

## **ICTS Pilot project**

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**Title:** Safety and efficacy of 2- arachidonoyl-*sn*-glycerol in treatment of end stage renal disease (ESRD)-related cachexia

**Abstract:** Currently there are more than 450,000 patients with ESRD in the United States who require weekly dialysis. The number of patients with ESRD is expected to increase to more than 750,000 by 2020. In spite of many improvements in dialysis treatment and the adherence of patients and physicians to the quality measures set forth by guidelines, ESRD patients continue to experience an annual mortality rate of approximately 20%, a rate worse than many cancers. In addition, currently there are no therapies available which have proven to be effective in improving survival in ESRD patients. For instance, three large randomized clinical trials failed to show that HMG CoA reductase inhibition (statin therapy) improves survival in patients on maintenance hemodialysis (MHD). Accordingly, the main risk factors responsible for the disproportionately elevated risk of death in these patients may be different than the general population. In fact, traditional risk factors such as obesity and hypertriglyceridemia cannot explain the magnitude of the risk observed in patients with ESRD given that they are paradoxically associated with better survival. **Moreover, there is accumulating evidence that nontraditional risk factors, such as cachexia/wasting caused by impaired/inefficient energy metabolism, may play a more important role in the higher risk of death in ESRD patients than traditional risk factors. Hence, therapies which address the latter pathologic pathways may provide a more effective strategy for improving survival in this patient population.**

In this regard, one novel and promising area which has not been fully explored is the endocannabinoid (ECB) system. There is accumulating evidence that the ECB system plays a major role in energy homeostasis and its activation can prevent cachexia via several different mechanisms. **Recently, we discovered that serum levels of 2-arachidonoyl-*sn*-glycerol (2-AG), a major endocannabinoid transmitter, are significantly increased in patients with ESRD. In addition, the highest serum levels of 2-AG were associated with significantly reduced risk of death. Furthermore, increased serum 2-AG levels were associated with reduced markers of cachexia and wasting.** *We have filed a record of invention as these novel findings raise the intriguing possibility that overactivity of the EC system as indicated by increased serum 2-AG levels may play a protective role in ESRD patients by preventing cachexia/wasting. Furthermore, 2-AG may be an effective potential therapeutic target for treatment of ESRD-related cachexia/wasting which can improve survival these patients.* The next step in the development of this novel idea is to provide proof of concept and mechanistic preclinical data to determine the mechanisms by which EC system can be protective in ESRD and safety/efficacy of 2-AG infusion in an animal model of kidney disease. *We hypothesize that*

1. Elevation of serum 2-AG and overactivity of the endocannabinoid system prevents cachexia and protein energy wasting in ESRD;
2. Infusion of 2-AG may prevent ESRD-related cachexia and wasting in a safe and effective manner.

Based on above hypotheses we propose the following two aims,

Aim I- Determine the impact of ESRD on activity of the renal, hepatic and adipose tissue endocannabinoid system. This will be done in a well-accepted and established rat model of chronic kidney disease (ESRD by 5/6 nephrectomy) with known cachexia/wasting.

Aim II- Determine the effectiveness and safety of 2-AG administration in this animal model of ESRD with wasting. Different dosages of 2-AG will be administered via infusion pumps to assess (i) the effectiveness of 2-AG administration in preventing cachexia, muscle wasting and adipose browning in an animal model of ESRD; and (ii) the safety profile of 2-AG dose regimens that were found to be effective.