Hybrigenics' inhibitor of Ubiquitin-Specific Protease 7 (USP7) shows activity in preclinical models of Chronic Lymphocytic Leukemia (CLL)

- A team of researchers led by Prof. Stankovic in Birmingham, United Kingdom, has published results on the death of human CLL cells induced by inhibition of USP7 *in vitro* and *in vivo*
- HBX 19,818, a USP7 inhibitor patented by Hybrigenics, kills human CLL cells *in vitro* and *in vivo*
- HBX 19,818 synergizes with DNA alkylating chemotherapeutic agents like cyclophosphamide
- HBX 19,818 also kills chemo-resistant human CLL cells *in vitro* and *in vivo*

Paris, France, on May 18th, 2017 – Hybrigenics (ALHYG), a bio-pharmaceutical company listed on the Alternext 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. T. Stankovic in Birmingham, United Kingdom, of a scientific article[1] in the prestigious journal "*Blood*" of the American Society of Hematology. This publication describes the cytotoxic activity of the inhibition of Ubiquitin-Specific Protease 7 (USP7) on human Chronic Lymphocytic Leukemia (CLL) cells *in vitro* and *in vivo*.

Researchers from the Institute of Cancer and Genomic Sciences of the University of Birmingham, and from the Centre for Clinical Hematology of the Queen Elizabeth Hospital in Birmingham, United Kingdom, under the leadership of Prof. T. Stankovic, have studied the impact of USP7 inhibition on human CLL cells in culture *in vitro*, or *in vivo* when xenografted to mice. They have used either RNA interference to knock-down the expression of the USP7 gene or HBX 19,818, a small molecule discovered and patented by Hybrigenics which specifically inhibits USP7, on primary CLL cells collected from 52 CLL patients or on the human Mec1 CLL cell line.

Inhibition of USP7 by HBX 19,818 alone resulted in CLL cell death by accumulation of damaged unrepaired DNA. This mechanism of action based on impairing DNA repair is the basis for a strong synergism with DNA-alkylating chemotherapeutic agents such as cyclophosphamide, one of the three components of the standard FCR (for Fludarabine-Cyclophosphamide-Rituximab) immuno-chemotherapy for CLL.

Furthermore, HBX 19,818 alone was also able to kill chemo-resistant CLL cells, such as the Mec1 cell line. When xenografted to immune-compromised mice, the Mec1 cells spread in the whole body and especially accumulate in the spleen. HBX 19,818, given alone twice weekly for two weeks by intravenous injections at the dose of 5 or 10 mg/kg, managed to reduce the increase in weight and the density of Mec1 cells of the spleen of treated mice.

Hybrigenics has discovered two different series of specific inhibitors of USP7, one reversible and the other irreversible, also called "suicide inhibitors". HBX 19,818 is the lead compound of the irreversible "suicide" series, patented worldwide until 2031. A lead compound of the reversible series, patented worldwide until 2032, will soon be tested in the same CLL models by the same English team.

[1] Agathanggelou et al., Blood 2017

"*This study validates the importance of Ubiquitin-Specific Protease 7 (USP7) as a new therapeutic target to potentially treat Chronic Lymphocytic Leukemia. Hybrigenics owns two patented series of small molecules specifically inhibiting USP7, one reversible and the other irreversible, to which HBX 19,818 belongs. HBX 19,818 is the first USP7 inhibitor showing the potential to kill human Chronic Lymphocytic Leukemia cells both* in vitro *and* in vivo *in preclinical mice models, alone or in synergy with cyclophosphamide, a key component of the standard immuno-chemotherapy of Chronic Lymphocytic Leukemia. Furthermore, HBX 19,818 showed single agent activity on chemo-resistant Chronic Lymphocytic Leukemia cells*," summarized Remi Delansorne, Hybrigenics' CEO who added: "*These results, published in the prestigious journal* Blood*, represent a very encouraging preclinical demonstration of therapeutic potential. The path forward now for Hybrigenics is to select our best series and chemically optimize it, prior to choosing a drug candidate to develop.*"

The publication abstract can be viewed online at: https://www.ncbi.nlm.nih.gov/pubmed/28495793

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 metastastic 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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