

DECEMBER 8TH 2008

INTERNATIONAL SYMPOSIUM

# Cancer immunotherapy / Immunothérapie et cancers

## SCIENTIFIC COMMITTEE :

- **Dr Marc Bonneville**, Head of Inserm U892, Cancer Regional Research Centre,  
University of Nantes

Doctor in Veterinary Medicine and Director of research at CNRS, is heading a Center for Cancer Research (Inserm unit U892) located in Nantes.

He was trained in transplantation immunology under the supervision of JP Souillou (1983-1987). He joined the laboratory of S. Tonegawa at MIT, Cambridge, Massachusetts and worked as a post doctoral fellow on the immunobiology of a particular murine T lymphocyte subset from 1987 to 1989. Back to France in 1990, he has been working since then on the characterization of cellular immune responses against infectious agents and tumors in the human.

Marc Bonneville authored more than 180 scientific papers, is a co-inventor of eight patents and the co-founder of a biotechnology company developing innovative immunotherapeutics in oncology and infectiology. He has been involved in over 20 scientific advisory boards and scientific committees and worked as advisor for the General Director of Inserm in the field of immunology and biotherapies from 2000 to 2007.

- **Pr Fabien Calvo**, Director of Research Programmes at French National Cancer Institute (INCa),  
Director of the Inserm Cancer Institute, Paris

Director of Research programmes at INCa and Director of the Inserm cancer Institute. Previously resident and senior registrar of Paris Hospitals, research associate of the National Cancer Institute in Bethesda (NIH / NCI / DCT, USA), he specialised in oncology and haematology. He is also a professor of pharmacology at the Denis Diderot Medical University in Paris.

He has been the director of the Saint-Louis Hospital CIC (clinical investigation centre) and the director of INSERM unit 716 on the identification of new molecular targets for the treatment of cancer since 1995. He is a member of the post-graduate school "oncogenesis fundamental basis". He also headed the clinical research programmes in cancer in the Paris area. He has published more than 200 original and review articles.

His spheres of activity and interest are the biology of metastatic processes, especially proteases, translational research, preclinical pharmacology and early clinical trials in haematology and oncology.

He also worked as a coordinator of the cancer mission for the Director of the Research and Innovation department, Ministry of Research and Higher Education in 2006 and 2007.

- **Dr Robin Fahraeus**, Laboratory of functional targets in antitumoral pharmacology,  
Inserm U716, Paris

Dr Robin Fahraeus did his MD-PhD at the Karolinska Institute in Stockholm in 1993. He joined the University of Dundee, Scotland, to work on developing techniques for studying the cell biological response to targeting factors within the cell cycle regulatory machinery.

Dr Fahraeus was involved in starting the Cyclacel Biotech. company with Cancer Research UK and venture investment funds. After two years as Head of Research and Development, Dr Fahraeus went back to an academic life with a Senior Research Fellowship from the Cancer Research UK, continuing work on evaluation of intra cellular targets for anti-cancer therapies. He is currently the head of an Inserm team working on new pathways for controlling p53 activity and for identifying immunological targets for Epstein-Barr virus-carrying cancers.

Since a year, Dr Fahraeus' team is an active part of the INSERM C-Dithem consortium that is an infrastructure aimed at developing techniques and molecules for modifying and studying protein-protein interactions.

## VENUE :

- **Cité Internationale Universitaire de Paris**

Espace Adenauer  
17, boulevard JOURDAN  
75014 Paris

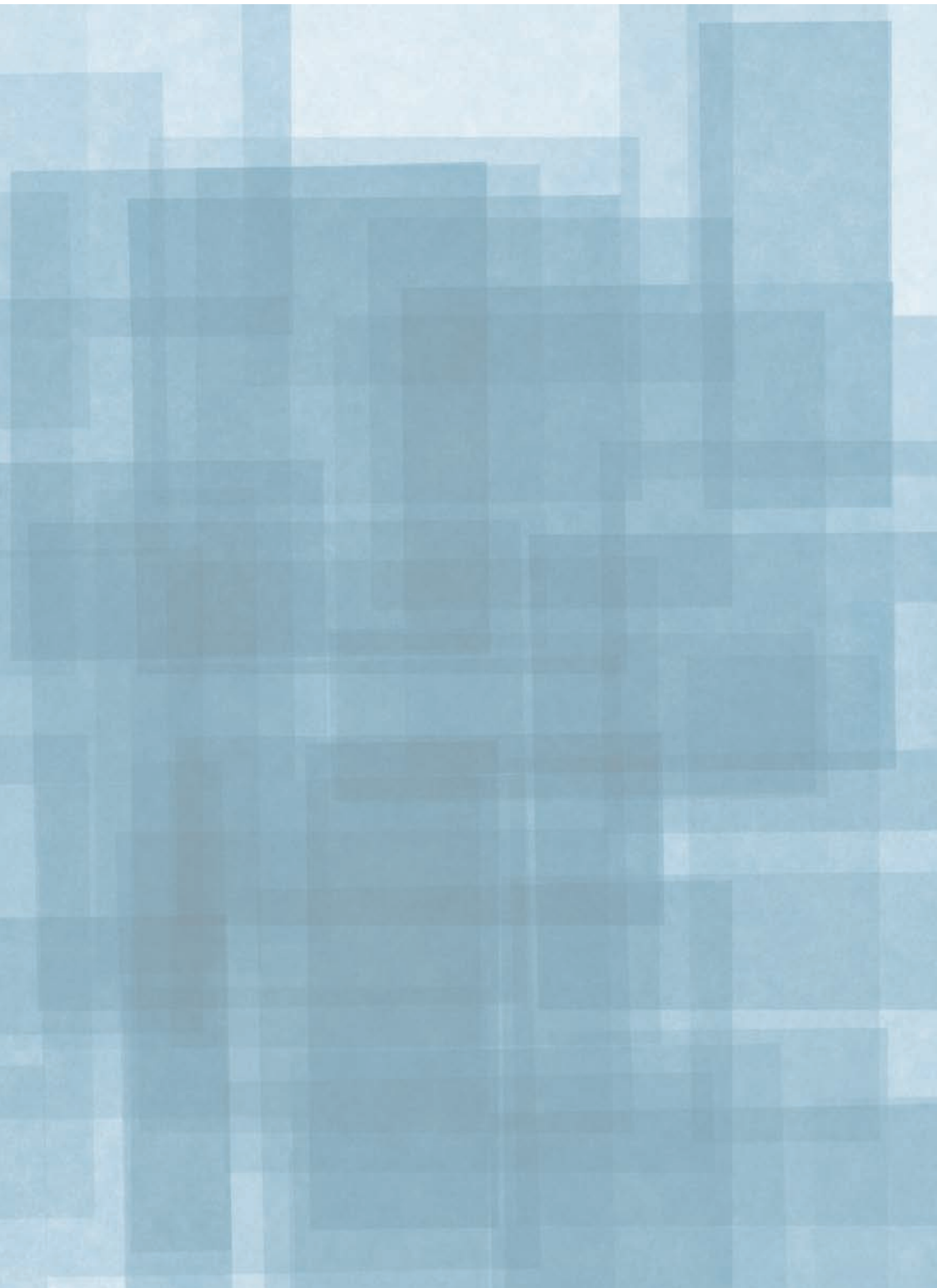


## INTRODUCTION

L'immunothérapie antitumorale vise à restaurer ou stimuler les mécanismes de défense immunitaire vis-à-vis des cellules cancéreuses. Les avancées récentes dans ce domaine font de l'immunothérapie un complément prometteur aux traitements antitumoraux basés sur la radiothérapie, la chimiothérapie ou les thérapies dites ciblées.

L'objectif du symposium est de dresser un état des lieux des stratégies immunothérapeutiques faisant l'objet d'études précliniques et cliniques dans le domaine du cancer, dont l'élaboration repose sur une connaissance de plus en plus fine des modalités du contrôle immunitaire des cellules tumorales. Dans cette optique, plusieurs sommités internationales s'attacheront à décrire les enjeux, les avancées les plus récentes et les perspectives cliniques dans leurs domaines respectifs, que sont l'étude des mécanismes de l'immunité antitumorale chez l'homme, l'identification de

nouveaux marqueurs immunitaires corrélant avec l'évolution clinique de certaines tumeurs et la réponse thérapeutique, et l'élaboration de nouvelles stratégies immunothérapeutiques basées sur l'administration de cellules immunes, de facteurs immunostimulants ou de vaccins thérapeutiques. Seront également abordées les stratégies de ciblage tumoral au moyen d'anticorps spécifiques de composés toxiques et les contributions possibles du système immunitaire à l'efficacité de certaines thérapies antitumorales conventionnelles et ciblées.



## PROGRAMME

<b>09:00 – 09:15</b>	<b>Fabien CALVO - Marc BONNEVILLE</b> Welcome – Introduction	
<b>09:15 – 10:00</b>	<b>Thierry BOON :</b> Tumor immune surveillance and immunotherapy : an overview	<b>06</b>
<b>10:00 – 10:45</b>	<b>Jerôme GALON :</b> Immune reaction and cancer prognosis : a novel paradigm	<b>07</b>
<b>11:00 – 11:45</b>	<b>Jean-Yves BONNEFOY :</b> Therapeutic vaccines against non-small cell lung cancer	<b>08</b>
<b>11:45 – 12:30</b>	<b>Carl H. JUNE :</b> Strategies for T cell adoptive transfer cancer therapy	<b>09</b>
<b>12:30 – 14:00</b>	Lunch break	
<b>14:00 – 14:45</b>	<b>Jacques BANCHEREAU :</b> Dendritic cell based immunotherapy	<b>10</b>
<b>14:45 – 15:30</b>	<b>Giorgio PARMIANI :</b> Cancer vaccines and their targets	<b>11</b>
<b>15:45 – 16:30</b>	<b>Jean François CHATAL :</b> Immunotoxins and radiolabelled tumor-specific mAbs in cancer treatment	<b>12</b>
<b>16:30 – 17:15</b>	<b>Laurence ZITVOGEL :</b> The anti-cancer immune response – A necessity for therapeutic success ?	<b>14</b>
<b>17:15 – 17:30</b>	<b>Marc BONNEVILLE :</b> Concluding remarks	<b>18</b>

## THIERRY BOON

Born in Belgium in 1944, Dr. Boon took his undergraduate degree at the University of Louvain and got his Ph.D. at the Rockefeller University in New York. He is now director of the Brussels branch of the Ludwig Institute for Cancer Research and professor at the University of Louvain.

Dr. Boon and his coworkers identified in 1991, the first human tumor-specific antigen recognized by T-lymphocytes. His present research is focused on the mechanisms that lead to anergy in tumor-infiltrating lymphocytes.

### ABSTRACT

#### **Tumor immune surveillance and immunotherapy : an overview**

Anti-tumoral vaccination of tumor-bearing melanoma patients has not yet provided satisfactory clinical results. It is possible that immunosuppression inside the tumor is a limiting factor for the efficacy of vaccination. There is growing evidence that melanoma metastases contain

large numbers of CD8 T lymphocytes directed against specific tumor antigens as a result of a spontaneous response of the patients. These lymphocytes appear to be anergic. A new mode of anergy involving separation of the T cell receptor and the CD8 receptor appears to be prevalent in cancer patients. New approaches involving both vaccination and local administration of agents that relieve this type of anergy should be considered.

## JERÔME GALON

Dr Jérôme Galon was a Ph.D. student in Immunology, Laboratory of Cellular and Clinical Immunology (Pr WH Fridman), at the Curie Institute, Paris, France (1994-1997), and he did post doctoral research with Dr JJ. O'Shea at the NIH in the Lymphocyte Cell Biology Section, Bethesda, USA from 1997 to 2001.

From 2001 to 2007, he worked as Research Scientist and Team Leader (INSERM) in the Laboratory of Cellular and Clinical Immunology (Pr WH Fridman), Paris, France.

Since 2007, Dr. Jérôme Galon is the Research Director and Principal Investigator (INSERM) of the Integrative Cancer Immunology Team, U872, Cordeliers, Paris, France.

He has been awarded several national and international prizes; in 2008, he received the Colon Cancer Research Schaeferbeke Award, Fondation de France, and the Clinical Research Award, Rose Lamarca, Fondation pour la Recherche Médicale, 2008.

Dr. Galon authored 38 scientific papers and 3 book chapters. He is the co-inventor of 2 patents.

### ABSTRACT

#### **Immune reaction and cancer prognosis : a novel paradigm**

The clinical outcome of a cancer involves interactions of the tumor with the immune defense mechanisms of the host, at all stages of tumor growth. Lymphocytic infiltration of tumor or peritumoral tissue may be indicative of a host immunologic response to the invasive malignancy and has been shown in studies to be a favorable prognostic factor. In Human colorectal cancers, we showed that intratumoral memory T-cells may control the early steps of the metastatic process. We evidenced that the effector-memory T cells (TEM), may have a central role in the control of tumor spreading to lymphovascular and perineural structures but also to lymph node or distant organs. Our data outline the delayed anti-tumor activity of TEM through a systemic immunosurveillance (Pagès et al. N Engl J Med 2005).

We used high-throughput quantitative measurement of cellular and molecular differences among colorectal cancers. This allowed a detailed characterization of the tumor

microenvironment and to identify associations with clinical outcomes. We provided evidence that, the type, the density and the location of immune cells within tumor samples strongly influenced the behavior of human CRC (stage I-IV). Thus, adaptive immune reaction within the tumor was a better predictor of survival than traditional staging (Galon et al, Science 2006). High density of adaptive immune cells correlated with an equally favorable prognosis regardless of the cancer size and spread. Conversely, a weak adaptive immune response correlated with a very poor prognosis even in patients with minimal tumor invasion. Understanding of the host-tumor relationship leading to the establishment of memory T cell reaction within the tumor will now be needed.

The data suggests that time to recurrence and overall survival times might be governed in large part by the state of the local adaptive and memory response, challenging our understanding of cancer progression. This could have important consequences in clinical practice, in particular in clinically localized colorectal cancers.

## JEAN-YVES BONNEFOY

Dr Jean-Yves Bonnefoy, VP, Research and Development was appointed Vice President, Research in February 2005 and Vice President, Research and Development in March 2006 in charge of Research, Clinical Development, Regulatory Affairs and Intellectual Property at Transgene.

Prior to joining Transgene, he was Head of the Canceropôle Lyon Rhône-Alpes.

From 1997 to 2002, he was Director of the Immunology Center of the Pierre Fabre Group in Saint-Julien en Genevois, France. He previously was responsible for the Immunology Department of the Biomedical Research Institute of the Glaxo-Wellcome Group in Geneva, Switzerland.

Jean-Yves Bonnefoy holds a PhD in immunology from the Lyons Claude Bernard University and has completed the Senior Management Program of the London Business School.

### ABSTRACT

#### **Therapeutic vaccines against non-small cell lung cancer**

Transgene is developing innovative therapeutic vaccines in the fields of infectious diseases and cancer. Likewise all other treatment modalities, patient response to therapeutic vaccines is heterogeneous. Therefore Transgene has launched an exhaustive program of immunomonitoring, transcriptomics and proteomics analysis of patients treated or not before, during and after therapeutic vaccines administration. This should allow us to define a signature predictive of response to those new therapies.

TG 4010, is a viral vector (MVA) encoding a tumor associated antigen (MUC-1) and a cytokine (IL-2). TG4010 is an active immunotherapy for MUC-1 expressing cancers including NSCLC, breast and prostate. We recently repor-

ted at ASCO (Chicago 2008) and ESMO (Stockholm 2008) that the primary endpoint of a clinical phase 2b in 148 NSCLC patients was met. The PFS at 6 months was >40% in the TG4010+chemotherapy arm and the RR was significantly increased with TG4010+chemotherapy (43% versus 27%). As far as biomarkers are concerned, preliminary data indicate a significant correlation between levels of activated NK cells in patient's peripheral blood prior to therapy, and survival in TG4010+chemotherapy arm only. Those important findings pave the way for further characterization of TG4010 mechanism of action and optimal design of the phase III clinical development. Latest results on those biomarkers signature in Transgene's products under clinical development will be presented.

## CARL H. JUNE

Dr Carl H. June received his B.S. degree in chemistry from the United States Naval Academy and his M.D degree from the Baylor College of Medicine. He was a research fellow at the World Health Organization Immunology Research and Training Center, Geneva, Switzerland, a resident in internal medicine at the National Naval Medical Center, Bethesda, Maryland.

He was a fellow in oncology at the University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington, where he did post doctoral research with Dr. Paul Martin and Dr. John Hansen from 1983 to 1986.

From 1986 to 1999 Dr. June was at the Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland, where he was promoted to the rank of Professor in 1995.

From 1999, Dr. June has been at the University of Pennsylvania where currently he is Director of translational Research Programs and Professor in the Department of Pathology and Laboratory Medicine.

Dr. June authored more than 200 scientific papers and book chapters.

His research interests are in the area of lymphocyte biology and adoptive immunotherapy for cancer and infectious diseases.

### ABSTRACT

#### **Strategies for T cell adoptive transfer cancer therapy**

While there are exciting examples of successful clinical strategies to mobilize the immune system to attack cancer cells, overall the results have been disappointing in randomized clinical trials. We are exploring the use of engineered T cells bearing chimeric receptors and strategies to augment their antitumor efficacy in adoptive transfer settings. The surface membrane glycoprotein mesothelin is a promising target for the immunotherapy of mesothelioma, ovarian, and pancreatic tumors due to the uniform overexpression of mesothelin and the benign phenotype of mesothelin null mice. We hypothesize that previous trials of adoptive immunotherapy for cancer that have used CTL have failed due to poor trafficking to sites of tumor, and insufficient effector functions to self antigens. Our preclinical data indicates that use of lentiviral engineered T cells with chimeric receptors that incorporate a 'tumor resistance genotype' should have improved function for cancer immunotherapy. We have tested mesothelin redirected T cells in humanized mouse models bearing

tumor xenografts. The T cells are able to eradicate large, well established tumors at an in vivo E:T ratio of at least 1:70. As a complementary strategy, we have engineered artificial antigen presenting cells (aAPC) to express ligands for either CD28 or ICOS. These aAPC appear to be useful to reprogram T cells, and increase the antitumor efficacy of adoptively transferred T cells. In ongoing clinical trials testing adoptive transfer of T cells after retroviral or lentiviral gene transfer we find that 1) the T cells engraft and persist at high levels for 10 years or more, indicating that central memory T cells with "stem cell like qualities" can be transduced, and 2) rectal mucosal biopsy studies taken from patients after adoptive transfer indicate that the T cells traffic with high efficiency to IEL. Finally, our preclinical studies with B. Jakobsen testing TCRs engineered for high affinity indicate the ability to "convert" polyclonal T cells to monoclonal T cells with potent redirected specificity for surrogate antigens, suggesting that tumor antigens for which substantial repertoire limitations in the natural pool of available T cells can be targeted with the adoptive transfer of engineered T cells.

## JACQUES BANCHEREAU

Dr. Jacques Banchereau is the Director of the Baylor Institute for Immunology Research (BIIR) in Dallas and holds the W.W. Caruth, Jr. Chair in Organ Transplantation Immunology. In December, 2007, BIIR became the first INSERM unit in the United States and Dr. Banchereau serves as the Director of BIIR/ANRS/INSERM Unit #899 “Center for Human Vaccines” that is working to develop therapeutic and preventive HIV vaccines. He received his Ph.D. in biochemistry from the University of Paris in 1980 and later served as director of the Schering Plough Laboratory for Immunological Research near Lyon, France, where he was among the first to discover how to grow human dendritic cells.

Dr. Banchereau came to Baylor in 1996 to develop the Baylor Institute for Immunology Research. He is an Adjunct Professor of Microbiology and a Member of the Cancer Immunobiology Center at The University of Texas Southwestern Medical Center. Dr. Banchereau also holds an Adjunct Professorship in Biomedical Studies at Baylor University Medical Center in Waco, TX. He is also a Professor at Mount Sinai School of Medicine in the Department of Gene and Cell Medicine, Department of Medicine (Clinical Immunology Division) as well as the Immunology Institute and Experimental Therapeutics Institute. He has served on the National Institutes of Health's Experimental Immunology Study Section, Center for Scientific Review, in the area of Experimental Immunology. He has published more than 275 papers and 150 book chapters and reviews in major international journals, reviews manuscripts for various scientific journals and is a frequent speaker at national and international scientific conferences. His research interests center around various areas of immunology and cancer including dendritic cells, novel cytokines and antibody-producing B lymphocytes. His extensive work significantly contributed to the understanding of dendritic cell biology.

### ABSTRACT

#### Dendritic cell based immunotherapy

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## GIORGIO PARMIANI

Giorgio Parmiani holds an MD from University of Milan. He was trained in tumor immunology at the Institute for Cancer Research of Philadelphia (1970-1) under the supervision of Richmond T. Prehn, one of the founders of the modern tumor immunology. Back to Italy he has been working at the Istituto Nazionale dei Tumori where in 1984 he has been appointed Director of the Division of Experimental Oncology then (1998) Deputy Scientific Director and Head and of the Department of Innovative Therapies. In 1994 he started the PhD Program in Molecular Oncology at the same institution.

On January 2007 he moved to the San Raffaele Foundation Scientific Institute where he is the Head of the Unit of Immuno-Biotherapy of Melanoma and solid Tumors.

Dr Parmiani research interests have been focused on studies of molecular characterization of human tumor antigens and the T cell response to them, particularly in melanoma patients, and on studies of immunotherapy in melanoma, colorectal and prostate cancer patients, first with gene-modified cellular vaccines and then with peptide or heat-shock protein-based vaccines. Dr. Parmiani has published over 400 papers in the field of tumor immunology, mostly in internationally peer reviewed journals. He is acting as reviewer for the major scientific journals in immunology and oncology. He has been awarded several national and international prizes. He has participated as invited speaker in many international meetings and has served as expert in several scientific committees and Scientific Advisory Boards.

### ABSTRACT

#### Cancer vaccines and their targets

The immunogenic strength and tissue distribution of human tumor associated antigens (TAAs) are crucial for a successful immunization of cancer patients. Such TAAs include peptide epitopes recognized by T cells in the context of class I or II HLA. The group of shared/ self TAAs have been largely used as vaccines in patients with different forms of cancer. While the first trials of phase I and II have been conducted with one or two such peptides, during the last few years multiple peptides have been administered simultaneously to improve targeting and reduce selection of TAA-negative tumor cells by T lymphocytes elicited by vaccination. These phase I-II trials have resulted into a variable frequency (20-60%) of patients developing an anti-vaccine specific T cell response, while tumor regression were reported in a minority of cases. In an attempt to vaccinate patients with a more immunogenic, individualized TAAs pool, we used autologous tumor-derived gp96 heat shock proteins (HSPPC-96; potentially binding tumor-specific, mutated TAAs) that led to TAA-specific T cell response in 50-60% metastatic melanoma and colon carcinoma patients with evidence of better survival in immune

responders as compared to non-responders subjects. A recent phase III trial comparing vaccination with HSPPC-96 (Vitespen) with physician choice treatment fared similarly in ITT though patients that could receive at least 10 vaccinations and had an early metastatic disease (M1a/M1b) did better than others. To further explore the mechanism of action of HSPPC-96 we performed experiments showing that gp96 may activate innate immune responses by a specific interaction with the CD91 receptor of plasmacytoid dendritic cells. A potential new target of therapy is represented by cancer stem cells (CSC). We have evaluated the TAA profile of glioblastoma CSC which showed an impaired expression of HLA as compared with non-CSC neoplastic counterparts accompanied by resistance to T or NKT cytotoxicity. As for immune deviation that prevents a better clinical outcome, we have found and characterized myeloid-derived suppressor cells in the blood and tumor tissue of patients with metastatic melanoma and colon cancer. Mechanism underlying such suppressive activity will be described. This new information has now been incorporated in the design of new vaccination protocol and early findings obtained by such protocols will be presented.

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Giorgio Parmiani<sup>1</sup>, Licia Rivoltini<sup>2</sup>, Lorenzo Pilla<sup>1</sup>, Rossella Galli<sup>1</sup>, Cristina Maccalli<sup>1</sup>

1 Unit of Immuno-Biotherapy of Solid Tumors, San Raffaele Scientific and University Institute, Milano  
and 2 Unit of Immunotherapy of Human Tumors, National Tumor Institute Foundation, Milano.

## JEAN FRANÇOIS CHATAL

Jean-François Chatal is a Distinguished Professor of Nuclear Medicine at the University of Nantes, France.

In 1975 he created a research team devoted to diagnostic (scintigraphic imaging) and therapeutic (radioimmunotherapy) use of radiolabeled monoclonal antibodies in oncology. This research team was a part of a larger group specialized in immunology and oncology and affiliated to INSERM (National Institute of Health and Medical Research) and University of Nantes. The first patient with a colorectal carcinoma was injected in Nantes with a <sup>131</sup>I-labeled anti-tumor monoclonal antibody in June 1981.

At the end of the 1980's, he developed a strong collaboration with Immunotech company in Marseille for the preclinical and clinical application of an original and innovative pretargeting technology based on the use of unlabeled bispecific antibody and radiolabeled bivalent hapten and which had just been patented by Immunotech. After a clear documentation of the efficacy of this technology in diagnostic application (immunoscintigraphy) at the beginning of the 1990's, the first phase I radioimmunotherapy study was initiated in 1996 in patients with medullary thyroid cancer and small cell lung cancer. Recently, in 2006, a paper published in the Journal of Clinical Oncology reported, for the first time, a survival benefit of pretargeted radioimmunotherapy in an advanced solid tumor (medullary thyroid carcinoma).

Currently the research team, headed by Jacques Barbet, one of the inventors of the pretargeted technology in Immunotech and who moved from Marseille to Nantes, is composed of 45 members including 21 researchers specialized in radionuclide and bioconjugate chemistry, experimental radioimmunotherapy (including alphaimmunotherapy) and radiobiology, radiophysics-dosimetry and clinical research.

Jean-François Chatal initiated, with 2 other colleagues, the project of installation in Nantes in 2008, of a high energy/high intensity cyclotron, termed ARRONAX, for the production of innovative radionuclides for nuclear medicine research in Europe.

He wrote 175 original papers and presented more than 100 invited lectures.

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JEAN FRANÇOIS CHATAL

## ABSTRACT

### **Immunotoxins and radiolabelled tumor-specific mAbs in cancer treatment**

The tumor cell-killing effect of antibodies can be enhanced by coupling them with potent cytotoxic agents such as toxins and radionuclides.

Immunotoxins are composed of a plant or bacterial toxin along with an antibody or a growth factor. They work by enzymatically inhibiting protein synthesis after being internalized by tumor target cells. Theoretically, once in the cytosol, one molecule can kill a tumor cell making immunotoxins among the most potent killing agents. A large variety of immunotoxins have been preclinically and clinically evaluated in the past 3 decades. More than 15 tumor antigens have been targeted with roughly the same number of antibodies or other ligands. Hematologic cancers have been preferably considered because malignant cells are rapidly accessible to intravenously injected drugs which fits well with the relatively short half-lives of immunotoxins. Moreover, in this clinical setting, patients tend to lack sufficient immunity to make neutralizing antibodies against the toxin. However, despite these favorable conditions, only one immunotoxin made of human interleukin-2 and truncated diphtheria toxin, has been approved by Food and Drug Administration. This immunotoxin, called denileukin diphtitox or Ontak is indicated for treatment of cutaneous T cell lymphoma and allowed to obtain, in a pivotal phase III trial in 71 patients, a response rate of 30%. A limited clinical effectiveness has been observed in several types of solid tumors. Currently the development of immunotoxins is severely limited by several problems including immunogenicity, toxicity and limited half-life. Neutralizing antibodies are detected in up to 40% of patients with hematologic malignancies and in 50% to 100% of patients with solid tumors after a single cycle of treatment. Toxicity combines vascular leak syndrome related to the need for immunotoxins to traverse endothelial cells before exiting blood cells and

hepatotoxicity. The future of immunotoxins remains uncertain and will need to consider combination with other treatment modalities.

The coupling of a radionuclide, instead of a toxin, to an antibody molecule has the main advantage of what is called the « cross-fire » effect. In this effect the electron emission from the radionuclide can, unlike immunotoxins, damage not only tumor cells expressing the targeted antigen but also tumor cells that are not accessible to the mAb, may not express the targeted antigen or may be resistant to the effects of unlabeled antibody.

The clinical effectiveness of radioimmunotherapy has been clearly documented in the clinical setting of minimal residual disease in which the tumor size (a few millimeters) fits well with the path length of electrons emitted by commonly used radionuclides (iodine-131 or yttrium-90). Moreover the best clinical results have been obtained in radiosensitive tumors like Non Hodgkin's Lymphoma for which a moderate tumor dose (less than 40 Gy) is sufficient to eradicate the targeted tumors. For radioresistant solid tumors the main challenge is the delivery of tumoricidal doses of the radiolabelled mAb while sparing normal tissues of unmanageable toxicities. One approach to solve this problem is pretargeting which involves the separation of the tumor localization with an anticancer mAb from the subsequent delivery of the therapeutic radionuclide. With the use of a bispecific antibody followed by radiolabelled bivalent hapten we have shown evidence of improved survival in patients with rapidly growing metastatic medullary thyroid cancer.

Another approach to increase the delivery of tumoricidal doses is to inject myeloablative activities of the radiolabelled mAb with stem cell rescue.

Finally the current main field of research is the preclinical and clinical evaluation of alpha-immunotherapy with the use of highly potent alpha particle-emitting radionuclides such as bismuth-213 and astatine-211 which should be able to efficiently kill disseminated, isolated and radioresistant tumor cells.

## LAURENCE ZITVOGEL

Pr L. Zitvogel, MD (clinical oncology), PhD (tumor immunology), PU-PH Faculty Paris Sud, University Paris XI (Clinical Biology), graduated in Medical Oncology from the School of Medicine of the University of Paris in 1992.

She started her scientific career when she was at the University of Pittsburgh in the USA in Michael Lotze's laboratory. She became Research Director at Institut National de la Santé et Recherche Médicale U805, in a laboratory located at Institut Gustave Roussy, a large cancer Center in Villejuif/France and the Head of the Center for Clinical Investigations CICBT 507 for vaccine developments at Villejuif.

She has been actively contributing to the field of cancer immunology and immunotherapy, and she brought together basic and translational research, including the design of cancer therapies through combined animal studies and Phase I patient trials. Her expertise is mainly dendritic cell and innate effector biology and relevance during tumour development as well as exosome-based vaccine designs.

She has been awarded several national and international prizes.

### ABSTRACT

#### **The anti-cancer immune response – A necessity for therapeutic success ?**

Although the impact of tumor immunology on the clinical managements of most cancers is still negligible, there is increasing evidence that anti-cancer immune responses may contribute to the control of cancer after conventional chemotherapy. Thus, radiotherapy and some chemotherapeutic agents, in particular anthracyclines, oxaliplatin and X Rays can induce specific immune responses (Obeid et al. Nat. Med 2007, Apetoh et al. Nat Med 2007) that result either in immunogenic cancer cell death, in

tumor sensitization to effector attack, in immunostimulatory “side effects” or in suppression of regulatory cells. This anti-cancer immune response then helps to eliminate residual cancer cells (that failed to be killed by chemotherapy) or maintains micrometastases in check, keeping them in a stage of dormancy.

Based on these premises, we will discuss how it may be possible to ameliorate conventional therapies by stimulating the anti-cancer immune response. Moreover, we will discuss the rationale of clinical trials to evaluate and eventually increase the contribution of anti-tumor immune responses to the therapeutic management of neoplasia.

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Laurence Zitvogel<sup>1,2,3,4</sup>, Lionel Apetoh<sup>1,3,4</sup>, François Ghiringhelli<sup>1,2,3</sup>, Fabrice André<sup>3</sup>, Antoine Tesniere<sup>3,4,5</sup> and Guido Kroemer<sup>3,4,5</sup>

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5 INSERM, U848, F-94805 Villejuif, France



# A NATIONAL HEALTH AND SCIENCE AGENCY,

## THE INSTITUTE:

The French National Cancer Institute was created through the Public Health Act of 9 August 2004, under the Cancer Plan, and implemented in July 2005 to enable a long-lasting, coordinated national policy against cancer. Placed under the tutelage of the Ministry of Health and the Ministry of Research, it brings together all of the players involved in the fight against cancer in France. The Institute is a health and science agency dedicated to oncology.

## ITS MISSIONS:

- ➔ To observe and assess the system in place to fight cancer;
- ➔ To define benchmarks for good practices and care in the field of oncology and the criteria for certifying institutions and professionals in the field of oncology;
- ➔ To inform professionals and the public;
- ➔ To participate in the implementation and validation of continuing education for doctors and paramedical personnel;
- ➔ To implement, finance and coordinate research projects in collaboration with the relevant public research organisations and charitable associations;
- ➔ To develop and monitor public/private actions in the areas of prevention, epidemiology, screening, research, education, care and evaluation;
- ➔ To participate in developing European and worldwide actions;
- ➔ To prepare expert reports in oncology and cancer issues at the request of the relevant ministries.

## A PUBLIC EXPERTISE AGENCY:

The Institute is a **public expertise agency** whose means of actions are the implementation of partnerships with and through the existing public and/or private structures of Care, Public Health and Research, and calls for proposals. The Institute covers the whole spectrum of the fight against cancer and has four main areas of interventions (below); the Institute's budget in 2007 was about 100 millions € dedicated to actions related to health, research, treatment and information

## 4 ACTION DOMAINS:

- ➔ **PUBLIC HEALTH:** Implement a better cancer prevention strategy and diagnose cancer earlier;
- ➔ **CARE:** Guarantee access to top-quality care for all, in line with the principle of equity;
- ➔ **RESEARCH:** Make innovation and progress more accessible;
- ➔ **INFORMATION:** population, patients and health care professionals.

## THE GOVERNANCE:

The National Cancer Institute is governed by a board of directors, which defines the overall strategy, and is made of public, private and associative stakeholders in the fight against cancer. An independent international scientific advisory board ensures the cohesion of scientific and medical policies. A committee of patients and a committee of health professionals are consulted on a regular basis, they advise on all actions of the Institute and actively participate to working groups on specific issues.

# DEDICATED TO CANCEROLOGY

## CANCER RESEARCH ORGANISATION:

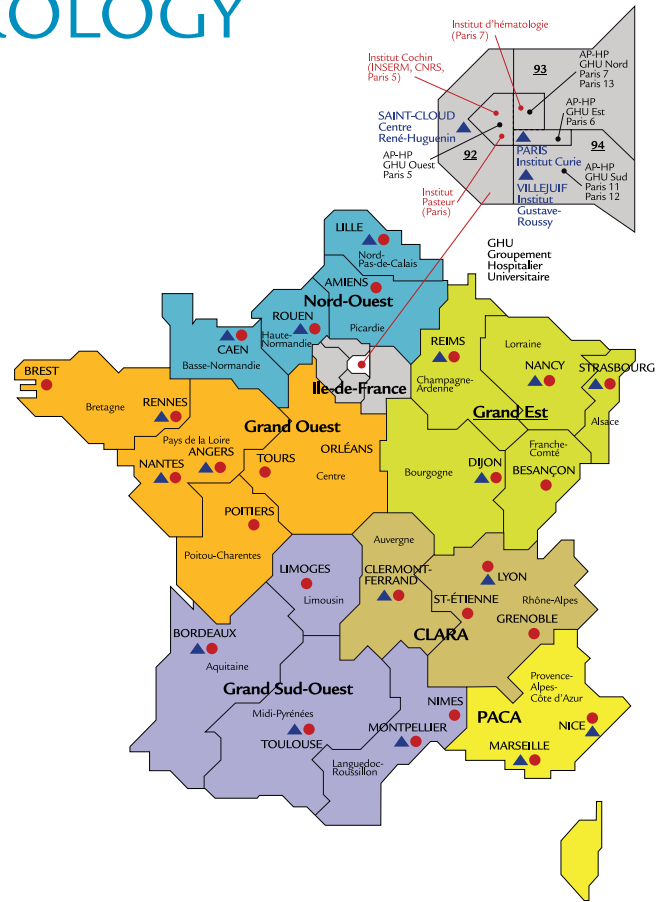
In 2003, 7 comprehensive cancer regions called “canceropôles” were created. These regional structures bring together the research units of scientific organisations, university hospitals with the aim of strengthening the coordination of research.

Research networks concentrated over 950 cancer research teams spread over France.

## FUNDING OF RESEARCH:

To ensure the care-research continuum, translational research is strongly supported by the Institute. From 2005 to 2007, 65.6 millions € were allocated to 211 projects which included an objective of translation; these projects represent more than 50% of the projects funded by the Institute. Since 2005, there is a constant increase in the funding of translational research projects;

- ➔ 2005: 50 projects, 16.7 M €;
- ➔ 2006: 60 projects, 19.5 M €;
- ➔ 2007: 78 projects, 29.4 M €.
- ➔ From 2008, a specific complementary programme will be dedicated to translational research.



**Clinical research** is supported by a yearly highly competitive cancer research programme sponsored by the Ministry of Health (16 millions €) and managed by INCa: 338 projects (clinical trials, epidemiological and clinical practice surveys, etc) were sponsored between 2003 and 2008. In addition, support is provided to 10 data management centres dedicated to cancer and to 140 clinical research nurses in cancer to help in collecting data and including patients into clinical trials.

**Integrated research programmes** covering all research areas from biology to clinical and social sciences are developed in specific types of cancer. In the last two years, two such specific research programmes were focused on early stages of colorectal cancer (5 M €) and lymphomas (5 M €). Hepatocarcinoma will be the next cancer type targeted in a 2009 call.

**Cancer genomics** is strongly supported, not only through specific calls but also through strengthening of networks, biological platforms and biobanks. The Institute is the French member of the **ICGC International Cancer Genome Consortium** which plans to sequence and analyse the genome of 50 different tumour types in the next five years.





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