LS21-010 - Mechanistic target elucidation by systematic stochastic tagging of antiproliferative compounds

Zusammenfassung

Key to understanding the direct targets of small molecules is their chemical derivatization to enable pull-down and crosslinking experiments. The success of these approaches depends on the careful selection of a tagging site so that the molecule of interest retains bioactivity, so far precluding unbiased studies of large compound sets. Herein, we propose to develop a universal approach for tagging molecules of interest regardless of their chemical structure. We aim to generate a set of chemical biology reagents featuring complementary radical, carbene and strong electrophilic reactivities that enable stochastic 'messy' tagging of different molecules. This technology shall be benchmarked on novel antiproliferative compounds identified in cell-based screens of the 90k CeMM compound library. First, we will profile the gene expression effects of those >1000 antiproliferative molecules to cluster them in comparison to molecules with known cytotoxic mechanisms. For 10 well-characterized drugs and 10 compounds with apparently novel antiproliferative mechanisms, including novel immunosuppressants from the FR-molecule family, we will then directly compare targeted and stochastic labeling in chemical proteomics. This project shall develop transformative technology enabling even scientists not well-versed in synthetic chemistry to rapidly derivatize small molecules of interest, at the same time identifying and validating a novel target of at least one antiproliferative compound.

Wissenschaftliche Disziplinen:
Organic chemistry (50%) | Chemical biology (50%)

Keywords:
target elucidation, chemical reactivity, stochastic tagging, chemical proteomics

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Weiterführende Links zu den beteiligten Personen und zum Projekt finden Sie unter
https://wwtf.at/funding/programmes/ls/LS21-010/