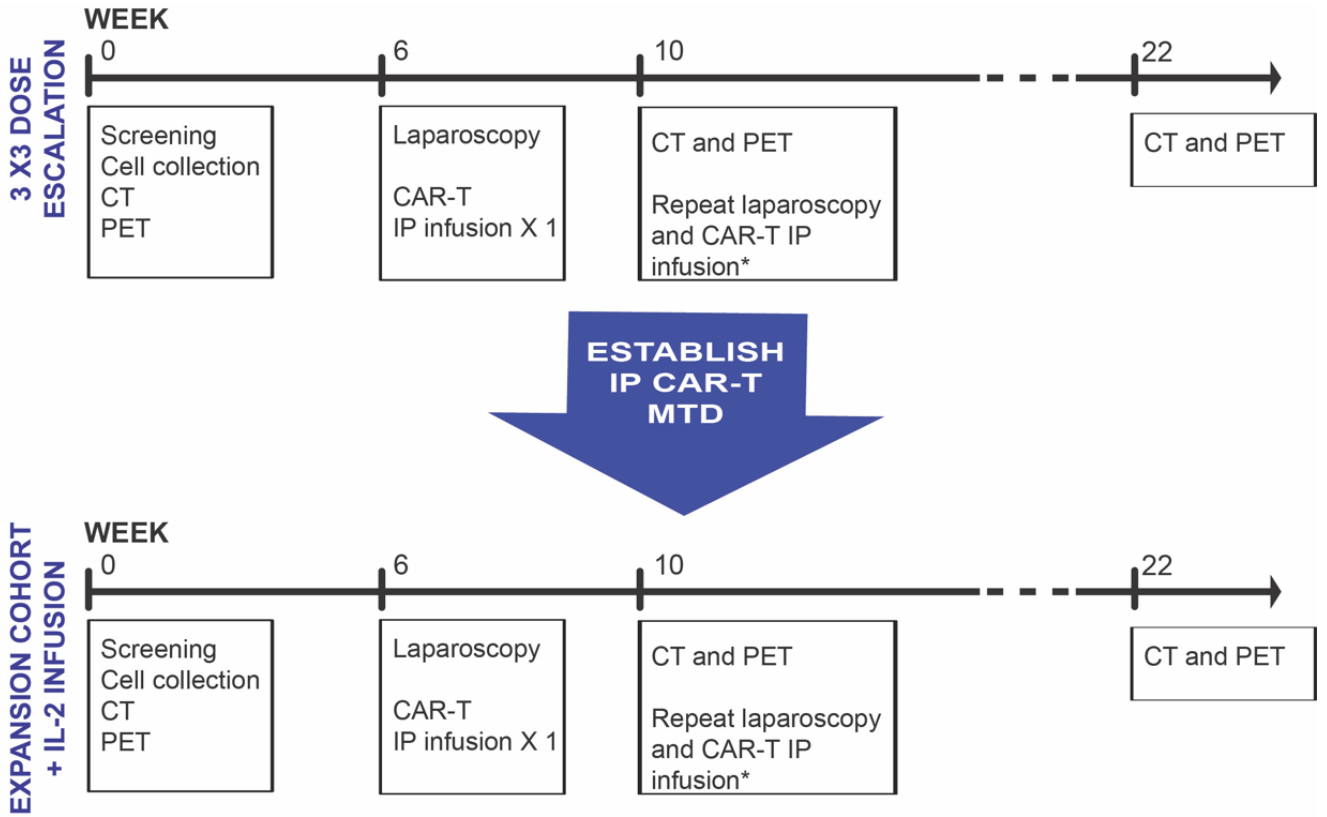




SC Katz et al. Cancer Gene Therapy (2016) 23, 142–148

IPC Phase I Study

CAR-T Intraperitoneal Infusions for CEA-Expressing Adenocarcinoma Peritoneal Metastases or Malignant Ascites (IPC)



**Additional discretionary 28-day IP infusion cycles may be initiated if criteria are met.*

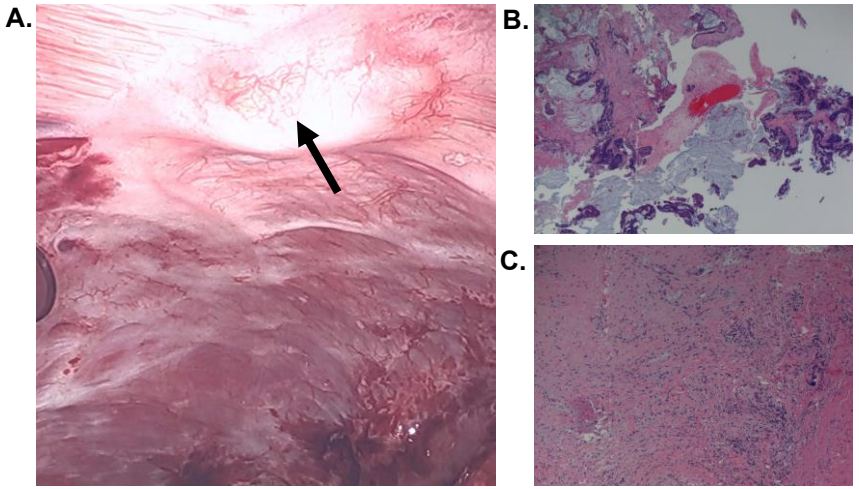
SSO Society of Surgical Oncology | Advanced Cancer Therapies

NIH U.S. National Library of Medicine

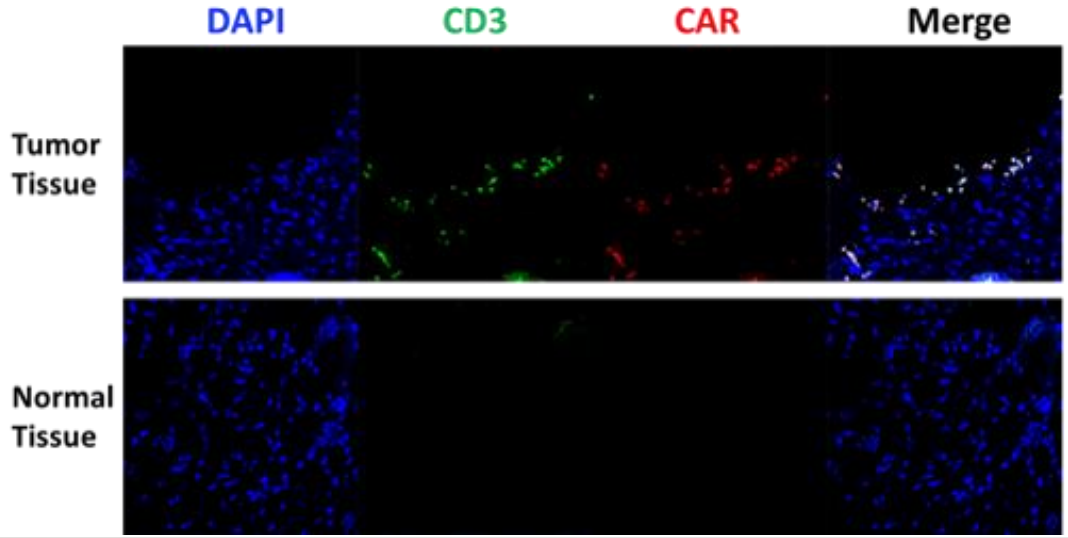
ClinicalTrials.gov

PI - Steven C. Katz (2020)

IPC Study – Delivery & Response



TIL counts/10 high power fields		
	Pre	Post
CD3+	12	36
CD4+	7	23
CD8+	5	13



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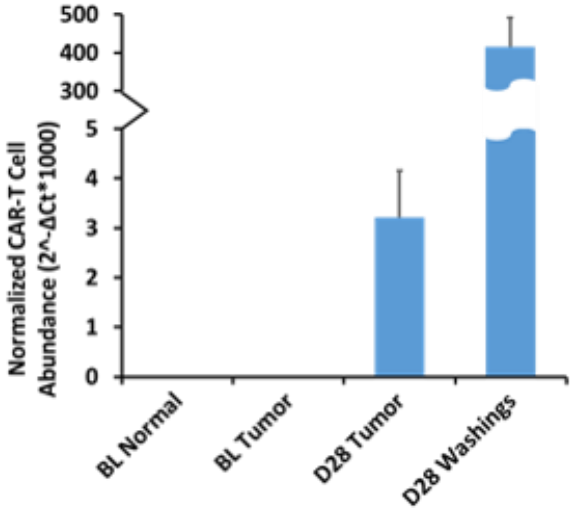
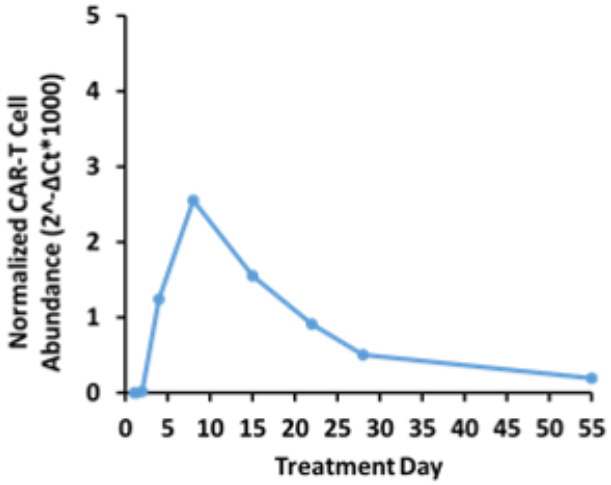
IPC Study

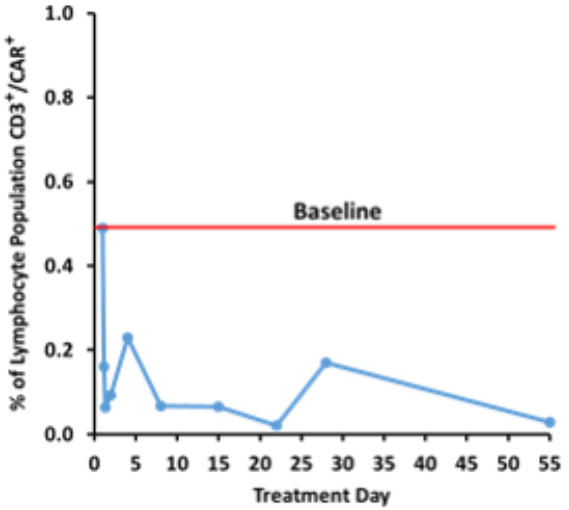
Tissue qPCR



Blood qPCR



Blood FC



Accumulation of CAR-T in peritoneal tumor and ascites.

Low systemic exposure.

SSO SOCIETY OF SURGICAL ONCOLOGY
ADVANCED CANCER THERAPIES

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ClinicalTrials.gov

PI - Steven C. Katz (2020)

CAR-T studies for peritoneal malignancies

Cancer Type	Treatment	Target	Model	Author (Year)
Gastric and Ovarian	chA21-4-1BBz CAR-T cells	HER2	Murine	Han et al. [60] (2018)
Ovarian cancer	CE7^{+}R T_{CM} CAR-T cells	L1-CAM	Murine	Hong et al. [61] (2016) Daponte et al. [62] (2008)
Colorectal cancer	Anti CEA CAR-T cells with anti Gr1/GITR and anti PD-L1	CEA, Gr1 and PD-L1	Murine	Katz et al. [59] (2016)
Ovarian cancer	Anti MUC16 CAR-T cells	MUC16	Human	Koneru et al. [63,64] (2015)
Breast and gastric cancer	Anti CEA CAR-T cells	CEA	Human	NCT02349724 (2015)
Ovarian, Breast and Colorectal cancer	Anti FRα CAR-T cells	FRα	Murine	Song et al. [57] (2011)

Abbreviations: PM, peritoneal metastasis; CAR-T, chimeric antigen receptor expressing T cells; CEA, carcinoembryonic antigen; PD-L1, programmed cell death protein-ligand 1; MUC16, mucin 16 associated with membrane; FRα, folate receptor α; HER2, human epidermal growth factor receptor 2; L1-CAM, L1 cell adhesion molecule; NCT, national clinical trial identifier.

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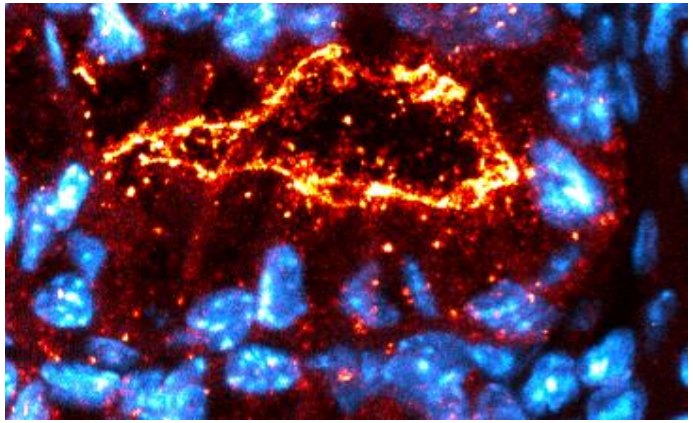
Thadi, Khalili, Morano…Bowne. Vaccines. 2018

Compartmentalized Antigens

- Cancer Mucosa Antigens

  - Intestinal tumor-associated antigens
  - Expression restricted to normal intestinal mucosa and derivative tumors
  - Immune independence from systemic surveillance



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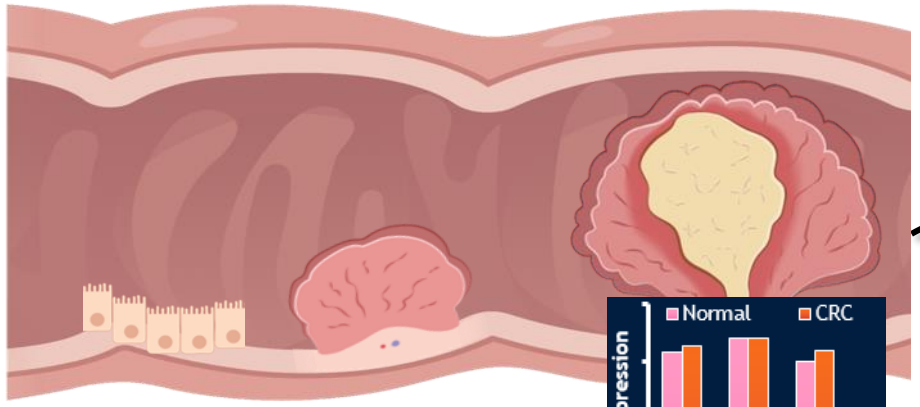
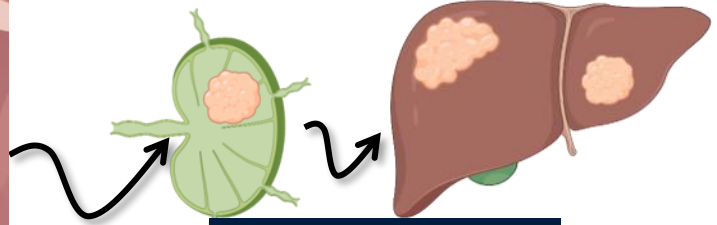
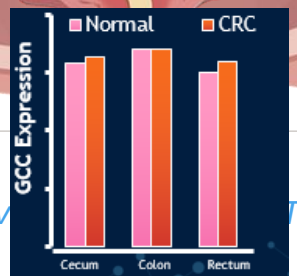
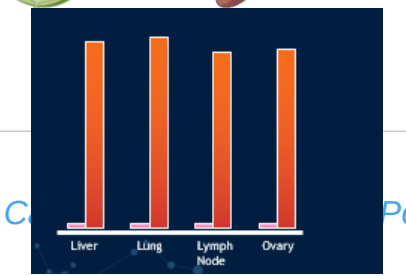


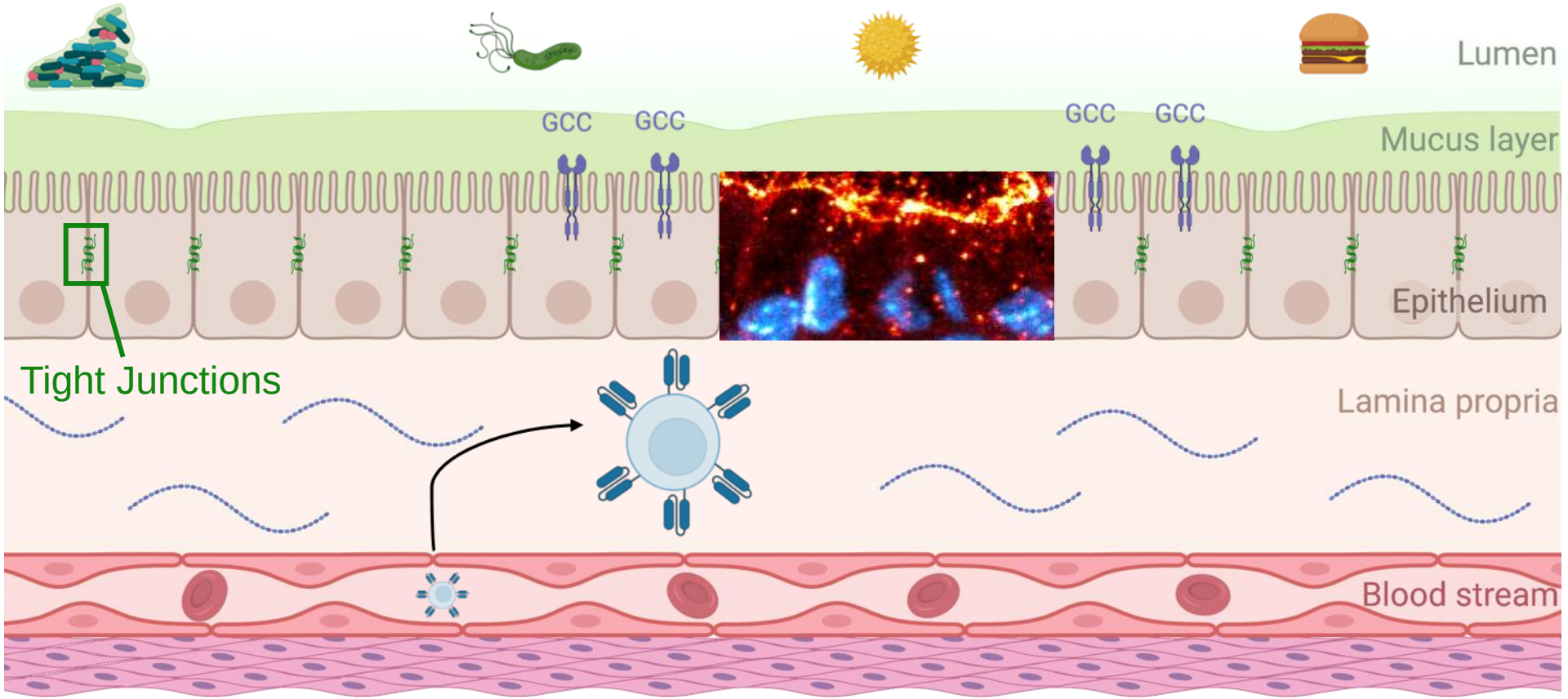






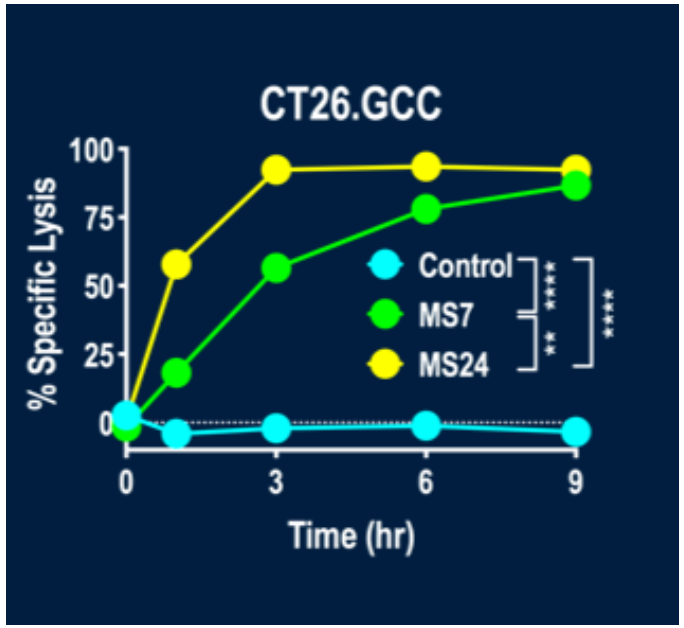
MS Magee et al. Cancer Immunol Res. (2018) 6, 509-516
AN Lisby et al. Expert Rev Precis Med Drug Dev. (2021) 6, 117-129

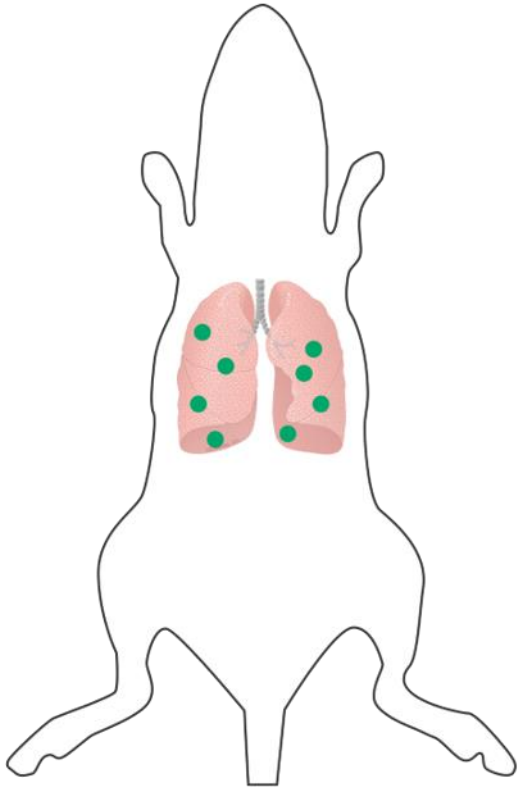
GCC Compartmentalization

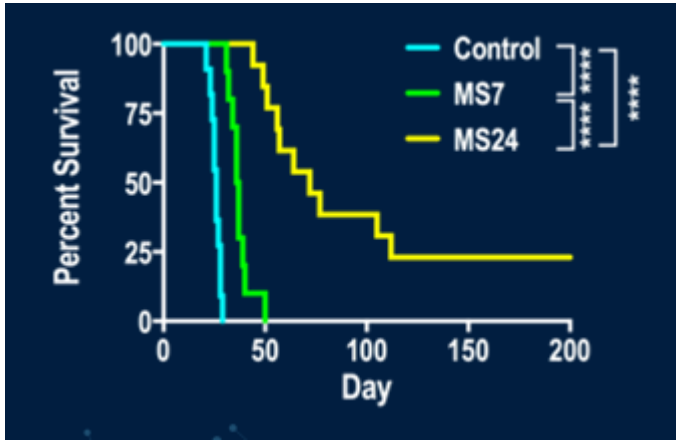


MS Magee et al. Cancer Immunol Res. (2018) 6, 509-516
AN Lisby et al. Expert Rev Precis Med Drug Dev. (2021) 6, 117-129

Syngeneic Model

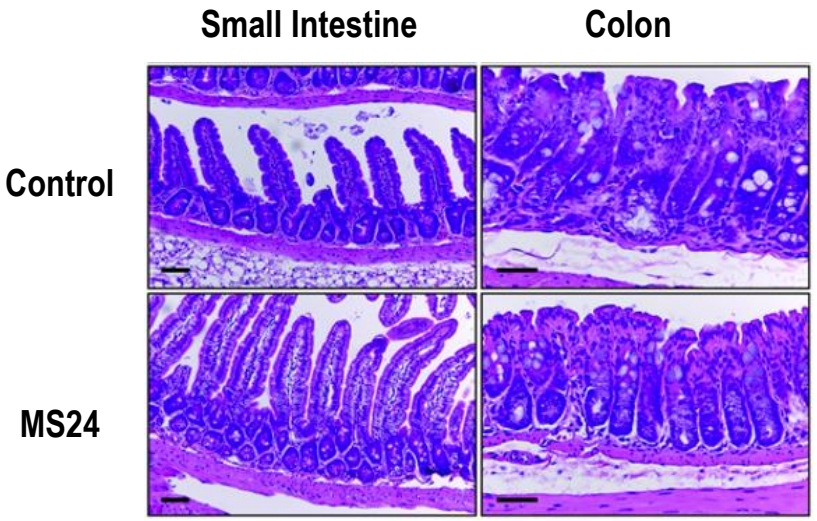


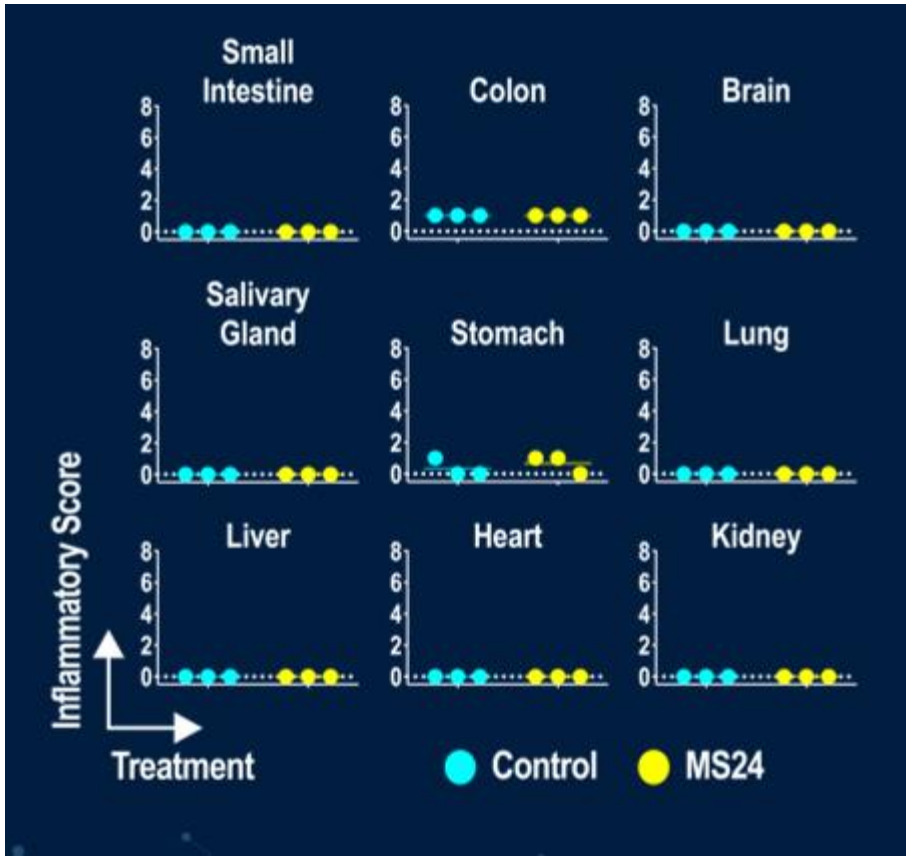




MS Magee et al. OncoImmunology (2016) 5, e1227897

Syngeneic Model



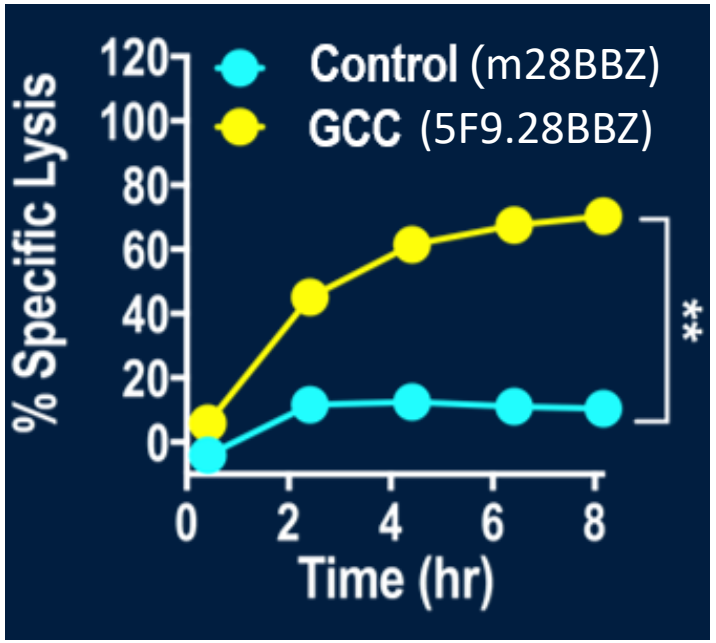


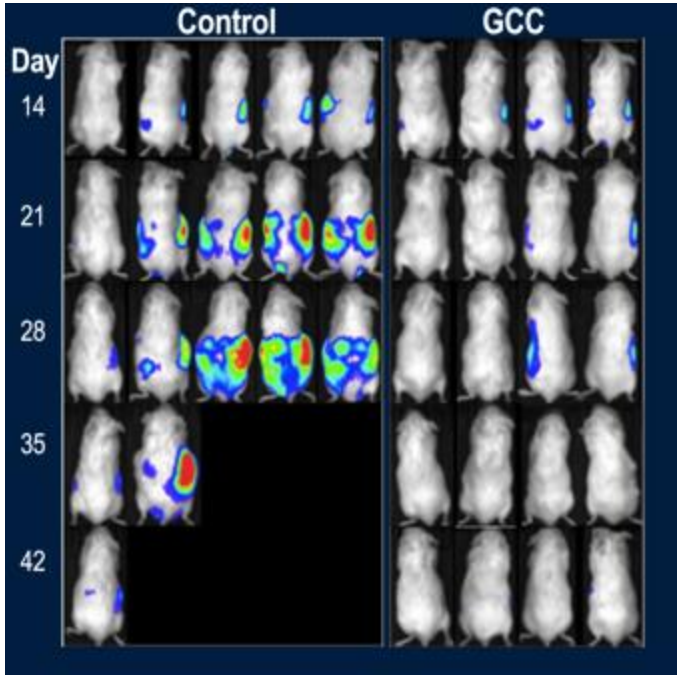
Low systemic toxicity

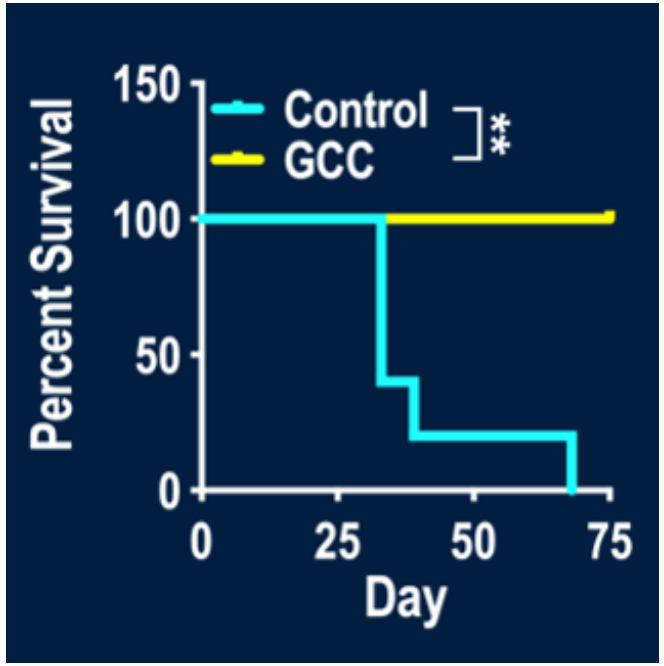
Absence of on-target / off- tumor autoimmunity

MS Magee et al. OncoImmunology (2016) 5, e1227897

Human Model (T84 / T84-Luc)







** Intraperitoneal (IP) regional delivery*

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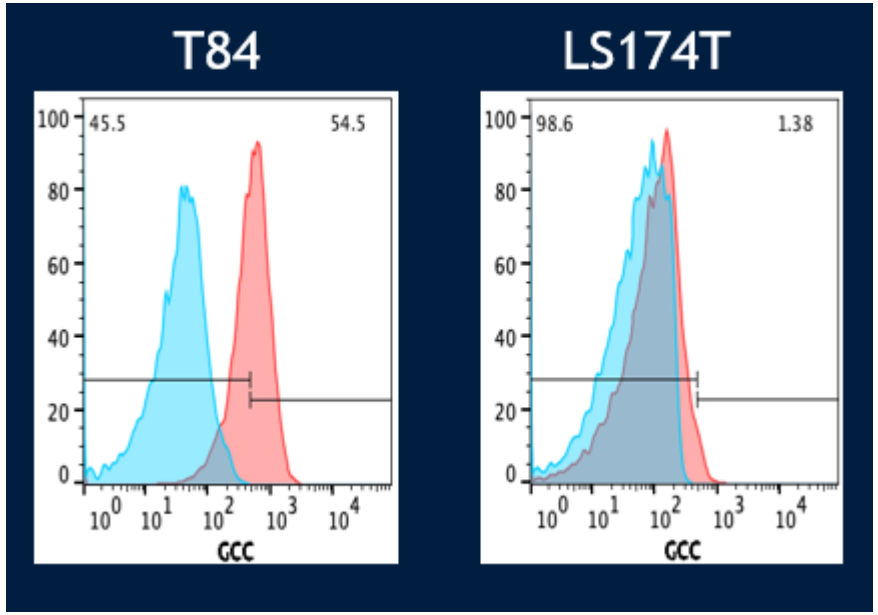
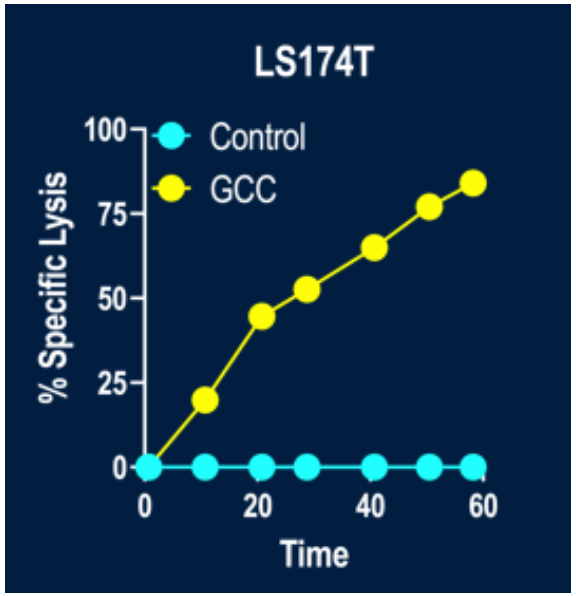
GCC CART-Cell Sensitivity



Cell Line	Surface GUCY2C Molecules
T84	8067
LS174T	875

Mathur D, et al. Clin Cancer Res. 2020;26(9):2188–2202.



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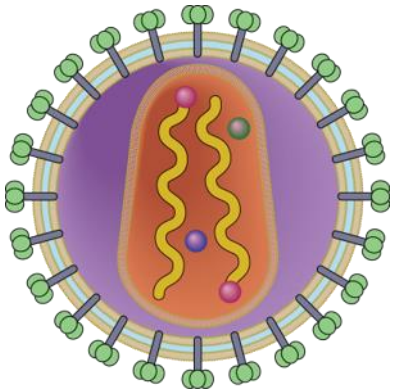
Translation

GMP Lentivirus



GMP CAR-T Production

Patients

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Future Directions

"CRS and HIPEC are a solution looking for a problem…."

- Jesus Esquivel

RESEARCH ARTICLE

WILEY

Clinical studies in CRS and HIPEC: Trials, tribulations, and future directions—A systematic review

William F. Morano MD[1] | Marian Khalili MD[1] | Dennis S. Chi MD[2] | Wilbur B. Bowne MD[1] | Jesus Esquivel MD[3]

Conclusions

- Intraperitoneal immunotherapy exploiting tumor-associated antigens offers a potential treatment strategy for peritoneal surface malignancies.
- Regional delivery of tri-functional antibodies and genetically modified T cells are promising forms of immunotherapy for metastases.
- Exploiting immune compartmentalization of intestinal tumor associated antigens mediates tumor immunity, obviating off-target autoimmunity.

Acknowledgements

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Scott A. Waldman (& Laboratory)