



## **Immutep Announces That ImmuFact<sup>®</sup> IMP321 Has Entered A Phase I Chemoimmunotherapy Trial In Breast Cancer**

**Orsay, August 3, 2006**, Immutep S.A. announced today that its lead product, ImmuFact<sup>®</sup> IMP321, has entered a Phase I chemoimmunotherapy clinical trial in metastatic breast carcinoma. ImmuFact IMP321 is a potent natural human T cell immunostimulatory factor designed to amplify the T cell immune response.

The Company believes that this is the first time that chemoimmunotherapy, chemotherapy followed by immune stimulation, is being used in metastatic breast cancer.

The study is being conducted at the René Huguenin Cancer Centre, Saint Cloud, near Paris. The design of the study is an open-label non-randomised fixed dose-escalation trial assessing IMP321 following paclitaxel. One of the Centre's main Principal Investigators, Maya Gutierrez, is leading the team carrying out the trial.

Chemoimmunotherapy is a new approach to the treatment of cancer. Chemotherapy drugs induce tumour cell apoptosis and cause modulation of the immunological environment combined with a burst of tumour antigen release. The resulting T cell immune response contributes to the regression of the tumour and, importantly, may seek out and destroy metastases. However, this initial immune response needs to be sustained and amplified by a T-cell booster that is non-toxic and could be given repeatedly, such as ImmuFact IMP321.

Patients will receive 6 cycles of low-dose weekly paclitaxel at Day 1, Day 8 and Day 15 of a 4-week cycle as first line chemotherapy with, in addition, bi-weekly IMP321 administered the day after the paclitaxel to make a total of 12 injections of IMP321 over 24 weeks. Two dose levels of IMP321 will be studied in two cohorts of 8 patients each. The objectives of the study are i) to evaluate clinical and laboratory safety and tolerability profiles, and ii) to determine pharmacodynamic parameters, including CD8 T cell responses.

"We are very pleased to start testing this innovative therapeutic approach at our Institute," said Dr Maya Gutierrez, Principal Investigator of this Phase I trial, "Such sequential chemo- and then non-toxic immunotherapeutic combos may be a way to improve the response rate and/or consolidate or stabilize the partial tumour responses obtained with chemotherapy alone.

"We are delighted to announce our first combination therapeutic trial with IMP321 in advanced cancer" said Frédéric Triebel, Scientific & Medical Director of Immutep. "Immunotherapy trials have shown their limitations in the past in metastatic breast cancer, but this new sequential design may provide a much greater benefit without adding toxicity to this already well-tolerated, low-dose chemotherapy regimen".

For further information please visit the web-site [www.immutep.com](http://www.immutep.com) or e-mail John Hawken, CEO, at [JBHawken@immutep.com](mailto:JBHawken@immutep.com).

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## **Notes to Editors**

### **Metastatic Breast Cancer and Chemoimmunotherapy**

Metastatic breast cancer remains incurable. The failure of current approaches is generally attributed to the outgrowth of breast tumour cells that are inherently resistant to standard treatments. Manipulating the immune system to recognize and eradicate breast tumour cells is a highly attractive alternative approach to disease management. Active immunization offers multiple theoretical advantages over all other therapies, including low toxicity and exquisite specificity. More importantly, the potential for a sustained antitumour effect due to immunological memory would obviate the requirement for prolonged, repetitive cycles of therapy.

Thus the objective is to amplify *natural pre-existing* T cell responses specific for any known or unknown tumour antigen and to recruit and amplify *new* tumour-specific T cell responses occurring during a chemotherapy cycle using cytotoxic drugs known to induce tumour cell apoptosis. The direct cytolytic effect of some cytotoxic drugs, such as paclitaxel, can enhance antigen presentation by inducing tumour cell apoptosis. This mechanism of therapeutic synergy has been shown with cyclophosphamide, doxorubicin, or paclitaxel when given with dendritic cell-based vaccines. Until 5 years ago, it was thought that the T cell depletion caused by chemotherapy would make immunotherapy ineffective. However it has now been shown that, on the contrary, the vigorous T cell repopulation following depletion can be directed against the tumour, the so-called "rebound" effect. Notably, one clinical study showed that, even in the absence of concurrent vaccination, the first dose of neoadjuvant paclitaxel induced an apoptotic response within the tumour that correlated with the induction of TIL in 67% of locally advanced breast cancer patients who developed a complete clinical response (Demaria et al, 2001. Clin Cancer Res 7:3025-3030).

As an example of the potential of such a chemoimmunotherapy protocol, Coley Pharmaceutical Group, Inc. obtained promising results in a randomised Phase II study of CPG 7909 (a TLR9 agonist that activates the DC network) combined with standard chemotherapy in the first-line treatment of advanced non-small cell lung cancer. The objective response rate was 37 percent among patients who received CPG 7909 plus chemotherapy against 19 percent in patients who received chemotherapy alone. These findings were further supported by a difference in reported median overall survival - 11.7 months for patients who received CPG 7909 plus chemotherapy against 6.8 months for patients who received chemotherapy alone.

### **Soluble LAG-3 protein is a prognostic factor in breast cancer**

ImmuFact IMP321 is closely related to the soluble form of the LAG-3 (Lymphocyte Activation Gene-3) protein which is a prognostic indicator for survival in breast cancers expressing oestrogen or progesterone receptors. This was shown in a study carried out by researchers at the René Huguenin Cancer Centre and Pr. Frédéric Triebel when he was at the Pharmacy Faculty of University Paris 11. These results paved the way for the current clinical trial. (Immutep Press Release No 6, April 2006)

### **Centre René Huguenin de Lutte contre le Cancer**

The René Huguenin Centre for the Fight against Cancer is a comprehensive cancer centre that treats more than 3,000 new cases of cancer each year, with more than 2,000 new cases of breast cancer. It has a medical staff of 66 practitioners. Besides participation in therapeutic trials, the Centre has developed special expertise in the field of tumorigenesis and pharmacogenetics of breast cancers. Professor Jean-Nicolas Munck is the Directeur-Général of the Centre.

### **Immutep S.A.**

Immutep S.A. is a biopharmaceutical company developing technologies for novel immunotherapies for the treatment of cancer and chronic infectious diseases and new approaches to immune response modulation. The Company's technologies are based on the properties of LAG-3. Immutep is developing its products both in-house and in partnership with pharmaceutical and biotech companies. The Company was formed in 2001 by Frédéric Triebel, the scientific founder, and John B. Hawken, a specialist in the management of biotech companies, and has its headquarters and research facilities near Paris, France. Immutep is backed by the Paris-based venture capital firm Innoven Partenaires and the venture capital fund H2I, a specialist Biotech fund managed by Unicorn Biotutors/Equitis (Paris).

## **The Technology**

The Company's range of products is derived from LAG-3 (CD223), an immunomodulatory protein expressed on the surface of activated T cells. The three unique proprietary product platforms make use of the key roles played by this natural human protein in the regulation of the immune system.

### **ImmuFact<sup>®</sup> - T cell Immunostimulatory Factors for amplifying the T cell response**

The lead product, ImmuFact IMP321, is a highly potent T cell immunostimulatory factor derived from the soluble form of LAG-3 that binds, with high affinity, to MHC class II molecules expressed by dendritic cells (DC). This binding leads to DC maturation, migration to the lymph nodes and enhanced cross-presentation of antigens to T cells. As a result, strong and sustained anti-tumour or anti-viral cytotoxic T cell responses are obtained when IMP321 is injected alone or in combination with antigens.

### **ImmuCcline<sup>®</sup> – Immunostimulatory Vaccines**

The Company is developing a second technology that will make it possible to design novel therapeutic vaccines with even greater potency and efficacy. Covalently linking an antigen to IMP321 in a fusion protein results in both vectorisation of the antigen to the DC as well as the immunostimulatory effect described above. These "dual action" vaccines will be reserved for very difficult cases like HIV.

### **ImmuTune<sup>®</sup> – Fine Tuning of the Immune Response**

The third technology uses LAG-3-specific antibodies to control signalling of the membrane-bound LAG-3 molecule into activated effector T cells or regulatory T cells (Tregs) to modulate the T cell response.

## **Clinical Development (ImmuFact)**

Immutep has completed two randomised single-blind escalating-dose Phase I studies in 108 healthy individuals with IMP321 alone and combined with two well-defined standard types of antigens to show safety of the product alone and as an adjuvant in therapeutic vaccines. A Phase I clinical trial in metastatic renal cell carcinoma started in September 2005 with IMP321 injected alone. The current breast cancer study is thus the fourth clinical trial with ImmuFact IMP321 in two years.

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