CURRICULUM VITAE

NAME: Stefania Canè

DATE AND PLACE OF BIRTH: 25 March 1974, Castel San Pietro Terme, Bologna, Italy

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NATIONALITY: Italian

EDUCATION: 1995-2000: bachelor degree in Biology, University of Bologna, Italy
2000-2002: master degree in Immunology, University of Bologna, Italy
2002-2006: Specialization School in Biochemistry, University of Brescia, Italy
2006-2011: Ph.D. in Immunology and Microbiology, University of Arkansas for Medical Sciences, Little Rock, AR, USA,

CURRENT POSITION: from December 2017 to current, Research Assistant University of Verona, Italy

MEMBERSHIPS OF SCIENTIFIC SOCIETIES: Member of the Belgium Immunological Society (www.bims.be)

RESEARCH ACHIEVEMENTS

1. PUBLICATIONS:

1. Stefania **Canè**, Jacques Van Snick, Catherine Uyttenhove and Benoît J. Van den Eynde. Neutralization of TGFβ 1 but not TGFβ 3 increases survival in a mouse model of inducible melanoma by decreasing the epithelial-to-mesenchymal transition. Under revision in Cancer Research.
2. Stefania **Canè**, JingJing Zhu, Céline Powis de Tenbossche, Didier Colau, Nicolas van Baren, Anne-Marie Schmitt-Verhulst, Peter Liljeström, Catherine Uyttenhove and Benoit J. Van den Eynde. Resistance to cancer immunotherapy mediated by apoptosis of tumor-infiltrating lymphocytes. Nat Commun. 2017 Nov 10;8(1):1404. doi: 10.1038/s41467-017-00784-1
3. Hennequart M, Pilotte L, **Canè S**, Hoffmann D, Stroobant V, Plaen E, Van den Eynde B. Constitutive IDO1 Expression in Human Tumors Is Driven by Cyclooxygenase-2 and Mediates Intrinsic Immune Resistance. Cancer Immunol Res. 2017 Aug;5(8):695-709. doi: 10.1158/2326-6066.CIR-16-0400.
4. Arts N, **Cané S**, Hennequart M, Lamy J, Bommer G, Van den Eynde B, De Plaen E. microRNA-155, induced by interleukin-1β, represses the expression of microphthalmia-associated transcription factor (MITF-M) in melanoma cells. PLoS One. 2015 Apr 8;10(4):e0122517.doi:10.1371/journal.pone.0122517. eCollection 2015.
5. **Cane' S**, Ponnappan S, Ponnappan U. Altered regulation of CXCR4 expression during aging contributes to increased CXCL12-dependent chemotactic migration of CD4+ T cells. Aging Cell. 2012 Aug;11(4):651-8 doi: 10.1111/j.1474-9726.2012.00830.x. Epub 2012 Jun 4.
6. **Cane' S**, Ponnappan S, Ponnappan U. Impairment of Non-Muscle Myosin IIA in human CD4+ T cells contributes to functional deficits in the elderly. Cell Mol Immunol. 2011 Oct10. doi:10.1038/cmi.2011.41.
7. Rank RG, Bowlin AK, **Cané S**, Shou H, Liu Z, Nagarajan UM, Bavoil PM. Effect of Chlamydiaphage phiCPG1 on the course of conjunctival infection with "Chlamydia caviae" in guinea pigs. Infect Immun. 2009 Mar; 77(3):1216-21. Epub 2009 Jan 12.
8. Bellone S, Watts K, **Cane' S**, Palmieri M, Cannon MJ, Burnett A, Roman JJ, Pecorelli S, Santin AD. High serum levels of interleukin-6 in endometrial carcinoma are associated with uterine serous papillary histology, a highly aggressive and chemotherapy-resistant variant of endometrial cancer. Gynecol Oncol. 2005 Jul;98(1):92-8.
9. Santin AD, **Cané S**, Bellone S, Palmieri M, Siegel ER, Thomas M, Roman JJ, Burnett A, Cannon MJ, Pecorelli S. Treatment of chemotherapy-resistant human ovarian cancer xenografts in C.B-17/SCID mice by intraperitoneal administration of Clostridium perfringens enterotoxin. Cancer Res. 2005 May 15;65(10):4334-42.
10. Santin AD, Diamandis EP, Bellone S, Soosaipillai A, **Canè S**, Palmieri M, Burnett A, Roman JJ, Pecorelli S. Human kallikrein 6: a new potential serum biomarker for uterine serous papillary cancer.

Clin Cancer Res. 2005 May 1;11(9):3320-5.
11. Santin AD, Zhan F, **Cane' S**, Bellone S, Palmieri M, Thomas M, Burnett A, Roman JJ, Cannon MJ, Shaughnessy J Jr, Pecorelli S. Gene expression fingerprint of uterine serous papillary carcinoma: identification of novel molecular markers for uterine serous cancer diagnosis and therapy. Br J Cancer. 2005 Apr 25;92(8):1561-73.
12. Santin AD, Zhan F, Bignotti E, Siegel ER, **Cané S**, Bellone S, Palmieri M, Anfossi S, Thomas M, Burnett A, Kay HH, Roman JJ, O'Brien TJ, Tian E, Cannon MJ, Shaughnessy J Jr, Pecorelli S. Gene expression profiles of primary HPV16- and HPV18-infected early stage cervical cancers and normal cervical epithelium: identification of novel candidate molecular markers for cervical cancer diagnosis and therapy. Virology. 2005 Jan 20;331(2):269-91.
13. Santin AD, Zhan F, Bellone S, Palmieri M, **Cane' S**, Bignotti E, Anfossi S, Gokden M, Dunn D, Roman JJ, O'Brien TJ, Tian E, Cannon MJ, Shaughnessy J Jr, Pecorelli S. Gene expression profiles in primary ovarian serous papillary tumors and normal ovarian epithelium: identification of candidate molecular markers for ovarian cancer diagnosis and therapy. Int J Cancer. 2004 Oct 20;112(1):14-25.
14. Santin AD, **Cane' S**, Bellone S, Bignotti E, Palmieri M, De Las Casas LE, Roman JJ, Anfossi S, O'Brien T, Pecorelli S. The serine protease stratum corneum chymotryptic enzyme (kallikrein 7) is highly overexpressed in squamous cervical cancer cells. Gynecol Oncol. 2004 Aug; 94(2):283-8.
15. Santin AD, Zhan F, Bellone S, Palmieri M, **Cane' S**, Gokden M, Roman JJ, O'Brien TJ, Tian E, Cannon MJ, Shaughnessy J Jr, Pecorelli S.Discrimination between uterine serous papillary carcinomas and ovarian serous papillary tumours by gene expression profiling. Br J Cancer. 2004 May 4;90(9):1814-24.
16. Santin AD, Bellone S, Palmieri M, Bossini B, **Cane' S**, Bignotti E, Roman JJ, Cannon MJ, Pecorelli S. Restoration of tumor specific human leukocyte antigens class I-restricted cytotoxicity by dendritic cell stimulation of tumor infiltrating lymphocytes in patients with advanced ovarian cancer. Int J Gynecol Cancer. 2004 Jan-Feb;14(1):64-75.
17. **Cane' S**, Bignotti E, Bellone S, Palmieri M, De las Casas L, Roman JJ, Pecorelli S, Cannon MJ, O'brien T, Santin AD. The novel serine protease tumor-associated differentially expressed gene-14 (KLK8/Neuropsin/Ovasin) is highly overexpressed in cervical cancer. Am J Obstet Gynecol. 2004 Jan;190(1):60-6.
18. Santin AD, **Cane' S**, Bellone S, Bignotti E, Palmieri M, De Las Casas LE, Anfossi S, Roman JJ, O'Brien T, Pecorelli S. The novel serine protease tumor-associated differentially expressed gene-15 (matriptase/MT-SP1) is highly overexpressed in cervical carcinoma. Cancer. 2003 Nov 1;98(9):1898-904.
19. Kass R, Bellone S, Palmieri M, **Cane' S**, Bignotti E, Henry-Tillman R, Hutchins L, CannonMJ, Klimberg S, Santin AD. Restoration of tumor-specific HLA class I restricted cytotoxicity in tumor infiltrating lymphocytes of advanced breast cancer patients by in vitro stimulation with tumor antigen pulsed autologous dendritic cells. Breast Cancer Res Treat. 2003 Aug;80(3):275-85.
20. Kass R, Agha J, Bellone S, Palmieri M, **Cane' S**, Bignotti E, Henry-Tillman R, Hutchins L, Cannon MJ, Klimberg S, Santin AD. In vitro induction of tumor-specific HLA class I restricted CD8+ cytotoxic T lymphocytes from patients with locally advanced breast cancer by tumor antigen-pulsed autologous dendritic cells. J Surg Res. 2003 Jun15;112(2):189-97.
21. Santin AD, Bellone S, Palmieri M, Bossini B, Roman JJ, Cannon MJ, Bignotti E, **Cane' S**, Pecorelli S. Induction of tumor-specific cytotoxicity in tumor infiltrating lymphocytes by HPV16 and HPV18 E7-pulsed autologous dendritic cells in patients with cancer of the uterine cervix. Gynecol Oncol. 2003 May;89(2):271-80.
22. Honorati MC, Meliconi R, Pulsatelli L, **Cane' S**, Frizziero L, Facchini A. High in vivo expression of interleukin-17 receptor in synovial endothelial cells and chondrocytes from arthritis patients. Rheumatology (Oxford). 2001 May;40(5):522-7.

2. GRANTED PATENT: mouse anti-human TGFβ1 13A1 2A6 monoclonal antibody and mouse anti-human TGFβ3 1901/16 monoclonal antibody. Patent applications submitted by Prof. Jacques Van Snick and Benoit Van den Eynde, Ludwig Institute for Cancer Research, Brussels, Belgium.

3. INVITED PRESENTATIONS:
1. Stefania Cane', Jacques Van Snick, Catherine Uyttenhove, Benoît Van den Eynde. "Neutralization of TGFß1 but not TGFβ3 decreases the amount and inhibitory function of CD11+ Gr-1+Ly6C+ cells in a mouse model of inducible melanoma". Séminaire des chercheurs Télévie 2015, Université de Liège. Oral and

poster presentation. December 2015
2. Stefania Cane', Jacques Van Snick, Catherine Uyttenhove, Benoît Van den Eynde. "Neutralization of TGFß1 but not TGFβ3 increases survival in a mouse model of inducible melanoma by decreasing the epithelial-mesenchymal transition". TGFβ International meeting Leiden 8-10 May 2014. Oral and poster presentation.
3. Stefania Cane', Jacques Van Snick, Catherine Uyttenhove, Benoît Van den Eynde. "Neutralization of TGFß1 but not TGFβ3 increases survival in a mouse model of inducible melanoma by decreasing the epithelial-mesenchymal transition". Séminaire des chercheurs Télévie 2014, Université Catholique de Louvain, Bruxelles. Oral and poster presentation.
4. Stefania Cane', Céline Powis de Tenbossche, Jacques Van Snick, Catherine Uyttenhove, Benoît Van den Eynde. "Neutralization of TGFß1 increases survival in a mouse model of inducible melanoma by decreasing the epithelial-mesenchymal transition". Séminaire des chercheurs Télévie 2013, Université Catholique de Louvain, Bruxelles. Poster presentation
5. Cane' S, Ponnappan S, Sullivan D. H, Ponnappan U. "Age-associated changes in nonmuscle myosin IIA and CXCR4 regulate increased migration induced by SDF-1α in CD4+ T lymphocytes from elderly human donors." American Association of Immunologists meeting. 2011, San Francisco, CA, USA. Oral and poster presentation
6. Graham J, Ponnappan S, Cane' S, Palmieri M, Ponnappan U. "Regulation of P62/Sequestosome 1 during oxidative stress, proteasomal inhibition and aging". INBRE, 2010, Fayetville, AR, USA. Poster presentation
7. Cane' S, Das R, Ponnappan S, Ponnappan U. "Contribution of Hsp90 to the proteasomal dysfunction accompanying immune senescence." American Association of Immunologists meeting, 2009, Seattle, WA, USA. Poster presentation
8. Cane' S, Crew D. "Sequence and genomic organization of pULBP1, a porcine gene encoding a major ligand for the human NK cell activating receptor NKG2D." Joint Conference of CTS, IPITA and IXA of The Transplantation Society, 2007, Minneapolis, MN, USA. Poster presentation
9. Santin AD, Cane' S, Bellone S, Palmieri M, Siegel ER, Thomas M, Roman JJ, Burnett A, Cannon MJ, Pecorelli S., "Treatment of chemotherapy-resistant human ovarian cancer xenografts in B.B 17/SCID mice by intraperitoneal administration of clostridium perfringens enterotoxin (CPE)". Society of Gynecology Oncologist (SGO), 2005, Miami Beach, FL, USA. Poster presentation
10. Santin AD, Bellone S, Palmieri M, Cane' S, Roman JJ, Cannon MJ, Pecorelli S. "HPV16/18 E&-pulsed dendritic cell vaccination in patients with recurrent cervical cancer refractory to standard salvage therapy". International Gynecological Cancer Society Conference, 2004, Edinburgh, Scotland. Poster presentation
11. Santin AD, Zhan F, Bellone S, Palmieri M, Cane' S, Godken M, Roman JJ, O'Brien T, Tian E, Cannon MJ, Shaughnessy J, Pecorelli S. "Discrimination between uterine serous papillary carcinomas and ovarian serous papillary tumors by gene expression profiling". American Association for Cancer Research, 2004, Orlando, FL, USA. Poster presentation

4. PRIZES AND AWARDS:
1. Stefania Cane', Jacques Van Snick, Catherine Uyttenhove, Benoît Van den Eynde. "Neutralization of TGFß1 but not TGFβ3 decreases the amount and inhibitory function of CD11+ Gr-1+Ly6C+ cells in a mouse model of inducible melanoma". Séminaire des chercheurs Télévie 2015, Université de Liège. Oral and poster presentation. December 2015. Best Poster.
2. Stefania Cane', Jacques Van Snick, Catherine Uyttenhove, Benoît Van den Eynde. "Neutralization of TGFß1 but not TGFβ3 increases survival in a mouse model of inducible melanoma by decreasing the epithelial-mesenchymal transition". Séminaire des chercheurs Télévie 2014, Université Catholique de Louvain, Bruxelles. Oral and poster presentation. Best oral presentation.

5. FUNDING:
Pre-doctoral fellowship UAMS-NIH, USA, 2006-2011
De Duve Postdoctoral Fellowship, UCL, Brussels, Belgium, 2012
FNRS-Télévie postdoctoral fellowship, Belgium, 2013 to 2016

6. SUPERVISING AND MENTORING ACTIVITIES:

During my post-doctoral fellowship at the Ludwig Cancer Research Institute, UCL, Brussels, Belgium I mentored and trained 3 Ph.D. students. I both supervised them in designing and executing experiments and in preparing the Ph.D. dissertation.

7. NARRATIVE RESUME:

Stefania Canè is a research assistant in Prof. Bronte's laboratories at the University of Verona, Italy. In Prof. Bronte's team she investigates how to switch off immunosuppressive PMN-MDSC by targeting ARG1 in a humanized mouse model of cancer breast and pancreatic cancer. Her research interest has been in immunology, particularly cancer immunotherapy. Since her master degree, she has been spending her career on learning and understanding how to boost the immune system, both in the contest of cancer and aging. She had a coherent professional career and aims at continuing her research in the field of immunology, by further understanding the mechanisms regulating tumor-associated immunosuppression. During her postdoctoral fellowship in the laboratories of Prof. Benoît Van den Eynde, she dealt with restoring an anti-tumor CD8+ T response by targeting immunosuppressive molecules like TGFβ, IDO/TDO expressed by myeloid-derived suppressor cells (MDSC), in a mouse model of inducible melanoma.

8. POSITIONS AND HONORS

2001-2007 Fellow, UAMS, Little Rock, AR, USA.
2007-2011 Ph.D. student UAMS, Department Immunology/Microbiology, Little Rock, AR, USA.
2012-November 2016 Postdoctoral fellow, Ludwig Cancer Research Institute, Brussels, Belgium.
2016 December to December 2017 Postdoctoral fellow, University of Verona, Italy.
December 2017 to current research assistant, University of Verona, Italy

9. CONTRIBUTIONS TO SCIENCE

From 2001 to 2006, she worked as Research Fellow in the laboratory of tumor immunotherapy, under the supervision of Dr. Alessandro Santin and Prof. Roger Rank, division of Obstetrics and Gynecology Oncology and Immunology/Microbiology, University of Arkansas for Medical Sciences, USA. She evaluated the gene expression differences between different type of ovarian cancers, employing microarrays analysis, and she mastered the production of recombinant *Clostridium Perfringens* Enterotoxin A for the treatment of ovarian cancer patients. She also played a role in the evaluation of the eligibility of cervical cancer patients to approved FDA vaccine trial, by analyzing the HPV16 and/or HPV18 positivity of paraffin embedded as well as primary tissue culture of cervical tumor samples by PCR. This vaccine, based on patient derived (i.e., autologous) dendritic cells loaded *in vitro* with HPV16/18 E6/7 proteins is showing great promise for the treatment of cervical cancer patients refractory to standard treatment modalities. For this project, she mastered her ability to isolate, differentiate and pulse DCs *in vitro,* as well as how to isolate human CD3+ T cells, to perform several immunological assays such as CFSE assay, Elispot, cytotoxicity assay, flow cytometry analysis, T cell activation and conjugation, recombinant protein expression and purification. The results of this research was used to prepare Specialization thesis manuscript in Biochemistry.

From August 2006 to August 2011, she worked to achieve the Ph.D. degree in the laboratory of Dr. Usha Ponnappan, Department of Microbiology/Immunology, University of Arkansas for Medical Sciences, USA. The major focus of her project was directed to understand the regulatory role of a chaperone protein, heat shock protein 90 (Hsp90), during immune senescence in primary human CD4+ T cells. Aging is characterized by irreversible and stochastic accumulation of damaged and aberrant proteins that impact most physiological functions. Accumulating evidence suggests that longevity is closely tied to the ability of the organism to effectively overcome stress. To deal with stress, organisms have evolved specific mechanisms, including the heat shock stress response, unfolded protein response and the ubiquitin proteasome system, all of which ensure the maintenance of protein homeostasis. In the heat shock response system, Hsp90 plays a key role as a chaperone in protecting the folding of newly synthesized proteins, while directing the damaged ones to degradation. Dr. Canè demonstrated that aging affects Hsp90 function by

altering the landscape of co-chaperone and client protein interactome, through specific posttranslational modifications. These results demonstrated that age-associated alterations in Hsp90-client protein interactions directly contribute to the altered kinetics of ligand-induced TCR internalization, intracellular Ca2+ flux and F-actin polymerization, influencing T cell functional responses. Surprisingly, despite defects in the interaction and function of Hsp90 and non-muscle myosin IIA, increased migration towards SDF-1α was observed in T cells from the elderly. The increased chemotactic migratory index in T cells correlates with increased surface expression of CXCR4, attributable to altered ubiquitination dynamics. Thus, age-associated alterations in the regulation of Hsp90 contribute to immune senescence, directly through its regulation of signaling networks within T lymphocytes and indirectly, through its impact on folding and release of client proteins. Therefore, manipulation of Hsp90 may serve as a potential target to ameliorate immune dysfunctions accompanying aging.

From December 2011 to October 2016, she was a postdoctoral fellow in the laboratory of Prof. Van den Eynde at the Ludwig Cancer Research Institute in Brussels, Belgium. Her major project was directed to dissect mechanisms of immunosuppression occurring in mouse and human melanomas. Particularly, we investigated the role of different TGFβ isoforms to initiate and sustain tumor growth and spreading by directly regulating tumor-associated EMT and recruitment of MDSC with suppressive phenotype at the tumor site. We found that, in mice, TGFβ1 but not TGFβ3 was mainly involved in mastering the immunosuppressive tumor microenvironment and blockade of TGFβ1, with newly generated mouse monoclonal neutralizing antibody, partially restored the antitumor specific CD8+ T cell response obtained by ACT. We also found that a combinatorial therapy with anti-TGFβ1 and check point blockade inhibitors, like anti-CTLA4 and anti-PD1, leads to a significant increase in the survival of mice carrying and inducible melanoma (Tirp mice) and receiving a prophylactic anti-tumor vaccine.

Dr. Canè work was also directed to dissect the molecular mechanisms regulating the expression/induction of IDO and TDO in several human cancer cell lines and tissues, and to test/validate in NSG mice the efficacy of therapies, combining new generation IDO/TDO inhibitors and ACT. The results of these researches are currently in preparation for manuscripts.

Stefania Canè is author of 21 articles published in peer-reviewed journals. Her H-index is 14 with an amount of 867 citations, considering 20 cited documents by Scopus database. She is a member of the Belgium Immunological Society (www.bims.be)