



PRESS RELEASE  
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FOR IMMEDIATE RELEASE

### **SOLUBLE LAG-3 MOLECULE AMPLIFIES TUMOR-SPECIFIC IMMUNITY**

Immutep S.A. announced today the publication of a research paper showing that a soluble human LAG-3 protein amplifies the *in vitro* generation of type 1 tumor-specific immunity.

The study (Cancer Research 2006; 66: (8): 4450-60) was carried out by Chiara Castelli and coworkers in Pr. Giorgio Parmiani's group of Italy's National Tumor Institute in Milan. This group has belonged to the top tier of European tumor immunology groups for more than 20 years, in terms of both basic and clinical research activities.

The adjuvant activities of the human Lymphocyte Activation Gene-3 (LAG-3) molecule were evaluated in a human setting by investigating the ability of a soluble recombinant human LAG-3 protein (hLAG-3Ig) to enhance the *in vitro* induction of viral and tumor-specific CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs). The researchers found that soluble human LAG-3 significantly sustained the generation and expansion of CD8<sup>+</sup> T lymphocytes against influenza matrix protein antigen or tumor antigens (Melan-A/MART-1 and survivin) in peripheral blood mononuclear cells (PBMCs) of healthy donors or cancer patients.

This shows that hLAG-3Ig has a unique ability to prime naïve CD8<sup>+</sup> T cells against a new antigen and to boost antigen-specific CD8<sup>+</sup> T cell memory response *in vitro*. The peptide-specific T cells generated in the presence of hLAG-3Ig were endowed with cytotoxic activity, enhanced release of type-1 cytotoxic T (Tc1) cytokines and were able to recognize tumor cells expressing their nominal antigen. Phenotype and cytokine/chemokines produced by antigen presenting cells (APC) in PBMCs exposed *in vitro* for 2 days to hLAG-3Ig indicate that the LAG-3-mediated adjuvant effect may depend on direct activation of circulating APCs.

The data revealed the activity of hLAG-3Ig in inducing tumor-associated, antigen-specific CD8<sup>+</sup> T cell responses in a human setting and strongly support the conclusion that this recombinant protein is a potential candidate adjuvant for cancer vaccines.

“These results taught us that a soluble human receptor protein, which is not a TLR agonist or a cytokine, could be used to expand tumor-specific CTL in humans, paving the way to its use as a cancer vaccine adjuvant” said Professor Giorgio Parmiani, Director of the Unit of Immunotherapy of Human Tumors of the National Tumor Institute in Milan.

The hLAG-3Ig, in the form of IMP321 (a GMP-grade recombinant protein), was supplied by Immutep. “Following years of preclinical and now clinical studies, these results are a direct proof that IMP321 is a powerful immunostimulant for patients' blood cells,” said Frédéric Triebel, the Company's Scientific and Medical Director. “These results have encouraged us to conduct several clinical trials with repeated s.c. injections of IMP321 mixed with numerous tumor antigen epitopes in patients with mostly incurable diseases, including advanced melanoma and ovarian cancer.”

LAG-3 was discovered by Frédéric Triebel and is a key mediator of the immune system expressed on the surface of activated T cells. Immutep has an exclusive licence to the molecule and related applications.

Immutep and the National Tumor Institute are planning to conduct a clinical trial in metastatic melanoma with the Company's sLAG-3 immunostimulatory factor, *ImmuFact*<sup>®</sup> IMP321, associated with peptide epitopes. Apart from the research work discussed here, the National Tumor Institute in Milan has no other links with Immutep and no member of its staff has a financial interest in the Company.

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).

## **Notes to Editors**

### **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 start-ups, 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*<sup>®</sup> 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.

#### ***ImmuCine*<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 particularly useful in 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 is completing 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: soluble influenza virus antigens and particulate hepatitis B surface antigen. The clinical phase of the first study in 60 subjects is complete and has shown good tolerability with no adverse events. A Phase I clinical trial in metastatic renal cell carcinoma started in September 2005 with IMP321 injected alone.

### **Istituto Nazionale Tumori, Milano**

The National Tumor Institute in Milan is the major comprehensive cancer center of the country with almost 200 people working at the pre-clinical level and 300 in the clinic. The Institute is running several immunotherapy trials in melanoma, lymphoma, colorectal and prostate cancer and has long-standing experience in this as well as in other therapeutic approaches in the major forms of cancer.