Target fishing with peptide natural products by chemogenomics

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Here, we present the anti-flaviviral and anti-malarial activities of the peptide natural product cavinafungin. Cavinafungin is a potently active compound against Zika and all four dengue virus serotypes. Unbiased, genomewide genomic profiling in human cells using a novel CRISPR/Cas9 protocol identified the endoplasmic reticulum-localized signal peptidase as the efficacy target of cavinafungin. Orthogonal profiling in *Saccharomyces cerevisiae* followed by the selection of resistant mutants pinpointed the catalytic subunit of the signal peptidase SEC11 as the evolutionary conserved target. Biochemical analysis confirmed a rapid block of signal sequence cleavage of both host and viral proteins by cavinafungin. Moreover, we prepared a small series of cavinafungin analogs by chemical synthesis and assessed their activities against single cell parasites. Cavinafungin and the related natural product WF10225A displayed potent inhibition of blood-stage *Plasmodium falciparum*. This study provides effective, peptidic natural product leads against the eukaryotic signal peptidase and thus confirms its critical role in the replication of various human pathogens.