COMPUTATIONAL MODELING OF IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY SYNDROME (ICANS)

Fund Information:
Engineering in Medicine Seed Grant, University of Virginia

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Abstract

CAR T-cell therapy has impressive anti-tumor activity in a variety of hematologic cancers including pediatric acute lymphoblastic leukemia (ALL), diffuse large B-cell non-Hodgkin's lymphoma (NHL), mantle cell NHL, multiple myeloma, and chronic lymphocytic leukemia (CLL), leading to the commercial approval of four CD19-directed CAR T-cell products. While CAR T-cells are promising treatments for relapsed/refractory hematologic cancers, they are limited by two significant toxicities, CRS and ICANS. Proven management options for CRS and ICANS are limited to tocilizumab and corticosteroids. Testing other currently available cytokine mediators or drugs for efficacy in controlling CRS/ICANS is expensive and cumbersome. The field would benefit from an *in silico* modeling system of CAR T-cells interacting with other immune components so that only promising CRS/ICANS mediators are tested in the clinic. We hypothesize that information in literature on the clinical applications of CAR T-cell therapy, immune cell-based research, animal models, and pre-clinical data will inform a computational model of immune system interactions during CRS and ICANS, allowing for future development of targeted therapies to treat these devastating side effects.

Better understanding of CRS and ICANS necessitates a prioritized, combinatorial exploration of underlying cell type distribution and physiological mechanisms. Principal components of clinically associated metadata were explored to define a hypothesis testing framework using biochemical and cellular modeling. Medical literature was reviewed for phase I/II trials of CAR T-cell therapy to extract and combine clinical data regarding patient demographics, CAR T-cell therapy indications, cellular therapy product information, toxicities, and disease outcomes. Adult and pediatric recipients of CAR T-cell therapy for all disease indications (ALL, mantle cell NHL, diffuse large B-cell NHL, and multiple myeloma) from 2009 to present were included in the data set.

A concept map was developed in CellDesigner, presenting a procedural and interaction-based view of the underlying systems involved in CRS and ICANS (Figure 1)[1]. Components were added through a systematic review of papers discussing the potential pathophysiology of ICANS, CRS, and neuroinflammation. In this view, cellular and molecular components of the system interact locally with other components, as well as across compartments. Behavior of cell types, cytokines, and chemokines are described in relation to the tumor microenvironment, lymph system, and blood-brain-barrier. This concept map, along with the clinical metadata, will be used to determine the parameters and primary focus of future computational models and allow multiple hypothesis testing as to the potentially multiple, underlying causes and mechanisms for symptom presentation.

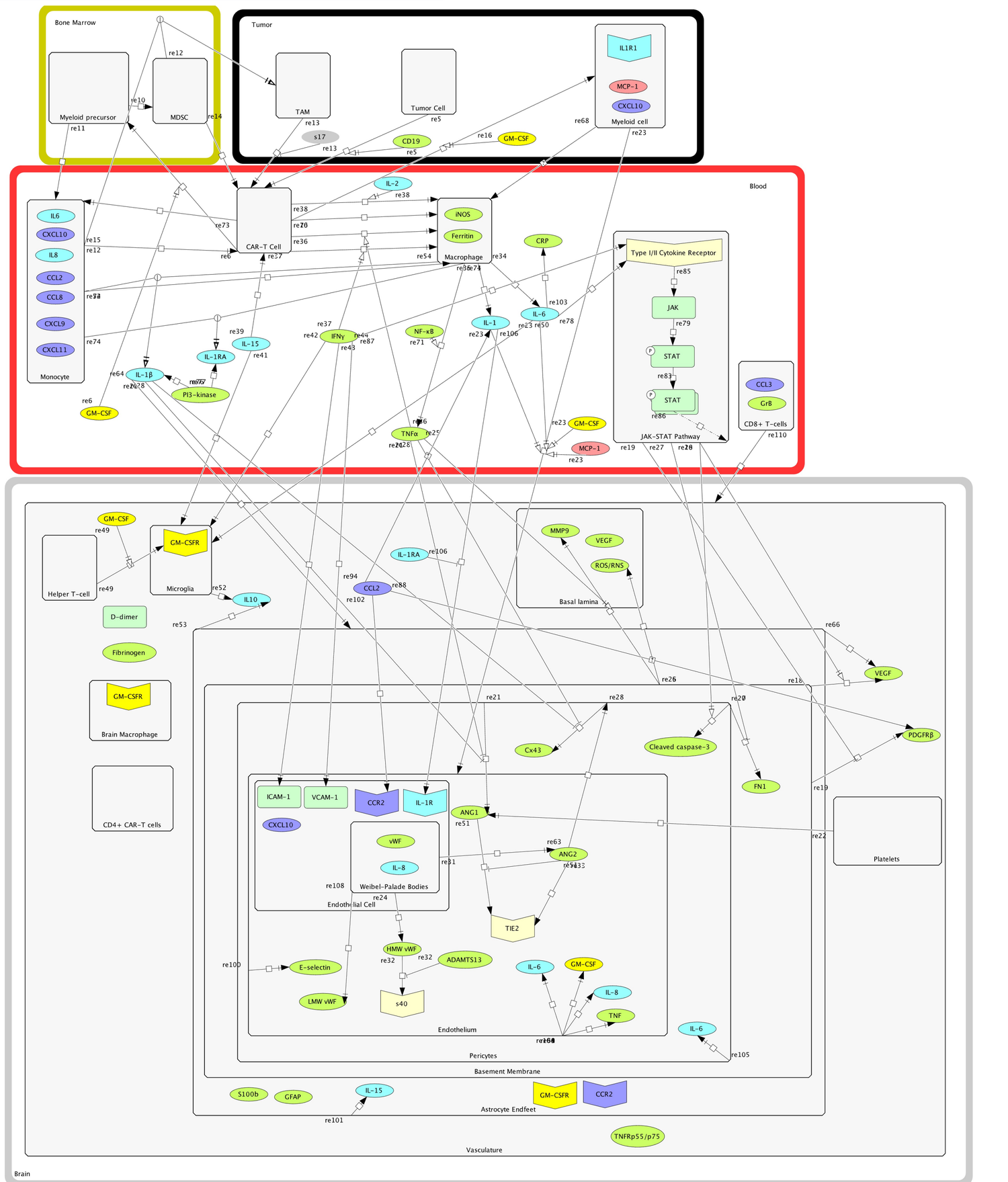

Figure 1: ICANS Concept Map

CAR-T Proximal:
MAP2K1, PIK3CG, trIL1A, NFKB1_p50*, IL1RN, p110-beta-gamma*, IFNG, IL1RAP, MEK*, IL1B, CSF2, IL8, NFKB1, MAP2K2, trIL1B, CXCL8, TNF-_alpha_*, TNF, PI3KC1-catalytic*, NFKB1_p105*, IL-6*, CXCL12, IL8*, MERTK, IRAP, p110*, IL6, IL1A

Symptom Proximal:
MCP1*, IL-6*, VEGFC, IL8*, CXCL8, VEGFA, PGF, VEGF*, CCR2, CCL2, VEGFD, IL6, ANGPT1, IL8, IL10, VEGFB

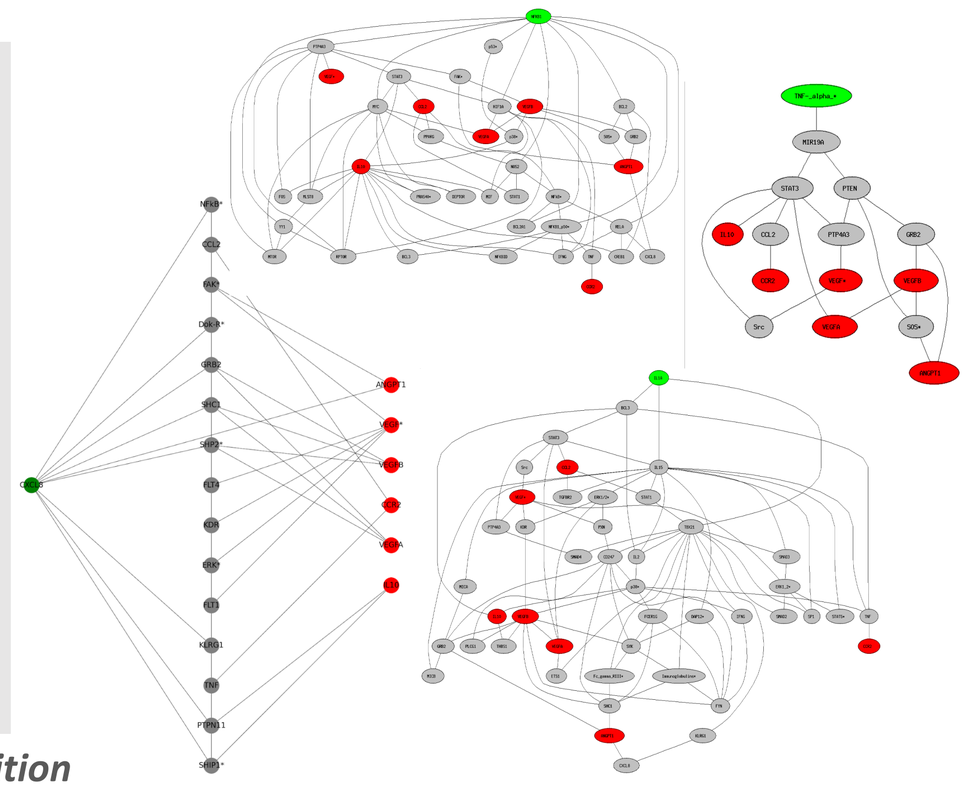

Figure 2: Network Decomposition

Methods

- Used original, fully referenced concept map to inform a list of input and output molecules for a multilayer model
- Traced the path from one molecule to another through the layers to determine potential pathways in the pathogenesis of ICANS
- Multilayer model was created using the Navicell Molecular Mapping Database and NetworkX software for complex networks [2,3].
- A large molecular network was obtained from the Navicell project which describes the hallmarks of cancer, curated based on literature review, and has multi-scale organization. Navicell Network: Nodes 2,774; Edges 14090; Layers 13
- Genes were labelled based on proximity to CAR-T treatment GREEN or possible symptom endpoints RED using expert curation
- The network is decomposed based on shortest path analysis via molecular networks and the labelled actors
- We are using the resulting graph components as attractors in knowledge graph mining to associate with possible causes of ICANS.
- Goal of Project: Relate symptoms to possible modes of action. e.g. simultaneous recruitment of inflammatory response and increase in vascular permeability

Relevance

ICANS presentation varies, but typically includes some combination of headaches, confusion, tremors, and delirium. More severe and potentially lethal symptoms include seizures, increased intracranial pressure, and cerebral edema [6]

Conclusions

- Biomedical literature analysis is a required component for the creation of knowledge graphs to establish probabilistic associations between molecules and symptoms
- Given the current understanding of ICANS, entity recognition and semantic tagging are potentially valuable in relating clusters of symptoms to biomolecular markers; enabling counterfactual elimination of possible mechanisms for symptom presentation.

References

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