LS21-015 - Chemical Reprogramming of Autophagy Receptors

Zusammenfassung

Neurodegeneration, muscle disorders and other devastating human diseases are driven by the accumulation of aberrant intracellular substructures such as dysfunctional organelles or protein aggregates (1). In non-pathological settings, cells are able to eliminate such assemblies via the multi-faceted process of autophagy, yet fail to do so in disease. In this proposal, we want to develop a chemical strategy to instruct key autophagy effectors, so-called autophagy receptors (ARs), to recognize and eliminate disease-causing cargo in a targeted and mechanistically understood manner. To that goal, we will combine cellular and biochemical assays with unbiased proteomics to find and optimize covalent ligands for selected ARs. We will then incorporate these AR binders into heterobifunctional compounds that recruit selected ARs to disease-causing cargo, thus licensing its autophagic clearance. If successful, this proposal will generate proof of concept for the first AR-driven, all-chemical, rational solution to prompt autophagic clearance of pathogenic cargo in a targeted manner. It will thus not only provide innovative tools for basic research, but also motivate further translational investigation aimed to find treatment options for unmet medical needs. This ambitious goal is made feasible by the highly complementary know-how of the two applicants, which provide world-leading expertise in targeted protein degradation, chemical biology and selective autophagy.

Wissenschaftliche Disziplinen:
Medical chemistry (20%) | Cell biology (40%) | Chemical biology (40%)

Keywords:
Autophagy, targeted protein degradation, autophagy receptors, proteomics, heterobifunctionals

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Principal Investigator:	Georg Winter
Institution:	CeMM - Research Center for Molecular Medicine of the Austrian Academy of Sciences
Co-Principal Investigator(s):	Sascha Martens (University of Vienna, Max Perutz Labs)

Status: Laufend (01.11.2022 - 30.10.2025)

Weiterführende Links zu den beteiligten Personen und zum Projekt finden Sie unter
https://wwtf.at/funding/programmes/ls/LS21-015/