HYBRIGENICS

Press Release

Hybrigenics presented expanded *in vitro* results on inecalcitol in multiple myeloma and acute myeloid leukemia

- **Hybrigenics' complete results on the stimulation of the CD38 antigen by inecalcitol have been presented at the annual ASH meeting in San Diego, USA**

- **It has been confirmed that inecalcitol increases the expression of CD38 at the surface of five multiple myeloma (MM) cell lines *in vitro*; therefore, inecalcitol could potentiate the clinical response of MM patients to a therapeutic anti-CD38 monoclonal antibody**

- **It has also been confirmed that inecalcitol induces the expression of the CD38 antigen at the surface of four acute myeloid leukemia (AML) cell lines *in vitro*; as a result, inecalcitol could render AML patients sensitive to a therapeutic anti-CD38 monoclonal antibody**

Paris, France, 05 December 2016 – Hybrigenics SA (ALHYG), a bio-pharmaceutical company listed on the Alternext market of Euronext in Paris, with a focus on research and development of new treatments against proliferative diseases, presented on December 4th at the 58th Annual Meeting of the American Society of Hematology (ASH) in San Diego, United States, expanded *in vitro* results showing that inecalcitol reproducibly stimulates the expression of the CD38 antigen at the surface of human multiple myeloma (MM) or acute myeloid leukemia (AML) cell lines in culture.

The initial results have already been published on line (cf Hybrigenics' press release of November 03, 2016; https://ash.confex.com/ash/2016/webprogram/Paper90126.html). Hybrigenics' research team has shown that, in normal *in vitro* culture conditions, the two human MM cell lines, MM1.S and L-363, showed a different mix of CD38 positive (CD38+) and CD38 negative (CD38-) cells. After treatment by inecalcitol, all MM cells became CD38+ and the total concentration of CD38 at their surface was multiplied by 5. It was also found that, despite being mostly CD38- in normal *in vitro* culture conditions, all cells from the two human AML cell lines, U-937 and HL-60, became CD38+ after treatment by inecalcitol and the intensity of their CD38 labelling was multiplied by 5 and 12, respectively.

Since these initial observations, similar results have additionally been reproduced on three more MM cell lines (MM.1R, H929 and RPMI-8226) and two more AML cell lines (MOLM-13 and THP1). Only the U266B1 MM cell line remained insensitive to inecalcitol. The time-course of the activity of inecalcitol has also been investigated: its maximal effect is observed as early as 48 hours after the start of treatment of the AML HL-60 cell line and 72 hours with the MM MM.1S cell line. Taken altogether, these results demonstrate an early, potent and reproducible induction of CD38 by inecalcitol at the surface of MM and AML cell lines.

CD38 is the target of daratumumab, the first therapeutic anti-CD38 monoclonal antiboby approved one year ago for relapsed refractory MM (Darzalex®, Genmab and Janssen). Increasing the concentration of CD38 at the surface of CD38+ MM cells can be expected to enhance the efficacy of daratumumab. Similarly, inducing the presence of CD38 at the surface of otherwise CD38- MM or AML cells may render them sensitive to daratumumab.

"*Five out of six human multiple myeloma cell lines and all four human acute myeloid leukemia cell lines tested have responded within 2 to 3 days by a strong and reproducible increase in the expression of the CD38 surface antigen to* in vitro *treatment by inecalcitol. These results strongly support the idea to test in the clinics the combination of inecalcitol with an anti-CD38 therapy such as daratumumab. Inecalcitol may strengthen the use of daratumumab in multiple myeloma and could also open acute myeloid leukemia as a new therapeutic indication for daratumumab*," said Remi Delansorne, Hybrigenics' CEO.

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 steps have been reached and additional milestones may be achieved until registration of a potential drug.
Hybrigenics Corp., based in Cambridge, Mass., is the American subsidiary of Hybrigenics.

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HYBRIGENICS is listed on the Alternext market of Euronext Paris

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