

Hybrigenics will present new *in vitro* results on inecalcitol in chronic myeloid leukemia (CML) at the ASH meeting in Orlando, USA

- **Inecalcitol synergizes with imatinib, dasatinib and nilotinib to better inhibit the *in vitro* growth of CML stem cells isolated from patients**
- **Inecalcitol alone has also been shown to exert growth inhibition on leukemic stem cells isolated from 15 out of 18 CML patients**
- **A panel of macrophage genes has been identified, which could be used as potential biomarkers predictive of clinical response to inecalcitol**
- **These data result from a collaboration between hemato-oncologists and researchers from several French University Hospitals and Inserm Units**

Paris, 19 November 2015 – Hybrigenics (FR0004153930 - ALHYG), a bio-pharmaceutical company listed on the Alternext market of Euronext Paris, with a focus on research and development of new treatments of proliferative diseases, today announces new *in vitro* results of inecalcitol on human chronic myeloid leukemia (CML) progenitors and stem cells in culture which will be presented at the 57th Annual Meeting of the American Society of Hematology (ASH) in Orlando, United States.

A collaboration between Hybrigenics, hemato-oncologists from the University Hospitals of Caen, Nancy and Paris-Sud and researchers from Inserm Units in Villejuif and Paris, led by Prof. A. Turhan, Head of Hematology and Inserm U935, Paris-Sud University, has confirmed the inhibitory synergy on leukemic stem cells isolated from CML patients between inecalcitol and either imatinib (Gleevec[®], Novartis), dasatinib (Sprycel[®], Bristol-Myers Squibb) or nilotinib (Tasigna[®], Novartis), three different Bcr-Abl tyrosine kinase inhibitors widely used to treat CML. By contrast, the combination of inecalcitol and any of these three Bcr-Abl inhibitors had no effect on normal myeloid progenitor cells.

Inecalcitol has been tested on *in vitro* cultures of CML stem cells isolated from a total of 18 different patients and shown to exert growth inhibition by itself, without any Bcr-Abl inhibitor, on CML stem cells from 15 out of these 18 patients. In addition, under the *in vitro* effect of inecalcitol alone, a panel of genes characteristic of differentiation of CML stem cells into macrophages has been identified, which could potentially be used as biomarkers predictive of clinical response to inecalcitol.

"The synergy between inecalcitol and the usual Bcr-Abl inhibitors indicated to treat chronic myeloid leukemia (CML) is a consistent and reproducible observation on CML stem cells isolated from patients and grown in vitro. The effect of inecalcitol alone is characteristic of differentiation of CML stem cells into macrophages; this means that a selection of macrophage genes specifically induced by inecalcitol could represent a "signature" of inecalcitol activity," said Prof. Ali Turhan, Head of Hematology and Inserm U935, Paris-Sud University.

"A panel of macrophage genes, if validated, could potentially be used to interpret the results of the present ongoing clinical Phase II study of inecalcitol in combination with imatinib, or of future studies which could also include dasatinib or nilotinib," said Jean-François Dufour-Lamartinie, Hybrigenics' Chief Medical Officer.

The meeting abstract can be viewed online through the ASH website at:
<https://ash.confex.com/ash/2015/webprogram/Paper79613.html>

About chronic myeloid leukemia

Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is a type of cancer that starts in the bone marrow, invades the blood and then other parts of the body such as the spleen. CML evolves slowly at the beginning and, without treatment, ends by deteriorating into acute ("blast") phases, causing deadly anemia, coagulation impairment or lack of defense against infections.

CML is an orphan adult leukemia. In the United States, 6,700 new cases are diagnosed every year and a total of about 34,000 patients are presently living with the disease; the 5-year survival rate is 60% and about 1,100 patients die from CML every year (Cancer Facts and Figures, 2015). In Europe, the incidence is 1.02 patient per year per 100,000 inhabitants (EuTOS, 2014). CML has orphan disease regulatory status in Europe, Japan and the United States.

CML is characterized by the over-production of all types of white blood cells (except lymphocytes) originating from a single stem cell, which starts escaping proper regulations. In all CML patients, the loss of cell control results from the same accidental "exchange" of "bits" of chromosomes (translocation between chromosomes number 9 and 22), which gives rise to the abnormal fusion gene called BCR-ABL. The product of this gene, the Bcr-Abl protein is a hyper-functional tyrosine-kinase which continuously stimulates cell proliferation. The inhibitors of the Bcr-Abl tyrosine-kinase, such as imatinib (Gleevec®), are used to treat CML patients and the BCR-ABL gene transcripts are well-established biomarkers of the blood concentration of residual CML cells.

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 and providing cutting-edge proteomic and genomic scientific services. Hybrigenics' current 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. A clinical Phase II study of inecalcitol is currently ongoing in chronic myeloid leukemia patients.

Hybrigenics has a research collaboration with Servier on deubiquitinating enzymes (DUBs) and their inhibitors in oncology, neurology, psychiatry, rheumatology, ophthalmology, diabetes and cardiovascular diseases. A first milestone has been achieved in a drug discovery program targeting one DUB in oncology.

Hybrigenics Services (www.hybrigenics-services.com) is the market leader in Yeast Two-Hybrid (Y2H) and related services to identify, validate and inhibit protein interactions for researchers in all areas of life sciences, using its ISO 9001-certified high-throughput Y2H screening platform.

Helixio (www.helixio.com), Hybrigenics' genomic branch, provides state-of-the-art services specialized in DNA chips, DNA or RNA target enrichment and next generation sequencing with an Illumina NextSeq500. Hybrigenics Corp., based in Cambridge, Mass., is the American subsidiary of Hybrigenics.

HYBRIGENICS is listed on the Alternext market of Euronext Paris

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