Small Molecule Drug Conjugate Cancer Therapeutic platform:

The use of cytotoxic drugs for cancer therapy has spawned the development of targeted drug delivery in attempts to reduce toxicity to normal tissues, sparing life-threatening side effects and improving therapy. Apoptosis and necrosis are two distinct pathways of cell death. However, both cell death processes converge on one critical biomarker, that is, externalization of phosphatidylserine (PS). PS is abundant in the tumor microenvironment, possibly due to the stress conditions, such as hypoxia, acidity, thrombin, inflammatory cytokines, and reactive oxygen species. Our strategy takes advantage of the bulk expression of PS at the tumor site as an apparent biomarker for the spatial- and temporal-controlled delivery of therapeutics to treat cancer. Since many disorders and pathological conditions, such as cancer, are the result of deregulation of cell death, PS has become a key target for the delivery of therapeutics. Agents that can selectively target PS on membrane surfaces and distinguish them from the near-neutral membrane surfaces of normal human cells have promising potential as imaging probes, drug delivery agents, and targeted molecular therapeutics.

Molecular Targeting Technologies, Inc. (MTTI) has licensed a technology platform developed by Dr. Bradley Smith at the University of Notre Dame which is based on synthetic zinc(II)-dipicolylamine (Zn-DPA) coordination complexes that specifically target PS. Smith and coworkers have shown that fluorescently labeled Zn-DPA probes were able to target the dead and dying cells within xenograft tumors in rat and mouse models. Based on these proof-of-concept studies demonstrating the localization/targeting ability of Zn-DPA probes to tumors, MTTI in collaboration with NHRI in Taiwan, designed and synthesized several T1-based molecules for cancer therapy.

The lead product candidate consists of Zn-DPA conjugated to the potent anti-cancer agent SN-38, a topoisomerase I inhibitor, with a proprietary novel linker group. The linker group is designed to provide stability in plasma but be susceptible to enzymatic cleavage in the tumor microenvironment. Characterization of this product candidate included successful demonstration of retention of PS binding affinity, plasma stability, cellular toxicity to colon and gastric cancer cells (nontoxic to normal cells), and a relatively high tolerated dose in mice. Of particular significance was the ability of the compound to inhibit tumor growth in a mouse colon cancer xenograft model. Our product candidate was compared directly to Irinotecan, a SN-38 prodrug, with both drugs dosed intravenously at 40 mg/kg, twice weekly for two weeks. Equivalent drug weight dosing results in the Zn-DPA drug conjugate containing only 40% of the Irinotecan dose. Results showed distinct advantage in the drug conjugate-dosed mice compared to Irinotecan-dosed mice at 22 days post treatment initiation. The tumors in the drug conjugate-dosed mice did not appear to grow beyond the size at initiation of treatment. Additionally, our SMDC was shown to have an “amplification” effect with the initial cytotoxicity

causing elevated levels of PS which in turn increases recruitment of the Zn-DPA conjugate to the tumor site, further enhancing its therapeutic effectiveness.

The SMDC cancer therapeutic, designated T1, will be further developed with the goal of entering phase I clinical trials in twenty months.

Product Candidate	**Potential indication**	**Development Status**	**Available License Territories**
T1	Colon, gastric, lung and others	Preclinical Research	World-wide