



Society for Immunotherapy of Cancer

Improving Benefit Profile of Adoptive Cellular Therapy

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Framework

- Improve the product
- Improve the manufacturing process
- Improve accessibility



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Improving the ACT product

- Issues and challenges
- Solutions



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Challenges of ACT

- Product specific:
 - Proliferation and persistence
 - Potency
 - Exhaustion
 - toxicity
- Tumor specific
 - Tumor heterogeneity
 - Antigen escape
 - Immune escape mechanisms
- Challenges specific to solid tumors
 - Trafficking to tumor sites
 - Tumor infiltration
 - Physical barriers
 - Immunosuppressive tumor microenvironment
 - Tumor heterogeneity between primary and metastatic sites



Improving expansion and persistence

- Cytokine expression (Il-15, Il-12, Il-21..)
- Lymphodepleting chemotherapy
- Strategies to avoid rejection, induce tolerance
- Don't eat me signal (CD47)
- Memory phenotype



Improving potency and addressing exhaustion

- Carefully choosing what CAR for what disease
 - Costimulatory domains
- Genetic engineering
 - KO checkpoint molecules, inhibitory pathways
 - KI activating genes
- Combination therapies
 - Checkpoint inhibitors
 - Immunomodulatory agents
 - Oncolytic viruses
- Metabolic reprogramming



Addressing antigen escape

- Dual antigen targeting
- Multiple antigen targeting (multiple TAA)
- Increasing affinity of CAR
 - enhance potency even with low antigen density



ACT in solid tumors

- Understanding the tumor microenvironment
 - Biomarkers, immunoscore...
- Immunosuppressive molecules (TGFB, adenosine)
 - Genetic engineering (TGFB2 KO, A2AR KO)
- Immunosuppressive cells
 - Tregs, Bregs, MDSC's
- Combination therapies:
 - Checkpoint blockade
 - Anti-angiogenesis
 - Radiation/chemo
 - Targeted therapy
- Trafficking: chemokine receptors
- Infiltration: overcoming the ECM (heparanase, collagenase, targeting fibroblasts...)



Improving the manufacturing process

- Issues:
 - Time consuming
 - Labor intensive
 - Issues with contamination
 - Variable quality
- Solutions:
 - Automation
 - Closed systems
 - Standardization
 - Quality testing including functional testing



Beyond autologous products

- Allogeneic T cells
 - KO TCR
- Alternatives that are not alloreactive
 - NK cells
 - NKT cells
 - Virus specific CAR's
- Off the shelf sources
 - Cord blood
 - iPSC



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Improving accessibility

- Decreasing the cost
 - Non viral transduction technologies
 - Transposons
 - Off the shelf universal products
- Understanding regulatory processes better

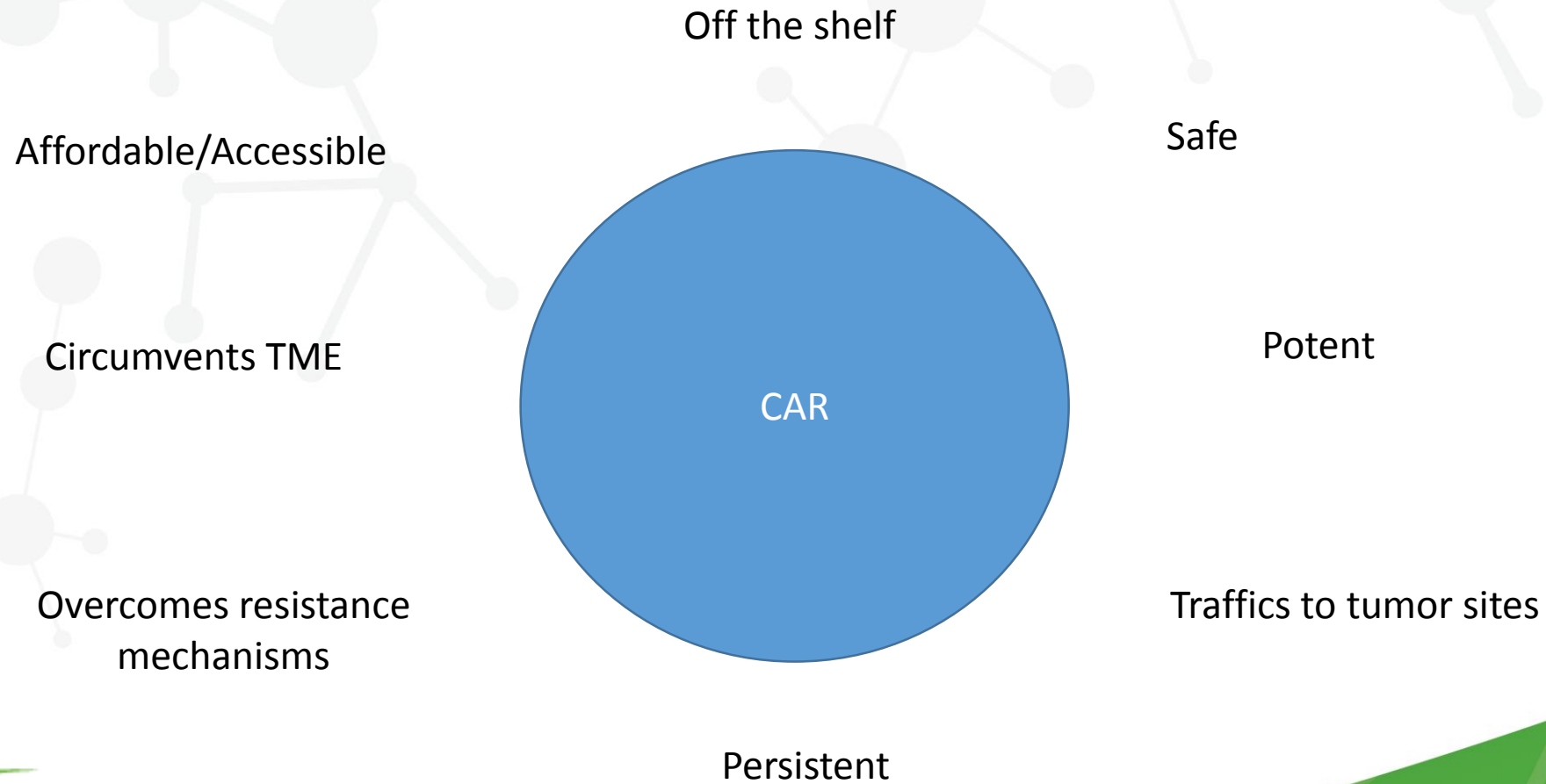


Take home messages

- A lot to learn:
 - Tumor/disease aspect
 - Immune effector cell aspect
 - One product does not fit all
- Very exciting possibilities
 - A lot of room for innovation
- Collaboration is needed



Ideal ACT product



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Thank you!

Questions?