Identification of a potent, orally bioavailable and selective MCT4 inhibitor for the treatment of solid Warburg tumors


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One of the most critical publications in the cancer research field by Hanahan & Weinberg acknowledges metabolic reprogramming as one hallmark of cancer. A key metabolic alteration in tumor cells is an elevated glycolysis rate. While non-transformed cells mainly utilize the citric acid cycle and oxidative phosphorylation for energy production and anabolic growth, tumor cells employ aerobic glycolysis. These alterations of cellular metabolism are by far more common in solid tumors compared to hematological malignancies[1].

Due to the enhanced glycolysis rate, cancer cells often produce increased amounts of lactate (up to 40-50%) leading to lactic acidosis within the tumor microenvironment (TME). Recent studies support the critical role of this metabolite in tumorigenesis and demonstrate versatile tumor-promoting effects of lactate. As one major contribution the stimulation of angiogenesis is discussed, an effect at least in part mediated through the activation of the VEGF/VEGFR signaling pathway in endothelial cells, which is the central player in the cellular response to hypoxia[10]. Thus, MCT4 activity is involved in hypoxia-inducible factor 1α (Hif1α) transcriptional activity leading to lactic acidosis within the tumor microenvironment. Recent publications support the notion that high intratumoral lactate levels are highly correlated with cancer cell migration, and intratumoral lactate levels are considered an effect at least in part mediated through the activation of the VEGF/VEGFR signaling pathway in endothelial cells, which is the central player in the cellular response to hypoxia[10]. Thus, MCT4 activity is involved in hypoxia-inducible factor 1α (Hif1α) transcriptional activity leading to lactic acidosis within the tumor microenvironment.

Lactate is transported across the plasma membrane by the monocarboxylate transporters 1 and 4 (MCT1/4) in symport with a proton. While MCT4 is expressed almost ubiquitously at low levels, MCT1 expression is regulated by hypoxia-inducible factor 1α (Hif1α), which is the central regulator of angiogenesis[5]. Furthermore, lactate has been implicated in cancer cell migration, and intratumoral lactate levels are highly correlated with cellular response to hypoxia[10]. Thus, MCT4 activity is involved in hypoxia-inducible factor 1α (Hif1α) transcriptional activity leading to lactic acidosis within the tumor microenvironment.

Since MCT4 has the strongest implication on the development and aggressiveness of diverse cancer types it has emerged as a new target for the treatment of solid tumors. Blockade lactate export by inhibition of MCT4 is expected to impair tumor metabolism and reduce lactate in the TME. Recent publications support the notion that this will result in:

- Tumor cell growth arrest
- Radio-sensitivity
- Chemo-sensitivity
- Restoration of cancer immunosurveillance

We have identified MCT4 specific inhibitors (MCT4i) and significantly improved activity and selectivity of MCT4 by an extensive medicinal chemistry program. These efforts resulted in the identification of highly potent, orally bioavailable and selective MCT4i. MCT4i CICl ≤ 2000 with MCT1i CICl ≤ 150 µM.

Introduction

Results

Phenex MCT4 inhibitor screening path

Conclusion & Outlook

- A phenotypic screening campaign identified several compounds that were inhibitors of lactate efflux via MCT4.
- Medicinal chemistry efforts led to a significant improvement of MCT4 inhibitor potency and metabolic stability.
- Cellular target engagement of early tool compounds was confirmed.
- Optimization of one series yielded PX-788 which shows single-digit nanomolar potency in the NCI-H358 mouse xenograft model. Synergy with anti-angiogenic therapies will be evaluated in subsequent studies.
- Human CD3+CD8+ T cell proliferation is not impaired by MCT4 inhibition. Therefore, MCT4 inhibitors represent promising single-agent or combination partners for immunomodulatory drugs due to the relief of lactate-mediated immunosuppression in the TME.

In the future, we will further analyze if MCT4 inhibitors are able to enhance response to checkpoint inhibition in pre-clinical models.

References

1. Hanahan & Weinberg; Cell (2011)