

EXECUTIVE SUMMARY [NON-TECHNICAL ABSTRACT FOR PUBLIC INFORMATION OR PROGRAM PROMOTION]:

State **in layman's terms** the application's broad, long-term objectives and specific aims, making reference to the potential public benefits of the project relevant to California. Kynureninase is an enzyme involved in metabolism of the amino acid tryptophan. It acts upon the intermediate metabolite kynurenine, converting it to anthranilic acid. Kynurenine, which builds up in certain medical conditions such as Alzheimer's disease and AIDS-related dementia, has neurotoxic effects, as does its downstream product, quinolinic acid. The long-term goal of this research is to identify suitable inhibitors of kynureninase in order to prevent these neurotoxic effects. Currently, there is no published structural information indicating the manner in which kynurenine or potential inhibitors bind in the active site, which is critical for improvement of inhibitors for clinical applications. We have paved the way for these experiments by determining the crystal structures of both human and yeast kynureninase. We have also obtained high-resolution diffraction data with the less potent inhibitor D-kynurenine bound in the active site of yeast kynureninase. The goal of this proposal is to understand how two more potent inhibitors bind to the active site of yeast and human kynureninase by obtaining diffraction data for both enzymes with each of the inhibitors bound. The two inhibitors, 3-hydroxydesaminekynurenine, and S-(2-aminophenyl)-L-cysteine-S,S-dioxide, were chosen because of their ability to probe certain predicted features of the enzyme-substrate binding and because they each bind to kynureninase with very high affinity, making them good pharmaceutical targets.