NIMBUS
THERAPEUTICS

Selective ACC Inhibitors Dramatically Impact Tumor Growth

First-time data are being presented showing application of selective ACC inhibitors in pre-clinical models of small cell lung cancer and liver cancer

Company successfully leverages cancer metabolism strategy to achieve potent anti-tumor effects in difficult-to-treat cancers; potential for whole new treatment approach

CAMBRIDGE, Mass. – April 1, 2014 – Nimbus Discovery LLC, a biotechnology company discovering novel medicines against exciting but previously inaccessible drug targets, today announced that data on its Acetyl CoA Carboxylase (ACC) program will be presented at the 105th Annual Meeting of the American Association for Cancer Research. Nimbus will present data in two abstracts showing activity with ND-646 and ND-654 in non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC) respectively. The conference will take place on April 5–9that the San Diego Convention Center, San Diego, California.

Continuous formation of fat as a source of energy is a common feature of tumor cells and is required to meet the demands of a growing tumor. ACC is the rate-limiting enzyme in the synthesis of new fat, and is up-regulated in many types of cancer, making ACC an attractive target for the prevention of tumor growth. Nimbus is the first company that has successfully designed allosteric inhibitors targeting ACC. The Nimbus small molecules have excellent drug-like properties, high potency, and are tissue-targeted, leading to outstanding pharmacology in preclinical models of disease. These preclinical anti-tumor data are especially encouraging given the lack of treatment options available to combat NSCLC and HCC. In particular, a highly potent and targeted treatment for HCC would be a welcome alternative to currently available drugs that have significant side effects and modest efficacy.

Abstract #1427
Title: Liver Selective Acetyl-CoA carboxylase inhibition by ND-654 Decreases

Hepatocellular Carcinoma Development in Cirrhotic Rats
Authors: Danielle K. DePeralta[1], Lan Wei[1], Geraldine Harriman[2], Jeremy Greenwood[3], Sathesh Bhat[3], William Westlin[2], H. James Harwood, Jr.[2], Rosana Kapeller[2], Kenneth K. Tanabe[1], Bryan C. Fuchs[1].
[1]Massachusetts General Hospital, Boston, MA; [2]Nimbus Discovery, Cambridge, MA; [3]Schrödinger, New York, NY
Date: Monday, April 7, 2014
Presentation Time: 8:00 AM – 12:00 PM (PT)
Location: Hall A-E, Poster Section 18

Summary

- ND-654, an allosteric inhibitor, inhibited the enzymatic activity of both ACC1 (IC_{50} = 3 nM) and ACC2 (IC_{50} = 8 nM), and inhibited fatty acid synthesis in HepG2 cells (IC_{50} = 14 nM) and in rats (ED_{50} = 0.3 mg/kg)
- This hepatoselective inhibitor reduced tumor burden in hepatocellular carcinoma model by 65%, when rats were treated with 10 mg/kg PO daily for 5 weeks; similar exposures in cirrhotic and tumor tissue were achieved at steady state
- ND-654 significantly improved survival rate of DEN-treated rats with hepatocellular carcinoma
- In conclusion, these results provide further evidence that de novo lipogenesis is an important mediator of hepatic carcinogenesis and that selective inhibition of hepatic ACC is a potential therapeutic strategy for HCC

Abstract #2679
Title: Acetyl-CoA Carboxylase Inhibition by ND-646 Reduces Fatty Acid Synthesis and Inhibits Cell Proliferation in Human Non-Small Cell Lung Cancer Cells
Authors: Robert Svensson[1], Geraldine Harriman[2], Jeremy Greenwood[3], Sathesh Bhat[3], H. James Harwood[2], Rosana Kapeller[2], Reuben Shaw[1].
[1]Salk Institute for Biological Studies, San Diego, CA; [2]Nimbus Discovery, Cambridge, MA; [3]Schrödinger, New York, NY
Date: Monday, April 7, 2014
Presentation Time: 1:00 PM – 5:00 PM (PT)
Location: Hall A-E, Poster Section 32

Summary

- ND-646, a potent and selective allosteric ACC inhibitor, demonstrated significant anti-proliferative effects in several NSCLC cell types

- This effect was enhanced in de-lipidated media and attenuated when media was supplemented with palmitate, suggesting that the anti-proliferative effects ND-646 is induced by depletion of cellular fatty acids
- A novel PD biomarker has been identified that can be used to determine target engagement in NSCLC and other tissues *in vivo* and *in vitro*
- ND-646 is currently being tested in NSCLC pre-clinical models

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. The company has been named by FierceBiotech as one of 2013's Fierce 15, designating it as one of the most promising private biotechnology companies in the industry. For more information please visit www.nimbustx.com.