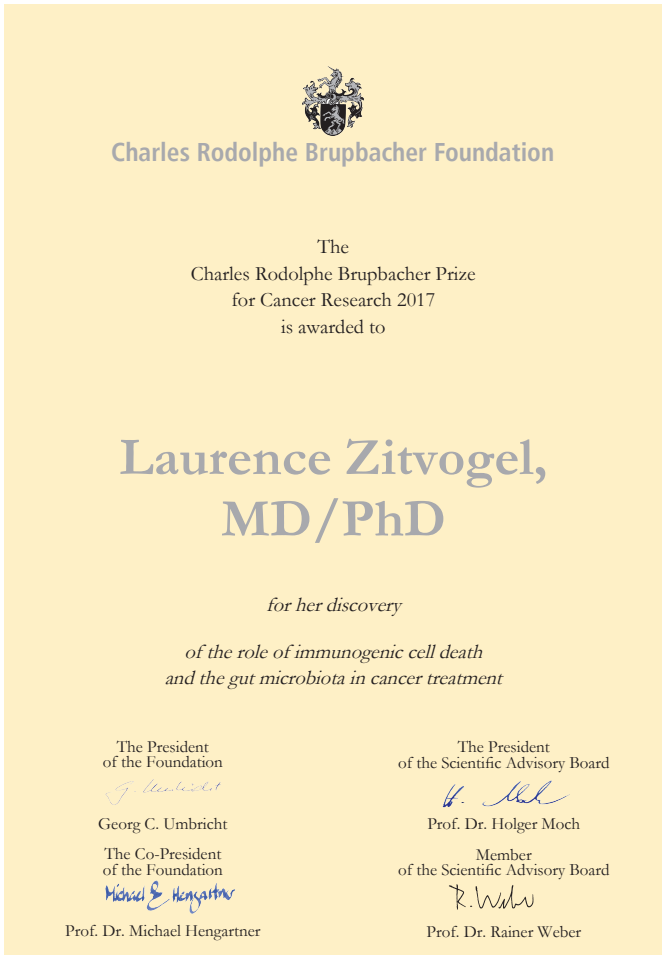


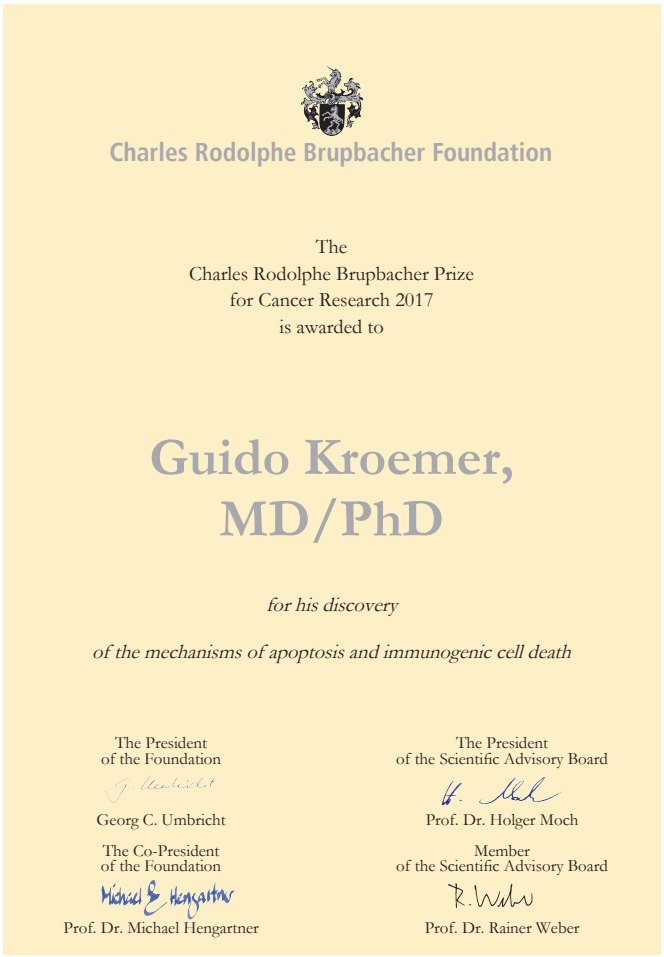


## Laudatio

*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 go. 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 Brc-Abl, c-Abl and c-Kit, promotes tumor response partly though its ability to stimulate natural killer (NK) cells to attack tumor cells, a findig that was to dramtically 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 impotant 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 regimen, 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 chemo-immunotherapy regimen 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 comensal 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 checkppoint 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 scientitists throughout the world.

## Guido Kroemer

*Summary Curriculum vitae*

**Appointment** Professor, University Paris Descartes

**Address** Centre de Recherche des Cordeliers
15 rue de l'Ecole de Médecine
F-75006 Paris, France

**Date of Birth** June 11, 1961.

**Education**

1985 MD-PhD (Immunology), University of Innsbruck, Austria
1990 Habilitation (Pathology), Medical University of Innsbruck, Austria
1992 PhD (Molecular Biology), Autonomous University of Madrid, Spain

**Academic Appointments/Affiliations**

1982-1985 Student Professor, University of Innsbruck, Austria
1984 Instructor, Wayne State University, Detroit, MI, USA
1985-1988 Assistant Professor, University of Innsbruck, Austria
1988-1990 Postdoctoral Fellow, Collège de France, Nogent-sur-Marne, France
1990-1992 Group Leader, Center of Molecular Biology, Madrid, Spain
1992 Visiting Research Scientist, University of California (UCSF); San Francisco, CA, USA
1992-1993 Group Leader, National Center for Biotechnology, Madrid, Spain
1993-1996 Senior Scientist (INSERM), CNRS, Cancer Research Center; Villejuif, France
1996-1999 Research Director (INSERM), CNRS, Cancer Research Center, Villejuif, France
1999-2001 Burnham Fellow, Burnham Institute La Jolla, CA, USA
2000-2010 Research Director, Institut Gustave Roussy/ INSERM, Villejuif, France
2010-present Full Professor, University of Paris Descartes, Paris, France
2013-2014 Visiting Professor, University of Rome, Tor Vergata, Rome, Italy
2015-present Foreign Adjunct Professor, Karolinska Institute & Hospital, Stockholm, Sweden

**Medical Appointments**

1990-2000 Associate Professor, Medical University of Innsbruck, Innsbruck, Austria
2000-2010 Consultant, Institut Gustave Roussy Villejuif, France
2003-2010 Interface contract, INSERM/Institut Gustave Roussy, Paris/Villejuif, France
2010-present Hospital Practitioner, Hôpital Européen Georges Pompidou, Paris, France

**Administrative Appointments**

1993-present Scientific Director, Laboratory "Apoptosis, Cancer & Immunity", Villejuif + Paris, France
2002-present Board of Directors, European Cell Death Organization, Ghent, Belgium
2007-2014 Director, INSERM Unit 848, Villejuif, France

2010-present Director, Metabolomics & Cell-Biology platforms, Gustave Roussy, Villejuif, France
2011-present Director, LabEx Immuno-Oncology, Paris, France
2011-present Founding President, European Academy of Tumor Immunology (EATI), Paris, France
2012-2014 President, European Cell Death Organization (ECDO), Ghent, Belgium
2013-present Director, Paris Alliance of Cancer Research Institutes (PACRI), Paris, France
2014-present Deputy Director, Cordeliers Research Center (CRC), Paris, France
2016-present Board of Directors, European Network for Cancer Immunotherapy, Mainz, Germany

**Appointments in Pharmaceutical Industry and Biotechnology**

1994-1997 Permanent consultant, Kabi Pharmacia, Lund, Sweden
2000-2002 Permanent consultant, Institut Scientifique Aventis, Ivry-sur-Seine, France
2003-2006 Scientific Advisory Boardn Apogenix Biotechnology Co., Heidelberg, Germany
2004-2010 Scientific Advisory Board, IOM Ricerca Catania, Italy
2005-present Permanent consultant, Bayer-Schering/Bayer-Healthcare, Berlin, Germany
2008-2010 Permanent consultant, Enzo Lifesciences Inc., Lausen, Switzerland
2009-present Advisor, Discovery Oncology Board, Bayer Healthcare, Berlin, Germany
2014-present Oncology Scientific Advisory Board, Hoffmann-La Roche Ltd., Basel, Switzerland
2015-present Scientific Advisory Board, Lytix Ltd., Oslo, Norway
2015-present Chairman of Scientific Advisory Board, Medicenna Therapeutics, Vanvouver, Canada
2015-present Board of Directors/Executive Board, Bristol Meyers Squibb Foundation, Paris, France
2016-present Permanent consultant, Genmab SA, Kopenhagen, Denmark
2016-present Founder, EverImmune (Biotech company), Paris, France

**Major editorial appointments**

2010-2016 Editor-in-Chief, Cell Death & Disease (Springer/Nature), London, UK
2012- Editor-in-Chief, OncoImmunolog (Francis & Taylor), Philadelphia, PA, USA
2013-2017 Editor-in-Chie, Microbial Cell (Shared Science Publishers), Graz, Austria
2014- Editor-in-Chief, Molecular & Cellular Oncology (Francis & Taylor), Philadelphia, PA, USA
2016- Deputy Editor, Cell Death & Differentiation (Springer/Nature), London, UK
2017- Founding Editor-in-Chief, Cell Stress (Shared Science Publishers), Graz, Austria

**Other editorial appointments (selection)**

1996-2002 Executive Editor, Immunology Letters (European Federation of European Societies)
1998-2016 Receiving Editor, Cell Death and Differentiation (Nature Publishing Group)
2000-2007 Associate Editor, Mitochondrion (Elsevier)
2000-2009 Associate Editor, Cancer Research (American Association for Cancer Research)
2002- Editorial Board Member, EMBO Journal (Nature Publishing Group)
2002-2011 Editorial Board Member, EMBO Reports (Nature Publishing Group)
2005- Editorial Board Member, Autophagy (Landes Bioscience Publisher)
2005-2010 Regional Editor, American Journal of Immunology (Science Publications, NY)
2007- Editorial Board Member, Cell Cycle (Landes Bioscience, Taylor & Francis)
2008- Editorial Board Member, Aging-US (Impact Journals)
2008- Editor, Biochemical and Biophysical Research Communications (Elsevier)

2009- Editorial Board Member, Cancer Research (American Association for Cancer Research)
2009- Associate Editor, Autophagy (Landes Bioscience, Taylor & Francis)
2009- Reviews Editor, Oncogene (Nature Publishing Group)
2009- Associate Editor , Journal of Molecular Cell Biology (Oxford University Press)
2010- Founding Editor, American Journal of Cancer Research (e-Century Publishing)
2010- Founding Editor, Oncotarget (Impact Journals)
2011- Editorial Board Member, Molecular Oncology (Elsevier)
2011-2013 Specialty Chief Editor, Frontiers in Oncology (Frontiers, Lausanne, Switzerland)
2012-2013 Advisory Board Member, Seminars in Immunopathology (Springer)
2013- Editorial Board Member, EMBO Molecular Medicine (Wiley)
2013- Editorial Board Member, Molecular & Cellular Biology (American Society for Microbiology)
2013- Reviewing Editor Science Signaling (American Assoc. for the Advancement of Science)
2015- Editorial Board Member, Oncogenesis (Nature Publishing Group)
2015- Editorial Board Member, Cell Research (Nature Publishing Group)
2015- Editorial Board Member, Cell Discovery ( Nature Publishing Group)
2016- Editorial Board Member, Signal Transduction and Targeted Therapy (Nature Publishing Group)

**Honors/Awards (selection)**

1984 Kamillo Eisner Award, Kamillo Eisner Foundation, Hergiswil, Switzerland
1985 Prize for the best MD/PhD thesis, Austrian Society for Allergology & Immunology, Vienna, Austria
1988 Erwin Schrödinger Fellowship, Austrian National Research Foundation, Vienna, Austria
1988 Hoechst Prize, University of Innsbruck, Austria
1996 Annual Research Prize, Ligue Nationale contre le Cancer, Paris, France
1997 Jean Valade Prize, Fondation de France, Paris, France
1997 Charles Oberling Prize, Senate of the French Republic, Paris, France
1998 Research Prize, Conseil Général des Yvelines, Versailles, France
1998 Monika Kutzner Cancer Research Prize, Academy of Sciences of Berlin-Brandenburg, Berlin, Germany
1999 Gallet & Breton Prize, National Academy of Medicine, Paris, France
1999 Medical Research Prize, Fondation pour la Recherche Médicale, France
2000 Jacques Sylvain Bourdin Prize, Ligue Nationale contre le Cancer, Paris, France
2000 Elected EMBO member, European Molecular Biology Organization, Heidelberg, Germany
2000 INSERM Prize for Pathophysiology, French Medical Research Council (INSERM), France
2003 Novum Lecture, Karolinska Institute & Nobel Assembly, Stockholm, Sweden
2006 Severo Ochoa Centennial Lecture, Spanish Society for Biochemistry, Alicante, Spain
2006 Descartes Prize, European Commission, Bruxelles, European Union
2007 Elected foreign member, Austrian Academy of Sciences, Vienna, Austria
2007 Elected member (Academician), German Academy of Sciences (Leopoldina), Halle, Germany
2007 Carus Medal, German National Academy of Sciences (Leopoldina)
2007 Elected member (Academician), Academia Europaea, London, UK
2007 Grand Prix Mergier-Bourdeix, French Academy of Sciences, Institut de France, Paris, France
2008 Carus Prize, City of Schweinfurth, Germany
2008 John Humphrey Lecture, Imperial College, London, UK
2008 Elected member (Academician), European Academy of Sciences and Arts, Salzburg, Austria

2009 Charles Darwin Lecture, Leopoldina Symposium on Cell Death, Wurzburg, Germany
2009 Dautrebande Prize, Belgian Royal Academy of Medicine, Bruxelles, Belgium
2009 Elected member (Academician), European Academy of Cancer Sciences, Amsterdam, Netherlands
2010 AXA Chair for Longevity Research, AXA Research Foundation, Paris, France
2010 Elected member (Academician), European Academy of Sciences, Liège, Belgium
2010 Jesus Montoliu Honorary Lecture, Institute of Biomedical Research of Lleida, Spain
2010 Elected member (Academician), European Academy of Tumor Immunology, Paris, France
2010 Duquesne Prize, National League against Cancer, Paris, France
2010 ECDO Career Award, European Cell Death Organization (ECDO), Ghent, Belgium
2011 Doctor honoris causa, University of Buenos Aires, Argentina
2011 ICDS Lifetime Achievement Award, International Cell Death Society (ICDS), New York, NY, USA
2011 Coup d'élan Prize, Bettencourt-Schueller Foundation, Neuilly, France
2012 Lambertsen Honorary Lecture, University of Pennsylvania, Philadelphia, PA, USA
2012 Ramalingaswami Memorial Lecture, National Institute of Immunology, New Delhi, India
2012 Léopold Griffuel Prize, Association for Cancer Research, Paris, France
2013 ERC Advanced Investigator Award, European Research Council (ERC), Bruxelles, European Union
2014 Karolinska Research Lecture, Medical Nobel Institute and Nobel Assembly, Stockholm, Sweden
2014 Mitjavile Prize, National Academy of Medicine, Paris, France
2015 Senior member, Institut Universitaire de France, Paris France
2015 Ohdang Distinguished Award, Pharmaceutical Society of Korea, Seoul, South Korea
2015 Galien Award for Pharmacological Research, Prix Galien de la Recherche Pharmaceutique, Paris, France
2016 International Prize for Oncology 'Ramiro Carregal', Rosaleda Foundation, Santiago de Compostela, Spain
2016 Leopoldina Lecture, International Conference on Innate Immunity, Berlin, Germany
2016 Grand Prix Claude Bernard, Science and Medicine Prize of the City of Paris, France
2016 Honorary professor, Center of Systems Medicine, Chinese Academy of Science, Suzhou

## Cancer cell stress and death: cell-autonomous and immunological considerations

Guido Kroemer

Cancer can be viewed in two rather distinct ways, namely (i) as a cell-autonomous disease in which malignant cells have escaped control from cell-intrinsic barriers against proliferation and dissemination or (ii) as a systemic disease that involves failing immune control of aberrant cells. The first vision has been prevailing in the area of cancer research over the last 50 years, while the latter has gained vast support only during the past few years.

In the cell-autonomous vision of cancer, the supreme goal of cancer research is to identify drugs that selectively kill cancer cells, much like antibiotics kill microbial pathogens yet spare host cells. This can be achieved by cytotoxic chemotherapies that kill rapidly proliferating cells (and hence induce the death of cancer cells more efficiently than normal host cells) or more elegantly – at least in theory – by identifying tumor cell specific signal transduction pathways that are responsible for the malignant phenotype and that can be regarded as cancer cell-specific therapeutic targets. Such tumor-specific targets would allow for "personalized" therapeutic interventions guided by the rules of "precision" medicine. Although some "personalized" therapies have undoubtedly been successful (such as the utilization of imatinib and its follow-up drugs for the treatment of Philadelphia-positive chronic lymphoid leukemia, CML, and gastrointestinal stromal tumors, GIST), thus far most "personalized" anticancer drugs have failed in clinical trials.

Adopting the view of cell biologists, my team has long been investigating one peculiar characteristic of cancer cells, namely their intrinsic resistance against lethal stimuli, meaning that malignant cells survive in conditions in which normal cells would succumb. This particular characteristic renders cancer cells resistant against otherwise lethal endogenous stress (such as lack of trophic transport, hypoxia, shortage of nutrients etc.) as well as against therapeutic interventions with cytotoxic chemotherapeutics and radiotherapy. We discovered in 1994 (and published for the first time in 1995) that, in programmed cell death, mitochondrial membrane permeabilization constitutes the point of no return of the lethal process and hence defines the cell death checkpoint. This discovery has initiated a scientific revolution in that it led to an operational redefinition of apoptosis (the prevalent form of regulated cell death), changed the method of apoptosis detection and conditioned the theoretical framework allowing for the ordering of pro-apoptotic signaling molecules. 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 has had far-reaching implications for the therapeutic manipulation of cell death, including the chemotherapeutic induction of cell death in cancer cells, which can be achieved by directly triggering mitochondrial permeabilization, as well as for the prevention of unwarranted cell death in stroke and infarction, which can only be achieved when targeting pre-mitochondrial or mitochondrial (but not post-mitochondrial) events. We explored the fine mechanisms of mitochondrial cell death control, as well as the molecular pathways that explain the inhibition of cell death in cancer cells, upstream of or at the level of mitochondria. We found that pro- and anti-apoptotic proteins of the BCL2 family regulate mitochondrial membrane permeability through interactions with proteins from the ATP synthasome and lipids. Beyond these mechanistic details, our work contributed to the comprehension of the mode of action of a series of oncogene products, in particular the proteins from the Bcl-2 family.

At a subsequent step of our work on the cell biology of cancer, we turned to autophagy, which is a bulk degradation pathway in which portions of the cytoplasm are enwrapped by membranes to form vesicles, so-called autophagosomes, which subsequently deliver their content to lysosomes. We noted that cell death is often preceded by cytoplasmic vacuolization with formation of autophagosomes, yet that suppression of autophagy by appropriate pharmacological and genetic interventions did not prevent cell death but rather accelerated the apoptotic or necrotic demise of stressed cells. We deciphered part of the molecular crosstalk between apoptosis and autophagy, showing that proteins with BH3 domains (BCL2 family members carrying BCL2 homology domains) can control both catabolic events and that activation of prominent elements of the classical NFκB activation pathway (in particular TAK1 and the proteins of the IKK complex) are required for the optimal induction of autophagy. We discovered that the pro-apoptotic tumor suppressor protein p53 plays a dual role in the control of autophagy, namely as an autophagy-inducing transcription factor and as an autophagy-repressing cytoplasmic factor. We also found that STAT3 can inhibit autophagy via the inhibition of PKR. We identified spermidine as a novel, non-toxic inducer of autophagy and

determined its mode of action as a life span-extending drug in yeast, nematodes, flies and mice. We accumulated extensive evidence that acetyl-coenzyme A and protein acetylation repress autophagy and that "caloric restriction mimetics" including spermidine induce autophagy via deacetylation reactions. We launched the (still valid) hypothesis that all longevity extending manipulations, be they metabolic, pharmacological or genetic, must induce autophagy to be efficient.

As we were working on the cell biology or apoptosis, autophagy and necrosis, we were wondering whether these cell stress and death mechanisms might influence the perception of cancer cells by the immune system. Driven by a discussion with my spouse, Laurence Zitvogel, as well as by our prior discovery that mitochondrial permeabilization constituted a lethal event that causes apoptosis accompanied by caspase activation as a default pathway, yet necrosis when caspases are inhibited, I launched a working hypothesis that a posteriori (and luckily) turned out to be wrong. I thought that, as the most prevalent pathway of physiological cell death execution, apoptosis would be immunologically silent (or even tolerogenic), while necrosis would be immunogenic. Hence, we injected CT26 colorectal cancer cells into immunocompetent BALB/c mice (which bear the same major histocompatibility locus as CT26 cells) and treated them with anthracycline-based chemotherapy alone, knowing that anthracyclines induce apoptosis, or anthracyclines plus a broad-spectrum caspase inhibitor (Z-VAD-fmk), knowing that this combination induces necrosis. We expected that the latter pro-necrotic regimen would be much more efficient than the pro-apoptotic treatment in stimulating an anticancer immune response and hence reducing tumor growth. To my dismay, the experiment yielded exactly the opposite result. Anthracyclines alone efficiently reduced tumor growth, while anthracyclines combined with caspase inhibitors failed to do so. Moreover, the capacity of anthracyclines to mediate tumor growth control were lost when CD8-positive cytotoxic T lymphocytes were depleted from the mice, indicating that their therapeutic action was entirely dependent on a cellular immune response. Driven by these unexpected results and a long-standing collaboration with Laurence Zitvogel, my group radically changed the working hypothesis to postulate that some chemotherapeutic agents including anthracyclines can stimulate a modality of cell death that we baptized "immunogenic cell death" (ICD) and that stimulates anticancer immunosurveillance through a partially caspase-dependent pathway.

In subsequent rounds of experiments, 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 ICD. We found that ICD is characterized by autocrine stimulation of type 1 interferon (IFN) receptors, 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 annexin A1 (ANXA1) and 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 annexin A1/HMGB1 exodus on secondary necrosis. CRT, ATP, ANXA1 and HMGB1 interact with four receptors (CD91 receptor, purinergic P2Y2 or P2X7 receptors, formyl peptide receptor-1 [FPR1], and toll-like receptor 4 [TLR4], respectively) that are present on the surface of dendritic cells or their precursors. CD91, P2Y2, FPR1, P2RX7 and TLR4 promote engulfment of dying cells, attraction of dendritic cells, juxtaposition of dendritic and dying cells, production of interleukin-1β and presentation of tumor antigens, respectively. Local induction of endoplasmic reticulum stress in the tumor bed and systemic induction of autophagy increase anticancer immune responses. 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. 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, among others.

Since macroautophagy/autophagy generally increases the fitness of cells (and entire organisms) as well as their resistance against endogenous or iatrogenic stress, it has been widely proposed that inhibition of autophagy would constitute a valid strategy for sensitizing cancer cells to chemotherapy or radiotherapy. Colliding with this cell-autonomous vision, however, we found that immunosurveillance against transplantable, carcinogen-induced or genetically engineered

cancers can be improved by pharmacologically inducing autophagy with caloric restriction mimetics, which are non-immunosuppressive but rather immunostimulatory. This positive effect depends on autophagy induction in cancer cells and is mediated by alterations in extracellular ATP metabolism, namely increased release of immunostimulatory ATP and reduced adenosine-dependent recruitment of immunosuppressive regulatory T cells into the tumor bed. The combination of autophagy inducers and chemotherapeutic agents is particularly efficient in reducing cancer growth through the stimulation of CD8+ T lymphocyte-dependent anticancer immune responses.

Altogether, our past and present research indicates that the efficacy of conventional and targeted anticancer agents does not only involve direct cytostatic/cytotoxic effects, but also relies on the (re)activation of tumor-targeting immune responses. Chemotherapy can promote such responses by increasing the immunogenicity of malignant cells, or by inhibiting immunosuppressive circuitries that are established by developing neoplasms. These immunological "side" effects of chemotherapy are desirable, and their in-depth comprehension will facilitate the design of novel combinatorial regimens with improved clinical efficacy.