Highly Selective Inhibitors of HDAC6 for the Treatment of Cancers and Neurodegenerative disease

RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

Researchers in RCSI and the Dana-Farber Cancer Institute have discovered a novel structural class of highly-selective HDAC6 inhibitors. These patented small molecules have a unique non-hydroxamic acid chemical structure and are >250-fold selective over the other HDACs. The lead compound BAS-2 has been shown to inhibit glycolysis in Triple Negative Breast Cancer Cells – a unique vulnerability independent of the mitochondrial apoptosis pathway which is one of the key drivers of chemoresistance.

BACKGROUND

Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer that lacks expression of estrogen receptor, progesterone receptor, and human epidermal growth factor 2 (HER2). The standard of care for recently diagnosed patients and patients with advanced disease is cytotoxic chemotherapy. While chemotherapy is effective for a subset of patients there is a large proportion of patients (60 to 70%) refractory to chemotherapy with poorer survival. Novel therapeutic strategies are urgently required for patients with chemoresistant TNBC disease.

A phenotypic small-molecule screen was undertaken to reveal vulnerabilities in TNBC cells that were independent of mitochondrial apoptosis. Using a functional genetic approach, the “hit” compound, BAS-2, was shown to have a similar mechanism of action to histone deacetylase inhibitors (HDAC). An in vitro HDAC inhibitor assay confirmed that the compound selectively inhibited HDAC6 with exquisite selectivity over the other HDAC subtypes. Inhibition or knockout of HDAC6 by BAS-2 has been shown to reduce glycolytic metabolism both in vitro and in vivo: a unique vulnerability in TNBC cells independent of the mitochondrial apoptosis pathway.

VALUE PROPOSITION

The majority of both cytotoxic and targeted therapeutics kill cells via the mitochondrial pathway of apoptosis which can lead to acquired chemoresistance and treatment failure in certain patient cohorts. Taking an unbiased approach via a small-molecule screen has identified HDAC6 as a new therapeutic target in apoptosis-resistant TNBC cells. This represents a paradigm shift from the conventional approach to TNBC drug discovery, which, intentionally or not, has been mainly effective at identifying therapeutics that kill via mitochondrial apoptotic mechanisms which rapidly develop chemoresistance.

Our representative small molecule lead compound BAS-2 (MW<300) is an attractive candidate for lead optimisation and a programme of medicinal chemistry is underway to progress towards pre-clinical studies. Additional unpublished data also suggests the potential for BAS-2 as a HDAC6-targeted therapeutic in neurodegenerative diseases.

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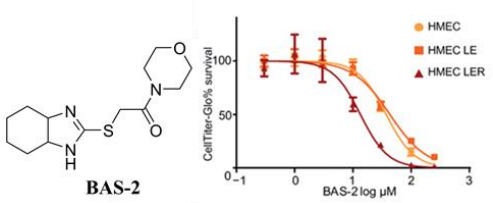

Figure 1. Transformed human mammary epithelial cells (HMEC LER cells, with oncogenic RAS), were more sensitive to BAS-2 than the non-transformed HMEC and HMEC LE cells indicating a selectivity of BAS-2 for cancer cells.

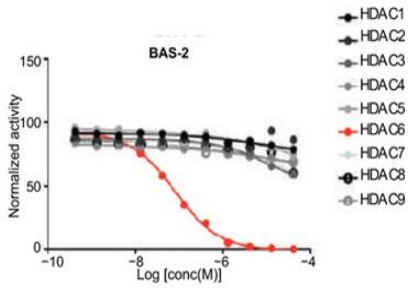

Figure 2. BAS-2 is highly selective against the other HDACs.

FEATURES	BENEFITS
>250 fold selectivity for HDAC6	Reduced off-target side effects
Novel anti-glycolytic mode of action	Synergy with other therapies. Reduced risk of chemoresistance
Novel chemotype and drug-like properties	Rapid lead optimization

TECHNOLOGY READINESS LEVEL

- PATENT APPLICATION FILED
- IN VIVO PROOF OF CONCEPT

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