

## OFFICIAL ABSTRACT and CERTIFICATION

### The Complete Structural Refinement and Analysis of the Protein Anaplasma phagocytophilum tRNA (guanine-N1)-methyltransferase

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Anaplasma phagocytophilum is the causative agent of Anaplasmosis, a septicemic vector-borne disease transmitted primarily by northeastern deer ticks. Infection results in nausea, general malaise, acute febrile illness, and even granulocytopenia. Hospitalization is not uncommon and the severity can be debilitating. Anaplasmosis is treated with the powerful broad-spectrum antibiotic doxycycline. However, when considering the ever-increasing incidence of widespread resistance to antibiotics, it is possible a superbug of Anaplasma could emerge. In this study, x-ray diffraction data from crystalized proteins of TrmD tRNA (guanine-N1)-methyltransferase previously isolated from the bacterium Anaplasma phagocytophilum were analyzed to provide insight into future antibiotic designs. Using previously gathered x-ray diffraction data from a synchrotron light source, an electron density map was computerized in order to create a novel model of the enzyme. The creation and refinement of the model were carried out with a variety of accredited computer programs such as PhaserMR, Refmac5, and Coot. The constructed model accurately includes an unfragmented amino acid sequence of the enzyme, which has not been seen in an unliganded Anaplasma TrmD until now. Using automated processing programs and manual structural refinement, elusive regions of the enzyme are accurately and completely modeled, allowing for striking novel observations. The model provided insight into the substrate-mediated changes in the catalytic domain, the consequent changes in the conformation of the elusive 'linker region' and 'halo region' of the enzyme, and observations that suggest possible pathways of competitive and allosteric inhibition. The complete model was published for review in the Worldwide Protein Data Bank.

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