SCIENCES & BIOENGINEERING SCIENCES

The Research Groups

General Chemistry (ALGC) and Structural Biology Brussels (SBB)

have the honor to invite you to the public defense of the PhD thesis of

Laura van Bergen

to obtain the degree of Doctor of Sciences

Title of the PhD thesis:

Insights into the architectural design of the active site of AhpE peroxiredoxin through an experimental and computational approach

Promotors:
Prof. Dr. Frank De Proft (ALGC)
Prof. Dr. Joris Messens (SBB)
Prof. Dr. Mercedes Alonso (ALGC)

The defence will take place on

Friday, February 3, 2017 at 17:00h

in Auditorium D.2.01 at the Campus Humanities, Sciences and Engineering of the Vrije Universiteit Brussel, Pleinlaan 2 - 1050 Elsene, and will be followed by a reception.

Members of the jury:

Prof. Dr. Steven Ballet (chairman)
Prof. Dr. Dominique Maes (secretary)
Prof. Dr. Gustavo J. Gutierrez
Dr. Julia Contreras-Garcia (CNRS and Univ. Pierre et Marie Curie, Paris, France)
Prof. Dr. Lennart Nilsson (Karolinska Inst., Huddinge, Sweden)

Curriculum vitae

2012 - 2016: PhD research at the Free University Brussels.

2009 - 2012: Master of Science studies in Drug Discovery and Safety (Farmacochemie), VU, Amsterdam, Nederland.

2006 - 2009: Bachelor of Science in Pharmaceutical Science (Farmaceutische wetenschappen), VU, Amsterdam, Nederland.

Abstract of the PhD research

The overall aim of this PhD-work is to understand the design of the active site architecture of alkyl hydroperoxide reductase E (AhpE) from *Mycobacterium tuberculosis*, the pathogen that causes tuberculosis. AhpE belongs to the peroxiredoxin enzyme family. Proteins from this family reduce peroxides to alcohols. Via this reduction reaction AhpE protects *M. tuberculosis* against the peroxides released by the human immune system. In most peroxiredoxins, the sulfenic acid cysteine forms a disulfide with another cysteine, the resolving cysteine. However, AhpE has only one cysteine, the peroxidatic cysteine. The lack of a resolving cysteine makes AhpE an ideal enzyme for studying the oxidation step of the thiolate within the peroxiredoxin family.
In this thesis the peroxide used to study the reaction is hydrogen peroxide (H_2O_2). We combined kinetics and structure analysis with computational techniques to investigate this reaction. One of questions that we addressed is how the environment influences the reduction reaction. With quantumchemical calculations of the reaction as a small model system in the presence of various environmental ligands, we found that the environmental chemical groups lower the activation barriers of the reaction with 10 to 30 kcal mol^{-1}. With MD simulations on active site mutants of AhpE, structural changes were correlated to changes in hydrogen bonding network and reaction rates. Our results showed that the conserved residues play a pivotal role in excluding water molecules from the active site of AhpE.
Secondly, we evaluated the current established methods for hydrogen bond detection in proteins. Three established methods that use geometrical criteria were compared with the NCI index method, which uses the electron density and the reduced density gradient. This comparison led to the proposal of an improved equation for detecting H-bonds in proteins using geometrical criteria.
Finally, we looked at the structure of the oxidized AhpE. We found that the architecture of the active site is designed to avoid further oxidation of the sulfenic acid. Most likely, it is a state that can quickly relax to allow disulfide formation with either of the reducing agents mycothiol or mycoredoxin-1.