HYBRIGENICS

Press Release

Hybrigenics' inecalcitol inhibits the growth of human hormone-dependent prostate cancer cells *in vitro* and *in vivo*

Results from Prof Koeffler's laboratory at the Cedars-Sinai Medical Center, University of California at Los Angeles, are published on-line in the International Journal of Cancer

Paris, 12 July 2011 – Hybrigenics (ALHYG), a bio-pharmaceutical company listed on Alternext (NYSE-Euronext) in Paris, with a focus on research and development of new treatments of proliferative diseases, announces today the on-line publication of a scientific article by Dr Ryoko Okamoto and co-authors in the peer-reviewed International Journal of Cancer*. Their preclinical results demonstrate the potential of inecalcitol to inhibit the proliferation of human cancer cells *in vitro*, as well as the growth of hormone-dependent prostate cancer xenografts *in vivo* in mice. Dr Okamoto works in Prof Phillip Koeffler's Division of Hematology and Oncology at the Cedars-Sinai Medical Center of the UCLA School of Medicine.

The results showed that inecalcitol was 11 times more potent than calcitriol, the naturally active metabolite of vitamin D, in inhibiting the growth *in vitro* of the human hormone-dependent prostate cancer cell line named LNCaP. The results also showed that, *in vivo*, inecalcitol was 480 times less toxic than calcitriol in mice. Inecalcitol was administered at the dose of 1.3 mg/kg by intraperitoneal injection three times per week for 42 days to nude mice bearing LNCaP xenografts; tumor growth was reduced by half as a result of inecalcitol treatment.

Interestingly, some molecular markers of activity were particularly responsive to inecalcitol treatment: ETS transcription factor variant 1 (ETV1) and Pim-1 kinase were down-regulated, while cytochrome P24A1 (24-hydroxylase), the main enzyme involved in the inactivation of vitamin D, was up-regulated. In addition, the same 11-fold difference in *in vitro* potency between inecalcitol and calcitriol was confirmed on the human promyeloid leukemia HL-60 cell line. Moreover, inecalcitol was 14 times more potent on this HL-60 cell line than on the hormone-dependent prostate cancer LNCaP cell line.

"*Although still preliminary, these results from a leading international laboratory in the field of cancer are very promising for three reasons:*

1) *inecalcitol may be active against hormone-dependent prostate cancer in addition to hormone-refractory prostate cancer for which it is currently being developed in combination with Taxotere® chemoterapy,*
2) *inecalcitol might also have a role in the treatment of some hematological malignancies exquisitely sensitive to vitamin D receptor agonists, such as myeloid or lymphocytic leukemias,*
3) *24-hydroxylase could be a positive biomarker of exposure to inecalcitol and of the effective activation of vitamin D receptors by inecalcitol*," said Remi Delansorne, Hybrigenics' CEO.

*Okamoto *et al.*, Int. J. Cancer, 2011 (doi: 10.1002/ijc.26279): Inecalcitol, an analog 1α,25$(OH)_2D_3$, induces growth arrest of androgen-dependent prostate cancer cells.

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About inecalcitol

Inecalcitol is a highly potent orally active agonist targeting the vitamin D receptor, with low hypercalcemic activity and toxicity. The therapeutic rationale behind its development in prostate cancer is to take advantage of its antiproliferative activity to enhance the established efficacy of the reference treatments of the two stages of this disease: in combination with anti-hormonals (LH-RH agonists and anti-androgens) for the hormone-dependent stage and with taxane-based chemotherapy (Taxotere® and Jevtana®, Sanofi) for the hormone-refractory stage. Other cancers expressing vitamin D receptors, such as some forms of myeloid or lymphocytic leukemias could also benefit from inecalcitol treatment. The safety profile of inecalcitol allows its use by oral administration in non-cancerous therapeutic indications for which its antiproliferative potential could prove effective, such as severe psoriasis.

About Hybrigenics

Hybrigenics (www.hybrigenics.com) is a bio-pharmaceutical company listed (ALHYG) on Alternext (NYSE-Euronext) in Paris, focusing its internal R&D programs on innovative targets and therapies for the treatment of proliferative cancerous or non-cancerous diseases.

Hybrigenics' current development program is based on inecalcitol, a vitamin D receptor agonist, for the first-line treatment of metastastic hormone-refractory prostate cancer in combination with Taxotere®, which is the current gold-standard chemotherapeutic treatment for this indication. Inecalcitol is also being developed to treat severe psoriasis by oral administration.

Hybrigenics' research program explores the role of enzymes known as ubiquitin-specific proteases (USP) in the degradation of onco-proteins, and the effectiveness of proprietary USP inhibitors in treating various types of cancer.

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Hybrigenics
Rémi Delansorne
CEO
Tel.: +33 (0)1 58 10 38 00
investors@hybrigenics.com

NewCap.
Financial communication
Axelle Vuillermet / Pierre Laurer
Tel.: +33 (0)1 44 71 94 94
hybrigenics@newcap.fr