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Translating novel NNMT inhibitors into new mechanism-of-action therapeutics to combat obesity and its comorbidities

Abstract:
There is a critical need for new mechanism-of-action drugs that reduce the burden of obesity and associated chronic metabolic comorbidities (e.g., type 2 diabetes). A novel target to treat obesity and linked comorbidities is nicotinamide-N-methyltransferase (NNMT), a cytosolic enzyme with newly identified roles in cellular metabolism and energy homeostasis. To validate NNMT as an anti-obesity drug target, we developed a series of novel small molecule NNMT inhibitors and subjected them to rigorous permeability, selectivity, mechanistic, and physiological studies. Effects of potent NNMT inhibitors on obesity measures and plasma lipid were assessed in the translationally-relevant high fat diet-induced obese mouse model. Results from these studies validate NNMT as a viable target to treat obesity and motivate continued development of small molecule NNMT inhibitors as therapeutics to reverse diet-induced obesity and related metabolic conditions. Importantly, since NNMT inhibitors significantly modulated key regulators of cellular energy homeostasis and gene transcription (e.g., NAD+, SAM), these inhibitors are expected to be additionally beneficial in treating a broad spectrum of aging-related disorders.

Keck Seminar

Friday, October 6, 4pm

BioScience Research Collaborative

Room 280 (2nd Floor)

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