# Small Molecule Inhibitors of P13 Kinase Signaling

Published date: Feb. 12, 2014

## Technology description

Why is the target important?

The PI3 lipid kinase (PI3K) pathway is an important target for anti-cancer drug development because:

It’ s activated by growth factors, oncogenes (RAS), GPCRs, etc.

It regulates an array of critical cellular functions, including survival, proliferation, metabolism and cell motility.

PI3K and its downstream effectors are frequently over-activated in human cancer (in some types comparably to p53).

Activity of PI3K contributes to survival, invasiveness and profound metabolic changes in cancer cells.

PIP3/PH domain binding is a critical non-redundant step in PI3K signaling, easily amenable to inhibition by a small molecule.

Structural differences in binding pockets could be exploited to achieve selectivity

What data do we have?

Through a screening and drug development program, Dr. Alexei Degterev of Tufts University and his collaborators have identified a potent, non-phosphoinositide inhibitor of PIP3/protein binding termed YK-NCL-240 that displays significant anti-tumor activity in vitro and in vivo.

Toxicity of YK-NCL-240 was tested in human ovarian (A2780), glioblastoma (U87MG), breast (T47D) and prostate (DU145) cancer cells. In these cancer types, YK-NCL-240 can effectively inhibit cell growth and induce cell deathin vitroin both free and micellar formulations. Addition of TRAIL leads to synergistic induction of cell death.

YK-NCL-240 can be incorporated into PEG-PE micelles in combination with TRAIL to get a synergistic effect between the two compounds. TRAIL-resistance is reversed in multiple TRAIL-resistant cancer cell lines.

In a mouse xenograft study, YK-NCL-240 significantly inhibited A2780 tumor growth in a subcutaneous mouse model. Combination effect with TRAIL was also observed. Studies using higher dose of YK-NCL-240 are ongoing.

YK-NCL-240 inhibits cellular migrationin vitro,which may translate into the inhibition of angiogensis within tumors as well as inhibition of metastasis. The inhibition of migration byYK-NCL-240 has also been shown in T47D, U87MG and DU145 cells.

YK-NCL-240 robustly suppresses the mTOR pathway downstream from Akt (in U87MG cells). Further characterization of the inhibition of Akt targets by YK-NCL-240 is ongoing.

Why is it competitive?
Previous efforts in developing PIP3 antagonists have focused on phosphoinositide-like molecules. However, as these molecules lack phosphate groups they require phosphorylation by endogenous kinases in the cells which creates a difficulty to achieve significant selectivity for PIP3 versus other phosphoinositides using this approach. Other issues, such as bioavalability and metabolic stability may also limit utility of these molecules.

## Institution

Tufts University

## Inventors

Alexei Degterev
Assistant Professor
MED
Yadagiri Kommagalla
Chepuri Venkata Ramana
Jinbo Lee

邮 箱：yeyingsheng@zf-ym.com