Iron-sulfur enzymes as candidates for antibiotic development

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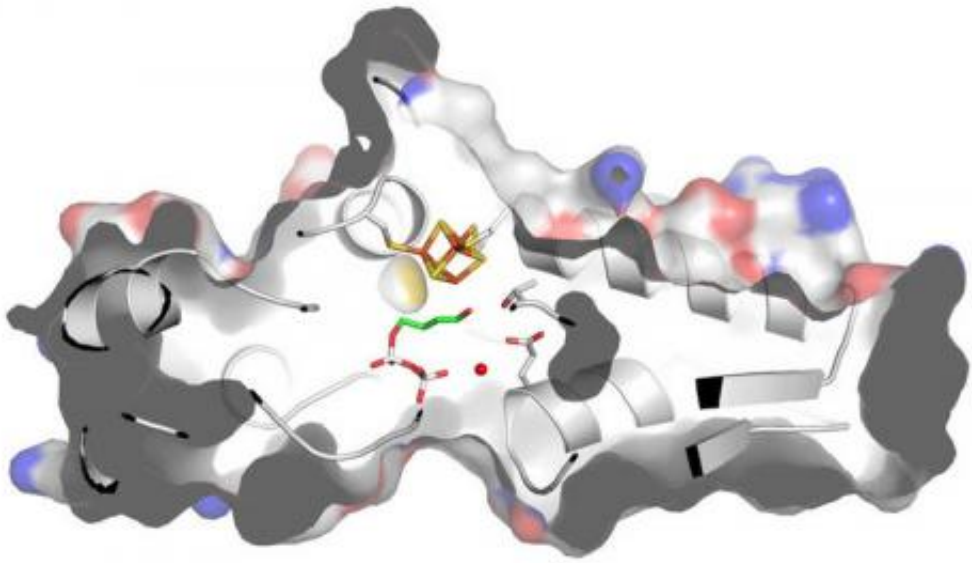
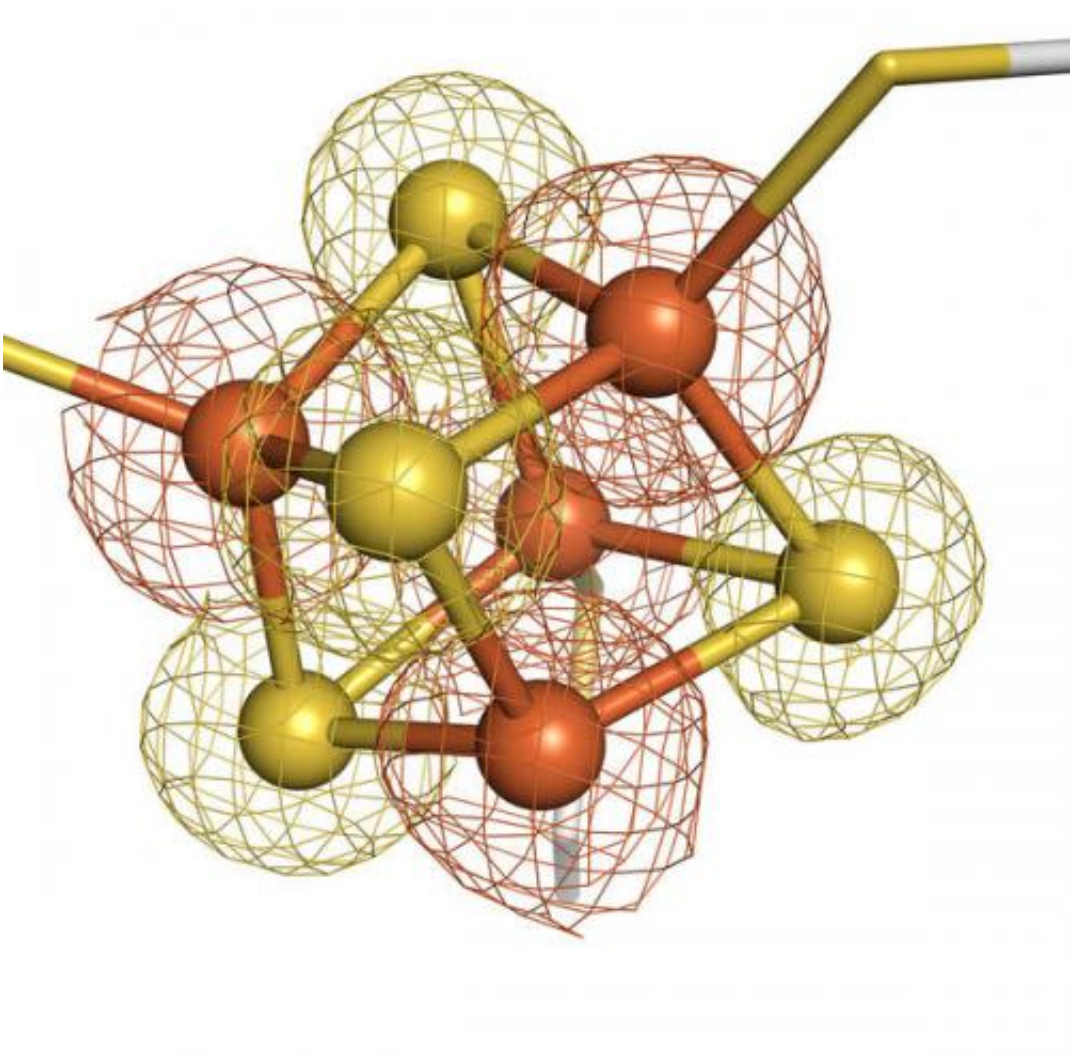


This is a close-up view of the active site of IspH in which one of the reactants is bound. Credit: TUM

The iron-sulfur protein IspH plays a central role in the terpene metabolism of several pathogens. The mechanism of the reaction provides an approach for developing new antibiotics, particularly against malaria and tuberculosis. While researching this enzyme, biochemists at the Technische Universitat Munchen discovered a previously unknown reaction: IspH accepts two completely different classes of molecules as partners. This surprising insight, published in *Nature Communications*,

opens up new perspectives in combating infectious diseases.

Terpenes constitute one of the largest and most versatile classes of natural compounds – familiar examples are cholesterol and estrogen. In all organisms the biosynthesis of terpenes starts from the two building blocks isopentenyl-diphosphate (IPP) and dimethylallyl diphosphate (DMAPP); however, mammals and bacteria use different biosynthetic pathways to do this. In bacteria and pathogenic microorganisms the enzyme IspH catalyzes the last step in the production of IPP and DMAPP. Thus for several years scientists have recognized the potential of IspH as a point of attack in developing drugs against malaria and tuberculosis.



Iron-sulfur cluster of IspH. Credit: TUM

Now Prof. Michael Groll and Dr. Ingrid Span at the TUM Chair of Biochemistry have made a significant breakthrough in this area. They have been working with Prof. Eric Oldfield and his group at the University of Illinois to characterize certain acetylene compounds that inhibit the IspH enzyme. With the aid of X-ray crystallography, they discovered that the enzyme not only binds several of these molecules to its active site but also modifies them: Through the additionof water to the acetylene groups (hydrocarbons with triple bonds), the compounds

are converted to aldehydes or ketones. "In general enzymes react with only one specific substrate," explains Ingrid Span. "So we were surprised to find that IspH, in contrast, accepts two completely different classes of molecules."

IspH owes its flexibility to the structure and location of its active site. The enzyme is composed of three structural units that harbor a cubic iron-sulfur cluster at their center. This unusual structure enables the enzyme to accomplish a challenging reaction: converting an allyl alcohol to a mixture of the two isoprene components. While iron-sulfur proteins normally act as electron transmitters (), the IspH enzyme binds the substrate directly to the iron-sulfur cluster.

Apart from acetylene hydratase and nitrogenase, IspH is just the third enzyme known to convert acetylene compounds. In addition, until now there were no known iron-containing catalysts that could carry out this reaction. Thus the newly discovered property of IspH could enable the development of new active pharmaceutical ingredients, particularly for the battle against malaria and tuberculosis.

This work was carried out in the bioinorganic department of the Chair of Biochemistry. Bioinorganic chemistry is concerned with elucidating the function of classical "inorganic" elements, especially metals, in biological processes and in nature. Here, metalloproteins (proteins with one or more metal ions or clusters) play a particularly important role as they combine the advantages of proteins (acid/alkaline catalysis, proximity of reaction partners, enclosed reaction space) with the versatile catalytic properties of metals. "The aim of our research is to understand enzymatic reactions and to produce new catalysts, to establish the foundation for applications in the chemical and pharmaceutical industries," explains Michael Groll.

More information: Span I., Wang K., Wang W., Zhang Y., Bacher A.,

Eisenreich W., Li K., Schulz C., Oldfield E. and Groll M. (2012). Discovery of an Acetylene Hydratase Activity of the Iron-Sulfur Protein IspH. *Nat Commun.*, 3 (1042), 1-8.