



Eric VIVIER,
DVM, PhD, PU-PH, Director of the CIML
Group leader: Natural Killer cells and Innate Immunity

Background

I was trained as a Doctor in Veterinary Medicine at the Maisons-Alfort Veterinary School. I obtained my PhD and HDR at the University of Paris. Thanks to the help of my mentors, I decided to work in basic research to understand the immune response. I moved then to Harvard Medical School (Dana-Farber Cancer Institute) with a Fogarty International Center fellowship, and started to be interested by a very enigmatic population of cytolytic lymphocytes, the Natural Killer (NK) cells.

Since then, my work has been focused on elucidation of the role and mode of action of NK cells, leading not only to a better understanding of these cells, but also more generally to unveiled new concepts in the regulation of cell activation (the ITIM-ITAM paradigm) and to finally work on NK cells as a model system of innate immunity.

Awards

- 1996 National League against Cancer (LNCC) Award
- 1999 National Award and Tremplins Rhône-Poulenc Award for Biotech start-ups
- 1999 Lucien Tartois Award, Fondation pour la Recherche Médicale
- 2003 Jacques Oudin Award, French Society for Immunology
- 2004 National League against Cancer (LNCC) Award
- 2004 Deutsche Gesellschaft für Immunologie / EFIS Award
- 2008 Fondation Del Duca Award-National Academy of Sciences
- 2010 Turpin Award in Cancerology - National Academy of Sciences
- 2010 Charles Oberling Award in Cancerology

Membership

- 1996-2001 Member of the Institut Universitaire de France (Junior)
- 2007-Present Member of the Institut Universitaire de France (Senior)



Selected funding

- European Research Council Advanced grants (2010-2015)
- Ligue Nationale contre le Cancer (Equipe Labellisée, 2000-present)
- Agence Nationale de la Recherche

Present committees

- Scientific Advisory Board of the LNCC
- Counselor of the INSERM Institute of Hematology-Immunology-Pneumology
- Member of the expert panel for the European Research Council Starting Grant
- Human Frontier Science Program (HFSP) Review Committee

Boards

- Science Signaling (Board of Reviewing Editors)
- Frontiers in NK cell biology (Speciality chief editor)
- Nature Reviews Immunology (Highlight advisory panel 2001-2011)
- J. Immunol. (Associate Editor, 2001-2005)
- Int. Immunol. (Associate Editor)
- Faculty 1000 (Contributing Member)

Industry

Co-founder and member of the scientific committee of Innate Pharma (www.innate-pharma.com)

Main achievements and questions

The balance between activating and inhibitory signaling pathways

Four review articles (Vivier and Daëron, 1997; Vély and Vivier, 1997; Vivier et al., Science 2004; Daëron et al., Immunol. Rev. 2008) summarized this major area of our work.

At Harvard in 1990, we showed that the engagement of CD16, the NK cell Fc receptor, activates a transduction pathway dependent on protein tyrosine kinases, which phosphorylates the CD3 ζ subunit associated with CD16. This article marked the starting point of the dissection of signal transduction cascades in NK cells, and highlighted the conservation of the proximal transduction machinery associated to antigen and antibody receptors.

We then studied the transduction of inhibitory signals in these cells. One of the major discoveries in NK cell research was the demonstration that MHC class I molecules engage inhibitory receptors expressed on NK cells, the "missing self model". We showed that these receptors exert their inhibitory function via an intracytoplasmic motif, the immunoreceptor tyrosine-based inhibition motif (ITIM).

We then proposed a model that fine tunes cell activation, based on the balance between activating and inhibitory signaling pathways. This discovery was key, not only for the understanding of NK cell function, but also for the extension of ITIM model to many inhibitory molecules widely expressed within and outside of the hematopoietic system.

These studies also led to the development of clinical trials aimed at manipulating inhibitory receptors, such as the use of blocking anti-KIR (killer cell Ig-like receptor) antibodies against cancers.

Definition and role of NK cells *in vivo*

The conservation of cytotoxicity across evolution as a mean for metazoans to fight against various assaults is one of the elements that advocate for a better understanding of NK cells.

A major bottleneck in the study of NK cell biology resided in the lack of homogenous markers for this cell lineage across mammalian species, and the lack of mouse models in which NK cells could be selectively depleted.

We developed several strains of transgenic mice that allowed addressing the relevance of NK cells and NK cell receptors *in vivo*. In particular, we generated the first mice transgenic for a human inhibitory KIR (Cambiaggi et al., PNAS 1997). This study provided the first demonstration of the activity of human KIR to inhibit graft rejection *in vivo*, as well as a pre-clinical model for clinical applications of KIR-HLA mismatch in innovative anti-tumor protocols.

More recently, we generated the first models of selective and inducible NK cell depletion (Walzer et al., PNAS 2007; Narni-Mancinelli et al., PNAS 2011). These mice have been already distributed in many laboratories over the world.

We also identified NKp46 as a marker of NK cells across mammalian species. Thanks to this finding, we have been able to reveal that a subset of NKp46+ cells in the gut produce the cytokine IL-22 that participates to the maintenance of mucosal integrity (Luci et al., Nature Immunology 2009).

These studies also unexpectedly revealed similarities between the lymphoid tissue-inducer cells and NK cells. Altogether, these data prompt new areas of research in lymphoid development, mucosal immunity and tissue repair.

Identification and function of the KARAP/DAP12 polypeptide

We discovered that a tyrosine phosphorylated polypeptide associates with activating KIR receptors, and named this new polypeptide KARAP (killer cell-activating receptor-associated protein, Olcese et al, 1997).

The identification of KARAP/DAP12 has been the first step for a new area of research linking protein tyrosine kinase-dependent pathways and many topics such as bone remodeling, granuloma formation or sepsis. Interestingly, other groups identified of KARAP/DAP12 deficiency in humans, which leads to a rare and fatal disease, Nasu-Hakola/PLOSL.

Education and tolerance to self: mechanisms that control NK cell functions

Results obtained in humans and mice show that NK cells are able to adapt to the level of expression of the MHC class I in their microenvironment to set up their level of reactivity. In this context, we propose to identify the molecular mechanisms and the cellular interactions implied in this modulation of NK cell functions, as well as the space-time conditions that are determining for this developmental program. One of our approaches is to use random mutations (ENU-mutagenesis) in the mouse (Narni-Mancinelli et al., Science 2012).

Selected publications (Total publications 228, h-Index:59)

Original publications

- Ugolini S., Arpin C., Anfossi N., Walzer T., Cambiaggi A., Förster R., Lipp M., Toes R. E. M., Melief C. J., Marvel J., Vivier E. Involvement of inhibitory NKRs in the survival of a subset of memory-phenotype CD8+ T cells. *Nature Immunology* 2001, 2: 430-435
- Diefenbach A., Tomasello E., Lucas M., Jamieson A. M., Hsia J., Vivier E.*, Raulet DH*. Selective associations with signaling proteins determine stimulatory versus costimulatory activity of NKG2D. *Nature Immunology* 2002, 3:1142-1149
- Saulquin X., Gastinel L., Vivier E. Crystal structure of the human natural killer cell activating receptor, KIR2DS2 (CD158j). *J. Exp. Med.* 2003, 197:933-938
- Stewart C. A., Laugier-Anfossi F., Vély F., Saulquin X., Tisserant A., Gauthier L., Romagné F., Ferracci G., Moretta A., Sun P., Ugolini S., Vivier E. Recognition of peptide-MHC class I complexes by activating Killer Ig-like Receptors. *Proc. Natl. Acad. Sci. USA* 2005, 102: 13224-13229
- Anfossi N., André P., Guia S., Falk C., Stewart C. A., Breso V., Roetyncck S., Frassati C., Reviron D., Middleton D., Romagné F., Ugolini S., Vivier E. Human NK cell education by inhibitory receptors for MHC class I. *Immunity* 2006, 25: 331-42
- Walzer T, Bléry M., Chaix J., Fuseri N., Chasson C., Robbins S. H., Jaeger S., André P., Gauthier L., Daniel L., Chemin K., Morel Y., Dalod M., Imbert J., Pierres M., Moretta A., Romagné F., Vivier E. Identification, activation and selective *in vivo* ablation of mouse NK cells via NKp46. *Proc. Natl. Acad. Sci. USA* 2007, 104: 3384-3389
- Walzer T., Chiossone L., Chaix L., Calver A., Carozzo C., Garrigue-Antar L., Jacques Y., Baratin M., Tomasello E., Vivier E. Natural killer cell trafficking *in vivo* requires a dedicated sphingosine 1-phosphate receptor. *Nature Immunology* 2007. 8: 1337-1344
- Luci C., Reynders A., Ivanov I.I., Cognet C., Chasson L., Hardwigsen J., Anguiano E., Banchereau J., Chaussabel D., Dalod M., Littman D.R., Vivier E.*, Tomasello E*. Influence of the transcription factor ROR γ t on the development of NKp46+ cell populations in gut and skin. *Nature Immunology* 2009 10:75-82
- Brandt CS., Baratin M., Yi EC., Kennedy J., Gao Z., Fox B., Haldeman B., Ostrander CD., Kaifu T., Chabannon C., Moretta A., West R., Xu WF., Vivier E.*, Levin SD*. The B7 Family Member B7-H6 is a tumor cell ligand for the activating Natural Killer cell receptor NKp30 in humans. *J. Exp. Med.* 2009. 206:1495-503
- Sola C., André P., Lemmers C., Fuseri N., Bonnafous C., Bléry M., Wagtmann N.R., Romagné F., Vivier E.*, Ugolini S*. Genetic and antibody-mediated reprogramming of natural killer cell missing-self recognition *in vivo*. *Proc. Natl. Acad. Sci. USA* 2009.106: 12879-12884.
- Guia S., Jaeger B.N., Piatek S., Mailfert S., Trombik T., Fenis A., Chevrier N., Walzer T., Kerdiles Y.M., Marguet D., Vivier E.*, Ugolini S*. Activating receptor confinement at the plasma membrane controls Natural Killer cell tolerance. *Science Signaling* 2011, 4:ra21.

- Reynders A., Yessaad N., Vu Manh T.P., Dalod M., Fenis A., Aubry C., Nikitas G., Escalière B., Renaud J.C., Dussurget O., Cossart P., Lecuit M., Vivier E.*, Tomasello E*. Differential function of NKp46+ROR γ t+ and NKp46+ROR γ t- gut lymphoid cells. *EMBO J.* 2011, 30:2934-47.
- Narni-Mancinelli E., Chaix J., Fenis A., Yessad N., Reynders A., Grégoire C., Ugolini S., Tomasello E., Walzer T., Vivier E. Fate mapping analysis of lymphoid cells expressing the NKp46 cell surface receptor. *Proc. Natl. Acad. Sci. USA.* 2011, 108: 18324–18329.
- Narni-Mancinelli E., Jaeger B.N., Bernat C., Fenis A., Kung S., De Gassart A., Mahmood S., Gut M., Heath S., Estellé J., Bertosio E., Vély F., Gastinel L.N., Beutler B., Malissen B., Malissen M., Gut I.G., Vivier E.*, Ugolini S.*. Tuning of Natural Killer Cell Reactivity by NKp46 and Helios Calibrates T Cell Responses. *Science*, 2012, 335: 344-348.
- *: corresponding authors

Reviews and Essays

- Ugolini S, Vivier E. Multifaceted roles of MHC class I and MHC class I-like molecules in T cell activation. *Nature Immunology* 2001, 2: 198-200
- Vivier E., Biron CA. A pathogen receptor on Natural Killer cells. *Science* 2002, 296:1248-1249
- Vivier E., Anfossi N. Inhibitory NK cell receptors on T cells: witness of the past, actors of the future. *Nature Reviews Immunology* 2004, 4: 190 –198
- Vivier E., Nunes J., Vély F. Natural killer cell signaling pathways. *Science* 2004, 306:1517-1519
- Vivier E., Malissen B. Innate and adaptive immunity: specificities and signaling hierarchies revisited. *Nature Immunology* 2005, 6: 17-21
- Vivier E., Romagné F. Good news, bad news for missing-self recognition by NK cells: autoimmune control but viral evasion. *Immunity* 2007. 26: 549-551
- Vivier E., Tomasello E., Baratin M., Walzer T., Ugolini S. Functions of Natural Killer cells. *Nature Immunology* 2008. 9: 503-510
- Ugolini S., Vivier E. Natural killer cells remember. *Nature* 2009. 457: 544-545
- Vivier E., Spits H., Cupedo T. Interleukin-22-producing innate immune cells: new players in mucosal immunity and tissue repair? *Nature Reviews Immunology* 2009, 9:229-234
- Vivier E. and Ugolini S. Regulatory Natural Killer cells: new players in the IL-10 anti-inflammatory response. *Cell Host and Microbe* 2009, 6:493-495
- Vivier E., Ugolini, S. Poster on NK cells: receptors and functions. *Nature Reviews Immunology* 2010, 10: 12
- Vivier E., Raulet D.H., Moretta A., Caligiuri M.A., Zitvogel L., Lanier L.L., Yokoyama W.M., Ugolini S. Innate or adaptive immunity? The example of Natural Killer cells. *Science* 2011, 331: 44-49.

