Inhibitors for Treatment of Metabolic Syndrome and Diabetes

Company successfully discovered and optimized the first small molecule allosteric inhibitors of ACC achieving excellent potency, selectivity and drug-like properties within 12 months

CAMBRIDGE, Mass. – January 28, 2013 – Nimbus Discovery LLC, a biotechnology company discovering novel medicines against exciting but previously inaccessible drug targets, will present preclinical data today at the Keystone Symposia Conference: Adipose Tissue Biology in Keystone, Colo., that show that the company has identified a series of novel, highly potent, and highly selective Acetyl CoA Carboxylase (ACC)1/2 allosteric inhibitors. Inhibition of ACC reduces fatty acid synthesis and stimulates fatty acid oxidation and has the potential to favorably affect the morbidity and mortality associated with obesity, diabetes, and fatty liver diseases.

Most efforts to discover ACC inhibitors have focused on interactions within the carboxyltransferase (CT) domain of the enzyme active center resulting in poor drug-like properties and have thus failed to provide benefit to patients. In contrast, Nimbus focused on the biotin carboxylase (BC) domain where the natural product soraphen interacts. Nimbus ACC allosteric inhibitors demonstrate excellent drug-like properties and show liver-muscle exposure that is aligned with driving outstanding pharmacology in preclinical models of disease.

Key findings of the Nimbus compounds presented at the conference include:

- Development of this series of ACC inhibitors has yielded deep structure-activity relationships, sub-nanomolar enzyme inhibition, functional activity in cellular assays and favorable drug-like properties leading to *in vivo* proof of concept.
- ND-630, the Nimbus lead compound, potently inhibits hepatic fatty acid synthesis (ED_{50} = 0.14 mg/kg) in a highly dose-dependent manner and stimulates whole

body fatty acid oxidation (minimum effective dose 3 mg/kg) in preclinical models of disease.

"Using our state-of-the art structure-based drug design approach, Nimbus was able to identify potent small molecule ACC inhibitors, with excellent pharmaceutical properties, 12 months after hits were generated from an *in silico* screen. We believe that we are the first company to create drug-like allosteric inhibitors against ACC. The impressive potency and selectivity of our molecules could translate into significant safety and efficacy benefits in the clinic," said Rosana Kapeller, M.D., Ph.D., Chief Scientific Officer of Nimbus. "We are now conducting a detailed pharmacological evaluation of this broad portfolio of potent allosteric inhibitors, including ND-630, and will provide an update on these data in metabolic disease, diabetes and cancer tumor metabolism models in the near future."

About Nimbus

Nimbus Discovery, a biotechnology company, harnesses cutting-edge computational technologies to uncover breakthroughs in small molecule pharmacology. We focus on medically important and highly sought-after disease targets that have proven inaccessible to traditional industry approaches. Our robust pre-clinical pipeline includes novel agents for the treatment of cancer, metabolic disease and inflammation. Nimbus is organized as a constellation of small, nimble teams of experienced drug-hunters deployed across program-focused subsidiary companies. Each team is freed from conventional barriers to scientific success, chartered to create solutions, and geared for program asset deals with leading pharmaceutical companies. Founded in 2009, Nimbus partnered with Schrödinger to invent and apply a physics-based approach that establishes a new standard for rational drug design. Nimbus is backed by world-class life science investors, including Atlas Venture, SR One, Lilly Ventures and Bill Gates. For more information please visit www.nimbustx.com.