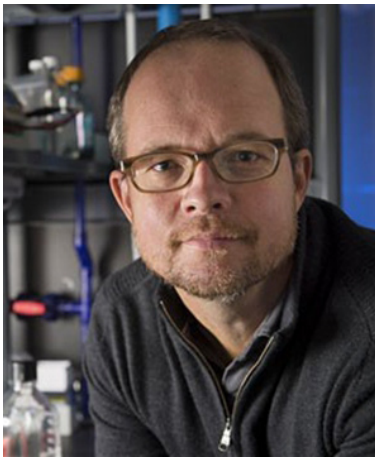
CARNEGIE MELLON UNIVERSITY
BME 2021 SPRING SEMINAR SERIES

Systems Immunology in Low-sample Regimes: Modeling and Guiding Cancer Immunotherapies with Machine Learning



PRESENTED BY

Newell Washburn
William J. Link Chair and Professor
Department of Biomedical Engineering
Department of Chemistry
Carnegie Mellon University

SCHEDULE

Thursday, April 1
(10:45-11:45AM)

Clinical outcomes are correlated with B and T cell receptor diversity (the adaptome) in a range of infectious diseases and cancers. Advances in massively multiplexed PCR followed by next-generation sequencing have enabled highly accurate measurements of immune repertoire diversity and clonality. The current approach to evaluate such datasets includes collapsing/consolidating/minimizing a space of 1015-1025 possible sequences into a low-dimensional space of a limited number of descriptors of sequence diversity and entropy, which models specific information on amino acid usage. Here I will discuss approaches to modeling millions of sequences acquired on the B-cell IgH, Igκ, and Igλ receptors and T-cell Vα, Vβ, Vγ, Vδ receptors based on clinical data. In a pilot trial, 29 patients with metastatic clear cell renal carcinomas (RCC) treated with high dose interleukin-2 (IL-2) and the autophagy inhibitor, hydroxychloroquine had their adaptomes measured by dimer avoidance multiplex PCR. In the original study, responses were monitored and outcomes assessed by retrospectively assigning to four states (progressive disease, stable disease, partial or complete response) one year following initiation of treatment based on changes in tumor size. Here, Markov chains based on calculation of conditional probabilities of amino acid dimer prevalence in whole receptor sequences were calculated for three purposes:

(1) intermediate-dimensionality representations of CDR3 repertoires as compact 20x20 transition probability matrices of amino acid usage that capture dimer-specific information from the adaptome;
(2) predictive classification of final patient clinical outcome following first dose of IL-2 treatment that correctly assigned >90% of patients as either responsive or non-responsive based on their repertoires after only two weeks of treatment;
(3) quantitatively monitoring changes in patient state from the initial progressive-disease condition with shifts in T-cell or B-cell chains following treatment to provide mechanistic insight into coordination in the adaptive immune system.

These results suggest that complex immunological responses can be modeled through analysis of multiple receptors, and Markov chain models can be a powerful tool to enable robust serial assessment of adaptive immunity, enhancing precision medicine. I will also discuss local collaborations with UPMC and the cancer therapeutics startup Nurix.

BIOMEDICAL ENGINEERING
Carnegie Mellon University