Breast Cancer

**Major finding:** The 1q21.3 amplification can be detected in cfDNA from most patients with recurrent breast cancer.

**Mechanism:** 1q21.3 harbors S100A7/8/9 which promote IRAK1 phosphorylation and cell growth.

**Impact:** 1q21.3 amplification may serve as a biomarker of recurrence and confer sensitivity to IRAK inhibitors.

Drug Discovery

**Major finding:** A virtual ligand screen led to generation of A-485, a potent selective p300/CBP catalytic inhibitor.

**Mechanism:** A-485 competes with acetyl-CoA for p300/CBP active site binding to inhibit H3K27 and H3K18 acetylation.

**Impact:** Targeting p300/CBP may be effective in some transcription-driven malignancies.

INHIBITION OF p300/CBP SUPPRESSES CASTRATION-RESISTANT PROSTATE CANCER

The paralogous histone acetyltransferases (HAT) p300 and CREB-binding protein (CBP) are transcriptional coactivators that have been implicated in cancer. However, selective potent inhibitors of p300 and CBP have not been developed, although the tool compound C6-46 has suggested the potential for therapeutic targeting of HATs in cancer. To identify small-molecule inhibitors of p300/CBP, Lasko, Jakob, and colleagues conducted a virtual ligand screen of 800,000 compounds in silico and evaluated 1,300 commercially available compounds in a direct radioactive p300/CBP HAT assay. Hydantoin emerged as a compound class and further optimization yielded A-485, a selective small-molecule inhibitor that was at least 1,000-fold more potent than C6-46 in inhibiting p300. Determination of the X-ray crystal structure of the p300 HAT domain in complex with A-485 at 1.95 Å demonstrated that A-485 competed with acetyl coenzyme A (acetyl-CoA) for binding to the catalytic active site of p300. A-485 reduced acetylation of H3K27 and H3K18, but not H3K9, in prostate cancer cells, indicating a selectivity for p300/CBP over other HATs. Further, A-485 suppressed proliferation of a number of cancer cell lines, including multiple myeloma, acute myeloid leukemia, and non-Hodgkin lymphoma. Most solid tumor cell lines were less sensitive, but A-485 potently suppressed the growth of androgen receptor (AR)-positive, but not AR-negative, prostate cancer cell lines. The A-485-mediated reduction in H3K27Ac deposition led to a reduction in AR transcriptional activity. In vivo, A-485 suppressed the growth of AR-positive castration-resistant prostate cancer xenografts. In addition to developing a highly potent and selective p300/CBP small-molecule inhibitor, these findings suggest that inhibitors of HAT catalytic activity may have antitumor activity in multiple tumor types including AR-positive castration-resistant prostate cancer.


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Chromosome 1q21.3 Amplification Is Linked to Breast Cancer Recurrence

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