

## Using 'Succilators' as potential treatment for IBD and other GI diseases

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### Technology

Succinate is a metabolic intermediate of the tricarboxylic acid (TCA) cycle and a pivotal inflammatory and ischemia-reperfusion signaling molecule. Succinate stimulates the selective G-protein coupled receptor, SUCNR1, which is linked to Diabetes, Hypertension, Arthritis and Inflammatory bowel disease (IBD). Intriguingly, several studies show that intracellular succinate reprograms macrophages (M $\phi$ ) to the pro inflammatory M1 state. Recent appreciation of M $\phi$  heterogeneity, with respect to both development and metabolism, indicates that different lineages of tissue-resident M $\phi$  respond divergently to microbial, environmental and immunological stimuli. Hence, trans epithelial absorption of succinate, which is produced by several bacterial strains of the gut microbiota, may potentially stimulate M $\phi$  polarization causing chronic inflammation.

Research in Dr. Ohana's lab demonstrated that bio-specimens from IBD patients and IBD mouse models contain high concentrations of succinate and are enriched with succinate producing bacteria. In addition, elevated succinate absorption in the kidney leads to hypertension and is associated with kidney stone formation.

Dr. Ohana and his team have used an established enzymatic succinate assay to successfully monitor succinate concentrations in human IBD and kidney stone patients, IBD mouse models, and knockout mice which developed kidney stones and hypertension. The therapeutic goal is to utilize recombinant hSUCNR1 proteins as succinate chelators ('succilators') to treat pathologies associated with high succinate concentrations, predominantly IBD. In parallel, biochemical and mass spectrometry methods will be used to measure succinate concentrations in biological specimens for a better diagnosis of IBD and related additional intestinal symptoms.

### Advantages

- Specificity – The human SUCNR1 is highly specific for succinate binding
- Safety - Since succilators are modified human proteins they are expected to evade immune responses
- Efficiency – Ability to modify the affinity of succilators to succinate by point mutations to generate improve and robust succinate chelators.

### Application

- Treatment for IBD and other diseases associated with high succinate concentrations
- Novel improved diagnostic method of IBD and intestinal symptoms
- Ability to monitor the efficiency of succinate treatment

### Patent

PCT submitted: WO2019/053731A1