Small molecule compound developed that can degrade the cancer promoting protein SUMO1

October 14 2021, by Bob Yirka

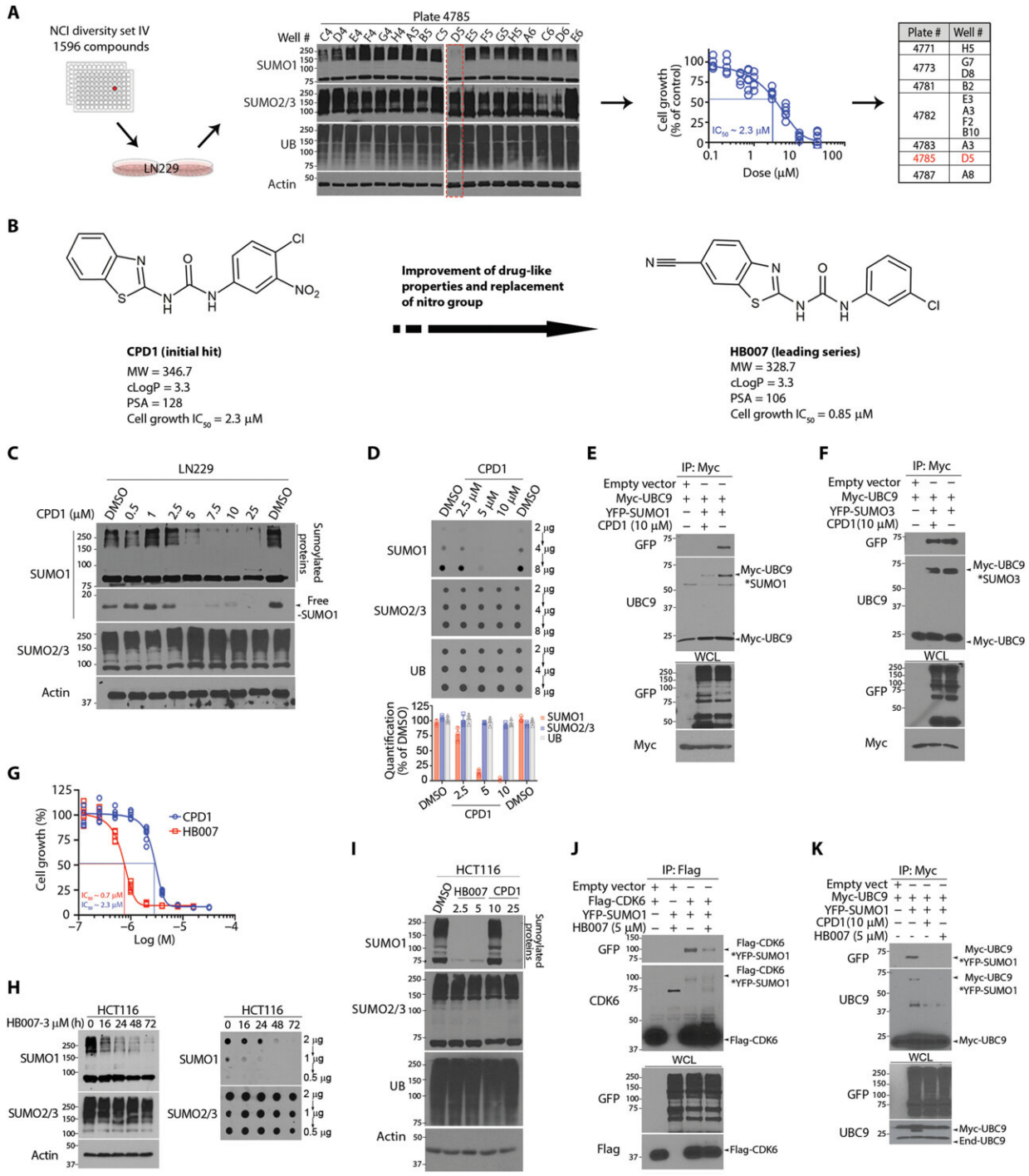

Fig. 1. Discovery of the hit compound CPD1 and chemical lead HB007.(A) Workflow in LN229 cell–based drug screening of the NCI library through Western blots and cell viability assay with the identification of 11 active compounds with D5 characterized as the hit compound (highlighted in red). (B) The chemical structures and pharmacological properties of the hit compound

CPD1 and the lead compound HB007. cLogP, partition coefficient log P; PSA, polar surface area. (C) LN229 cells were treated for 72 hours with indicated doses of CPD1 and analyzed by Western blots for conjugated and unconjugated/free SUMO1 as indicated (right). SUMO2/3 and β-actin were used, respectively, as the selectivity and the loading control. (D) LN229 cells were treated with CDP1 for 72 hours and examined by dot blots for total SUMO1 concentrations with the amounts of loading proteins indicated (right). Dot intensity was evaluated using ImageJ (bottom). (E and F) LN229 cells were cotransfected with Myc-UBC9 and YFP-SUMO1 or YFP-SUMO3 or empty vector as control and subjected to myc IP and Western blotting for UBC9-SUMO1 (E) and UBC9-SUMO3 conjugates (F) as indicated (right) with whole-cell lysate (WCL) as the loading control. (G) LN229 cells were treated with a series of dilutions of CPD1 or HB007 for 5 days and examined by cell viability for cell growth inhibition with the IC50 values indicated (points: n = 6). (H) HCT116 cells were treated with HB007 for the time indicated and analyzed by Western (left) and dot blots (right) for conjugated and total SUMO1 concentrations. (I) HCT116 cells were treated with DMSO (control), CPD1, or HB007 for 72 hours with the indicated doses (micromolar) and analyzed by Western blotting using the indicate antibodies (left). (J) LN229 cells were cotransfected with Flag-CDK6 and YFP-SUMO1, treated with HB007 for 24 hours, and subjected to Flag IP and Western blotting using CDK6 and green fluorescent protein (GFP) antibody (that recognizes YFP) for SUMO1-CDK6 conjugates as indicated (right). (K) Myc IP and Western blotting for SUMO1-UBC9 conjugates as indicated (right) in myc-UBC9– and YFP-SUMO1–transfected LN229 cells after CPD1 and HB007 treatment for 24 hours. Credit: DOI: 10.1126/scitranslmed.abh1486

A team of researchers working at the Indiana University School of Medicine, has developed a compound that can degrade the cancer-promoting protein SUMO1. In their paper published in the journal *Science Translational Medicine*, the group describes their work in attempting to find a degrader for what has been described as an undruggable cancer-related protein.

Prior research has shown that there are some proteins that change cancer proteins in ways that help it form and spread, but which are considered to be undruggable, meaning that it appears unlikely that a drug could be developed that would prevent it from doing its job. Such proteins are considered to be chemically challenging. SUMO1 is one such protein. In 2014 it was found to drive the cell cycle for certain cancers by promoting tumor growth. It does so by attaching to other cancer-forming proteins, and it was the focus of the work by the team in Indiana.

To find a drug that might degrade SUMO1, the researchers screened a drug library of data regarding 1,596 compounds related to protein degradation. They found a molecule called CPD1 that appeared to be a likely candidate for study. After learning more about its characteristics, the researchers developed a new lead compound called HB007. The researchers tested the new protein under real-world conditions. In mouse models, they found administration of the protein suppressed the development of breast, lung and colon tumors. Further testing also showed that the protein increased survival rates in mouse models compared to control groups. The findings highlight the importance of proteins like SUMO1 in promoting tumor growth, and why more research is required to find ways to counteract them.

The researchers suggest that their work could lead to new ways to fight cancer in humans—two of them have co-founded a startup with that goal in mind. They also suggest that their work could be used as a template for other scientists seeking ways of dealing with 'undruggable' protein degraders.

More information: Anita C. Bellail et al, Ubiquitination and degradation of SUMO1 by small-molecule degraders extends survival of mice with patient-derived tumors, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abh1486