Looking Inward: Tweaking Our Own Immune System to Target Gastroesophageal Cancers

Matthew R. Strickland, MD
Medical Oncology Fellow, DFCI/MGB
December 17th, 2021
Agenda

• Introduction

• Immunotherapy for Gastroesophageal cancers
  – Background
  – Brief Snapshot: Current, approved immunotherapies
  – CAR T cells
  – Re-engineered T cells
  – Tumor Infiltrating Lymphocyte (TIL)-based therapies
  – Questions
Introduction

- 3rd year medical oncology fellow
  - Massachusetts General Hospital
  - Dana–Farber Cancer Institute
  - Brigham and Women’s Hospital

- Internal Medicine Residency
  - Boston Medical Center

- Boston University School of Medicine

- Clinical: Gastroesophageal Cancer

- Research:
  - Cancer immunology
  - Tumor microenvironment

- Mentor: Dr. Sam Klempner
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William Coley: Father of Immunotherapy

- William B. Coley, MD
- Bone service Chief Surgeon, Memorial Hospital, NY
- Lost 17 year old female patient to sarcoma
- Early clinical/translational investigator

William Coley: Father of Immunotherapy

- 1891: Intratumoral live *Streptococcus* injections
- Later: “Coley’s toxins”
- Tumor shrinkage noted
- Inconsistent methods, reporting
- Overshadowed by rise in radiation and later chemotherapy
Immunosurveillance gains ground over 20th century

Olivera J. Finn, J Immunol 2018
Immune system 101

Next: Innate versus adaptive immune response
Innate immune system

Quick, non-specific

Adaptive immune system

1. Virus infects and replicates within the epithelium
2. Dendritic cell activation
3. T and B cell priming in the lymph node
4. Adaptive immunity

- Dendritic cells take infection to the lymph node
- Inflamed tissue
- Activated dendritic cell
- Lymph node
- B cell
- Plasma cell
- T cell
- Antibodies and T cells attack viruses and virus-infected cells
Adaptive immune system

Long-term, highly specific

How are immune cells trained to identify a specific target and execute a precision attack?
Antigen-presenting cells train T cells to recognize cancer

1. Antigen shedding by tumor

2. Antigen presentation by DC (APC)

3. APC activates T cell

4. Activated T cell migrates to tumor

5. T-cell mediated tumor cell killing

Antigen = tag for foreign threat
So why do some tumors escape immune system attack?

Olivera J. Finn, J Immunol 2018
What is an immune checkpoint?
Preclinical work

Enhancement of Antitumor Immunity by CTLA-4 Blockade

Dana R. Leach, Matthew F. Krummel, James P. Allison

Science

A

Average tumor size (mm²)

Control
Anti-CD28
Anti-CTLA-4

Days after tumor injection

Sa1N only
Control
Anti-CTLA-4

Average tumor size (mm²)

Days after tumor injection
Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade

Yoshiko Iwai*, Masayoshi Ishida†‡§, Yoshimasa Tanaka†‡§, Taku Okazaki*, Tasuku Honjo*, and Nagahiro Minato†¶

*Department of Medical Chemistry, Graduate School of Medicine, †Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Corporation, and ‡Department of Immunology and Cell Biology, Graduate School of Biostudies, Kyoto University, Kyoto 606-8501, Japan
Nobel Prize!
Clinical Efficacy: Phase I

Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates


Table 2. Treatment Characteristics and Clinical Response to Therapy

<table>
<thead>
<tr>
<th>Tumor histology</th>
<th>No. of Patients</th>
<th>Total No. of Doses</th>
<th>Best Response (duration in months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td></td>
<td>1  2  3  5  11</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>14</td>
<td>35.9</td>
<td>N/A</td>
</tr>
<tr>
<td>Melanoma</td>
<td>10</td>
<td>25.6</td>
<td>1 MXR (1)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>8</td>
<td>20.5</td>
<td>1 CR (21+)†</td>
</tr>
<tr>
<td>NSCLC</td>
<td>6</td>
<td>15.4</td>
<td>2 PR (3+, 16+)‡§</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>1</td>
<td>2.6</td>
<td>1 MXR (1)</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>27 2 7 2 1</td>
<td>1 CR, 2 PR, 2 MXR</td>
</tr>
</tbody>
</table>
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FDA approvals for ICIs have exploded since discovery

**Figure 2.** FDA-approved immune checkpoint inhibitors (copyright owned by Raju Vaddepally, et al.). Vaddepally et al, Cancers 2020
FDA approvals for ICIs have exploded since discovery

Checkpoint inhibitor approvals for GE cancers

Adapted from: cancerresearch.org

Timeline of Anti-PD-1/L1 Antibody Approvals by the FDA
Updated December 3, 2021
Sources: CRI, CRI Analytics, and FDA
Clinical Trials Resource

Website: cancerresearch.org
There are many types of immunotherapy
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What is a CAR T cell?

- Chimeric antigen receptor
- MHC unrestricted
- CAR can bind more extensive target list
- Also has T cell activating functions

Credit: Raquel Baranow; TwoColoredRoseChimera.jpg
Overview of CAR T cell & therapy

Entire process: 3 weeks
Preparation of CAR T cells: 2 weeks
## Side Effects

<table>
<thead>
<tr>
<th>More common</th>
<th>Less common</th>
</tr>
</thead>
<tbody>
<tr>
<td>- rash</td>
<td>- cytokine release syndrome</td>
</tr>
<tr>
<td>- fatigue</td>
<td>- neurotoxicity</td>
</tr>
<tr>
<td>- fever, chills</td>
<td>- on target, off tumor toxicity</td>
</tr>
<tr>
<td>- weakness</td>
<td>- CAR T cell exhaustion</td>
</tr>
<tr>
<td>- nausea</td>
<td></td>
</tr>
<tr>
<td>- vomiting</td>
<td></td>
</tr>
<tr>
<td>- dizziness</td>
<td></td>
</tr>
</tbody>
</table>
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  – **Re-engineered T cells**
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What is an engineered T cell?

- TCR itself is engineered to target of interest
- Depends on MHC
  Thus, “MHC restricted”
- Can recognize intracellular antigens
- More specific and higher affinity to tumor antigens

Zou et al, Adoptive Cell Therapy of Gastric Cancer 2017
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What is TIL-based therapy?

1. Isolation from tumor and host patient
2. Harvest and infuse back into patient
3. Growth and proliferation
4. IL-2 MIRACLE GROW
5. Tumor-infiltrating lymphocytes
TIL-based therapy for GE cancers?

- Success demonstrated in melanoma, ovarian cancer
- TIL positivity correlates with better survival in EC

Gu et al, Front Oncol 2021
Yagi et al, Annals of Surgery 2019
TIL-based therapy for GE cancers?

- Proof of principle in a single patient with esophageal cancer
- Awaiting additional trials with larger patient cohorts!
- Combines TIL and TCR T cell approaches

Isolation of T cell receptor specifically reactive with autologous tumour cells from tumour-infiltrating lymphocytes and construction of T cell receptor engineered T cells for esophageal squamous cell carcinoma

Qin Tan, Chaoting Zhang, Wenjun Yang, Ying Liu, Palashati Heyilimu, Dongdong Feng, Liying Xing, Yang Ke and Zheming Lu

- TIL-PRE
  - CD137 identification
  - Stimulate for 2 weeks

- TIL-POST
  - CD137 identification
  - Single-cell RT-PCR

TIL PRE-List

1. LVRGQGKTVQL
2. AAVPQPDIERTN
3. UPDGQSOCTG

TIL POST-List

1. LVRGQGKTVQL
2. AAVPQPDIERTN
3. APILSQAAQT

TCR-vector construction

Donor

Apheresis

Peripheral blood T cells

Lentivirus

Lentivirus package

TCR-engineered T cells

In-vitro cytotoxicity assays

In-vivo infusion experiments

Autologous primary tumor cells

Patient-derived xenograft models
Thank you!

A special thank you to our patients and their families

Please reach out with questions 😊

mstrickland1@mgh.harvard.edu
Thank you to my mentors and colleagues!

- Sam Klempner
- Theodore Hong
- Justin Gainor
- Priscilla Brastianos
- Aki Smith

Figures created using biorender.com
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Please reach out with questions 😊
 mstrickland1@mgh.harvard.edu
How do I find cell therapy trials?

1, 2, & 3: Speak with your medical oncologist 😊

Our duty is to empower you to make well-informed, autonomous decisions

4. Get additional opinions at large, academic cancer centers

5. stocan.org

6. cancerresearch.org (see previous slide)

7. clinicaltrials.gov (built for clinicians)
Are T cell therapies ready for prime time in GE cancer treatment?

### Global Immuno-Oncology Drug Development Pipeline

Published by Samik Upadhaya & Annie Yu on Sep 18, 2020

Sources: CRI, CRI Analytics, Clinicaltrials.gov, CRI-iAtlas, and GlobalData.

#### Comparison of IO pipelines in 2017 versus 2020

233% Growth in 3 years.

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Year</th>
<th>2017</th>
<th>2020</th>
<th>Clinical stage</th>
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<tbody>
<tr>
<td>T-cell targeted immunomodulator</td>
<td>2017</td>
<td>332</td>
<td></td>
<td>(All)</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>829</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other immunomodulator</td>
<td>2017</td>
<td>436</td>
<td></td>
<td>Approved</td>
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<tr>
<td></td>
<td>2020</td>
<td>976</td>
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<td>Phase I</td>
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<tr>
<td>Cell therapy</td>
<td>2017</td>
<td>405</td>
<td></td>
<td>Phase II</td>
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<tr>
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<td>Cancer vaccine</td>
<td>2017</td>
<td>612</td>
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<tr>
<td></td>
<td>2020</td>
<td>855</td>
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</tr>
<tr>
<td>Oncolytic virus</td>
<td>2017</td>
<td>164</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>2020</td>
<td>250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3-targeted bispecific antibody</td>
<td>2017</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>213</td>
<td></td>
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</tr>
</tbody>
</table>

![Graph showing comparison of IO pipelines in 2017 versus 2020](https://example.com/graph.png)