Sensor Pharmaceuticals, Inc.

Discovering orally delivered, gut-restricted entities

The gut defines a boundary between self and non-self. The cells lining the gut lumen police this frontier, letting in useful nutrients while keeping microbes in check. Because of this, nutrition and inflammation are intimately connected: a high-fat diet can increase inflammation in the intestines, driving chronic metabolic disorders, such as obesity and diabetes, inflammatory bowel disease and even colorectal cancer. Sensor Pharmaceuticals aims to interrupt this harmful cascade by targeting these inflammation-causing pathways with oral, gut-restricted therapeutics.

Sensor's proprietary platform technology, Synitivity, allows oral delivery of small-molecule drugs, peptides and potentially proteins in a form that maintains them in the gut without significant systemic uptake. This may confer a safety advantage, as some of these nutrient-sensing receptors are also expressed in other organs, including the brain and liver. Retention of active agents in the gut lumen may also make Synitivity more appealing than naturally occurring (or supplemented) probiotics. Finally, according to James Hauske, Sensor's CEO and founder, the approach also delivers multiple agents that may act synergistically to combat multigenic, multifactor diseases, such as diabetes.

Sensor uses this approach targeting the complex molecular circuitry connecting diet, inflammation and disease. The gut contains diverse target cell populations, including intestinal epithelial cells, which serve both barrier and secretory functions, and L cells, which affect glucose tolerance and insulin sensitivity. Receptors expressed on these cells recognize by-products of gut microbiome metabolism. Intestinal T cell populations are also regulated in part by nutrient-sensing receptors. Multiple G-protein-coupled receptors (GPCRs), for example, are known to induce the release of proinflammatory cytokines in response to fatty acids, and Toll-like receptor 4 activates similar pathways in response to bacterial lipopolysaccharides.

Using both receptor-based and whole-cell models to assess anti-inflammatory activity, as measured by proinflammatory cytokine production, Sensor has identified candidate molecules with *in vitro* activity. These agents exert effects through varied receptor types, including GPR-109a, -41, -43 and -120, as well as the pattern-recognition receptor Toll-like receptor 4. In addition to activity *in vitro* against various molecular and cellular targets, several of these compounds inhibit disease induction *in vivo* in well-validated animal models, including diet-induced obesity, ob/ob mice and dextran sulfate sodium–induced colitis. Notably, gut-restricted multimediator compound SEN-18,438-2 has shown activity both *in vitro*, acting as a GPR-43 agonist (40 nM) and cannabinoid receptor 1 antagonist (25 nM), and *in vivo* in the rodent diet-induced obesity model, in which oral dosing at 250 mg/kg led to reductions in weight (27%) and amounts of tumor necrosis factor-α (12%). Additionally, SEN-943,081-2, a dual agonist active against GPR-43 and GPR-109a (90 and 100 nM, respectively), upon oral delivery at 350 mg/kg demonstrated better gut-mucosal healing in the rodent dextran sulfate sodium–induced colitis model than either azathioprine or cyclosporin A.

contact
Jim Hauske, President and Founder
Sensor Pharmaceuticals, Inc.
La Jolla, California, USA
Tel: +1-858-551-8294
Email:
jim.hauske@sensorpharmaceuticals.com