Project 9.2 Design of "stealth" asparaginases for the treatment of acute lympoblastic leukemia (ALL)

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www: https://shorturl.at/3inoD

Background:

Due to genetic linkage, acute lymphoblastic leukemia (ALL) cells make little asparagine synthetase. Therefore, the malignant cells, but not their somatic surroundings, are dependent on a supply of asparagine from the bloodstream. Therefore, the depletion of asparagine from serum by highly active bacterial asparaginases is a standard treatment for ALL. However, the clinically used asparaginases are from a non-human source. Therefore, they are recognized as "foreign" by the immune system of the patients. Nearly a quarter of the treated children develop an overt immune response against the drug that necessitates termination of treatment. Another quarter experience a silent immune response that renders the drug inactive. We suspect that immune haplotypes determine whether or not an immune response occurs, and therefore want to explore the design of asparaginases that are "stealth" for the immune system of a given patient or a model mouse of known immune haplotype.

Aim:

In the project, inverse folding tools based on Large Language Models (LLMs) or Denoising Diffusion Probabilistic Models (DDPMs) will be combined with immune prediction tools (MHCIIpan) to design asparaginases that are expected to be less immunogenic for a given haplotype than the clinically used wild-type protein. The asparaginases will be expressed in E. coli cells, engineered to select for high asparaginase activity. To select asparaginases in high-throughput manner, input and selected plasmid pools will be sequenced to identify the most enriched, and therefore presumably most active variants among the designed proteins. Finally, we plan to compare the predicted and actual immunogenicity of designed asparaginase variants in a mouse model of asparaginase treatment, using standard immunological readouts to experimentally quantify the extent of the induced immune response.

Requirements:

- Master's degree in biochemistry or related field,
- solid knowledge in at least one of the following disciplines: molecular biology, biochemistry, immunology, or animal (mouse) models,
- hands on experience in at least one of these areas,
- proficiency with LINUX and prior experience in machine learning welcome but not required,
- written and spoken fluency in English,
- willingness to learn and take new challenges, ability to work independently, analytical thinking,
- good interpersonal skills and a collaborative attitude.

Number of positions available: 1

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