

My research program focuses on investigating the effect of the interaction between dietary fatty acids and environmental toxicants on human health using chemical biology methods and state-of-the-art instrumentations. More specifically, we are interested in studying the molecular mechanism on how dietary omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) affects human diseases. The metabolites from omega-3 and omega-6 PUFAs are important lipid signaling molecules that play an important role in inflammation, blood pressure regulation, wound healing, cancer, pain, etc. Therefore, understanding the signaling mechanism of these potent lipid metabolites will lead to alternate treatments for diseases. Currently, we are focused on two different directions to elucidate the mechanism on how omega-3 and omega-6 PUFA metabolites affect human physiology:

1) Identification of the receptors of polyunsaturated fatty acid (PUFA) epoxides.

PUFA epoxides are potent lipid mediators with anti-inflammatory, anti-hypertensive, anti-fibrotic and analgesic properties. They also play a vital role in cancer biology. However, even after two decades of research, the signaling mechanism of PUFA epoxides remain largely unknown. To tackle this challenge, we will design analogs of PUFA epoxides. Currently, we have identified several active analogs which allows us to pursue the identification of highly specific and high affinity epoxyeicosatrienoic acid receptor(s).

2) Design and synthesis of analogs of omega-3 PUFA epoxide and inhibitor of soluble epoxide hydrolase with improved druglikeness to treat diseases.

Omega-3 PUFA epoxides are transient endogenous metabolites which are metabolically unstable and rapidly degraded by an enzyme called soluble epoxide hydrolase. In addition, these fatty acid epoxide are very lipophilic with poor physical properties. Therefore, they are poor drug candidates. Recently, our laboratory have employed a high-throughput screening in order to study the structure-activity-relationship of the omega-3 PUFA epoxides on fibrosis. By understanding the SAR of PUFA epoxides on fibrosis, we will be able to design analogs with better drug-like properties.

Because the soluble epoxide hydrolase (sEH) is the major metabolic enzyme for PUFA epoxides, inhibition of sEH is beneficial to human health through stabilization of PUFA epoxides *in vivo*. Thus, sEH becomes a prominent therapeutic target. Recently, it has been shown that sEH inhibitors are efficacious on diabetic neuropathic pain model in mice. Unfortunately, the properties of the current sEH inhibitors are not fully optimized. Therefore, we will redesign the structure of the sEH inhibitors to improve their drug-like properties particularly, the drug-target residence time because the drug-target residence time has been demonstrated to be an important drug parameter to predict *in vivo* efficacy of the drug. 🍎



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Molecular Mechanism of Dietary Lipids and Environmental Toxicants on Human Health

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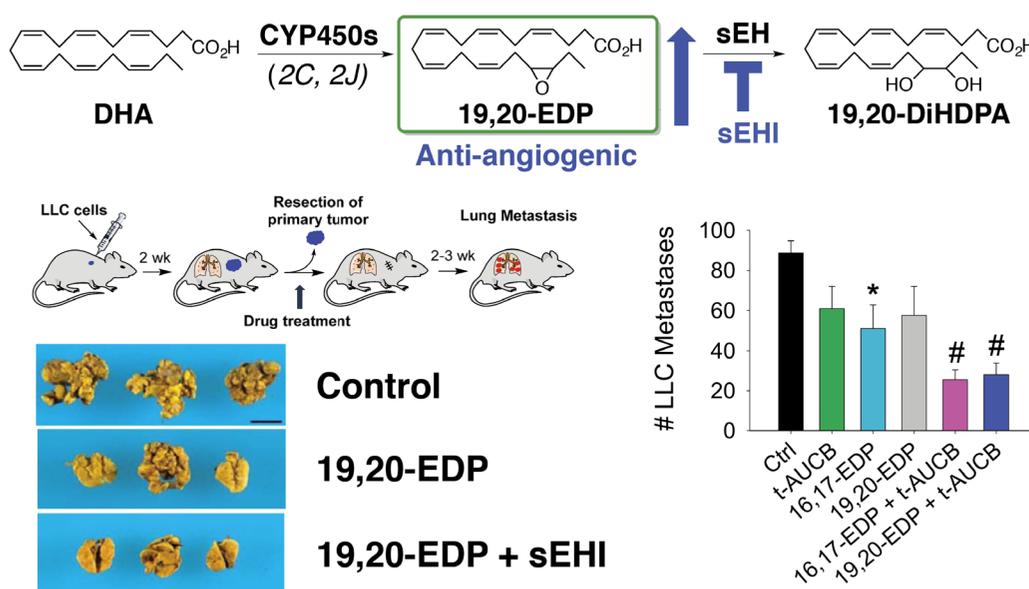
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