NIMBUS
THERAPEUTICS

Irak4 Inhibitors Synergize with Ibrutinib

Potential to increase durability and response rates in lymphoid malignancies

Novel genetically targeted therapy for tumors with activating L265P MyD88 mutation

Data presented at the 54th American Society of Hematology Annual Meeting

CAMBRIDGE, Mass. – December 9, 2012 – Nimbus Discovery LLC, a biotechnology company discovering novel medicines against exciting but previously inaccessible disease targets, will present preclinical data today that show that the novel Nimbus IRAK4 inhibitors (ND-2110 and ND-2158) when combined with the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, work synergistically to induce selective cell death in hematological tumors with the activating MyD88 mutation. This genetically-defined patient population can be identified in the clinic prior to treatment increasing the potential for positive response. These findings were generated in collaboration with Louis M. Staudt, M.D., Ph.D., Head, Molecular Biology of Lymphoid Malignancies Section at the National Cancer Institute.

IRAK4 and BTK are well-known signaling kinases required for tumor cell survival and proliferation. The synergism of IRAK4 and BTK inhibition was demonstrated in both ABC-DLBCL and Waldenström's macroglobulinemia tumor cells at the 54th American Society of Hematology Annual Meeting being held at the Georgia World Congress Center in Atlanta, Ga.

"Nimbus is the first drug developer to uncover the underlying drivers of potency and selectivity for IRAK4, enabling us to identify truly selective IRAK4 inhibitors in less than two years since the company was founded," said Rosana Kapeller, M.D., Ph.D., Chief Scientific Officer of Nimbus. "These data highlight that our novel compounds have the potential to treat a genetically identified patient population, who lack effective treatment options, with a highly targeted cancer treatment with improved likelihood of clinical

success. We expect to initiate clinical studies in patients with hematological tumors in 2014."

Abstract #62 IRAK4 Kinase As A Novel Therapeutic Target in the ABC Subtype of Diffuse Large B Cell Lymphoma

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B401-B402, Level 4, Building B (Georgia World Congress Center)

- The American Cancer Society estimates there will be 79,190 new patients diagnosed with lymphoma in 2012 and approximately 20,130 deaths
- Oncogenic MyD88 mutations are present in 39% of activated B-cell-like diffuse large B-cell lymphoma (ABC DLBCL), and many other lymphoid malignancies
- Oncogenic $MyD88^{L265P}$ constitutively engages IRAK4/IRAK1 kinases to activate the canonical NF-kB pathway and promote lymphoma cell division and survival
- IRAK4 kinase activity is obligatory for $MyD88^{L265P}$-driven oncogenic signaling
- IRAK4 inhibitors are universally toxic towards ABC DLBCL tumors containing $MyD88^{L265}$ but not cell lines with wild type MyD88 or germinal center B-cell-like (GCB) DLBCL, consistent with the highly specific mechanism of action.
- ND-2158 is well-tolerated in NOD-SCID mice, and shows single agent activity in a DLBCL xenograft (OCI-LY10)
- The compounds demonstrate good pharmacologic drug-like properties and are expected to have a suitable safety profile for clinical evaluation
- Preclinical data strongly support pharmacologic inhibition of IRAK4 kinase activity as a novel and promising therapeutic strategy for treatment of MyD88-mutated DLBCL, and potentially other lymphoid malignancies
- Combined inhibition of BTK and IRAK4 signaling should be explored as a novel therapeutic strategy in ABC DLBCL

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.