Thalidomide reveals path for targeting undruggable transcription factors for cancer treatment

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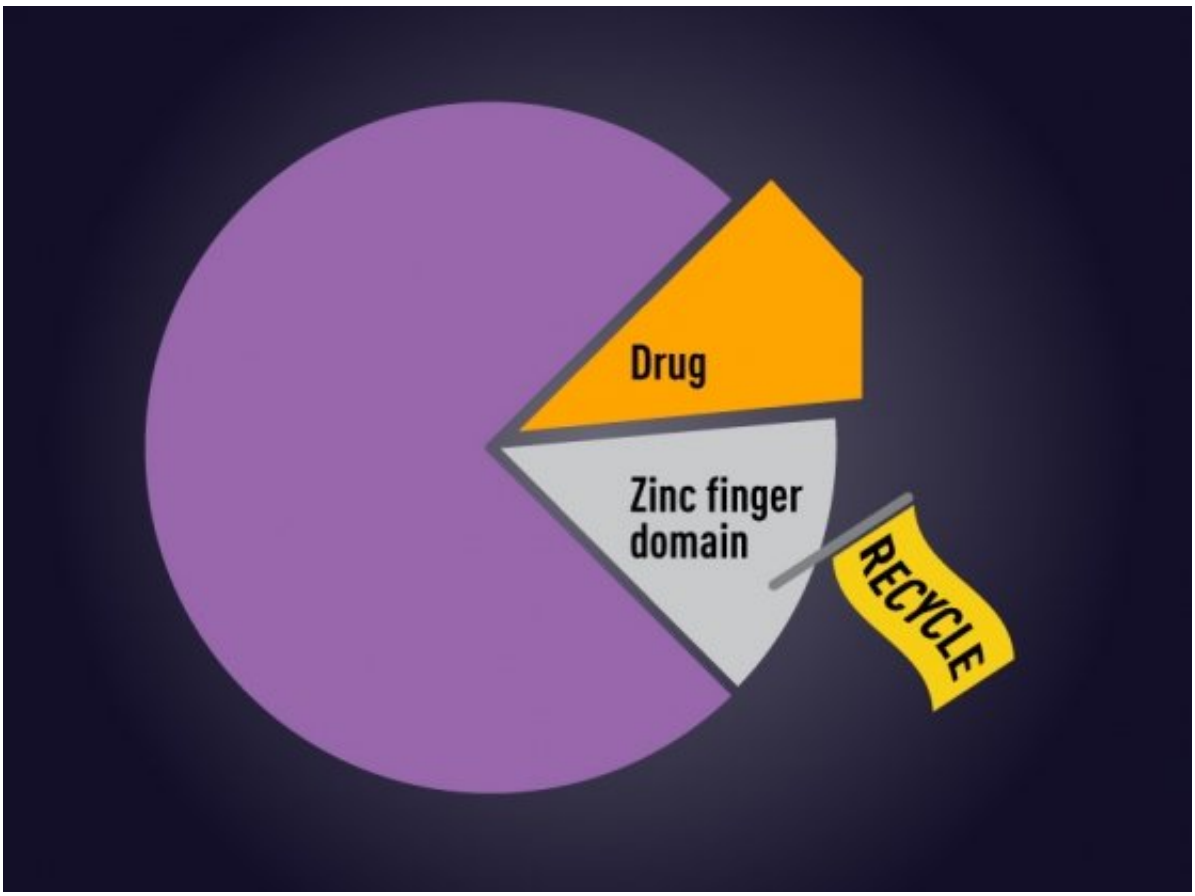

Credit: Susanna M. Hamilton, Broad Communications

Thalidomide, a morning-sickness drug recalled in the 1960s because it caused devastating birth defects, is now commonly used to treat multiple

myeloma and other blood cancers. It and its chemical relatives work by causing cells to destroy two proteins—members of a larger family of conventionally "undruggable" proteins called transcription factors—that feature a particular molecular pattern called a C2H2 zinc finger (ZF) motif.

Writing in the journal *Science*, researchers at the Broad Institute of MIT and Harvard, the Dana-Farber Cancer Institute, Brigham and Women's Hospital, and the University of Basel suggest that thalidomide and related drugs could provide a starting point for establishing a new class of cancer-fighting compounds, one that targets many more of the estimated 800 transcription factors that harbor the same motif.

Transcription factors bind to DNA and coordinate the expression of large numbers of genes, often in patterns specific to certain cell types or tissues. Errors in these proteins are linked to many cancers, but scientists have found them exceedingly difficult to target them for drug development. This is because transcription factors lack sites where drug molecules can bind directly.

Thalidomide and its chemical relatives, pomalidomide and lenalidomide, rather, attack their targets (two C2H2 ZF-bearing transcription factors called IKZF1 and IKZF3) indirectly, by conscripting a protein called cereblon. Cereblon is part of a molecular machine called an E3 ubiquitin ligase, which flags proteins for destruction by the cell's recycling system.

When thalidomide and its cousins are absent, cereblon ignores IKZF1 and IKZF3. When present, however, they allow cereblon to recognize these transcription factors and mark them for disposal.

"The discovery of thalidomide's mechanism of action was surprising in many ways, but it showed us how to trigger the rapid degradation of two zinc finger transcription factors that we otherwise had no idea of how to

drug," said Benjamin Ebert, an institute member in the Broad Cancer Program and the chair of medical oncology at DFCI.

The search for new roles for an old drug

The human genome encodes an estimated 800 transcription factors that, like IKZF1 and IKZF3, bear some variation of the C2H2 ZF motif. Recognizing an opportunity to open additional such factors up for drug development, the team—led by Ebert and Quinlan Sievers of the Broad, DFCI, and BWH; and Georg Petzold and Nicolas Thoma at the University of Basel—set out to discover whether other similar transcription factors might also be vulnerable to thalidomide-like drugs.

The team started by determining the precise C2H2 ZF features that cereblon "sees" when thalidomide-like drugs are present. They then screened thalidomide, pomalidomide, and lenalidomide for their ability to trigger degradation of 6,572 unique C2H2 ZF motif variations in cellular models. The screen revealed six C2H2 ZF-containing proteins that were vulnerable to the drugs, four of which scientists had not previously identified as targets for thalidomide or its relatives.

After conducting additional functional and structural studies of IKZF1 and IKZF3 to better understand how the transcription factors, cereblon, and thalidomide drugs interact, the team then ran computer models of 4,661 variations to see if they could predict additional transcription factors that might dock with cereblon in the presence of drug.

The computational data, together with follow-on biochemical studies, suggest that suitably modified thalidomide-like drugs should be able to "trick" cereblon into flagging specific subsets of C2H2 ZF transcription factors for recycling.

"It's extraordinary how specific these interactions are," Ebert said. "The

drugs prompt the cell to degrade specific zinc finger transcription factors, leaving the other zinc finger proteins alone. It's a highly selective mechanism."

New answers, new questions

The findings raise many more questions then they answer. For instance, scientists know little about many of the C2H2 ZF transcription factors highlighted in this study: which cell types they are active in, which genes they affect, which cancers may depend on them. This knowledge would help researchers prioritize the factors they might want to target, and set the stage for creating new thalidomide derivatives to target them.

"But the take-home message," Ebert said, "is that there is a much broader array of zinc finger transcription factors that may be amenable to drug-induced degradation than we had initially thought."

More information: Quinlan L. Sievers et al. Defining the human C2H2 zinc finger degrome targeted by thalidomide analogs through CRBN, *Science* (2018). DOI: 10.1126/science.aat0572

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