Design and Development of Serine Hydroxymethyltransferase-2 (SHMT2) Inhibitors Blocking Tumor Growth.

The growth and proliferation of cancer cells depend on boosted recircling of folates that make up the so-called one-carbon (1C) metabolism. 1C metabolism is vital to all living cells, but its turnover is abnormally accelerated in cancer cells due to the increased demand for nucleotides and methionine (utilized in downstream epigenetic marking). In fact, cellular reprogramming to accelerate 1C metabolism is one of the hallmarks of cancer.

One of the crucial intermediates in 1C metabolism is 5,10-methylenetetrahydrofolate (5,10-meTHF), which also is a direct co-substrate for *de novo* pyrimidine biosynthesis. 5,10-meTHF is the carrier of the 1C units, installed on tetrahydrofolate by serine hydroxymethyltransferases (SHMTs) with the concurrent and reversible transformation of serine to glycine. Because SHMT2 fuels 1C metabolism by supplying 5,10-meTHF, it has recently emerged as a promising target for developing new anti-cancer drugs. **This project will develop small molecules that will inhibit serine hydroxymethyltransferase-2 (SHMT2) and downregulate the turnover rate of 1C metabolism.** On the molecular level, inhibition of SHMT2 activity will impede nucleotide and methionine biosynthesis. Except for a direct impact on downstream biosynthetic pathways, SHMT2 inhibition will influence epigenetic maintenance, amino acid homeostasis, and redox defense.

Other enzymes in 1C metabolism are targets of antifolate chemotherapeutics that have cured millions of patients. However, despite the interest, a genuine drug targeted at SHMT2 has not yet been developed. We even do not have a good lead (candidate) molecule for an SHMT2-targeted drug, which is a missed opportunity to help cancer patients.

An opportunity has arisen from recent reports showing off-target inhibition of SHMT2 by antifolates in clinical use (methotrexate, pemetrexed, etc.). Modification of existing drugs having at least acceptable ADME-Tox (absorption, distribution, metabolism, excretion, and toxicity) properties is effective, as expressed by Sir James Whyte Black: “the most fruitful basis for the discovery of new drug is to start with an old drug.” Therefore, this project will explore two strategies: (i) further modifications to the antifolate scaffold and (ii) search for new scaffolds and new druggable sites for SHMT2 inhibitors. Future SHMT2-targeted drugs could work alone or in conjunction with other therapies (not only pharmacological) to maximize therapeutic outcomes.

The need for new chemotherapeutic agents is unquestionable, both for personalized therapies currently revolutionizing cancer treatment and for minimizing drug resistance, a problem that affects many chemotherapy patients. While usually only pharmaceutical companies can afford clinical trials and drug rollout, basic science projects, such as this one, are indispensable in finding new leads. With that in mind, this project will provide much-anticipated advances in the field by revealing new lead molecules for further development into SHMT2-targeting drugs. A blend of cutting-edge methods in high-throughput screening, structural biology, bioinformatics, machine learning, enzymology, and chemical synthesis with the experience and expertise of the research team maximize the chance for lead discovery and promise sustainability of the project results.