Regenacy Pharmaceuticals Demonstrates Reversal of Chemotherapy-Induced Peripheral Neuropathy with HDAC6 Inhibitor Ricolinostat in Preclinical Model

-- Results from Preclinical Studies of Selective HDAC6 Inhibitors Published Online in PAIN –

BOSTON – March 8, 2017 – Regenacy Pharmaceuticals, LLC, a clinical-stage biopharmaceutical company that is regenerating biological function by selective protein acetylation, today announced the publication of data demonstrating reversal of chemotherapy-induced peripheral neuropathy after treatment with HDAC6 inhibitors including ricolinostat in a preclinical model. The article, titled "HDAC6 Inhibition Effectively Reverses Chemotherapy-Induced Peripheral Neuropathy," was published online in *PAIN*, the official Journal of the International Association for the Study of Pain.

The studies were conducted in the laboratory of Annemieke Kavelaars, Ph.D. and Cobi J. Heijnen, Ph.D. at the University of Texas MD Anderson Cancer Center, in collaboration with scientists from the former Acetylon Pharmaceuticals and the Center for Systems Biology at Massachusetts General Hospital. Regenacy received an exclusive license from Celgene Corporation to the selective HDAC6 inhibitor, ricolinostat (ACY-1215), for the treatment of neuropathies and other non-cancer disease indications as part of the spin out of Regenacy from Acetylon Pharmaceuticals in December 2016 prior to the acquisition of Acetylon by Celgene.

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common adverse effects of cancer treatment, resulting in pain, numbness, tingling, and temperature sensitivity typically localized in the hands and feet. The occurrence of CIPN can disrupt cancer treatment and greatly reduce the quality of life for cancer survivors, but despite its high prevalence and severity, there are currently no effective FDA-approved drugs to prevent or reverse CIPN. Cisplatin, a platinum-based chemotherapeutic agent, as well as taxanes, are commonly used for the treatment of solid tumors but are associated with a high incidence of CIPN.

In a preclinical model of cisplatin-induced peripheral neuropathy, the highly selective HDAC6 inhibitor, ACY-1083, was shown to prevent and reverse pain in response to touch, known as mechanical allodynia. Reversal of cisplatin-induced mechanical allodynia in the preclinical model was also observed after treatment with the selective HDAC6 inhibitor ricolinostat (ACY-1215) that is currently in clinical trials for cancer treatment. These observations were extended to a rat model of taxol-induced neuropathy. Additionally, the data demonstrated a reversal of cisplatin-induced spontaneous pain and numbness after treatment with ACY-1083. This reversal of cisplatin-induced neuropathy by HDAC6 inhibition was associated with a restoration of intraepidermal nerve fiber density, which is reduced by cisplatin treatment, indicating that HDAC6 inhibition results in re-growth of nerves into the skin.

"These data demonstrate that HDAC6 is a novel therapeutic target for the treatment of chemotherapy-induced neuropathies, for which there are currently no FDA-approved drugs," said Matthew B. Jarpe, Ph.D., Associate Vice President of Biology at Regenacy. "These findings have implications for addressing the primary dose-limiting toxicity of cisplatin and taxanes. An HDAC6 inhibitor like ricolinostat could potentially be used in conjunction with platinum- or taxane-based chemotherapy to allow for higher and/or longer chemotherapy dosing regimens and potentially improved clinical outcomes for many patients with solid tumors. Additionally, the reversal of both pain and numbness in this preclinical model suggests that an HDAC6 inhibitor could be used after a course of chemotherapy is completed to treat and potentially reverse resultant debilitating CIPN symptoms that impact function and quality of life for many patients. Preclinical results seen with the clinical candidate ricolinostat highlight the translational potential of these findings to the clinic."

"The utility of selective HDAC6 inhibition for the treatment of neuropathy was previously demonstrated in a study evaluating ricolinostat as a pharmacologic therapy for a comparatively rare inherited motor neuropathy, axonal Charcot-Marie-Tooth disease,[1] and the peer reviewed article published today in the medical journal *PAIN* provides further validation of the potentially broad applicability of HDAC6 inhibition for a range of neuropathies," said Walter C. Ogier, President and Chief Executive Officer of Regenacy. "These studies support the continued clinical development of ricolinostat to provide potential functionally restorative therapy to patients with diseases including peripheral neuropathy in which intracellular protein function and organelle transport is dysregulated. As ricolinostat has completed Phase 2 clinical development in cancer, it is now poised for the initiation of Phase 2 clinical trials in neuropathy and other non-cancer disease indications."

About Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most commonly and widely reported adverse side effects of cancer treatment, with the overall incidence of CIPN ranging from 30%–80% in patients treated for cancer, depending on the chemotherapy regimens used and the duration of treatment. The symptoms of CIPN include pain, numbness, tingling, and temperature sensitivity, and the occurrence of CIPN can limit chemotherapeutic dosage, delay additional treatment cycles, and lead to early termination of treatment – each potentially reducing the benefit of chemotherapy. Moreover, CIPN frequently persists or even worsens after completion of chemotherapy, reducing long-term quality of life for cancer survivors. Despite the high prevalence and severity of CIPN, there are currently no effective FDA-approved drugs to prevent or reverse CIPN.

About HDAC6 Inhibition

Regenacy's lead clinical candidate, ricolinostat (ACY-1215), and the non-clinical proof-of-concept compound, ACY-1083, each selectively inhibit the intracellular enzyme HDAC6, a histone deacetylase that is known to have specificity for cytoplasmic, non-histone cellular proteins. Those proteins include α-tubulin, a principal structural component of microtubules which, inside peripheral neurons, are up to several feet in length. HDAC6 is thought to regulate multiple intracellular processes such as protein degradation, cell motility, and cell-cell interactions and has been implicated in the regulation of mitochondrial and protein transport along microtubules. Selective inhibition of HDAC6 as a therapeutic

target thus may have positive implications for the treatment of malignancies, neuropathies, and ciliopathic diseases such as polycystic kidney disease.

About Regenacy

Regenacy Pharmaceuticals, LLC is a clinical-stage biopharmaceutical company regenerating biological function by protein acetylation for the treatment of peripheral neuropathies, ciliopathic/polycystic diseases, hemoglobinopathies, cognitive disorders and oncology indications. The company's selective inhibition technology provides superior safety profiles and potential enhanced efficacy compared to non-selective HDAC inhibitors. Regenacy's programs selectively inhibit histone deacetylase 6 (HDAC6) to restore normal intracellular protein and organelle transport in diabetic and other peripheral neuropathies and in ciliopathic/polycystic diseases, and selectively inhibit HDACs 1 and 2 to restore oxygen transport in orphan blood disorders such as sickle cell disease and beta-thalassemia, regenerate normal cognitive function in patients with psychiatric disorders, and restore normal bone marrow function through differentiation of acute myeloid leukemia (AML) cells. www.regenacy.com

References:

[1]Benoy, V. et. al. 2016. Development of Improved HDAC6 Inhibitors as Pharmacological Therapy for Charcot-Marie-Tooth Disease. *Neurotherapeutics*. DOI: 10.1007/s13311-016-0501-z

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