

Curriculum vitae Claudio Isella

Personal details

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Educations

2008: Doctor of Philosophy: Complex System applied to post genomic biology. University of Turin, Italy. Supervisor: Prof. Enzo Medico.

2005: Master Degree in Molecular Biotechnology. 110/110 cum Laude. University of Turin, Italy. Supervisor: Prof. Enzo Medico. -D.M.509/199

Professional experiences and current position

01/03/2023 – Present – Associate professor, Department of Oncology, University of Turin.

01/03/2020 – 28/02/2023 - Fixed-term Researcher type B, Department of Oncology, University of Turin.

06/01/2018 - 02/28/2020 - Collaboration contract: "Global evaluation of the stromal contribution to the progression and response to treatments of colorectal and mesenchymal tumors." Candiolo Institute, FPO.

04/01/2018 - 05/31/2018 - Research fellow: "Development of a public data portal for the European collection of patient-derived xenografts from the EDIReX project." Department of Oncology - University of Turin.

04/01/2017 - 01/31/2018 - Research fellow: "Systematic study of tumor-stroma interactions through transcriptomic analysis of preclinical models of colorectal carcinoma." Department of Oncology - University of Turin.

04/01/2016 - 03/31/2017 - Research fellow: "Study of tumor-stroma interaction mechanisms through transcriptomic analysis of preclinical models of colorectal carcinoma." Department of Oncology - University of Turin.

03/01/2015 - 03/31/2016 - Collaboration contract: "AIRC 5 2010 special program molecular clinical oncology 5 per mille coordinator Paolo Maria Comoglio" - AIRC - Piedmont Foundation for Cancer Research.

05/01/2014 - 02/28/2015 - Research fellow: "Mechanisms of resistance to anti-angiogenic therapy: bioinformatic analysis of expression data." Department of Oncology - University of Turin.

11/01/2013 - 04/30/2014 - Research fellow: "Regulatory circuits between stroma and tumor, an integrated system approach to improve knowledge of neoplastic progression mechanisms and response to target drugs." Department of Oncology - University of Turin.

02/01/2013 - 10/31/2013 - Research fellow: "E-lab: Miniaturized laboratory for early diagnosis of colon rectal cancer." Department of Oncology - University of Turin.

02/01/2012 - 01/31/2013 - Research fellow: "Large-scale functional screening for tumor transformation and progression." Department of Oncology - University of Turin.

02/01/2011 - 01/01/2012 - Research fellow: "Large-scale functional screening for tumor transformation and progression." Department of Oncology - University of Turin.

01/01/2010 - 01/31/2011 - Extension of project contract: "Large-scale functional screening for tumor transformation and progression" at the Piedmont Foundation for Cancer Research.

06/01/2009 - 12/31/2010 - Project contract: "Large-scale functional screening for tumor transformation and progression" at the Piedmont Foundation for Cancer Research.

02/01/2008 - 05/31/2009 - Conclusion of the scholarship funded by CINECA for the development of an integrated genomic platform at the Italian level. Activities carried out at the Oncogenomics Laboratory of the Candiolo Institute, Department of Oncological Sciences, University of Turin, Italy. Supervisor: Prof. Enzo Medico.

Participation to Directive Boards of Scientific Societies and/or Institutions:

Honors

- IRCC Intramural Award for Scientific Productivity 2010.
- AACR Training award 2015
- BITS travel grant 2016

Teaching activity:

- Holder of the Histology course, 2020/2021, Bachelor's Degree in Biotechnology, University of Turin, lectures and final exams.
- Holder of the Histology course, 2019/2020, Bachelor's Degree in Biotechnology, University of Turin, lectures and final exams.
- Holder of the Histology course, 2019/2020, Bachelor's Degree in Nursing, University of Turin, lectures and final exams.
- Complementary teaching activity, 2018/2019, histology module of biomedical sciences, Bachelor's Degree in Dental Hygiene, University of Turin, lectures and final exams.
- Member of the Teaching Board, PhD program in "Complex Systems for Quantitative Biomedicine", University of Turin from the academic year 2021-22.
- Laboratory supervision for three PhD students, University of Turin.
- *Co-tutoring, Master's Degree students at the University of Turin: 1 in Molecular Biology, 4 in Medical Biotechnology, 2 in Molecular Biotechnology.*

Research main topics

Over the past 15 years I have been interested in developing multidisciplinary approaches to the study of cancer biology. At the moment my research activity mainly focuses on the study of colorectal cancer, covering the role of both project manager and collaborator. During my master thesis, I acquired the genomics skills necessary to manage and interpret large-scale data (both at the DNA and RNA level), integrating standardized methodologies with original approaches aimed at resolving clinical and biological issues. (Can Disc 2011, PMID: 22586653; BMC Genomics 2008, PMID: 18510758; Can Res 2013 BMC Bioinformatics 2011, PMID: 21955789;). Working in the field of oncogenomics, I developed awareness of the challenges in the field of research and clinical practice. Thanks to those experiences, I joined collaborative activities and developed projects conducted in first person. In these projects I have applied genomic methods aimed at discovering agents of tumor aggressiveness and mechanisms of sensitivity and resistance to therapies. (Oncogene 2009, PMID: 19838208; Can Res 2007, PMID: 17875685; JBC 2009, PMID: 19561079; Clin Exp Met 2009, PMID: 19340593). In particular, I have investigated the study of signaling pathways involved in transcriptional control mediated by transcription factors and non-coding RNA, in activities carried out independently of my mentor. (Clin Cancer Res 2011, PMID: 22179665, Mol Onc 2015, PMID: 25306394, J Clin Invest 2018, PMID: 29953416; BMC Cancer 2018 PMID: 29970021; Mol Cancer Ther. PubMed PMID: 29483217.). These work have highlighted biological programs of sensitivity and resistance to targeted therapies that lay the foundations for therapeutic repositioning strategies rather than the development of innovative strategies aimed at cell signaling pathways and previously unexplored paracrine

mechanisms in solid tumors. Working with clinicians, I acquired applied bio-statistical skills. (Ann Surg 2011, PMID: 23665971; Clin Cancer Res 2011, PMID: 21447729; Nat Comm 2015, 6: 8878; Gut 2015, PMID: 25804630).

I recently developed a new integrated transcriptomics approach to colorectal cancer to investigate new tumor subtypes, and in particular to demonstrate the contribution of the stromal components. Specifically, it was possible to generate molecular signatures able to trace various mesenchymal cellular components in solid tumors, such as fibroblasts, endothelial cells and leukocytes and to associate a correlation with an ineffectual course of the disease. (Nat Jan 2015, PMID: 2570,627; Nat Comm 2017, PMID: 25926053). These studies have introduced the concept of "stromophilous" tumor, a subgroup of patients associated with an extreme aggressive pathology, characterized by a specific histological architecture, with a high dosage of stromal cells. These results have generated great excitement in the sector and are hesitated in various commentary work. (Nature Gen 2015, PMID: 25814306, Nature Rev Clin Oncol, 2015 PMID: 25781571, Nature 2015, PMID: 26343385, Nature Review 2017, PMID: 28050011). In parallel, for several years I have been part of my activities in the frame of Genobitus, an initiative wanted by the University of Turin with the aim of spreading genomics skills in the University's projects.

Main projects as PI

- 2020 – present: Project Manager for an animal experimentation project authorized by the Ministry of Health entitled "Identification of new therapies inhibiting tumor-stroma interaction in Colorectal Carcinoma." Number 21635.34. Ministerial Authorization No. 107/2021-PR of February 10, 2021.
 - 2017-2019: Italian Association for Cancer Research - My First AIRC Investigator Grant 18047 - Systematic assessment of stromal contribution to colorectal cancer progression and response to treatment - Principal Investigator -
 - 2018-2023: Ministry of Health - Finalized Research, young researchers - Systematic assessment of stromal contribution to progression and response to treatment in colorectal cancers (CRCs) and mesenchymal tumors (MTs) - Principal Investigator - Collaboration
 - 11/02/2018 - 31/01/2022: EDIRex: EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts
 - 31/12/2015 - 30/12/2018: Characterization and preclinical therapeutic validation of low-prevalence oncogenic drivers in colorectal cancer
 - 31/12/2012 - 30/12/2015: Targeting the NEDD8 pathway for colorectal cancer treatment
 - 21/11/2010 - 31/10/2013: E-LAB: Miniaturized laboratory for early diagnosis of colon-rectal cancer
 - 31/07/2010 - 31/12/2017: Targeting resistances to molecular therapies in metastatic colorectal carcinomas.
 - 31/12/2009 - 30/12/2012: Integrative functional genomics of cancer progression and response to targeted treatments
- 2004-2009: A Center for Functional Genomics of Cancer Progression.

Bibliometry (2007-present) (www.scopus.com)

10 best publications

1. Bertotti A, Migliardi G, Galimi F, Sassi F, Torti D, Isella C, Corà D, Di Nicolantonio F, Buscarino M, Petti C, Ribero D, Russolillo N, Muratore A, Massucco P, Pisacane A, Molinaro L, Valtorta E, Sartore-Bianchi A, Risio M, Capussotti L, Gambacorta M, Siena S, Medico E, Sapino A, Marsoni S, Comoglio PM, Bardelli A, Trusolino L. A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective

- therapeutic target in cetuximab-resistant colorectal cancer *Cancer Discov* 2011 10.1158/2159-8290.CD-11-0109
2. Isella C, Renzulli T, Corà D, Medico E. Mulcom: a multiple comparison statistical test for microarray data in Bioconductor *BMC Bioinformatics* 2011 10.1186/1471-2105-12-382
 3. Ling H, Pickard K, Ivan C, Isella C, Ikuo M, Mitter R, Spizzo R, Bullock M, Braicu C, Pileczki V, Vincent K, Pichler M, Stiegelbauer V, Hoefler G, Almeida MI, Hsiao A, Zhang X, Primrose J, Packham G, Liu K, Bojja K, Gafà R, Xiao L, Rossi S, Song JH, Vannini I, Fanini F, Kopetz S, Zweidler-McKay P, Wang X, Ionescu C, Irimie A, Fabbri M, Lanza G, Hamilton SR, Berindan-Neagoe I, Medico E, Mirnezami A, Calin GA, Nicoloso MS. The clinical and biological significance of MIR-224 expression in colorectal cancer metastasis *Gut* 2016 10.1136/gutjnl-2015-309372
 4. Zanella ER, Galimi F, Sassi F, Migliardi G, Cottino F, Leto SM, Lupo B, Erriquez J, Isella C, Comoglio PM, Medico E, Tejpar S, Budinská E, Trusolino L, Bertotti A. IGF2 is an actionable target that identifies a distinct subpopulation of colorectal cancer patients with marginal response to anti-EGFR therapies *Sci Transl Med* 2015 10.1126/scitranslmed.3010445
 5. Isella C, Terrasi A, Bellomo SE, Petti C, Galatola G, Muratore A, Mellano A, Senetta R, Cassenti A, Sonetto C, Inghirami G, Trusolino L, Fekete Z, De Ridder M, Cassoni P, Storme G, Bertotti A, Medico E. Stromal contribution to the colorectal cancer transcriptome *Nat Genet* 2015 10.1038/ng.3224
 6. Isella C, Brundu F, Bellomo SE, Galimi F, Zanella E, Porporato R, Petti C, Fiori A, Orzan F, Senetta R, Boccaccio C, Ficarra E, Marchionni L, Trusolino L, Medico E, Bertotti A. Selective analysis of cancer-cell intrinsic transcriptional traits defines novel clinically relevant subtypes of colorectal cancer *Nat Commun* 2017 10.1038/ncomms15107
 7. Sebastian C, Ferrer C, Serra M, Choi JE, Ducano N, Mira A, Shah MS, Stopka SA, Perciaccante AJ, Isella C, Moya-Rull D, Vara-Messler M, Giordano S, Maldí E, Desai N, Capen DE, Medico E, Cetinbas M, Sadreyev RI, Brown D, Rivera MN, Sapino A, Breault DT, Agar NYR, Mostoslavsky R. A non-dividing cell population with high pyruvate dehydrogenase kinase activity regulates metabolic heterogeneity and tumorigenesis in the intestine *Nat Commun* 2022 10.1038/s41467-022-29085-y
 8. Woo XY, Giordano J, Srivastava A, Zhao ZM, Lloyd MW, de Bruijn R, Suh YS, Patidar R, Chen L, Scherer S, Bailey MH, Yang CH, Cortes-Sanchez E, Xi Y, Wang J, Wickramasinghe J, Kossenkov AV, Rebecca VW, Sun H, Mashl RJ, Davies SR, Jeon R, Frech C, Randjelovic J, Rosains J, Galimi F, Bertotti A, Lafferty A, O'Farrell AC, Modave E, Lambrechts D, Ter Brugge P, Serra V, Marangoni E, El Botty R, Kim H, Kim JI, Yang HK, Lee C, Dean DA 2nd, Davis-Dusenbery B, Evrard YA, Doroshow JH, Welm AL, Welm BE, Lewis MT, Fang B, Roth JA, Meric-Bernstam F, Herlyn M, Davies MA, Ding L, Li S, Govindan R, Isella C, Moscow JA, Trusolino L, Byrne AT, Jonkers J, Bult CJ, Medico E, Chuang JH; PDXNET Consortium; EurOPDX Consortium. Conservation of copy number profiles during engraftment and passaging of patient-derived cancer xenografts *Nat Genet* 2021 10.1038/s41588-020-00750-6
 9. Lupo B, Sassi F, Pinnelli M, Galimi F, Zanella ER, Vurchio V, Migliardi G, Gagliardi PA, Puliafito A, Manganaro D, Luraghi P, Kragh M, Pedersen MW, Horak ID, Boccaccio C, Medico E, Primo L, Nichol D, Spiteri I, Heide T, Vatsiou A, Graham TA, Élez E, Argiles G, Nuciforo P, Sottoriva A, Dienstmann R, Pasini D, Grassi E, Isella C, Bertotti A, Trusolino L. Colorectal cancer residual disease at maximal response to EGFR blockade displays a druggable Paneth cell-like phenotype *Sci Transl Med* 2020 10.1126/scitranslmed.aax8313
 10. Isella C, Vaira M, Robella M, Bellomo SE, Picco G, Borsano A, Mignone A, Petti C, Porporato R, Ulla AA, Pisacane A, Sapino A, Simone M, Medico E. Improved Outcome Prediction for Appendiceal Pseudomyxoma Peritonei by

15 more relevant publication in the last 5 yrs (2018-2022)

1. Isella C, Vaira M, Robella M, Bellomo SE, Picco G, Borsano A, Mignone A, Petti C, Porporato R, Ulla AA, Pisacane A, Sapino A, Simone M, Medico E. Improved Outcome Prediction for Appendiceal Pseudomyxoma Peritonei by Integration of Cancer Cell and Stromal Transcriptional Profiles Cancers (Basel) 2020 10.3390/cancers12061495
2. Luraghi P, Bigatto V, Cipriano E, Reato G, Orzan F, Sassi F, De Bacco F, Isella C, Bellomo SE, Medico E, Comoglio PM, Bertotti A, Trusolino L, Boccaccio C. A Molecularly Annotated Model of Patient-Derived Colon Cancer Stem-Like Cells to Assess Genetic and Nongenetic Mechanisms of Resistance to Anti-EGFR Therapy Clin Cancer Res 2018 10.1158/1078-0432.CCR-17-2151
3. Lazzari L, Corti G, Picco G, Isella C, Montone M, Arcella P, Durinikova E, Zanella ER, Novara L, Barbosa F, Cassingena A, Cancelliere C, Medico E, Sartore-Bianchi A, Siena S, Garnett MJ, Bertotti A, Trusolino L, Di Nicolantonio F, Linnebacher M, Bardelli A, Arena S. Patient-Derived Xenografts and Matched Cell Lines Identify Pharmacogenomic Vulnerabilities in Colorectal Cancer Clin Cancer Res 2019 10.1158/1078-0432.CCR-18-3440
4. Arena S, Corti G, Durinikova E, Montone M, Reilly NM, Russo M, Lorenzato A, Arcella P, Lazzari L, Rospo G, Pagani M, Cancelliere C, Negrino C, Isella C, Bartolini A, Cassingena A, Amatu A, Mauri G, Sartore-Bianchi A, Mittica G, Medico E, Marsoni S, Linnebacher M, Abrignani S, Siena S, Di Nicolantonio F, Bardelli A. A Subset of Colorectal Cancers with Cross-Sensitivity to Olaparib and Oxaliplatin Clin Cancer Res 2020 10.1158/1078-0432.CCR-19-2409
5. Lafferty A, O'Farrell AC, Migliardi G, Khemka N, Lindner AU, Sassi F, Zanella ER, Salvucci M, Vanderheyden E, Modave E, Boeckx B, Halang L, Betge J, Ebert MPA, Dicker P, Argilés G, Tabernero J, Dienstmann R, Medico E, Lambrechts D, Bertotti A, Isella C, Trusolino L, Prehn JHM, Byrne AT. Molecular Subtyping Combined with Biological Pathway Analyses to Study Regorafenib Response in Clinically Relevant Mouse Models of Colorectal Cancer Clin Cancer Res 2021 10.1158/1078-0432.CCR-21-0818
6. Rospo G, Lorenzato A, Amirouchene-Angelozzi N, Magrì A, Cancelliere C, Corti G, Negrino C, Amodio V, Montone M, Bartolini A, Barault L, Novara L, Isella C, Medico E, Bertotti A, Trusolino L, Germano G, Di Nicolantonio F, Bardelli A. Evolving neoantigen profiles in colorectal cancers with DNA repair defects Genome Med 2019 10.1186/s13073-019-0654-6
7. Rizzolio S, Cagnoni G, Battistini C, Bonelli S, Isella C, Van Ginderachter JA, Bernards R, Di Nicolantonio F, Giordano S, Tamagnone L. Neuropilin-1 upregulation elicits adaptive resistance to oncogene-targeted therapies J Clin Invest 2018 10.1172/JCI99257
8. Alderdice M, Richman SD, Gollins S, Stewart JP, Hurt C, Adams R, McCorry AM, Roddy AC, Vimalachandran D, Isella C, Medico E, Maughan T, McArt DG, Lawler M, Dunne PD. Prospective patient stratification into robust cancer-cell intrinsic subtypes from colorectal cancer biopsies J Pathol 2018 10.1002/path.5051
9. Orzan F, Pagani F, Cominelli M, Triggiani L, Calza S, De Bacco F, Medicina D, Balzarini P, Panciani PP, Liserre R, Buglione M, Fontanella MM, Medico E, Galli R, Isella C, Boccaccio C, Poliani PL; on behalf of the Neuro-Oncology group of Spedali Civili of Brescia. A simplified integrated molecular and immunohistochemistry-based algorithm allows high accuracy prediction of glioblastoma transcriptional subtypes Lab Invest 2020 10.1038/s41374-020-0437-0

10. Sebastian C, Ferrer C, Serra M, Choi JE, Ducano N, Mira A, Shah MS, Stopka SA, Perciaccante AJ, Isella C, Moya-Rull D, Vara-Messler M, Giordano S, Maldi E, Desai N, Capen DE, Medico E, Cetinbas M, Sadreyev RI, Brown D, Rivera MN, Sapino A, Breault DT, Agar NYR, Mostoslavsky R. A non-dividing cell population with high pyruvate dehydrogenase kinase activity regulates metabolic heterogeneity and tumorigenesis in the intestine *Nat Commun* 2022 10.1038/s41467-022-29085-y
11. Woo XY, Giordano J, Srivastava A, Zhao ZM, Lloyd MW, de Bruijn R, Suh YS, Patidar R, Chen L, Scherer S, Bailey MH, Yang CH, Cortes-Sanchez E, Xi Y, Wang J, Wickramasinghe J, Kossenkov AV, Rebecca VW, Sun H, Mashl RJ, Davies SR, Jeon R, Frech C, Randjelovic J, Rosains J, Galimi F, Bertotti A, Lafferty A, O'Farrell AC, Modave E, Lambrechts D, Ter Brugge P, Serra V, Marangoni E, El Botty R, Kim H, Kim JI, Yang HK, Lee C, Dean DA 2nd, Davis-Dusenbery B, Evrard YA, Doroshow JH, Welm AL, Welm BE, Lewis MT, Fang B, Roth JA, Meric-Bernstam F, Herlyn M, Davies MA, Ding L, Li S, Govindan R, Isella C, Moscow JA, Trusolino L, Byrne AT, Jonkers J, Bult CJ, Medico E, Chuang JH; PDXNET Consortium; EurOPDX Consortium. Conservation of copy number profiles during engraftment and passaging of patient-derived cancer xenografts *Nat Genet* 2021 10.1038/s41588-020-00750-6
12. Lupo B, Sassi F, Pinnelli M, Galimi F, Zanella ER, Vurchio V, Migliardi G, Gagliardi PA, Puliafito A, Manganaro D, Luraghi P, Kragh M, Pedersen MW, Horak ID, Boccaccio C, Medico E, Primo L, Nichol D, Spiteri I, Heide T, Vatsiou A, Graham TA, Élez E, Argiles G, Nuciforo P, Sottoriva A, Dienstmann R, Pasini D, Grassi E, Isella C, Bertotti A, Trusolino L. Colorectal cancer residual disease at maximal response to EGFR blockade displays a druggable Paneth cell-like phenotype *Sci Transl Med* 2020 10.1126/scitranslmed.aax8313
13. Miller IS, Khan S, Shiels LP, Das S, O' Farrell AC, Connor K, Lafferty A, Moran B, Isella C, Loadman P, Conroy E, Cohrs S, Schibli R, Kerbel RS, Gallagher WM, Marangoni E, Bennett K, O' Connor DP, Dwyer RM, Byrne AT. Implementing subtype-specific pre-clinical models of breast cancer to study pre-treatment aspirin effects *Cancer Med* 2022 10.1002/cam4.4756
14. Avanzato D, Pupo E, Ducano N, Isella C, Bertalot G, Luise C, Pece S, Bruna A, Rueda OM, Caldas C, Di Fiore PP, Sapino A, Lanzetti L. High USP6NL Levels in Breast Cancer Sustain Chronic AKT Phosphorylation and GLUT1 Stability Fueling Aerobic Glycolysis *Cancer Res* 2018 10.1158/0008-5472.CAN-17-3018
15. Corso S, Isella C, Bellomo SE, Apicella M, Durando S, Migliore C, Ughetto S, D'Errico L, Menegon S, Moya-Rull D, Cargnelutti M, Capelôa T, Conticelli D, Giordano J, Venesio T, Balsamo A, Marchiò C, Degiuli M, Reddavid R, Fumagalli U, De Pascale S, Sgroi G, Rausa E, Baiocchi GL, Molfino S, Pietrantonio F, Morano F, Siena S, Sartore-Bianchi A, Bencivenga M, Mengardo V, Rosati R, Marrelli D, Morgagni P, Rausei S, Pallabazzer G, De Simone M, Ribero D, Marsoni S, Sottile A, Medico E, Cassoni P, Sapino A, Pectasides E, Thorner AR, Nag A, Drinan SD, Wollison BM, Bass AJ, Giordano S. A Comprehensive PDX Gastric Cancer Collection Captures Cancer Cell-Intrinsic Transcriptional MSI Traits *Cancer Res* 2019 10.1158/0008-5472.CAN-19-1166