UNIVERSITÀ DEGLI STUDI DI UDINE

Prof. Gianluca Tell
Full Professor of Molecular Biology
Head of the Laboratory of Molecular Biology and DNA repair
Deputy Head of the Department of Medicine
Department of Medicine
University of Udine - Italy

Udine, May 2rd 2025

Prof. Gianluca Tell

Curriculum Vitae

Name – Gianluca Tell

Position Title – Full Professor of Molecular Biology, Department of Medicine, University of Udine, Italy

Education/Training –

- Academic years 1988-1992 University of Trieste, Laurea a ciclo Unico in Scienze Biologiche, magna cum Laude (13th March 1993). Field of Study: Regulation of gene expression in human cells through biochemical and molecular biology approaches
- 1993 Centro di Riferimento Oncologico Aviano – I.R.C.C.S. Research Fellow. Field of study: Molecular mechanisms of cancer cell migration
- 1996 NIH, NCI, Experimental Immunology Branch-Division of Basic Science. Visiting Scientist. Field of study: Molecular mechanisms of ScFv folding

A. Personal Statement

Gianluca Tell was born on March 6th 1968. His prevailing interests is the study of molecular mechanisms of gene expression particularly in the field of redox signalling and cell oxidative stress. Now, he is focusing on some aspects linking gene expression and DNA repair and its relevance in molecular oncology and cancer. In particular, from 1998, he contributed to the understanding of the molecular mechanisms, involving the main mammalian Apurinic/Apyrimidinic Endonuclease, i.e. APE1, in coordinating cellular responses to oxidative stress in different cell models. His background includes molecular and cellular biology as well as biochemistry techniques and –OMICS technologies to characterize the relationship between structure and function of proteins involved in gene expression and DNA repair. He coordinated several research projects granted from Telethon, AIRC, PRIN, ASI and worked as a Referee for several different International Journals, including: Oncogene, Nucleic Acids Research, Proteomics, Cancer Research, Clinical Cancer Research, etc. Actually, from 2010, his research activity is focused on characterizing the non-canonical roles of DNA repair enzymes of the Base Excision Repair pathway in association with RNA metabolism. He is currently head of the Laboratory of Molecular Biology and DNA repair of the Department of Medicine at the University of Udine, Italy, coordinating the work of three Post-Doctoral fellows and two PhD students.

Prof. G. Tell authored more than 180 publications in international peer reviewed journals and several international congress communications, concerning control of gene expression and DNA damage response during response to oxidative stress and genotoxic treatments. In 55%

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of these publications Prof. Tell gave a central contribution, acting as a first or last name. Total Impact Factor >500. The value of citation index (h-index) according to Scopus is 50.

MAJOR ACHIEVEMENTS IN SCIENCE. Prof Tell has contributed to the understanding of the molecular mechanisms, involving the main mammalian Apurinic/Apyrimidinic Endonuclease APE1, in coordinating cellular responses to oxidative stress using different cancer cell models. He discovered one of the most important non-canonical roles of this protein in miRNA processing highly relevant in cancer biology.

Website: https://www.researchgate.net/profile/Gianluca_Tell
Lab Web site: https://gianlucatell.wixsite.com/labtell
ORCID Identifier: https://orcid.org/0000-0001-8845-6448
Scopus Author ID: 7005032283

B. Positions, Scientific Appointments and Honors

- From December 2024 to December 2026, panel member of the National Committee for habilitations evaluations in the "Commissioni Nazionali per il conferimento dell'Abilitazione Scientifica Nazionale (ASN)" for the MUR, Italian Ministery of University and Research;
- From December 2018-present he is Full Professor (tenure track) of Molecular Biology, at the Department of Medicine, University of Udine, Udine, Italy.
- From October 2017-present he is Deputy of the Head of the Department of Medicine for Research, at the Department of Medicine, University of Udine, Udine, Italy;
- From January 2017-November 2018 he is Associate Professor of Molecular Biology and Head of the Laboratory of Molecular Biology and DNA repair, at the Department of Medicine, University of Udine, Udine, Italy
- From 25th October 2015 to 30th September 2019, he is member of the Technology Transfer Commission of the University of Udine, Italy;
- From January 2011-December 2016, he is Associate Professor of Molecular Biology and Head of the Laboratory of Molecular Biology and DNA repair, at the Department of Medical and Biological Sciences, School of Medicine, University of Udine, Udine, Italy.
- From November 2005-December 2010, he is Associate Professor of Molecular Biology, at the Department of Biomedical Sciences and Technologies, School of Medicine, University of Udine, Udine, Italy.
- From November 2012-September 2018, he is Head of the School of Biotechnology at the University of Udine, Italy;
- July-September 2011, Visiting Research Scholar in the lab of Prof. Bruce Demple. Department of Pharmacological Sciences, Stony Brook University, Stony Brook, NY, USA.
- July 2009, Visiting Professor in the lab of Prof. Pablo Radicella. CEA, Institut de Radiobiologie Cellulaire et Moléculaire, UMR217 CNRS, F-92265 Fontenay-aux-Roses, France.
- June-August 2006, Visiting Professor in the lab of Prof. Sankar Mitra.
School of Medicine-Sealy Center For Molecular Science And Department Of Human Biological Chemistry And Genetics. University of Texas, Galveston, TX, USA.
- September 2003-October 2005, Assistant Professor of Molecular Biology, Department of Biomedical Sciences and Technologies, School of Medicine, University of Udine, Italy;

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- March 2000-September 2003, Assistant Professor of Molecular Biology, Department of Biochemistry, Biophysics and Macromolecular Chemistry, School of Medicine, University of Trieste, Italy;
- 1996, visiting scientist in the lab of Dr. David Segal, Experimental Immunology Branch, Division of Basic Sciences, NCI, NIH, Bethesda (MD) USA;
- Staff fellow, April 1995-March 2000, Department of Biomedical Sciences and Technologies, School of Medicine, University of Udine, Italy;

Others:

1998 – 1999 Deputy Associate Professor, General Pathology, Department of Biomedical Sciences and Technologies, Udine University Medical School, Udine – Italy
1997 – 1999 Teaching assistant, Molecular Immunology, Department of Biomedical Sciences and Technologies, Udine University Medical School, Udine – Italy
1997 – 1998 Teaching assistant, Biochemical and Molecular Gene Expression Techniques, Department of Biomedical Sciences and Technologies, Udine University Medical School, Udine – Italy
1994 (January) -1995 (May) Second lieutenant, Italian Army, anti-aircraft artillery, Sabaudia (Rome) and 5th Regiment Udine, Italy
1993 – 1994 Research Scientist (Postgraduate fellow) supported by Oncological Research Center (C.R.O.) Aviano, PN, Italy

Professional memberships

2000- American Association for Biochemistry and Molecular Biology (ASBMB)
2000 Italian Society for Biochemistry and Molecular Biology (SIB)
2003-2008 American Society for Bone and Mineral Research (ASBMR)
2004 Human Proteome Organization (HUPO)
2004 Italian Human Proteome Organization (IHUPO)
2011- Visiting Research Scholar at Stonybrook University, Stonybrook, NY-USA
2014-2020 Scientific Board of the Italian Research Cancer Association (AIRC)
2015 Member of the Scientific Board of the Fondazione Italiana Fegato, FIF-ONLUS, Trieste, Italy

Panel review board member for National and International granting agencies

- 2008-2012. Consultant Ministry of Science (Georgia)
- 2011-present. Consultant, Ministry of University and Research (Italy);
- 2014-2020. Reviewer and Scientific Board member of the Italian Research Cancer Association (AIRC) for PostDoc Fellowships
- 2022, Reviewer for grant Projects applications for the National Science Center, Poland
- 2023-present. Panel review member, Plan Cancer et Stratégie Décennale Cancer Inserm, France
- 2024. Reviewer for Austrian Science Fund (FWF), ESPRIT Program
- 2025. Reviewer UK Research and Innovation (UKRI), United Kingdom
- 2025, Reviewer for PhD fellowships project, Fonds de la Recherche Scientifique – FNRS Bruxelles, Bruxelles
- 2024-2025. Panel review member Agence Nationale de Recherche (ANR), France
- 2024-2025 Panel review member for French National Cancer Institute, France

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Honors and Awards including invitations as speaker in International Congresses

- 2008 Invited Speaker at "Anticancer Research Congress" in Kos, Greece;
- 2009 Invited Speaker at "3rd US/EU-DNA repair meeting" in Galveston, TX-USA;
- 2010 Invited Speaker at INBB meeting in Rome, Italy;
- 2011 UICC Yamagiwa-Yoshida Memorial International Cancer
- Study Grant funded by the Kyowa Hakko Kogyo Company Ltd., Tokyo and the Japan National Committee for UICC
- March 2018, Inviter Speaker at EEMGS International Conference, Potsdam, Germany;
- August 2018, Invited Speaker by the Institute of Chemical Biology and Fundamental Medicine, SB, RAS, NSU Novosibirsk Russia, to give a lecture at the 11th International Multiconference BGRS/SB-2018 "Bioinformatics of Genome Regulation and Structure/Systems Biology", at Novosibirsk, Russia.
- July 2nd, 2024; FEBS2024 Conference, Milan Italy, Lecture in a Special Symposium.
- December 4th, 2024, Translational Trends in Natural and Health Sciences (TTNHS-2024), Central University of Punjab, VPO Ghudda, Bathinda, Punjab INDIA, Lecture in a Special Symposium
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Invited seminars and International teaching courses

- October 11th, 1997; Udine University - Medical School, Department of Biomedical Sciences and Technologies, Udine – Italy;
- April 5th, 1998; Udine University - Medical School, Department of Biomedical Sciences and Technologies, Udine – Italy;
- February 20th, 1999; Naples University - Medical School, Department of Molecular and Cellular Pathology 'L. Califano', Naples - Italy;
- March 7th, 2001; Florence University - Chemistry School, CERM and Department of Chemistry, Title: "Role of APE/Ref-1 in the transcriptional control of eukaryotic cells", Florence – Italy;
- October 1st, 2004; Trieste, AREA Science Park – EASL International Workshop 'The Molecular Basis of Bilirubin Encephalopathy and Neurotoxicity' – Title: "Redox regulation of cellular functions: new perspectives for the antioxidant role of bilirubin", Trieste – Italy;
- July 20th, 2007; Trieste, AREA Science Park – Summer School in Molecular Medicine – Title: "Proteomics in the new post-genomic era", Trieste – Italy;
- November 14th, 2007, Indiana University Melvin and Bren Simon Cancer Center; Title: "The many faces of APE1/Ref-1: molecular journey to unveil the secrets of this multifunctional protein", Indianapolis, IN (USA);
- November 23rd (2010); Department of Molecular Embriology, DKFZ, Heidelberg, D, Title: 'New insights into the unusual DNA repair protein APE1 and implications for cancer";
- April 7th, 2011; Naples University - Medical School, Department of Molecular and Cellular Pathology 'L. Califano', Naples - Italy; Title: 'New insights into the unusual DNA repair protein APE1 and implications for cancer";
- September 17th, 2012; College of Medicine, Graduate Center for Toxicology, University of Kentucky, Lexington, KY 40536-0305, USA –Title: "New insights into the unusual DNA repair protein Ape1 and relevance for Base Excision Repair and cancer";

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- June 13th, 2018; Fondazione Istituto Italiano di Tecnologia (IIT), Genova Italy; Title: 'Non canonical roles of BER enzymes in RNA processing: novel perspectives in cancer biology through the study of APE1 RNA- and protein-interactomes' (Host: Stefano Gustincich);
- September 24-29, 2018; Savitribai Phule, Pune University, Pune, INDIA; Teaching course of 15 hours: "Genome integrity and DNA repair in cancer" under the GIAN scheme of MHRD, Government of India.
- September 25th, 2018; National Centre for Cell Science S.P. Pune University Campus, Pune, INDIA; Title: "Non canonical roles of BER enzymes in RNA processing: novel perspectives in cancer biology through the study of APE1 protein - and RNA –interactomes"
- September 27th, 2018; Indian Institute of Science Education and Research, Pune, India; Title: "Non canonical roles of BER enzymes in RNA processing: novel perspectives in cancer biology through the study of APE1 protein - and RNA –interactomes"
- April 3rd, 2019; School of Biological Sciences, Georgia Institute of Technology, Atlanta (GA), USA (Host. Prof. Francesca Storici);
- April 5th, 2019; Department of Biochemistry, St Louis University, St Louis (MO) USA, (Host: Prof. Alessandro Vindigni);
- April 9th, 2019; NIEHS/NIH, Triangle Park (VA), USA (Host. Prof. Samuel Wilson)
- May 11th, 2019; Opening Lecture at the '5th Liangjiang Meeting on the tumor and transformation research', Chongqing, China;
- September 24th, 2019; Istituto Superiore di Sanità, Rome, Italy (Host: Dr. Eugenia Dogliotti).
- November 6th-9th 2022, VII EU/US DNA Repair Conference Stony Brook, NY, USA. Plenary Lecture
- May 30th, 2024; Norwegian University of Science and Technology NTNU, Trondheim, Norway, Host: Prof. Barbara van Loon)
- July 2nd, 2024; FEBS2024 Conference, Milan Italy, Lecture in a Special Symposium.
- December 4th, 2024, Translational Trends in Natural and Health Sciences (TTNHS-2024), Central University of Punjab, VPO Ghudda, Bathinda, Punjab INDIA, Lecture in a Special Symposium
- May 28th 2025, Department of Life Sciences, University of Cagliari, Italy. Invited Seminar.
- October 5th-9th 2025, VIII EU/US DNA Repair Conference Trondheim Norway. Plenary Lecture
- November 1th-3rd 2025, VII FARM-DNA meeting (Fundamental Aspects of DNA Repair and Mutagenesis) at the University of São Paulo, Brasil. Plenary Lecture

Research Support

In the Last 10 years, Prof. Tell received grants in support of his research activities, for an overall budget of more than 2 MEuros from different granting agencies including: the National Institutes of Health (NIH), MIUR, MAE, Telethon, AIRC, Regione FVG, Private Companies

Ongoing Research Support

- 2025-2027 Research Grant MUR-PRIN (Grant # 20224F7P9Y), titled: "*Improving drug discovery strategies targeting Apurinic Apyrimidinic Endoribonuclease-1 in miR processing through integrated molecular approaches on cancer cell lines and tumor organoids*"**.** Project location: University of Udine, Italy. Total funding: € 199.424.
- 2024-2026 Research Grant MINSAL, PNRR-POC Mission 6 (PNRR-POC-2023-12377143), titled: "*Proteoglycan-4 as coadjuvant treatment to overcome resistance to Sorafenib and Regorafenib in*

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patients with Hepatocellular carcinoma". Project location: University of Udine, Italy. Total funding to Dr Tell: € 230.000.

- 2025-2030 Research Grant AIRC (Grant # IG-30399), titled: "*Understanding the role of APE1 in the regulation of oncomiR containing G-quadruplex structures for cancer treatment*" Project location: University of Udine, Italy. Total funding to Dr Tell: € 534.000.

Completed Research Support

- 2021-2022 Research Grant MUR, FISR2020IP_01563 (D.D. n.562 del 5.5.2020), titled: "*A system approach platform, based on Artificial Intelligence (AI) / Machine Learning (ML), for serum proteomics, radiomics and clinical data analysis to identify diagnostic and prognostic biomarkers in SARS-CoV-2 (SCV2) infection*". Project location: University of Udine, Italy. Total funding to Dr Tell: € 52.967,91.
- 2018-2022 Research grant AIRC #IG19862 (*Unveiling the role of Ape1 in regulating tumor cell resistance to chemotherapy through miRNAs processing in HCC and NSCLC*). The goal of this proposal is to characterize new Ape1 functions in cancer resistance associated with miRNAs and gene expression regulation. This project will evaluate the roles of Ape1 and Ape1-regulated miRNAs as predictive biomarkers in NCSLC and HCC. Project location: University of Udine, Italy. Total funding to Dr Tell: € 454.000
- 2016-2021 Research Grant R01 NIH (1R01ES026243-01), National Institutes of Health agency: National Cancer Institute Special Emphasis Panel (Ribose-seq profile and analysis of ribonucleotides in DNA of oxidatively-stressed and cancer cells). PI: Prof. Francesca Storici, Georgia Technology Institute, Atlanta, GA, USA. Co-PI: Prof. Gianluca Tell Project. Total fundings to Dr. Tell: $388,190. The goal of this project is to map ribonucleotides embedded in DNA in normal and cancer cells and identify the mechanisms for their repair. Project location: Georgia Technology Institute, Atlanta, GA, USA and University of Udine, Italy
- 2017-2019 Crossborder cooperation program Interreg V Italia Austria Bando 2016 funded by the European Regional Development Fund (ERDF) and the National Funds, implemented by the Autonomous Region Friuli Venezia Giulia, in quality of Managing Authority (PreCanMed: Generation of a Precision Cancer Medicine platform). Total funding to Dr Tell: € 205.450
- 2015-2017 Research Grant R21 NIH, National Institutes of Health agency: National Cancer Institute Special Emphasis Panel (The Ape1-NPM1 Axis and Telomere Maintenance). PI: Prof. Bruce Demple, Stony Brook University, NY, USA. Co-PI: Prof. Gianluca Tell Project. Total fundings: $429,642. The goal of this project is to unveil the role of the Ape1-NPM1 axis in telomere maintenance for development of new anticancer drugs. Project location: Stony Brook University, NY, USA and University of Udine, Italy
- 2015-2017 Research Grant R21 NIH, National Institutes of Health agency: National Cancer Institute Special Emphasis Panel (The Ape1-NPM1 Axis and Telomere Maintenance). PI: Prof. Bruce Demple, Stony Brook University, NY, USA. Co-PI: Prof. Gianluca Tell Project. Total fundings: $429,642. The goal of this project is to unveil the role of the Ape1-NPM1 axis in telomere maintenance for development of new anticancer drugs. Project location: Stony Brook University, NY, USA and University of Udine, Italy
- 2014-2016 Research grant AIRC #IG14038 (*Base Excision Repair dysregulation and cancer: Ape1 as a therapeutic target*)

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- 2012-2015 Crossborder cooperation program Italy- Slovenia 2007- 2013 funded by the European Regional Development Fund (ERDF) and the National Funds, implemented by the Autonomous Region Friuli Venezia Giulia, in quality of Managing Authority (*Environmental pollutants and neurodegenerative diseases*).
- 2010-12 Research grant AIRC #IG10269 – three years (*Understanding the functional regulation of APE1 for development of new specific inhibitors*)
- 2010-12 Telethon, Grant # GGP10051B (*New diagnostic and therapeutic approaches for the Crigler−Najjar Syndrome Type I*)
- 2010-12 Research grant PRIN2008 #2008CCPKRP (*Molecular networks involving APE1 and role of post-translational modifications in fine-tuning the APE1 different functions for development of new drugs for cancer treatment*)
- 2009-2010 ITALY/FRANCE 'Galileo' exchange grant from the Università Italo-Francese.
- 2008-11 Grant FIRB-National Proteomics Network RBRN07BMCT (Italian Human ProteomeNet)
- 2008-10 EU/USA Exchange Grant by Ministry from Foreign Affairs: *Role of Ape1 in Neurotoxicity of Cancer Treatments*
- 2006-08 Telethon, Grant #GGP06208 (*DJ-1 in neurodegeneration*)
- 2005-09 Private grants from Procter & Gamble and Abiogen
- 2005-07 AIRC, (*New approaches for studying genetics, early molecular diagnosis and prognostic factors relevant for HCC)*
- 2005-07 Telethon, Grant #GGP05062 (*Genetic determinants of bilirubin encephalopathy*)
- 2005-07 National coordinator grant PRIN2005 (*Molecular mechanisms of cell response to oxidative stress*)

Meeting/Courses organization and invited chairman

- - September 8th-11th 2003. European Science Foundation Programme on integrated approaches for functional genomics. *Biocrystallography course: from gene to drug*, Trieste, Italy. Chairman and course organizer in collaboration with Prof. Silvano Geremia
- - February 29th-March 1st 2012. EASL Basic School of Hepatology, course 7: *Hepatocyte damage and Liver metabolism*, Trieste, Italy. Chairman and course organizer in collaboration with Prof. Claudio Tiribelli.
- - September 24th-28th 2017, 6th EU-US International Meeting on Endogenous DNA Damages, Udine, Italy. Chairman and Congress organizer in collaboration with Prof. Robert Sobol, Alexander Buerckle, Eugenia Dogliotti;
- - March 21st 2018, Chairman and invited speaker at EEMGS International Conference, Potsdam, Germany.

Referee for the following journals

- Antioxid. Redox. Signal.
- Biochemical Journal
- Biochimica and Biophysica Acta
- Biotechnology Progress
- Biochimie
- Cancer Research
- Cell Biology International

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- Cell Death and Differentiation
- European Journal of Pharmacology
- Experimental Cell Research
- Gastroenterology
- Gene
- Hepatology
- International Journal of Biochemistry & Cell Biology
- International Journal of Cancer
- J. Proteome Res.
- Molecular and Cellular Endocrinology
- Molecular Biosystems
- Mutation Research
- Nucleic Acids Research
- Nucleic Acids Research-Cancer
- Nucleic Acids Research-Methods
- Nature Metabolism
- Oncogene
- Oncology
- PlosONE
- PNAS
- Proteomics
- RNA

Associate Editor of the following Journals

- Annals of Hepatology
- Biomolecules
- BMC Research Notes
- BMC Biochemistry
- DNA Repair
- Proceedings of the National Academy of Sciences (PNAS)
- Scientific Reports

Institutional assignments

- Academic Years 2010-2012: Representative of Associate Professors in Academic Senate of the University of Udine;
- Academic Years 2009-2012: Member of the Teaching Commission for the Degree in Biotechnologies of the University of Udine;
- Academic Years 2012-2018: Director of the B.Sc. in Biotechnologies of the University of Udine;
- From 2010-present, Head of the Laboratory of Molecular Biology and DNA repair of the Department of Medicine at the University of Udine, Italy;
- From October 2015-present, member of the Technology Transfer Commission of the University of Udine, Italy;

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- Academic Years: 2014-present: Representative of the Rector of the University of Udine within the "Consortium of Molecular Biomedicine" of the Regione Friuli Venezia Giulia (CBM S.c.r.l. http://www.cbm.fvg.it);
- From January 2018-2020: member of the Scientific Committee for the organization of ESOF2020 (https://www.euroscience.org/tag/esof-2020/ and http://www.proesof2020.eu/).

C. Contributions to Science

Prof Tell has more than 190 scientific publications. Peer reviewed Publications and citations parameters:

- First author publications: 25
- Last/corresponding author publications: 63
- Total publications in peer reviewed international journals: 190
- Peer-reviewed publications at this link: ORCID ID: https://orcid.org/0000-0001-8845-6448.
- Scopus Author ID: 7005032283
- Sum of the Times Cited (Scopus): 8666
- Average Citations per Item (Scopus): 43.33
- **h-index (Scopus): 50**

Most cited paper: The intracellular localization of APE1/Ref-1: More than a passive phenomenon? Tell, G; Damante, G; Caldwell, D; et al. ANTIOXIDANTS & REDOX SIGNALING (2005), 7, 367-384. **Number of citations:** 264 with a mean of 21.82/year.

Paper with highest Impact Factor:

1. Fantini D, Vascotto C, Marasco D, D'Ambrosio C, Romanello M, Vitagliano L, Pedone C, Poletto M, Cesaratto L, Quadrifoglio F, Scaloni A, Radicella JP, **Tell G**. *Critical lysine residues within the overlooked N-terminal domain of human APE1 regulate its biological functions*. **Nucleic Acids Res**. 2010 38(22):8239-56. **Impact Factor: 9.1**

2. Antoniali G, Serra F, Lirussi L, Tanaka M, D'Ambrosio C, Zhang S, Radovic S, Dalla E, Ciani Y, Scaloni A, Li M, Piazza S, **Tell G**. *Mammalian APE1 controls miRNA processing and its interactome is linked to cancer RNA metabolism.* **Nature Communications (2017) Oct 6;8(1):797**. doi: 10.1038/s41467-017-00842-8. PubMed PMID: 28986522; PubMed Central PMCID: PMC5630600. **Impact Factor: 12.1**

3. Bellina A, Malfatti MC, Salgado G, Fleming AM, Antoniali G, Othman Z, Gualandi N, La Manna S, Marasco D, Dassi E, Burrows CJ, **Tell G** *Apurinic/Apyrimidinic Endodeoxyribonuclease 1 modulates RNA G-quadruplex folding of miR-92b and controls its expression in cancer cells*. **Proc Natl Acad Sci U S A**. 2024 Nov 12;121(46):e2317861121. doi: 10.1073/pnas.2317861121. Epub 2024 Nov 4.PMID: 39495925. **Impact Factor:9.4**

4. Dall'Agnese G, Hannett NM, Overholt KJ, Platt JM, Henninger JE, Marcos-Vidal A, Othman Z, Salgado G, Antoniali G, **Tell G.** *APE1 condensation in nucleoli of non-cancer cells depends on rRNA transcription and forming G-quadruplex RNA structures.* **Nucleic Acids Res.** 2025 Feb 27;53(5):gkaf168. doi: 10.1093/nar/gkaf168. **Impact Factor:16.7**

Journals with mid-high Impact Factor in which Prof. G. Tell published as first or as corresponding author:

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1. Nature Communications
2. Nucleic Acids Research
3. Molecular and Cellular Biology
4. Oncogene
5. Genome Biology
6. Antioxidants and Redox Signalling
7. Journal of Biological Chemistry
8. Molecular Biology of the Cell

Referee for the following granting agencies:
1. NSERC (Canada)
2. Wellcome Trust (UK)
3. Cancer Research (UK)
4. Georgia Ministry of Science
5. National Medical Research Council (NMRC), Singapore
6. Italian MIUR
7. Italian Association for Cancer Research (AIRC)

The narrative below touches on the key achievements embodied in some of these papers.

Gene expression and molecular mechanisms of transcriptional control: Transcription Factors and gene expression molecular mechanisms during cell response to stresses.

This has been the main interest of my early scientific activity. The main model, where these arguments have been dealt with, has been the thyroid cell. In this cell, proliferative and differentiative events are modulated, in particular, by hormonal stimulation by TSH (thyrotropin). Two of the main Transcription Factors, which are involved in this kind of regulation, are TTF-1 and Pax-8. The molecules, which I have been studied, are the TTF-1 *homeodomain* and the Pax-8 *paired* domain. These molecules mediate the interaction of the whole molecule with DNA in a sequence specific manner on the promoter of thyroid specific genes such as Tg (Thyroglobulin) and TPO (thyroperoxidase). All these studies were made both from a structural point of view by using Circular Dichroism and Nuclear Magnetic Resonance spectroscopy and by the isolation of specific DNA-sequences (by using common biochemical techniques). Data obtained in these ways revealed of fundamental interest to the comprehension of how these classes of proteins recognize specific DNA-sequences.

Then, I focused on the redox-based mechanisms responsible for tissue specific transcription factors regulation in the thyroid cell model and in particular on the role of ROS species. I demonstrated, in 1998, that also thyroid specific TFs may be involved in this kind of regulation. In fact, Pax-8 transcription factor, involved in thyroglobulin gene expression control, is redox regulated. This is exerted through APE1/Ref-1 protein, a transcriptional co-activator also involved in the redox control of Egr-1, p53, NF-κB, AP-1, Myb and HIF-1α TF.

Key papers:

1. Damante, G., Pellizzari, L., Esposito, G., Fogolari, F., Viglino, P., Fabbro, D., **Tell, G.**, Formisano, S. and Di Lauro, R. "*A molecular code dictates sequence-specific DNA recognition by homeodomains*". (1996) EMBO J. 15, 4992-5000.
2. **Tell, G.**, Fabbro, D., Leonardi, A., Pellizzari, L., Pucillo, C., Lonigro, R., Formisano, S. and Damante, G. "*In the TTF-1 homeodomain the contribution of several amino acids to DNA*

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Control of Gene expression in osteoblasts mediated by mechanical stress and by anti-osteoporotic drugs.

Extracellular nucleotides such as ATP are locally released, short-lived, yet potent extracellular signaling molecules for bone cells. The provision of a mechanism to induce the activation of osteoblasts above a threshold attained by systemic factors alone may facilitate focal remodeling and could represent the basis of new pharmacological strategies designed to counteract several forms of bone disease. Within this context, I deeply contributed to understanding the molecular mechanisms involved in response to purinergic stimulation upon mechanical stress, by defining a signal transduction pathway able to control the activity of Egr-1 transcription factor and the expression of its own target gene, i.e. collagen II(I), together with the activity of another tissue specific transcription factor, i.e. Cbfa-1/Runx2.

Nitrogen-containing bisphosphonates (N-BPs) are used to relieve bone pain and to prevent skeletal complications in bone metastasis, most commonly in breast and prostate cancer. Until now, their mode of action has been almost entirely unknown. The group I coordinated, during years 2002-2010, used high-throughput technologies based on gene expression, proteomics and functional genomics approaches on osteoblasts, osteocytes and yeast to identify new biological processes involved in the cellular response to N-BPs, opening up opportunities for the development of new anticancer drugs.

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Application of Redox Proteomics in studying molecular mechanisms involved in gene expression control during early cellular response to oxidative stress**.**

Reactive oxygen species (such as H_2O_2, $OH^{\cdot}$, $O_2^{\cdot-}$, collectively known as ROS) play important physiological functions and can also cause extensive cellular damage. Oxidative stress, an imbalance between the generation of ROS and the antioxidant defense capacity of the cell, can affect major cellular components, including lipids, proteins, and DNA. This phenomenon is closely

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associated with a number of human diseases such as many degenerative diseases, including cardiovascular disease, diabetes, cancer and neurodegenerative disorders. These pathologies seem to be mostly related to chronic oxidative stress, however also exposure to acute levels of ROS seems to be responsible for different pathologies such as the development of osteoporosis and tissues damages as a consequence of ischemia/reperfusion (I/R) in different organs such as liver. Information regarding the nature of ROS, as well as the localization and the effects of oxidative stress, may be gleaned from the analysis of discrete biomarkers isolated from tissues and biological fluids. Biomarkers are cellular indicators of the physiological state and changes during a disease process, at a specific time. However, the presence of oxidatively damaged molecules could simply reflect secondary epiphenomena rather than having a causal role. A clear delineation of the causal connections cannot be given at present, but a growing body of evidence indicates that high levels of ROS induce distinct pathological consequences that greatly amplify and propagate injury, leading to irreversible cell and tissue degeneration. With the aim of characterizing early molecular mechanisms of cellular response to oxidative stress, I studied the effects of acute doses of H_2O_2 in different cell systems highly exposed to oxidative damage, i.e. human lens cells, osteoblasts and hepatocytes by means of modern approaches of Differential Proteomics. A recent field of investigation is the study of molecular mechanisms of Bilirubin toxicity in mammalian cells, which involve an impairment of the intracellular redox state. The role of cellular redox state in the pathogenesis of hepatocellular carcinoma, osteoporosis and Gaucher disease has also been a field of interest.

Key papers:

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Role of APE1/Ref-1 functions on DNA-repair, Gene expression regulation and on RNA metabolism in cancer cells.

Apurinic/apyrimidinic endonuclease 1 (APE1), an essential protein in mammals, is known to be involved in base excision DNA repair (BER), acting as the major abasic endonuclease; the protein also functions as a redox co-activator of several transcription factors that regulate gene expression. Recent findings obtained by my Lab, highlighted a novel role for APE1 in RNA metabolism through interaction with NPM1 protein, which is involved in ribosomal processing. Such findings on the role of APE1 in the post-transcriptional control of gene expression could explain its ability to influence diverse biological processes and its re-localization to cytoplasmic compartments in some tissues and tumors. I recently demonstrated that an altered APE1/NPM1 interaction is associated with the

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genomic instability of Acute Myeloid Leukemia cells providing the first basis for a role of a BER impairment in tumor transformation. In addition, I proposed that APE1 may serve as a "cleansing" factor for oxidatively damaged abasic RNA, establishing a novel connection between DNA and RNA surveillance mechanisms. These recent discoveries of the novel functions of APE1 in controlling RNA metabolism opened up new paradigms that perhaps explain its cytoplasmic distribution, new areas of investigation to define the biological contributions of its multiple functions, and future avenues for translational research. Now, a possible involvement of APE1 in miRNA metabolism is currently under investigation as well as the high-throughput screening for the identification of small molecules able to interfere with this new function of the protein that may have great relevance for tumor biology and anticancer therapies.

A recent topic that I developed in my Lab is the study of the crosstalk between BER and RER and its relevance in Acardi Goutieres Syndrome (AGS). AGS belongs to type I interferonopathies, characterized by constitutive activation of the antiviral type I interferon (IFN) axis, in which both the accumulation of ribonucleotides (rNMPs) in genomic DNA and an oxidative stress conditions contribute to AGS pathogenesis by generating a vicious cycle. The majority of AGS patients bear mutations in ribonucleases genes, including RNase H2 belonging to the ribonucleotide excision repair (RER) pathway, and are characterized by both the accumulation of cytosolic nucleic acid leading to the activation of the IFN-pathway and by genomic instability. Whereas RNase H2 can process rNMPs in DNA, in my Lab we discovered its inability to remove 8-oxoguanosine (r8oxoG) and ribose monophosphate abasic (rAP) sites, produced during oxidative stress conditions and involved in AGS. Recently, we found that the base excision repair (BER) pathway is actively involved in the removal of r8oxoG as well as rAP sites embedded in DNA and plays an important role in inflammatory processes in response to oxidative stress through non-canonical. Currently, since not only rNMPs but also r8oxoG and rAP are generated during oxidative stress conditions, it is central to understanding which molecular mechanisms are responsible for the repair of those lesions in AGS cells carrying RNase H2 mutation/deletion.

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Book Chapters

- **Tell G.,** *Early molecular events during response to oxidative stress in human cells by differential proteo*mics in 'Redox Proteomics' Editors I. Dalle Donne, A. Scaloni, A. Butterfield, WILEY 2006
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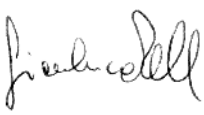

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