

BIOGRAPHICAL SKETCH

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NAME: Alberto Bardelli

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

POSITION TITLE: Full Professor, Department of Oncology – Università degli studi di Torino and Scientific Director, IFOM ETS – The AIRC Institute of Molecular Oncology

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
Università degli studi di Torino, Torino	Laurea 110/110 cum laude	07/1991	Biological Sciences
University College London, London	PhD	11/1996	Biochemistry and Molecular Biology
Università degli studi di Torino, Torino	Board Certified Specialist	08/1999	Clinical Pathology
Johns Hopkins University, Baltimore	Post-Doctoral Training	01/2004	Cancer Genetics

A. Personal Statement

I graduated Cum Laude at the University of Turin and after I moved to the Ludwig Institute for Cancer Research in London where I obtained a Ph.D. in Biochemistry and Molecular biology from the University College London (UCL). I moved to the United States in 1999 for a post-doctoral fellowship in the laboratory directed by Bert Vogelstein at the Howard Hughes Medical Institute, Johns Hopkins University (Baltimore). Here I began studying the genomics of cancer. One of the most significant publications from that period identified for the first-time mutations in kinase genes (the kinome) that are associated with colorectal cancer.

As an independent investigator, I pioneered the combined use of genomics, patients' avatars and liquid biopsies to accurately predict tumor's response and resistance to targeted agents.

My group showed that the analysis of circulating tumor DNA (liquid biopsies) allows monitoring tumor's evolution and resistance to targeted therapies and was the first to pinpoint the emergence of KRAS/NRAS mutations in the blood of patients during EGFR blockade.

My recent publications pinpointed molecular mechanisms which sustain generation of neoantigens in colorectal cancer cells, and unveiled innovative approaches to increase response to immunotherapy. Notably, some of the most prominent strategies have been successfully tested in clinical trials in which his group provided preclinical support (AIRC 5x1000 program Metastatic disease: the key unmet need in oncology). My current work aims at uncovering pharmacological strategies to increase colorectal cancer antigenicity and to convert immune 'cold' into 'hot' tumors (ERC Advanced Grant). Moreover, my group is researching new approaches to diagnose early metastatic tumors, eligible for a more tailored treatment (AIRC Investigator Grant), and is characterizing the molecular causes responsible of the onset of colorectal tumors in young individuals.

My discoveries are published in over 250 scientific articles - over 100 as an independent investigator - in international journals such as Nature, Science, Cancer Cell, Cell, Nature Genetic, Nature Medicine, Journal of Clinical Oncology, JAMA and Lancet Oncology. My studies led to international clinical trials such as CHRONOS,

PEGASUS and ARETHUSA. Since 2014 I have been in the ranking of the most cited researchers in the world "Web of Science".

Member of authoritative scientific associations such as EACS - European Academy of Cancer Sciences and EMBO - European Molecular Biology Organization, I was President of EACR - European Association for Cancer Research (2018-2020) and member of the Scientific Committee of the AIRC Foundation (2013-2023). In 2020 I was awarded the Guido Venosta Award assigned by AIRC and conferred by the Presidency of the Italian Republic for research aimed at developing new therapeutic approaches to neoplasms. Since 2022 I have been appointed as Scientific Director of IFOM ETS – The AIRC Institute of Molecular Oncology, Milan.

B. Positions, Scientific Appointments, and Honors

IRCC Candiolo and Università degli studi di Torino, School of Medicine, Candiolo (To), Italy	Postdoctora I Fellow	1996-1999	
The Johns Hopkins University; Baltimore MD USA	Postdoctora I Fellow	1999-2004	
Università degli Studi di Torino, Italy	Assistant Professor	1998-2005	
Laboratory of Molecular Oncology, Candiolo Cancer Institute IRCCS, Candiolo (To), Italy	Director	2004-2022	
Università degli Studi di Torino, Italy	Associate Professor	2005-2016	
Università degli Studi di Torino, Italy	Full Professor	2016-Present	
IFOM ETS – The AIRC Institute of Molecular Oncology, Milano, Italy	Scientific Director	2022-Present	
Laboratory of Genomics of Cancer and Targeted Therapies, IFOM ETS, Milan	Group Leader	2022-Present	
Laboratory of Genomics of Cancer and Targeted Therapies, Molecular Biotechnology Center (MBC2), Università degli Studi di Torino, Italy	Group Leader	2022-Present	

Fellowships, awards and academy memberships

2024 CORE Oncology Award, Centro Oncoematologico Reggio Emilia, Italy
 2022 TEFAF Honourable Chair, University of Maastricht, The Netherlands
 2021 ERC Advanced Grant
 2020 Guido Venosta Award, FIRC AIRC, Presidenza della Repubblica Italiana
 2019 Member of the Johns Hopkins Society of Scholars
 2018-2024 Highly Cited Researcher, Web of Science, Claryvate
 2017 European Society for Medical Oncology (ESMO) Translational Research Award
 2017 Fellow of European Molecular Biology Organization (EMBO)
 2016 Grant for Oncology Innovation Research Project
 2015 Fellow of the European Academy of Cancer Sciences
 2015 Fellow of the Turin Academy of Sciences
 2014 Thomson Reuters Highly Cited Researcher - Beautiful Minds List
 2004 The Alfred Blalock Research Award - Johns Hopkins Medical School, Baltimore USA
 1999-2004 Fellowship, Howard Hughes Medical Institute, Baltimore MD USA
 1996 Cecilia Cioffrese -Cancer Research Award, Carlo Erba Foundation
 1994 Francesca e Ferdinando Quartero, Cancer Research Prize, Italian Cancer Association
 1994 VIII Mascia Brunelli-Award, Italian Cell Culture Association
 1991 Graduated with Honor and Distinction (*Laude, Menzione d'Onore*), University of Torino

Supervision of graduate students and postdoctoral fellows

2003-pres. n. 22 PhD Students
 2006-pres. n. 40 Graduate Students

2004-pres. n. 40 Postdoctoral fellows

Editorial boards

2020-pres. Editorial Board member, ESMO Journal Immuno-Oncology and Technology
2019-pres. Editorial Board member, Genome Medicine
2017-pres. Editorial Board member, Nature Reviews Clinical Oncology
2016-pres. Editorial Board member, Cancer Discovery
2014-pres. Editorial Board member, Molecular Oncology
2014-pres. Editorial Board member, Clinical Cancer Drugs
2013-pres. Editorial Board member, Cancer Treatment Reviews
2011-pres. Editorial Board member, BMC Gastroenterology
2010-pres. Executive Editors, Molecular Cancer
2007-pres. Editorial Board member, International Journal of Oncology

Reviewer

Science, Nature, Cancer Cell, Cancer Discovery, Cancer Research, Clinical Cancer Research, Science Signaling, Nature Medicine, The EMBO Journal, Proceedings Of The National Academy Of Sciences (PNAS), The Journal of Clinical Investigation, NEJM, Nature Cancer.

Commissions of trust

2024-pres. Member of the Executive Council of the School of Higher Studies Ferdinando Rossi of the University of Turin
2023-pres. Scientific Advisory Board member, Institute of Oncology Research (IOR), Bellinzona (Switzerland)
2022 TEFAF Oncology Chair and Visiting Professor in Oncology at the Faculty of Health, Medicine and Life Sciences / GROW school of Oncology and Reproduction, Maastricht (NL)
2021-pres. Scientific Advisory Board member, Onco Institute, Utrecht (The Netherlands)
2019-pres. The Johns Hopkins Society of Scholars, Baltimore (USA)
2018-pres. Scientific Advisory Board member, MD Anderson Moon Shots Program, Houston (USA)
2018-pres. Scientific Advisory Board member, Neophore, Cambridge (UK)
2018-2020 President, EACR (European Association for Cancer Research)
2017-pres. Scientific Advisory Board member, Cancer Research UK Manchester Institute, Manchester (UK)
2015-pres. Board Member, European Association for Cancer Research (EACR)
2013-pres. Scientific Committee, Pezcoller Foundation
2013-2023 Scientific Committee, AIRC (Italian Association for Cancer Research)
2012-pres. Director, Basic Research, Candiolo Cancer Institute, Candiolo (To), Italy
2008-pres. Scientific Advisory Board member, Horizon Discovery, Cambridge (UK)

C. Contributions to Science

After his undergraduate studies, Alberto Bardelli moved to the Ludwig Institute for Cancer Research in London where he obtained a Ph.D. in Biochemistry and Molecular biology from the University College London (UCL). He moved to the United States in 1999 for a post-doctoral fellowship in the laboratory directed by Bert Vogelstein at the Howard Hughes Medical Institute, Johns Hopkins University (Baltimore). Here, professor Bardelli began studying the genomics of cancer. One of his most significant publications from that period identified for the first-time mutations in kinase genes (the kinome) that are associated with colorectal cancer (1).

As an independent investigator, he pioneered the combined use of genomics, patients' avatars and liquid biopsy to accurately predict tumor response and resistance to targeted agents in patients. Bardelli's group discovered that *KRAS*-, *NRAS*- and *BRAF*-mutated colorectal cancer patients lack response to anti-EGFR antibodies (2, 3). His lab has systematically used genomic screens of CRC preclinical models to define new actionable targets in this tumor type. In the past ten years, the laboratory defined mutant *BRAF* (4), translocated *TRK* and *ALK* (5, 6), amplified *HER2*(7), and combinatorial inhibition of EGFR and mutant *KRAS* p.G12C (8) as clinically-validated targets in colorectal cancer. These findings led to clinical trials aimed at targeting deregulated *BRAF*, *NTRK*, and *HER2* in which Bardelli's unit was actively engaged. The HERACLES trial was a paradigmatic example of these activities (9).

His work also led the development of diagnostic tests, based on the pioneering use of liquid biopsies (10). He showed that the analysis of circulating tumor DNA (liquid biopsies) allows longitudinal monitoring of tumor evolution and resistance to targeted therapies. The Bardelli's lab was the first to pinpoint the emergence of *KRAS/NRAS* mutations in the blood of patients during EGFR blockade (11, 12). These discoveries represent the first example of personalized therapies for colorectal cancer patients (13, 14). Moreover, the efficacy of this promising approach in driving clinical decision-making for the treatment of colorectal cancer patients is currently being tested in the CHRONOS trial (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002597-12/IT>), where the Bardelli team has a pivotal role.

The hype generated by the so-called personalized oncology, based on the use of targeted therapies in molecularly stratified patient populations, was soon counteracted by the awareness that in nearly all patients, treatments are only transiently effective due to onset of secondary resistance. The Bardelli lab defined several mechanisms of acquired resistance, including elucidation of how CRC escape from EGFR, BRAF, TRK, and HER2 blockade. Genetic tracking of cancer cell populations showed how the development of resistance can be restrained *in vitro* and *in vivo*. For example, we recently reported that dependency on the WNT/APC/ β -catenin signaling axis, an ancestral CRC oncogenic event, is maintained through development of resistance to multiple targeted therapies. These results suggest the use of trunk mutations as targets to restrain, or possibly prevent, the emergence of resistance in CRC (15).

Again, liquid biopsies can be used to monitor clonal evolution and tumor heterogeneity, and to intercept the emergence of resistant clones non-invasively in patients (11). Recent studies from the Bardelli team demonstrated that analysis of ctDNA is able to detect heterogeneous mechanisms of resistance to targeted therapies in CRCs, and that this approach can be used for the longitudinal follow up of patients (11, 12, 16, 17). Specifically, we optimized technologies (double DNA barcoding) to analyze with high sensitivity plasma ctDNA thus revealing detailed molecular maps of resistance mechanisms (7).

Understanding how tumors evolve heterogeneous mechanisms of acquired resistance to targeted therapies is crucial in order to find effective strategies to prolong treatment efficacy and possibly prevent tumor relapse. Recently, the Bardelli Lab focused on the study of drug-tolerant persister cells, which are cancer cells that survive to targeted agents through non-genetic mechanisms, and maintain a reservoir from which genetic drivers of resistance eventually emerge (18). Inspired by the notion that bacteria exposed to antibiotics activate a stress response (called "adaptive mutability") that leads to increased mutagenesis, ultimately fueling antibiotic-resistance, the Bardelli lab discovered that colorectal cancer cells activate a similar response under therapeutic stress (18, 19). Indeed, in a recent study they reported that cancer cells treated with targeted therapies downmodulate several DNA repair mechanisms, and switch from a high-fidelity to an error-prone DNA replication system. This, in turn, creates a permissive *milieu* which leads to increased mutability, which has been observed both in cells and in patient-derived samples obtained during treatment with targeted agents (19).

Extensive efforts have been placed at developing drugs capable of restoring the function of tumor suppressor proteins in the hope that they could act as anticancer agents. Our data indicate that permanent inactivation (rather than reactivation) of certain tumor suppressors involved in DNA repair could instead be pursued for therapeutic purposes (20). Specifically, Bardelli's studies suggest that targeting genes involved in DNA mismatch repair pathway facilitates the acquisition of neoantigens. The latter can be recognized by the immune system and restrict cancer growth (20, 21). More recently, Bardelli lab pursued the interest on DNA repair mechanisms, focusing on pharmacological modulation of mismatch repair activity and its impact towards improving tumor immune surveillance and response to immunotherapy (22, 23).

References

1. Bardelli A, Parsons DW, Silliman N, Ptak J, Szabo S, Saha S, et al. Mutational analysis of the tyrosine kinome in colorectal cancers. *Science*. 2003;300(5621):949.
2. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, Zanon C, Moroni M, Veronese S, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. *Cancer Res*. 2007;67(6):2643-8.
3. Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol*. 2008;26(35):5705-12.
4. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature*. 2012;483(7387):100-3.
5. Medico E, Russo M, Picco G, Cancelliere C, Valtorta E, Corti G, et al. The molecular landscape of colorectal cancer cell lines unveils clinically actionable kinase targets. *Nature Communications*. 2015;6.
6. Russo M, Misale S, Wei G, Siravegna G, Crisafulli G, Lazzari L, et al. Acquired Resistance to the TRK Inhibitor Entrectinib in Colorectal Cancer. *Cancer Discov*. 2016;6(1):36-44.
7. Siravegna G, Lazzari L, Crisafulli G, Sartore-Bianchi A, Mussolin B, Cassingena A, et al. Radiologic and Genomic Evolution of Individual Metastases during HER2 Blockade in Colorectal Cancer. *Cancer Cell*. 2018;34(1):148-62.e7.
8. Amodio V, Yaeger R, Arcella P, Cancelliere C, Lamba S, Lorenzato A, et al. EGFR Blockade Reverts Resistance to KRAS. *Cancer Discov*. 2020;10(8):1129-39.
9. Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(6):738-46.
10. Diaz LA, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol*. 2014;32(6):579-86.
11. Misale S, Yaeger R, Hobor S, Scala E, Janakiraman M, Liska D, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature*. 2012;486(7404):532-6.
12. Siravegna G, Mussolin B, Buscarino M, Corti G, Cassingena A, Crisafulli G, et al. Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients. *Nat Med*. 2015.
13. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol*. 2017;14(9):531-48.
14. Di Nicolantonio F, Vitiello PP, Marsoni S, Siena S, Tabernero J, Trusolino L, et al. Precision oncology in metastatic colorectal cancer - from biology to medicine. *Nat Rev Clin Oncol*. 2021;18(8):506-25.
15. Russo M, Lamba S, Lorenzato A, Sogari A, Corti G, Rospo G, et al. Reliance upon ancestral mutations is maintained in colorectal cancers that heterogeneously evolve during targeted therapies. *Nature Communications*. 2018;9(1):2287.
16. Van Emburgh BO, Arena S, Siravegna G, Lazzari L, Crisafulli G, Corti G, et al. Acquired RAS or EGFR mutations and duration of response to EGFR blockade in colorectal cancer. *Nat Commun*. 2016;7:13665.
17. Russo M, Siravegna G, Blaszkowsky LS, Corti G, Crisafulli G, Ahronian LG, et al. Tumor Heterogeneity and Lesion-Specific Response to Targeted Therapy in Colorectal Cancer. *Cancer Discov*. 2016;6(2):147-53.
18. Russo M, Sogari A, Bardelli A. Adaptive Evolution: How Bacteria and Cancer Cells Survive Stressful Conditions and Drug Treatment. *Cancer Discov*. 2021;11(8):1886-95.
19. Russo M, Crisafulli G, Sogari A, Reilly NM, Arena S, Lamba S, et al. Adaptive mutability of colorectal cancers in response to targeted therapies. *Science*. 2019;366(6472):1473-80.
20. Germano G, Lamba S, Rospo G, Barault L, Magri A, Maione F, et al. Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. *Nature*. 2017;552(7683):116-20.
21. Germano G, Lu S, Rospo G, Lamba S, Rousseau B, Fanelli S, et al. CD4 T Cell-Dependent Rejection of Beta-2 Microglobulin Null Mismatch Repair-Deficient Tumors. *Cancer Discov*. 2021;11(7):1844-59.
22. Crisafulli G, Sartore-Bianchi A, Lazzari L, Pietrantonio F, Amatu A, Macagno M, et al. Temozolomide Treatment Alters Mismatch Repair and Boosts Mutational Burden in Tumor and Blood of Colorectal Cancer Patients. *Cancer Discov*. 2022;12(7):1656-75.
23. Amodio V, Lamba S, Chila R, Cattaneo CM, Mussolin B, Corti G, et al. Genetic and pharmacological modulation of DNA mismatch repair heterogeneous tumors promotes immune surveillance. *Cancer Cell*. 2023;41(1):196-209 e5.