HYBRIGENICS

Press Release

Hybrigenics will present new *in vitro* results on inecalcitol in multiple myeloma and acute myeloid leukemia at the annual ASH meeting in San Diego, USA

- **It has been shown that inecalcitol increases the expression of the CD38 antigen at the surface of CD38 positive 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 discovered that inecalcitol induces the expression of the CD38 antigen at the surface of CD38 negative acute myeloid leukemia (AML) cell lines *in vitro*; therefore, inecalcitol could make AML patients sensitive to a therapeutic anti-CD38 monoclonal antibody.**

Paris, France, 03 November 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, today announces new *in vitro* results showing that inecalcitol stimulates the expression of the CD38 antigen at the surface of human multiple myeloma (MM) or acute myeloid leukemia (AML) cell lines in culture. These results are already on line: https://ash.confex.com/ash/2016/webprogram/Paper90126.html and will be presented on December 4th, 2016 at the 58th Annual Meeting of the American Society of Hematology (ASH) in San Diego, United States.

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 for 3 days, 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 3 days of treatment by inecalcitol and the intensity of their CD38 labelling was multiplied by 5 and 12, respectively.

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.

"*The strong and reproducible effect of inecalcitol to stimulate the expression of the CD38 surface antigen on human multiple myeloma or acute myeloid leukemia cell lines makes its combination with an anti-CD38 therapy such as daratumumab an obvious next clinical step to test. 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. 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. Inecalcitol has also 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.

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 also 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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