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The Therapeutic Potential Of Targeting Histone Deacetylase For Pituitary Neuroendocrine Tumors By High-throughout Drug Screening

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Background: A growing awareness regarding all molecular mechanisms involved in both tumor shrinkage and hormonal control might allow for medical treatment of pituitary neuroendocrine tumors (PitNETs), especially macroadenomas, rather than surgery. However, there are still no effectively therapeutic targets and corresponding drugs for all subtypes of PitNETs. **Methods:** To identify druggable cell-intrinsic vulnerabilities and correspondingly promising therapeutic agents, we examined 3 PitNETs cell lines and 21 PitNETs patient-derived primary cell cultures in sequential quantitative high-throughput screens (HTS) of 2149 FDA-approved and bio-active targeted drugs. Furthermore, we verified the most effective drug which targeted the class of mechanistic vulnerabilities, histone deacetylase (HDAC) in vitro and in vivo PitNETs models. Further RNA sequencing was employed to reveal underlying molecular mechanisms following treatment with the most effective HDAC inhibitor, panobinostat. **Results:** The HTS effort generated a total of 55296 single-agent dose responses which were enriched among multiple inhibitors for relevant PitNETs oncogenic targets, including HDAC, Akt/mTOR, proteasome, mitogenactivated protein kinase (MEK), and phosphoinositide-3-kinase (PI3K). Inhibitors from these mechanistic classes demonstrated a relatively wide potency-range, with HDAC inhibitors being, on average, the most potent drug class. Further in vitro and In vivo testing in PitNETs models validated HDACi, especially panobinostat as a promising therapeutic approach. Transcriptional surveys revealed substantial alterations to the oxidative redox mediated by the Akt/mTOR1/4EBP1/Nuclear factor-E2-related factor 2 (Nrf2) antioxidant signaling pathway following treatment with panobinostat. **Conclusion:** The current study revealed a class of newfound anti-tumor drugs, HDACi based on the HTS technology, which may be potential drugs for the treatment of PitNETs.

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