Mapping CAR-T Cell Therapy Associated Neurotoxicity

Aubrey Winger
Dr. Andrew Warren

Background & Context

CAR-T Cell Therapy

- The first effective CAR-T Cells were developed in 2002
- CD19-directed CAR-T cells were FDA approved in 2017
- Often used to treat relapsed or refractory patients who have tried >=3 other lines of therapy
- Lasting remission is achieved by about 30-40% of patients
- Can be accompanied by extreme neurological and physical side effects that limits usage in critically ill patients

Therapy Process

- Immune cells (T cells) are extracted from the patient
- Cells are engineered with chimeric antigen receptors (CAR) to target cancer cells
- Patient is infused with CAR-T cells, and often receives chemotherapy in conjunction
- CAR-T cells recognize, bind, and eliminate cancer cells

Cytokine Release Syndrome (CRS)

- One of the most common side effects of CAR-T therapy
- CAR-T cells release inflammatory cytokines that trigger other immune cells in the body
- Ranges from mild to life threatening

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

- Associated with, but not caused by CRS
- Thought to be caused by a disruption of the blood brain barrier
- Side effects include headaches, confusion, seizures, tremors, and delirium
- Pathophysiology is poorly understood

Specific Aims & Hypothesis

Hypothesis:

- Clinical data and medical literature can inform a computational model of the immune system interactions that take place during CRS and ICANS

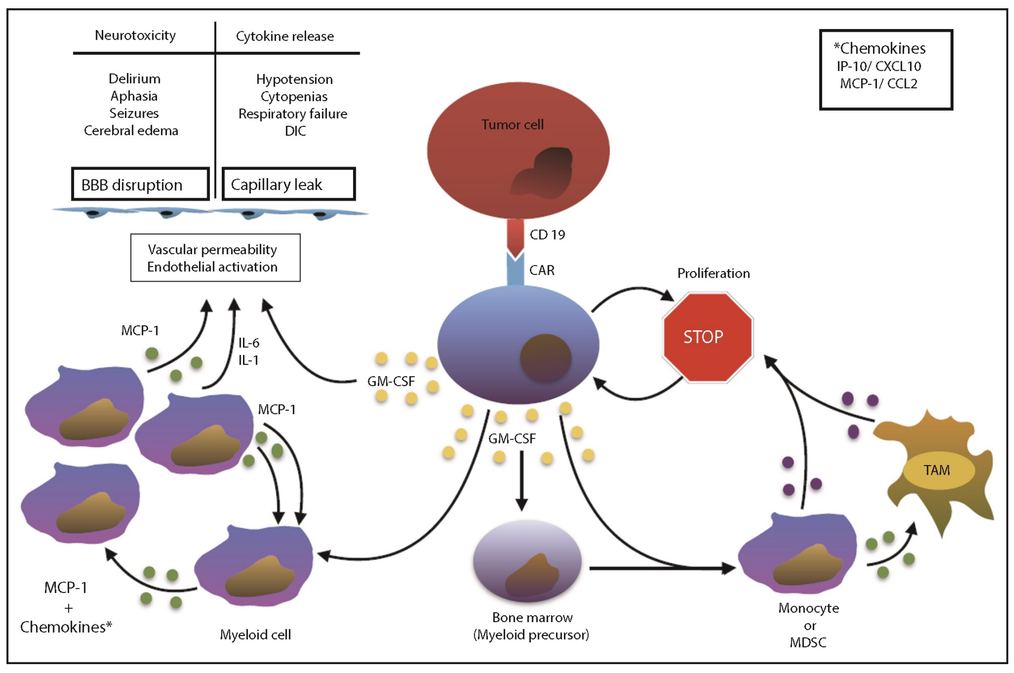
Overall Aim:

- Determine the principal risk predictor or best combination of predictors for CRS and ICANS to drive hypothesis generation for model formation and perturbation
- Identify potential targets for reducing patient risk associated with CRS/ICANS

Specific Aims of this Project:

1. Collect metadata from CAR-T therapy clinical trials
2. Organize metadata so that it can be utilized in a machine learning model
3. Collect literature related to ICANS, CRS, and immune pathways
4. Create a concept map from the literature, in order to predict possible molecular pathogeneses for ICANS

Figure 1: Current conceptual understanding of the generation of ICANS from CAR-T Cells. GM-CSF is produced by CAR-T cells and triggers an immune reaction (Ahmed, 2019)



Images
https://www.istockphoto.com/search/2/image?mediatype=illustration&phrase=iv+therapy
https://www.cellandgene.com/doc/car-t-cell-therapies-current-limitations-future-opportunities-0001
https://www.shutterstock.com/image-vector/tissue-engineering-linear-icon-repair-damaged-1457029913
http://goldfieldupc.com/

Current Work

Collecting Metadata from Clinical Trials

Thirty papers were reviewed, and information was collected in the following categories:

1. Clinical Trials: Demographic and clinical information about the cohort, CAR T construct and dose levels, and clinical trial information such as duration and general responses
2. Heme Side Effects: Blood related side effects
3. Non-Heme Side Effects: All other side effects, including those related to CRS and ICANS
4. Responses: All the response data for the patient cohort, some of which is also included in the Clinical Trial category. Common data included median duration of response, and the number of patients who achieved complete or partial remission
5. CAR T: Molecular and cellular information about the CAR-T therapy, including the median duration of the cells, number of days until maximum expansion, and highest level of CAR-T cells in the blood

The data, represented generally as raw counts, was cleaned and compiled into an Excel spreadsheet for future use

Mapping CAR-T Associated Neurotoxicity

- A general compartment model was used to define parameters of interest (Figure 2)
- Each compartment has a corresponding Zotero folder with all the papers used to define interactions within that compartment
- A concept map was developed using CellDesigner, an SBML based application with extensive diagramming capabilities
- Since this map represents cellular interactions, and CellDesigner is meant for illustrating biochemical networks, the graphical notation system is interpreted slightly differently (Figure 3-5)
- Interactions and molecules are cited using PubMed ID, and additional information is provided within the map notes (Figure 6)

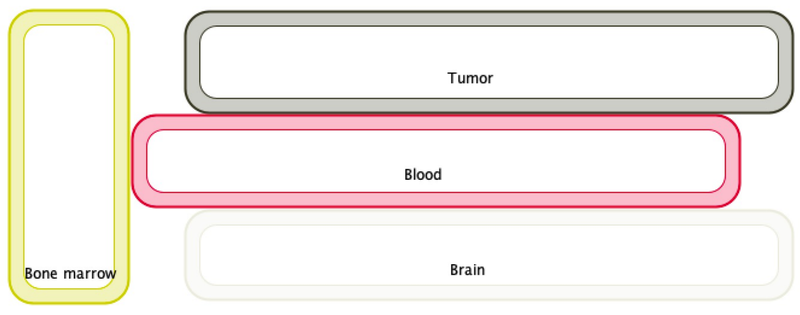


Figure 2. *General compartment model used to start the concept map*

Figure 3. *Color coding used in the concept map. The cyan (top) designates any interleukin (IL), and the periwinkle designates chemokines (CCL/CXCL). GM-CSF and MCP-1 have specific colors since they are expressed by multiple players in the diagram.*

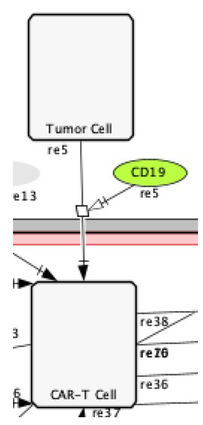


Figure 4. *CD19 Is transported to CAR-T Cells where it has an effect specified in the notes*

Figure 5. *ANG2 and ANG1 both bind to the TIE2 receptor, inducing changes in extracellular stability. However, ANG2 can inhibit ANG1 from binding*

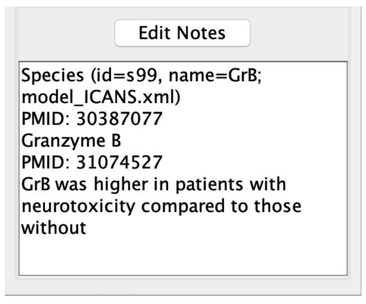


Figure 6. *Example of notes for molecule GrB*

Future Work

Build a computational immune system model

- Combine the clinical metadata with temporal data from clinics investigating CAR-T cell therapy to develop a dynamic model of events that occur during CRS and ICANS
- Use the concept map to determine key molecular/cellular interactions that should contribute to the computational model

References

- Ahmed, Omar. "CAR-T–Cell Neurotoxicity: Hope Is on the Horizon." *Blood* 133, no. 20 (May 16, 2019): 2114–16. https://doi.org/10.1182/blood-2019-03-900985.
- Bartosch, Jamie. "Three Years after CAR T-Cell Therapy For Lymphoma, Patient Still Cancer-Free." *UChicago Medicine*, UChicago Medicine, 17 Oct. 2019, www.uchicagomedicine.org/forefront/cancer-articles/a-walking-miracle-car-t-cell-therapy.
- "Car t Cells: Timeline of Progress." *Memorial Sloan Kettering Cancer Center*, www.mskcc.org/timeline/car-t-timeline-progress.
- "Car t-Cell Therapy and Its Side Effects." *American Cancer Society*, www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/car-t-cell1.html.