Immunotherapy for the treatment of GIST

Division of Surgical Oncology
Office of Therapeutic Development
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Associate Professor of Surgery
Boston University Medical Center

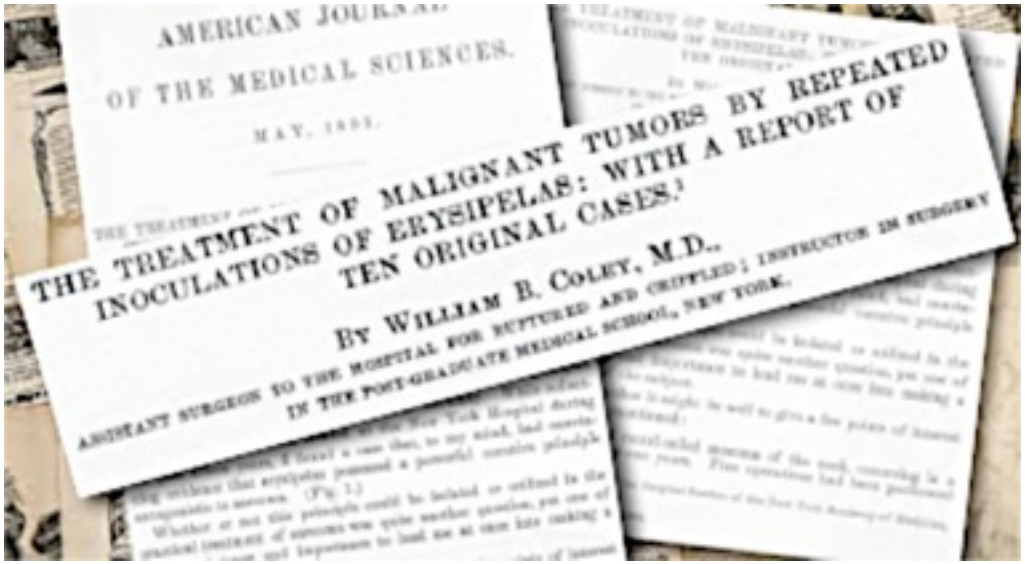
Steven C. Katz, MD

en.wikipedia.org

Outline

- **Immunotherapy for solid tumors**
- Unmet clinical need
- Immune response to GIST
- Building an anti-KIT CAR

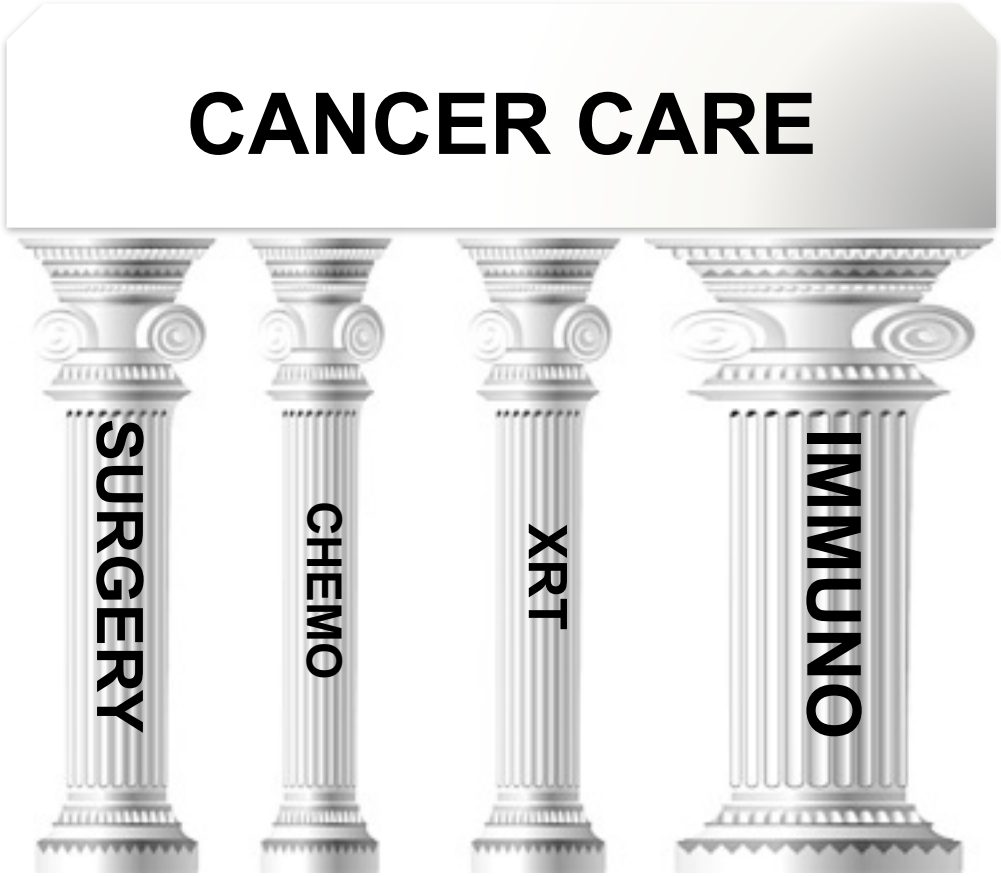
1890


OF THE MEDICAL SCIENCES.
THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF TEN ORIGINAL CASES.
By William B. Coley, M.D.,

2003

2015

2020



$25-40 billion market

50% of medical oncology market share

U.S.

Cancer Immunotherapy Treatment Shows More Promise

Treatment Eradicated Tumors in 14 of 16 Patients With Advanced Leukemia in Study

BUSINESS

New Immunotherapy Drug Data Show Promise in Treating Cancer

Drugs From Bristol-Myers and Merck Shown to Prolong Lives of Some Cancer Patients

MARKETS

New Cancer Technology Gives Investors a Shot in the Arm

Immunotherapy's promise is drawing some marquee financiers

The New York Times

BUSINESS DAY

F.D.A. Allows First Use of a Novel Cancer Drug

By ANDREW POLLACK SEPT. 4, 2014

HEALTH

Breaking Through Cancer's Shield

By GINA KOLATA OCT. 14, 2013

HEALTH

New System for Treating Cancer Seen as Hopeful

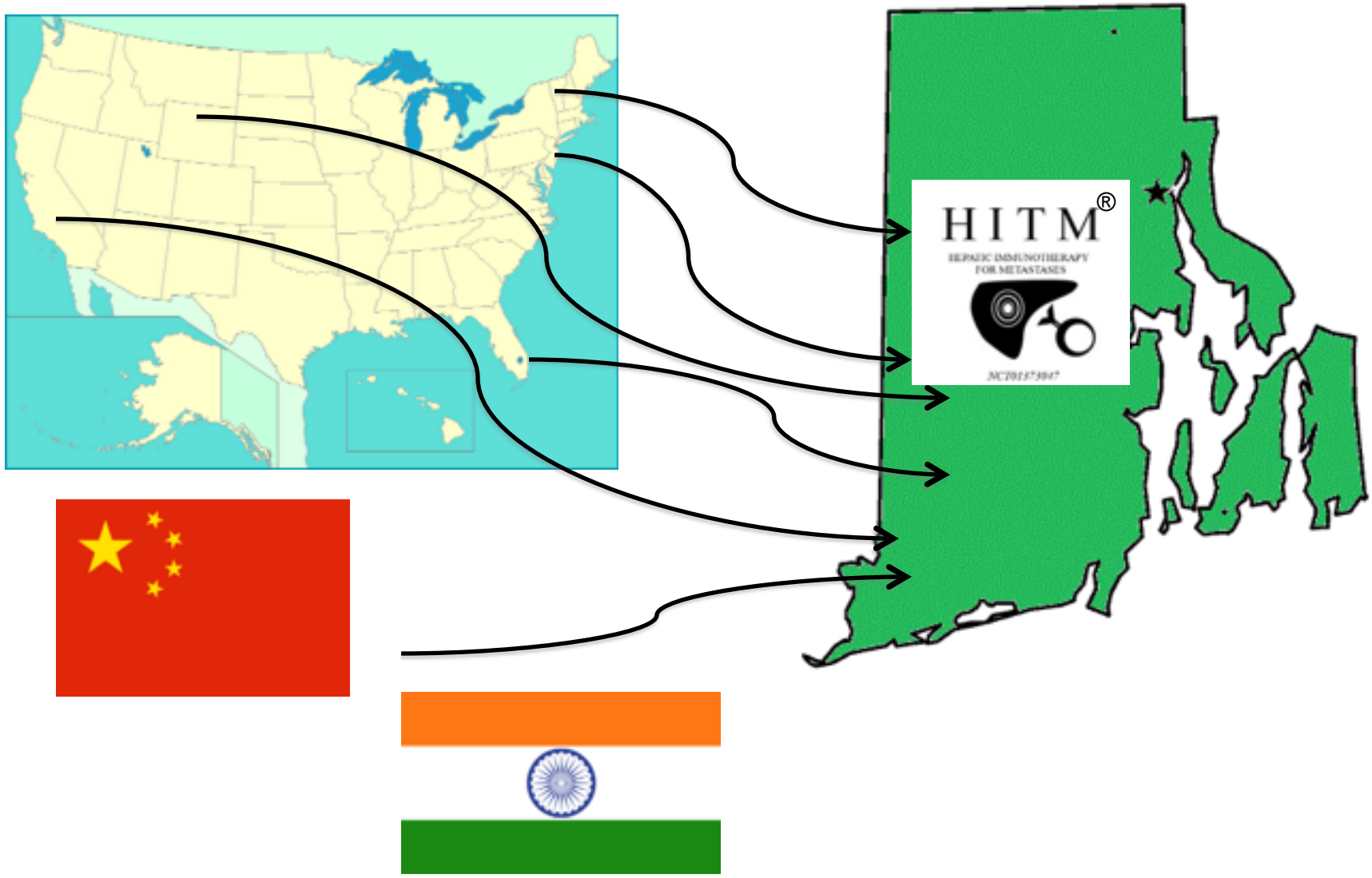
By ANDREW POLLACK JUNE 2, 2014

Science

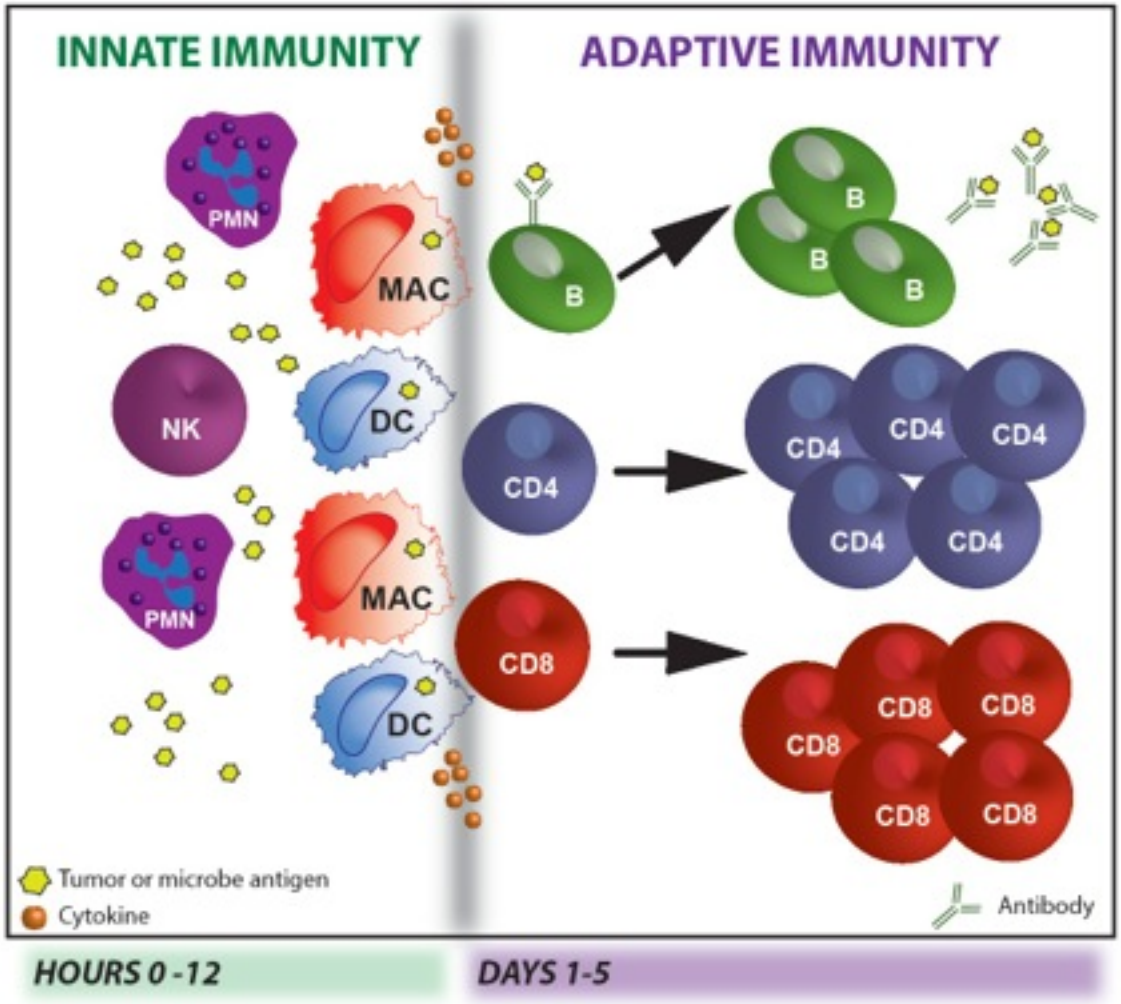
AAAS

Breakthrough of the Year 2013

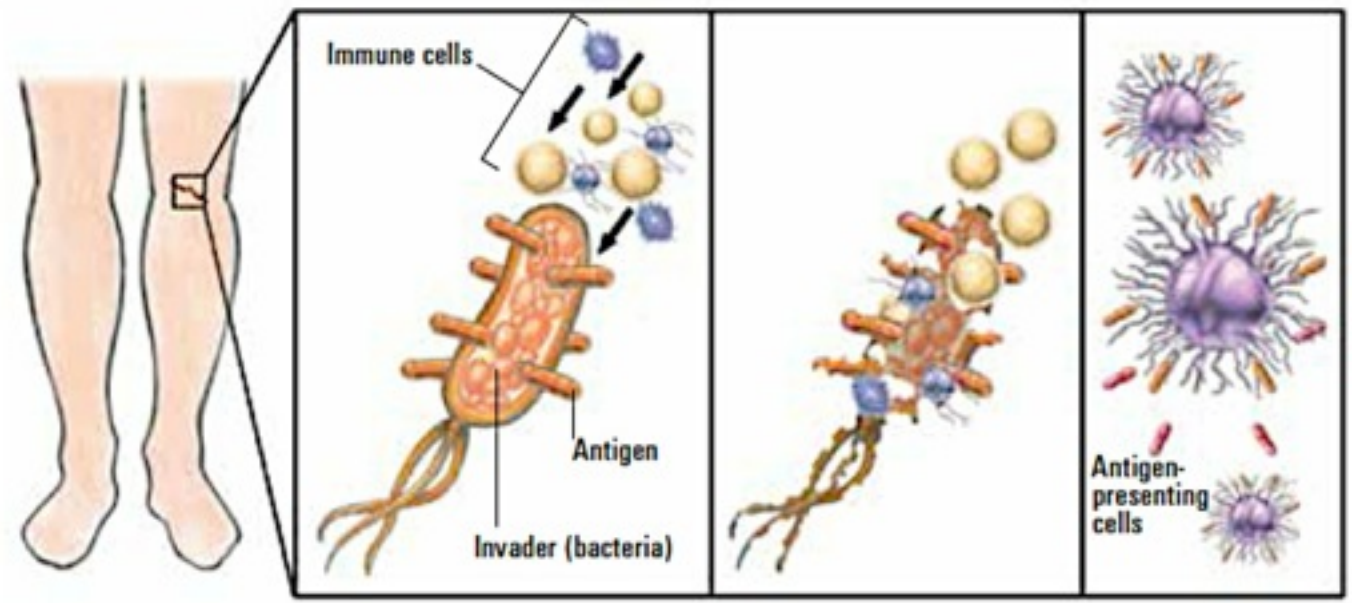
Broad Interest



Normal Immune Response



Normal Immune Response



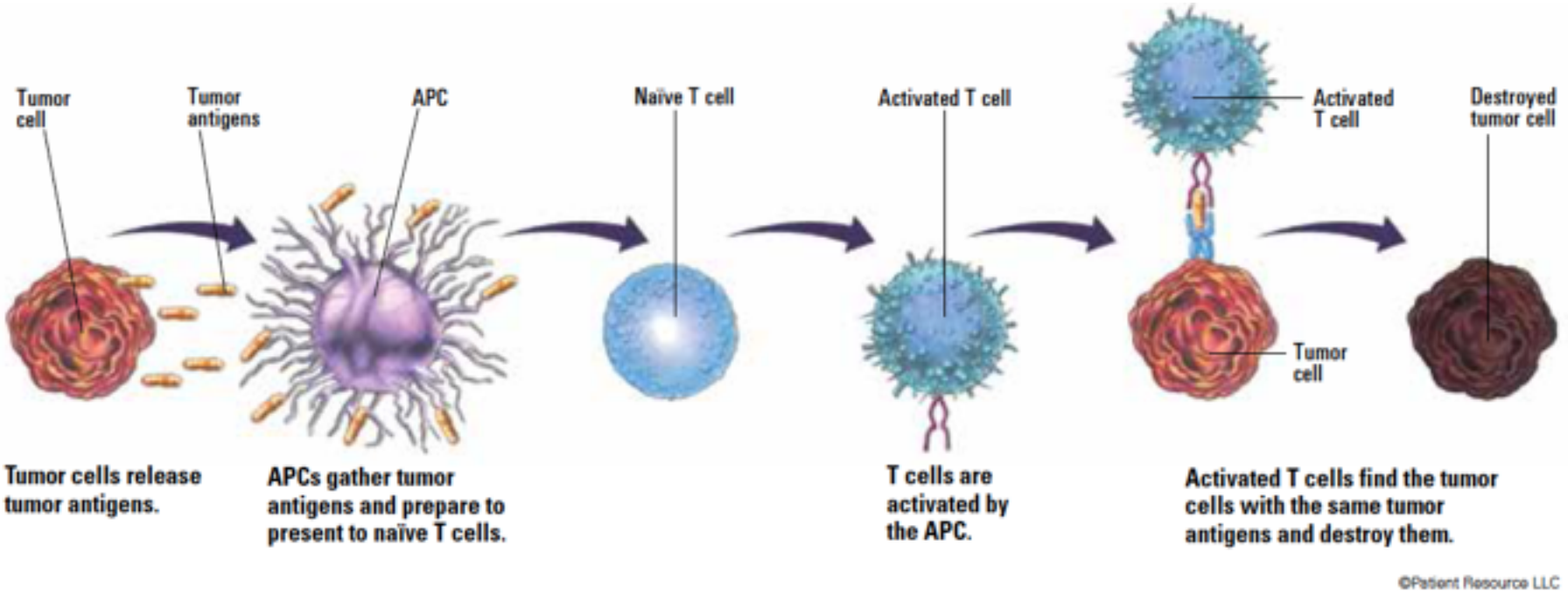
Skinned knee: First barrier of protection is broken.

An invader enters the body through the cut, where immune cells have begun to gather to protect the body.

The immune cells begin to destroy and digest the invader and its antigens.

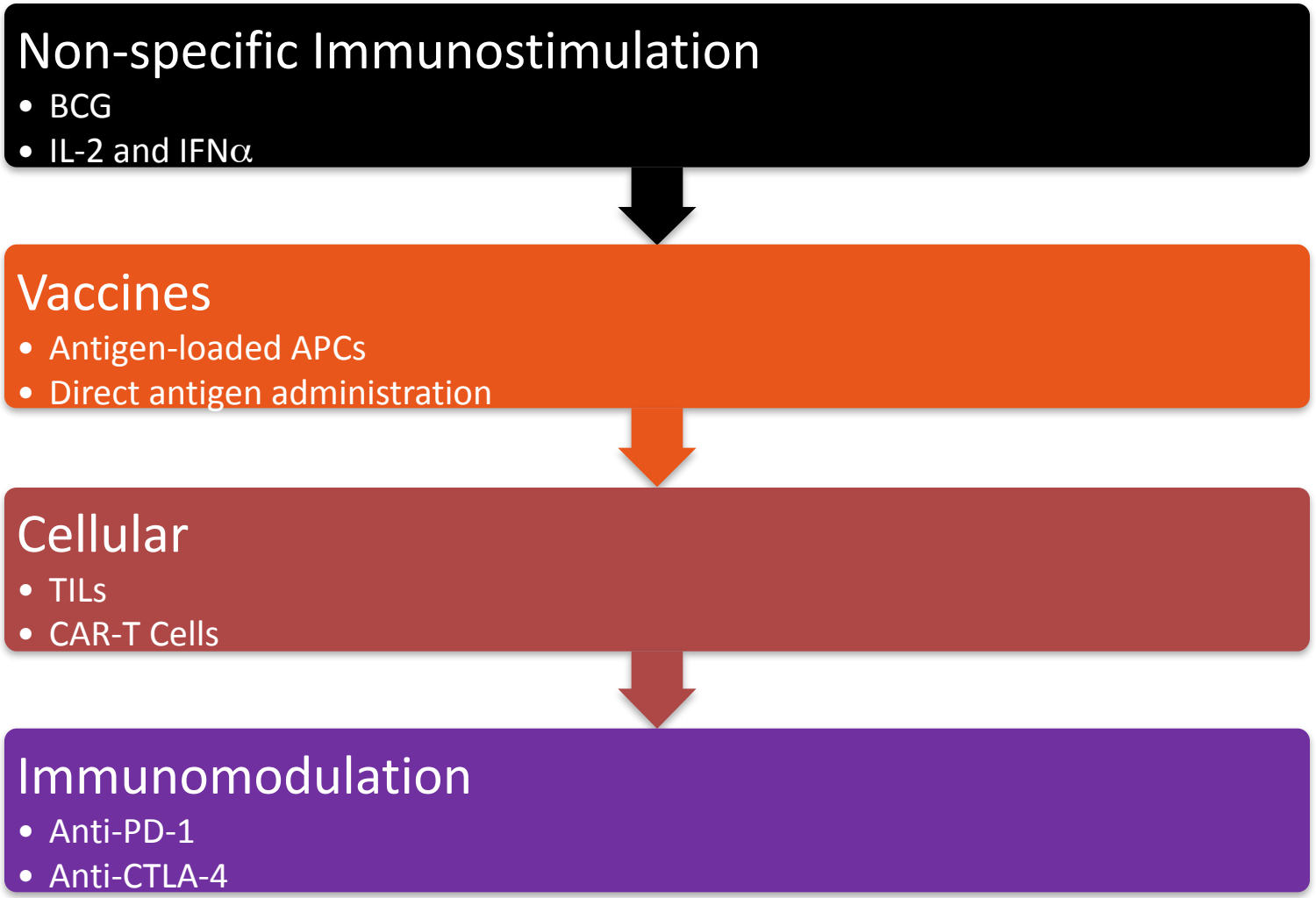
Some of the immune cells transform into antigen-presenting cells that tell the T cells about the invader.

Anti-Tumor Immune Response



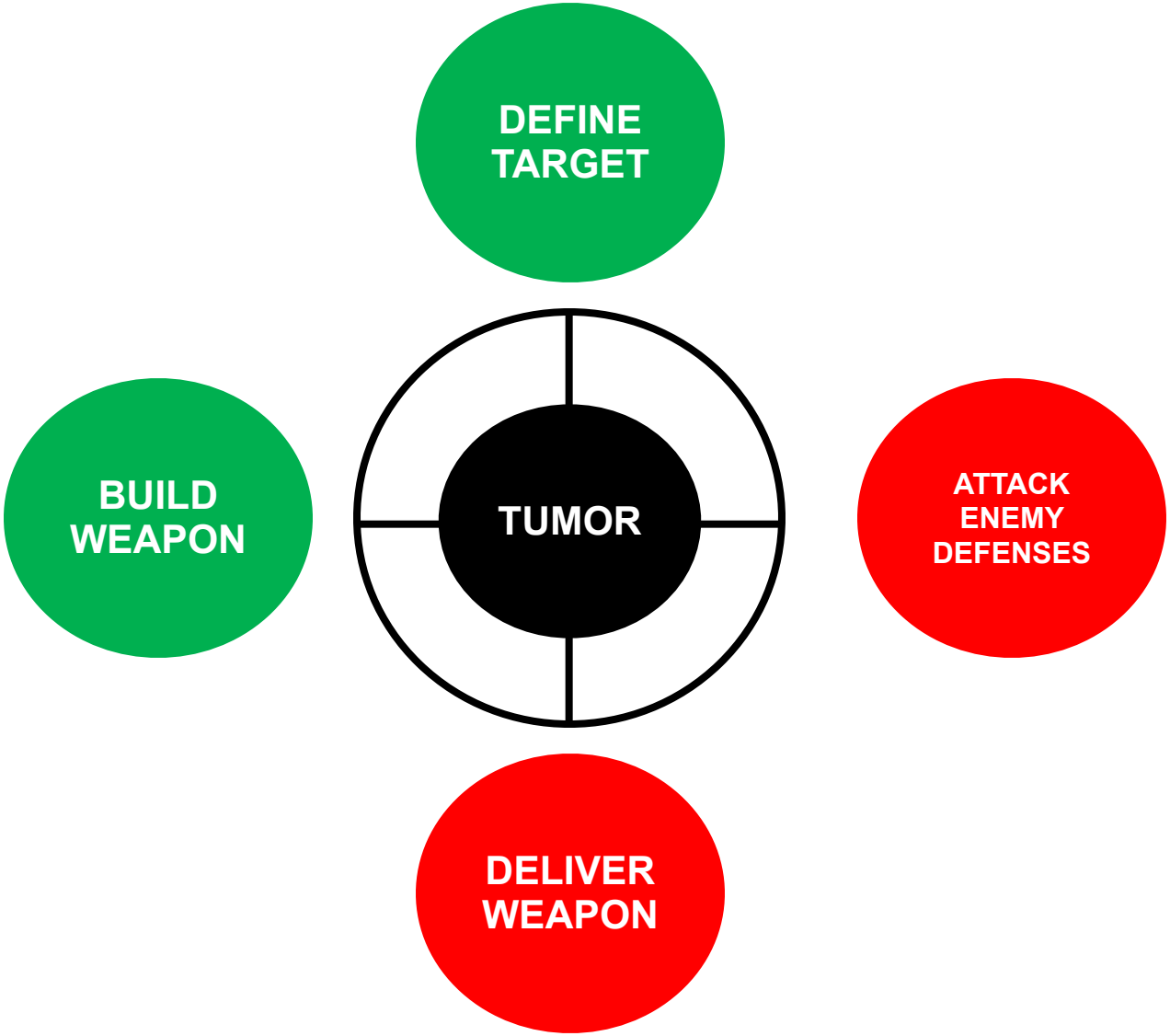
www.sitc.org

Immunotherapy Categories



Caspi.Nat Rev Imm.2008

Core Principles of Immunotherapy

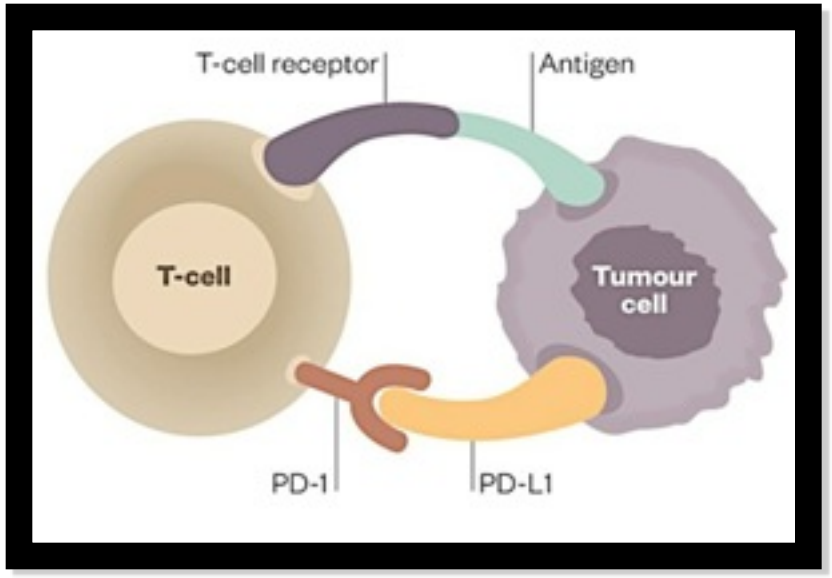


Is the enemy thyself?

- Cancer tissue is a variant of normal
- Immune cells may not be able to distinguish
- *KIT present on tumor and normal cells*
- ***Delicate balance between immune attack and organ damage***

thoughtsbeforecoffee

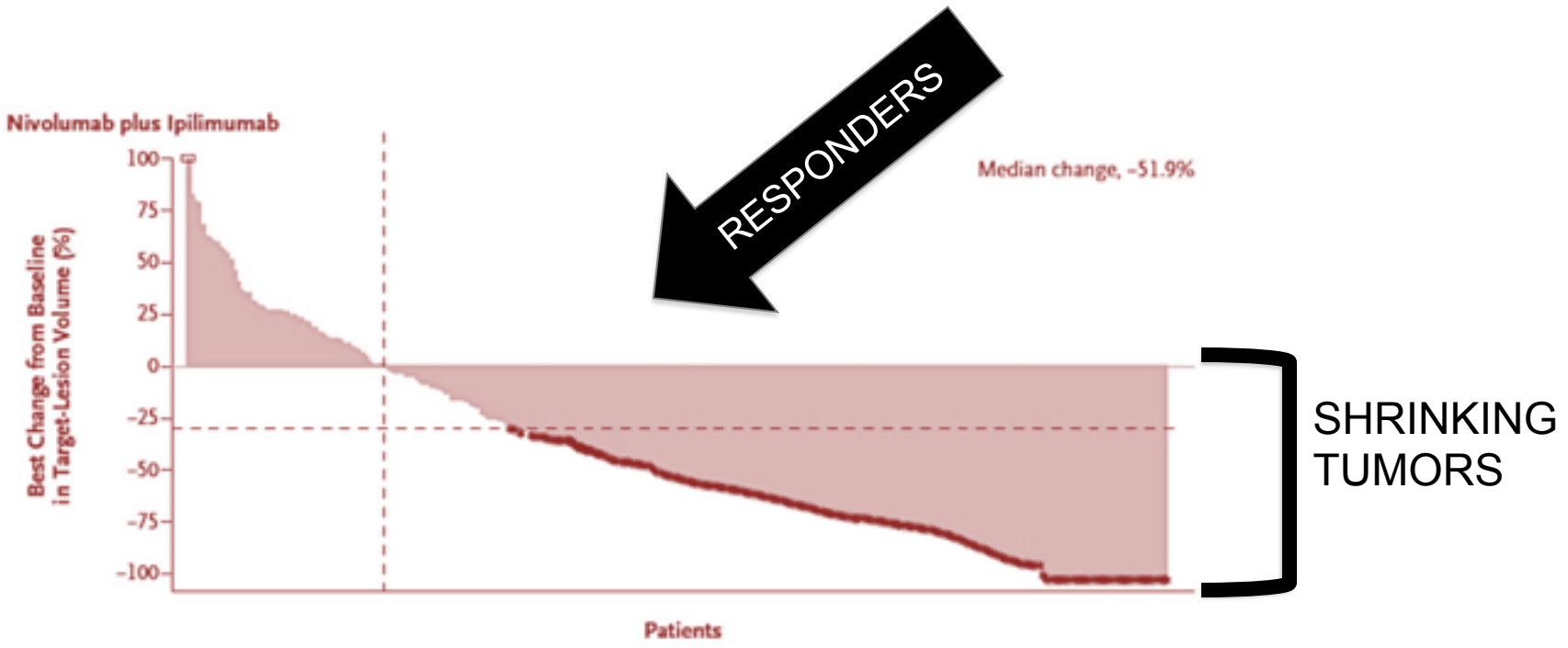
Checkpoint Inhibitors



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

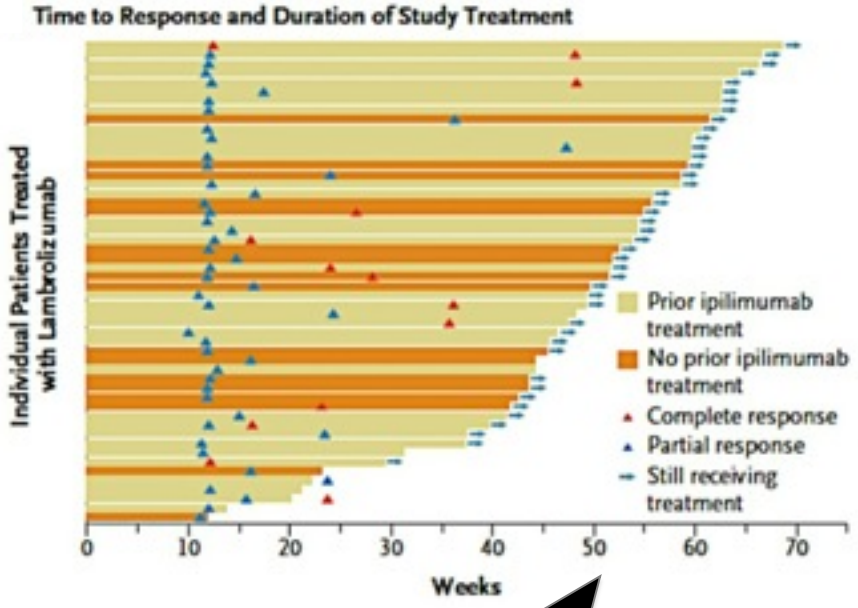
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

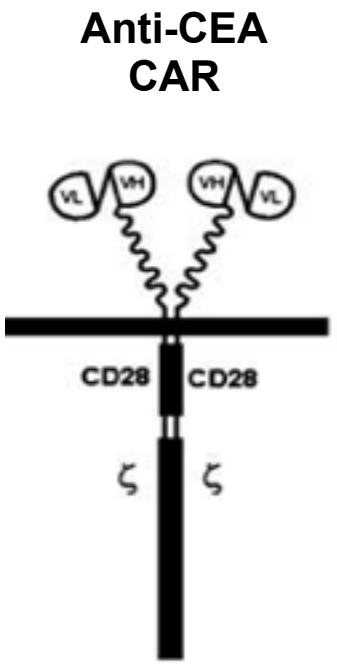
Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma



DURABLE

CAR-T Cells

- Genetic re-engineering of patient T cells
- Chimeric antigen receptor (CAR)
  - Fusion protein
  - Antibody confers tumor antigen specificity
  - T cell receptor components
  - Co-stimulatory components
- Focus on CD19 CAR for leukemia and lymphoma
- Solid tumors more challenging



LIQUID ≠ SOLID

≠

Pattern of GIST Metastases

Site	n	% of total
All liver	61	65
Liver only	50	53
Any peritoneal	20	21
Any node	6	6
Any bone	6	6
Any lung	2	2

Liver and peritoneal cavity main sites of GIST metastases.

Gold & Dematteo Ann Surgery 2006
Katz & Dematteo J Surg Onc 2008

Published OnlineFirst April 7, 2015; DOI: 10.1158/1078-0432.CCR-14-1421

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]

Cancer Gene Therapy (2014) 21, 457–462

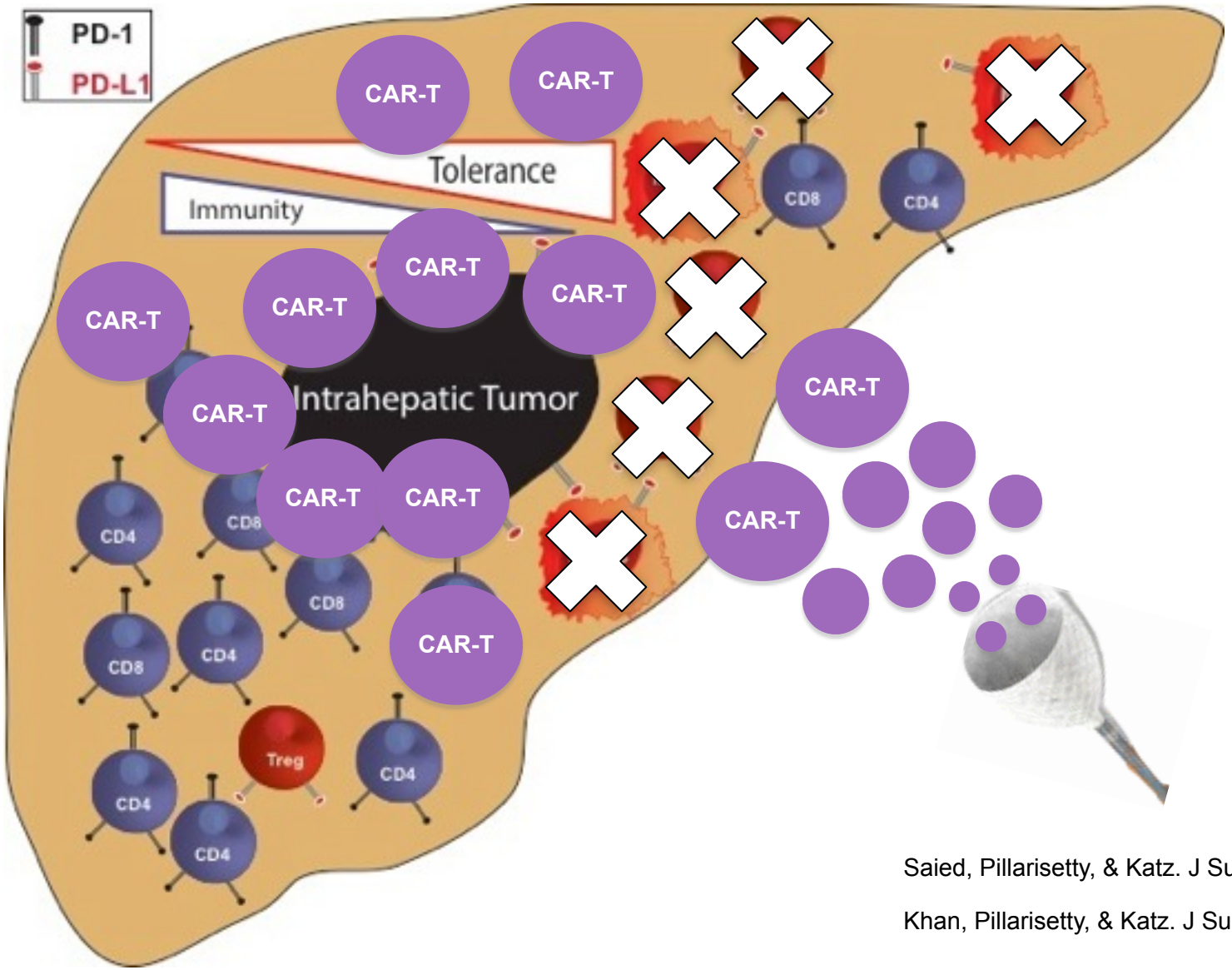
www.nature.com/cgt

ORIGINAL ARTICLE

Neutrophil:lymphocyte ratios and serum cytokine changes after hepatic artery chimeric antigen receptor-modified T-cell infusions for liver metastases

A Saied[1], L Licata[1], RA Burga[1], M Thorn[1], E McCormack[2], BF Stainken[3], EO Assanah[3], PD Khare[4], R Davies[4], NJ Espat[1], RP Junghans[2] and SC Katz[1]

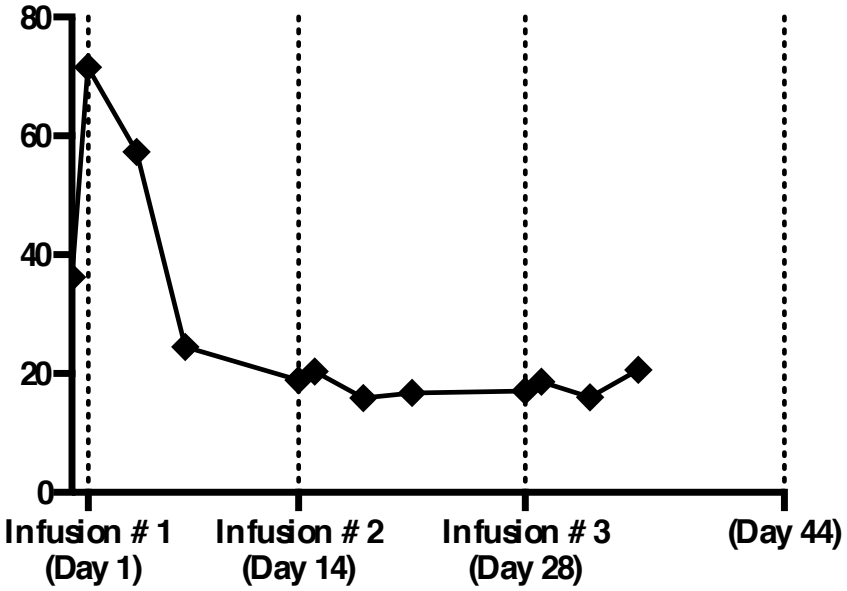
Plan of Attack



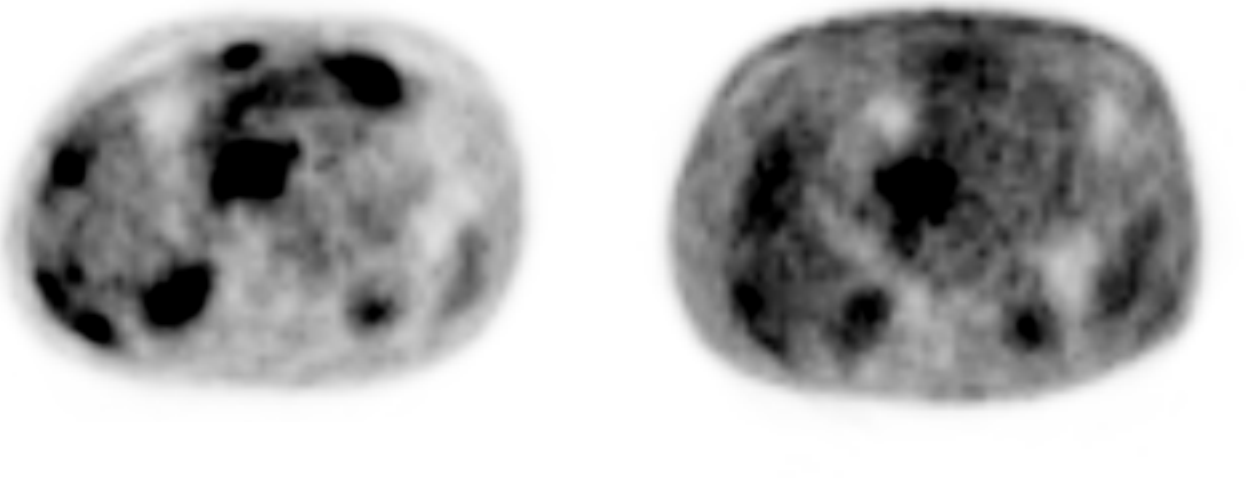
Saied, Pillarisetty, & Katz. J Surg Res 2014

Khan, Pillarisetty, & Katz. J Surg Res. 2014

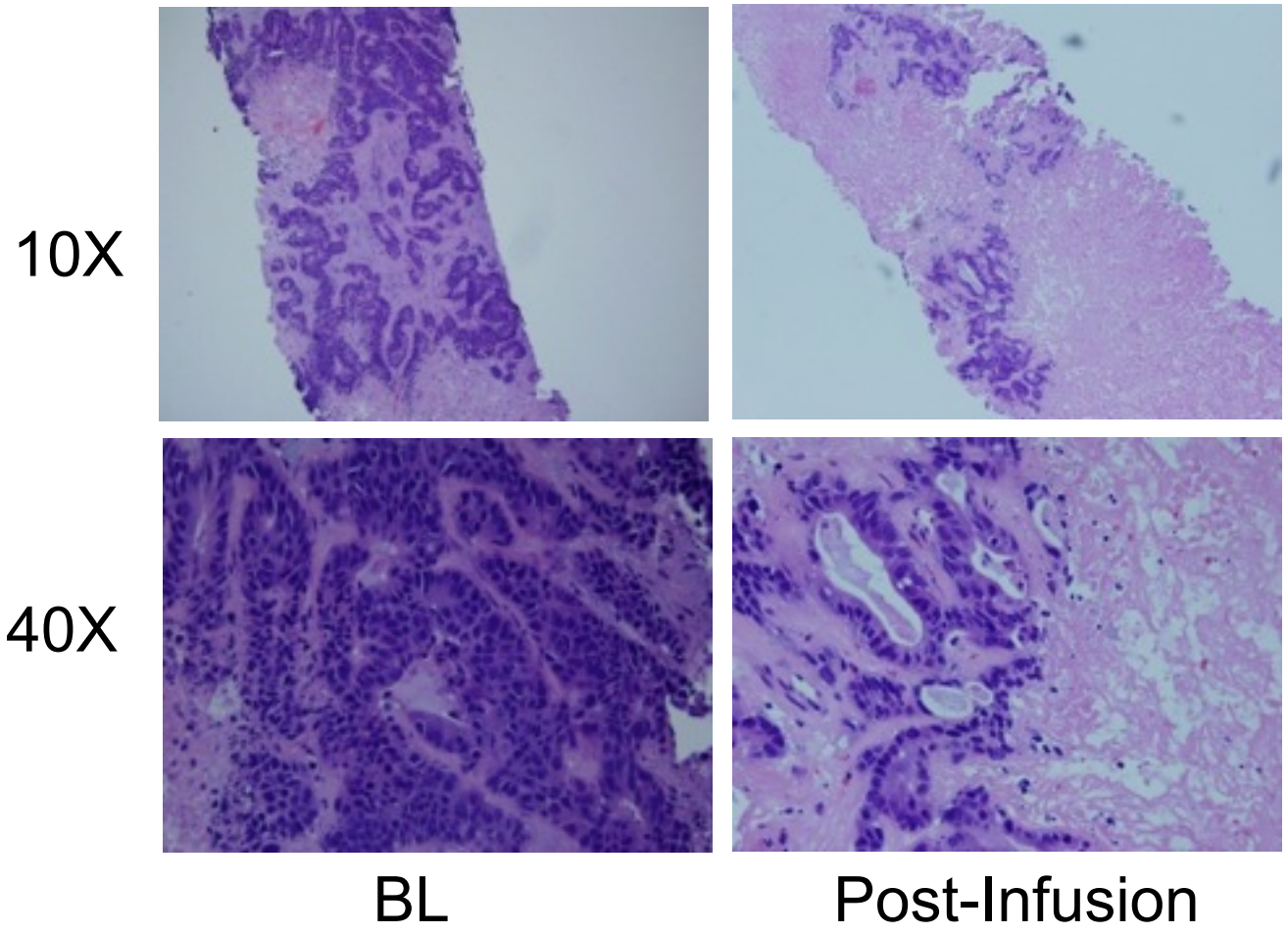
Tumor Marker Response to CAR-T Cells



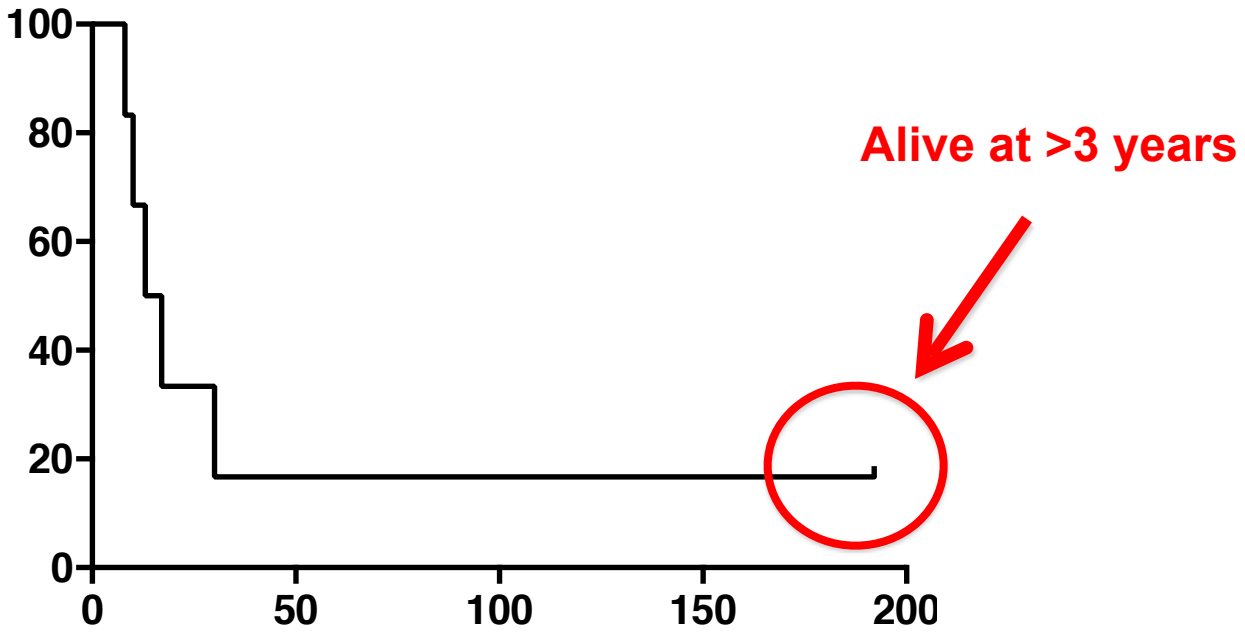
Response to CAR-T Cells



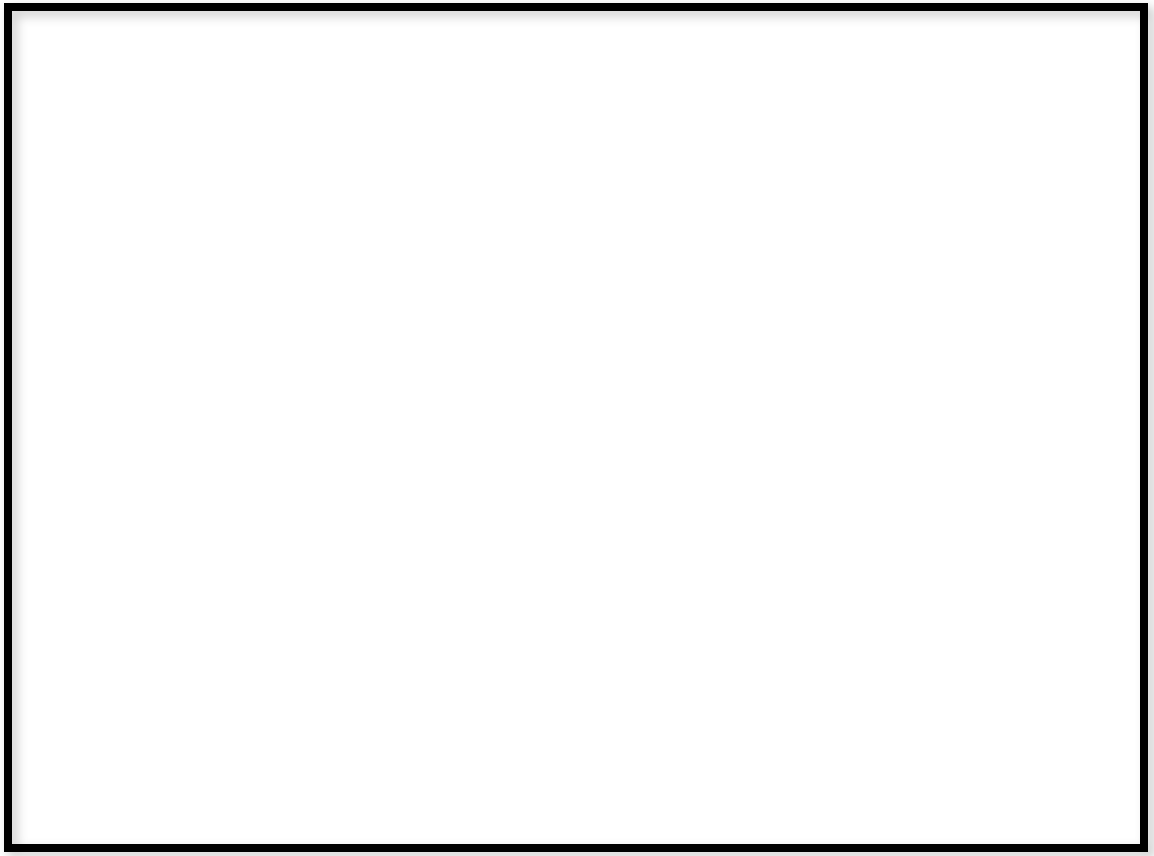
CAR-T Cells Mediated Tumor Cell Death



This is why we are all here…



Intraperitoneal CAR-T delivery
IPC



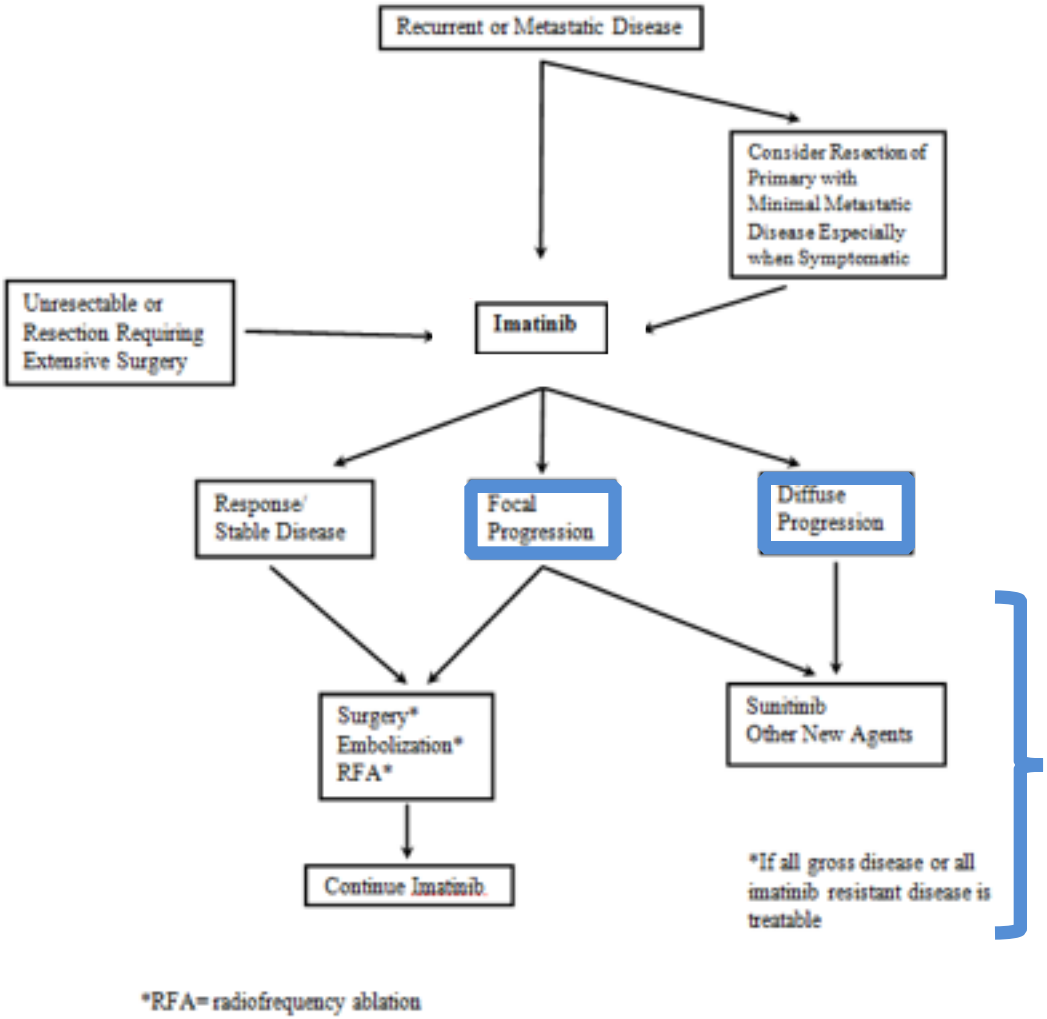
Outline

- Immunotherapy for solid tumors
- **Unmet clinical need**
- Immune response to GIST
- Building an anti-KIT CAR

Rationale for GIST Immunotherapy

- 30% recur within 2 years after surgery
- Resistance to TKIs
- No advances in first-line therapy since 2002
- Immune infiltrate in GIST demonstrated
- TKI and immunotherapy may be synergistic

Gastrointestinal Stromal Tumor (GIST)



LIMITED OPTIONS FOR ADVANCED TKI RESISTANT DISEASE

Gold & Dematteo Ann Surgery 2006
Katz & Dematteo J Surg Onc 2008

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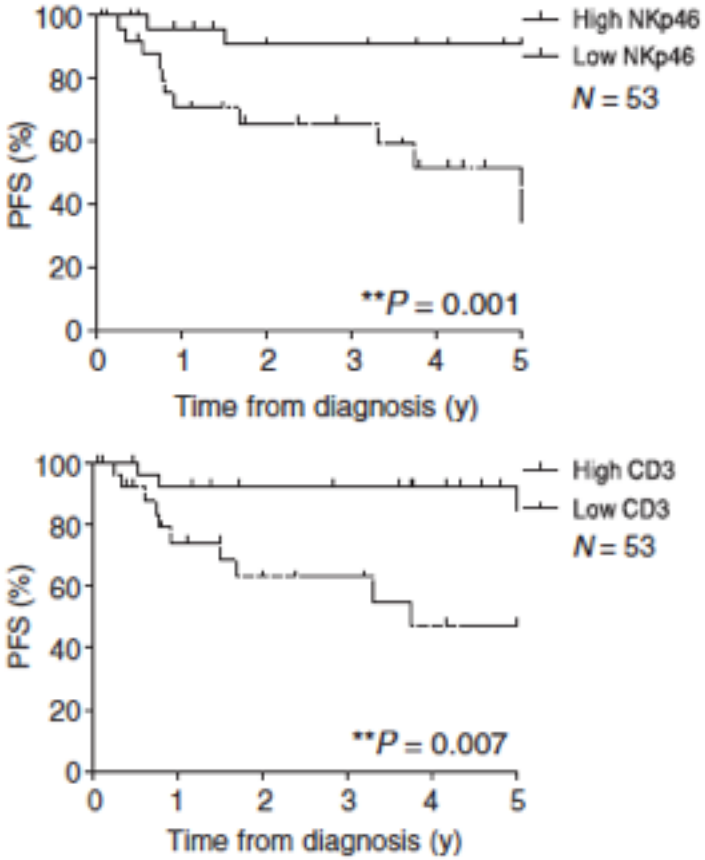
GIST Immune Cells Predict Outcome

- NK cell density predicts progression
- T cell density predicts progression
- Immuno-surveillance is occurring
- Potential biomarkers

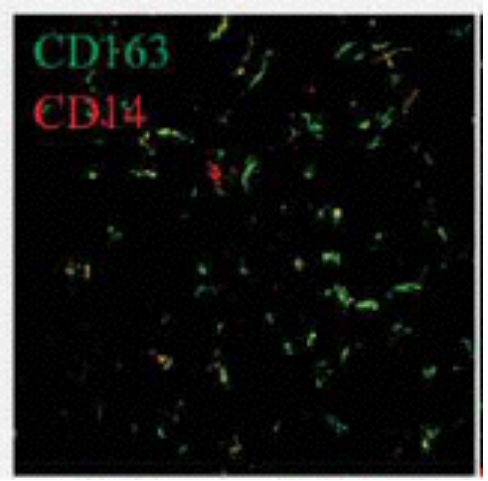


Rusakiewicz. Cancer Research. 2013

Immune Cells in GIST

In need of assistance

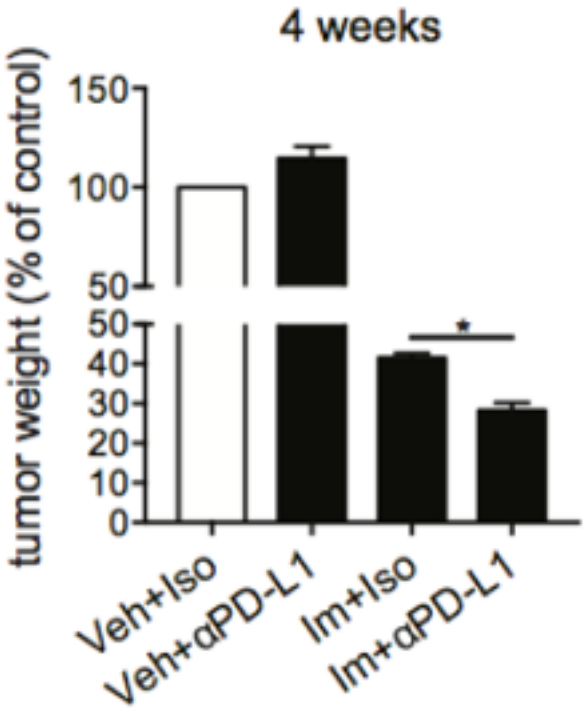
- High level of macrophages and T cells
- T cell balance skewed toward suppression
- Abundance of M2 anti-inflammatory macrophages
- Level of M2 cells correlated with Treg
- More M2 cells in metastatic GIST



van Dongen, et al. Int J Cancer. 2009

Checkpoints Exploited

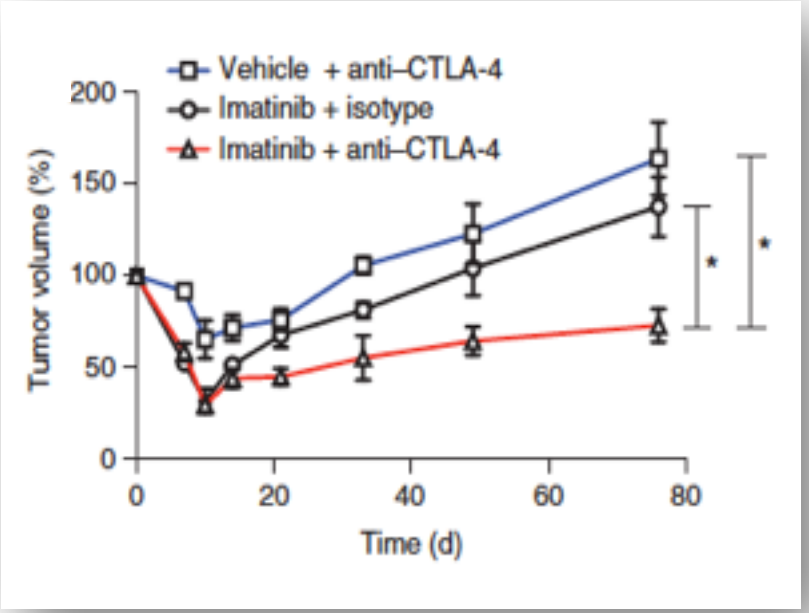
- T cells in GIST tumors express checkpoint molecules
  - PD-1, TIM-3, LAG-3
- Imatinib increases GIST TIL PD-1 expression
- Imatinib decreased GIST tumor PD-L1 expression



Seifert, et al. Clin Can Res. 2016; in press.

TKI Effect on Immune Cells

- More than direct effect on tumor cells
- KIT expressed on immune cells
- Targeting tumor and patient
- Enhances immune response to GIST
- Improved T cell tumor killing
- Reverses immunosuppression
- Synergy with checkpoint blockade



Balachandran, et al. Nature medicine. 2011;17(9):1094-100.

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- Immunotherapy for solid tumors
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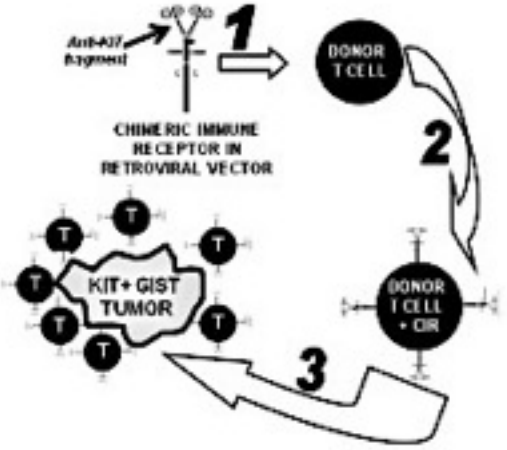
- **Building an anti-KIT CAR**

Adoptive Cell Immunotherapy – Renewed Optimism

- Tumor infiltrating lymphocyte (TIL) therapy
  - Derived from resected specimens or biopsies
  - Response rates up to 51-72% in patients with melanoma[1,2]
  - Applicable to a limited number of diseases and patients
- CAR-T cells
  - Applicable to wide variety of cancer types
  - Need to define surface target
  - Derived from peripheral blood leukocytes
  - Introduction of genes for chimeric antigen receptors (CAR)
  - Success with CLL (anti-CD19 CAR with CD137)[3]



1 Dudley. JCO; 23: 2346 (2005)
2 Dudley. JCO; 26: 5233 (2008)
3 Porter. NEJM; 365: 8 (2011)

Katz et al. Journal of Translational Medicine 2013, 11:46
http://www.translational-medicine.com/content/11/1/46

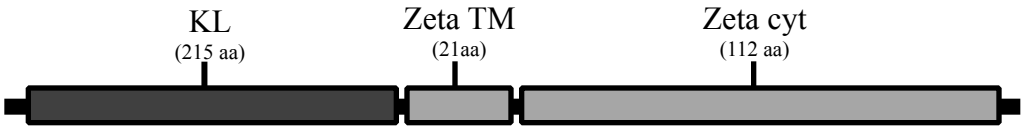
JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

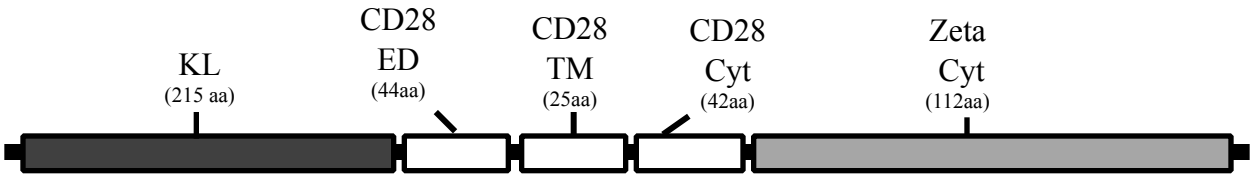
Anti-KIT designer T cells for the treatment of gastrointestinal stromal tumor

Steven C Katz[1*], Rachel A Burga[1], Seema Naheed[1], Lauren A Licata[1], Mitchell Thorn[1], Doreen Osgood[1], Cang T Nguyen[1], N Joseph Espat[1], Jonathan A Fletcher[3] and Richard P Junghans[2]

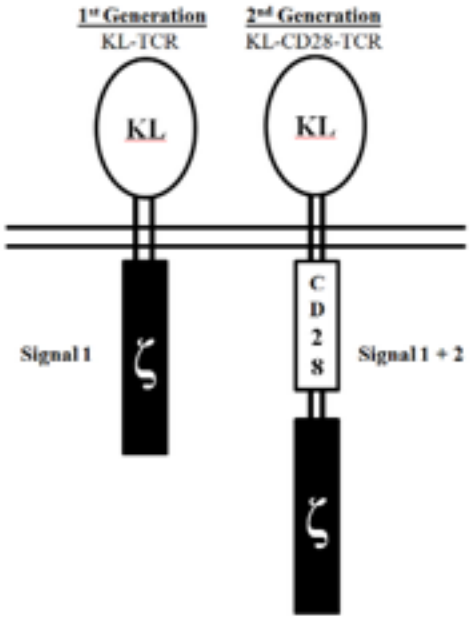
Anti-KIT CAR Constructs



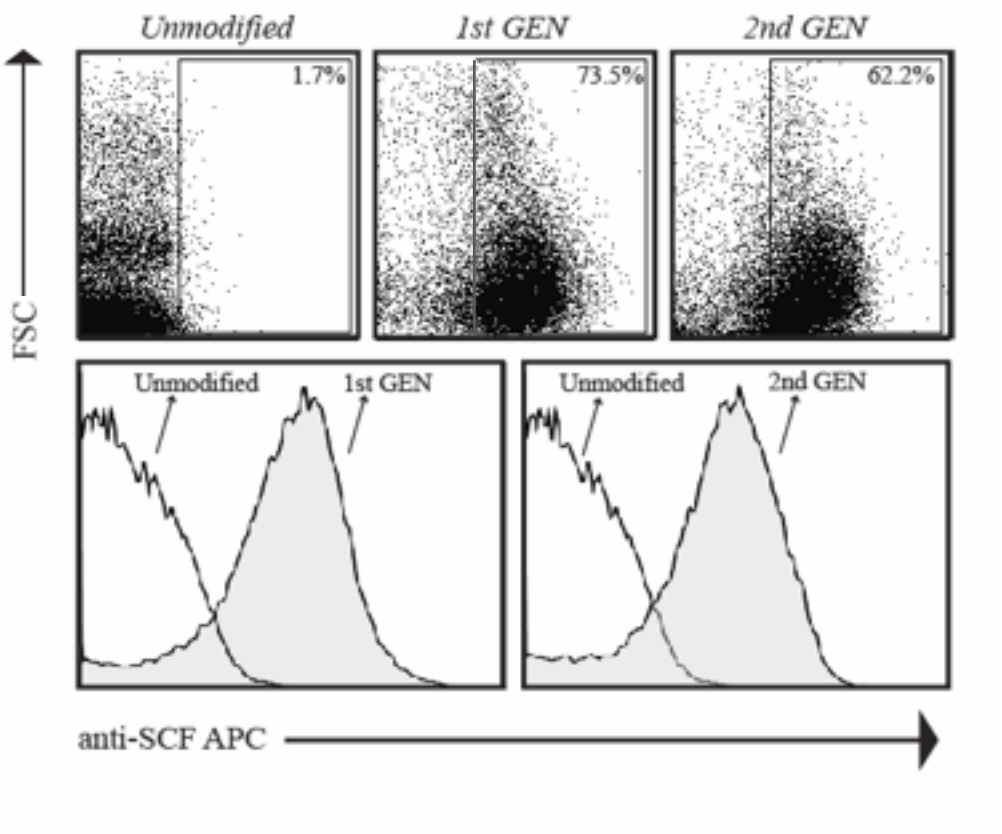
KL-TCR (1st Generation)

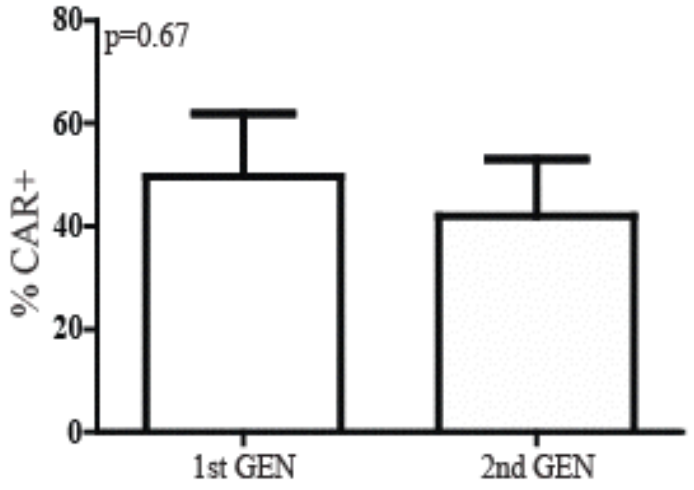


KL-CD28-TCR (2nd Generation)

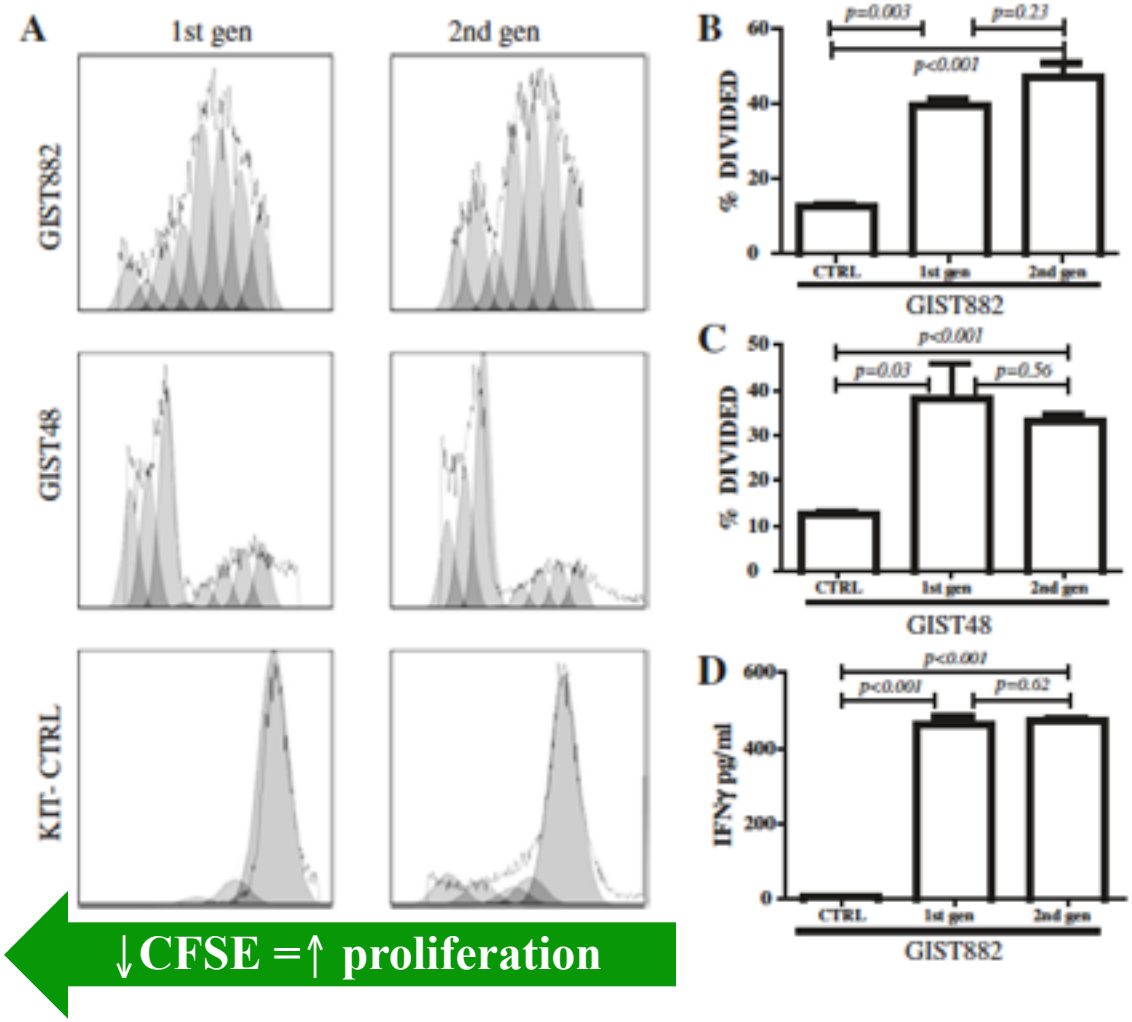


anti-KIT CAR-T Transduction Efficiency

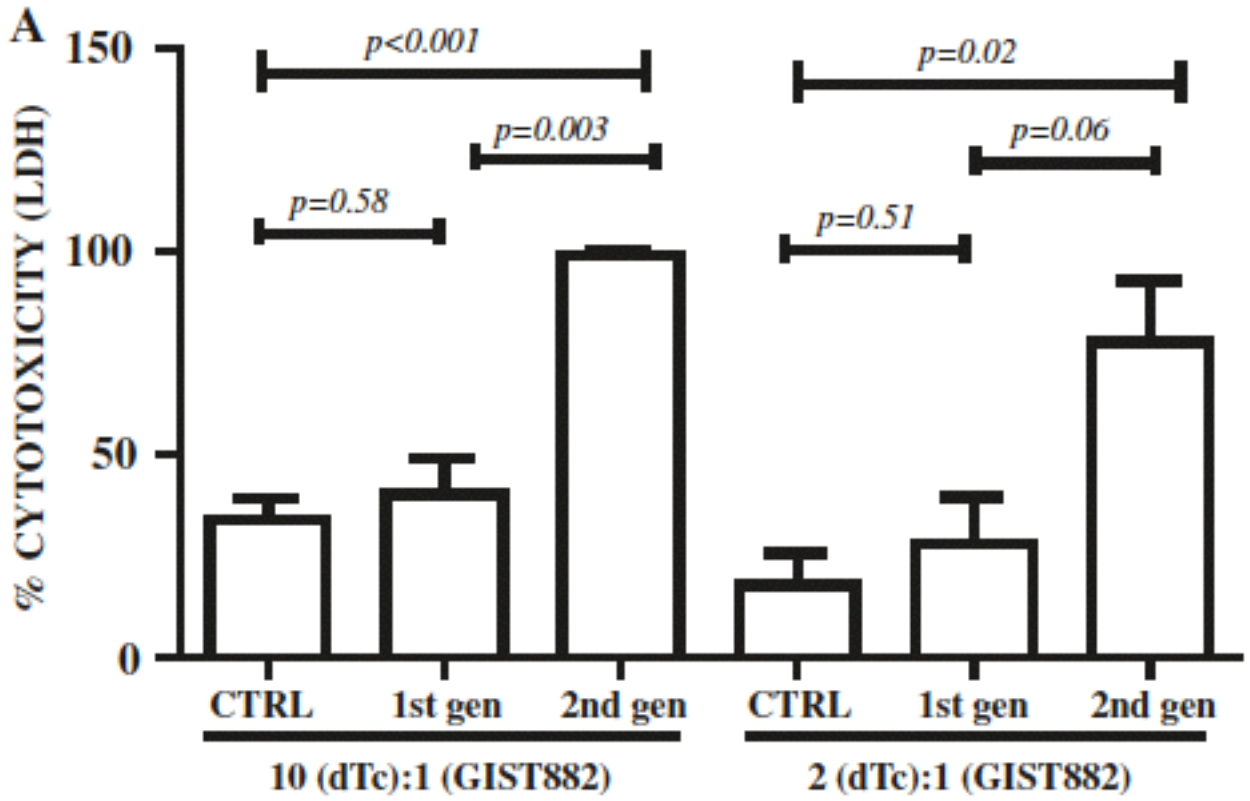




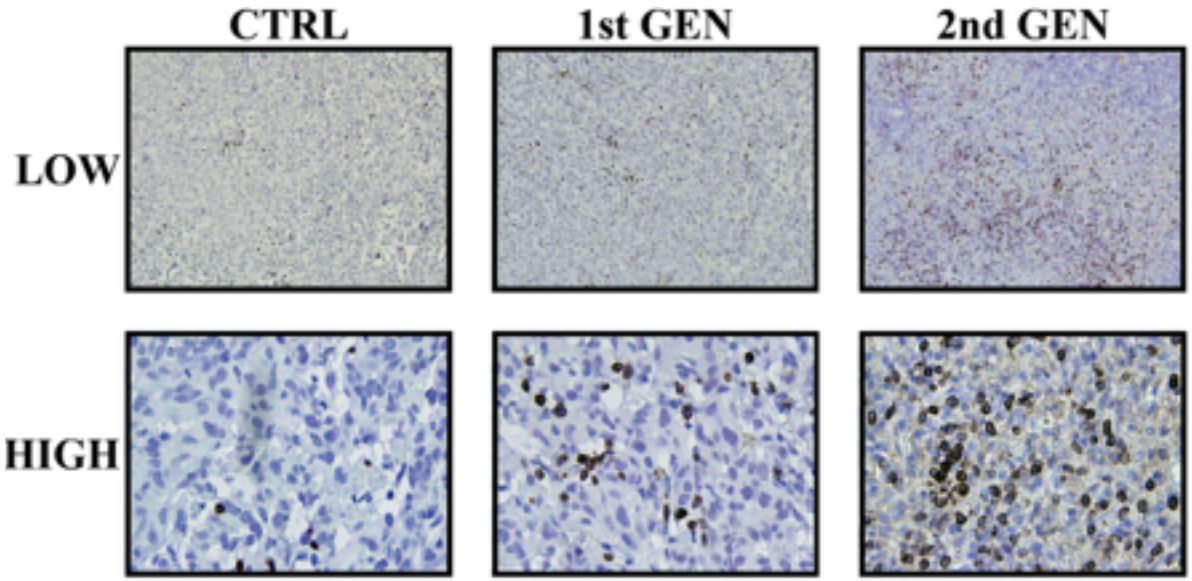
anti-KIT CAR-T 1st & 2nd Generation Proliferate on exposure to KIT+ tumor

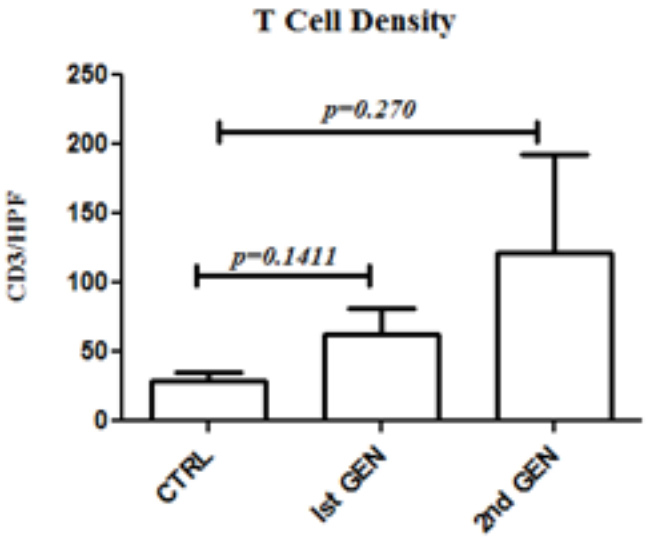


anti-KIT CAR-T Kill KIT+ Tumor Cells

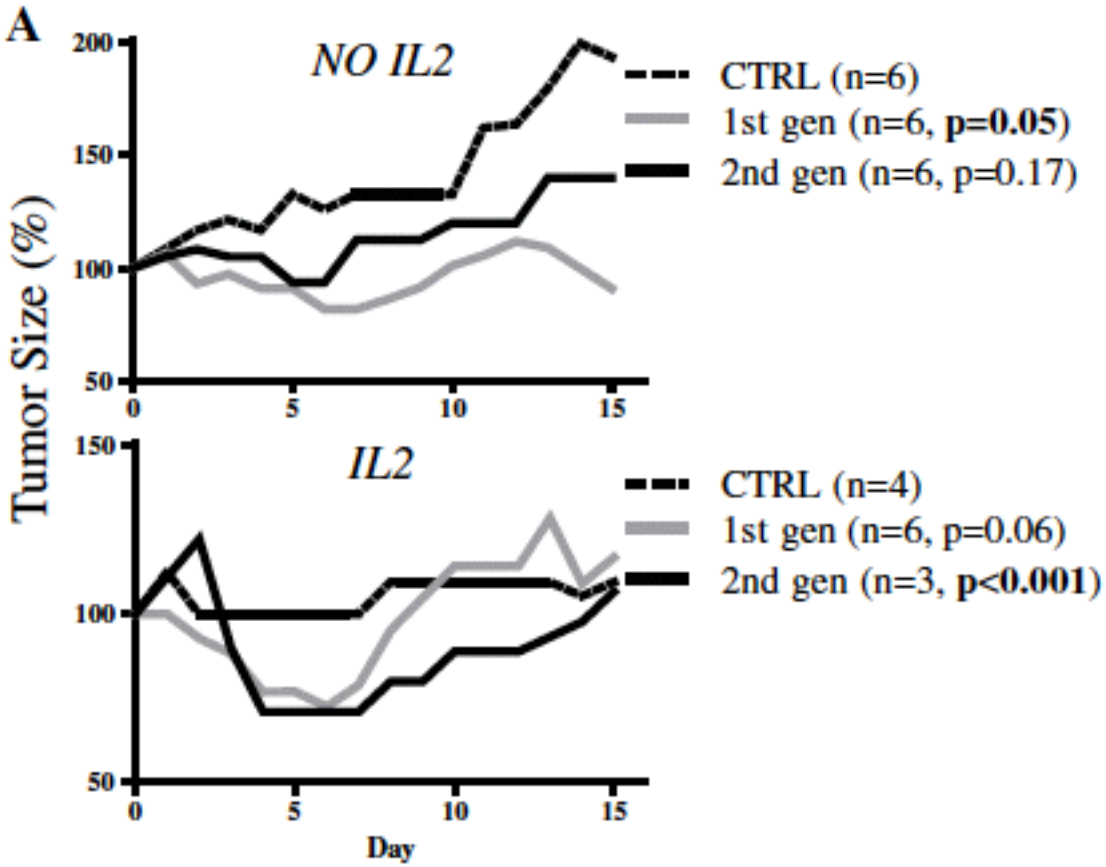


Infiltration of anti-KIT CAR-T Within GIST Xenografts

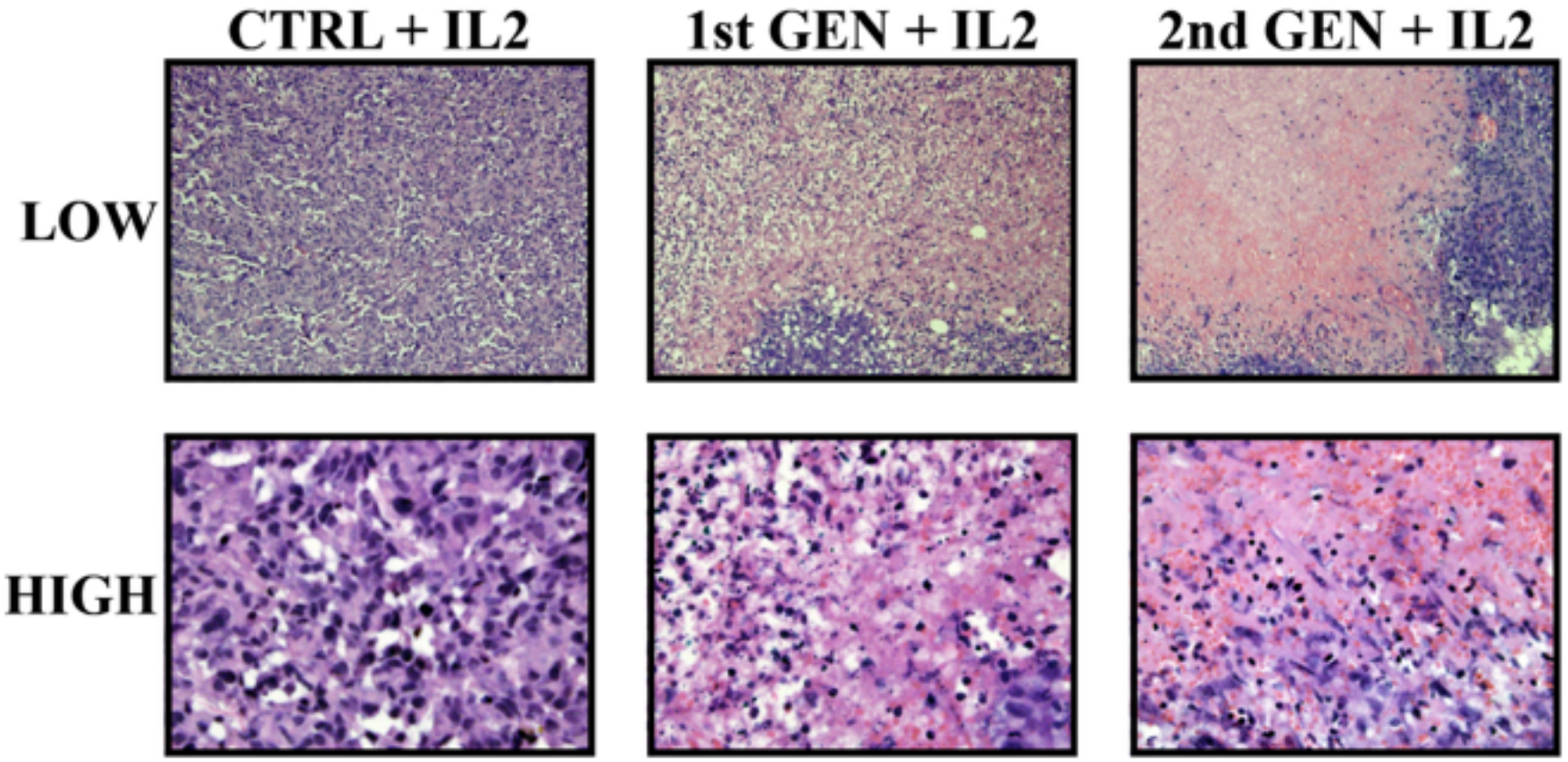




In Vivo Activity in Xenograft Model



Necrosis of GIST Xenografts Induced By anti-KIT CAR-T With IL-2



Summary

- Immunotherapy for solid tumors promising
- Regional delivery for GIST metastases
- Immune response to GIST biologically meaningful
- Anti-KIT CAR-T for GIST under development
- **Target the tumor and the host**

Thank you

MENTORS

- Ron DeMatteo
- Murray F. Brennan
- Sam Singer
- Richard P. Junghans
- N. Joseph Espat

COLLABORATORS

- Jonathan A. Fletcher

The Kristen Ann Carr Fund

Sarcoma SFA Foundation of America
finding the cure in our time