PS-111

Preclinical and first-in human development of SGM-1019, a first-in-class novel small molecule modulator of inflammasome activity for the treatment of nonalcoholic steatohepatitis (NASH)

Karim Dabbagh[1], G. Steven Dodson[2], Lynn Yamamoto[2], Bernat Baeza-Raja[2], Andrew W Goodyear[2]
[1]; [2]*Second Genome, Inc, South San Francisco*
Email: karim@secondgenome.com

Background and Aims: Preclinical studies suggest that inflammasome activation in response to diverse stimuli drives liver inflammation and fibrosis in models of NASH. These stimuli include cellular damage in the liver and bacterial products that originate from the gastro-intestinal tract that appear to be increased in the context of western diets associated with chronic liver diseases. The study aimed to confirm that inflammasome activity in rodent NASH models and efficacy of inflammasome inhibition to reduce inflammation and fibrosis in the liver. We also sought to demonstrate the safety and pharmacological activity of SGM-1019, a novel small molecule inhibitor of inflammasome activation, in a non-human primate (NHP) model of liver inflammation and fibrosis, and in healthy human volunteers enrolled in a phase I clinical study.

Methods: Inflammasome activity in animals fed a high fat diet (HFD) was evaluated by measuring IL-1β levels from *ex vivo* stimulated whole blood and in *ex vivo* liver culture supernatants. The effect of inflammasome blockade on the development of liver inflammation and fibrosis was evaluated in the streptozotocin (STZ)-HFD-induced steatosis model of NASH following 10 weeks of treatment. The efficacy of SGM-1019 was evaluated in a 6-week carbon tetrachloride (CCl_4) exposure model of liver fibrosis in NHP. We also evaluated the pharmacokinetics, safety and pharmacodynamic effects of SGM-1019 on inflammasome activation in a phase I single and multiple ascending dose trial in healthy human volunteers.

Results: HFD fed rodents displayed enhanced whole blood IL-1β responses to LPS/ATP stimulation *in vitro* (581 pg/ml chow, 2685 pg/ml HFD, $p<0.0001$). Cultured liver slices from these animals also displayed increased IL-1β secretion (6.58 pg/ml chow, 73.6 pg/ml HFD, $p<0.001$) that was inhibited by inflammasome blockers (34.6 pg/mg IB-1 $p< 0.01$; 33.1 pg/ml IB-2 $p<0.05$). 10-week treatment of diabetic mice on a HFD (STZ-HFD) treated with an inhibitor of inflammasome activation reduced liver histological fibrosis scores by 44% (2 vs 1.125, $p=0.01$). Furthermore, in a 6-week NHP CCl_4 model, bi-daily SGM-1019 treatment for 4 weeks improved total histology scores ($p<0.01$) driven primarily by improvements in fibrosis, hepatocyte degeneration and inflammation. Finally, SGM-1019 was safe and well tolerated in healthy human volunteers dosed for 2 weeks at all doses evaluated. Pharmacodynamic evaluation demonstrated that at the doses tested, SGM-1019 significantly inhibited inflammasome activation over the dosing period as measured by IL-1β release from *ex vivo* stimulated whole blood.

Conclusion: These studies demonstrate that the inflammasome plays a critical role in the pathogenesis of liver fibrosis and NASH, and that inhibition of inflammasome activation with SGM-1019 is a novel and potentially safe and effective way of treating patients with chronic liver diseases.