

**VINCENZO COSTANZO, MD-Phd****BIOGRAPHICAL SKETCH**

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| NAME<br>Vincenzo Costanzo                                                                                            |                                                                                                                             | ADDRESS                                                                                                |                                                                      |
| CONTACT DETAILS<br>Tel.: +3902574303875                                                                              |                                                                                                                             | IFOM ETS, the AIRC Institute of Molecular Oncology<br>Foundation Via Adamello 16 20139 - Milan - ITALY |                                                                      |
| EDUCATION/TRAINING                                                                                                   |                                                                                                                             |                                                                                                        |                                                                      |
| INSTITUTION AND LOCATION                                                                                             | DEGREE                                                                                                                      |                                                                                                        | FIELD OF STUDY                                                       |
| University of Naples Federico II, Naples - Italy                                                                     | Undergraduate training                                                                                                      |                                                                                                        | Molecular and Cellular biology; Biochemistry                         |
| University of Naples Federico II, Naples - Italy                                                                     | Clinical Rotations                                                                                                          |                                                                                                        | Internal Medicine, Oncology, Endocrinology, Gynecology and Pathology |
| University of Naples Federico II, Naples – Italy                                                                     | Medical Doctor degree (MD) – Final mark: 110/110<br><i>Magna Cum Laude with special dean mention and thesis publication</i> |                                                                                                        | Medicine and Surgery                                                 |
| University of Naples Federico II, Naples – Italy                                                                     | Italian Board certification for medical practitioner. Final mark: 100/100                                                   |                                                                                                        | Medicine and Surgery                                                 |
| University of Naples Federico II, Naples – Italy<br>Joint with Columbia University, Dep. Of Genetics and Development | PhD                                                                                                                         |                                                                                                        | Cellular and Molecular Biology and Pathology                         |

**A. Personal Statement**

I am full professor in General Pathology at University of Milan and Senior investigator in DNA metabolism at IFOM where I lead a group of 15 scientists, including postdocs, PhD students and staff scientist. My research journey started during the studies to obtain my medical degree when I became intrigued by molecular medicine's potential health impacts. I spent most of my early formative years at Columbia University in NY specializing in molecular mechanisms of tumor suppressor genes. Under Dr. Jean Gautier's mentorship at the Columbia University Department of Genetics and Development, I

made substantial contributions to the field of genome integrity by developing a cell-free system that accurately simulated the ATM and ATR dependent DNA damage response, identifying novel DNA damage checkpoints.

In 2004, I became a group leader at Clare Hall Laboratories, the London Research Institute, now The Francis Crick Institute, where I started the Genome Stability Laboratory. I worked side by side with Nobel laureates colleagues Tomas Lindal and Tim Hunt on several aspects of DNA damage response and repair. I made important findings, which have been widely reproduced and expanded upon other groups over the years. A major breakthrough has been the discovery that RAD51 prevents ssDNA gap accumulation and Mre11 nuclease dependent degradation of nascent DNA during DNA replication. These findings introduced the concept of recombination protein-mediated replication fork protection. This breakthrough significantly impacted the scientific community, providing a major contribution to understanding genome instability and chemoresistance in cancer cells.

Further research conducted in my lab demonstrated that DNA degradation products leak in the cytoplasm. I also identified new cell cycle and DNA replication fork stability regulators and established a link between ATM checkpoint gene and cellular metabolism. These findings helped explaining neurodegeneration in Ataxia Telangiectasia.

In 2010, I was promoted to Tenured Senior Investigator by an international panel appointed by Cancer Research UK.

In 2013, I moved to IFOM and the University of Milan, where I continued my research. I unveiled the replication, protein composition, and loop structure of the human centromeres' chromatin, illustrating how repetitive DNA is replicated. I demonstrated that BRCA1 and BRCA2 also prevent ssDNA gap accumulation and extensive DNA degradation showing that this is triggered by SMARCAL1 dependent fork reversal. Recently, I discovered a new function for Polymerase Theta in gap filling and replication fork rupture prevention, contributing to explain the widespread base substitution in BRCA1 and BRCA2 defective cancer cells.

Overall, these findings expanded our understanding of DNA replication stress and its role in early cancer formation. Related to this we have recently shown that replication stress influences cell fate, pushing stem cells towards totipotency, a pathway reactivated in tumors to increase cell plasticity. This pathway is suppressed in somatic cells by epigenetic mechanisms, which we showed to control replication origin assembly coupled to cell cycle and growth development.

Throughout my career, my work has significantly advanced the field of DNA damage response, DNA repair and DNA replication, resulting in numerous invitations to international conferences and several awards, including the prestigious Lister Institute Research Prize, the Harvard-Armenise Career Development award, and two consecutive European Research Council grants. Several of my former students and postdocs have achieved independent careers at prestigious institutions and companies. My work over the years has been highlighted in several News and Views and review articles and has led to major advance in the field of genome integrity maintenance as confirmed by work from many labs that reproduced and expanded upon my initial observations.

## **B. Positions, Scientific Appointments, and Honors**

### **Positions and Scientific Appointments:**

1999-2004: Research Scientist Department of Genetics and Development, Columbia University NY

2004: Tenure-Track Junior Group leader, Cancer Research UK, London Research Institute, Clare Hall Laboratories

2004: Honorary fellow, University College of London

2010 Senior Tenured Group Leader, London Research Institute, Clare Hall Laboratories

2010 : Honorary Full Professor, University College of London

2013-Present: Senior Tenured Group leader, DNA metabolism laboratory, IFOM, Milan, Italy

June 2018: Associate Professor, University of Milan

2023-Present: Full Professor, University of Milan

### **Honors and Awards:**

2004 Cancer Research UK core funding grant 2004-2013,

2006 Nominated member of the Lister Institute for Preventive Medicine

2006 Awarded the Lister Institute for Preventive Medicine

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2007 Nominated member of the European Molecular Biology Organization as Young Investigator

2007 Awarded the European Research Council ERC Start up grant (1.5 M Euros) to “AAMDR, Studying the role of ATM, ATR and MRE11 in vertebrate DNA damage response”

2013 Awarded the Armenise-Harvard Foundation career development award (\$ 750.000) to study DNA replication fork protection

2013 Awarded the European Research Council Consolidator grant ((2 M Euro) to study RAD51, BRCA1 and BRCA2's role in maintaining genome stability during DNA replication

2023 Elected to the European Molecular Biology Organization as Senior EMBO Investigator

### **C. Contribution to Science**

An ATR- and Cdc7-dependent DNA damage checkpoint that inhibits initiation of DNA replication.

Costanzo V, Shechter D, Lupardus PJ, Cimprich KA, Gottesman M, Gautier J.

Mol Cell. 2003 Jan;11(1):203-13.

Mre11 assembles linear DNA fragments into DNA damage signaling complexes.

Costanzo V, Paull T, Gottesman M, Gautier J.

PLoS Biol. 2004 May;2(5):E110.

Mre11 protein complex prevents double-strand break accumulation during chromosomal DNA replication.

Costanzo V, Robertson K, Bibikova M, Kim E, Grieco D, Gottesman M, Carroll D, Gautier J.

Mol Cell. 2001 Jul;8(1):137-47.

Reconstitution of an ATM-dependent checkpoint that inhibits chromosomal DNA replication following DNA damage.

Costanzo V, Robertson K, Ying CY, Kim E, Avvedimento E, Gottesman M, Grieco D, Gautier J.

Mol Cell. 2000 Sep;6(3):649-59.

CEP63 deficiency promotes p53-dependent microcephaly and reveals a role for the centrosome in meiotic recombination.

Marjanović M, Sánchez-Huertas C, Terré B, Gómez R, Scheel JF, Pacheco S, Knobel PA, Martínez-Marchal A, Aivio S, Palenzuela L, Wolfrum U, McKinnon PJ, Suja JA, Roig I, Costanzo V, Lüders J, Stracker TH.

Nat Commun. 2015 Jul 9;6:7676. doi: 10.1038/ncomms8676.

RAD51- and MRE11-dependent reassembly of uncoupled CMG helicase complex at collapsed replication forks.

Hashimoto Y, Puddu F, Costanzo V.

Nat Struct Mol Biol. 2011 Dec 4;19(1):17-24.

Brca2, Rad51 and Mre11: performing balancing acts on replication forks.

Costanzo V.

DNA Repair (Amst). 2011 Oct 10;10(10):1060-5.

ATM activates the pentose phosphate pathway promoting anti-oxidant defence and DNA repair.

Cosentino C, Grieco D, Costanzo V.

EMBO J. 2011 Feb 2;30(3):546-55.

Rad51 protects nascent DNA from Mre11-dependent degradation and promotes continuous DNA synthesis.

Hashimoto Y, Ray Chaudhuri A, Lopes M, Costanzo V.

Nat Struct Mol Biol. 2010 Nov;17(11):1305-11.

GEMC1 is a TopBP1-interacting protein required for chromosomal DNA replication.

Balestrini A, Cosentino C, Errico A, Garner E, Costanzo V.

Nat Cell Biol. 2010 May;12(5):484-91.

Tipin/Tim1/And1 protein complex promotes Pol alpha chromatin binding and sister chromatid cohesion.

Errico A, Cosentino C, Rivera T, Losada A, Schwob E, Hunt T, Costanzo V.

EMBO J. 2009 Dec 2;28(23):3681-92.

An ATM- and ATR-dependent checkpoint inactivates spindle assembly by targeting CEP63.

Smith E, Dejsuphong D, Balestrini A, Hampel M, Lenz C, Takeda S, Vindigni A, Costanzo V.

Nat Cell Biol. 2009 Mar;11(3):278-85.

Polo-like kinase 1 reaches beyond mitosis, cytokinesis, DNA damage response, and development.

Takaki T, Trenz K, Costanzo V, Petronczki M.

Curr Opin Cell Biol. 2008 Dec;20(6):650-60.

Mre11-Rad50-Nbs1-dependent processing of DNA breaks generates oligonucleotides that stimulate ATM activity.

Jazayeri A, Balestrini A, Garner E, Haber JE, Costanzo V.

EMBO J. 2008 Jul 23;27(14):1953-62.

Plx1 is required for chromosomal DNA replication under stressful conditions.

Trenz K, Errico A, Costanzo V.

EMBO J. 2008 Mar 19;27(6):876-85.

Tipin is required for stalled replication forks to resume DNA replication after removal of aphidicolin in *Xenopus* egg extracts.

Errico A, Costanzo V, Hunt T.

Proc Natl Acad Sci U S A. 2007 Sep 18;104(38):14929-34.

ATM and ATR promote Mre11 dependent restart of collapsed replication forks and prevent accumulation of DNA breaks.

Trenz K, Smith E, Smith S, Costanzo V.

EMBO J. 2006 Apr 19;25(8):1764-74.

RAD51 protects abasic sites to prevent replication fork breakage.

Hanthi Y, Ramirez-Otero MA, Appleby R, De Antoni A, Joudeh L, Sannino V, Waked S, Ardizzoia A, Barra V, Fachinetti D, Pellegrini L, Costanzo V

Mol Cell. 2024 Aug 22;84(16):3026-3043.e11. doi: 10.1016/j.molcel.2024.07.004.

POL $\theta$  processes ssDNA gaps and promotes replication fork progression in BRCA1-deficient cells.

Schrempf A, Bernardo S, Arasa Verge EA, Ramirez Otero MA, Wilson J, Kirchhofer D, Timelthaler G, Ambros AM, Kaya A, Wieder M, Ecker GF, Winter GE, Costanzo V, Loizou JI.

Cell Rep. 2022 Nov 29;41(9):111716. doi: 10.1016/j.celrep.2022.111716. Epub 2022 Nov 17.

POL $\theta$  prevents MRE11-NBS1-CtIP-dependent fork breakage in the absence of BRCA2/RAD51 by filling lagging-strand gaps.

Mann A, Ramirez-Otero MA, De Antoni A, Hanthi YW, Sannino V, Baldi G, Falbo L, Schrempf A, Bernardo S, Loizou J, Costanzo V. Mol Cell. 2022 Nov 17;82(22):4218-4231.e8. doi: 10.1016/j.molcel.2022.09.013.

REV1-Pol $\zeta$  maintains the viability of homologous recombination-deficient cancer cells through mutagenic repair of PRIMPOL-dependent ssDNA gaps.

Taglialatela A, Leuzzi G, Sannino V, Cuella-Martin R, Huang JW, Wu-Baer F, Baer R, Costanzo V, Ciccio A.

Mol Cell. 2021 Oct 7;81(19):4008-4025.e7. doi: 10.1016/j.molcel.2021.08.016. Epub 2021 Sep 10.

The Cohesin Ring Uses Its Hinge to Organize DNA Using Non-topological as well as Topological Mechanisms.

Srinivasan M, Scheinost JC, Petela NJ, Gligoris TG, Wissler M, Ogushi S, Collier JE, Voulgaris M, Kurze A, Chan KL, Hu B, Costanzo V, Nasmyth KA. Cell. 2018 May 31;173(6):1508-1519.e18. doi: 10.1016/j.cell.2018.04.015.

SAMHD1 acts at stalled replication forks to prevent ssDNA-mediated induction of type I interferons

Coquel F, Silva MJ, Técher H, Zadorozhny K, Sharma S, Nieminuszczy J, Mettling C, Dardillac E, Barthe A, Schmitz AL, Promonet A, Cribier A, Sarrazin A, Niedzwiedz W, Lopez B, Costanzo V, Krejci L, Chabes A, Benkirane M, Lin YL and Pasero P. Nature. 2018 May;557(7703):57-61.

Smarcal1-mediated fork reversal triggers Mre11-dependent degradation of nascent DNA in the absence of Brca2 and stable Rad51 nucleofilaments. Kolinjivadi AM, Sannino V, De Antoni A, Zadorozhny K, Kilkenny M, Técher H, Baldi G, Shen R, Ciccio A, Pellegrini L, Krejci L and Costanzo V. Mol Cell 2017 Sep 7;67(5):867-881

Restoration of Replication Fork Stability in BRCA1- and BRCA2-Deficient Cells by Inactivation of SNF2-Family Fork Remodelers. Taglialatela A, Alvarez S, Leuzzi G, Sannino V, Ranjha L, Huang JW, Madubata C, Anand R, Levy B, Rabadan R, Cejka P, Costanzo V, Ciccio A.

Mol Cell. 2017 Oct 19;68(2):414-430.e8. doi: 10.1016/j.molcel.2017.09.036.

Fanconi-Anemia-Associated Mutations Destabilize RAD51 Filaments and Impair Replication Fork Protection.  
Zadorozhny K, Sannino V, Beláň O, Mlčoušková J, Špírek M, Costanzo V, Krejčí L.  
Cell Rep. 2017 Oct 10;21(2):333-340. doi: 10.1016/j.celrep.2017.09.062.

Xenopus laevis as Model System to Study DNA Damage Response and Replication Fork Stability.  
Sannino V, Pezzimenti F, Bertora S, Costanzo V.  
Methods Enzymol. 2017;591:211-232

Moonlighting at replication forks - a new life for homologous recombination proteins BRCA1, BRCA2 and RAD51.  
Kolinjivadi AM, Sannino V, de Antoni A, Técher H, Baldi G, Costanzo V.  
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Structure of human Cdc45 and implications for CMG helicase function.  
Simon AC, Sannino V, Costanzo V, Pellegrini L.  
Nat Commun. 2016 May 18;7:11638. doi: 10.1038/ncomms11638.

Centromeric DNA replication reconstitution reveals DNA loops and ATR checkpoint suppression.  
Aze A, Sannino V, Soffientini P, Bachi A, Costanzo V.  
Nat Cell Biol. 2016 Jun;18(6):684-91. doi: 10.1038/ncb3344.

Epigenetic regulation of replication origin assembly: A role for histone H1 and chromatin remodeling factors.  
Falbo L, Costanzo V.  
Bioessays. 2021 Jan;43(1):e2000181. doi: 10.1002/bies.202000181. Epub 2020 Nov 9.

SSRP1-mediated histone H1 eviction promotes replication origin assembly and accelerated development.  
Falbo L, Raspelli E, Romeo F, Fiorani S, Pezzimenti F, Casagrande F, Costa I, Parazzoli D, Costanzo V.  
Nat Commun. 2020 Mar 12;11(1):1345. doi: 10.1038/s41467-020-15180-5.

ATR expands embryonic stem cell fate potential in response to replication stress.  
Atashpaz S, Samadi Shams S, Gonzalez JM, Sebestyén E, Arghavanifard N, Gnocchi A, Albers E, Minardi S, Faga G, Soffientini P, Allievi E, Cancila V, Bachi A, Fernández-Capetillo Ó, Tripodo C, Ferrari F, López-Contreras AJ, Costanzo V.  
Elife. 2020 Mar 12;9:e54756. doi: 10.7554/eLife.54756.

Exploring the links between cancer and placenta development.  
Costanzo V, Bardelli A, Siena S, Abrignani S. Open Biol. 2018 Jun;8(6). pii: 180081. doi: 10.1098/rsob.180081. Review

## **BIBLIOMETRICS**

Total number of publications: 82

Citations: 4705

H-Index: 42

(Google Scholar)