Society for Immunotherapy of Cancer

Welcome to
SITC 2019 Adoptive Cell Therapy Workshop

Organizers:

Katayoun Razvani, MD, PhD – The University of Texas MD Anderson

Alessandra Cesano, MD, PhD – ESSA PHarmaceuticals

Alessandra Cesano - disclosure

- I am a full time employee of ESSA Pharmaceuticals
- I am a consultant of Nanostring Inc. and Refuge Biotechnologies Inc.

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CAR-T a rapidly emerging approach to immuno-therapy: from theoretical construct to a therapeutic reality

2017 brought landmark approvals for the first CAR-T products

- Approved August 2017
- Indicated for patients up to 25 years of age with B-ALL that is refractory or 2nd or later relapse
- 2nd approval in May 2018
- Indicated for patients with r/r DLBCL after 2 or more lines of systemic therapy

- Approved October 2017
- Indicated for patients with r/r DLBCL after 2 or more lines of systemic therapy

- 600 clinical trials worldwide; ~ 100+ biotech and cancer centers developing ACT

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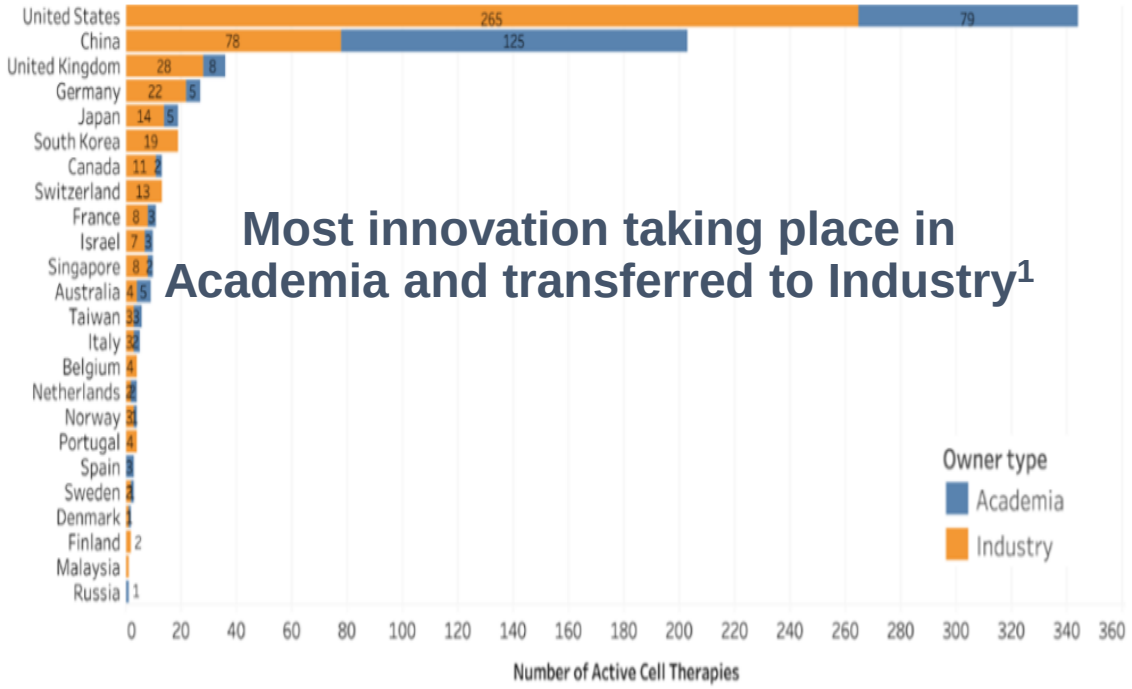
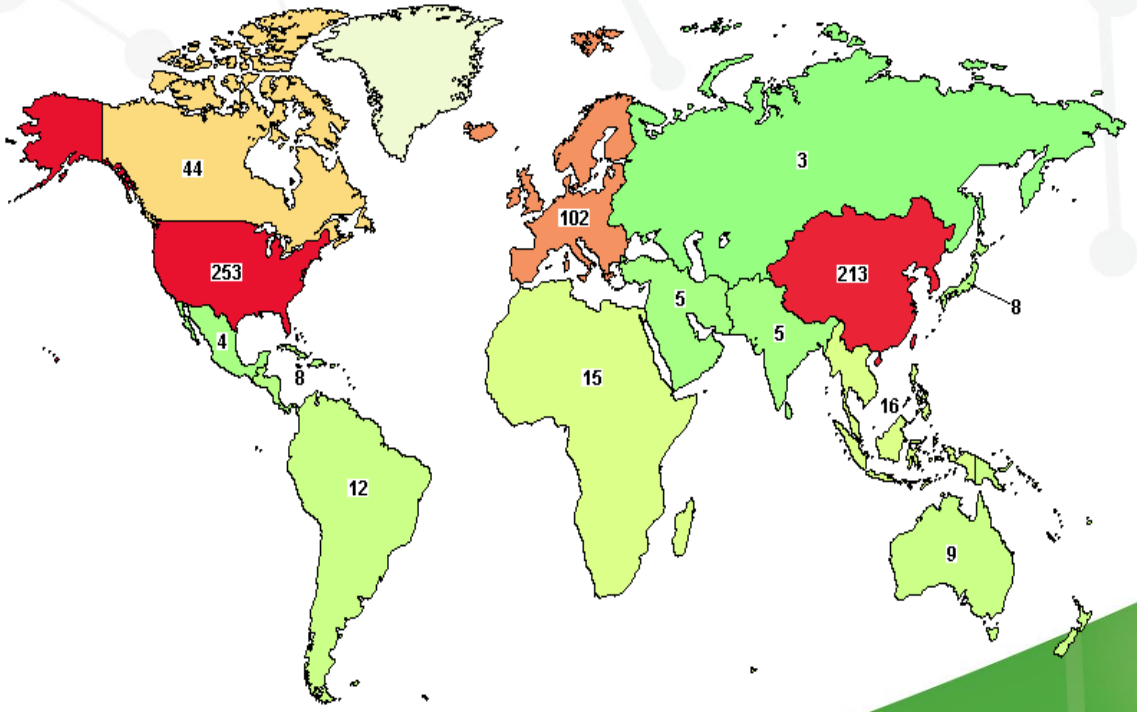
ACT is continuing to explode with US and China leading the way

Number of ongoing Cell Therapy studies



Most innovation taking place in Academia and transferred to Industry[1]

Global Clinical Trials for CAR-T



US and China are leading in active Clinical Trials[2]

1. Tang et al. (doi:10.1038/nrd.2018.74)
2. Clinical Trials.Gov: CAR-T search term, October 28, 2018

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Momentum is here and so are the challenges…..

December 12, 2017

The Promise and Challenges of CAR-T Gene Therapy

Bridget M. Kuehn, MSJ

JAMA. 2017;318(22):2167-2169. doi:10.1001/jama.2017.15605

Successes in CAR T translation have propelled their commercial launch but expanding their impact remain challenging

CAR T-Cell Therapies: Overcoming the Challenges and New Strategies

Partow Kebriaei, MD
Department of Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, Houston, TX, USA

Extended Abstract: 045-PLENI-01

Human Gene Therapy, Vol. 29, No. 5 | Review Articles

Free Access

CAR T Cells in Trials: Recent Achievements and Challenges that Remain in the Production of Modified T Cells for Clinical Applications

Ulrike Köhl, Stanislava Arsenieva, Astrid Holzinger, and Hinrich Abken

Published Online: 1 May 2018 | https://doi.org/10.1089/hum.2017.254

SITC 2019 Adoptive Cell Therapy (ACT) workshop - Objectives

- SITC is proud to host an Adoptive Cellular Therapies Workshop to support both continued momentum and clinical advancement in this field.
- This two-day workshop will bring together cancer immunotherapy experts to discuss and address challenges concerning the use and development of adoptive cellular therapies for the treatment of cancer patients.
- Throughout seven didactic sessions and participation in collaborative working groups, attendees will discuss a number of topics, including:
  - Development of novel strategies to improve the overall risk/benefit profile for adoptive cellular therapies
  - Clinical development and regulatory challenges
  - Real world hurdles that impact scalability and patient access
- Since some of the challenges related to CIR to ACT are shared with other forms of immunotherapy two of this morning sessions (External Circumstantial Factors and Emerging ideas and new concepts) will be in common with the SITC 2019 CIR workshop
- It is anticipated that the efforts of this workshop, and the resulting manuscript, will help fuel innovative collaborative efforts as well as the dissemination of knowledge throughout the field.

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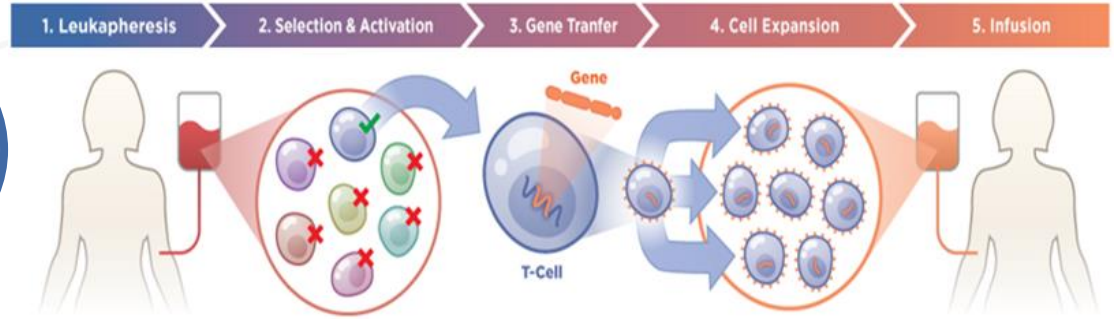
Current challenges with ACT development and commercialization

Realizing the full potential of ACT will require <u>parallel scientific progress</u> overcoming biologic challenges and addressing practical challenges related to scalability and affordability



ACT

Efficacy

- Primary Resistance (solid tumors)
- Acquired Resistance (hematologic malignancies)

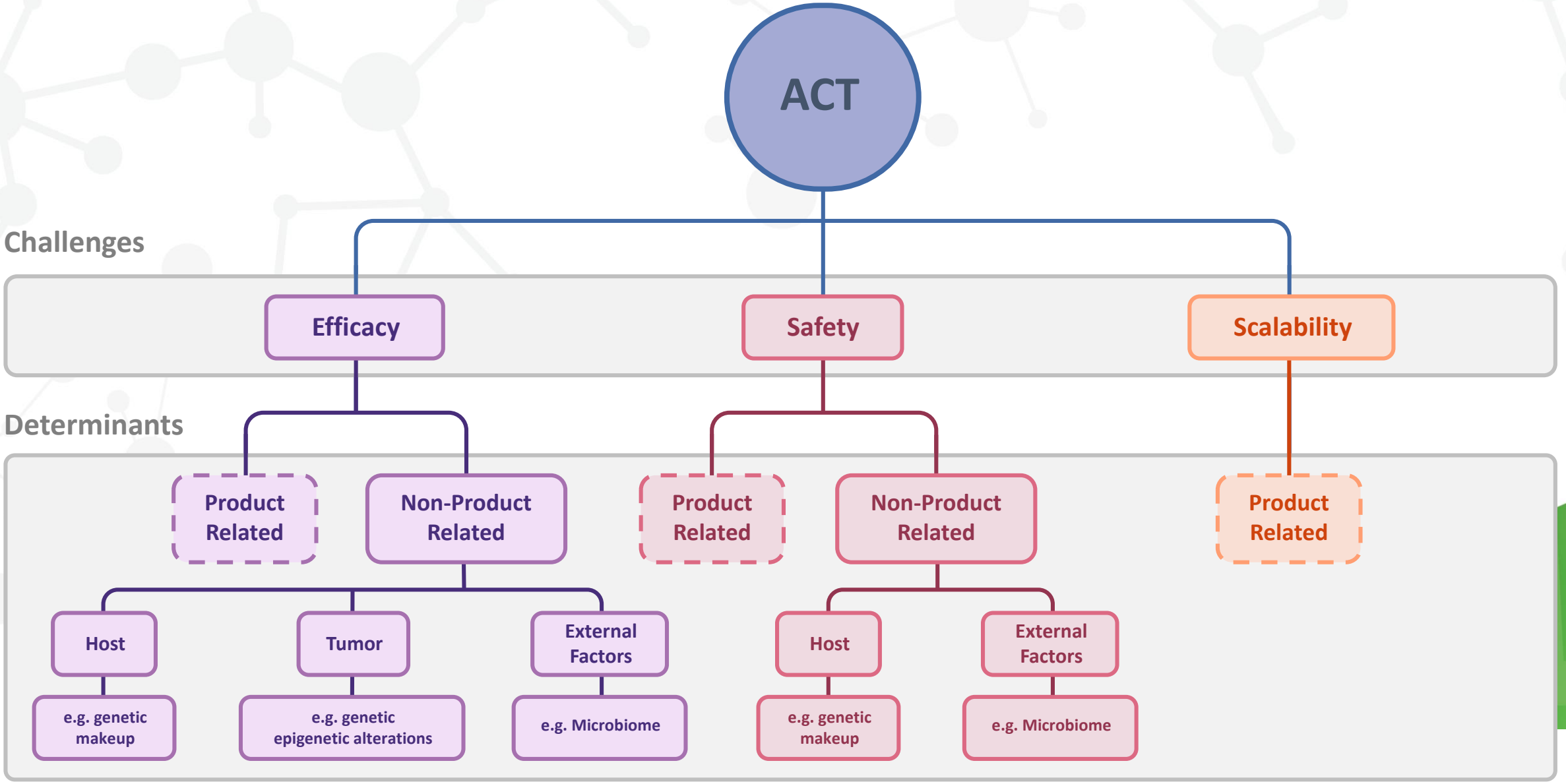
Safety

- On target/off tumor (B cell lymphopenia)
- Off target/off tumor (CRS, Neurotox, oncogenicity, GVHD)

Scalability

- Patient Access
- Turn around Time
- Cost

Current challenges with ACT development and commercialization



Non-Product Related Modifiers

Factors that may affect the success of ACT independently from product quality and its PK/PD/MOA:

HOST

Genetic make up of the host – complex to follow with current technologies but evolving

- Should germ-line DNA for genetic studies be collect in all patients enrolled in CAR-T cell trials?

Tumor

Genetic/epigenetic and transcriptional profiles of the cancer and associated influences on TME

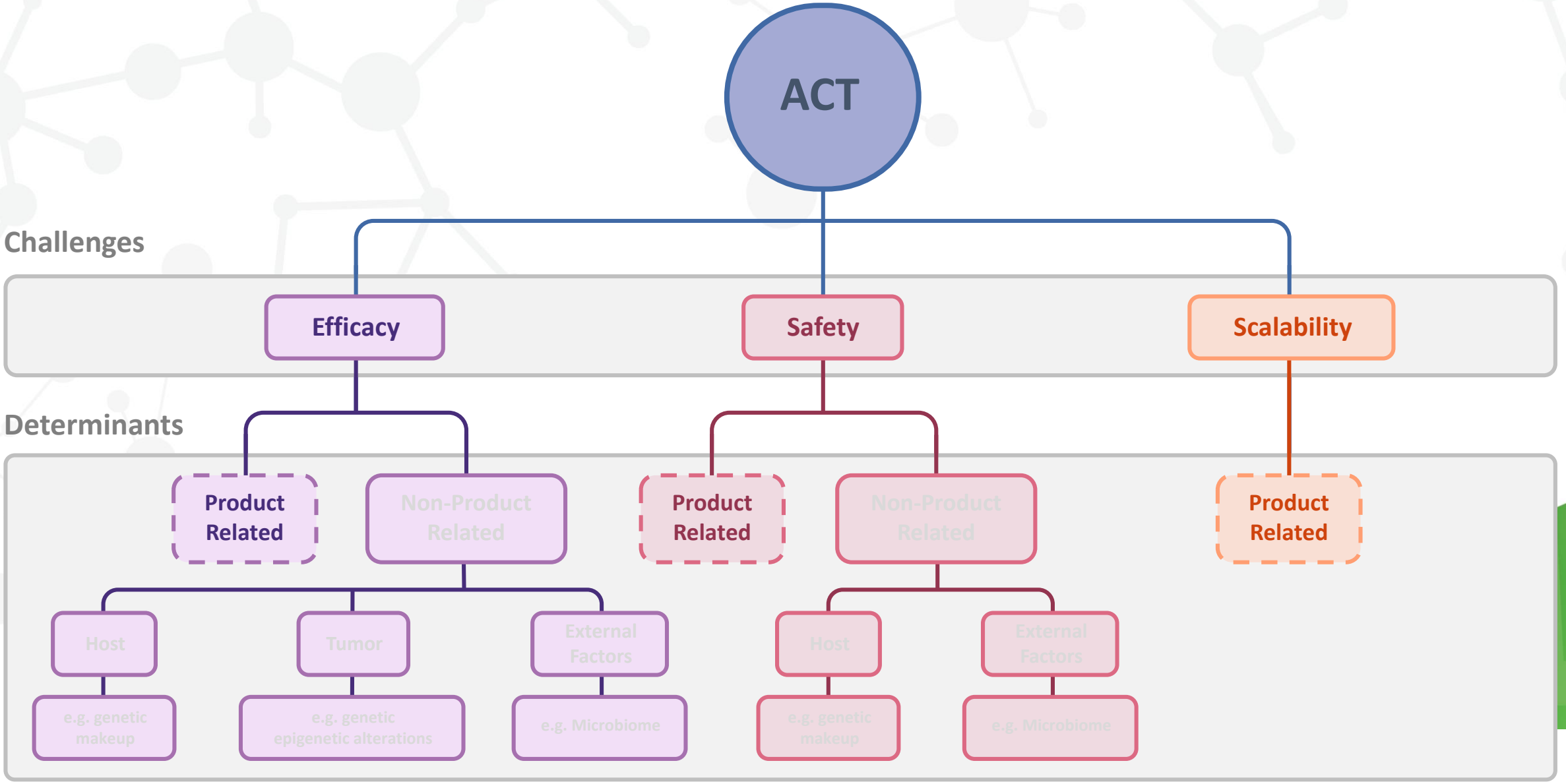
- Implications for CAR-T cell trafficking to solid tumor?

External Factors

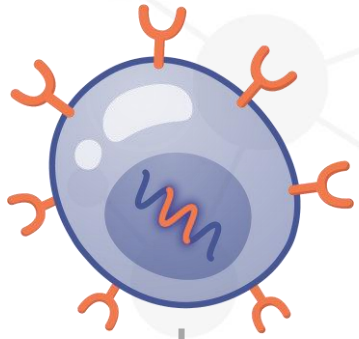
Environmental factors such as microbiome, co-morbidity and associated therapies

- Are adoptively transferred cells once infused subjected to the same immune modulatory effects that endogenous immune cells?

Current challenges with ACT development and commercialization: Product Related Challenges



Product Related Challenges/Considerations



Product Design

- Selection of Ag target
- Selection of mechanisms
- of Ag recognition
- Selection of construct design
- Selection of cellular product

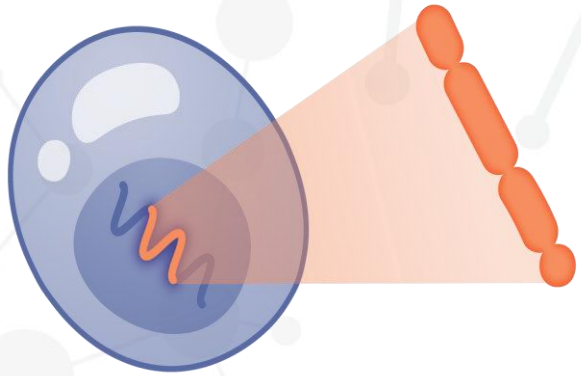
Product Development

- Analysis of non-Ag specific characteristics determining “fitness” and toxicity
- Modulation of cellular function

Product Manufacturing QA

- Assessment of product specifications

Product Design Key Challenges



Selection of Ag Target	• CD19 was an ideal target, how will CD22, CD20, and BCMA compare? • How to select/validate targets for solid tumors?
Selection of Mechanism of Ag Recognition	• Surface molecule recognized in natural conformation (scFv) • Antigens processed and presented in the context of HLA
Selection of Construct Design	• What are the characteristics that determine optimal construct design? • Signal 2: CD28 vs 4-1BB or others as Co-stim?
Selection of Cellular Product	• T cells (Appropriate composition of CD4/CD8 cells?) • NK cells • Autologous vs allogeneic?

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Product Development Key Challenges

Analysis of non-Ag specific characteristics determining "fitness" and toxicity

- **T cell characteristics determining product "fitness":**
  - Level of T cell differentiation
  - Stage of T cell maturation
  - T cell metabolism
  - Range of function and respective cytokine profile
  - Others?
- **How does T-cell fitness determine efficacy and toxicity?**
- **How does the fitness of the starting material effect efficacy of the finished product?**
- **How can we change/polarize product cell composition and function during manufacturing process?**
- **What are the tools available today to determine T-cell fitness throughout the MFG process?**
- **What are the optimal points during the MFG process to sample fitness?**
  - Starting material?
  - Pre-cell expansion?
  - Pre-infusion?
  - All the above?

Modulation of cellular function

- **What are the product-inherent engineering of synthetic mechanisms that modulate cellular function in response to stimulus?**
  - E.g. CRISPR-based gene targeting
- **Intrinsic versus extrinsic modulation?**
- **Suicide switches vs. mAb depletion**
- **Armored CARs**

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In vivo validation of product function

Understanding parameters of product effectiveness in vivo:

- Immune-responsiveness: Product quality versus intrinsic biology of the tumor

Validation of MOA

- Efficacy: PK/PD parameters (i.e. CAR T cell expansion, CAR T cell persistence, T cell clonality?) in relation to clinical outcome
- Safety:
  - PK/PD parameters in relation to on target/ off tumor (e.g. B cell aplasia)
  - PK/PD parameters in relation to off target/off tumor (e.g. CRS, neurotoxicity, oncogenicity)

Tissue Sampling

- Types: PB, BM, Tumor, Affected tissue (toxicity)
- Time points (pre and post-infusion)

Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting

- **Remarks by Scott Gottlieb, M.D.**
  Commissioner of Food and Drugs
  Alliance for Regenerative Medicine's Annual Board Meeting
  May 22, 2018
  Washington, DC

- ***"…..In contrast to traditional drug review, where 80 percent of the review is focused on the clinical portion of that process, and maybe 20 percent is focused on the product issues, I'd say that this general principal is almost completely inverted when it comes to cell and gene therapy. The initial clinical efficacy is often established early, and sometimes in small series of patients. The more challenging questions relate to product manufacturing and quality, or questions like how much you can change in the manufacturing process before the entire product's safety or performance is affected…..***

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SITC 2019 ACT Workshop – Day 1

- Session I
  - State of the Field of Adoptive Cell Therapy
    - Invited speaker: Helen Heslop MD – Baylor College of Medicine
- Session II
  - External Circumstantial Factors*
    - Co-Chairs:
      - Christina Spencer, PhD – PICI
      - Alessandra Cesano, MD PhD – ESSA Pharma
- Session III:
  - Emerging ideas and New Concepts*
    - Co-chairs:
      - Kyung-Ho Roh, PhD – University of Alabama in Huntsville
      - Francesco M. Marincola – Refuge Biotechnologies
- Session IV
  - Improving Risk and Benefit profile of ACT
    - Co-chairs:
      - David M. Barrett – Children Hospital of Philadelphia
      - Prasad S. Adusumilli, MD, FACS, FCCP - MSKCC

* In common with SITC 2019 CIR workshop

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