



DEPARTMENT
OF PHARMACEUTICAL SCIENCES

Seminars on Drug Sciences (SDS)

Lecture of

Dr. Claudia Jessen-Trefzer

Faculty of Chemistry and Pharmacy, University of
Freiburg, Freiburg i. Br., Germany

Intra- and Extracellular Prodrug Activation with the Help of Protein Capsids

Encapsulins (Enc) are virus-like particles and conserved prokaryotic compartments. They self-assemble inside the cell from protein monomers and present a highly attractive platform for intracellular compartmentalization of chemical reactions by design. The smallest representatives of Encs assemble into 60-subunit icosahedral nanocompartments (~240 Å) and are therefore the smallest example of bacterial compartments identified to date. Enc nanocompartments usually have a 5-, 3-, or 2-fold symmetry, where at each point of symmetry uncharged, positively charged, and negatively charged pores are formed, respectively. Interestingly, coexpressed genes are targeted to the interior of Enc, via a conserved c-terminal sequence. We have previously isolated the Enc orthologue from *Mycobacterium smegmatis* and successfully installed non-natural guest proteins inside Enc. Additionally, we investigate the covalent targeting of small molecules inside Enc, by coexpressing HaloTag and a monomeric rizavidin variant. By equipping these guest-proteins with two synthetic organometallic catalysts, encapsulin serves as a host for a linear, sequential two-step reaction cascade. A ruthenium catalyzed alloc deprotection is followed by a gold-catalyzed, ring-closing hydroamination reaction leading to indoles and phenanthridines with up to 67 % overall yield in biological media. We are able to perform this reaction cascade inside a proteinaceous capsid opening up exciting possibilities in the field of designing artificial organelles with compartmentalized reaction pathways or pro-drug activation purposes.

References

- [1] Lohner P, Zmyslia M, Thurn J, Pape JK, Gerasimaitė R, Keller-Findeisen J, Groer S, Deuringer B, Süss R, Walther A, Lukinavičius G, Hell SW, Hugel T, Jessen-Trefzer C, Inside a shell - Organo-metallic catalysis inside encapsulin nano-reactors, *Angew.Chem.Int.Ed.* 2021, 60, 23835–23841.
- [2] Ebensperger P, Jessen-Trefzer C, Artificial Metalloenzymes in a Nutshell: The Quartet for Efficient Catalysis, *Biological Chemistry*, 2022, 403, 4, 2022, 403-412.
- [3] Ebensperger P, Zmyslia M, Lohner P, Braunreuther J, Deuringer B, Becherer A, Süss R, Fischer A, Jessen-Trefzer C, A dualmetal catalyzed sequential cascade reaction in an engineered protein cage, *Angew. Chem.Int. Ed.* 2023, 62, e202218413.

Wednesday, May 29, 2024

17:15 - 18:15

Lecture Hall 1, Pharmacenter, Klingelbergstrasse, 50, Basel

Host: Prof. R. Teufel

Pharmaceutical Biology



University
of Basel