

2016 Research Week Proposal Instructions and Template
Posters and Presentations

Title – DAGL inhibitors' role in the progression towards the treatment of metabolic DAGL issues

Program of Study – Biology and Chemistry

Presentation Type – Print Poster

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Category – **Choose one of the following:** Experimental (Applied)

Abstract: Obesity is a significant health problem that has been increasing steadily in the past several years. The investigation of obesity and its accompanying cardiometabolic complications is of critical importance. The endocannabinoid system serves to regulate both the central control of energy balance and peripheral metabolic processes. This regulation affects factors of risk associated with cardiometabolic processes. The endocannabinoid system (ECS) affects the transport of nutrients as well as metabolism and other physiologic processes. The ECS regulates these processes through endogenous ligands such as anandamide, 2-AG and CB1 receptors which are located in various places throughout the body. CB1 receptors can be found in the brain, digestive tract, muscle, and adipose tissue; the ECS has both central and peripheral components which are integrated through neuronal and hormonal signaling. Specifically, our focus will be on the peripheral components of the ECS to discover the plausibility of developing peripherally restricted DAGL inhibitors to play an important role in balancing energy levels. When the ECS is stimulated, one's food intake and adiposity is increased. By extension, when CB1 receptors are not accessible, the food intake and adiposity is decreased. When specifically considering the stimulation of the ECS in the liver, it is apparent that lipogenesis occurs via the

activation of hepatic lipogenic enzymes. There is also increased synthesis of fatty acids. The dysregulation of the metabolism can lead to many different harmful symptoms such as obesity, high blood pressure, resistance to insulin, etc.

DAGL (diacylglycerol lipase) inhibitors have the potential to treat these aforementioned symptoms that result from the dysregulation of metabolism. In addition to this, it may also treat neuroinflammation, addictions, and pathological pain. The effectiveness of DAGL inhibitors needs to be investigated further and more in-depth to include more information about the possibility of developing subtype-selective (peripherally restricted) DAGL inhibitors. **We propose that the discovery of peripherally restricted inhibitors' ability to be developed will hold important headway in the treatment of certain metabolic disorders that are controlled by DAGLs.** These compounds should not penetrate the central nervous system (CNS) due to the known adverse CNS side effects of CB1 antagonists.

The purpose of this research is to review the quantity and effectiveness of DAGL inhibitors to discover their potential to dissipate the affects, and possibly treat metabolic disorders and neurodegeneration. Increasing knowledge about this topic will help us to find out the plausibility of developing peripherally DAGL inhibitors. To do this, it is necessary to analyze the current assays that measure DAGL activity, of which there are several. The assay to be used employs activity-based protein profiling (ABPP). Of the six inhibitor classes identified, glycine sulfonides (reversible inhibitors of DAGL) have been found to be optimized to several compounds that have been found to be peripherally restricted, highly potent, and a dual DAGL α / β inhibitor. More information on compounds such as this can be invaluable in the progress and development of treatments for the metabolism disorders that are regulated by DAGL.