Hybrigenics' compound inhibits Ubiqitin-Specific Protease 10 (USP10) and shows activity in preclinical models of Acute Myeloid Leukemia (AML)

- **A team of researchers at Harvard Medical School and Dana-Farber Cancer Institute, has published in the prestigious journal *Nature Chemical Biology* results with HBX 19,818, an inhibitor patented by Hybrigenics, demonstrating its efficay to inhibit USP10 and to kill human FLT3-mutated AML cells *in vitro***
- **HBX 19,818 synergizes with midostaurin (Rydapt®), the FLT3 inhibitor recently approved and launched by Novartis for FLT3-mutated AML**

Paris, France, on October 9th, 2017 – Hybrigenics (ALHYG), a bio-pharmaceutical company listed on the Euronext Growth market of Euronext Paris, with a focus on research and development of new anticancer treatments, today announces the publication by a team of researchers led by Prof. James D. Griffin, from Harvard Medical School and the Dana-Farber Cancer Institute in Boston, Mass., USA, of a scientific article[1] in the prestigious journal "*Nature Chemical Biology*". This publication identifies USP10 "*as a critical effector enzyme of tumor growth and survival in subjects with FLT3-mutated AML*" and reports that "*the top hit from our screen, HBX 19,818, led to striking and selective antiproliferative effects against mutant-FLT3-positive* [AML] *cells*".

FLT3 is a gene coding for the fms-related tyrosine kinase #3 (FLT3-kinase) which is involved in the stimulation of hematopoiesis, the process by which blood cells are formed. AML is a blood cancer characterized by the rapid uncontrolled proliferation of myeloblasts, precursor cells of the myeloid lineage in the early stage of hematopoiesis. In about 30% of AML cases, proliferating myeloblasts have an activating mutation of the FLT3-kinase, which becomes an oncoprotein. In April 2017, the FLT3-kinase inhibitor midostaurin has been launched for mutant-FLT3-positive AML by Novartis (Rydapt®), the first new product approved for AML in more than 25 years.

However, resistance to midostaurin, like to all kinase inhibitors in general, may develop overtime. An alternative strategy has been discovered by the team of researchers at Harvard: they found that the FLT3-kinase is "recycled", *i.e.* rescued from natural intracellular degradation by the proteasome, by Ubiquitin-Specific Protease #10 (USP10). They further found that HBX 19,818, an inhibitor discovered and patented by Hybrigenics, was a good inhibitor of USP10 and able to markedly inhibit the "recycling" of FLT3-kinase, thereby forcing its degradation. With much less or no FLT3-kinase activity left as a result of HBX 19,818 activity, myeloblasts stopped proliferating. Similarly, with less FLT3-kinase to inhibit, midostaurin showed *in vitro* efficacy at lower concentrations when combined with HBX 19,818: this is the basis of the synergy between the two compounds acting by two distinct and complementary mechanisms of action.

"*This study validates the importance of Ubiquitin-Specific Protease 10 (USP10) as a new therapeutic target to potentially treat Acute Myeloid Leukemia cases characterized by mutations of the FLT3-kinase. Hybrigenics holds a pioneering position in the field of USP research and owns several patents protecting diverse series of small molecule USP inhibitors. One of them, HBX 19,818 was already well known to inhibit USP7 and to kill human Chronic Lymphocytic Leukemia cells both* in vitro *and* in vivo *in preclinical mice models* (cf. Hybrigenics'

[1] Weisberg et al., Nature Chem. Biol. 2017

press release of May 18, 2017). *HBX 19,818 has now been shown to be a dual inhibitor of both USP7 and USP10 with a potent effect on human FLT3-mutated AML cells and a synergistic activity with midostaurin, a FLT3-kinase inhibitor recently launched for mutant-FLT3-positive AML,"* summarized Remi Delansorne, Hybrigenics' CEO who added: "*These results, published in the prestigious journal* Nature Chemical Biology*, represent another very encouraging proof that inhibition of de-ubiquitinating enzymes to force the degradation of oncoproteins is a valid strategy. It also highlights the potential of HBX 19,818 as a lead compound to optimize for Chronic Lymphocytic Leukemia and/or Acute Myeloid Leukemia.*"

The publication abstract can be viewed online at: https://www.ncbi.nlm.nih.gov/pubmed/28967922

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 company listed (ALHYG) on the Euronext Growth 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 Euronext Growth market of Euronext Paris

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