Hybrigenics gets European patent protection for inhibitors of Ubiquitin-Specific Protease 8 (USP8)

- A European patent covering new small molecules inhibiting USP8 has been granted to Hybrigenics
- USP8 is involved both in the resistance of lung cancer to anti-EGFR therapies and in the genetic cause of many Cushing's disease cases
- HBX 96,819, Hybrigenics' USP8 inhibitor, has shown activity in both preclinical models of EGFR-resistant lung cancer and Cushing's disease

Paris, France, on June 6th, 2017 – Hybrigenics (ALHYG), a bio-pharmaceutical company listed on the Alternext market of Euronext Paris, with a focus on research and development of treatments against proliferative diseases, today announces the grant of a European patent protecting a series of new small molecules inhibiting Ubiquitin-Specific Protease 8 (USP8). On this occasion, Hybrigenics emphasizes the potential of USP8 as an innovative target for drug discovery in lung cancer and in Cushing's disease.

Hybrigenics' pioneer research in the field of USPs has already resulted in worldwide granted patents covering two different series of specific inhibitors of USP7. One of these compounds showed activity in preclinical models of human chronic lymphocytic leukemia (cf. press release of May 18, 2017). Now, Hybrigenics has discovered an innovative chemical modification which switches inhibition from USP7 to USP8 and recently secured European patent protection for a series of USP8 inhibitors derived from its own proprietary USP7 inhibitors. HBX 96,819, Hybrigenics' lead USP8 inhibitor, is the basis for further chemical optimization.

USP8 is a key factor in the cell recycling of the receptor for Epidermal Growth Factor (EGFR) which is an important target in oncology: small molecule EGFR inhibitors, such as gefitinib (Iressa®, AstraZeneca) or erlotinib (Tarceva®, Roche), are widely used for the treatment of advanced lung cancer. A collaboration between American and Korean researchers[1,2] have demonstrated that this recycling contributes to the resistance of lung cancer cells to EGFR inhibitors. They showed that HBX 96,819 effectively killed human lung cancer cell lines, irrespective of their resistance to gefitinib, both *in vitro* and in *in vivo* xenografts in mice.

In a totally different field, activating mutations of USP8 have recently been found in at least 35% of human Cushing's disease (CD) cases. CD is characterized by the non-cancerous proliferation of certain cells of the pituitary gland in charge of secreting adrenocorticotrophic hormone (ACTH). The physiological role of ACTH is to stimulate the secretion of cortisol by the adrenal glands. In CD patients, in addition to forming benign tumors, these cells secrete too much ACTH, and CD patients suffer from too high levels of cortisol, leading to a "moon face" appearance, obesity, diabetes, reproductive disorders and increased cardiovascular risk. In the *in vitro* model of CD, the AtT20 cells in culture, HBX 96,819 managed to inhibit cell proliferation and to decrease the secretion of ACTH[3].

"*USP8 has emerged in the last few years as a very attractive new therapeutic target with two totally different applications: lung or other cancers when they have developped resistance to previously effective anti-EGFR therapies and, much more surprisingly, Cushing's disease. Hybrigenics, with its recently granted European patent, positions itself at the forefront of USP8 inhibition by small molecules in these two new indications, in addition to its long standing interest in USP7 inhibitors in hemato-oncology*," said Remi Delansorne, Hybrigenics' CEO.

1 Jeong C.H., J. Cancer Prev., 2015; [2] Byun et al., Clin. Cancer Res., 2013; [3] Jian et al., Chin. Med. J., 2016

About deubiquitinylating enzymes (DUBs) and ubiquitin-specific proteases (USPs)

Ubiquitins are small intracellular regulatory peptides which, when “stuck” by ligases to proteins, “label” them for destruction by the proteasome, the protein “shredder” present in each living cell. The role of DUBs is to remove ubiquitins from proteins, preventing them from degradation: DUBs are “protein-recycling” enzymes. The class of USPs is part of the wider family of DUBs. Some USPs can recycle oncoproteins, the proteins involved in cancer initiation or progression. Inhibiting such USPs results in the forced degradation of oncoproteins and therefore in a totally new mechanism of anticancer action.

About Hybrigenics

Hybrigenics (www.hybrigenics.com) is a bio-pharmaceutical group listed (ALHYG) on the Alternext market of Euronext Paris, focusing its internal R&D programs on innovative targets and therapies for the treatment of proliferative diseases.

Hybrigenics’ development program is based on inecalcitol, a vitamin D receptor agonist active by oral administration. Inecalcitol has been tested in chronic lymphocytic leukemia patients, an indication for which inecalcitol has received orphan drug status in Europe and the United States. Two clinical Phase II studies of inecalcitol are currently ongoing in chronic myeloid leukemia and acute myeloid leukemia. Oral inecalcitol has shown excellent tolerance and strong presumption of efficacy for the first-line treatment of metastatic castrate-resistant prostate cancer in combination with Taxotere®, which is the current gold-standard chemotherapeutic treatment for this indication.

Hybrigenics’ research program is exploring the role of enzymes called Ubiquitin-Specific Proteases (USP) in the balance between degradation and recycling of proteins called onco-proteins due to their involvement in various cancers. Hybrigenics is evaluating the interest of inhibitors of USP as anti-cancer drug candidates. Hybrigenics has collaborated with Servier on one particular USP in oncology. In this R&D program, two milestones have been reached and additional milestones may be achieved until registration of a potential drug.

Hybrigenics Pharma Inc., based in Cambridge, Mass., is the U.S. subsidiary of Hybrigenics.

Hybrigenics is listed on the Alternext market of Euronext Paris

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