Stopping Runaway CAR-T Cells

John Miller
University of Rochester
Department of Microbiology & Immunology
America’s Got Regulatory Science Talent Student Competition
CAR-T cells are a promising cancer treatment

1. In the clinic, the patient’s T cells are separated from the rest of their blood and sent to the lab.
2. A viral vector delivers CAR-encoding gene into the T cells.
3. The T cells now express CAR on their surfaces and are known as CAR T cells.
4. CAR T cells are multiplied and put back into the patient’s bloodstream.
5. The CAR T cells identify the cancer cells with target antigen and kill them.

CAR-T cell mediated cancer cell death
Regulatory Science Focus Area

Individualized therapies and precision medicine

Goal: Provide new regulatory guidelines to address off-target effects of CAR-T cell therapies and improve the CAR-T cell review process

• Important for increasing review efficiency and the safety of these treatments
The Problem with Runaway CAR-T cells

• Overactive CAR-T cells > Cytokine release syndrome, neurotoxicity

On-target effects

Off-target effects

On-target off-tumor effects

Tumor cell

Healthy cell

Healthy cell

Killing of cells with non-target antigen

Recognition of target antigen on healthy cells
The CAR-T Safety Switch

• Once infused, CAR-T cells are difficult to modulate compared to traditional oral and IV cancer drugs, where dosage can be changed to mitigate toxicity
• Currently used in investigational clinical trials
Requiring Safety Switches in CAR-T Cell Products

Regulatory Science Solution: With adequate data from preclinical trials, the FDA should move towards requiring CAR-T cell manufacturers to incorporate a safety switch mechanism in these therapies.

Benefits
- Efficient review - speed up regulatory processes
  - Accelerate risk mitigation and clinical risk monitoring processes
- Improved safety and effectiveness
  - Benefit/risk profile
- Advancing the safety of CAR-T cell therapies

Potential Limitations
- May be difficult to require all manufacturers to incorporate this into their products
  - There are multiple methods of producing Safety Switches for CAR-T cells
- If the manufacturer can show there are no off-target effects, this requirement could be waived
Conclusion

Incorporation of safety switches into CAR-T cell products will allow for an efficient method for increased regulatory capacity and safety.
Acknowledgements

FDA Advisors – Center for Biologics Evaluation and Research
Sakshi Tomar, PhD
Maitreyi Chattopadhyay, PhD

University of Rochester CTSI
Joan Adamo, PhD