New tricks for an old system – Bacterial system enables site-specific ubiquitylation of proteins in living cells

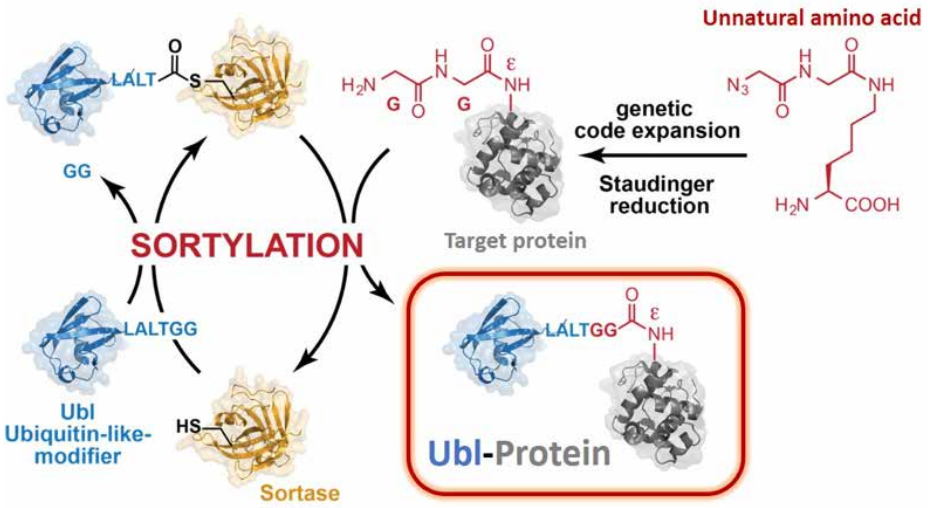
Reference No: B78098

CHALLENGE

The covalent attachment of **ubiquitin (Ub)** to target proteins represents one of the most versatile and common **post-translational modifications** in eukaryotic cells. Ubiquitylation plays a crucial role in many fundamental cellular processes ranging from **protein degradation, DNA repair, nuclear transport, endocytosis to chromosomal organization.** Importantly, many diseases including **different types of cancer and neurodegenerative diseases** such as Parkinson's link to dysfunctions in ubiquitylation. However, how these essential modifications influence biological processes is not fully understood. The process of ubiquitylation is catalyzed by a complex and specialized cascade involving **E1/E2/E3 ligases**. Similarly, target proteins can also be covalently modified by **ubiquitin-like-proteins (Ubls)** such as **SUMO.** As a major obstacle for a detailed *in-vitro* analysis of ubiquitylation, chemical generation of Ub- and Ubl-conjugates has proven to be difficult and are **often limited** to easy and refoldable target proteins.

INNOVATION

We present a new method allowing for the **site-specific ubiquitylation and SUMOylation of target proteins** - both *in vitro* and *in cellulo**. By genetic code expansion, a modified amino acid is incorporated into the target protein serving as the platform for a *bacterial enzyme*, named "sortase". In a **transpeptidation** step, the enzyme attaches an ubiquitin or ubiquitin-like molecule to the target protein thereby generating **cleavage-resistant** and **ligase-independent Ubs and Ubls.**



The process of **"sortylation"** provides a powerful tool to modify non-refoldable and multidomain proteins whilst retaining their physiological integrity and biological function. This allows for a detailed analysis of ubiquitin marks in cellular processes as well as potential involvement in different human diseases.

COMMERCIAL OPPORTUNITIES

- **Inducible** attachment of ubiquin-modifiers to complex proteins independent of ligase-system
- Potential to **site-specifically** conjugate **other polypeptide** to proteins of interest
- Synthesized proteins allow for **quantitative characterization of cellular interactions**

DEVELOPMENT STATUS

Proof of concept *in vitro* and *in cellulo.*

REFERENCES:

*Nat Chem Biol. 2019 Mar;15(3):276-284. doi: 10.1038/s41589-019-0227-4. Epub 2019 Feb 15

BayPAT

Technische Universität München

Technology from TECHNISCHE UNIVERSITÄT MÜNCHEN

IP rights:
PCT filed 2019

Contact:
Dr. M. Charlotte Hemmer
+49 (0) 89 5480177 - 29
chemmer@baypat.de

Bayerische Patentallianz GmbH
Prinzregentenstr. 52
80538 München
www.baypat.de