CONTENT AND IMPACT OF THE SCIENTIFIC CONTRIBUTIONS

Pr Laurence ZITVOGEL MD, PhD
Gustave Roussy Cancer Center, Villejuif-Grand Paris

Current positions : Full Professor, Immunology Biology, Medical School, Paris-Saclay, France
Scientific Director of OncoImmunology, Gustave Roussy
Director of U1015 INSERM : Label since 2002
Co-Director CIC BT507 Biotherapies of Cancer : Label since 2004
Research Director, sponsored team by LIGUE contre le Cancer : Label since 2002
Title of the expertise : Tumor Immunology and Cancer Immunotherapy
Career Summary : Pr L. Zitvogel, clinical oncologist and research director, has been actively contributing to the field of cancer immunology and immunotherapy since 1992. 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 pioneered the concept of immunogenic cell death and showed that chemotherapy, radiotherapy and inhibitors of tyrosine kinase mediate their tumoricidal activity, at least partly through the immune system. She recently uncovered the role of gut microbiota in regulating antitumor immunity during therapy with cyclophosphamide and ipilimumab. She received numerous Prizes and awards (Brupbacher, ASCO-SITC, ESMO,…) from the National Academies (of medicine or Sciences, Elected Member of Academia Europaea), from INSERM (Translational Research Grand Prize), was nominated “Chevalier à l’Ordre de la Légion d’honneur” by the Health Ministery, and member of the National Academy of Medicine and of the European Academy of Cancer Sciences. Her H factor is 104, with >390 publications on PubMed, 52 000 quotations, and ranked by LabTimes Magazine, June 2013, the first female immunologist in Europe, based on N=111 papers issued from 2005-2011 cited N=7598 from 2005-2011, and by Thomson Reuters, one of the three top french scientists of the last 5 years. Currently directing the Research Department of ImmunoOncology at Gustave Roussy Cancer Center, Grand-Paris, France, and the TORINO-LUMIERE RHU microbiome-cancer network.

Curriculum vitae Laurence ZITVOGEL

PERSONAL INFORMATION

Family name, First name: **ZITVOGEL, Laurence**
Date + Place of birth: 25-12-1963, Suresnes, France;
Nationality: French
Languages: English, French

EDUCATION

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

CURRENT POSITIONS

2014- Scientific Director, OncoImmunology Programms, Gustave Roussy Cancer Center (GRCC)
2000- Director, Laboratory "Tumor immunology and immunotherapy" INSERM U1015, GRCC
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
1998-2016 Hospital Practioner, Breast Cancer Department, Clinical attending, GRCC
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 of tumors, Prof. Fridman's lab., Institut Curie, Paris

FELLOWSHIPS AND AWARDS

2018 Best article 2017 Prize: Prix de la Recherche, Science et Avenir
2018 Jakob Herz Prize, Erlangen
2018 Price of the journal « La Recherche » 2017
2017 ESMO Award for Immuno-Oncology
2017 Elected Member of Academia Europaea, London
2017 ASCO-SITC Award Keynote address Tumor Immunology, Orlando, USA
2017 Prize from the C.R. Brupbacher Foundation, Zürich, Switzerland
2016 Award from the Earle A Chiles Research Institute, Portland, OR, USA
2014 Swiss Bridge Award for Cancer Research, Swizerland
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 recherché 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

SUPERVISION OF GRADUATE STUDENTS AND POST-DOCTORAL FELLOWS

Until now I have directed 28 PhD theses and 39 post-doctoral fellows. Among these, thus far 6 have become Full Professors of Medicine (François Ghiringhelli, Antoine Tesnière, Fabrice André, Christophe Borg, Julien Taieb) or Pharmacy (Nathalie Chaput), 2 became INSERM research directors (Lionel Apetoh, Florent Ginhoux), 1 INSERM senior scientist (Magali Terme), 2 international group leaders abroad (Miriam Merad and Florent Ginhoux).

ORGANIZATION OF SCIENTIFIC MEETINGS

2017 Organizing comittee, AACR Conference, Washington DC, DC, USA
2017 Editing the first Bible of Immuno-Oncology (Springer, English version)
2016 Organizing comittee, Cold Spring Harbor, Shuzhu, China
2015 Editing the first Bible of Immuno-Oncology (EDPSciences, version française)
2015-2016 Organizing comittee, 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 comittee, AACR Conference on Tumor Immunology, San Diego, CA, USA
2013 Organizing comittee, ECDO Conference, Paris, France

INSTITUTIONAL RESPONSIBILITIES

2016- Director, TORINO-LUMIERE, Programm project, Paris, France
2014- Scientific Director, OncoImmunology Programms, Gustave Roussy Cancer Center (GRCC)
2011- Member of Co-Directorate, Gustave Roussy Cancer Campus, Villejuif, France
2002- Co-Director, Center of Clin. Investigations in Biotherapies of Cancer, GRCC-Curie, Paris
2000- Director, INSERM Unit 1015, Villejuif, France

PRINCIPAL COMMISSIONS OF TRUST

2017- SAB, Tusk Therapeutics Ltd., Stevenage, UK
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 Helmoltz Foundation, research committee
2001-2003 French Medical Research Council (INSERM)
1997 EORTC, Immunology Scientific Commitee

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)

ORGANIZATION OF SCIENTIFIC SOCIETIES

2011- Founding Director, European Academy of Tumor Immunology (EATI), Paris, France
1996-2002 Founding Member of the Club Francophone des Cellules Dendritiques.

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. Judes 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, Singapour, 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. Wolchock, MSKCC, NYC, USA, Dr M. Maio, University of Siena, Italy, Dr B. Weide University of Tübingen, Germany), and the exosome team (Dr S. Amigorena, INSERM, Institut Curie, Dr Clotilde Théry, Institut Curie, Dr O. Lantz, Institut Curie).

Preambule

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, first at the University of Pittsburgh, Pennsylvania, US and later on, established her own lab at 38 years- old at 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 pilars.

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/IFNγ) has been completed and submitted to JCI. It demonstrates the bioactivity of DC IFNγ 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 (IFNγ□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 (HGNB).

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° 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° 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-1β 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 (oxaliplatine, cis-platine) 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). In September 20 2017, the demonstration of the deleterious role of antibiotics in the clinical efficacy of PD-1 blockade in lung, kidney and bladder cancer patients was brought up, highlighting the role of *Akkermansia muciniphila* as the main player in the immunomodulatory effects of pembrolizumab or nivolumab (Routy et al. Science 2017 Nov2).

Most significant publications these last 10 years

- Liu P, Zhao L, Loos F, Iribarren K, Lachkar S, Zhou H, Gomes-da-Silva LC, Chen G, Bezu L, Boncompain G, Perez F, Zitvogel L, Kepp O, Kroemer G. Identification of pharmacological agents that induce HMGB1 release. ***Sci Rep.*** 2017 Nov 2;7(1):14915. doi: 10.1038/s41598-017-14848-1.

- Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelot N, Qu B, Ferrere G,Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V,Gonin P, Soria JC, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. ***Science.*** 2017 Nov 2. doi: 10.1126/science.aan3706.

- Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV,Prieto PA, Vicente D, Hoffman K, Wei SC, Cogdill AP, Zhao L, Hudgens CW,Hutchinson DS, Manzo T, Petaccia de Macedo M, Cotechini T, Kumar T, Chen WS,Reddy SM, Sloane RS, Galloway-Pena J, Jiang H, Chen PL, Shpall EJ, Rezvani K,Alousi AM, Chemaly RF, Shelburne S, Vence LM, Okhuysen PC, Jensen VB, Swennes AG, McAllister F, Sanchez EMR, Zhang Y, Le Chatelier E, Zitvogel L, Pons N,Austin-Breneman JL, Haydu LE, Burton EM, Gardner JM, Sirmans E, Hu J, Lazar AJ, Tsujikawa T, Diab A, Tawbi H, Glitza IC, Hwu WJ, Patel SP, Woodman SE, Amaria RN, Davies MA, Gershenwald JE, Hwu P, Lee JE, Zhang J, Coussens LM, Cooper ZA,Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff MT, Sharma P, Allison JP,Jenq RR, Wargo JA. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. ***Science.*** 2017 Nov 2. doi: 10.1126/science.aan4236.

- Bloy N, Garcia P, Laumont CM, Pitt JM, Sistigu A, Stoll G, Yamazaki T, Bonneil E, Buqué A, Humeau J, Drijfhout JW, Meurice G, Walter S,

Fritsche J, Weinschenk T, Rammensee HG, Melief C, Thibault P, Perreault C, Pol J, Zitvogel L, Senovilla L, Kroemer G. Immunogenic stress and death of cancer cells: Contribution of antigenicity vs adjuvanticity to immunosurveillance. **Immunol Rev.** 2017 Nov;280(1):165-174. doi: 10.1111/imr.12582.

- Jacquelot N, Roberti MP, Enot DP, Rusakiewicz S, Ternès N, Jegou S, Woods DM, Sodré AL, Hansen M, Meirow Y, Sade-Feldman M, Burra A, Kwek SS, Flament C, Messaoudene M, Duong CPM, Chen L, Kwon BS, Anderson AC, Kuchroo VK, Weide B, Aubin F, Borg C, Dalle S, Beatrix O, Ayyoub M, Balme B, Tomasic G, Di Giacomo AM, Maio M, Schadendorf D, Melero I, Dréno B, Khammari A, Dummer R, Levesque M, Koguchi Y, Fong L, Lotem M, Baniyash M, Schmidt H, Svane IM, Kroemer G, Marabelle A, Michiels S, Cavalcanti A, Smyth MJ, Weber JS, Eggermont AM, Zitvogel L. Predictors of responses to immune checkpoint blockade in advanced melanoma. **Nat Commun.** 2017 Sep 19;8(1):592.

- Gao Y, Souza-Fonseca-Guimaraes F, Bald T, Ng SS, Young A, Ngiow SF, Rautela J, Straube J, Waddell N, Blake SJ, Yan J, Bartholin L, Lee JS, Vivier E, Takeda K, Messaoudene M, Zitvogel L, Teng MWL, Belz GT, Engwerda CR, Huntington ND, Nakamura K, Hölzel M, Smyth MJ. Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells. **Nat Immunol.** 2017 Sep;18(9):1004-1015.

- Fridman WH, **Zitvogel L,** Sautès-Fridman C, Kroemer G. The immune contexture in cancer prognosis and treatment. **Nat Rev Clin Oncol**. 2017 Jul 25. Review.

- Zitvogel L, Pietrocola F, Kroemer G. Nutrition, inflammation and cancer. **Nat Immunol**. 2017 Jul 19;18(8):843-850. doi: 10.1038/ni.3754. Review. PubMed PMID: 28722707.

- Zitvogel L, Ayyoub M, Routy B, Kroemer G. Microbiome and Anticancer Immunosurveillance. **Cell.** 2016 Apr 7;165(2):276-87.

- Zitvogel L, Pitt JM, Daillère R, Smyth MJ, Kroemer G. Mouse models in oncoimmunology. **Nat Rev Cancer**. 2016 Dec;16(12):759-773.

- Zitvogel L, Daillère R, Roberti MP, Routy B, Kroemer G. Anticancer effects of the microbiome and its products. **Nat Rev Microbiol**. 2017 May 22. Review.

- Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. **Nat Rev Immunol**. 2017 Feb;17(2):97-111. Review.

- Daillère R, Vétizou M, Waldschmitt N, Yamazaki T, Isnard C, Poirier-Colame V, Duong CP, Flament C, Lepage P, Roberti MP, Routy B, Jacquelot N, Apetoh L, Becharef S, Rusakiewicz S, Langella P, Sokol H, Kroemer G, Enot D, Roux A, Eggermont A, Tartour E, Johannes L, Woerther PL, Chachaty E, Soria JC, Golden E, Formenti S, Plebanski M, Madondo M, Rosenstiel P, Raoult D, Cattoir V, Boneca IG, Chamaillard M, Zitvogel L. Enterococcus hirae and Barnesiella intestinihominis Facilitate Cyclophosphamide-Induced Therapeutic Immunomodulatory Effects. **Immunity.** 2016 Oct 18;45(4):931-943.

- 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, Becharef S, Formenti S, Golden E, Cording S, Eberl G, Schlitzer A, Ginhoux F, Mani S, Yamazaki T, Jacquelot 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.

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