SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Structural Biology Brussels

has the honor to invite you to the public defence of the PhD thesis of

Tzu Keng Shen

to obtain the degree of Doctor of Bioengineering Sciences

Joint PhD with Université libre de Bruxelles

Title of the PhD thesis:
The H_2S-persulfidation axis as a critical regulator of redox homeostasis in chronic metabolic liver disease

Supervisors:
Prof. dr. Joris Messens (VUB)
Prof. dr. Esteban Gurzov (ULB)
Co-supervisor:
Prof. dr. Daria Ezerina (VUB)

The defence will take place on:

Friday, June 19, 2026 at
2 p.m. in Promotiezaal D.2.01

The defence can be followed through a live stream: https://teams.microsoft.com/meet/322315970626191?p=woAgBXptfMDE5e3BW8

Members of the jury

Prof. dr. Remy Loris (VUB, chair)
Dr. Inès Dufait (VUB)
Prof. dr. Bruno André (ULB)
Prof. dr. Hennie Valkenier (ULB)
Prof. dr. Rachel Deplus (ULB)
Prof. dr. Marc Fransen (KU Leuven)
Prof. dr. Hozumi Motohashi (Tohoku University, JP)

Curriculum vitae

Tzu Keng Shen obtained his master degree at Heidelberg University. After, he relocated to Brussels, Belgium to continue his research in redox biology supervised by Joris Meseesns in VUB/VIB and Esteban Gurzob in ULB. He's awarded the FNRS-ASP grant to support his research. With a strong foundation in biochemistry and molecular biology, he investigates the molecular mechanisms underlying oxidative stress and protein persulfidation, aiming to uncover potential therapeutic targets for metabolic diseases.

Abstract of the PhD research

Metabolic dysfunction–associated steatotic liver disease (MASLD) is a prevalent and progressive chronic liver disorder characterized by metabolic dysregulation, inflammation, and oxidative stress. Although disturbances in redox balance are central to MASLD pathogenesis, the contribution of sulfur-based signaling pathways, which constitute the core cellular redox-regulatory mechanism, remains poorly understood. Cysteine persulfidation (PSSH), a reversible post-translational modification mediated by hydrogen sulfide (H_2S), has recently emerged as an important regulator of protein function and cellular redox homeostasis. However, how this modification is regulated during MASLD development and progression remains largely unknown.

In this thesis, I characterize the hepatic H_2S–persulfidation axis across the MASLD spectrum. By integrating proteomics, persulfidomics, and biochemical approaches, I demonstrate that MASLD is associated with a pronounced reduction in hepatic H_2S production capacity and global PSSH levels, accompanied by a selective remodeling of the hepatic persulfidome. These findings indicate that PSSH is not merely a passive by-product of oxidative stress but rather a dynamically regulated redox modification.

To investigate the functional contribution of endogenous H_2S production, I studied liver-specific cystathionine β-synthase (CBS) KO mice in a dietary model that recapitulates human MASLD. Despite substantial loss of CBS, global hepatic PSSH remained preserved, while a selective, protein-specific reprogramming of the persulfidome was observed. This suggests the presence of compensatory sulfur metabolic pathways and reveals a previously underappreciated layer of redox adaptation.

Furthermore, non-targeted pharmacological supplementation with the slow-releasing H_2S donor GYY4137 failed to improve metabolic or hepatic outcomes in a diet rich in fat, fructose, and cholesterol, highlighting the context-dependent and limited efficacy of non-targeted H_2S donor strategies. Finally, this work validates PersIc, a genetically encoded fluorescent biosensor, for real-time monitoring of intracellular persulfide dynamics in hepatocytes.

Collectively, this work establishes the H_2S–persulfidation axis as a critical regulator of redox homeostasis in chronic metabolic liver disease.