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 patients (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, plasmamembrane citrate carrier) to be responsible for citrate uptake in cancer cells. PmCiC expression is detected in a wide variety of human cancer cell lines, as well as in human tumor tissue sections with differences in expression 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 specialized 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 cancer cells
- 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

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