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Inhibition of HDAC6 as targeted therapy for breast cancers

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Due to their unique biology, the homeostasis of cancer cells presents different requirements from non-transformed cells. Targeted therapies that interfere with these requirements have been successfully used as highly selective and low toxic anticancer strategies. Recently, we have identified and validated that viability of inflammatory breast cancers (IBC) depends on histone deacetylase 6 (HDAC6) function (Putcha et al. Breast Cancer Res.). Thus, HDAC6 inhibitors, which are currently being tested in advanced clinical trials for other tumor types, represent a novel targeted therapeutic option for these patients. We reasoned that additional breast cancers, other than IBCs, may present the same dependency and that identification of patient populations that can benefit from HDAC6 targeted therapy would be necessary in order to rapidly transition this finding into the clinic. By using system biology strategies to interrogate the regulatory circuit of breast cancer cells we have found that HDAC6 activity is highly increased in HDAC6-dependent cells, acting as a master regulator. We have also developed an algorithm (HDAC6-score) based on mRNA expression profiling to evaluate the HDAC6 activity of individual tumor samples. Thus, the HDAC6-score works as a biomarker to easily identify cancers with high HDAC6 activity that are likely to depend on HDAC6 function. Using our HDAC6-score algorithm we have analyzed ~3,000 primary breast cancers. Interestingly, we have found that a group of ~20% of breast cancers that is enriched in hormone receptor positive (HR+) and HER2 positive (HER+) tumors presents an HDAC6-score predictive of good response to HDAC6 inhibitors. To validate our findings, we correlate the HDAC6-score and the growth inhibitory response to the leading HDAC6 inhibitor, Ricolinostat, in preclinical breast cancer models *in vitro* and *in vivo*. Our preclinical studies confirmed the high levels of HDAC6 activity in HR+ and HER2+ breast cancer cells as well as their sensitivity to HDAC6 inhibition. Clinical considerations: Despite the success of Pan-histone deacetylase inhibitors (HDACis) against cutaneous T-cell lymphoma, these inhibitors suffer from ineffectively low concentrations in solid tumors and cardiac toxicity due to its activity against HDAC1, HDAC2 and HDAC3, hindering their progress in the clinic. More-selective HDAC inhibitors represent a novel and promising class of anticancer drugs with wider therapeutic indexes. The leading HDAC6 inhibitor Ricolinostat, which is in Phase II trials for multiple myeloma and lymphoma, has a 20-fold more potency for HDAC6 inhibition than other class-I/II histone deacetylases. Thus, Ricolinostat can be dosed more frequently with better tolerability than non-selective FDA-approved HDACis.

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