**Project Title:** Targeting growth factors and cytokine secretion in tumor associated fibroblasts to counter therapeutic resistance in non-small cell lung cancer

**Abstract:** Targeted therapies have transformed the treatment of many lung cancers. Unfortunately, while in most cases patients initially respond well, acquisition of resistance leads to relapse. New drugs recently developed can tackle some of the resistance but in many cases options are limited. Tumors are a mixture of cancer cells and non-cancer cells that functionally interact with each other. Recent studies have shown that factors secreted by the other cells in the tumor can make cancer cells resistant to drugs. We have been studying the role of non-cancer cells in lung cancer and how they promote resistance. We have observed a variety of behaviors in these models with several different secreted factors inducing drug resistance. This variety complicates the design of therapies that would benefit most patients as each factor must be targeted and we would need to know which factors are at play for each patient. As an alternative strategy, we propose to use the Ipsen TSI approach to tackle resistance caused by secreted factors broadly. We hypothesize that TSI has the potential to suppress the secretion of multiple factors that concomitantly induce resistance. We will test the potential for this approach using a large collection of models (cancer cells and associated cells) derived from clinical trial biopsies. We already know that these clinically relevant models induce resistance through multiple factors some of which we have identified and thus constitute a good laboratory system to test our hypothesis