**“Activation of Natural RTK Inhibitors in Cancer Therapy”**

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Funding Category: A

**Abstract:** A large fraction of tumors rely for their growth and survival on the aberrant activation of various Receptor Tyrosine Kinases (RTKs) signaling pathways. Our ever-increasing understanding of the mechanisms that drive tumorigenesis, and the role of RTK signaling within it, has lead to the development of smart drugs that target RTK activities as one of the core modern therapeutic approaches to cancer treatment. However, the effectiveness of such drugs depends on the specific tumor genetic context, and treatment frequently results in appearance of drug resistance both through compensatory mutations and through the activation of alternative signaling pathways. We have identified a large number of novel secreted soluble decoy RTKs isoforms that could act as powerful natural dominant negatives of RTK signaling and promise to be very effective in overcoming acquired drug resistance to current RTK inhibitors. We have also developed an innovative general method to specifically activate such secreted variants that could lead to a new generation of drugs targeting RTK activities, especially in the context of resistant or relapsing tumors. We will characterize the activity of such natural soluble decoy receptors, and develop compounds to induce their activation *in vitro* and *in vivo*, initially in the context of lung and brain tumors, and we will investigate their role and potential as anti-cancer drugs in situations where deregulated activation of RTK signaling is a key contributor to tumor progression and maintenance.