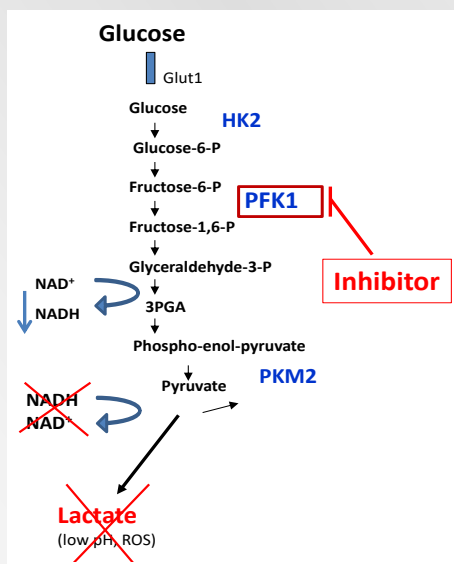


## SMALL MOLECULE-INHIBITORS OF 6- PHOSPHOFRUCTO-1-KINASE FOR SUPPRESSING



Consistent characteristic of malignant cells is the consumption of a larger amount of glucose compared to the normal cells and conversion of majority of glucose into lactic acid. Lactate that is transported out of the cells causes acidification in tumors that contributes to immune escape, besides lactate induces angiogenesis and migration of cancer cells. Manipulation of glycolysis in the cancer cells with an aim to reduce lactate.

### Technology

In cancer cells post-translational modification of 6-phosphofructo-1-kinase (PFK1), the key regulatory enzyme of glycolysis, is responsible for deregulation of glycolysis and redundant NADH formation. In the cells lactate formation is needed for redox balancing where surplus of NADH is re-oxidized by reducing pyruvate into lactate. By inhibiting highly active cancer specific form of PFK1, lactate generation may be prevented. We used three dimensional crystal structure of PFK-P iso-enzyme as a model to virtual screen ZINC Drugs NOW database by docking the compounds to the ATP binding site. Thirty three compounds were selected and purchased for testing. First, the inhibitory capacities of compounds were determined followed by evaluation of selected inhibitors for preventing lactate generation by different tumorigenic cell lines. Seven compounds showed strong inhibitory capacities and effectively prevented lactate generation. By analytical methods, PFK1 enzyme has been confirmed to be a target for inhibition.

### Main advantages

- Partial inhibition of cancer specific PFK1 enzymes reduces glycolytic flux to that of the normal cells.
- Reduced glycolytic flux prevents lactate generation.
- Minimal or no negative cytostatic and cytotoxic effects of inhibitors are detected.
- Inhibitors are effective at low (5-15  $\mu$ M) concentrations when administered periodically and low cost of compounds.

### Key words

Cancer treatment, deregulated glycolysis, lactate generation, small molecule-inhibitors, suppressed lactate generation

#### TYPE OF COOPERATION

Technology licensing opportunities

#### INTELLECTUAL PROPERTY

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#### MORE INFORMATION ABOUT THE INVENTION

