Systems Immunology - From Cells, to Mice, to Humans

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Understanding the operation of complex biological systems at the basic level and applying such understanding to promoting human health by preventing or treating disease (including drug discovery efforts) requires moving beyond the limited data gathering and information integration of conventional laboratory research efforts. Recent experimental and computational advances now permit high density, multiplex interrogation of cell, tissue, and organism states followed by thorough analysis of the resulting large and complex datasets using statistical and quantitative modeling tools. This presentation will review our integrated approach to data gathering and computational analysis of immune function and host-pathogen interaction. It will emphasize our team-based efforts that have led to the development of novel computational tools for multiscale modeling and the integration of this modeling effort with technologies for network node discovery, parameter determination, and molecular identification and quantification in support of fine-grained modeling. It will also discuss our use of a lethal mouse influenza infection system as a paradigmatic model for multiplex data collection and informatic analysis at a coarse-grained level. Association of fine-grained models of individual subnetworks with each other to produce larger scale models and the importance of connecting these higher order, but fine-grained models with coarser-grained statistical models that relate phenotype with genotype and control of gene expression will be highlighted. Finally, these more basic efforts will be put in the context of the use of parallel, high-density, multiparameter data gathering for the more complete definition of the state of the normal human immune system (the 'immunome') and the use of perturbation analysis, especially by timed interventions such as vaccination, for inferring how the human immune system operates in health and disease. How these various systems approaches can be used to enhance identification of potential drug targets, optimize lead candidates, and stratify subjects for trials will be noted.

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