Curriculum vitae Tiziana Crepaldi

Personal details

Born in Turin
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Education

1984-1988	PhD in Human Genetics, University of Turin, Italy.
1976-1980	Master's Degree in Biological Sciences, University of Turin, Italy, 110/110 cum laude

Professional experiences and current position

2022-pres	Full Professor, University of Turin, School of Medicine
2005-2022	Associate Professor, University of Turin, School of Medicine
1996-2004	Research Assistant, University of Turin
1994-1995	Research Fellow, Curie Institute, Paris, France
1989-1995	Research Fellow, University of Turin
1984	Research Fellow, University of Tubingen, Germany.
1984	Research Fellow, N.Y.S. College of Veterinary Medicine, Cornell University, Ithaca, N.Y., USA
1983	Research Fellow, College of Physicians and Surgeon, Columbia University, N.Y., USA

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

2021-pres	Member of Research Commetee, Department of Oncology, University of Turin
2014-2016	Member of AQ Committee, MD in Dentistry
2007-pres	Member of Educational Commetee, School of Medicine
1998-2001	Scientific Consultant for Animal Welfare, Candiolo Cancer Institute, Candiolo (Torino)

Honors

1990	Fellowship from Farmitalia
1989	Fellowship from Sorin Biomedica
1988	Fellowship from "Fondazione Gigi Ghirotti"
1984	Award from "Comitato Sanremo Genetica Umana"
1983	Travel Grant, "Fulbright program Fellowship for Italian-American Exchange"
1983	Fellowship from "Fondazione A. Bossolasco"
1981	Fellowship from "Fondazione A.V. Rusconi"

Teaching activity:

2010-pres	Organic Chemistry and Biochemistry, MD in Dentistry, University of Turin
2008-pres	General and Inorganic Chemistry, MD in Dentistry, University of Turin
2007-pres	Chemistry and Biochemistry, MSc in Medical Radiology Technician for Imaging and Radiotherapy, University of Turin
2006-2011	Chemistry and Biochemistry, MSc in Nursing, University of Turin
2002-2014	Practical courses of Biochemistry, MSc in Biotechnology

Research main topics

Over the last three decades, Tiziana Crepaldi has investigated the molecular and cellular mechanisms that control the signaling of Hepatocyte Growth Factor (HGF) and its receptor tyrosine kinase (MET) in development, tissue repair and cancer.

Her first research activity in immunogenetics and experience in the production of hybridomas and monoclonal antibodies (mAbs), was instrumental to generate useful anti-MET mAbs for tumor diagnosis, basic research, and human therapy. She applied these mAbs to identify overexpression of the MET in tumor cells of several cancers (Prat et al., Int J Cancer 1991; Di Renzo et al., Int J Cancer 1994; Grigioni et al., Hepatology 1995). She firstly reported (Prat et al., Mol Cell Biol 1991) the C-terminal truncated forms of MET receptor, now well-known as "MET decoy" molecules, which

interfere with both HGF binding to MET and MET homodimerization, and thus were subsequently exploited to inhibit MET in cancer (International Patent -US-5571509). Then, she demonstrated (Crepaldi et al., J Cell Biol 1994) that the MET receptor is selectively exposed at the basolateral plasmamembrane domain of polarized epithelial cells. Next, she focused on membrane peripheral proteins able to convey the signals elicited by HGF receptor to the actin cytoskeleton machinery. She reported that Ezrin is critical for engagement of actin cytoskeleton in apical domain morphogenesis and cell migration promoted by HGF (Crepaldi et al., J Cell Biol 1997; International Patent-US-6399584). She produced and characterized for the first-time monoclonal antibodies (mAbs) directed against the extracellular domain of MET, able to behave as either full or partial agonists of MET (Prat et al., J Cell Sci 1998). One of these antibodies (DN30) was further developed in the Paolo Comoglio's lab, deprived of agonistic activity and recently patented as a potent, selective, and irreversible inhibitor of ligand-dependent and ligand-independent MET activation (International Patent-US-20210395372).
She discovered a new MET Interactor (Fap68) which is able to couple MET with p70S6K, by performing a genetic screen with the yeast two-hybrid system (Grisendi et al., J Biol Chem 2001). She helped starting a new approach to inhibit MET through shRNA, which is useful to suppress MET-mediated transformation in cancer (Taulli et al., Cancer Res 2006). By collaborating with Aldo Fasolo's lab, she discovered that HGF contributes to the migration of GnRH-1 neurons (Giacobini et al., J Neurosci 2007; Garzotto et al., J Neurosci 2008). By using the tetracycline-dependent regulatory (tet-off) system, she generated transgenic mice with inducible targeted expression of either MET or HGF in skeletal and cardiac muscle (Crepaldi et al., J Biol Chem 2007; Riess et al., Trans Res. 2011; Leo et al., Plos One 2011; Sala et al., J Mol Cell Cardiol 2016; Morena et al., ELife 2016). These animal models provided powerful tools for assessing the effect of an extra-dose of HGF or activated MET in muscle tissues under pathological conditions (Sala and Crepaldi, Cell Mol Life Sci 2011). She exploited the MET agonistic mAbs as deliverable drugs that can substitute HGF in protection against apoptosis and autophagy (Gallo et al., Cell Death Dis 2014; Modica et al., Cancers, 2020). She showed the potency of MET agonists for tissue repair through in vivo administration of DO24 mAb in a model of doxorubicin-induced cardiotoxicity (Gallo et al., Br J Pharm 2020) and in the experimental autoimmune encephalomyelitis mouse model (Desole et al., Front Immunol 2021). By next-generation sequencing, she identified novel circulating microRNAs in advanced heart failure (Galluzzo et al., ESC Heart Fail., 2021). By collaborating with Denis Vivien's lab, she discovered a new interaction between MET and the glutamate NMDA receptor in neurons (Hedou at el., Int J Mol Sci 2021). Recently, she demonstrated that MET co-opts NMDAR neuronal signaling in cancer (Gallo et al, Cancers 2022).

Main funded projects as PI:

2018-2021	"Activation of the Met receptor as therapeutic tool in MS: a new neuroprotective mechanism involving the glutamatergic system", Fondazione Italiana per la Sclerosi Multipla (FISM)
2014-2020	"New Biomarkers of Heart Failure", CRT and Compagnia di SanPaolo
2012-2014	"Cardiac cachexia and cardiac effects of muscular atrophy: a cross-talk of autophagic wasting", Association Francaise contre les Myopathies (AFM)
2012	"Study of the mechanisms involved in cardiac cachexia", University of Turin (ex 60%)
2010-2012	"EM safety by sensors developments and Hazards Mitigation by proper EV design", FP7-2010-ICT-GC
2009	"The role of HGF/MET pathway during heart development", University of Turin (ex 60%)
2008-2010	"Role of growth factors in cardiomyogenesis and development of novel therapies to regenerate the injured myocardium", French-Italian University Program
2008-2009	"HGF and c-Met receptor in heart development and cardiac function", Association Francaise contre les Myopathies (AFM)
2007-2009	"Use of conditional transgenic model to express HGF in the heart and develop novel therapies for myocardial infarction", CRT and Compagnia di SanPaolo
2007-2008	"New targets for prevention and therapy of muscular atrophy in cancer", PRIN 2007
2007-2008	"Cardiac expression of HGF to promote neovascularization and to recruit stem cells into myocardial infarction", University of Turin (ex 60%)
2006	"Intracellular signaling pathways involved in skeletal muscle atrophy", Regione

	Piemonte
2004	"New approaches in melanoma diagnosis and therapy", Regione Piemonte
2004-2007	"RIGHT - RNA Interference Technology as Human Therapeutic Tool", FP6 European Community
2002-2003	"An inducible in vivo model for metastatic melanoma and rhabdomyosarcoma", Compagnia di San Paolo Oncology Program
1997-1999	"Structural and biochemical analysis of Met receptor enzymatic function", The Armenise - Harvard Foundation
1994-1996	"Membrane-cytoskeleton interactions and tumour suppression", European Union Biomedical and health research program

Bibliometry (1994-present) (*www.scopus.com*)
H-index 27
Citations 6,751

Publications (selected)

Gallo S, Vitacolonna A, Comoglio P, **Crepaldi T**. 2022. MET Oncogene Controls Invasive Growth by Coupling with NMDA Receptor. *Cancers*. 14:4408.
DOI: 10.3390/cancers14184408

Hedou E, Douceau S, Chevilley A, Varangot A, Thiebaut AM, Triniac H Bardou I, Ali C, Maillasson M, **Crepaldi T**, Comoglio P, Lemarchand E, Agin V, Roussel BD, Vivien D. 2021. "Two-Chains Tissue Plasminogen Activator Unifies Met and NMDA Receptor Signalling to Control Neuronal Survival". *Int J Mol Sci*. 22:13483.
DOI: 10.3390/ijms222413483

Desole C, Gallo S, Vitacolonna A, Vigna E, Basilico C, Montarolo F, Bardou I, Ali C, Maillasson M, **Crepaldi T**, Comoglio P, Lemarchand E, Agin V, Roussel BD, Vivien D. 2021. "Engineering, Characterization, and Biological Evaluation of an Antibody Targeting the HGF Receptor". *Front Immunol*. 12:775151.
DOI: 10.3389/fimmu.2021.775151

Galluzzo A, Gallo S, Pardini B, Birolo G, Fariselli P, Boretto P, Vitacolonna A, Peraldo-Neia C, Spilinga M, Volpe A, Celentani D, Pidello S, Bonzano A, Matullo G, Giustetto C, Bergerone S, **Crepaldi T**. 2021 "Identification of Novel Circulating Micrornas in Advanced Heart Failure by Next-Generation Sequencing". *ESC Heart Fail*. 8:2907-2919.
DOI: 10.1002/ehf2.13371

Modica C, Gallo S, Chiriaco C, Spilinga M, Comoglio PM, **Crepaldi T**, Basilico C, Vigna E. 2020. "Molecular Engineering Strategies Tailoring the Apoptotic Response to a MET Therapeutic Antibody". *Cancers* 12: e741.
DOI: 10.3390/cancers12030741

Gallo S, Spilinga M, Albano R, Ferrauto G, Di Gregorio E, Casanova E, Balmativola D, Bonzano A, Boccaccio C, Sapino A, Comoglio PM, **Crepaldi T**. 2020. "Activation of the Met Receptor Attenuates Doxorubicin-Induced Cardiotoxicity in Vivo and in Vitro." *Br J Pharmacol.* 177:3107-3122.
DOI: 10.1111/bph.15039

Vigna, E, Basilico C, **Crepaldi T**, Comoglio P. inventors. 2019. "Anti-MET Fab-Fc For The Treatment Of A Tumor And/Or Metastasis". METIS Precision Medicine SB S.R.L. assignee, PCT/EP2019/077116.

Morena D, Maestro N, Bersani F, Forni PE, Lingua MF, Foglizzo V, Šćepanović P, Miretti S, Morotti A, Shern JF, Khan J, Ala U, Provero P, Sala V, **Crepaldi T**, Gasparini P, Casanova M, Ferrari A, Sozzi G, Chiarle R, Ponzetto C, Taulli R. 2016. "Hepatocyte Growth Factor-Mediated Satellite Cells Niche Perturbation Promotes Development of Distinct Sarcoma Subtypes." *ELife* 5: 1–24.
DOI: 10.7554/eLife.12116

Sala V, Gallo S, Gatti S, Medico E, Vigna E, Cantarella D, Fontani L, Natale M, Cimino J, Morello M, Comoglio PM, Ponzetto A, **Crepaldi T**. "Cardiac Concentric Hypertrophy Promoted by Activated Met

Receptor Is Mitigated in Vivo by Inhibition of Erk1,2 Signalling with Pimasertib." *J Mol Cell Cardiol.* 93: 84–97.
DOI: 10.1016/j.yjmcc.2016.02.017

Gallo S, Gatti S, Sala V, Albano R, Costelli P, Casanova E, Comoglio PM, **Crepaldi T**. 2014. "Agonist Antibodies Activating the Met Receptor Protect Cardiomyoblasts from Cobalt Chloride-Induced Apoptosis and Autophagy." *Cell Death Dis.* 5: e1185.
DOI: 10.1038/cddis.2014.155

Riess I, Sala V, Leo C, Demaria M, Gatti S, Gallo S, Fitou A, Boero O, Levi R, Cuccovillo I, Molla F, De Angelis N, Staszewsky L, Latini R, **Crepaldi T**. 2011. "A Mouse Model for Spatial and Temporal Expression of HGF in the Heart." *Trans Res.* 20: 1203–1216.
DOI: 10.1007/s11248-011-9485-y

Leo C, Sala V, Morello M, Chiribiri A, Riess I, Mancardi D, Schiaffino S, Ponzetto C, **Crepaldi T**. 2011. "Activated Met Signalling in the Developing Mouse Heart Leads to Cardiac Disease." *PLoS One* 6: e14675.
DOI: 10.1371/journal.pone.0014675

Garzotto D, Giacobini P, **Crepaldi T**, Fasolo A, De Marchis S. 2008. "Hepatocyte Growth Factor Regulates Migration of Olfactory Interneuron Precursors in the Rostral Migratory Stream through Met-Grb2 Coupling". *J Neurosci*. 28:5901-5909.
DOI: 10.1523/JNEUROSCI.1083-08.2008

Giacobini P, Messina A, Wray S, Giampietro C, **Crepaldi T**, Carmeliet P, Fasolo A. 2007. "Hepatocyte Growth Factor Acts As A Motogen And Guidance Signal For Gonadotropin Hormone-Releasing Hormone-1 Neuronal Migration." *J Neurosci.* 27:431-445.
DOI: 10.1523/JNEUROSCI.4979-06.2007

Crepaldi T, Bersani F, Scuoppo C, Accornero P, Prunotto C, Taulli R, Forni PE, Leo C, Chiarle R, Griffiths J, Glass DJ, Ponzetto C. 2007. "Conditional Activation Of MET In Differentiated Skeletal Muscle Induces Atrophy". *J Biol Chem*. 282:6812-6822.
DOI: 10.1074/jbc.M610916200

Taulli R, Scuoppo C, Bersani F, Accornero P, Forni PE, Miretti S, Grinza A, Allegra P, Schmitt-Ney M, **Crepaldi T**, Ponzetto C. 2006. "Validation of Met as a Therapeutic Target In Alveolar And Embryonal Rhabdomyosarcoma". *Cancer Res.* 66:4742-4749.
DOI: 10.1158/0008-5472.CAN-05-4292

Grisendi S, Chambraud B, Gout I, Comoglio PM, **Crepaldi T**. 2001. "Ligand-Regulated Binding of FAP68 to the Hepatocyte Growth Factor Receptor." *J Biol Chem.* 276: 46632–46638.
DOI: 10.1074/jbc.M104323200

Prat M, **Crepaldi T**, Pennacchietti S, Bussolino F, Comoglio PM. 1998. "Agonistic Monoclonal Antibodies against the Met Receptor Dissect the Biological Responses to HGF." *J Cell Sci.* 111: 237–247.
DOI: 10.1242/jcs.111.2.237

Crepaldi T, Gautreau A, Comoglio P, Louvard D, Arpin M. 1997. "Ezrin Is an Effector of Hepotocyte Growth Factor-Mediated Migration and Morphogenesis in Epithelial Cells." *J Cell Biol.* 138: 423–434.
DOI: 10.1083/jcb.138.2.423

Grigioni WF, Fiorentino M, D'Errico A, Ponzetto A, **Crepaldi T**, Prat M, Comoglio PM. 1995. "Overexpression of c-Met Protooncogene Product and Raised Ki67 Index in Hepatocellular Carcinomas with Respect to Benign Liver Conditions". *Hepatology*. 21:1543-1546.

Crepaldi T, Pollack AL, Prat M, Zborek A, Mostov K, Comoglio PM. 1994. "Targeting of the SF/HGF Receptor to the Basolateral Domain of Polarized Epithelial Cells." *J Cell Biol.* 125: 313–320.
DOI: 10.1083/jcb.125.2.313

Di Renzo MF, Olivero M, Katsaros D, **Crepaldi T**, Gaglia P, Zola P, Sismondi P, Comoglio PM. 1994. "Overexpression of the Met/HGF Receptor in Ovarian Cancer". *Int J Cancer*. 58:658-662. DOI: 10.1002/ijc.2910580507

Prat M, **Crepaldi T**, Gandino L, Giordano S, Longati P, Comoglio P. 1991. "C-Terminal Truncated Forms of Met, the Hepatocyte Growth Factor Receptor." *Mol Cell Biol.* 11: 5954–5962. DOI: 10.1128/mcb.11.12.5954-5962.1991

Prat M, Narsimhan RP, **Crepaldi T**, Nicotra MR, Natali PG, Comoglio PM. 1991. "The Receptor Encoded by the Human c-MET Oncogene Is Expressed in Hepatocytes, Epithelial Cells and Solid Tumors". *Int J Cancer*. 49:323-328. DOI: 10.1002/ijc.2910490302

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Tiziana Crepaldi