27O-ISMS42 **Discovery of Novel and Potent Stearoyl Coenzyme A Desaturase 1 (SCD1) Inhibitor T-3764518 as Anticancer Agent**

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Stearoyl-CoA desaturase-1 (SCD1) is one of the iron-containing endoplasmic reticulum (ER) enzyme, which assumes a rate-limiting step in the synthesis of unsaturated fatty acid (UFA) from saturated fatty acid (SFA). SCD1 expression and activity are closely related to cancer pathogenesis and tumor malignancy, and the homeostasis of the ratio in UFA to SFA has been implicated in the regulation of cell growth/death and differentiation. Therefore, inhibition of SCD function induces imbalance of fatty acid composition in intracelullar lipids, leading to cell death via lipotoxicity and ER stress responses in certain types of cancer.

Our lead compound showed moderate SCD1 binding affinity, but a poor pharmacokinetic profile and limited chemical accessibility, making it suboptimal for use in anticancer research. To identify potent SCD1 inhibitors with promising PK profiles, we newly designed a series of 4, 4-disubstituted piperidine derivatives based on molecular modeling studies. Optimization around new lead was accelerated by analyzing Hansch–Fujita and Hammett constants to obtain 4-phenyl-4-(trifluoromethyl)piperidine. Final fine-tuning of profile led to our candidate **T-3764518**, which retained potent affinity and exhibited an excellent PK profile. Reflecting these profiles, orally administrated compound **T-3764518** showed significant PD reduction and tumor growth suppression (at 1 mg/kg, bid) in mouse xenograft model.

In our presentation, we would like to discuss about molecular design, synthesis and biological studies of new compounds. We also discuss about therapeutic potential of SCD1 inhibitors for cancer and other disease.