# Small molecule hdac6 inhibitors

Reference No: B74064

## CHALLENGE

For **malignant tumors** to successfully grow and metastasize, cancer cells use an extracellular **citrate supply** as an important energy source and substrate for the synthesis of critical cellular building blocks (e.g. fatty acids). Several metabolomic studies indicate that blood citrate levels decrease in cancer pa- tients (e.g. lung, bladder, pancreas). Recent studies show that a significant portion of **citrate is taken up by cancer cells** from the extracellular space. In contrast, normal cells do not take up citrate except some specialized (liver, kidney, sperm) normal cells.

## INNOVATION

The inventors found a highly specialized plasma membrane protein (**pmCiC, plamsamembranecitrate carrier**) to be **responsible for citrate uptake in cancer cells.** PmCiC expression is detetcted in a wide variety of human cancer cell lines, as well as in human tumor tissue sections with differences in ex- pression levels among cancers, and within the different areas of individual cancers (invasion front and invading cells are often more stained that the cells in the central part of the tumor). The transporter is also present in normal prostate secretory cells (apically), but works in opposite directions, as citrate ex- porter, and is responsible for maintaining high extracellular citrate levels in the prostate gland. The spe- cialized normal cells (liver, kidney, sperm) that also take up citrate use a different channel (not pmCiC).

## COMMERCIAL OPPORTUNITIES

- pmCiC is a **novel and specific marker of cancercells**
- pmCiC expression **correlates with tumor grade:** the more aggressive regions of the cancer appear to have the most intense expression
- pmCiC as **new therapeutic target:** inhibitors, openers, antibodies, cytotoxic drugs

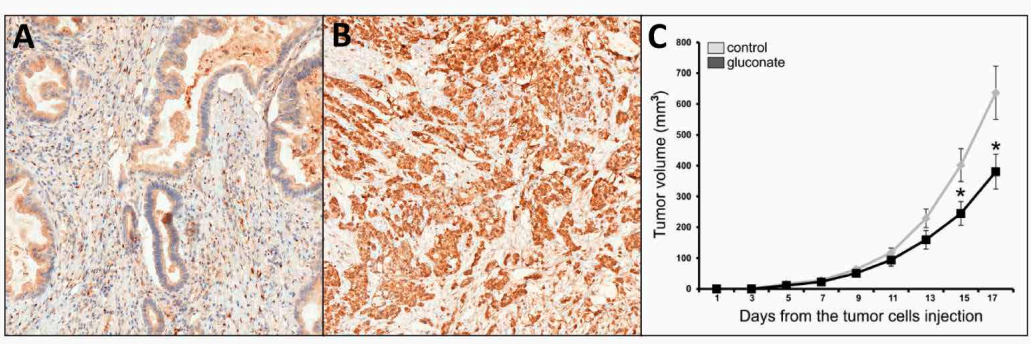


**Figure A,B:** different pmCiC expression levels in human cancerous tissues (100x); Pancreatic adenocarcinoma, moderately (A) and poorly (B) differentiated; **Figure C:** Gluconate reduces tumor growth; Mice were injected subcutaneously with human pancreatic L3.6pl cancer cells. Tumor growth was significantly decreased in the group injected daily ip with 10 mg of sodium gluconate (in 100 µl)

## DEVELOPMENT STATUS

- The inventors have initial indications that pmCiC in tumor cells (importer) and healthy prostate secretory cells (exporter) offers different epitopes for Ab binding
- Human tissue staining revealed pmCiC detection in a variety of tumors, e.g. prostate, urothelium, pancreas, breast, gastric
- Experiments with siRNA to inhibit pmCiC expression in vivo confirmed the importance of citrate uptake for tumor growth and metastasis
- Small molecule inhibitor which irreversibly blocks pmCiC has been identified and successfully tested in vivo, resulting in decreased angiogenesis and stroma transformation and collapsing of subcutaneous tumor.

**REFERENCE:**

(1) Mycielska et al, Cancer Research 2018 May 15;78(10):2513-2523

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