

University of Groningen

Novel Approaches for Developing Small Molecules to Target Histone Deacetylases

Cao, Fangyuan

DOI:
[10.33612/diss.157448844](https://doi.org/10.33612/diss.157448844)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Cao, F. (2021). *Novel Approaches for Developing Small Molecules to Target Histone Deacetylases*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.157448844>

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1. Histone deacetylases (HDACs) are better called lysine deacetylases (KDAC), to describe their biological function rather than their protein target, since they also deacetylate non-histone proteins. 2. HDAC isoenzymes may not only be involved in regulation of inflammatory gene transcription through their lysine deacetylase catalytic activity but also through non-catalytic interactions. 3. Proteolysis targeting chimera (PROTAC) molecules are different from the traditional occupancy-driven inhibitors. PROTACs act in an event-driven manner and degrade the targeted protein from the cells. 4. The side effects of Cereblon-recruiting PROTACs should be assessed carefully, because the E3-ligase binding components, alone or incorporated into PROTACs, can induce downregulation of NF- κ B signaling pathway. 5. For multifactorial diseases such as cancer and inflammation, approaches to manipulate multiple targets might be more beneficial than approaches directed at a single target. Sometimes, one plus one equals more than two. 6. All men by nature desire to know. —Aristotle 7. When you are lost during a project, think about its beginning and recapitulate your original aims. Stay true to your original intentions.