

BIOGRAPHICAL SKETCH

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NAME: Tommasi, Stella

eRA COMMONS USER NAME (credential, e.g., agency login): stommasi

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Bari, Bari, Italy	Sc.D.	02/1987	Biological Sciences
University of Bari, Bari, Italy	Diploma	05/1989	Genetics
MIUR-University of Bari, Italy	Ph.D.	02/1993	Molecular Biology
City of Hope, CA, USA	Post-doc	03/1999	Cancer Biology

A. Personal Statement

The studies proposed in this grant application will investigate, for the first time, the mechanistic involvement of secondhand smoke (SHS) in the genesis and progression of non-alcoholic fatty liver disease (NAFLD), one of the most prevalent forms of chronic liver disorders, worldwide. Throughout my career, I have acquired a broad knowledge in the field of cancer genetics and epigenetics, an interest that dates back to my graduate and postgraduate research at the Genetics Institute, University of Bari, Italy, and at the Biology Department, Beckman Research Institute of the City of Hope, California. While studying the molecular basis of X-chromosome inactivation, I have analyzed the CpG methylation pattern at promoters of X-linked genes using state-of-the-art genomic sequencing techniques. In subsequent years, I have expanded my research in the areas of DNA damage and repair, cell cycle regulation, and chemical & physical carcinogenesis, as well as genomics and epigenomics. Apart from being a skilled molecular biologist, I am also an expert in mouse biology and pathobiology, with a well-established record in the generation/treatment of transgenic mice modeling after smoking-associated human cancer. Of relevance to this proposal, I have acquired extensive knowledge on the analysis of microarray and next-generation sequencing (NGS) data and functional interpretation of the results. Over the years, I have successfully constructed and analyzed the genome-wide profile of methylated CpG islands (MIRA-chip) and histone modifications (ChIP-chip) in relation to gene expression in a variety of human/rodent cell types and tumor specimens. These include human breast and lung cancer, melanoma, as well as immortalized cell lines and mice/cells treated *in vivo/in vitro* with various carcinogens, including secondhand smoke. These studies have all resulted in high quality publications in top scientific journals. Using state-of-the-art NGS techniques and Partek Flow pipeline, my laboratory is currently investigating the epigenetic changes, namely hydroxymethylation and histone modifications, induced by SHS in a mouse model of human cancer (TRDRP26IP-0051). We are also investigating whether *in vivo* exposure of mice to electronic cigarette vapor can cause DNA damage, gene mutation, and/or aberrant DNA methylation (TRDRP25IP-0001). I have all the credentials, expertise and resources needed to direct this project, and lead a research team that is uniquely qualified to undertake this work, and has all the skills, tools, and technologies (all being routinely used by us) to carry out this project, and the experience to deal with any unforeseen challenges, should they arise.

B. Positions and Honors

Positions and Employment

1989-1992	Visiting Scientist, Department of Biology, Beckman Research Institute of the City of Hope, Duarte, CA, USA
1992-1993	Research Fellow, Genetics Institute, University of Bari, Italy
1993-1999	Research Fellow, Department of Biology, Beckman Research Institute of the City of Hope, Duarte, CA, USA
1999-2001	Senior Research Fellow, Department of Biology, Beckman Research Institute of the City of Hope, Duarte, CA, USA
2001-2007	Assistant Research Professor, Department of Biology, Beckman Research Institute of the City of Hope, Duarte, CA.
2007-2013	Associate Research Professor, Department of Cancer Biology, Beckman Research Institute of the City of Hope, Duarte, CA
2013-2014	Research Scientist, Department of Preventive Medicine, University of Southern California, USC/Norris Comprehensive Cancer Center, Los Angeles, CA
2014-present	Assistant Professor, Department of Preventive Medicine, University of Southern California, USC/Norris Comprehensive Cancer Center, Los Angeles, CA

Patents

2013	Rossi J.J., Castanotto D., Pfeifer G., Tommasi S. , Morris K.V., Kim D.H. "Double stranded nucleic acid targeting low copy promoter-specific RNA". US Patent 8,513,401, filed May 3, 2010, and issued August 20, 2013.
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Training

2003	<i>FloCyte DNA Flow Cytometry</i> Course, City of Hope, Duarte, CA
2006	" <i>Analyzing Microarray Data Using Gene Ontology and Pathway Analysis Tools</i> " workshop, Department of Biomedical Informatics, City of Hope, Duarte, CA
2007	Partek Microarray Workshop " <i>Statistical analysis and visualization tools for microarray data analysis using Genomic Suite software</i> ", Partek Inc., Duarte, CA
2009	Partek Microarray Workshop " <i>Integration of Gene Expression and Copy Number Data in Partek GS & Integration of Solexa ChIP-Seq and Microarray ChIP-Chip Data in Partek GS</i> ", Partek Inc., Duarte, CA
2009	<i>Pathobiology of the Mouse</i> (Tier 1A, 3.0 Academic Units, A+), UC Davis Extension, University of California, Davis, CA
2010	<i>Pathobiology of the Mouse</i> (Tier 1B, 3.0 Academic Units, A), UC Davis Extension, University of California, Davis, CA
2011	Partek Microarray Workshop " <i>Microarray data analysis with Partek® Genomic Suite™</i> ", Partek Inc., Duarte, CA
2013	Partek on-site training, " <i>Microarray data analysis with Partek Genomic Suite & RNA-seq data analysis with Partek Flow</i> ", HSC, USC (Nov. 5-6)
2014	Partek webinar, " <i>Learn how to analyze RNA-seq data the fast and easy way</i> ", Partek Inc. (Oct. 2)
2015	Partek on-site training, " <i>RNA-seq and DNA-seq Data Analysis with Partek Flow; Data visualization and Microarray Data Analysis with Partek Genomics Suite™</i> ", Partek Inc., HSC, USC (Nov. 4-5)
2017	Qiagen webinar, " <i>Formatting and Uploading your RNA-seq data into IPA - Part 2</i> ", Qiagen Genomics (May 10)
2017	IPA on-site training, " <i>Ingenuity Pathway Analysis (IPA): Maximizing the Biological Interpretation of Gene, Transcript & Protein Expression Data with IPA</i> ", Qiagen Advanced Genomics, HSC, USC (Oct. 26)
2017	IVA on-site training, " <i>Finding Causal Variants using Ingenuity Variant Analysis (IVA)</i> ", Qiagen Advanced Genomics, HSC, USC (Oct. 26)
2017	Partek on-site workshop, " <i>Omics Data Analysis using Partek Software: Overview of Partek Flow and Partek Genomics Suite</i> ", Partek Inc., HSC, USC (Nov. 8-9)
2018	NML Workshop #1: " <i>R for Bioinformatics</i> ", HSC, USC (April 3)
2018	NML Workshop #2: " <i>R for Bioinformatics</i> ", HSC, USC (April 10)

Other Experience and Professional Memberships

1988-1989	Instructor, Istituto Professionale "Fabio Besta", Treviso, Italy
2001-2012	Instructor, Irell & Manella Graduate School of Biological Sciences, City of Hope, Duarte, CA
Spring 2015	Instructor, University of Southern California, Los Angeles, CA
Fall 2015	Instructor, University of Southern California, Los Angeles, CA
1990-present	Ordine Nazionale dei Biologi (National Board of Biologists, Italy), ONB member# 033388
2018-	The Epigenetics Society

Honors

1988	IBM Fellowship, Italy
1988	Passed the State Board Exam, Italy
1989	National Fellowship Award, Ministry of University and Research (MIUR), Italy
1992	R.A.I.S.A. (Advanced Research for the Innovation of the Agricultural System) Fellowship Award, National Research Council (C.N.R.), Italy
2014	National Academic Qualification as a Full Professor in Applied Biology (Abilitazione Scientifica Nazionale, Biologia Applicata, Prima Fascia), Italy

C. Contribution to Science

I am an expert in cancer biology and bioinformatics, with specialization in processing, analysis, and interpretation of high-dimensional genomic, epigenomic, and transcriptomic data. I actively investigate the underlying mechanisms of carcinogenesis with a special emphasis on genetic and epigenetic determinants. Using a broad range of analysis and visualization tools, including Partek Flow, Partek Genomic Suite, BIOBASE, and Ingenuity Pathway Analysis, I have integrated high-throughput data from genetics, epigenetics, and transcriptomics studies to elucidate the molecular mechanisms of chemical carcinogenesis (Tommasi et al., *Carcinogenesis* 2014; Tommasi et al., *Int. J. Cancer* 2015) and cellular senescence and immortalization (Tommasi et al., *Nucleic Acids Res.* 2013). My work on sunlight mutagenesis showed that ultraviolet (UV) -induced pyrimidine dimers, formed at promoter regions, can significantly alter transcription factor binding and therefore gene transcription. This was the first study demonstrating that UV damage, besides being mutagenic, exerts its biological effects by perturbing gene expression (Tommasi et al. *Biochemistry* 1996). In another landmark study, I was able to show that 5-methylcytosine increases the sensitivity to hot spots for damage in the *TP53* gene; this was an early demonstration of the interplay of genetics and epigenetics in human carcinogenesis (Tommasi et al., *Cancer Res.* 1997). I was the first investigator to generate single and double knockout mice for *Rassf1a* (*Rassf1a*^{-/-} and *Rassf1a*^{-/-} *p53*^{-/-} KO mice). These mouse models were instrumental in understanding the role of *Rassf1a* as a tumor suppressor gene and guardian of mitosis (Tommasi et al., *Cancer Res.* 2005; Tommasi et al., *Oncogene* 2011). My studies on epigenetic inactivation of the *RASSF1A* tumor suppressor gene, a major component of the Hippo pathway, in cutaneous malignant melanoma and lung cancer are among the first investigations of the role of epigenetics in human carcinogenesis. My work on reversing gene silencing by demethylating agents (5-AzaCdR) was one of the first applications of epigenetic therapy in human melanoma (Spugnardi, Tommasi et al., *Cancer Res.* 2003). Throughout the years, I have also contributed to the development of cutting-edge methodologies for detecting mutations (Tommasi et al., *Nucleic Acids Res.* 2012) and aberrant DNA methylation (Tommasi et al., *Methods in Mol. Biology* 2018). I am also one of the inventors for a short-hairpin RNA approach to target CpG methylation (Castanotto et al., *Mol. Ther.* 2005) (US Patent #8,513,401). Below is a list of peer reviewed publications (in chronological order) that best represent five areas of my research accomplishments:

(I) Tobacco carcinogenesis

1. **Tommasi, S.**, Kim, S.I., Zhong, X., Wu, X., Pfeifer, G.P., and Besaratinia, A. (2010) Investigating the epigenetic effects of a prototype smoke-derived carcinogen in human cells. *PLoS One* 5(5): e10594. PMID: 20485678
2. **Tommasi, S.**, Zheng, A., Yoon, J.I., Li, A.X., Wu, X., and Besaratinia, A. (2012) Whole DNA methylome profiling in mice exposed to secondhand smoke. *Epigenetics* 7(11):1302-14. PMID:23051858
3. Besaratinia, A., and **Tommasi, S.** (2013) Genotoxicity of tobacco smoke-derived aromatic amines and bladder cancer: current state of knowledge and future research directions. *FASEB J*, **27**, 2090-100. PMID: 23449930

4. Besaratinia, A., and **Tommasi, S.** (2014) Electronic cigarettes: The road ahead. *Prev Med*, 66: 65-7. PMID: 24952095
5. Besaratinia, A., and **Tommasi, S.** (2017) An opportune and unique research to evaluate the public health impact of electronic cigarettes. *Cancer Causes Control*, **28**,1167-1171. PMID: 28861656
6. **Tommasi, S.**, Bates, S.E., Behar, R.Z., Talbot, P., and Besaratinia, A. (2017) Limited mutagenicity of electronic cigarettes in mouse or human cells *in vitro*. *Lung Cancer*, 112: 41-46. PMID: 29191599

(II) High-dimensional data analysis

7. **Tommasi, S.**, Karm, D.L., Wu, X., Yen, Y., Pfeifer, G.P. (2009) Methylation of homeobox genes is a frequent and early epigenetic event in breast cancer. *Breast Cancer Res.* 11(1): R14. PMID:19250546
8. **Tommasi, S.**, Zheng, A., Weninger, A., Bates, S.E., Li, X.A., Wu, X., Hollstein, M., and Besaratinia, A. (2013) Mammalian cells acquire epigenetic hallmarks of human cancer during immortalization. *Nucleic Acids Res.* 41(1): 182-195. PMID: 23143272
9. **Tommasi, S.**, Zheng, A., Yoon, J.I., and Besaratinia, A. (2014) Epigenetic targeting of the Nanog pathway and signaling networks during chemical carcinogenesis. *Carcinogenesis* 35(8): 1726-1736. PMID: 24480805
10. **Tommasi, S.**, Zheng, A., and Besaratinia, A. (2015) Exposure of mice to secondhand smoke elicits both transient and long-lasting transcriptional changes in cancer-related functional networks. *Int J Cancer* 136 (10): 2253-2263. PMID: 25346222

(III) Other relevant epigenetic studies

11. **Tommasi, S.**, Denissenko, M.F., and Pfeifer, G.P. (1997) Sunlight induces pyrimidine dimers preferentially at 5-methylcytosine bases, *Cancer Res.* 57: 4727-4730. PMID: 9354431
12. Spugnardi, M.,* **Tommasi, S.**,* Dammann, R., Pfeifer, G.P., and Hoon, D.S. (2003) Epigenetic inactivation of RAS association domain family protein 1 (RASSF1A) in malignant cutaneous melanoma, *Cancer Res.* 63: 1639-43. PMID: 12670917. * Equal authorship.
13. **Tommasi, S.**, Zheng, A., and Besaratinia, A. (2015) Expression of epigenetic modifiers is not significantly altered by exposure to secondhand smoke. *Lung Cancer*, 2015 Oct 27. pii: S0169-5002(15)30092-1. PMID: 26525280

(IV) Hippo pathway studies

14. **Tommasi, S.**, Dammann, R., Jin, S-G., Zhang, X.F., Avruch, J., and Pfeifer, G.P. (2002) *RASSF3* and *NORE1*: identification and cloning of two human homologues of the putative tumor suppressor gene *RASSF1*. *Oncogene* 21(17): 2713-20. PMID: 11965544
15. **Tommasi, S.**, Dammann, R., Zhang, Z., Wang, Y., Liu, L., Tsark, W.M., Wilczynski, S.P., Li, J., You, M., and Pfeifer, G.P. (2005) Tumor susceptibility of *Rassf1a* knockout mice *Cancer Res.* 65(1): 92-8. PMID: 15665283 ‡ Featured on front page of Cancer Research
16. Pfeifer, G.P., Dammann, R., and **Tommasi, S.** (2010) *RASSF* proteins *Curr. Biology* 20(8): R344-5. PMID: 21749948
17. **Tommasi, S.**, Besaratinia, A., Wilczynski, S.P., and Pfeifer, G.P. (2011) Loss of *Rassf1a* enhances p53mediated tumor predisposition and accelerates progression to aneuploidy. *Oncogene* 30(6):690-700. PMID: 20890300

(V) Method development

18. Castanotto, D*, **Tommasi, S***, Li, M., Li, H., Yanow, S., Pfeifer, G.P., and Rossi, J.J. (2005) Short hairpin RNA-directed cytosine (CpG) methylation of the *RASSF1A* gene promoter in HeLa cells *Mol. Ther.* 12(1): 179-83. PMID: 15963934. * Equal authorship
19. Besaratinia, A., Li, H., Yoon, J.I., Zheng, A., Gao, H., and **Tommasi, S.** (2012) A high-throughput nextgeneration sequencing-based method for detecting the mutational fingerprint of carcinogens. *Nucleic Acids Res.* 40(15) e116. PMID: 22735701
20. **Tommasi S.**, and Besaratinia A. (2018) A Versatile Assay for Detection of Aberrant DNA Methylation in Bladder Cancer. *Methods Mol Biol.* 1655: 29-41. PMID: 28889375

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/pubmed/?term=Tommasi+S>

D. Research Support

Ongoing Research Support

TRDRP – 25IP-0001 (PI: Tommasi) 07/01/2016 – 06/30/2019 (no-cost extension)
University of California Tobacco Related Disease Research Program (TRDRP)
Investigating the carcinogenicity of e-cig
The major goal of this project is to determine whether sub-chronic exposure of mice to electronic cigarettes (ecig) aerosol can result in carcinogenic effects.
Role: Principal Investigator (PI)
Total direct costs: \$ 240,000

TRDRP – 26IP-0051 (PI: Tommasi) 08/01/2017 – 07/30/2019
University of California Tobacco Related Disease Research Program (TRDRP)
Does secondhand smoke induce epigenetic changes?
The major goal of this project is to determine whether secondhand smoke can induce changes in the epigenome *in vivo*.
Role: Principal Investigator (PI)
Total direct costs: \$ 240,000

1R01DE026043-01 (PI: Besaratinia) 03/03/2016 – 28/02/2022
National Institutes of Health (NIH)
Genetic epigenetic and transcriptomic effects of e-cig on oral epithelium
The major goal of this project is to determine whether chronic use of electronic cigarettes (e-cig) in adults can lead to oral cancer.
Role: Co-Investigator (Co-I)
Total direct costs: \$ 1,000,000

Pending

1R01CA239096-01 (PI: Besaratinia) 04/01/2019 - 03/31/2024 (*pending review*)
National Institutes of Health (NIH)
National Cancer Institute (NCI), National Institute on Drug Abuse (NIDA), National Institute of Dental & Craniofacial Research (NIDCR)
Epigenetic biomarkers for assessing cancer risk in electronic cigarette users and cigarette smokers
The major goal of this randomized control trial is to compare the health risks or benefits of e-cig use and cigarette smoking using epigenetic biomarkers.
Role: Co-Investigator (Co-I)
Total Direct Costs: \$2,489,562

TRDRP –29IP-0519 (PI: Tommasi) 04/01/2019 – 03/31/2021 (*pending review*)
University of California Tobacco Related Disease Research Program (TRDRP)
The harmful effects of secondhand smoke on hepatic lipid metabolism
The major goal of this project is to investigate the mechanistic involvement of secondhand smoke (SHS) in chronic liver disease.
Role: Principal Investigator (PI)
Total Direct Costs: \$ 400,000

TRDRP-29IR- (PI: Besaratinia) 07/01/2019 –06/31/2022 (*pending review*)
University of California Tobacco Related Disease Research Program (TRDRP)
The use of epigenetic biomarkers for assessing cancer risk in electronic cigarette users
The major goal of this project is to determine the magnitude of cancer risk associated with e-cig use relative to smoking tobacco cigarettes.
Role: Co-Investigator (Co-I)
Total Direct Costs: \$750,000