



Immutep

## **Immutep Announces That ImmuFact<sup>®</sup> IMP321 Induces Activation of a Wide Range of Human Effector Cytotoxic Cells**

***Research paper describes IMP321's potency as a new immunopotentiator in cancer patients***

**Orsay, September 17, 2007** - Immutep S.A., a biopharmaceutical company specialised in immunostimulatory and immunomodulatory treatments of cancer and infectious or autoimmune disease, announced today the publication of a research paper showing that its lead product, IMP321, induces activation of a wide range of human effector cytotoxic cells.

ImmuFact<sup>®</sup> IMP321 is a potent natural human immunostimulatory factor designed to amplify the T cell immune response. It can be used either as an immunopotentiator in therapeutic vaccines or alone at higher doses as a monotherapy or in combination with chemotherapy. Six clinical trials have been initiated with ImmuFact IMP321 in the last 30 months.

Immutep's ImmuFact research team carried out the study described in the research paper at its laboratories near Paris.

The principal anti-tumour immune response is mediated through the activation of type 1 cytotoxic (Tc1) CD8<sup>+</sup> T cells, NK cells and monocytes/macrophages. The research team investigated the potency of IMP321 at inducing such a cytotoxic-type response in short term *ex vivo* assays on human blood cells.

The research team found that IMP321, a soluble recombinant form of the human LAG-3 protein, binds to all circulating dendritic cells and a fraction of MHC class II<sup>+</sup> monocytes. Four hours after addition of IMP321 to blood cells these antigen-presenting cells (APC) produce cytokines important for initiating the immune response. At 18 hours, following this activation of the APC, a significant number of CD8<sup>+</sup> T cells and NK cells are fully activated in their turn and produce Tc1 cytokines such as IFN- $\gamma$  or TNF- $\alpha$ . Similar induction was observed in metastatic cancer patients.

In contrast to IMP321, TLR agonists, another class of immunostimulatory factors, all induce the immunosuppressive IL-10 cytokine, and are therefore unable to achieve the Tc1 IFN- $\gamma$ <sup>+</sup> response that is crucial to an effective anti-tumoral effect.

Thus, IMP321 has properties that confirm its uniqueness and potency as a new immunopotentiator in cancer patients.

"It is remarkable that 92 per cent of blood donors or patients respond at clinically-significant levels to a first short exposure of IMP321." said Chrystelle Brignone, ImmuFact Project Manager and first author of the paper.

"This timely and orderly activation of both innate and adaptive immunity by this potent endogenous APC activating agent shows great promise for a new era of more effective immunotherapies in cancer patients," said Frédéric Triebel, Immutep's Scientific and Medical Director. "Similar strong induction of both innate and adaptive immunity effector arms has been already observed with IMP321 administered for six months in metastatic cancer patients, without side effects. This shows that immune activation could be safely induced over a long period of time to high levels using this unique and natural signalling pathway into APC."

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

## **Notes to Editors**

### **The Published Paper**

“A Soluble Form of Lymphocyte Activation Gene-3 (IMP321) Induces Activation of a Large Range of Human Effector Cytotoxic Cells”, Chrystelle Brignone, Caroline Grygar, Manon Marcu, Knut Schäkel, and Frédéric Triebel, *Journal of Immunology* 2007 179: 4202-4211

### **The LAG-3 immune control mechanism**

The Lymphocyte Activation Gene-3 (LAG-3) immune control mechanism plays a role in both the upregulation of the immune system through antigen presenting cells like dendritic cells and in the downregulation of the immune system through different types of lymphocytes. The lymphocyte activation gene-3 (LAG-3 or CD223) binds to the MHC class II molecule which is at the centre of immune response induction. LAG-3 is evolutionarily related to CD4 and has retained an affinity 2 log higher than CD4 for their common ligand, MHC class II molecules on antigen presenting cells such as dendritic cells. LAG-3 was discovered by Frédéric Triebel. Immutep has an exclusive licence to the molecule and related applications.

### **MHC class II**

MHC Class II molecules are found only on a few specialised cell types, including monocytes and dendritic cells, all of which are professional antigen-presenting cells (APCs). Initially it was thought that their only role was to present antigens to CD4<sup>+</sup> T cells but it later became clear that they also play a major role in mediating the competence of the immune response and cooperation among different immune cells. They are extremely polymorphic families of glycoproteins including the -DR, -DQ and -DP designations, of which HLA-DR is most studied. Some of these glycoproteins are associated with certain diseases of immune aetiology (e.g. auto-immune diseases like diabetes).

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

Immutep S.A. is a biopharmaceutical company developing immunostimulatory factors for the treatment of cancer and chronic infectious diseases and immunomodulatory therapeutic antibodies for the treatment of cancer or autoimmune disease. The Company's technologies are based on a key immune control mechanism that mediates T cell immune responses. 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 Technologies**

The Company's range of products is derived from LAG-3 (CD223), an immunomodulatory protein expressed on the surface of activated T cells. The 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*<sup>®</sup> IMP321, is a highly potent T cell immunostimulatory factor. It is a 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 coinjected with antigens or alone.

IMP321 is currently being tested by a wide range of therapeutic vaccine companies as an adjuvant to their proprietary technologies.

### **Clinical Development**

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. Four new clinical trials are in progress: a Phase I/II clinical trial in metastatic renal cell carcinoma with IMP321 injected alone, a Phase I/II study in metastatic breast cancer combining IMP321 with paclitaxel in a chemoimmunotherapy protocol, a disease-free melanoma study with IMP321 as an adjuvant to peptide antigens and a lympho-depletive/adoptive transfer metastatic melanoma study.

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