“Stealth” asparaginases as improved protein drugs
for the treatment of childhood acute lymphoblastic leukemia (ALL)

Lymphoblastic (also called lymphocytic) leukemia is a cancer of the blood and bone marrow that leads to an overproduction of white blood cells. Its acute form, ALL, is the most common malignancy in children, accounting for about one-quarter of all childhood cancers and about three-quarters of childhood leukemia cases. If left untreated, the disease is fatal within months, with death typically resulting from the patient's inability to fight off infection. Fortunately, advances over the decades have dramatically improved the prognosis for ALL patients: pediatric ALL is now curable in > 90% of cases. For adult patients, the prognosis is worse, but still about half of all patients survive for five years or more.

Bacterial asparaginases are therapeutic proteins for the treatment of childhood ALL. They work by depleting the blood of the amino acid asparagine, thereby starving the tumor. The therapy is tumor selective because genetic and epigenetic factors make the leukemic clone less able than healthy cells to compensate for the reduced supply of asparagine from the bloodstream by upregulating cellular asparagine synthetase. Unfortunately, complete starvation of the tumor clone requires prolonged asparaginase treatment (typically 30 weeks, with biweekly asparaginase injections). This repeated exposure to a non-human protein tends to induce unwanted immune responses in about half of all patients. In 30% of treated patients, the immune system has overt adverse effects. In another 20% of treated patients, there are no overt effects, but there is a sufficient immune response to render the asparaginase treatment ineffective.

Recent advances in immunology should make it possible to predict a patient's immune response if genetic information about their personal immune arsenal (the HLA haplotype) is available. In this project, we will test this in a (humanized) mouse model of asparaginase treatment. Given a mouse's haplotype, we will identify minimally and (as a negative control) maximally immunogenic asparaginases for the mouse strain. Next, we will attempt to use recent advances in machine learning to design asparaginases that are (predicted to be) less visible to the immune system of a given mouse or patient than the naturally occurring enzymes. Specifically, we will use tools conceptually similar to ChatGPT for natural language modeling and DALL-E2 for image generation to design "optimal" asparaginases for a given patient/mouse.

If successful, this would be a proof of principle for another case of patient-specific precision medicine. Ideally, one would like to have asparaginases that are minimally visible not only to the immune system of a given patient, but to the immune systems of many different patients, so that the needs of the population could be addressed with a finite and hopefully small number of different enzymes. Evading the human pan-immune system is probably unrealistic (otherwise viruses would have done that long ago), but it may be possible to make asparaginases that could be used in groups of patients. In this project, we will use modern computational techniques to explore the possibility.