Technical summary

Until recently, vaccine development has involved little immunology due to limited understanding of the mechanisms by which protective immunity arises, though traditional vaccine design approaches have regardless proven successful against many diseases. Yet several classes of problems in vaccinology remain unsolved today that may require interdisciplinary approaches across engineering and immunology to solve them. In this thesis, we combine theoretical approaches with protein sequence and clinical data to address two contemporary problems in vaccinology: 1. understanding how the many immune components work collectively to effect the immune response; and 2. developing an antibody vaccine against HIV, an example of a highly mutable pathogen.

The human immune system consists of many different immune cells that coordinate their actions to fight infections. The balance between these cell populations is determined by direct interactions and soluble factors such as cytokines, which serve as messengers between cells. To investigate whether differences in immune response could be explained by variation in immune composition across individuals, we analyzed experimental measurements of various immune cell population frequencies in a cohort of healthy humans. We demonstrated that human immune variation in these parameters is continuous rather than discrete. Furthermore, we showed that key combinations of these immune parameters can be used to predict immune response to diverse stimulations, namely cytokine stimulation and vaccination. This result highlights a previously unappreciated connection between immune cell composition and systemic immune responses, and can guide future development of therapies that aim to collectively, rather than independently, manipulate immune cell frequencies.

In HIV-infected individuals, antibodies produced by the immune system bind to specific parts of an HIV protein called Envelope (Env). However, the virus evades the immune response due to its high mutability, thus making effective vaccine design a huge challenge. To predict the mutational vulnerabilities of the virus, we developed a model (a fitness landscape) to translate sequence data into viral fitness, a measure of the ability of the virus to replicate and thrive. The landscape accounts explicitly for coupling interactions between mutations at different positions within the protein, which often dictate how the virus evades the immune response. We developed new computational approaches that enabled us to tackle the large size and mutational variability of Env, since previous approaches have been unsuccessful.

A small fraction of HIV-infected individuals produce a class of antibodies called broadly neutralizing antibodies (bnAbs), which neutralize a diverse number of HIV strains and can thus tolerate many mutations in Env. To investigate the mechanisms underlying breadth of these bnAbs, we combined our landscape with 3D protein structures to gain insight into the spatial distribution of binding interactions between bnAbs and Env. In conjunction with a previously published vaccination strategy, we designed an optimal set of immunogens (i.e. Env sequences), with mutations at key residues, that are most likely to lead to the elicitation of bnAbs via vaccination.

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