



## Charles Rodolphe Brupbacher Foundation

The  
Charles Rodolphe Brupbacher Prize  
for Cancer Research 2017  
is awarded to

**Laurence Zitvogel,  
MD/PhD**

*for her discovery*

*of the role of immunogenic cell death  
and the gut microbiota in cancer treatment*

The President  
of the Foundation

Georg C. Umbricht

The Co-President  
of the Foundation

Prof. Dr. Michael Hengartner

The President  
of the Scientific Advisory Board

Prof. Dr. Holger Moch

Member  
of the Scientific Advisory Board

Prof. Dr. Rainer Weber



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The  
Charles Rodolphe Brupbacher Prize  
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is awarded to

**Guido Kroemer,  
MD/PhD**

*for his discovery*

*of the mechanisms of apoptosis and immunogenic cell death*

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of the Foundation

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### Laudatio

*Miriam Merad*

It is my great pleasure to give the laudation for Laurence Zitvogel and Guido Kroemer, winners of the Brupbacher Prize for Cancer Research in recognition of their contribution to cancer immunology research.

I am standing here presenting this eulogy today because of a fortunate encounter I have made with Laurence Zitvogel 20 years ago. In 1996, I was a 3rd resident in hematology/oncology at the Gustave Roussy Cancer Institute in Paris, when I was introduced to Laurence, a new

attending clinician who had just returned from the United States after 3 years spent in a cancer immunology research lab. Laurence's passionate teaching of cancer immunotherapy, which contrasted so much with the discussions we had on the clinical floors, inspired me to learn immunology and, twenty years later, there is still so much to learn and discover.

Laurence was born in France in a suburb of Paris from a family of Artisans. When she was six-years old, she announced to her family that she will become a doctor, and the long suffering and early death of a father she adored strengthened her intention. To this day, Laurence's vocation to seek novel cures and alleviate suffering has remained intact.

Laurence attended La pitie Salpetriere's Medical School in Paris and very early decided to specialize in Oncology. Frustrated by her training in clinical oncology and saddened by the bleak outcome of her patients, Laurence decided to take some time off from the clinical training to learn about immunology, as she had become fascinated by the process of vaccination and immune protection. Intrigued by the work of Steven Rosenberg, a surgical oncologist at the NIH and a pioneer of tumor immunotherapy, she decided to join the laboratory of Michael Lotze, a former Rosenberg's trainee, who was leading a Cancer Immunology laboratory in Pittsburgh University. After a successful time there, she returned to Paris to start her own laboratory at Gustave Roussy Cancer Research Institute, where she has been since. Soon after starting her laboratory, she became interested in the role of targeted and conventional therapy on the immune system. She discovered that imatinib (Glivec), a tyrosine kinase inhibitor targeting the oncogenic kinases Bcr-Abl, c-Abl and c-Kit, promotes tumor response partly through its ability to stimulate natural killer (NK) cells to attack tumor cells, a finding that was to dramatically influence her subsequent research with Guido Kroemer. It is at Gustave Roussy that Laurence met Guido for the first time, a meeting that was to transform their personal and professional lives.

Guido is a trained pathologist, immunologist and molecular biologist. In the mid 90's he discovered that mitochondrial membrane permeabilization constitutes the central checkpoint of apoptosis, thereby laying the grounds for the comprehension of regulated cell death. Kroemer's team discovered that, in mammalian cell death, mitochondrial membrane permeabilization constitutes the point-of-no-return of the lethal process and thus defines the lethal checkpoint. Instead of considering apoptosis as a process dominated by proteases and nucleases, cell death is now viewed as a process that is largely controlled by mitochondria. This discovery has had important implications for the understanding of cell death. A prolific author and one of the most cited biologist in the world, Guido obtained many scientific awards including the International Cell Death Society Life Achievement Award and the European Cell Death Society Career Award.

In contrast to most immunologists at that time, who focused mainly on tumor vaccines or T cell adaptive therapies, Laurence and Guido inspired by Laurence's finding on the immunogenic role of Glivec and Guido's work on the mechanisms of cell death started to question whether all types of cell death were equal and searched for compounds that could induce tumor cell death in a way that could be recognized

by the immune system. They tested hundreds of compounds for more than 10 years and together they finally discovered that anthracyclines and oxaliplatin, two common chemotherapy agents, can induce a type of cancer cell death that elicits an anticancer immune response, hence allowing the immune system to control residual tumor cells. They identified the distinct molecular alterations that lead a dying cell to induce an immune response, distinguish this type of cell death from conventional apoptosis and showed that the immune response against dying tumor cells controls the clinical outcome of many chemotherapy regimens, both in mouse models and in cancer patients. These results led to a novel paradigm they named immunogenic cell death, a paradigm that revolutionizes our understanding of anti-cancer chemotherapies and should influence the development of combination chemio-immunotherapy regimens for the treatment of cancer patients.

During the course of these studies, Laurence became fascinated by the differential effects of chemotherapy on the immune system and she started systematically to monitor immune responses induced upon administration of chemotherapy. Soon she discovered that cyclophosphamide induced the release of interleukin-17, which was essential for the induction of antitumor immunity and that IL-17 release was dependent on the presence of gut commensal microbes. This led her to hypothesize for the first time the key role of the gut microbiome in the control of chemotherapy-mediated antitumor immunity. This work, published in "Science" in 2013, was soon followed by another breakthrough. Prompted by the finding that the checkpoint blockade of CTLA4 leads to gut tissue damage, Laurence then searched whether the gut microbiota was also instrumental in inducing tumor response to CTLA4 blockade. In a subsequent study, also published in "Science", she showed that, in mouse experimental tumor models, CTLA4-mediated antitumor immunity was also dependent on the presence of gut commensals. The discovery of the role of the gut microbiome in cancer treatment had enormous implications for the field and ignited a worldwide effort in academia and industry to develop novel microbe-based therapies to potentiate antitumor therapies.

I have met many physicians and scientists throughout my professional life, but to date I have not met scientists as passionate and as engaged as the Zitvogel & Kroemer team. They have dedicated their intellectual and personal lives to the finding of a cure for cancer and their passion has transformed our understanding of antitumor immune response and dramatically influenced and inspired generations of scientists throughout the world.

## Laurence Zitvogel

It is my distinct pleasure today, Laurence and Guido, to present you this well-deserved Charles Rodolphe Brupbacher Prize for Cancer Research in recognition of your contribution to cancer immunology research.



### *Summary Curriculum vitae*

**Appointment** Scientific Director of OncoImmunology,  
Gustave Roussy Cancer Center (GRCC)

**Address** 114 Rue Edouard Vaillant  
94800 Villejuif, France

**Date of Birth** December 25, 1963

### **Current Positions**

- 2016– Director, Torino-Lumiere, Program Project, Paris, France
- 2011– Member of Co-Directorate, Gustave Roussy Cancer Campus, Villejuif, France
- 2003– Full Professor, Immunology & Biology, Kremlin Bicêtre School of Medicine, University Paris XI
- 2002– Co-Director, Center of Clinical Investigations in Biotherapies of Cancer, GRCC-Curie, Paris
- 2000– Director, Laboratory “Tumor immunology and immunotherapy” INSERM U1015, GRCC
- 1998– Hospital Practitioner, Breast Cancer Department, Clinical attending, GRCC

### **Previous Positions**

- 1995-2000 Associate Professor, Clinical attending, Medical University of Paris XI, Villejuif
- 1995-1998 Post-doctoral fellowship, Adenovirus Gene Therapy, Pr Pericaudet’s lab, Villejuif, France

1994-1995 Assistant Professor, University of Pittsburgh,  
Pittsburgh Cancer Institute, USA  
1992-1994 Instructor, University of Pittsburgh,  
Pittsburgh Cancer Institute, USA  
1990 Master in Tumor Immunology, Prof. Fridman's  
lab. Institut Curie, Paris

### Education

1987 MD, School of Medicine, Pitié Salpêtrière,  
University of Paris VI, France  
1992 Board Certificate, Medical Oncology,  
University Paris VII, France  
1995 PhD, Immunology, University Paris VII, France -  
Pittsburgh Cancer Institute, Pittsburg, PA, USA  
1998 Habilitation, University Paris XI, France

### Fellowships and Awards

2014 Swiss Bridge Award for Cancer Research, Switzerland  
2013 Ligue Française contre le Cancer, Research Prize,  
Conseil Général des Yvelines, Versailles  
2012 Member of the National Academy of Medicine,  
Biology Division, Paris, France  
2012 Permanent member of the European Academy of  
Cancer Sciences, ECCO  
2011 Medical Research Prize, Price Raymond Rosen  
Fondation pour la recherche médicale, France  
2007 INSERM Prize for Translational Research,  
French Medical Research Council (INSERM)  
2007 Gallet & Breton Prize, National Academy of  
Medicine, Paris, France  
2005 Charles Oberling Prize, Senate of the French  
Republic, Paris, France  
2000 Gustave Roussy Prize, National Academy of Sciences,  
Paris, France  
1999 Prize of the Chancellery, University of Paris  
City Hall Paris  
1996 Ligue Française contre le Cancer, Research Prize,  
Conseil Général Haute Loire, France  
1995 Merit Award, Society for Biological Therapy,  
Nappa Valley, CA, USA

1994 Presidential Award, American Society of Clinical  
Oncology, LA, CA, USA  
1992 Vocation Prize, Bleustein Blanchet Foundation,  
Paris, France  
1992 Gold Medal, Internal Medicine, first Prize,  
Assistance Publique-Hôpitaux de Paris

### Principal Commissions of Trust

2016– Scientific Advisory Board (SAB), Transgene,  
Paris-Illkirch, France  
2015– SAB, Lytix Ltd., Oslo, Norway  
2015– SAB, NeoVacs, Paris, France  
2015– SAB, GSK, Philadelphia, PA, USA  
2014– Board of Directors/Executive Board, Transgene,  
Paris, France  
2014– Board of Directors/Executive Board, National  
Institute of Cancer (INCA), Paris  
2011-2014 SAB, DKFZ, Heidelberg, Germany  
2011 Helmholtz Foundation, research committee  
2001-2003 French Medical Research Council (INSERM)  
1997 EORTC, Immunology Scientific Committee

### Organization of Scientific Meetings

2017 Organizing committee, AACR Conference,  
Washington DC, DC, USA  
2016 Organizing committee, Cold Spring Harbor,  
Shuzhu, China  
2015-2016 Organizing committee, AACR/CIMT/CRI/EATI  
Conf. Tumor Immunology NYC, USA  
2013 Co-Organizer, Keystone Symposium, Vancouver,  
British Columbia, Canada  
2013 Coordinator, Cancéropôle Ile-de-France,  
Microbiota Conf, Paris, France  
2011 Co-Organizer, Keystone Symposium, Santa Fe,  
New Mexico, USA  
2006-2016 President and co-organizer, Miltenyi Immunology  
Annual Conferences, Paris, France  
2015 Organizing committee, AACR Conference on  
Tumor Immunology, San Diego, CA, USA

2013 Organizing committee, ECDO Conference, Paris, France

and the exosome team (Dr S. Amigorena, INSERM, Institut Curie, Dr Clotilde Théry, Institut Curie, Dr O. Lantz, Institut Curie).

### **Principal Editorial Activities**

2012– Editor-in-Chief, OncoImmunology (Landes Bioscience), Austin, Texas, USA  
2010-2016 Editor (Immunology), Cell Death & Disease (Nature Publishing Group), London, UK  
2005-2012 Associate Editor, Cancer Research (AACR), Philadelphia, PA, USA

### **Guest Editor**

2016 J. Clinical Investigations (series on exosomes biology)  
2008 Current Opinion in Immunology (Springer)  
2008 Cell Death Differentiation (Nature Publishing Group)  
2007 Immunological Reviews (Munksgaard-Springer)

### **Major Collaborations**

Together with some hundreds of collaborators/co-authors, our team has published close to 360 PubMed-indexed papers (search Zitvogel\_L). The most important collaborative efforts include G. Kroemer from Les Cordeliers, University Paris Descartes (230 common publications) on the immunogenic cell death concept (together with Dr D. Green, St. Jude's Hospital in Memphis, Dr M. Pittet, Harvard Medical School), Mark J. Smyth from QIMR Berghofer Medical Research Institute in Australia (>20), the Dendritic cell team (Dr Miriam Merad, Mont Sinai, NYC, USA, Dr Florent Ginhoux, A\*Star, Singapore, Dr Federica Sallusto, Bellinzona, Switzerland, Dr Dhodapkar, University of Yale, Connecticut, USA) the Microbiota team (Dr Ivo Gomperts Boneca, G. Eberl, and Dr Mathias Chamaillard, Institut Pasteur, Lille and Paris, France, Dr Joel Doré and Dr P. Lepage, Metagenopolis, INRA, Jouy-en-Josas, France), the Clinical team for breast cancer and melanoma (Dr F. André, Dr S. Delaloge, Gustave Roussy Cancer Center, Dr D. Jaeger, DKFZ, Heidelberg, Germany, Dr J. Wolchok, MSKCC, NYC, USA, Dr M. Maio, University of Siena, Italy, Dr B. Weide University of Tübingen, Germany),

## Acceptance Speech

Laurence Zitvogel

### Preamble

Prof. L. Zitvogel, MD, PhD, is 52 and graduated in Medical Oncology, School of Medicine, University of Paris in 1992 before starting her scientific career at the University of Pittsburgh, Pennsylvania, US. She established her own lab at the Institut Gustave Roussy in Villejuif. She developed her career in the field of cancer immunology and immunotherapy and reconciled basic and translational research to design novel cancer vaccines and conduct Phase I and II trials. Her scientific discoveries over the last 20 years rely on 4 pillars.

### 1: The role of dendritic cells and their exosomes in cancer immunology and immunotherapy

Having triggered the therapeutic potential of DC for cancer therapy, Pr Zitvogel investigated the cellular mechanisms whereby DC mediated tumor regression in vivo. She unraveled four novel and critical biological pathways: DC not only elicit T cell responses but also trigger the activation of innate effectors such as NK and NKT cells (Ikarashi et al. J. Exp. Med. 2001, Zitvogel L, J Exp Med 2002, Fernandez et al. Nat. Med. 1999, Fernandez et al. Eur. Cyt. Netw. 2002, Terme et al J. Immunol. 2004, Borg et al. JCI, 2004, Walzer et al. Blood 2005). DC/NK cell cross-talks appeared critical to dictate cognate immune responses (in the context of viruses or tumors) and control certain types of human malignancies (such as leukemia, gastrointestinal sarcoma and neuroblastoma), DC directly interact with T cells but also secrete membrane vesicles called “exosomes” that bear major complex histocompatibility molecules and heat shock proteins inducing, on their own, antitumor effects (Zitvogel et al Nat Med 1998, Wolfers et al Nat Med 2001, Thery, Zitvogel, and Amigorena, Nat Rev Immunol 2002, André et al The Lancet, 2002, André et al J Immunol 2004, Chaput et al, J Immunol 2004, Taieb J, J. Immunol 2006). Having demonstrated the immunogenicity of DC-derived exosomes in vitro and mouse models, Pr Zitvogel conducted two clinical trials based on patents and support from a Biotech Cie at first. Indeed, in collaboration with Institut Curie, she launched a Phase I trial using autologous DC derived-exosomes in stage IV melanoma patients in an academic cell therapy unit (Escudier et al J Transl Medicine 2004, results confirmed in parallel by an American team (Morse et al J Transl Med 2004). Exosomes were able to restore NKG2D-expression levels in both CD8+ T cells and

NK cells due to their high contents in IL-15R and MICA/B (Viaud et al PloS One, 2009). A Phase II in non small cell lung cancer using second generation exosomes (from DC propagated in GM-CSF/IL-4/IFN $\gamma$ ) has been completed and submitted to JCI. It demonstrates the bioactivity of DC IFN $\gamma$  exosomes on NK cell functions in NSCLC, specifically on NKp30 effector functions due to B7-H6 expression on exosome membranes. This illustrates that therapeutic intervention on the host immune system using exosomes may be of therapeutic value. A novel DC subset (called “IKDC” for IFN producing killer DC), with a unique morphology and unique potentials (IFN $\gamma$  secretion and TRAIL-dependent lysis in contact with a variety of transformed cells) involved in tumor immunosurveillance (J. Taieb, Nature Med, Feb. 2006).

Moreover, facing the reality of tumor-induced tolerance, she undertook the investigation of DC pathophysiology during tumor progression in mouse and human specimen. She discovered two novel concepts of immunosuppression: i) tumor cells pervert DC and convert them into TGF- secreting cells promoting the expansion and accumulation of naturally occurring regulatory T cells (suppressor T cells, Treg) (Ghiringhelli et al J Exp Med 2005a), ii) such Treg interfering with not only conventional T cells but also blunting all NK cell functions in tumor bearing hosts (Ghiringhelli et al J Exp Med 2005b).

### 2: The role of NK cells in human malignancies and discovery of NKp30-associated biomarkers

Her team valued the study of a potential impact of NK cells in tumor immunosurveillance. She conducted mouse models of transplantable tumors and studied human malignancies. In addition to the well recognized prognostic value of NK cells in leukemias, her team contributed to highlight for the first time the critical prognostic role (and predictive value of NKp30 isoforms) of NK cells in gastrointestinal sarcoma (GIST) and high grade neuroblastoma (HGNC).

She first characterized various subsets of NK cells in mouse models of expanding tumors such as IKDC (a subset of CD11b+ class II+ NK capable of APC functions, Terme et al. Cancer Res. 2008, a subset of regulatory NK cells CD27+ Kit+, dictated by IL-18, Terme et al. Cancer Res. 2010, Cancer Res. 2011).

Next, she reported that NK cells are major components of human gastrointestinal sarcoma and high grade neuroblastoma and are endowed with prognostic value in large cohorts of metastatic patients (Borg C, J.Clin. Invest 2004, Ménard C et al Cancer Res. 2006).

Based on the finding that the NK specific Nkp30 receptor was selectively downregulated in tumors, her team was the first to describe a post-transcriptional regulation of three distinct Nkp30 isoforms and their functional consequences on NK cell effector properties and patients prognosis (Delahaye, Nat Med 2011, Rusakiewicz, Cancer Res 2013, Semeraro, Sci Transl Med in press, Rusakiewicz, JCI submitted). Importantly, her medical background and constant preoccupation for clinical care in oncology led her to highlight a novel mode of action of the c-Kit tyrosine kinase inhibitors (the paradigmatic STI571/ imatinib mesylate/Gleevec<sup>o</sup> used for chronic myeloid leukemia and gastrointestinal sarcoma (GIST)). Her team showed that STI571, in addition to cell autonomous effects on tumor cells, exerts potent NK cell-mediated tumor regression in vivo in tumor models resistant to the antiproliferative effects of STI571 in vitro. This statement also applies to humans since GIST-bearing patients treated with STI571 exhibit enhanced NK cell effector functions after 2 months of therapy (Borg et al J. Clin Invest 2004, Ménard C, Cancer Res 2009). Moreover, STI571-induced NK cell triggering is an independent surrogate marker of efficacy of Gleevec<sup>o</sup> associated with prolonged disease free survival (Borg et al J Clin Invest 2004, Ménard et al. Cancer Res 2009). This discovery prompted her to find a biomarker of response to imatinib, by describing isoforms of Nkp30 activating receptors dictating the prognosis of GIST (Delahaye N et al. Nat. Med. 2011, Rusakiewicz S, Cancer Res 2013). Together with Novartis Pharma, she launched a Phase I/II study combining STI571 to drugs enhancing NK cell activation (Cyclophosphamide and IL-2, Locher C, OncoImmunology, 2013, Chaput N, OncoImmunology 2013).

3: The concept of immunogenic cell death: how chemotherapy can be viewed as a cancer vaccine?

Our groups (Zitvogel L in collaboration with G. Kroemer) invalidated the dogma that apoptosis is a non-immunogenic cell death modality. We demonstrated that, depending on the upstream triggers, apoptosis can be immunogenic and hence alert the innate immune system and instruct it to stimulate a cognate response against dead-cell antigens. This has opened a new field of research at the frontier between immunology and cell biology, allowing us to define the molecular properties of immunogenic cell death (ICD). We found that ICD is characterized by autocrine stimulation of type 1 interferon (IFN) receptors (and the TLR3/TRIF pathway), the pre-apoptotic exposure of calreticulin (CRT) on the cell surface, release of ATP during the blebbing phase of apoptosis, and post-apoptotic exodus of the chromatin-binding

protein high mobility group B1 (HMGB1). Type 1 interferon secretion depends on the stimulation of TLR3, CRT exposure on an endoplasmic reticulum stress response, ATP release on pre-mortem autophagy, and HMGB1 exodus on secondary necrosis. CRT, ATP and HMGB1 interact with three receptors (CD91 receptor, purinergic P2Y2 or P2X7 receptors, and toll-like receptor 4, respectively) that are present on the surface of dendritic cells or their precursors. CD91, P2Y2, P2RX7 and TLR4 promote engulfment of dying cells, attraction of dendritic cells, production of interleukin-1 $\beta$  and presentation of tumor antigens, respectively. We have launched and then proven the hypothesis that the immune response against dying tumor cells dictates the therapeutic success of anticancer chemotherapy, both in mouse models and in cancer patients (Obeid et al. Nat Med. 2006, Apetoh et al Nat. Med. 2007, Ghiringhelli et al. Nat. Med. 2009, Ma Y, JEM 2011, Michaud M et al. Science 2011, Menger L, Sci. Transl. Med 2012, Senovilla L, Science 2012, Sistigu et al. Nat Med 2015).

Obviously, this discovery has had major consequences for the comprehension, conception and implementation of anticancer chemotherapies. Indeed, we postulate that, at least in certain cases, both classical and targeted anticancer therapies require an active contribution of the immune system to be optimally efficient. We obtained clinical evidence that this hypothesis holds true for anthracycline-treated breast cancer, oxaliplatin-treated colorectal cancer, and imatinib-treated gastrointestinal stromal tumors.

4: The unsuspected role of gut microbiota in cancer therapies

Her team has recently highlighted the crucial role of gut microbiota in eliciting innate and adaptive immune responses beneficial for the host in the context of effective therapies against cancer (chemotherapies, immunotherapy based on immune checkpoint blockers).

1/ Context of cyclophosphamide (CTX):

Chemotherapeutic agents, by compromising, to some extent, the intestinal integrity, facilitate the gut permeability and selective translocation of Gram positive bacteria in secondary lymphoid organs. There, anti-commensal pathogenic TH17 T cell responses are primed, facilitating the accumulation of TH1 helper T cells in tumor beds post-chemotherapy as well as tumor regression. Importantly, the redox equilibrium of myeloid cells contained in the tumor microenvironment is also influenced by the intestinal microflora, contributing to tumor responses. Hence, the anticancer efficacy of alkylating agents is compromised in germ-free mice or animals treated with antibiotics. These findings represent a paradigm shift in our understanding of

the mode of action of many compounds having an impact on the host-microbe mutualism (Viaud S, Science 2013). These findings have been extended to platinum salts (oxaliplatin, cis-platin) as well as to a combination of anti-IL-10R mAb+CpG for Iida et al. Science Nov 2013 (Trinchieri's group at the NIH, USA).

2/ Context of CTLA4 blockade :

The immune checkpoint blocker (ICB) anti-CTLA4 Ab is a first-in class compound approved for reinstating cancer immunosurveillance and prolonging survival in metastatic patients. However, this clinical benefit is often associated with immune-related side effects at sites exposed to commensal flora such as the large intestine. Uncoupling efficacy from toxicity is a challenging issue for the future development of ICB. Her team showed (and submitted to Science) that the antitumor effects of CTLA4 blockade, largely dependent upon Toll like receptor (TLR)2/TLR4 receptors, markedly rely on the regulatory commensal *Bacteroides fragilis* (Bf) (in coordination with *Burkholderia cenocepacia*). Innate signaling induced by specific TLR2/TLR4 agonists failed to compensate the lack of tumoricidal activity mediated by CTLA4 blockade in germ free (GF) or antibiotics-treated mice while the IL-12-dependent cognate immunity directed against Bf could do so. Hence, anti-CTLA4 Ab elicited protective Bf-specific Th1 immune responses in specific pathogen free (SPF) mice that could be substituted, in GF animals, by oral Bf, purified Bf-associated polysaccharides or a Bf-specific adoptive T cell transfer, without triggering overt colitis. Ipilimumab could also restore Bf-specific Th1 immune responses in a fraction of advanced melanoma patients. This study unravels the key role of *B. fragilis* in the immunostimulatory effects of anti-CTLA4 Ab, opening up novel strategies to safely broaden its clinical efficacy (Vétizou et al. Science Nov. 2015). At the same time, Gajewski's group in Chicago showed that *Bifidobacteria* from the gut influence the tumor microenvironment in such a way that anti-PDL-1 Ab can induce a prominent anticancer immune responses (Sivan et al. Science Nov. 2015).

Most significant publications

- Zitvogel L, Ayyoub M, Routy B, Kroemer G. Microbiome and Anticancer Immunosurveillance. *Cell*. 2016 Apr 7;165(2):276-87.
- Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, Rusakiewicz S, Routy B, Roberti MP, Duong CP, Poirier-Colame V, Roux A, Becharaf S, Formenti S, Golden E, Cording S, Eberl G, Schlitzer A, Ginhoux F, Mani S, Yamazaki T, Jacquelinot N, Enot DP,

Bérard M, Nigou J, Opolon P, Eggermont A, Woerther PL, Chachaty E, Chaput N, Robert C, Mateus C, Kroemer G, Raoult D, Boneca IG, Carbonnel F, Chamaillard M, Zitvogel L. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science*. 2015 Nov 27;350(6264):1079-84.

- Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillère R, Hannani D, Enot DP, Pfirschke C, Engblom C, Pittet MJ, Schlitzer A, Ginhoux F, Apetoh L, Chachaty E, Woerther PL, Eberl G, Bérard M, Ecobichon C, Clermont D, Bizet C, Gaboriau-Routhiau V, Cerf-Bensussan N, Opolon P, Yessaad N, Vivier E, Ryffel B, Elson CO, Doré J, Kroemer G, Lepage P, Boneca IG, Ghiringhelli F, Zitvogel L. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science*. 2013 Nov 22;342(6161):971-6.
- Zitvogel L, Galluzzi L, Viaud S, Vétizou M, Daillère R, Merad M, Kroemer G. Cancer and the gut microbiota: an unexpected link. *Sci Transl Med*. 2015 Jan 21;7(271):271ps1.
- Vacchelli E, Ma Y, Baracco EE, Sistigu A, Enot DP, Pietrocola F, Yang H, Adjemian S, Chaba K, Semeraro M, Signore M, De Nino A, Lucarini V, Peschiaroli F, Businaro L, Gerardino A, Manic G, Ulas T, Günther P, Schultze JL, Kepp O, Stoll G, Lefebvre C, Mulot C, Castoldi F, Rusakiewicz S, Ladoire S, Apetoh L, Bravo-San Pedro JM, Lucattelli M, Delarasse C, Boige V, Ducreux M, Delaloge S, Borg C, André F, Schiavoni G, Vitale I, Laurent-Puig P, Mattei F, Zitvogel L, Kroemer G. Chemotherapy-induced antitumor immunity requires formyl peptide receptor 1. *Science*. 2015 Nov 20;350(6263):972-8.