Curriculum vitae

Silvia Giordano

Personal details

Born in: Torino
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Educations

Oct 1990/ Jul 1993 Hematologist - Hematology Università degli Studi di Modena e Reggio Emilia, Modena Italy
Oct 1988/ Jul 1991 PhD in Morphogenetic and Cytological Sciences - "La Sapienza", Roma Italy
Oct 1979/ Jul 1985 MD, summa cum laude and special award - The src oncogene Università degli Studi di Torino, Torino Italy

Professional experiences and current position

Oct 2007/ now Full Professor Università degli Studi di Torino (Torino Italy) and Director of the Cancer Molecular Biology Laboratory at the IRCCs, Candiolo (Torino)
Oct 2001/ Jul 2007 Associate Professor Università degli Studi di Torino - Torino Italy
Oct 1990/ Oct 2001 Research Assistant Università degli Studi di Torino - Torino Italy
Oct 1988/ Jul 1991 PhD Student Università degli Studi di Roma "La Sapienza" - Roma Italy
Feb 1988/ Oct 1988 Visiting fellow National Cancer Institute - NCI - Frederick, Maryland United States of America
Jan 1985/ Jan 1987 AIRC fellow Università degli Studi di Torino - Torino Italy
Jan 1980/ Jul 1985 Graduate student Università degli Studi di Torino - Torino Italy

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

Feb 2022/ today, Member of Italian Supreme Court of Health, Ministry of Health
2004 – 2013; 2019-today Member of the scientific board of AIRC
2014 - 2018 President of the Italian Society of Cancerology
2014 – 2018 Member of EACR Advisory Council
Consultant for Petzcoller Foundation

2010-2014 Member of the Nucleo di Valutazione, University of Torino
2022- today AQ delegate for the Oncology Dept.

Honors

2009 Francesco de Luca International Prize, for a MD doing cancer research, awarded by Accademia Nazionale dei Lincei.

Teaching activity:

Teaching activity since 1986
1986-1990 Anatomy at “scuola di tecniche di radiologia medica” (Torino)
1994 Neuro-Anatomy at “scuola di tecniche di radiologia medica” (Chieti)
1986-2017 Histology and Embriology at Scuola di Medicina, Ospedale San Luigi, Orbassano (Torino)
2013-2015 Histology at Scienze Infermieristiche (Cuneo)
2015-2022 Histology at Scienze Infermieristiche, (Torino)
2017-2022 Histology at Tecnici della riabilitazione psichiatrica
2017-2021 Molecular Oncology at Scuola di Medicina, Ospedale San Luigi, Orbassano (Torino)
2017- today Histology at Medicine and Surgery, Ospedale San Luigi, Orbassano (Torino)

2017- today Embriology at Medicine and Surgery, Ospedale San Luigi, Orbassano (Torino)
Teaching at Specialization schools of Oncology and cardiology

Research main topics

Silvia Giordano has an established record in the field of cancer where she focused on signal transduction, with a progressive shift from basic cancer research to translational oncology.

Her major accomplishments include:

- Identification and biochemical/biological characterization of the tyrosine kinase encoded by the MET gene: (i) determination of the structure of the receptor and identification of its constitutive activation in human cells (Giordano, Nature, 1989); (ii) study of its biosynthesis and post-translational modifications (Giordano, Oncogene, 1989) and of the mechanism of signal transduction (Ponzetto, Cell, 1994); (iii) characterization of the biological activities promoted by the activation of the MET receptor (Giordano, PNAS, 1993).; (iv) documentation of MET overexpression in primary tumors and gene amplification in secondary lesions (Di Renzo, Clin. Cancer Res, 1995); (v) study of the biochemical and biological properties of constitutively active mutant forms of MET, identified in patients with Hereditary Renal Papillary Carcinoma (Giordano, FASEB, 2000; Michieli, Oncogene 1999; Bardelli, PNAS, 1998); (vi) identification of MET addiction in tumors with MET constitutive activation (Corso, Oncogene, 2008); (vii) identification of a new mechanism that controls receptor degradation (Petrelli, Nature, 2002; Foveau, Mol. Cell. Biol, 2009; Ancot, Traffic, 2012). These studies have laid the groundwork to identify structural and functional alterations of this receptor, have helped to demonstrate an altered regulation of the MET gene in different types of human tumors and have identified MET as a therapeutic target.
- Identification of ligand-independent mechanisms of MET activation: activation due to interaction with Plexins (membrane receptors devoid of tyrosine kinase activity); the role of this mechanism in cancer cells (Giordano, Nature Cell Biol., 2002; Barberis, Faseb J., 2004; Artigiani, EMBO. Rep., 2004; Conrotto, Oncogene, 2004); pro-angiogenic role of Plexin-mediated MET activation (Conrotto, Blood, 2005; Sierra, J. Exp. Med., 2008). These studies have identified a new mode of MET activation and imply that MET inhibition may have both a direct antineoplastic effect in tumor cells and an anti-angiogenic effect in endothelial cells.
- Identification of molecular lesions involved in the early phases of hepatocellular carcinoma development (Kowalik, Hepatology, 2011; Petrelli, Oncogene, 2012 and Hepatology 2014; Perra, J. Hepatology, 2014; Frau, Hepatology, 2015; Zavattari, Hepatology, 2015; Kowalik, Oncotarget, 2015,2016; Mattu, J Hepatology, 2016; Orru, Cancers, 2020; Kowalik, J Hepatol. 2020; Mattu, Cell Mol Gastroeterol Hepatol, 2022). These papers have identified the role of genes and microRNAs in the onset of human and experimental HCCs, highlighting new therapeutic targets.
- Identification of mechanisms of resistance to targeted therapies directed toward tyrosine kinases: role of activation of members of the EGFR receptor family, and of MET and KRAS amplification in resistance to MET inhibitors (Apicella, Oncogene, 2016; Martin, Mol. Onc. 2014; Corso, Mol Cancer, 2010; Cepero, Cancer Res, 2010; Apicella, Cell Metabolism, 2018; Migliore, EMBO Mol Med. 2018); role of MET amplification in resistance to EGFR inhibitors (Bardelli, Cancer Discovery, 2013); Mechanisms of resistance to FGFR2 inhibition in cholangiocarcinoma (Cristinziano, J. Hepatology, 2021). These studies can help in preventing the onset of resistance and, in the case of colon cancer patients with MET-driven acquired resistance and of gastric cancer patients with MET amplification, can offer patients new therapeutic options.
- Generation of a gastric cancer Patient-derived Xenograft platform and identification of new molecular targets (Apicella, Oncogene, 2017; Pietrantonio, Clin. Cancer Res, 2018; Corso, Neoplasia, 2018; Corso, Cancer Res, 2019, 2021; Ughetto, Gastric Cancer, 2021,

Pietrantonio, Clinical Cancer Research 2022; Chiriaco, J. Exp Clin Rearch, 2022; Petrelli, Cancer Research, 2023).

Main projects as PI:

The postulate of precision oncology is to exploit treatments targeting the molecular characteristics of a specific tumour. At present, only around 5-10% of cancer patients can benefit from targeted therapies. Delivering the right drug to the right cancer patient requires a detailed understanding of how genomic alterations are coupled to drug response. Thus, to improve the value of a target therapy it is mandatory to molecularly annotate tumors, to properly select patients that could benefit from that therapy, to validate the real biological relevance of the identified targets in a specific tumor type and to identify molecular alterations that could affect the responsiveness to treatment.
Targeted therapies licenced to treat GC are restricted to Trastuzumab and its derivative Trastuzumab deruxtecan, Ramucirumab and nivolumab or pembrolizumab. Most of the clinical trials performed during the last years in GC patients to identify new targets and to test new drugs failed. The reason for this failure, in many cases, can be ascribed to the lack of proper patient selection and/or to the inadequacy of robust preclinical data.
These considerations imply that, before going to clinic, we need a better knowledge of the genomic environment associated to each oncogenic driver and necessitate predictive biomarkers to better select patients.
The acute need for new therapeutic options and the possible presence of 'druggable' targets prompted us to investigate and validate potential targeted therapies for GC, in order to implement patient selection and improve treatment.
We aim to:
1) Prospectively evaluate the therapeutic efficacy of HER2 inhibitors to improve the effectiveness of HER2 blockade;
2) Evaluate EGFR as a therapeutic target in a subgroup of GC patients;
3) fight drug-resistance through targeting of persister cancer cells;
4) investigate genetic dependencies guiding response to PARP1 inhibitors;
5) explore cell-autonomous sensitivity to chemotherapy of microsatellite instable (MSI) vs microsatellite stable (MSS) GC cells;
6) dissect intratumor mismatch repair (MMR) heterogeneity in GC.
For our project we will take advantage from a proprietary, molecularly annotated platform of 250 GC Patient-Derived Xenografts (PDXs) and in vitro-derived material.
We will perform in vitro experiments and in vivo preclinical trials on selected PDXs and validate our results in patients enrolled in clinical trials.
We expect to get results that could lead to practice changing trials and improve the treatment of subgroups of GC patients.

Bibliometry (*www.scopus.com*)
HI 67
Publications 156
Total IF 2160,808; average 13.9
Citations 15256

10 best publications

S. Giordano, et al., TYROSINE KINASE RECEPTOR INDISTINGUISHABLE FROM THE *c-Met* PROTEIN. Nature, 339, 155-156, 1989.
C. Ponzetto, et al., A MULTIFUNCTIONAL DOCKING SITE MEDIATES SIGNALING AND TRANSFORMATION BY THE HEPATOCYTE GROWTH FACTOR / SCATTER FACTOR RECEPTOR FAMILY. Cell, 77, 261-271, 1994
Petrelli A., et al., THE ENDOPHILIN/CIN85/CBL COMPLEX MEDIATES LIGAND-DEPENDENT HEPATOCYTE GROWTH FACTOR RECEPTOR DOWN-REGULATION Nature, 416: 187-190, 2002
Carrolo M, et al., HEPATOCYTE GROWTH FACTOR AND ITS RECEPTOR ARE REQUIRED FOR MALARIA INFECTION. Nature Medicine. 11:1363-9, 2003

Pennacchietti S., et al., HYPOXIA PROMOTES INVASIVE GROWTH BY TRANSCRIPTIONAL ACTIVATION OF THE MET PROTO-ONCOGENE. Cancer Cell, 3: 347-361, 2003
Comoglio PM., S.Giordano, L.Trusolino. DRUG DEVELOPMENT OF MET INHIBITORS: TARGETING ONCOGENE ADDICTION AND EXPEDIENCE Nature Reviews Drug Discovery, 7:504-516, 2008
Corso S, et al., ACTIVATION OF HER FAMILY MEMBERS IN GASTRIC CARCINOMA CELLS MEDIATES RESISTANCE TO MET INHIBITION, Mol Cancer. 26;9:121, 2010
Bardelli A, et al., AMPLIFICATION OF THE MET RECEPTOR DRIVES RESISTANCE TO ANTI-EGFR THERAPIES IN COLORECTAL CANCER. Cancer Discovery, 3(6):658-73, 2013
Corso S. Giordano S. CELL-AUTONOMOUS AND NON-CELL-AUTONOMOUS MECHANISMS OF HGF/MET-DRIVEN RESISTANCE TO TARGETED THERAPIES: FROM BASIC RESEARCH TO A CLINICAL PERSPECTIVE. Cancer Discov. 3(9):978-92, 2013
Apicella M, et al., INCREASED LACTATE SECRETION BY CANCER CELLS SUSTAINS NON-CELL-AUTONOMOUS ADAPTIVE RESISTANCE TO MET AND EGFR TARGETED THERAPIES, Cell Metabolism, 28: 848-865, 2018

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

Petrelli et al., *BRCA2* Germline Mutations Identify Gastric Cancers Responsive to PARP Inhibitors. Cancer Res. 2023, in press
Pietrantonio F, et al., HER2 COPY NUMBER AND RESISTANCE MECHANISMS IN PATIENTS WITH HER2-POSITIVE ADVANCED GASTRIC CANCER RECEIVING INITIAL TRASTUZUMAB-BASED THERAPY IN JACOB TRIAL.Clin Cancer Res. Feb 1;29(3):571-580. 2023
Chiriaco C, et al., EFFICACY OF CAR-T IMMUNOTHERAPY IN MET OVEREXPRESSING TUMORS NOT ELIGIBLE FOR ANTI-MET TARGETED THERAPY J Exp Clin Cancer Res. Oct 21;41(1):309. 2022
Carlos Sebastián, et al., A NON-DIVIDING POPULATION WITH HIGH PYRUVATE DEHYDROGENASE KINASE ACTIVITY REGULATES METABOLIC HETEROGENEITY AND TUMORIGENESIS IN THE INTESTINE Nat Commun. Mar 21;13(1):1503. 2022
Puliga et al., MICROSATELLITE INSTABILITY IN GASTRIC CANCER: BETWEEN LIGHTS AND SHADOWS. Cancer Treat Rev. Apr;95:102175. 2021
Cristinziano G, et al., FGFR2 FUSION PROTEINS DRIVE ONCOGENIC TRANSFORMATION OF MOUSE LIVER ORGANOIDS TOWARDS CHOLANGIOCARCINOMA. J Hepatol. Vol. 75, 2:351–362 2021
Woo XY, et al., CONSERVATION OF COPY NUMBER PROFILES DURING ENGRAFTMENT AND PASSAGING OF PATIENT-DERIVED CANCER XENOGRAFTS. Nat Genet. Jan;53(1):86-99. 2021
Kowalik MA, et al., THYROID HORMONE INHIBITS HEPATOCELLULAR CARCINOMA PROGRESSION VIA INDUCTION OF DIFFERENTIATION AND METABOLIC REPROGRAMMING. J Hepatol. Jun;72(6):1159-1169. 2020
Simona Corso, et al., A COMPREHENSIVE PDX GASTRIC CANCER COLLECTION CAPTURES CANCER CELL INTRINSIC TRANSCRIPTIONAL MSI TRAITS. Cancer Res. Nov 15;79(22):5884-5896. 2019
Apicella M, et al., INCREASED LACTATE SECRETION BY CANCER CELLS SUSTAINS NON-CELL-AUTONOMOUS ADAPTIVE RESISTANCE TO MET AND EGFR TARGETED THERAPIES, Cell Metabolism, 28: 848-865, 2018
Migliore C, et al., MIR-205 MEDIATES ADAPTIVE RESISTANCE TO MET INHIBITION VIA ERRFI1 TARGETING AND RAISED EGFR SIGNALING., EMBO Mol. Med, EMBO Mol Med.10: pii: e8746, 2018
Pietrantonio F, et al., BIOMARKERS OF PRIMARY RESISTANCE TO TRASTUZUMAB IN HER2-POSITIVE METASTATIC GASTRIC CANCER PATIENTS: THE AMNESIA CASE-CONTROL STUDY. Clin Cancer Res. 24: 1082-1089, 2018
Sanlorenzo M, et al., BRAF AND MEK INHIBITORS INCREASE PD1-POSITIVE MELANOMA CELLS LEADING TO A POTENTIAL LYMPHOCYTE-INDEPENDENT SYNERGISM WITH ANTI-PD1 ANTIBODY. Clin Cancer Res. 24: 3377-3385 2018
Rizzolio S, et al., DOWNREGULATING NEUROPILIN-2 TRIGGERS A NOVEL MECHANISM ENABLING EGFR-DEPENDENT RESISTANCE TO ONCOGENE-TARGETED THERAPIES. Cancer Res. 78: 1058-1068, 2018
Rizzolio S, et al., NEUROPILIN-1 UPREGULATION ELICITS ADAPTIVE RESISTANCE TO ONCOGENE-TARGETED THERAPIES. J Clin Invest. 128: 3976-3990, 2018

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