Forward Looking Statement

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Ziopharm’s Platforms Positioned to Target Solid Tumors

- Targeting solid tumors where target is known
  - The T-cell is the most potent drug platform, and the TCR is the best targeting molecule
  - Sleeping Beauty is the most clinically advanced non-viral gene transfer technology
  - TCR-T: “Play book” for targeting neoantigens – Sleeping Beauty and neoantigen library are the keys to uniquely position Ziopharm
  - CAR-T: “Play book” commercial adoption involves rapid and cost-effective manufacturing

- Our trial with the NCI is positioned to be the first non-viral TCR-T trial in the clinic
Ziopharm is Well-Positioned and Addressing the Largest Cancer Market

TCR-T is the gating technology to target solid tumors

1.5M+ solid tumors

174,250 blood cancers

Recent Milestones Dramatically Advance Ziopharm’s TCR-T Program

• Today’s call will focus on the TCR-T program and recent news:
  – **May 28, 2019** announcement of Ziopharm’s exclusive license with NCI for T-cell receptors (TCRs) reactive to neoantigens within the KRAS, p53 and EGFR gene families with transposons
  – **June 11, 2019** announcement of the IND clearance for *Sleeping Beauty* TCR-T trial at the NCI

• Two shots on goal:
  – NCI’s trial for mid-2019 “TCRs from the patient, for the patient”
  – Trials targeting mutations in KRAS, p53, EGFR gene families using established TCR library

*In partnership with NCI, Ziopharm is front and center with a significant TCR library*
A Scientific Primer - Targeting Neoantigens with T cells is the Key to Curing Solid Tumors

• All cancers arise from mutations in DNA
• Targeting mutations that are specific to tumors attacks the very foundations (building blocks) that cause cancer and avoids targeting normal cells
• By targeting tumor-specific mutations Ziopharm has:
  – A broad approach applicable to many cancers
  – Increased the chance of achieving anti-tumor effects as the tumors are “addicted” to these mutations
  – Limited toxicity due to cross-reactivity with normal/healthy cells
A subset of these mutations are “immunogenic” and referred to as neoantigens

The majority of mutations are unique, not shared between types of tumor or between patients

However, some of these mutations can be predicted and are shared between patients in “hotspots”
Two Ways to Specifically Target Neoantigens in Solid Tumors

**Vaccinate**
- They may trigger an immune response inside the body, *but do they result in tumors going away?*
- Years of research and many trials have demonstrated that vaccines cannot eliminate bulky tumors
- Vaccines may make immune checkpoint inhibitors work better, but overall market will be limited to the “box” that immune checkpoint inhibitors have baseline activity

**Infuse T Cells**
- Proven to eliminate bulky or metastatic tumor
- Can operate independent of immune checkpoint inhibitors
- Gives Ziopharm the ability to go after solid tumor market in its entirety
How Do We Know That T cells Can Target Bulky Metastatic Tumors?

Melanoma – Example of infused T cells targeting large amounts of solid tumor

- Resect tumor
- Tumor infiltrating lymphocytes (TIL)
- Propagate
- Infuse
- T cells (killing by native TCRs)
- Lymphodepletion
- Targeting neoantigens
Do the Lessons of T-cell Therapy for Melanoma Extend to Other Tumors?
T cells can Target Neoantigens in Solid Tumors Beyond Melanoma, but...

- Metastatic cholangiocarcinoma
- Colorectal, lung cancers
- Metastatic breast cancer

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Science. 2014 May 9;344(6184):641-5


Limitations of Non-Genetically Modified T Cells

These examples are proof-of-concept, but:
- Anti-tumor responses are not predictable
- Technology is difficult to scale

- Metastatic cholangiocarcinoma
- Colorectal, lung cancers
- Metastatic breast cancer

Science. 2014 May;344(6184):641-5
Why do Non-Genetically Modified T cells Fail to Reproducibly Target Solid Tumors?

1. Resect tumor
2. Tumor infiltrating lymphocytes (TIL)
3. Propagate
4. Neoantigen-specific T cells
5. Infuse Neoantigens

- Neoantigens (targets)
- Native TCRs (specificity)
- T cells (limited killing)

Why?

T cells are exhausted (old)
Solution: Using *Sleeping Beauty* to Manufacture TCR-T Targeting Neoantigens

- Neoantigens (targets)
- Introduced TCRs (specificity)
- T cells (repeated killing by young cells)
Stable, Nonviral Expression of Mutated Tumor Neoantigen-specific T-cell Receptors Using the Sleeping Beauty Transposon/Transposase System

Drew C Denlinger, Anna Pauletto, Eric Tran, Maria R Pankhurst, Cyrille Cohen, Paul F Robbins, Laurence J Cooper and Steven A Rosenberg

Neoantigens unique to each patient’s tumor can be recognized by autologous T cells through their T cell receptor (TCR) but the low frequency and/or terminal differentiation of mutation-specific T cells in tumors can limit their utility as adoptive T cell therapies. Trans- fect of TCR genes into younger T cells from peripheral blood with a high proliferative potential could obvi- ate this problem. We generated a rapid, cost-effective strategy to genetically engineer cancer patient T cells with TCRs using the clinical Sleeping Beauty transposon/transposase system. Patient-specific TCRs reactive against HLA-A*0201-restricted neoantigens AASSH575 or EBBD272 or the HLA-A*0101-restricted neoantigen EEMK954 were co-transduced with murine constant chains and cloned into Sleeping Beauty transposons. Patient peripheral blood lymphocytes were co-transduced with Sleeping Beauty transposase and transposase-transduced T cells were enriched by sorting on murine TCRs (enTCR) expression. Rapid expansion of enTCR T cells with irradiated allogeneic peripheral blood lymphocytes feeder, OKT3, interleukin-2 (IL-2), IL-15, and IL-21 resulted in a proportionate increase (CD7/CD45RA+) and less-differentiated (CD7/CD45RA−) T cells. Transposase-transduced T cells specifically mounted a polyfunctional response against cognate mutated neoantigens and tumor cell lines. Thus, Sleeping Beauty transposition of mutation-specific TCRs can facilitate the use of personalized T cell therapy targeting unique neoantigens.

INTRODUCTION

Mutation-specific T cells likely play a key role in resolving long-term tumor regressions, in adaptive T cell therapy using tumor-specific T cell receptors (TILs). In excision, 39-50% of the patients treated with TILs and interleukin (IL)-2 following en- rollment into clinical trials achieved durable, complete regression of metastatic disease.12 Interventions analysis of these “young” T cells revealed that TILs, generated patient-specific, non-enzymously transduced immune by tumors,12m Prospectively administered TILs specifically reactive with EBBD272,12n were used in a trial of patients with a high tumor burden. This trial included a large well-documented cohort of patients, which could provide an opportunity for the expression of a range of TCRs.12s Clinical trials with T cell-receptor directed against neoantigens in T cells has been safely customarily limited to the development of targetable neoantigens.12t 12u 12v 12w 12x 12y 12z 12AA 12BB 12CC 12DD 12EE 12FF 12GG 12HH 12II 12JJ 12KK 12LL 12MM 12NN 12OO 12PP 12QQ 12RR 12SS 12TT 12UU 12VV 12WW 12XX 12YY 12ZZ 12aa 12bb 12cc 12dd 12ee 12ff 12gg 12hh 12ii 12jj 12kk 12ll 12mm 12nn 12oo 12pp 12qq 12rr 12ss 12tt 12uu 12vv 12ww 12xx 12yy 12zz 12A 12B 12C 12D 12E 12F 12G 12H 12I 12J 12K 12L 12M 12N 12O 12P 12Q 12R 12S 12T 12U 12V 12W 12X 12Y 12Z

Mol Ther. 2016 Jun;24(6):1078-1089
Clinical Trial Under Newly Cleared IND at NCI – “TCRs from the patient, for the patient”

Neoantigens and TCRs identified in real time

Genetically modified SB manufacture of TCR-T

Identification of neoantigens

Identification of TCRs

Infusing TCR-T cells targeting solid tumor neoantigens with Sleeping Beauty technology
Some TCRs Recognize Neoantigens in Hotspots
Library of TCRs Against Shared Neoantigens; Size of Library is Key
Tumor- and Neointegron-Reactive T-Cell Platforms Can Be Identified by Natural Frequency in Their Tumor

Introduction

The prevalence of actionable neoantigens in tumors refers to the number of mutations that occur in a tumor's DNA. The identification of these mutations can help in the development of personalized therapies. When considering the expression of neoantigens, it is essential to understand the context in which they are expressed.

Materials and Methods

Studies involving mouse models and human tumor samples were performed in the live mouse and human tissues, respectively. The collected data were analyzed using various statistical tools and software, which included single-cell RNA sequencing, which is a powerful technique for analyzing the transcriptome of individual cells. The results were then interpreted to provide insights into the mechanisms underlying cancer immune responses.

Results and Discussion

The use of neoantigens as cancer immunotherapy targets is an emerging field of research. The results from the studies presented in this paper highlight the potential of using neoantigens as therapeutic targets. The findings suggest that the identification of neoantigens in tumors can lead to the development of effective immunotherapies.

Dr. Sarah Johnson, Director of Cancer Research, University of California, San Francisco

References


Sleeping Beauty Platform Expresses TCRs Specific for Neointegrons in Hotspots


Tumor- and Neointegron-Reactive T-Cell Platforms Can Be Identified by Natural Frequency in Their Tumor

Introduction

The importance of immunotherapy for the treatment of cancer cannot be overstated. Over the past decades, several immunotherapeutic strategies have been developed, including checkpoint inhibitors, vaccines, and adoptive cell therapies. However, despite these advances, there is a need for more effective and targeted immunotherapies.

Materials and Methods

Studies involving mouse models and human tumor samples were performed in the live mouse and human tissues, respectively. The collected data were analyzed using various statistical tools and software, which included single-cell RNA sequencing, which is a powerful technique for analyzing the transcriptome of individual cells. The results were then interpreted to provide insights into the mechanisms underlying cancer immune responses.

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New Trial Targeting Neoantigens in Hotspots

Neoantigens and TCRs identified ahead of time

- Build, curate and maintain TCR library against (shared) neoantigens in hotspots
- Faster Screening of neoantigens
- Selection of TCRs from library
- Genetically modified SB manufacture of TCR-T
- More TCRs, greater success
Sleeping Beauty is the Non-Viral Solution to Targeting Neoantigens with TCR-T

• DNA plasmids are needed to scale for the large number of TCRs needed by anyone in this field
  – We do not believe genetically modifying T cells with virus can be commercially achieved

• Ziopharm has two shots on goal:
  – Identify neoantigens and TCRs for patients in real time with broad applicability
    o TCRs “from and for the patient” which are not shared (one-time use, multiple TCRs/patient)
  – Screen patients and use TCRs prepared ahead of time with rapid applicability
    o TCRs that are shared between patients in a library of sufficient size
    o Success enrolling patients is dependent on the size of the TCR library
Ziopharm Oncology: 
the right technology, 
the right trials, 
and the right market.
Thank you