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ERIC VIVIER'S TEAM AT THE MARSEILLE-LUMINY IMMUNOLOGY CENTRE AND INNATE PHARMA RESEARCHERS ANNOUNCE THE DEVELOPMENT OF A NEW ANIMAL MODEL DEDICATED TO STUDYING NK CELL ACTIVITY

Marseille, February 28, 2007

NK cells are now recognised as key players in anti-tumour and anti-infectious immunity. Even so, their exact contribution among the numerous cells and molecules involved in the immune response remained to be established. This required the development of a representative, flexible animal model, a milestone that has just been achieved. The last issue of the "Proceedings of the National Academy of Sciences USA" ("PNAS") described the first mouse whose NK cells can be manipulated at will. Developed in collaboration by the Eric Vivier laboratory at Inserm^I and researchers from Innate Pharma, this model will be extremely useful in precisely characterising the role of this innate immunity compartment with high therapeutic potential.

Discovered at the beginning of the 80s, NK cells have since then been the subject of many scientific publications worldwide. It is now known that these cells directly kill cancer cells or cells infected by viruses, but also trigger and influence the adaptive immune response, which is the base of immunological memory. It is equally known that their activity depends on a balance between the different activator and inhibitor receptor families. Lastly, other researches have shown that abnormally-activated NK cells could contribute to the development of certain autoimmune pathologies (rheumatoid arthritis, Basedow's disease, etc.).

"Though NK cell anti-tumour and anti-infectious activity is now clearly established," declared Professor Eric Vivier, in charge of the NK research at the Marseille-Luminy Immunology Centre, "we still have to precisely define their contribution to the immune response, which is based on the coordinated action of a large number of cells and molecules (dendritic cells, NK cells, T and B cells, etc.). Mutant models without B or T cells are already being used, but NK-cell-free mice had yet to be obtained. The only murine model available thus far involved monoclonal antibodies targeting antigens mainly expressed by NK cells (GM1, NK1.1) but also found on the surface of macrophage and T cell sub-populations, which made results very difficult to interpret."

Following the discovery of the NKp46 molecule in humans by Professor Alessandro Moretta's team in Genoa, Inserm and Innate Pharma researchers have shown that this molecule and its counterparts form a specific molecular signature for NK cells in several mammal species (humans, monkey and mice). They also demonstrated that a minimum sequence of this gene's^{II} promoter sufficed to drive the specific expression of any gene in the NK cells.

^I INSERM U631, CNRS UMR 6102, Université de la Méditerranée UMR 6546
Vivier lab: <http://www.ciml.univ-mrs.fr/Lab/vivier.htm>

^{II} A short DNA sequence placed at the beginning of the gene makes it possible to trigger and regulate the transcription of information carried by the gene.



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Different transgenic mice have been produced either by transferring the diphtheria toxin receptor or the NKp46 human gene or of the green fluorescent protein ("GFP"), under control of this promoter sequence. By using the diphtheria toxin in transgenic mice for this toxin's receptor, the selective ablation of NK cells can be achieved. Conversely, NK cells in transgenic mice for the GFP emit a fluorescent signal, which is used to study their dynamics *in vivo*.

"Obtaining such a mouse gives us a double satisfaction," declared Doctor François Romagné, Executive Vice President and CSO of Innate Pharma. *"Firstly, from a scientific viewpoint, these models will be extremely useful in refining NK cell contribution in normal and pathological conditions. Secondly, the monitoring of the manipulation of NK cells by NK immuno-modulator drug candidates developed by Novo Nordisk A/S in collaboration with Innate Pharma will be greatly simplified."*

About CIML:

The *Centre d'Immunologie de Marseille-Luminy* ("CIML"), or Marseille-Luminy Immunology Centre, is a CNRS mixed research unit run by Inserm and the *Université de la Méditerranée*, which was created in 1976. This immunology centre is part of the Luminy Science & Technology Park in Marseille. The centre has more than 230 staff members, which includes 20 research teams, administration, technical services, scientific core services (imagery, proteomics, transgenesis laboratory, etc.), as well as technical platforms and support centres dedicated to microscopy (PICsL with IBDM), bio-optics (MOSAIC in association with the *Institut Fresnel*) and functional investigation of the murine model (RIO-Marseille-Nice-Génopôle platform). Main research led by the immunology centre's teams focuses on key biological processes such as ontogeny, lymphocyte activation, phagocytosis, host-pathogen interactions and cell death. For more information on research by the Eric Vivier team, visit: <http://www.ciml.univ-mrs.fr/Lab/vivier.htm>

About Innate Pharma:

Founded in 1999 and funded by reference venture capitalists up to its IPO on Euronext in Paris in 2006, Innate Pharma S.A. (Euronext Paris: FR0010331421 – IPH) is a biopharmaceutical company developing first-in-class^{III} drugs targeting innate immunity.

The pioneering work of Innate Pharma's scientific founders and research groups has led to the development of three product platforms (gamma delta T cells, NK^{IV} cells and TLR), each directly or indirectly validated in clinical oncology settings.

In addition to cancer, Innate Pharma's drug candidates have development potential in the treatment of infectious disease and chronic inflammation. The company's most advanced molecule is in Phase II clinical trials in cancer.

With its strong scientific position in innate immunity pharmacology, its robust intellectual property portfolio and its R&D expertise, Innate Pharma intends to become a leading player in the rapidly growing immunotherapeutics market.

Based in Marseilles, France, Innate Pharma had 67 employees as of December 31, 2006.

Learn more about Innate-Pharma at: www.innate-pharma.com

^{III} *With new mechanisms of action.*

^{IV} *The NK platform is part of an exclusive strategic partnership for the research & development of drug candidates between Innate Pharma and the Danish pharmaceutical group, Novo Nordisk A/S.*



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For more information, please contact:

Innate Pharma

Stéphane Boissel, EVP and CFO
Tel: +33 (0)4 96 19 05 58
stephane.boissel@innate-pharma.fr

Alize Public Relations

Caroline Carmagnol
Tel: +33 (0)6 64 18 99 59
caroline.carmagnol@wanadoo.fr

François Romagné, EVP and CSO
Tel: +33 (0)4 96 19 05 50
francois.romagne@innate-pharma.fr