Characterization of the Effects of the Anti-Tumorigenic Drug TPCK on the Substrates of the Pro-Proliferative Kinase PDK1.

Jaye L. Grundy¹, Rana Anjum², John Blenis² and Bryan A. Ballif¹
¹Department of Biology, University of Vermont, Burlington, VT. 05405. USA.
²Department of Cell Biology, Harvard Medical School, Boston, MA. 02115. USA.

Cancer is characterized by uncontrolled cell division, often caused by increased activity in growth signaling pathways. A challenge to cancer chemotherapy is that when one pathway is blocked by a chemotherapy agent, the cells can evolve resistance to the drug. However, new therapies hope to target multiple signaling pathways at once to reduce the ability of the cancer to evolve resistance. The drug N-α-tosyl-L-phenylalanyl chloromethyl ketone (TPCK) has recently been characterized as an anti-tumor agent capable of blocking several of the signaling pathways involved in growth and proliferation that are down stream of the kinase Phosphoinositide-Dependent Kinase 1 (PDK1). TPCK has been shown to inhibit these pathways by forming adducts on and blocking the activity of PDK1 substrates RSK, AKT, MSK, and S6K. Recent data have shown that while TPCK inhibits the activity of these proteins, it actually increases their binding to PDK1 significantly. Our data show this increased binding and further characterizes the mechanisms by which TPCK acts to inhibit these pathways and how this might lead to its anti-tumorigenic properties.