1. **Abstract:**
Pancreatic ductal adenocarcinoma (PDAC) is characterized by a prominent desmoplastic or fibrotic reaction. It is well established that activated pancreatic stellate cells (PSCs) present in the tumor stroma are the principal source of desmoplasia and promotes cancer progression and hinders effective drug delivery. In PDAC, the PSCs or the myofibroblast like cells play critical roles in tumor progression, metastasis and chemo-resistance. Therefore, we hypothesized that a pharmacological approach to kill activated PSCs and cancer cells together would enhance the clinical efficacy. To address this hypothesis, the objectives of this study were to establish a novel cell based screening method to check the efficacy of 800 FDA approved drug molecules that could have growth-suppressive effects on activated PSCs in culture through drug repositioning approach and to characterize a homologous orthotopic model of pancreatic cancer desmoplasia in Syrian golden hamster to investigate the effect of selected drugs on desmoplastic/fibrotic tumors. Drug library screening identified 18 potential drugs that suppress the survival of activated PSCs *in vitro*. The HapT1 PC cells when implanted orthotopically in to hamster pancreas formed tumors with morphological, cellular and molecular similarities to human PC. Protein profiling of activated hamster pancreatic stellate cells (ha-PSCs) revealed expression of proteins involved in fibrosis, cancer cells growth and metastasis. Pirfenidone, suppressed growth of HapT1 cells and the desmoplastic response *in vivo*; these effects were enhanced by co-administration of NAC. Disulfiram alone or in combination with copper (Cu) was toxic to HapT1 cells and PSCs *in vitro*; but co-administration of DSF and Cu accelerated growth of HapT1 cells *in vivo*. Moreover, DSF had no effect on tumor-associated desmoplasia. The study identifies HapT1-derived orthotopic tumors as a useful model to study desmoplasia and tumor-directed therapeutics in PC. Pirfenidone in combination with NAC could be a novel combination therapy for PC and warrants investigation in human subjects.