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THE CANDIOLO CANCER INSTITUTE

The Candiolo Cancer Institute is a private non-profit institution founded and supported by the Fondazione Piemontese per la Ricerca sul Cancro-Onlus (FPRC) and operated by the Fondazione del Piemonte per l’Oncologia (FPO: a joint venture between the FPRC and the Regione Piemonte). It is linked to the University of Torino Medical School. Its mission is a significant contribution to fight cancer, by understanding the basics, and by providing state-of-the-art diagnostic and therapeutic services. At the core of the Institute is the interface between molecular biology and medicine. The FPRC provides enduring fund raising to complete and develop the Institute’s buildings and technologies to foster research.

From the left Paolo M Comoglio, Scientific Director of the Institute, Marco Boglione, President of the Fondazione del Piemonte per l’Oncologia (FPO)-IRCCS, Giampiero Gabotto, Managing Director of FPO, Margaret Foti, Chief Executive Officer of the American Association for Cancer Research (AACR) visiting the Institute, and Allegra Agnelli, President of the Fondazione Piemontese per la Ricerca sul Cancro Onlus (FPRC).

25 November 2014
The Candiolo Cancer Institute is a biomedical and clinical research center entirely devoted to the study and the treatment of cancer. Its mission is to transfer experimental preclinical information into clinical practice, through the continuous flow of knowledge from the fields of genetics, molecular and cell biology and pathology.

The Institute aims to offer a significant contribution to the defeat of the disease through scientific research and clinical practice of excellence. In order to fulfill these goals, the Institute: (i) capitalizes on knowledge by conducting scientific research in oncology and – at the same time – promoting fast transfer of knowledge to the clinical practice; (ii) provides assistance in cancer prevention, including the identification of genetic risk factors; (iii) performs diagnostic studies, using state-of-the-art instrumentation and technology; (iv) provides a full cycle of treatment on the premises, employing besides the best conventional therapies– protocols for novel targeted therapies and clinical trials for ‘precision medicine’.

Focus
Basic and clinical research make the Institute of Candiolo a center of excellence focussed on the study, prevention and treatment of the dreadful complication of cancer, metastasis.

Basic Research
The current knowledge about the mechanisms of cancer onset and progression is provided by basic disciplines, such as genetics, cell and developmental biology. Thanks to these studies, it is possible to classify tumors not only on the basis of their site of origin and histopathological features, but, notably, by the identification of the genetic lesion(s) that support their growth. The tasks of the Institute is basic research are aimed at understanding the mechanisms that control normal cell functions responsible for proliferation, and at analyzing how these mechanisms are corrupted during neoplastic transformation. The topics include signal transduction, DNA duplication, cell division, differentiation, senescence, apoptosis and cell motility. Recent studies suggest that anti-neoplastic therapy is really effective not only when it hits the appropriate molecular target (vide infra), but especially when it hits the cells feeding the tumor mass. Indeed, most of the cells of the neoplastic mass are quite innocuous and can be attacked with classical therapies, while only a small fraction of them are resistant to treatment and able to regenerate the tumor. This small subpopulation includes the “cancer stem cells” – strictly related to normal “stem cells” – which control the development of our organism during embryonic life and allow us to renew worn parts in adult life. The up-to-date conceptualization of Cancer defines it as a “somatic, genetic disease of the stem cells”.

Translational Research (ECMO: Experimental Clinical Molecular Oncology)
Translational research is the “heart” of the Institute, bridging the gap between basic and clinical research. Based on recent technological advances, genomic analysis makes possible –in a significant percentage of cases– the identification of genetic alteration(s) with a “driver” role in tumor development. However, the contribution of each lesion to the transformed phenotype remains elusive. Moreover, knowledge is still insufficient about the mechanisms that control the lack of response to targeted therapies, even in the presence of the molecular target (primary resistance), as well as on the mechanisms that lead to progressive attenuation of the response after prolonged treatment (acquired resistance).
ECMO research aims at the fulfillment of some ambitious Goals to integrate the traditional prognostic and diagnostic factors with a detailed characterization of the genetic and functional alterations of the tumor; to identify new malfunctioning regulatory pathways in cancer; to isolate and study cancer stem cells; to develop new preclinical platforms that can reliably disclose—and understand in detail—the prospective results of clinical practice. The generation of this kind of knowledge is necessary to design clinical trials that will no longer be based on empirical observations but on a strong rationale.

Investigational Clinical Oncology (INCO)
Cancer is a complex disease, tied to genetic lesions, that increase in number over time, as a consequence of genetic instability and exposure to environmental carcinogens. Thus, a cell clone proliferates and invades the adjacent tissues in an uncontrolled way. Since cancer cells contain several genetic anomalies, and tend to accumulate more anomalies as time passes, cancer is a heterogeneous and hard-to-attack disease, just because it would be necessary to aim at many targets that continuously change. The molecular lesions that cause and sustain most tumors are, however, finite in number (the bona fide oncogenes). These findings have driven clinical pharmacology to commit to an epochal effort to create drugs, called "targeted", able to contrast the function of specific oncogenes. The strategy of the Institute at Candiolo intends to make significant contributions to the field of cancer targeted therapy by: (i) identifying pathologies and recruiting patients sensitive to the therapies currently in use; (ii) planning and performing—in international networks—the related clinical trials; (iii) developing translational and preclinical research aimed at designing new targeted therapies.

Molecular diagnosis and "precision" medicine
The success of targeted therapies is based on the rationale that the target molecule is "druggable"—as a consequence of the genetic anomaly—in the tumor but not in healthy tissue, and therefore its deactivation has consequences restricted to the neoplastic mass, with a minimum of "off-target" consequences, leading to generic organ damage. This notion has two important clinical outcomes: first of all, before treating patients with a given targeted therapy, it is necessary to verify the presence of the genetic lesion "predictive" of sensitivity to the drug. Second—in the perspective of targeted therapies—tumors will be classified not only according to their site of origin and/or morphological features, but also by the molecular lesion(s) which earmark them and, at the same time, make them vulnerable to a targeted treatment. Therefore, new therapies are not only "targeted" but also "personalized". This new approach is called "precision medicine".

Clinical Research
At the Institute, oncologists, surgeons and radiotherapists cooperate with scientists to design clinical trials based on molecular data, intended to verify hypotheses and generate novel ones. In order to make this cooperation productive, the Institute manages a daily net of interactions involving formal aspects (seminars and meetings), training (refresher courses and lessons), operational efforts (contacts with pharmaceutical companies, and management of regulatory instruments). Clinical Research is the last and more direct haven to improve the assistance to cancer patients, providing them with the most appropriate, novel, safe and effective therapeutic approach, according to the genetic characteristic of their own tumor, as an ultimate means of increasing their life expectancy.

Paolo M. Comoglio MD
(Scientific Director)
Research Topic 1: Mechanisms of cancer onset and progression.

The current knowledge on mechanisms of cancer onset and progression has been provided by basic disciplines, such as cell biology, developmental biology and genetics. The tasks of Research Topic 1 are aimed at understanding the mechanisms controlling the normal cell functions responsible for the regulation of cell proliferation and at analyzing how these mechanisms are corrupted during neoplastic transformation. The topics include signal transduction, DNA duplication and cell division processes, differentiation, senescence, apoptosis and cell invasion. Special attention is given to the microenvironment and to the relations of the neoplastic cell with adjacent cells. In the past, the angiogenic process and the vascularization of the tumor mass have been studied in detail.

Research Topic 1 is focussed on:
1.1 The role of Semaphorins in invasiveness, metastases and angiogenesis
1.2 The plasma membrane in metastasis dissemination
1.3 Tumor angiogenesis

Confocal microscopy pictures of H1993 cells. This is a lung cancer cell line that carries amplification of the MET oncogene. Cells were stained with antibodies to reveal MET (shown in green in the merged images) and EEA1, a marker of the early endosomal compartment (in red in the merged images). Nuclei are in blue. Pictures were kept with identical settings. Left: the receptor accumulates at the plasma membrane in control cells. Right: treatment with the anti-MET therapeutic antibody (DN30Fab) abrogates MET accumulation at the cell surface. Bar is 10 μm.
Semaphorins: structure & functions

The elucidation of the functional role and molecular mechanisms by which Semaphorin genes control the invasiveness of tumor cells and the formation of metastases will prompt the development of innovative diagnostic and therapeutic approaches.

Team
Michael Rehman, Sabrina Rizzolio, Lorena Capparuccia, Chiara Battistini, Gabriella Cagnoni, Gurrapu Sreeharsha, Massimo Accardo

Research topic:
Semaphorins and Semaphorin Receptors in Cancer Progression.

Background:
Semaphorins and their receptors (Neuropilins and Plexins), beyond their role in embryo development and morphogenesis, are relevant players in cancer progression and emerging targets for innovative therapeutic approaches. Semaphorins form a conserved family of over 20 members in vertebrates, which include transmembrane molecules (thought to elicit bi-directional signaling upon cell-cell contact) and secreted members. Secreted semaphorins often act to restrict cell migration; for instance, they can negatively regulate angiogenesis, preventing its pathological role in cancer. Certain semaphorins can play diverse functional roles in different cell populations, due to the involvement of distinctive receptor complexes and signaling cascades. In particular, our lab demonstrated that Sema3A and Sema3E are relevant targets for innovative therapeutic approaches, as they can regulate cancer cells and stromal cells in concomitant manner in the tumor microenvironment. In addition to their role as semaphorin and VEGF receptors, we and others found that neuropilins represent receptor hubs on the cell surface, controlling the function of multiple signaling cascades supporting tumor growth, such as EGFR and integrins.

Research achievements:
The laboratory has been working on several aspects of the research topic. We studied the function of Plexin-D1 and Neuropilin-1 receptors in cancer cells and in the tumor microenvironment, and found that they can play multiple roles in cancer progression. For instance, oncogene addicted tumor cells use Nrp1 to uphold survival signaling cascades in response to targeted therapies. Moreover, Nrp1 mediates Sema3A-dependent recruitment and localization of tumor associated macrophages in hypoxic tumor areas, where they can deploy their pro-angiogenic and immune-suppressor activity. Beside secreted family members, transmembrane semaphorins are also presently being investigated in the lab, such as Sema4C and Sema6A. We accomplished novel and exciting results about their role in cancer cells, regulating their intrinsic metastatic potential and therapeutic response to targeted therapies. The lab is also a leader in semaphorin research at the international level, contributing expert know-how and reagents to frontline collaborative studies.

Conclusions and perspectives:
Semaphorins and their receptors are novel and exciting players in cancer progression. By understanding the specific role of different family members in human cancers, we could validate novel predictive markers of progression or response to innovative targeted therapies. Moreover, certain semaphorins (and receptors) have already been put forward as potential targets for functional interference approaches, aimed at regulating angiogenesis, cancer cell invasiveness and metastatic progression.

Biographical Sketch:
Luca Tamagnone, MD, PhD started his research activity with Paolo Comoglio. During his training in the lab of Kari Alitalo, he discovered new genes encoding tyrosine kinases, such as RYK and BMX (published in Oncogene, 1993 and 1994). On returning to Italy, Dr Tamagnone started working on a new family of receptors, the Plexins (described in PNAS-USA, 1996). Three years later he published the identification of plexin ligands, the Semaphorins (Cell 1999). As tenured Associate Professor at the University of Torino, and Young Investigator of the European Molecular Biology Organization, in 2001, Dr Tamagnone started his own lab in the Institute for Cancer Research of Candiolo-Torino (IRCC). He focused his attention on semaphorin/plexin activities in cancer cells, identifying fundamental signaling mechanisms and functional properties in the regulation of tumor progression (e.g. Neuron 2001; Nat Cell Biol 2002; Nature 2003; FASEB J 2004; J Cell Sci 2005). By exploiting experimental models in vivo, he found that semaphorin signals regulate multiple steps of tumor progression: from tumor growth, to angiogenesis, to the recruitment of tumor-associated leucocytes, to the formation of distant metastases (e.g. J Exp Med 2008; J Clin Invest 2010; EMBO Mol Med, 2012), validating their relevance as targets for molecular therapy. Moreover, recent findings have revealed novel functions of the semaphorin co-receptor Neuropilin-1 in the regulation of EGFR oncogene signalling (Cancer Res, 2012), as well as in the recruitment of tumor associated macrophages (Cancer Cell, 2013). To date (Jan 2015), Dr Tamagnone is author of more than 70 papers published in peer-reviewed journals, with over 8000 citations, and has an H-index of 41.

Selected references
Tamagnone L, Rehman M. “To Die or Not to Die: Sema3E Rules the Game”. Cancer Cell. 2013, 24:695-709
Dynamic control of cell adhesion: ‘normalization’ of tumor blood vessels

The pharmacological modulation of integrin function can be therapeutically exploited to improve the biodistribution of anti-neoplastic drugs and counteract the hypoxia-driven metastatic dissemination of cancer cells

Team
Donatella Valdembri, Chiara Camillo, Noemi Gioelli, Giulia Mana, Chiara Sandri, Giulia Villari

Research topic:
Grasping the molecular basis of cell adhesion dynamics to design effective ‘vascular normalizing’ drugs for anti-cancer therapy.

Background:
Tumor blood vessels are structurally and functionally aberrant, thus hampering the delivery of anti-cancer drugs and causing hypoxia-driven metastatic dissemination. Normalizing the vasculature of tumors could hence sizably improve anti-cancer therapy. The binding of vascular endothelial cells (ECs) to the extracellular matrix (ECM) is mediated by integrins, a class of adhesive receptors that can assume active or inactive conformations, respectively characterized by high or low affinity binding to ECM ligands. Blood fluid shear stress is the main determinant of normal vascular architecture and function, its foremost outcomes being that of triggering integrin activation and fostering EC-to-ECM adhesion. As a direct consequence, ECs modify their adhesive interactions and reciprocal positions in space, finally giving rise to a remodelled, mature, and functional vascular tree. In this framework, inhibitors of integrin function should warrant a swift responsivity of EC-to-ECM adhesion to variations in blood flow-elicited forces. Therefore, pharmacological modulation of integrin function might be therapeutically exploited to ‘normalize’ the tumor vasculature.

Research achievements:
We have previously shown how: (i) the chemorepulsive guidance cue semaphorin 3A (Sema3A) and its receptors plexins and neuropilin-1 (Nrp1) allow correct vascular morphogenesis by negatively modulating the conformational activation of integrins and inducing active/ECM bound integrin endocytosis; (ii) the abrogation of Sema3A-dependent integrin-inhibitory signals underpins the alterations that characterize tumor blood vessels; (iii) somatic gene transfer of Sema3A restores the physiological inhibition of endothelial integrins and effectively prevents cancer vascular abnormalities, thus improving the penetration of anti-neoplastic drugs and impairing metastases. Stemming from these findings, over the last two years, we rationally designed, generated, and purified a molecular variant of Sema3A protein that we dubbed Sema3A* and is endowed with a much higher (Kd 0.7 nM) affinity for its major signaling receptor plexin A4. Fittingly, we found that, when compared to its wild type counterpart, Sema3A* displays much more robust biochemical and biological activities on cultured ECs. Finally, in collaboration with the Laboratory of Transgenic Mouse Models of our Institute, we proved how intra peritoneal administration of recombinant mutant Sema3A* protein in transgenic and orthotopic mouse models of pancreatic cancer effectively normalizes the tumor vasculature and impairs liver metastatization.

Conclusions and perspectives:
Our data provide evidence of how the negative pharmacological modulation of endothelial integrins by Sema3A can be therapeutically exploited to improve the biodistribution of anti-neoplastic drugs and counteract the hypoxia-driven metastatic dissemination of cancer cells. It will therefore be crucial to further characterize the mechanisms and molecular determinants responsible for: (i) the inhibition of integrin-dependent EC adhesion by Sema3A; (ii) the selective Nrp1-dependent control of active integrin traffic in ECs.

Biographical Sketch:
Over the last two decades, Guido Serini has investigated the role of integrin-mediated cell adhesion in the control of tumor progression and angiogenesis. He firstly reported (Serini et al., J. Natl. Cancer Inst. 1996; 88:442-44) how the neo-expression of alpha6-beta4 integrin, now well-known for its pro-metastatic activity, as a hallmark of the transition of human benign adenomas into malignant carcinomas. He also demonstrated (Serini et al., J. Cell Biol. 1998; 142:873-881) how the generation of pro-invasive and pro-angiogenic cancer associated fibroblasts requires integrin-triggered signals. He then focused on the mechanisms that, by tuning the conformational activation of integrins, control physiological angiogenesis and are disrupted in cancer, finally resulting in hypoxia-driven metastatization. After reporting that autocrine VEGF is critical for integrin activation and vascular network formation (Serini et al., EMBO J., 2003; 22:1771-1779), he showed for the first time how endothelial class 3 semaphorins (SEMA3) signal through plexin receptors to inhibit integrins and allow vascular morphogenesis (Serini et al., Nature 2003; 424:391-397). Next, together with Dr. Giraudo, he discovered that SEMA3A is present in endothelial cells of pre-malignant lesions, lost during tumor progression, and, when therapeutically reintroduced, able to normalize the vasculature, inhibit tumor growth, and extend survival (J. Clin. Invest., 2009; 119:3356-3372). He recently unveiled how vascular morphogenesis relies not only on integrin activation, but also on dedicated signaling pathways that control active integrin traffic back and forth from adhesion sites (PloS Biol. 2009, 7(1): e1000025; Cell Res. 2012; 22:1479-501; Curr. Opin. Cell Biol. 2012; 24:582-591). He authored 58 papers in peer-reviewed journals and has an H-index of 28.

Selected references
New targets for anti-angiogenic therapy
The better understanding of the anti-metastatic and normalizing effects of Sema3s on tumor blood vessels, will allow design new strategies to overcome the resistance to anti-angiogenic therapy.

Team
Federica Maione, Stefania Capano, Yaqu Qiu, Donatella Regano

Research topic:
Semaphorin 3A: a new tool to normalize the tumor vasculature and to halt metastasis formation.

Background:
Angiogenesis is required for invasive tumor growth and metastasis. It is well described that tumor vessel normalization represents a remarkably advantageous anti-cancer strategy, reducing tumor hypoxia and also being able to favor chemotherapy delivery and response to radiotherapy. It is critical therefore to identify new “pro-normalizing” modulators to define new anti-angiogenic combinatorial regimens to block tumor growth. In these years, several studies have showed that class3 semaphorins (Sema3s), that act via receptor complexes binding neuropilins 1 and 2 (Nrp1/2) and transducing the signal by plexins (Plexns), represent new targets to inhibit tumor angiogenesis and cancer growth.

Research achievements:
By using mouse models of spontaneous pancreatic tumors (RIP-Tag2) and cervical carcinomas (HPV16/E2) it a role of Sema3A has been uncovered as an endogenous angiogenic inhibitor that impairs tumor growth and normalizes tumor vasculature. Interestingly, the treatment of mouse with adeno-associate virus (AAV)-8 Sema3A counteracted Sunitinib- and DC101-induced resistance to therapy by normalizing the tumor vasculature. Studies aimed it better defining the mechanisms of action of Sema3A, unveiled that the treatment of RIP-Tag2 mice with Sema3A inhibited c-Met phosphorylation both in vessels in tumor cells. In co-culture systems of human endothelial cells (ECs) and pericytes Sema3A attracted the pericytes toward ECs and down-modulated Nrp-1 in both cell types, with the consequent over-expression of PDGF-B and Ang 1, known to promote vessel maturation. Remarkably, Sema3A strongly inhibited HGF-induced Met phosphorylation in Nrp-1 silenced ECs, suggesting that this molecule could act directly binding Met or HGF. Notably, Sema3A impaired HGF-induced Met phosphorylation, not only in ECs, but also in several Nrp-1-silenced tumor cell lines and induced apoptosis similarly to the Met inhibitor JNJ-38877605. Finally the treatment of a mouse model of pancreatic ductal adenocarcinoma (PDAC) with Sema3A revealed a significant reduction of metastasis formation, a normalization of tumor vasculature and a selective impairment of Met phosphorylation both in vessels and in tumor cells.

Conclusions and perspectives:
Based on these findings the main focus of research are the following: (i) investigation of the molecular mechanisms by which Sema3A turns off the HGF/Met pathway in different stroma cell types and cancer cells; (ii) study of the ability of Sema3A to impair cancer dissemination in different Met-addicted tumor cells types in vivo; (iii) evaluation of the anti-metastatic and pro-vessel normalizing effects of a non-proteolyzable high-affinity version of Sema3A (in collaboration with the laboratory of Cell Adhesion Dynamics) in different mouse models of human tumors.

Biographical Sketch:
Enrico Giraudo has contributed with a high quality track record of publications to the research field of tumor angiogenesis. Since the beginning, he has contributed to the identification of the molecular mechanisms that regulate the motility and differentiation of angiogenic endothelial cells (Giraudo E. J. Biol. Chem, 1998; 157:2618-23; Nature Med. 1996; 2:1371-75; Giraudo E. J Biol Chem. 2003; 278:50702-13). His main focus has been the study of the mechanisms regulating tumor angiogenesis and cancer progression in transgenic mouse models of tumorigenesis. He described the molecular zip-code deciphering blood and lymphatic heterogeneity during tumorigenesis (Cancer Cell. 2003; 4:383-91). Next, he uncovered an important role of matrix metallo-proteases (MMP)-9 and macrophages on tumor angiogenesis in a transgenic model of cervical cancer, by employing an amino-bisphosphonate Zoledronic acid able to efficiently inhibit cancer growth (Giraudo E. J Clin Invest. 2004; 114:623-33). More recently he first demonstrated that the axon guidance cue Semaphorin 3A is an endogenous angiogenic inhibitor and that its therapeutically re-expression in cancers impairs angiogenesis, tumor growth and induced vessel normalization in mouse models of cancer (Maione F. J Clin. Invest. 2009; 119:3356-72). On these bases, he showed that Sema3A was able to overcome resistance to anti-angiogenic therapies, by normalizing tumor vessels and inhibiting hypoxia (Maione F. J. Clin. Invest. 2012; 122:1832-48). To date, he has authored 35 papers published in peer-reviewed journals.
Role of membrane receptor endocytosis in the dissemination of metastatic cells

Knowing the mechanisms that control the downregulation of receptors involved in metastatic cell dissemination provides the rationale for the generation of innovative anti-neoplastic drugs

Team
Emanuela Pupo, Nadia Ducano

Research topic:
Role of endocytosis in the regulation of signaling by oncogenic tyrosine kinase receptors.

Background:
Tumors, in order to grow and metastasize, activate pathways that largely depend on endocytic proteins as these molecules control receptor tyrosine kinase (RTKs) signaling and cell migration/invasion. Although mutations in endocytic genes have crucial roles in the manifestation of the neoplastic phenotype, the possibility to exploit endocytic proteins as targets of pharmacological intervention, alone or in combination with other treatments, are still poorly investigated. Work in our unit addresses the role of key endocytic players, the small GTPase Rab5 and its negative regulator RN-tre, as well as the effects of endocytosis inhibition, in the regulation of RTKs signaling and in cell invasion.

Research achievements:
Recently, we identified a novel molecular mechanism that prevents chemotactic cell migration of both normal and cancer cells. Endocytosis controls the downregulation of phosphorylated RTKs. We found that inhibition of the oncogenic MET kinase receptor by ATP-competitive drugs prevents receptor endocytosis resulting in MET accumulation at the plasma membrane. After inhibitor removal, MET phosphorylation recovers to levels higher than those displayed at steady-state and reactivates the downstream cascade. This generates a “rebound” effect pushing quiescent cancer cells back into the cell cycle.

Conclusions and perspectives:
Database analyses has revealed that RN-tre is amplified/overexpressed in 16% of breast tumors. Based on its function in receptor signaling and cell adhesion, we hypothesize that RN-tre overexpression in breast cancer cells might confer proliferative advantages by upregulating oncogenic tyrosine kinase receptors, and/or promoting anchorage-independent growth and cell survival. To determine the value of targeting RN-tre in breast cancer, we will investigate whether its downregulation reduces the oncogenic potential of breast cancer cell lines that carry RN-tre amplification. Based on our findings on MET kinase inhibition, we plan to address the effects of delayed endocytosis in tumor recurrence. We will study the rebound effects on proliferation of cancer cells that were initially subjected to ATP-competitive RTK inhibitors and then released from the inhibition, trying to mimic what might happen in patients treated with similar drugs in a time window. We will address whether alternate or metronomic treatment with RTKs inhibitors and therapeutic antibodies might counteract this harmful effect.

Selected references


Biographical Sketch:

Letizia Lanzetti did her training at the Department of Medical Genetic in Torino where she participated in the isolation of a novel gene family: the endophilins. Next, she joined the European Institute of Oncology in Milan to study the impact of endocytosis on the signal transduction cascade. Her work pioneered the existence of crosstalk between these processes as described in two of her major publications (Lanzetti et al., 2000, Nature 408:374-7), (Lanzetti et al., 2004, Nature 429:309-14).

In 2008 she established her laboratory at the Candiolo Cancer Institute. Here, she revealed a novel function for endocytic proteins in cancer cell division (PNAS 2011; 108:17337-42), and in cell migration and invasion (Curr. Biol. 2013; 23:2355-64).

Her work led to the identification of molecular pathways that control signaling and trafficking of receptors involved in cell transformation and invasion. Currently, she is widening her research looking at the feasibility of targeting endocytic molecules, in combination with other treatments, in cancer therapy.

RN-tre localizes to focal adhesions. Snapshot from Total Internal Fluorescence Microscopy in living RN-tre KO fibroblasts expressing cherry-RN-tre (red) and the focal adhesion marker GFP-paxillin (green). Bar, 10 μm.
From neuronal biology to neoplastic progression
The identification of ‘molecular keys’ that mediate the relationship between tumor cells, blood vessels and nerves will contribute to the definition of a new class of therapeutic targets

Team
Laura Bizzozzero, Margherita Pergolizzi, Elena Riccitelli, Grazia Vitagliano

Research topic:
Neuroligin: a novel modulator of cell transformation and cancer diffusion through nerves.

Background:
Neuroligin (NLGN) is a neuronal and tumoral adhesion protein that is a translational target of the mTOR (mechanistic target of rapamycin) kinase. mTOR plays a key role in tumorigenesis, but mTOR based therapies have had limited success, mainly because of evasive resistance and lack of predictive biomarkers of efficacy. Tumor-nerve interactions are a clinically significant but often underestimated way of cancer diffusion, including colorectal cancer (CRC). Tumor and nerve relations take place by Perineural Invasion (PNI), the invasion of nearby nerves by cancer cells, and neo-neurogenesis, or the stimulation of neurite outgrowth by the cancer through soluble signals. These obviously represent different aspects of a wide range of molecular interactions that are nevertheless poorly defined. Moreover, no specific therapy exists that will target tumor nerve interactions, so new molecular players and therapies are needed. Ultimately, finding novel proteins that provide insight into the tumorigenic properties of mTOR both in the tumor cell itself and in the microenvironment, as well as serving as predictive biomarkers, is paramount.

Research achievements:
This laboratory has been working on the extra-neuronal activities of NLGN for the last ten years. Since 2013 we have focused on the following questions on the role of tumoral NLGN (mainly in CRC): (a) How does it impact tumor cell phenotypes? (b) Does it modulate PNI and neo-neurogenesis? (c) Does it influence the cancer response (growth/invasion/PNI) to mTOR inhibition? The results obtained to date show that NLGN inhibits tumor cell proliferation, anchorage independent growth and in vivo xenograft growth but promotes PNI. This last effect is completely abolished by drug-mediated blockade of mTOR.

Conclusions and perspectives:
If broadly confirmed, our data reveal NLGN as a double-faced cue (i.e. growth suppressing but pro-invasive) that is targeted by an existing anti-tumoral drug, hence carrying potential clinical implications. We now want to exploit the knowledge coming from the neuronal field, the large amount of reagents present in this laboratory, and in vitro and in vivo experimental settings (mouse xeno- and ortho-transplants) in order to fully answer the questions stated above.

Biographical Sketch:
Marco Arese has dedicated his early research activities to the study of various mediators of intercellular communication that involve cancer and vascular cells (J Clin Invest. 1995 Aug;96:940-4). In the laboratory of Prof. Daniel B. Rifkin, at the New York University Medical Center (USA), he examined the mechanisms of action of two growth factors: Fibroblast Growth Factor-2 (FGF-2, Mol Biol Cell. 1999 May;10:1429-44) and transforming growth factor-beta (TGF-beta). During the last fifteen years, he has devoted himself to studying the “molecular parallels” between the nervous system and vascular and tumoral tissues, with the aim of finding new targets that drive the cooperation between the tumor and its “microenvironment” (specifically, infiltrating vessels and nerves). In turn, this cooperation is known to fuel disease progression. Initially, he discovered that two synaptic proteins, Neurexin and Neuroligin, have widespread functions in the vascular system, including tumor angiogenesis (Proc Natl Acad Sci U S A. 2009 Dec 8;106:20782-7; Arterioscler Thromb Vasc Biol. 2012 Jul;32:1563-72). He is currently devolving all efforts to focusing on the role of these two nervous proteins in the tumor/nerves connections, which mediate tumor growth and dissemination but are still widely underestimated in the clinic.

Selected references
Cellular and molecular mechanisms sustaining tumor angiogenesis

All target therapies, including antiangiogenic therapies, are far from the wished results. However antiangiogenic regimens are an important tool for solid tumor treatment. Our studies aim at understanding the complexity of angiogenic processes in physiology.

Team
Serena Marchiò, Elena Astanina, Valentina Comunanza, Gabriella D’oronto, Lucia Napione, Alessio Norghero, Davide Corà, Maria Alvaro, Anna Gualandris

Research topics:
Identification of early biomarkers of pancreatic ductal carcinoma (PDAC).

Background:
Elegant tracking studies of the genetic evolution of PDACs indicate at least 15 years between the occurrence of the initiating mutation and the acquisition of metastatic ability. This result demonstrates a broad time window of opportunity for early detection to prevent deaths from metastatic disease. We reasoned that an early biomarker had to play a necessary role in the onset of the disease and preferentially released from the cells. Therefore we performed a whole transcriptomic analysis of the early in situ carcinomas (PanIN) isolated by laser capture microdissection from a genetically engineered mouse model characterized by the expression of KRASG12V in acinar cells through the use of the elastase promoter (Elias-K-RasG12V).

Research achievements:
RNAs highly expressed in PanIN encode proteins involved in axon guidance cues and synaptogenesis that recently have been demonstrated to be altered in PDAC. We focused on neuroligins (Nlg), a family of adhesive molecules regulating synaptic activity. Anti-pan-Nlgs antibody showed a faint membrane signal of acinar and ductal cells whereas PanINs displayed a stronger staining that dropped in PDAC. Similar results were obtained in human lesions (a series of 6 Panin, 8 PDAC and 4 pancreaticis from the University of Verona). By analysing the expression of the 5 Nlgs we visualized a minute population of acinar cells carrying KRASG12V and expressing Nlg-2 associated with stemness markers (DCLK1, CD24, CD44, and CXCR4). The current hypothesis of the pathogenesis of PDAC relies on the differentiation of acinar precursors carrying KRAS mutation into ductal cells (acinar-ductal metaplasia). We demonstrated that KRASG12V acinar cells isolated from Elias-K-RasG12V underwent in vitro acinar ductal metaplasia with an increased expression of Nlg-2. An isogenic cell line carrying KRASG12V (provided by Prof. Bardelli) overexpressed Nlg-2 as compared with wild-type cells. Loss-of-function experiments showed that Nlg-2 ablation halted acinar-ductal metaplasia, supporting the concept that Nlg-2 is necessary in the early phase of PDAC. Then, we looked for the possibility that Nlg-2 was shed by the cells, supported by the presence of a Disintegrin And Metalloproteinase (ADAM) proteolytic cleavage site in the extracellular domain. Nlg-2 accumulated in the serum-free supernatant of pancreatic PT45 human cell line overexpressing Nlg-2. This phenomenon is blocked by ADAM inhibitors TAPE-2 and GM 6001.

Conclusions and perspectives:
We reported that Nlg2 (i) has an early role in PDAC by promoting the acinar-ductal metaplasia of precursors; (ii) is shed by an ADAM-dependent mechanism. To further support the role of Nlg2 as an early biomarker in PDAC, we will continue the following activities: (i) demonstration of the role of Nlg2 in stemness features of acinar precursors undergoing acinar-ductal metaplasia; (ii) analysis of PDAC progression in Elias-K-RasG12V model crossed-back with Nlg2/- mice (in collaboration with Prof. Arese); (iii) generation of mAb anti-Nlg2 to set-up an ELISA for Nlg2 quantification in biological fluids; (iv) increase of human samples to analyse Nlg2 expression and activities.

Biographical Sketch:
Federico Bussolino began his scientific career by investigating the cross-talks between the mediators of inflammation and vascular cells with the goal of understanding the cellular traffic across vascular walls. Then (1988), he was captured by the discovery of colony stimulating factors and their strict specificity during hematopoiesis. He has gone beyond this concept, showing that these molecules activate a pro-survival and pro-angiogenic program in endothelial cells (Nature 337: 471, 1989). After 20 years, the proangiogenic roles of these molecules have clarified their fundamental role in the bone marrow vascular niche, which is fundamental in the maturation of blood cells.

Then he moved to tumor angiogenesis showing the role of the MET receptor in cancer-associated vascularization (J Cell Biol 119: 629, 1992). This seminal observation supported the concept that Met is pivotal in the regulating the invasive growth. In 1996, he began to work on VEGFs showing that HIV-1 Tat activates the VEGF pathway. This result emphasizes the ability of the virus to directly support the progression of tumors appearing in AIDS (Nat Med 2:1371, 1996; Nat Med 8:225,2002). In Embo J. (18: 882,1999), he firstly demonstrated the existence of a dynamic platform constituted by adhesive and tyrosine-kinase receptors. In 2003, he funded a successful interdisciplinary PhD program on complexity in biology that has anticipated the concepts of Systems Biology. In 2003, he contributed to open a frontier in angiogenesis, by connecting the 3D architecture of the vascular bed with the mechanisms that wire neurons. (Nature 424: 391, 2003). Recently, he has added another piece of information about the cues shared by the brain and vascular system by demonstrating that two synaptic proteins, neurexin and neuroligin, regulate the assembly of vascular units.

Selected references
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Napione L et al. IL-12-dependent innate immunity arrests endothelial cells in G0-G1 phase by a p21(Cip1/Waf1) mediated mechanism. Angiogenesis. 2012, 15:713-25
Cell migration in tumor angiogenesis and invasion

The mechanisms of cancer onset and progression will allow the prevention of metastatic dissemination by pharmacological inhibition

Team
Laura Di Blasio, Alberto Puliafito, Giulia Chiaverina, Paolo Gagliardi, Desiana Somale

Research topic:
Molecular mechanisms that differentiate invasive cancer cells from their non-motile counterparts, and the relationship between tumor and non-tumor cells during cell migration.

Background:
Cancer cells spread from the initial site of tumor growth acquiring an invasive phenotype characterized by both the loss of cell-cell interactions and increased cell motility. Cells which undergo this epithelial to mesenchymal transition are then able to move and spread throughout the entire body as isolated and highly motile cells. Recent evidence shows that tumor cells also move as groups both in normal development and in cancer models, in a process named collective migration. Even vascular endothelial cells collectively migrate into tumor mass forming new vessels in a process called tumor angiogenesis.

Research achievements:
We are developing new three-dimensional (3D) culture systems that in combination with conventional cell biology approaches, allow the study of collective and directional cell migration. A new model for in vitro tumor angiogenesis studies has been described and cell spheroid cultures from breast and prostate cell lines have been developed. With these three-dimensional models we have been able to discover new mechanisms of PI3K regulation of collective migration and the role of the endothelial podosome in tumor angiogenesis.

Conclusions and perspectives:
We are convinced that spheroids/organoids 3D culture from cells and tissues could overcome limitations of established cell lines, such as adaptation to 2D growth, providing better models for studying collective migration, epithelial-to-mesenchymal transition and tumor vascularization, and for the identification of molecular mechanisms involved in these processes. Moreover, we are establishing 3D cell cultures from patient-derived xenograft (PDX) of colon cancer with a high percentage of in vitro engraftment. By combining our know-how in 3D cultures with the PDX platform developed in the Institute, we will implement an unprecedented in vitro platform for genetic functional and drug screening purposes.

Biographical Sketch:
Luca Primo has a remarkable experience in the field of vascular cell biology. He started his research experience characterizing the thrombospondin receptor CD36. He showed that this membrane protein was involved in the pathogenesis of cerebral malaria (Blood, 1993; J Immunol, 2001) and angiogenesis (Faseb J., 2005). During his post-doc he contributed to unveil the molecular mechanisms of several angiogenic growth factors, such as VEGF-A (J BiolChem, 1998) and GM-CSF (Blood, 1997). He then moved to the Candiolo Cancer Institute where he focused his research efforts on the PI3K signalling pathway in angiogenesis and cell motility (Oncogene, 2000). During a research experience at the Tuft University of Boston, he started to study the protein kinase PDK1, a downstream effector of PI3K. He discovered the central role of PDK1 in breast cancer growth (Neoplasia, 2012) and invasion (J Cell Biol, 2014). By gene expression analysis in endothelial cells he discovered the pro-angiogenic role of integrin α6 (Cancer Res, 2010) and the effects of miR126 on Angiopoietin1 signaling (BBA MolCell Res, 2012). Moreover, he developed a new model for the three-dimensional study of tumor angiogenesis, the Human Arterial Ring assay, which can be exploited for drug screening and gene function analysis on human vessels (Blood, 2013). More recently, he described regulatory mechanisms of integrin endocytosis (Traffic, 2010; J Cell Sci, 2015) and the role of endothelial podosomes in angiogenesis (Nat Cell Biol, 2014). Luca Primo is Associate Professor of Biochemistry and group leader of the Laboratory of Cell Migration. He is author of more than 40 papers published in peer-reviewed journals, with an H-index of 23.
Mechanisms of escape from anti-angiogenic therapy

**The development of novel approaches such as anti-metabolic therapy can open new avenues for the treatment of aggressive forms of colorectal cancer**

**Team**

Manuela Cazzanti, Federica Linty, Alessia Mira, Virginia Morello

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**Research topic:**
Opportunities and limitations of targeting the HGF/MET pathway for cancer therapy.

**Background:**
HGF and MET have been attracting increasing interest in the last two decades as appealing targets for cancer therapy, leading to the development of various targeted drugs. However, the initial enthusiasm has been partially mitigated by a number of realizations: (i) anti-HGF/MET drugs display cytostatic rather than cytotoxic activity even in the most MET-dependent systems; (ii) MET activation in cancer occurs through multiple and redundant mechanisms, often involving micro environmental signals; (iii) the patient population that can benefit from HGF/MET inhibition per se is less broad than anticipated. To date, no HGF or MET targeted drug is approved for clinical use.

**Research achievements:**
(i) Mechanism of action of tivantinib. Tivantinib is being tested in Phase III as a 'highly selective MET inhibitor'. We demonstrated that this drug is not a MET inhibitor at all but a microtubule active cytotoxic compound. (ii) Generation of antagonistic anti MET antibodies for cancer therapy. Using the SIMPLETM antibody platform and in collaboration with arGEN X BVBA (Zwijnaarde, Belgium), we generated and validated 68 different antagonistic anti MET antibodies. The most promising among them was selected for clinical development and is now in Phase I (clinicaltrial.gov ID #NCT02055066), (iii) Role of HGF/MET signaling in intrinsic and acquired resistance to targeted therapies. We have demonstrated that micro environment derived HGF plays a major role in the resistance to anti angiogenic, anti MET and anti MEK therapies. (iv) Gene therapy of cancer using a monovalent anti MET antibody. We had previously demonstrated in collaboration with the Laboratory of Gene Therapy that the DN 30 anti MET antibody is antagonistic only if in a monovalent form. To achieve delivery of DN 30 Fab to the tumor, a lentiviral vector based technique was employed.

**Conclusions and perspectives:**
The HGF/MET pathway remains an appealing but elusive target for cancer therapy. While several HGF/MET inhibitors are available with therapeutic potential, including those generated by this laboratory, their optimal employment has not been focused yet. Our results point at an important role of HGF as a master modulator of cancer cell survival and metabolism in adverse micro environmental conditions, suggesting a potential therapeutic strategy based on the association of HGF MET inhibitors with drugs that cause tumor energetic unbalance. Among the most interesting drugs of this kind are anti metabolic agents, which held promise for cancer therapy in combination with HGF/MET targeted drugs. This field of study is currently being actively investigated by this laboratory, particularly in colorectal cancer.

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**Selected references**


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**Biographical Sketch:**
Paolo Michieli graduated in Biological Sciences at the University of Milano in 1990. After a few years of training at the Mario Negri Institute for Pharmacological Research and the Istituto Nazionale dei Tumori, both in Milano, he carried out his post-doc in the Laboratory of Cellular and Molecular Biology at the National Cancer Institute in Bethesda, Maryland. During this period he contributed to several scientific publications in the field of oncogenes, growth factors and cell cycle. In 1997 he moved back to Italy to the newly founded Candiolo Cancer Institute in Candiolo, Torino. Since then he has been Group Leader of a small team committed to experimenting novel therapeutic strategies in oncology, with particular reference to the molecular targeting of growth factors and their receptors. In 2001 he specialized in Clinical Pathology at the University of Torino Medical School. In 2008 he received a Ph.D. in Cellular Sciences and Technologies from the same University, and in December 2011 he was appointed tenured Assistant Professor at the Department of Oncology. He is author of 36 scientific publications accounting for more than 4,000 citations, a total impact factor of 387, an H-index of 26 and a i10-index of 30.
Research topic 2
From Molecular Biology to “Precision Medicine”

Research topic 2 is the scientific core on which the projects of most laboratories of the Institute are focused.

Advances in genome sequencing and expression analysis have made it possible to quickly identify genetic alterations with a potential “driver” role in tumor development, with unprecedented informative power. Thanks to these studies, today it is possible to classify tumors, not only on the basis of their site of origin and histopathological features, but also – and especially – by the identification of the genetic lesions that support their growth and that, for this reason, provoke tumor death when deactivated by targeted therapies. However, the contribution of each lesion to the transformed phenotype remains elusive. Moreover, knowledge is still insufficient on the mechanisms that control the lack of response to targeted therapies, even in the presence of a molecular target (primary resistance), as well as on the mechanisms that lead to progressive attenuation of the response after prolonged treatment (acquired resistance). Translational Research is a multi-disciplinary task based on the expertise of a new generation of scientists, specifically trained to translate molecular information into more effective treatments. The goals are ambitious: to integrate the traditional prognostic and diagnostic factors with a very detailed characterization of the genetic and functional alterations of the tumor; to identify new malfunctioning regulatory pathways in cancer; to isolate and study cancer stem cells; to develop new preclinical platforms that can reliably disclose – and understand in detail – the prospective results of clinical practice. The generation of this kind of knowledge is instrumental to instructing clinical trials that will be no longer based on empirical information but on a strong rational connotation.

Research Topic 2 concerns:
2.1. Oncogenes and growth factors
2.2. Genes responsible for response to antineoplastic drugs
2.3. Preclinical models of “personalized” therapies
2.4. Resistance to targeted therapies
Oncogenes involved in invasive growth

Genetic and molecular biology beyond the metastatic process is largely unknown. It is mandatory to identify and to validate therapeutic targets to develop long-sought (and still missing) effective therapies.

Team
Cristina Basilico, Silvia Benvenuti, Alessandra Gentile, Federica Verginelli, Maria Rita Virzì, Chiara Modica

Research topic:
Oncogenes involved in invasive growth

Background:
Growing evidence prompted us to hypothesize that the metastatic process involves members of the gene ‘super-family’ of tyrosine kinase receptors for ‘scatter factor’, homologues to the Met oncogene (Ron, Axl, Mer and Tyro). Recently, other poorly characterized genes of the family have been identified, Ror1 and Ror2, that can possibly interfere with the response to drugs directed against Met (entered in the clinic), generating resistance.

Research achievements:
In the past we have shown that the Met oncogene encodes the receptor for the ‘scatter factor’ HGF. A series of studies –performed for two decades in this and other laboratories- revealed the involvement and the importance of this oncogene in human cancers, demonstrating its key role in the control of ‘invasive growth’, a genetic program driving the metastatic process. We contributed to the development of drugs that inactivate the Met tyrosine kinase: either chemical inhibitors or monoclonal antibodies. These drugs inactivate cancer stem cells in preclinical models of glioblastoma, colorectal and gastric carcinomas, and provide promising results in clinical trials.

Conclusions and perspectives:
We are now working on the characterization of tyrosine kinase receptors of the Met oncogene family (Ron, Axl, Mer and Tyro, Ror1-2) at the genetic, biochemical and functional levels. In particular, we are studying their possible interference -positive or negative- with the intracellular signaling triggered by Met during execution of the invasive growth program. Emphasis is given to the study of a hyper-metastatic syndrome, the so-called CUP, metastatic cancer from unknown primary origin.

Biographical Sketch
Paolo Comoglio has a long and distinguished record in the field of research on tyrosine kinase receptors and related oncogenes. He developed the first anti-phosphotyrosine antibody (Comoglio et al. 1984, EMBO J. 3:483-9); by this tool he identified the tyrosine kinase encoded by the rearranged Bcr-Abl oncogene, responsible for the onset of Chronic Myeloid Leukemia (Mol Cell Biol. 1986; 6:1803-11.) He focused his research efforts on the full mechanistic insight of the genetics, biochemistry and biology of the Met receptor, with a special emphasis on the role of this oncogene in human cancers. After a long standing career he is now acknowledged as a leader in the field.

He identified the tyrosine kinase receptor encoded by the Met oncogene (Nature. 1989; 339:155-6.), discovered that Hepatocyte Growth Factor (HGF) is the cognate ligand (Oncogene. 1991; 6:501-4.) and cloned the Plexin genes (Cell. 1999; 99:71-80), recognizing their role as receptors for Semaphorins, signals for cell-cell repelling clues.

He identified and elucidated the functions of two tyrosine kinase receptors, encoded by genes structurally related to Met: Ron, (EMBO J. 1994; 13:3524-32), and Ror (Cancer Res. 2011; 71:3132-41). On the translational front he generated the anti-Met antibody DN30, and its monovalent counterpart, to be used in cancer therapy, either conventional or by ‘gene transfer’ (Cancer Res. 2008; 68: 9176-83).

Paolo Comoglio expounded and introduced a number of wisdoms that are now largely accepted and widespread, notably the concept of ‘invasive growth’, a genetic program otherwise ‘physiological’ but ‘usurped’ by cancer cells to progress toward metastasis (Nature Rev. Cancer 2002, 2:289-300).

To date (Dec 2014), he is author of more than 350 papers published in peer-reviewed journals generating more than 25,000 citations.

Selected references


Preclinical models of oncogene ‘addiction’

We aim to identify ‘dominant’ genetic aberrations that drive tumorigenesis and put them in the context of concurrent ‘recessive’ alterations that may act as modifiers of response to targeted therapies.

Team
Andrea Bertotti, Barbara Lupo, Francesco Galimi, Francesco Sassi, Giorgia Migliardi, Francesca Cottino, Simonetta Maria Leto, Eugenia Zanella

Research topic:
Translational models of cancer precision medicine.

Background:
Advances in technologies have allowed the attainment of powerful insights into the molecular determinants of human tumours, and in many cases inactivation of individual oncogenic drivers results in tumor regression. However, this knowledge has been translated into effective treatments very slowly, due to difficulty in predicting how the complex mutational background and the adaptive resilience of cancer cells can influence the activity of the dominant oncogene and modify response to therapies.

Research achievements:
Our projects aim at exploring the mechanisms of tumor dependency on oncogenic drivers and how such dependency is affected by genomic or functional modifiers, with an emphasis on colorectal cancer (CRC). Our experimental pipeline entails the deployment of multi-dimensional data for discovery and hypothesis validation, followed by cell-based mechanistic investigation and preclinical validation in patient-derived tumorgrafts – ‘xenopatients’. By this approach, we have contributed to finding that hyperactivation of the HER2 and MET oncogenes correlate with resistance to anti-EGFR therapies (cetuximab and panitumumab). To examine the global effects of somatic genetic changes in CRC on sensitivity to EGFR-targeted therapies, we performed complete exome sequence and copy number analyses of 129 tumors and analyzed their response to anti-EGFR blockade in xenopatients. We identified several alterations as potential mechanisms of resistance to this therapy as well as genetic lesions segregating in tumors with increased sensitivity to anti-EGFR therapy. Resistance to EGFR blockade could be overcome in xenopatients through combinatorial therapies targeting actionable genes. A typical response of CRC patients sensitive to EGFR neutralization is stable disease rather than massive regression. Mining of candidate gene expression outliers – coupled with retrospective analysis of patient material and in vitro functional studies – identified IGF2 as a predictor of poor sensitivity to cetuximab and as a new target. One limitation of xenopatients is that human tumour stroma is substituted by host (murine) components. However, this drawback can be exploited analytically to dissect the representation of human (cancer-cell specific) versus mouse (stromal-cell specific) traits in CRCs. By doing so, we contributed to re-categorising the transcriptional classification of CRC by demonstrating that a subtype displaying features of epithelial-to-mesenchymal transition and poor prognosis is not an expression of aggressive cancer cell dedifferentiation (as originally argued) but rather a read-out of abundant stromal content.

Conclusions and perspectives:
Our studies provide a systematic functional approach to evaluate response to targeted therapies in human cancer, highlight new mechanisms of responsiveness to anti-EGFR therapies, and provide a new vocabulary for the molecular management of colorectal cancer with immediate clinical implications.

Biographical Sketch:
Since 2006, Livio Trusolino has been Associate Professor of Histology at the University of Turin Medical School, Italy. He received his M.D. (1993) from the University of Turin and a Ph.D. in Human Oncology (1997) from the San Raffaele Scientific Institute, Milan, Italy. Livio initially studied the cross-talk between growth factor receptors and adhesion molecules in tumour transformation and cancer progression. Later, his work concentrated on the characterisation of the molecular mechanisms underlying responsiveness to anti-cancer targeted therapies, using innovative preclinical models. The results of Livio’s research have been published in leading journals such as Cell, Nature Genetics, Science Translational Medicine, and Cancer Discovery. He has also written review articles for Nature Reviews Drug Discovery, Nature Reviews Cancer, and Nature Reviews Molecular and Cellular Biology.

Biographical Sketch:
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Selected references


The puzzling oncosuppressive function of oncogenes

Identification of novel therapeutic targets and predictive biomarkers responsive to chemotherapy or targeted drugs in ovarian cancer

Team
Annalisa Lorenzato, Martina Olivero, Jessica Erriguez, Daniele Musiani, John David Konda, Erica Torchiaro

Research topic:
Unleashing the intrinsic tumor suppressive properties of oncogenes to kill cancer cells.

Background:
Oncogenic tyrosine kinases (TKs) might harbor intrinsic tumor suppressive functions. They sit at the apex of multiple downstream signaling pathways that exert various biological effects depending upon cell type and context. While some of these pathways are mitogenic and pro-survival, others might restrain the oncogenic potential by promoting, for example, apoptosis and senescence. Obviously, the latter programs do not confer a selective advantage and thus are hidden in cancer cells. However, intrinsic tumor suppression of TKs might be unleashed to kill cancer cells. This Laboratory had demonstrated that activation of the MET TK by its ligand Hepatocyte Growth Factor (HGF) results in the commitment to death of ovarian cancer cells. This model has been exploited to identify actionable molecules, that could be targeted to treat ovarian cancer and to sensitize ovarian cancer to standard platinum and taxane based treatment, once they have developed resistance.

Research achievements:
Among the actionable molecules this laboratory has identified (i) CDT2, (ii) the small heat shock protein of 27 Kda (HSP27), (iii) the PIM 2 kinase and (iv) the 90 kDa ribosomal S6 kinases (RSKs) that is presently still under investigation. In detail, using transcriptomic and small scale proteomics we found that MET activation in ovarian cancer cells resulted in the down regulation of the anti-apoptotic small heat shock protein of 27 KDa (HSP27, HSPB1) while MET inhibition in addicted cancer cell lines resulted in the increase of HSP27 and cell protection from death. Likewise, in human cancer cells susceptible to EGFR inhibition, EGFR inhibitors induced HSP27 expression and were strengthened by HSP27 suppression. Therefore, in cancer therapies targeting the MET pathway, the induction of HSP27 might limit the efficacy of anti-MET agents. As HSP27 increase also impairs the effectiveness of EGFR inhibitors and is known to protect cells from chemotherapeutics, the induction of HSP27 by targeted agents might strongly impact the success of combination treatments. A SILAC-based approach combined with TiO2-based phosphopeptide enrichment allowed the identification of PIM2 as a kinase whose phosphorylation is regulated by DNA damaging agents in ovarian cancer cell lines. Targeting PIM2 kinase sensitized ovarian cancer cells to drug-induced apoptosis, while PIM2 over-expression resulted in cell resistance to DNA damaging agents.

Conclusions and perspectives:
Altogether data showed that pro-apoptotic pathways can be unveiled in cancer cells by studying the unexpected pro-death outcome of MET activation. This allowed the identification of actionable molecules for which inhibitors are available and may find clinical application as an alternative or an adjunct to standard chemotherapy.

Biographical Sketch:
Maria Flavia Di Renzo got an MD degree at the University of Torino Medical School in 1977 and then the residency in Neurology in 1981. Besides short periods spent working in another University and abroad, she has been working in the same University as professor since 1981 and as full professor of Histology since 1994 to date. In 1997 she became head of the Laboratory of Cancer Genetics of the Candiolo Cancer Institute. Since 1981 she has been involved in the study of oncogenes and tumor suppressor genes in human cancer with a particular focus on tyrosine kinase oncogenes, demonstrating for the first time the increased expression of the MET oncogenes in human cancer (Di Renzo et al, Oncogene 1991 and subsequent publications). Moreover, she identified mutations of the MET oncogene in lymph node metastases of head and neck squamous cell carcinomas, reinforcing the concept of a genetic basis of the cancer progression towards metastasis. In 2004 her major research interest turned in the study of human ovarian cancer with the aim of identifying suitable targets for molecular therapy. For this purpose the group led by Maria Flavia Di Renzo has used functional (Rasola et al, Cancer Res 2004; Bardella et al., Clin. Cancer res 2007), genomic (Olivero et al., Mol. Cancer Ther., 2006; Lorenzato et al., FASEB J 2012) and proteomic approaches (Musiani et al, FASEB J and J Proteome Res 2014), that have led to the identification of possibly actionable molecules.

Selected references


Cancer stem cells and resistance to standard and targeted therapies

To set up therapies targeted at 'cancer stem cells', that are cells that constitute the 'roots of tumors', that resist chemo- and radio-therapy, and, after these conventional treatments, can cause tumor relapse

Team
Francesca De Bacco, Paolo Luraghi, Federica Verginelli, Viola Bigatto, Antonio D’Ambrosio, Francesca Orzan, Raffaella Albano, Elena Casanova, Elia Cipriano, Roberta Neggia, Gigliola Reato

Research topic:
The MET oncogene in cancer stem cell resistance to standard and targeted therapies.

Background:
Like normal tissues, tumors such as colorectal cancer or glioblastoma are structured according to a hierarchy that includes two main components. At the hierarchy’s apex there is a (small) subpopulation of ‘cancer stem cells’ (CSC) able to self-renew, namely to proliferate endlessly, and to relentlessly support tumor regeneration, growth, and dissemination. At the hierarchy’s base there is an (ample) subpopulation of cells that, unlike CSC, have limited proliferative ability, and tend to aberrantly differentiate and die. This model implies that, to cure the tumor, CSC must be eradicated. This task is challenging, as CSC are often inherently resistant to therapies that so far have proven effective against the hierarchical basis of tumor cells, therapies that also include the most innovative agents, targeted at the molecular lesions responsible for cancer pathogenesis. To achieve better therapeutic outcomes, it is mandatory to identify and attack the molecular and genetic mechanisms underlying CSC resistance to conventional chemo- and radio-therapy, or to agents targeted at molecular lesions.

Research achievements:
In CSC isolated from human metastatic colorectal cancer or glioblastoma (CR-CSC or GBM-CSC, respectively), we’ve found that the wild-type MET oncogene - the HGF receptor - confers primary resistance to standard therapies. In CR-CSC, MET counteracts the proliferative blockade imposed by EGFR inhibitors. Thus, in mouse models of CR-CSC xenografting in the presence of human HGF, we’ve shown that concomitant inhibition of EGFR and MET results in a greater and more durable tumor regression as compared with EGFR inhibition alone. In GBM we’ve shown that MET is a functional marker of a specific subset of CSC, and activates a signalling pathway that protects CSC from DNA damage and cell death induced by ionizing radiation. Consistently, MET inhibition sensitizes GBM-CSC to radiotherapy in vitro and in vivo, leading to enhanced regression of tumors obtained by xenografting GBM-CSC, prolonged mouse survival, and eradication of the GBM-CSC subpopulation.

Conclusions and perspectives:
The MET oncogene is crucial to sustain CSC viability and long-term propagation. In metastatic CRC and GBM, we’ve provided preclinical evidence that MET targeting impairs CSC properties, and increases the effectiveness of current therapies aimed at affecting cell proliferation (e.g. EGFR inhibitors) or DNA integrity and cell survival (e.g. radiotherapy). These results can instruct clinical trials that associate MET inhibitors with standard therapeutic protocols. Current work is aimed at identifying (i) the genetic and molecular context that modulates the CSC response to MET inhibitors; (ii) the intratumoral CSC genetic and phenotypic heterogeneity, which must be recognized to refine the targeted treatment of each individual tumor.

Biographical Sketch:
From the beginning of her career, Carla Boccaccio has contributed to elucidate the signalling and transcriptional mechanisms by which the MET oncogene controls invasive growth, a physiological program of stem and progenitor cells, inappropriately activated during tumor onset and progression. She discovered that MET regulates a genetic program concomitantly driving a procoagulant and a neoplastic phenotype, thus helping to unravel the pathogenesis of Trousseau’s syndrome, the association of cancer and thrombosis frequently observed, but often unexplained, in patients. More recently she discovered that MET is a functional marker of cancer stem cells isolated from brain and colorectal tumors. In these cells, MET sustains self-renewal, invasion, and resistance against DNA damaging treatments, such as ionizing radiation, and biological agents targeting other tyrosine kinase receptors such as EGFR. She is now engaged in understanding the interactions among MET activity, the genetic lesions occurring in cancer stem cells, and the cellular response to standard and targeted treatments, to identify the clinical context where MET inhibition can be effective.

Selected references


From Molecular Biology to “Precision Medicine”
Integrative genomics of cancer progression and resistance to treatments

The integration of molecular profiles and clinical information enables accurate determination of cancer aggressiveness and response to treatment, to individualize therapeutic approaches (precision medicine)

Team
Claudio Isella, Consalvo Petti, Gabriele Picco, Sara Erika Bellomo, Andrea Mignone

Research topic:
Integrative genomics of cancer progression and resistance to treatment.

Background: Cancer progression involves accumulation by neoplastic cells of multiple molecular alterations conferring metastatic ability and resistance to treatment. Over the last years, large international consortia have been delivering multi-layer molecular data (gene mutation, expression, copy number, etc.) for large series of clinically annotated tumor samples. Integrative analysis of such data has two main outcomes: (i) improved patient stratification into subgroups with different prognosis and treatment sensitivity (“molecular subtyping”); (ii) identification of patient-specific alterations that at the same time drive the neoplastic phenotype and provide an effective therapeutic target (“precision medicine”).

Research achievements:
Over the last two years, the Laboratory of Oncogenomics has been focusing on colorectal cancer (CRC) and on the generation and analysis of multi-layer molecular and pharmacological data on large sets of CRC samples, patient-derived xenografts (PDXs) and cell lines. The main achievements are summarized here: (i) identification of MACC1 mRNA levels as a prognostic indicator for liver-metastatic colorectal cancer; (ii) species-specific genomics of CRC PDXs to distinguish the stromal transcriptome, contributed by murine cells, from the human epithelial cancer transcriptome; (iii) identification of mixed mRNA/microRNA networks associated with CRC subtypes; (iv) integrative pharmacogenomic profiling of a large collection of CRC cell lines (n=151), validating molecular subtypes and providing new actionable expression outliers in specific cases; (v) identification of RAF1 and BRAF truncations as mediators of resistance to RTK-targeted therapy; (vi) development of “Genome Cruzer”, a 3D-interactive platform for visualization and analysis of large cancer datasets with multiple molecular and clinical layers (www.genomecruzer.com); (vii) development of a procedure for high efficiency in vivo transduction of PDXs with lentiviral vectors; (viii) identification of NEDD8 pathway inhibition as an effective therapeutic option in KRAS- and BRAF-mutant CRC, and in vivo validation of a molecular response predictor.

Sharing the genomic expertise of the Laboratory with other groups inside and outside the Institute also led to publication of several collaborative works.

Conclusions and perspectives:
The Laboratory will continue exploiting integrative genomics for better molecular stratification and for highlighting actionable therapeutic targets in CRC and other neoplastic diseases.

Biographical Sketch:
Enzo Medico graduated in Medicine at the University of Torino in 1989 and got a PhD in Cell and Developmental Biology in 1994, University “La Sapienza” of Rome. Since 2005 he is associate professor at the University of Torino. Dr Medico has a long-standing activity in the field of tyrosine kinase receptor signaling and genomics.

In particular, he has worked on the MET family of tyrosine kinase receptors, showing their role in the control of epithelial morphogenesis and invasive growth. Since 1998, Dr. Medico has re-directed his research in the field of functional genomics. In collaboration with the Fred Hutchinson Cancer Research Center, Seattle, he developed a “gene trapping” approach for genome-wide exploration of transcriptional regulation. Dr. Medico has been among the first Italian users of DNA microarrays technology, exploiting it since 1999 to study alterations in transcriptional regulation, gene expression and function associated with cancer aggressiveness and resistance to treatment. In 2004 he became director of the Laboratory of Oncogenomics at the Candiolo Cancer Institute. Over the last ten years, he has been managing and coordinating functional oncogenomics projects led by the Institute and funded, among others, by the Italian Government, by AIRC and by the European Commission.

Selected references


Pharmacogenomics of colorectal cancer
The knowledge of specific molecular alterations in the tumor DNA repair pathway could define a novel context of susceptibility for alkylating agents

Team
Ludovic Barault, Daniele Oddo

Research topic:
Predictive and prognostic role of specific or global epigenetic variants in cancer.

Background:
Epigenetic regulation is key to many stages of tumor development. Epigenetic changes such as global DNA hypomethylation and promoter-specific hypermethylation are found in early-stage tumors, making ideal markers for tumor detection and monitoring disease burden. Epigenetic mechanisms regulate the plasticity of tumor cells and may underlie some forms of drug resistance. Most epigenetic modifications may be reversible (and/or preventable) by pharmacological targeting of DNA methylation and histone acetylation and methylation. This laboratory was set up in 2012 to study the predictive and prognostic role of specific or global epigenetic variants in cancer. On one hand we aim to assess whether and how epigenetic mechanisms cause drug resistance in colorectal cancer (CRC); on the other, we aim to develop non-invasive methods to monitor changes in DNA methylation in cancer patients undergoing therapy.

Research achievements:
We have implemented a new assay to quantify methylation both in tumor and plasma samples based on an ultra-sensitive two-step digital PCR (ddPCR) technique followed by detection via fluorocytometer. As a test case, we focused on methylation of the O6-Methyl-Guanine-Methyl-Transferase (MGMT) gene. MGMT silencing by promoter methylation is commonly found in multiple cancers, and is prognostic and predictive of response to alkylating agents in glioblastoma (GBM). However, its value in malignancies other than brain tumors remains highly controversial. Methylated status of MGMT as assessed by ddPCR better defined a GBM patient subset with longer overall survival (p<0.001) compared to other techniques (including methylation specific PCR or pyrosequencing). In CRC patients, MGMT methylated status by ddPCR in either tissue or circulating tumor DNA was associated with better disease control rate with dacarbazine, as well as significant improved median progression-free survival (p=0.006).

Conclusions and perspectives:
In conclusion, our ddPCR technology outperformed commonly used methods for detecting MGMT methylation and allowed tumor molecular characterization from plasma. In the future, we wish to apply the same technology to other genes to track tumor burden in CRC as well as to detect mechanisms of drug resistance in BRAF mutant CRC patients. We have previously shown that preclinical models of BRAF mutant CRC are resistant to BRAF/MEK targeted agents or EGFR inhibitors in monotherapy, but are sensitive to their combination. These combo regimens are being tested in 7 clinical trials. We have generated BRAF mutant CRC cells with acquired resistance to combinations of BRAF/MEK and EGFR inhibitors. These cells will undergo functional screening in the laboratory of Prof R. Bernards (NKI) by exploiting a ‘chromatin regulator’ library of shRNAs targeting 661 genes to unveil epigenetic mechanisms of drug resistance.

Biographical Sketch:
Federica Di Nicolantonio holds a PharmD degree (1999) and gained a PhD (Medicine) from University College London, UK, in 2004. Her research focuses on the molecular mechanisms underlying cancer cells’ response to antineoplastic drugs. In her previous work she has given a significant contribution to discovering and establishing several cancer pharmacogenomic relationships. She identified KRAS mutations and KRAS amplification as biomarkers of resistance to the mTOR inhibitor everolimus (Di Nicolantonio F et al., J Clin Invest. 2010 20(8):2858-66) and EGFR monoclonal antibodies (Valtorta E et al., Int J Cancer. 2013;133(5):1259-65), respectively. She is the leading author of a highly cited manuscript that first described BRAF mutations as a biomarker of adverse prognosis and of resistance to EGFR targeted therapies in colorectal cancer patients (Di Nicolantonio F et al., J Clin Oncol. 2008;26(35):5705-12). This paper has received over 1000 citations so far and lead to the special mention in the 2011 Lorini Prize. Dr Di Nicolantonio contributed as a co-first author to the discovery that lack of efficacy of BRAF inhibitors could be mediated by EGFR, hence leading to the design of clinical studies aimed at testing combinations of EGFR and BRAF inhibitors (Prahallad A*, Sun C*, Huang S*, Di Nicolantonio F* et al., Nature. 2012; 483(7387):100-3). This preclinical work has provided the rationale for testing BRAF and EGFR inhibitors in colorectal cancer patients. Dr Di Nicolantonio has co-authored over 60 publications in peer-reviewed journals (i-index=24), three patents, and has given several invited lectures at both national and international meetings.
Personalized therapy and non-invasive molecular diagnostics of colorectal cancer

To define the genetic and molecular characteristics of patients in order to lead and check the treatment of colorectal cancer

Team
Sabrina Arena, Giovanni Crisafulli, Giovanni Germano, Sebastian Hobor, Simona Lamba, Luca Lazzari, Sandra Misale, Mariangela Russo, Beth Van Emburgh, Giulia Siravegna, Carlotta Cancelliere, Benedetta Mussolin, Luca Novara, Giuseppe Rospo

Research topic:
Clonal evolution and drug resistance: from cancer avatars to liquid biopsies.

Background:
A central paradigm of modern oncology is that tumor-specific molecular alterations underlie ‘functional’ dependencies that can be therapeutically exploited. Remarkable results have been obtained by applying this paradigm in the clinic, and several targeted drugs have been approved to treat, among others, melanomas, lung and colorectal cancers. Unfortunately even when applied to the ‘right’ patient, that is when they are tailored to a molecularly defined subset of tumors, the efficacy of targeted drugs is transient. Virtually all patients undergoing treatment with targeted agents eventually acquire pharmacological resistance (‘secondary’ or ‘acquired’) and undergo tumor relapse or progression. Arguably, the rapid and apparently unavoidable emergence of resistance is the major limitation to further progress in the application of targeted therapies in oncology. How can we overcome the near-certainty of disease recurrence following treatment with targeted agents?

Research achievements:
We have used colorectal cancer (CRC) as a model system to test the hypothesis that the emergence of drug resistance can be controlled. To this goal, we studied how clonal evolution impacts the development of resistance in patients’ avatars (cell lines and tumor xenografts). In parallel, we analysed clonal evolution dynamics and drug resistance in the blood of patients (liquid biopsies) who receive targeted therapies. Our results indicate that acquired resistance is -for the most part- a ‘fait accompli’. Mathematical models based on our data suggest that each (traceable) metastatic lesion contains hundreds of cells with mutations to virtually any targeted agents. According to this model, the time to relapse is simply the interval required for mutant or otherwise altered subclones to re-populate the lesion. On the positive side, we found that resistance can be prevented when drug combinations are rationally used.

Conclusions and perspectives:
The awareness that in nearly all patients targeted drugs are only transiently effective due to the rapid emergence of resistance poses a formidable challenge. Although the overall picture is looming, our data and the concepts they underlie offer several opportunities for intervention. Genetic tracking of cancer cell populations can be used to study how the development of resistance can be restrained in vitro and in vivo. Furthermore, liquid biopsies can be exploited to monitor clonal evolution and to intercept the emergence of resistant clones non-invasively in patients. When applied together cancer avatars and liquid biopsies may identify, monitor and potentially overcome resistance to targeted therapies.

Biographical Sketch:
Prof. Bardelli received a PhD in Molecular Biology from the UCL (University College London, UK). As a postdoc at the Johns Hopkins University (Baltimore, USA, supervisor Dr Bert Vogelstein) he developed the first comprehensive mutational profile of kinases (Bardelli et al Science 2003). As an independent investigator Prof. Bardelli has then translated these findings into clinical practice (Moroni et al., Lancet Oncology 2005; Di Nicolantonio et al., JCO 2008). Recently, Prof. Bardelli’s work has defined mechanisms of acquired resistance to anti-EGFR therapies in colorectal cancer patients thus providing insights into new therapies aimed at overcoming resistance (Misale et al., Nature 2012; Bardelli et al., Cancer Discovery 2014). These studies involve an innovative methodology - named liquid biopsy - which allows the use of circulating tumor DNA to monitor patient’s response using a blood draw (Misale et al., Science translational Medicine 2014). The H factor of Prof Bardelli is 58.
In 2014 he has been listed in the Thomson Reuters List of Highly Cited Researchers (http://highlycited.com/).

Selected references
Antibody gene transfer for ‘active’ targeted cancer immunotherapy

Development of novel therapeutic strategies to generate, produce and deliver monoclonal anti-cancer antibodies

Team
Simona Cignetto, Cristina Chiriaco, Lara Fontani

Biographical Sketch:

Research topic:
Antibody gene transfer for targeted cancer immunotherapy.

Background:
Clinical evidence indicates that the MET oncogene plays a role in progression of cancer toward metastasis and/or resistance to targeted therapies. While mutations are rare, the common mechanism of MET activation is overexpression, either by gene amplification ('addiction') or transcriptional activation ('expedience'). In both instances ligand-independent kinase activation plays the major role in sustaining the transformed phenotype. Currently available MET antibodies are directed against the receptor binding site, behaving essentially as a ligand (HGF) antagonist, and are ineffective in ligand-independent activation.

Research achievements:
The monovalent chimeric MV-DN30 antibody, delivered as a purified protein, binds the fourth IPT extracellular domain and induces proteolytic cleavage of MET, dramatically inhibiting downstream signaling pathways, in both the absence or presence of ligand. As an inventive approach, Mv-DN30 was delivered by ‘gene therapy’ driven by a second generation bidirectional lentiviral vector. In vitro, the antibody displayed a strong inhibition of ligand independent invasive growth of MET ‘addicted’ cancer lines, and –notably- of primary cells from a MET amplified gastric ca. patient. In vivo the antibody strongly impaired the growth of a panel of MET ‘addicted’ human cancer lines, xenotransplanted in nude mice lacking HGF. In patient-derived RAS wt colorectal cancer xenografts, MET amplification was found to correlate with resistance to anti-EGFR therapy. By the gene therapy approach, direct Mv-DN30 gene transfer in nude mice, intra-tumor or systemic, was followed by a therapeutic response of MET addicted human glioblastomas and lung carcinomas.

Conclusions and perspectives:
To further develop the MV-DN30 antibody as a strong candidate for targeting tumors sustained by ligand-independent MET oncogenic activation, resulting from MET amplification or mutations, and for overcoming resistance to anti-EGFR therapies. These studies will also provide proof of concept for a gene transfer immunotherapy strategy and encourage clinical studies with Mv-DN30.

Biographical Sketch:
Mechanisms of resistance to tyrosine kinase receptor inhibitors

Design of strategies bypassing resistance to targeted therapies

Team
Simona Corso, Elena Ghiso, Valentina Martin, Silvia Menegon, Cristina Migliore, Annalisa Petrelli, Maria Apicella, Marilisa Cargnelutti, Elena Morando

Research topic:
Molecular mechanisms responsible for response/lack of response to molecular therapies targeting receptor tyrosine kinases.

Background:
The goal of delivering the right drug to the right cancer patient requires understanding how genomic alterations are linked to drug response. Hence, the clinical efficacy of targeted therapy depends on: (i) the validation of the true biological relevance of putative targets in the context of a specific tumor type; (ii) the context-specific identification of the active drug(s) and of additional molecular alterations affecting the responsiveness to treatment.

Research achievements:
We have studied the mechanisms responsible for response/lack of response to molecular therapies targeting receptor tyrosine kinases (RTK). In particular, we have shown that: (i) the amplification of the MET proto-oncogene is responsible for de novo and acquired resistance to anti-EGFR therapy in colorectal carcinomas. (ii) Resistance of MET-addicted cells to treatment with a MET-antibody (MV-DN30) can be sustained by an increase of MET gene copies and overexpression of the MET receptor. Notably, antibody-resistant cells became ‘drug-dependent’ since the removal of MV-DN30 led them to death due to excess of signal. Finally, MV-DN30 and MET kinase inhibitors (TKIs) showed a synergistic effect on tumor cells. These findings suggest that a discontinuous, combined treatment with antibodies and TKIs may increase the clinical response and bypass resistance to anti-MET targeted therapies. (iii) Activation of members of the RAS family can confer resistance to inhibitors of the ROS1 RTK. This has important clinical implications as: (a) RAS alterations in ROS1+ tumors are negative predictors of efficacy for targeted drugs and (b) this resistance is unlikely to be overcome by the use of more potent ROS1 targeting drugs. (iv) By exploiting a large colony of gastric PDX (Patient-derived xenopatients), we are generating a study population that will be profiled for biomarker assessment and prospectively tested with targeted agents. This project combines the flexibility of preclinical analysis with the informative value of population-based studies. Starting by targeting HER2, half of gastric cancer patients could be potentially treated with RTK-directed therapies against ‘druggable’ targets. Making use of PDXs, we will validate known potential actionable targets, performing ‘clinical’ trials in mice with matching targeted drugs. To assure the feasibility of the project, in the last year we: (i) established a network of 15 centers for sample collection; (ii) optimized tumor engraftment in NOD-SCID mice. So far 46 samples have been implanted with an engraftment-learning curve going from the original 30% to the current >60%; (iii) identified patients bearing HER2, EGFR, FGFR2, MET and KRAS amplification and generated the corresponding PDX; (iv) performed a pilot study, from a MET amplified gastric cancer.

Conclusions and perspectives:
Resistance is, at present, the major limit of the efficacy of target therapies. Deciphering the mechanisms sustaining resistance to targeted therapies could guide the design of new clinical trials based on combinatorial therapies and it might help to overcome, or possibly prevent, resistance onset.

Biographical sketch:
Silvia Giordano has a long experience in the field of research on tyrosine kinase receptors and related oncogenes. She has focused her research on the study of the tyrosine kinase receptor encoded by the MET gene. She identified this receptor (Nature, 1989; 339:155-6.) and contributed to the understanding of the signal transduction mechanisms and of the biological role in physiological as well as in pathological conditions. In particular, she has critically contributed to the understanding of the mechanisms controlling MET down-regulation (Nature 416: 187-190, 2002) and HGF-independent activation (Nature Cell Biol. 9, 720-724, 2002). Moreover, she showed that cancer cells may be dependent (“addicted”) on the constitutive activation of this oncogene (Oncogene; 27:684-93, 2008). Recently, she has been deeply involved in the study of the mechanisms of resistance to targeted therapies (Cancer Res; 70:7580-90, 2010; Cancer Discovery, 3:658-73, 2013). She has also performed studies of the role of miRNA targeting and tumorigenesis. (Proc Natl Acad Sci U S A. 103:5909-5, 2006). Silvia Giordano is author of more than 110 papers, published in peer-reviewed journals. In January 2014 she was elected as President of the Italian Society of Cancer Research.

Selected references


Experimental cancer immunotherapy with Cytokine-induced killer cells

Adoptive immunotherapy against solid tumors

Team
Loretta Gammaitoni, Lidia Giraudo Diego, Giulia Mesiano, Valeria Leuci

Research topic:
Immunotherapy with Cytokine-Induced Killer (CIK) cells for the treatment of solid tumors refractory to conventional treatments.

Background:
Adoptive immunotherapy holds promise for the treatment of solid tumors. Disease relapse and drug resistance are sustained by a subset of putative cancer stem cells (CSC), poorly responsive to conventional treatments. Immunotherapy is a promising approach capable of targeting putative CSC. Our group has focused over the last years on a subset of T lymphocytes known as Cytokine-induced Killer (CIK) cells. CIK cells are ex vivo expanded T lymphocytes generated from circulating mononuclear cells, endowed with MHC-independent antitumor activity. The aim of our research is to explore adoptive immunotherapy with CIK cells for sarcomas and melanoma.

Research achievements:
We demonstrated that immunotherapy with CIK cells is active against autologous sarcomas and melanoma, including putative CSC. Our main findings are summarized as follows. (i) Generation of CIK cells: clinically relevant rates of CIK cells were successfully expanded from patients with sarcomas and melanoma; (ii) tumor killing activity: patient-derived CIK cells were highly active against autologous sarcomas and melanoma in vitro and in vivo; (iii) activity against CSC: we developed a lentiviral CSC-detector capable of visualizing putative CSC based on their ability to re-activate stem gene Oct4. Immunotherapy with CIK cells efficiently killed autologous CSC in sarcoma and melanoma models, in vitro and in vivo.

Conclusions and perspectives:
Adoptive immunotherapy with CIK cells is potentially active against solid tumors and capable of eradicating CSC. We plan to explore synergism of immunotherapy with molecular targeted approaches and focus on countering drug resistance and disease relapse.

Biographical Sketch:
Dario Sangiolo is a physician scientist with research interest in the field of transplant immunology developed at the Fred Hutchinson Cancer Research Center (Seattle, WA). He contributed to the development and characterization of preclinical models based on Cytokine-Induced Killer (CIK) cells (Int Immunol. 2008; J Immunother. 2012). In preclinical studies he demonstrated the activity of CIK cells against melanoma and sarcomas (Clin Cancer Res. 2013; Cancer Res. 2014 ). He explored strategies to genetically engineer T lymphocytes to enhance antitumor activities and decrease the risk of GVHD across HLA barriers (Hum Gene Ther. 2009; Gene Ther. 2007). In the field of clinical research he investigated the efficacy and toxicity of Hematopoietic Cell Transplant in hematologic and solid tumors (Biol Blood Marrow Transplant. 2010; Blood. 2006 May).

Selected references
Todorovic et al. Ex vivo allogeneic stimulation significantly improves expansion of cytokine-induced killer cells without increasing their alloreactivity across HLA barriers J Immunother. 2012, 35:579-86
Over the past few years, the improved knowledge on the biological, genetic and molecular heterogeneity of tumors, together with the development of pharmacological technologies, has allowed the identification of molecular targets for novel therapeutic strategies. This fast process has led to the overall reconsideration of classical approaches to clinical oncology, traditionally oriented toward design of cancer treatments irrespective of the biological and genetic peculiarities that can make each tumor a pathology on its own. The identification of patients likely to respond to specific treatments according to the presence of relevant molecular targets (personalized medicine) and based on the expression of potential markers of sensitivity or resistance, needs clinical studies that result from a constant and productive interaction among the professionals with a significant background in the various disciplines. The goal of the “Investigational Clinical Oncology” team is to increase the therapeutic index of molecular targeted drugs, by the identification and clinical validation of biomarkers of sensitivity/resistance. This goal is pursued through the development of research programs aimed at designing hypothesis-driven clinical trials that directly derive from the Institute’s biological, genetic and molecular research. In order for these tasks to be implemented, an ad-hoc organizational structure favours the interchange and the synergy among preclinical researchers, oncologists and pharmaceutical companies – which are the potential providers of new drugs for clinical trials. Another of INCO’s goals will be the promotion of a clinical research culture based on the knowledge of molecular biology and tumor genetics, and particularly of the mechanisms of sensitivity or resistance to molecular targeted drugs. This organization is instrumental to the referral of patients for admission into top-priority clinical trials.

Research Topic 3 is focused on:
3.0 Rational design of clinical trials for targeted drugs.

AGNOSTOS is a precision medicine project aimed at addressing both clinical and translational needs of CUP, a heterogeneous clinical syndrome represented by metastatic tumors that are first-time diagnosed in the absence of a clinically detectable primary lesion. Three protocols are embedded in the project: AGNOSTOS Profiling, a non-treatment protocol to collect biological specimens from CUP patients for translational purposes; AGNOSTOS Trial, a multicenter, randomized phase 2 trial with a ‘Pick the Winner’ design in treatment-naive CUP patients; AGNOSTOS 2, an observational therapeutic protocol for previously chemotherapy treated patients aimed at selecting patients for target therapy according to the molecular profile of their CUP tumors.
HERACLES and ARES: trials for the ‘Precision Medicine’ of Cancer

Shaping the clinical validation path of new putative targets found in the Institute’s preclinical programs

Team
Antonella Balsamo, Cosimo Martino, Marilì Vitiello, Mario Spione

Research topic:
Design, implementation and conduction of ‘hypothesis-driven’, precision medicine trials based on the translational discoveries of the FPO-IRCC research laboratories

Background:
Precision medicine brings a new set of challenges to clinical application. To hasten the adoption of new therapies we need to achieve a deeper molecular understanding of cancers and reliably translate results from representative preclinical models into clinical trials enriched with suitably identified patients.

Research achievements:
At Candiolo we have started to confront precision medicine hurdles by creating a clinical platform integrating, under the same virtual roof, the efforts of surgeons, pathologists, radiologists, and medical oncologists from the IRCC clinical network (25 centers around Italy), in order to assemble the timely collection of high quality, clinically annotated biological samples at meaningful time points, to feed research projects and precision medicine trials. Five translational protocols are now feeding the translational Labs of the Institute (PROFILING, AGNOSTOS-Profiling, GEA, FUNNEL and CORNUCOPIA). Together with the translational scientists, we are also building a “cancer knowledge network” to store the resulting molecular and medical data in digital form and to deliver them, in comprehensible ways, to scientists, clinicians, and patients (Projects LAS and PROBUS). Three hypothesis driven clinical trials have been designed and implemented (HERACLES and ARES in colorectal cancer, AGNOSTOS in cancer of unknown origin). HERACLES has been the Institute first precision trial designed upon the discovery, based on PDX studies, that HER2 amplification in metastatic colorectal cancer (mCRC) associates with resistance to anti-EGFR therapy, and predicts response to the combination of lapatinib and trastuzumab for a dual blockade of the HER2 pathway. Accordingly, we conducted a proof-of-concept trial testing the combination in HER2 amplified mCRC patients failing standard therapies. The trial has proven the efficacy of the combination with 8 long lasting responders out of 23 patients treated, proving HER2 as the first bona fide actionable target in mCRC. Genotype/response correlation has shown that only patients with truly ‘HER2 addicted’ tumors benefit from this therapy. The tumor genomic landscape of non-responders and relapsing cases is under scrutiny to define the determinants of primary and secondary resistance.

Conclusions and perspectives:
In the next year we will focus on addressing the obstacles encountered in HERACLES: unexplained primary drug resistance, inadequacy of current criteria for monitoring tumor response and recurrence, limited knowledge of genomic heterogeneity of mCRC. We will also extend the dynamic research infrastructure which we have created for mCRC to gastric cancer and cancers of unknown origin. Two new resource-dense, hypothesis-driven trials deriving their rationale from the results of the Institute’s translational labs, will be embedded and nurtured by this infrastructure.

Biographical Sketch:
Silvia Marsoni has a distinguished career as a clinical trial methodologist, which started in the ’80 at the NCI-USA. Since then, she has focused her research efforts on the rationalization of oncology trials. In the nineties at the Mario Negri Institute she founded her first clinical network and designed pivotal phase 3 trials establishing the standard of care in the adjuvant setting of colon cancer. Currently, she still designs standard-defining trials for genotype selected populations. In 2000 she founded SENDO, a non-profit organization for the early development of new cancer drugs in Italy and Spain. SENDO, firstly in Italy, developed targeted drugs in biomarker enriched populations. While she also developed trabectedin in ovarian cancer. Since 2011 she directs the Clinical Trials Unit, and has built the clinical platform for genomic-driven trials serving the translational labs of the Institute. The first of these trials, HERACLES, is targeting HER2 in colorectal cancer with promising preliminary results. In the last 20 years she has authored more than 80 clinical research papers published in peer-reviewed Journals.

Selected references
Personalizing HER2-positive breast cancer treatment

To optimize HER2 molecular target therapies to avoid, if possible, standard cytotoxic chemotherapy in this subgroup of patients with breast cancer

Team
Elena Geuna, Andrea Milani, Valentina Rossi, Annamaria Nuzzo

Background:
Amplification of the human epidermal growth factor receptor 2 (HER2) gene, which results in overexpression of its transmembrane tyrosine-kinase receptor product, is found in about 15% of breast cancers. This abnormality drives an aggressive clinical phenotype. HER2-treatment in combination with chemotherapy has revolutionized the outcome of patients with this otherwise rapidly fatal disease. While newer achievements in this field have led to more and more complex forms of treatment (i.e. combination of multiple HER2-targeting agents with chemotherapy) as standard of care, anecdotal experience and some clinical and experimental evidence indicate that purely HER2-driven tumors may display exquisite sensitivity to simplified targeted therapies. Establishing molecular markers of sensitivity, which is the main purpose of our project, would provide the basis for a more rational utilization of the several anti-HER2 agents that are available and provide guidance for further refinement.

Research achievements:
We have shown that HER2-positive metastatic breast cancers respond differently to chemotherapy according to hormone receptor co-expression. In particular, the now called “triple-positive” breast cancer (HER2, ER and/or PgR positive) was found to be less responsive to chemotherapy and, possibly, better suited to free combinations of anti HER2-agents with endocrine therapy. This biological difference may also impact the scheduling and duration of anti HER2 therapy in the adjuvant setting.

In a clinical trial that we conducted (HERLAP), we observed that tumors belonging to the HER2-enriched breast cancer subtype and with a high HER2/p95 expression ratio are particularly sensitive to single agent anti HER2 therapy with trastuzumab or lapatinib. Patients whose tumor bears this biological profile may be suitable for simplified treatments (i.e. sequential use of single-agent anti HER2-treatments with or without chemotherapy).

Conclusions and perspectives:
Results of the HERLAP trial suggest that a molecular profile can identify patients where the current standard of combining chemotherapy with multiple HER2-targeting agents could represent an overtreatment and a potential waste of resources. We are now seeking to validate our preliminary findings in the currently ongoing HERLAP study. In this trial, 60 patients at their first diagnosis of HER2-positive, low-burden metastatic breast cancer receive trastuzumab and lapatinib without chemotherapy if the disease responds to biological therapy. The translational research plan includes extensive evaluation of molecular markers that can identify long-term responders, including but not limited to RNA expression profiles with the PAM50 test and whole genome analysis on tumor tissues and circulating DNA to establish mutated genes that could be related to outcome.

Biographical Sketch:
Dr. Filippo Montemurro is the Director of the Investigative Clinical Oncology Unit (INCO) at the Candiolo Cancer Institute - I.R.C.C.S. This recently created Unit is at the interface between basic, translational and clinical research and is strongly committed to designing clinical trials of cancer precision medicine. During his fellowship and his professional career, Dr. Montemurro has focused on breast cancer and biologically targeted therapies for the HER2-positive subset, where he has acquired competence and international visibility. In particular, he has pioneered reductive approaches aimed at sparing chemotherapy to patients with HER2-positive metastatic breast cancer whose disease shows molecular features of clinical addiction to the HER2 oncogene. Currently, he is Principal Investigator and steering committee member of a number of Phase II and III, multicentric international Clinical Trials in breast cancer. Furthermore, in the context of the activities of the INCO unit, he co-chairs a special program in patients with metastatic Cancer of Unknown Primary origin (CUP), which includes clinical and molecular investigations in this rare, but meaningful disease subset. Presently, Dr. Montemurro has published 90 papers in international medical journals, a substantial proportion of which as first, senior or corresponding author.

Selected references:
AGNOSTOS: Target Therapy and Cancer of unknown primary (CUP)

The project aims to build a genomic profile of CUPs, focusing on MET and selected oncogenes known to be frequently mutated in cancer

Team
Paola Cassoni, Rebecca Senetta, Claudio Valizia, Patrizia Morbini

Research topic:
Cancer of Unknown Primary (CUP).

Background:
Cancer of unknown primary (CUP) is defined as metastatic cancer in the absence of a clinically detectable anatomically defined primary tumor site, after an adequate diagnostic evaluation. This condition defines a highly malignant syndrome which accounts for up to 6% of the whole cancer population and - at present - is still lacking appropriate therapies. While the majority of CUP related studies are focused on how best track down the putative cancer of origin, the real enigma of this syndrome is related to its biological and genetic setting as supported by growing evidence suggesting that indeed the rationale for personalized targeted therapies is in the genomic alteration of cancer cells, rather than in the tissue of origin.

Research achievements:
Given the highly aggressive metastatic phenotype of CUPs we have focused on the Met oncogene, a key player of the ‘invasive growth program’, and have recently demonstrated a five-timess higher mutational incidence (15% vs 3% of unselected cancer population) in a cohort of about 50 CUP patients.

Conclusions and perspectives:
The activity of the CUPs Center is part of AGNOSTOS, a larger program to optimize the diagnosis and the treatment of CUP patients at our Institute. AGNOSTOS includes a comprehensive diagnostic algorithm and a phase 2 trial in which patients, whose metastases harbor an ‘actionable’ molecular alteration including MET, will be treated with the accordingly appropriate targeted drug. Treatment outcome will be monitored with both traditional methods and BEAMing, a ‘liquid biopsy’ technique that uses the putative ‘actionable’ target as a marker of therapeutic success. In addition, as part of this program, the tumor material of CUPs, which harbor specific genetic lesions, will be implanted in immuno-compromised mice to establish human-mouse (Xenopatients) models of CUPs for preclinical studies.

Biographical Sketch:
Dr Giulia Maria Stella graduated in Medicine and Surgery in 2001 at Pavia University Medical School. She got the MD European Qualification in 2002. She obtained the specialization in Respiratory System Diseases in 2005 and completed a PhD in Pharmacological Sciences in 2005. In 2011 she obtained a Master degree in Molecular Oncology at Turin University Medical School. She is now working. As a clinical research assistant (Hospital Medical staff) responsible for the pneumo-oncology DH at San Matteo Hospital Foundation in Pavia, she is a lecturer in Respiratory System Diseases at Pavia University Medical School. Her research interest is focused on cancers of Unknown Primary origin (CUPs). Her work has documented the activation in this syndrome by somatic mutations, of the MET oncogene. She is now involved in both selecting and following CUP patients and in analysing the genetic profile of these lesions, in a translational perspective. Her technical skills and Medical competences go from molecular and cellular biology, to biochemistry and bio informatics to clinical expertise (invasive and Medical procedures required for thoracic cancer patient management). She is author of 24 peer-reviewed indexed papers. She is a member of the Editorial Board of Ars Pneumologica and Translational Lung Cancer Research. She has active collaborations with the University of Pennsylvania and with the Norwegian University of Science and Technology.

Selected references


Research Topic 4: Applied Clinical Research

The ultimate task of the Institute is the development of clinical research integrated with health assistance, also through nationally- and internationally-controlled clinical trials. With the introduction of molecular therapies, it has been understood that a specific disease can have different characteristics that need different therapies. Treatments are therefore oriented toward personalized therapy, which needs a very sophisticated molecular diagnostics armamentarium that the Institute is able to provide. Ongoing clinical research integrates the Divisions, the Laboratories and the Facilities, in order to allow synergy among different highly-specialized technologies and complementary, diagnostic and therapeutic know-how. The research goal is the progress of science, but the figure and the well-being of the patient are an absolute priority. The participation in the experimental protocols is voluntary and is suggested to patients according to the biological and clinical characteristics of the disease. The Ethics Committee of IRCCS-FPO guarantees that patients receive only treatments having solid scientific bases and that they are monitored with the most serious attention. In compliance with the Declaration of Helsinki, patient who do not wish to participate in a trial receives the best “standard” therapy.

Oncologists, surgeons, radiologists and radiotherapists cooperate with researchers to design clinical trials based on molecular data, intended to verify and generate hypotheses. In order to make this cooperation productive, the Institute manages a daily net of interactions involving formal aspects (seminars and meetings), training (refresher courses and lessons) and operational efforts (contacts with pharmaceutical companies, regulatory and management instruments).

Clinical Research is the last and most important haven to improve the assistance to cancer patients, to increase their life expectancy and to provide them with the most appropriate, safe and effective therapeutic approach according to the genetic characteristics of their own tumor. The controlled clinical Protocol is the final product of the overall work of a multidisciplinary group composed of basic researchers, oncologists, surgeons, pathologists, pharmacologists, radiologists and nuclear medicine doctors, biostatistics and bioinformatics scientists, research healthcare assistants, data managers and legal experts. The main projects of the Applied Clinical Research are listed below, followed by the table of Controlled Clinical Trials.

Research Topic 4 concerns:

4.1. Colorectal cancer: onset and progression
4.2. Development of new therapeutic strategies
4.3. New approaches to surgical oncology
4.4. Laboratory Medicine, Imaging and Radiotherapy
Stochastic modelling of colorectal tumorigenesis
Identification of molecular and morphological markers of premalignant colon tumor lesions, to rationalize diagnostic and therapeutic strategies

Team
Laura Casorzo, Carmine Dell’Aglio, Ivana Sarotto, Elena Frangipane, Alberto Pisacane

Research topic:
Aurora Kinase Gene A in the Early Steps of Colorectal Tumorigenesis

Background:
A crucial role for the Aurora Kinase A (AURKA) gene has been demonstrated in the advanced steps of colorectal tumor progression, likely through the promotion of a CIN phenotype, but little is known about its involvement in the early steps of the adenoma-carcinoma sequence. Despite approximately 30% of colorectal cancers occur by means of the serrated neoplasia pathway, no data are currently available concerning Aurora Kinase A involvement in serrated tumorigenesis. The current investigation is aimed at evaluating the involvement of the AURKA gene and protein in the early, progressive and non-progressive steps of the conventional adenoma-carcinoma sequence and at clarifying their role in the serrated tumorigenesis of the large bowel.

Research achievements:
We demonstrated that the AURKA gene is involved in the adenoma-carcinoma sequence of the large bowel, acting solely in adenomas in which the malignant transformation actually occurs (progressive adenomas); in this setting, protein expression strictly parallels the increase in gene copy number. Conversely, the diploid status of the gene is maintained in non-progressive conventional adenomas and along the progression of serrated neoplasia. Aurora Kinase A protein expression in serrated polyps is uncoupled from gene status and is likely to reflect apoptotic dysregulation.

Conclusions and perspectives:
FISH evaluation of AURKA gene status could therefore potentially discriminate between progressive and non-progressive conventional adenomas of the large bowel. The clinical significance of the morphologically identifiable dysplasia in the natural history of serrated lesions has to be critically re-evaluated.

Biographical Sketch:
Mauro Risio has been director of the Division of Pathology at the Institute for Cancer Research and Treatment since 1999. He was visiting Professor of the Department of Pathology at the Memorial Sloan-Kettering Cancer Center, New York, in 1995. He was senior Scientist at the Strang Cancer Center, Cornell and Rockefeller University, New York 1996-2006. Most of his scientific activity is related to the pathology of premalignant colorectal lesions. Mauro Risio has supervised several international polycentric studies concerning the histological features of adenomas with invasive cancer (Histopathology 2012, 61: 562-575), and authored the most recent national and international guidelines for colorectal neoplasia pathological diagnosis (Dig Liver Dis 2011, 43: 344-55; Virchows Arch. 2011, 458: 21-30; Surg Endosc 2015).

Identification of potential targets in cancer of the biliary tract

Development of new cancer therapies to improve the prognosis of biliary carcinomas, a group of highly lethal malignances

Team
Renato Ferraris, Federica Colombi, Ilaria Depretis, Elisabetta Fenocchio, Roberto Filippi, Donatella Marino, Giuliana Cavalloni, Caterina Peraldo Neia

New strategies in advanced biliary cancer treatment

Background:
Biliary tract cancer (BTC) is a rare and lethal disease with very few therapeutic options. Previous studies suggest that Epithelial Growth Factor Receptor (EGFR) pathway activation could be involved in BTC pathogenesis, envisaging a potential role of anti-EGFR monoclonal antibodies.

Research achievements:
Our group has designed and coordinated a multicenter randomized phase II clinical study to evaluate the efficacy of the fully human monoclonal anti-EGFR panitumumab (P) in combination with standard chemotherapy (GEMOX) compared to GEMOX alone for the treatment of unresectable BTC with KRAS wild-type status (Vecti-BIL study, NCT01389414). The primary endpoint was to demonstrate that the P-GEMOX combination is able to prolong progression-free survival (PFS) from 6 months (estimated PFS of GEMOX arm) to 10 months. Enrolment in the study, which involved 10 Italian Cancer Centers, was completed in September 2013. On December 15th 2014 the database will be closed and final analysis will be published. Preliminary results demonstrated that the P-GEMOX combination showed a trend towards better PFS and response rates (RR) in KRAS wild-type BTC patients as compared to GEMOX alone. Even in the case of positive results, it is clear that anti-EGFR therapy may be only a step closer to better control of the disease and that the search for other targets remains an essential topic. To this aim, we have developed a large scale approach based on gene expression profiling, genome sequencing, miRNA and proteomic profiling of primary BTC to identify new potential druggable targets in these tumors. To build more suitable preclinical models to test new therapies, we are focusing on the xenograft model. To date we have achieved significant results in preclinical models with the use of both targeted agents such as Src inhibitors and alternative (non-target specific) chemotherapy such as ET-743. Recent advances in our work have demonstrated that in 9% of BTC a FIG-ROS fusion is detected. In particular, we have set up a new, quick, specific, and sensitive PCR test to screen for the FIG-ROS1 fusion.

Conclusions and perspectives:
On these bases we are planning new trials in patients relapsing after standard therapies where treatment will be driven by an extensive molecular analysis.

Biographical Sketch:
Francesco Leone is Assistant Professor at the University of Turin, Department of Oncology. Since 2006 he is coordinator of the activities of the multidisciplinary team for the treatment of digestive cancers at the Candiolo Cancer Institute and coordinator of translational research projects in this field between the Medical Oncology Division and the Oncology Laboratory at the Institute. In colorectal cancer, the major area of interest is represented by “conversion therapy” to maximize the possibility to offer surgery to metastatic patients (Crit Rev Oncol Hematol. 2014;92:218-26, Cancer. 2013;119:3429-35). He realized a significant synergy also for the multidisciplinary treatment of locally advanced pancreatic cancer (Cancer. 2013;119:277-84) and, in the metastatic setting, he participated in the pioneering of modern immunotherapy concepts (Ann Oncol. 2014;25:1750-5). In recent years, his main area of research has been the study of biliary tumors. He has contributed to exploring the feasibility of targeted therapies for these highly malignant cancers (Crit Rev Oncol Hematol. 2013;85:136-48, Clin Cancer Res. 2006;12:1680-5) and is currently engaged in the final analysis of a multicenter randomized clinical trial of panitumumab in combination with chemotherapy for advanced biliary tumors, coordinated by the Candiolo Cancer Institute (ASCO GI Proceedings 2015). Given the unsatisfactory results of the anti-EGFR based strategy, he developed insights in new directions such as the evaluation of new chemotherapists (BMC Cancer. 2014;14:918,) and the identification, through extensive molecular analysis, of specific genetic targets to be explored in future clinical trials (Genes Chromosomes Cancer. 2014;53:1033-40).

Selected references
Cell therapy for metastatic tumors
Application of new cell-therapy based strategies, to synergize with molecular targeted therapies

Team
Daniela Caravelli, Valentina Coha, Paolo Becco, Susanna Gallo

Research topic:
Hematopoietic Cell Transplantation (HCT): toward an immunological platform for cell and molecular therapy in the treatment of metastatic refractory cancers.

Background:
Allogeneic HCT, coupling to high dose chemotherapy a powerful donor immunological anti-tumoral effect, is a curative therapy for many hematological malignancies. However in the past years its broader application has been limited by two relevant obstacles: the first being represented by Graft versus host disease (GVHD) - the second being represented by the incapability of generating a specific graft versus tumor effect (GVT). Only when it will be possible to achieve a complete control of GVHD along with the generation of a specific GVT, allogeneic HCT will accomplish its extraordinary curative potential. Our research is focused on the clinical application of a strategy able to fully control GVHD and that transforms HCT into a safe platform for adoptive cell therapy.

Research achievements:
In regard to GVHD our group contributed to the study of conventional treatment and classification of this complication and is currently running an interventional study of post-transplant cyclophosphamide (PT-CY) as a safe strategy for GVHD control. In this context in the first 30 patients treated we reported an extremely low rate of acute GVHD and no incidence of cGVHD.

In regard to GVT (i) we at first revealed that following HCT it was possible to generate donor T cells specifically directed against patient-tumor antigens. (ii) We contributed to the demonstration that allogeneic HCT is an effective cell-therapy in the treatment of Multiple Myeloma. (iii) We have been involved in pre-clinical studies regarding a specific form of cell-therapy derived from the generation and infusion of Cytokine-induced Killer cells (CIK). In regard to Cell therapy regulatory issues and Law: cell therapy clinical application will be allowed only in Clinical centers that are JACIE-FACT accredited. Our Transplant center as part of the Turin metropolitan transplant network was accredited in July 2013.

Conclusions and perspectives:
The introduction in the clinical scenario of a safe strategy for GVHD control will allow HCT fully explored to be as a platform for tumor specific cell therapy and investigating if this platform might contribute to a future integration of cell therapy and molecular therapies. We plan to design and conduct clinical trials of cell-therapy (CIK and tumor specific T-cells) in the context of the Turin metropolitan transplant network both in solid tumors (melanoma and sarcomas) and in hematological malignancies.

Biographical Sketch:
Fabrizio Carnevale-Schianca has been working in the field of hematopoietic stem cell transplantation (HCT) since the time of fellowship (1997) accumulating robust clinical knowledge both in the biological rationale and clinical management of this strategy. As oncology fellow he contributed to the start-up of the clinical unit of Medical Oncology at the Candiolo Institute (1998). At the end of his fellowship he spent 18 months at Fred Hutchinson Cancer Research Center mentored by Rainer Storb. In Seattle he worked in the clinic, gaining deep experience of allogeneic HCT; in clinical research he has carried out studies on GVHD treatment and classification (Biol Blood Marrow Transplant 2000;6:613, Bone Marrow Transplant 2009;44:739, Biol Blood Marrow Transplant 2009;15:749). Once back in Candiolo he led the opening of the Medical Oncology Stem Cell Transplant Unit (2001); this unit is now part of a large metropolitan network that was JACIE-FACT accredited in 2013.

In clinical research since his return he was dedicated to mechanistically demonstrating that allogeneic HCT can generate a specific, long lasting graft versus tumor effect in hematological and solid tumors (Blood 2006;107:3795, NEJM 2007;356:1110, Blood 2009;113:3375, Biol Blood Marrow Transplant 2009;15:326, Blood 2011;117:6721). In the last years his group efforts have been aimed at exploring strategies for controlling GVHD and transforming HCT into a safe platform for specific anti-tumoral cell-therapies. In this regard he is collaborating with immunologists (Int Immunol 2008;20:841, J. immunother 2012;35:579). Since 2010 he and his group have been involved in the constitution of a melanoma-unit (BJC 2014;110;1721, Cancer Invest 2014;32:144). In metastatic melanoma, taking advantage of his experience in cellular therapies he is collaborating with immunologists to project clinical trials aimed at combining targeted therapies and check-point modulators to adoptive cell therapy (Clin Cancer Res 2013;19:4347, Expert Opinion Biol Ther 2014;14:1259).

Selected references


Cooperative trials for new therapeutic approaches

Team
Ymera Pignochino, Sandra Aliberti, Lorenzo D’Ambrosio, Danilo Galizia, Federica Capozzi, Paola Boccone, Sara Miano, Erica Palesandro, Marta Canta, Maja Todorovic

Integrated therapies for the treatment of sarcomas

Conclusions and perspectives:
The achieved results show the importance of dissecting B-STS heterogeneity to identify histotype specific Achilles’ heel. Moreover, we are developing a form of immunotherapy that can be combined with any of the multidisciplinary therapies that are the real backbone of sarcoma treatment. In perspective we look for an even greater integration with the other immunotherapeutic tools directed to reactivating patient anti-tumor activity directed against patients’ tumors. After ongoing AIFA protocol approval, a phase I/II trial will be run within the Italian Sarcoma Group.

Biographical Sketch:
Giovanni Grignani has been involved in clinical research focusing on the development of prognostic tools in oncology and later in the field of sarcomas. During his residency he worked on the identification of prognostic factors to improve multiple myeloma and lymphoma stratification as well as on several phase II trials exploring innovative chemotherapy combinations. Since he moved to the Candiolo Institute, he has been actively involved in translational research in the field of stem cells and sarcomas. In particular, he deepened understanding the mechanisms of metastatic seeding of osteosarcoma (Clin Cancer Res 2005;11:490-7) identifying the CXCR4/CL12 axis as one of the major determinants of the peculiar pattern of osteosarcoma diffusion. He took part in several pivotal trials of target therapies and took advantage of his large experience to develop preclinical models to test target therapies in sarcomas other than gastrointestinal stromal tumors (Cancer 2011;117:826-31). His group identified the role of the MAPK pathway in osteosarcoma progression and, on this original finding, he demonstrated the activity of sorafenib and mTOR inhibitor in the advanced stages of this tumor (Ann Oncol 2012;23:508-16 and Lancet Oncol 2015;17:1470-8).

In the last years, he set up a preclinical collaboration with immunologists in the attempt to overcome the intrinsic limit of target therapies related to tumor heterogeneity. In this setting, he has recently published an original model to expand patient derived lymphocytes showing that so-called cytokine induced killer cells selectively kill autologous sarcoma cells (Cancer Res 2014;74:119-29). In the forthcoming year this experience is going to be translated into the clinic in a phase I/II trial.

Research achievements:
We focused on the identification of key-pathways that can be exploited with innovative therapeutic tools. In osteosarcoma we identified the role of the mTOR pathway as a mechanism of resistance to sorafenib and showed the possibility of hitting this pathway with an innovative target combination therapy with sorafenib and everolimus. In this context we ran and completed a phase II trial. We identified on several B-STS the expression of specific antigens that can elicit a MHC-unrestricted T-cell immune-response. Thereafter, we demonstrated in B-STS patients that we could sort and ex-vivo expand a specific T-cell sub-population endowed with antitumor activity directed against patients’ tumors. After ongoing AIFA protocol approval, a phase I/II trial will be run within the Italian Sarcoma Group.

Research topic:
Integrated therapies for the treatment of sarcomas

Background:
Bone and soft tissue sarcomas (B-STS) are a rare and heterogeneous group of tumors. As of today, a multidisciplinary treatment encompassing complete surgical removal of the tumor +/- chemotherapy and radiotherapy cures roughly 50% of patients. Unfortunately, the most active chemotherapies may eradicate micro-metastatic disease, but do not cure non-resectable disease. Several second- and further-line treatments have been tested showing marginal activity at most. Therefore, innovative therapeutic strategies are urgently needed.

Research achievements:
We focused on the identification of key-pathways that can be exploited with innovative therapeutic tools. In osteosarcoma we identified the role of the mTOR pathway as a mechanism of resistance to sorafenib and showed the possibility of hitting this pathway with an innovative target combination therapy with sorafenib and everolimus. In this context we ran and completed a phase II trial. We identified on several B-STS the expression of specific antigens that can elicit a MHC-unrestricted T-cell immune-response. Thereafter, we demonstrated in B-STS patients that we could sort and ex-vivo expand a specific T-cell sub-population endowed with antitumor activity directed against patients’ tumors. After ongoing AIFA protocol approval, a phase I/II trial will be run within the Italian Sarcoma Group.

Conclusions and perspectives:
The achieved results show the importance of dissecting B-STS heterogeneity to identify histotype specific Achilles’ heel. Moreover, we are developing a form of immunotherapy that can be combined with any of the multidisciplinary therapies that are the real backbone of sarcoma treatment. In perspective we look for an even greater integration with the other immunotherapeutic tools directed to reactivating patient anti-tumor response. Secondly, several new compounds with improved selectivity to targets are in development. We have built a successful partnership with several pharmaceutical industries based on clinical trials designed and conducted by our team. On this ground, we will keep on joining international trials of important drugs, as we did with pazopanib, and investigating combination therapies based on our preclinical/translational research activity.

Selected references
Pignochino Y, et al., The Combination of Sorafenib and Everolimus Abrogates mTORC1 and mTORC2 upregulation in osteosarcoma preclinical models. Clin Cancer Res 2013, 19:2117-31
Hyperthermic intraperitoneal chemotherapy (HIPEC)

Treatment of peritoneal carcinomatosis

Team
Armando Cinquegrana, Patrizia Marsanic, Andrea Muratore, Demetro Siatis, Alfredo Mellano, Marco Vaira

Research topic:
Treatment of peritoneal carcinomatosis by surgical cytoreduction combined with HIPEC

Background:
Our clinical experience is focused on the treatment of peritoneal carcinomatosis and tumor recurrence. Since 1995, about 900 operations for peritoneal carcinomatosis have been performed; since January 2013 to date more than 150 patients with peritoneal carcinomatosis have been treated in our Institute. Our operative unit is specialized in the treatment of this kind of disease by cytoreductive surgery (CRS) combined or not with hyperthermic intraperitoneal chemotherapy (HIPEC) and secondary surgical cytoreduction of advanced cancers.

Research achievements:
In the last two years we have performed about 45 CRS + HIPEC (peritoneal mesothelioma = 8; colorectal carcinomatosis = 10; pseudomyxoma peritonei = 20; ovarian carcinomatosis = 6). Through the constant improvement of surgical and perioperative skills, we have achieved promising results in terms of long-term survival (median overall survival of 58 months for peritoneal mesothelioma, 42 months for ovarian cancer, 55 months for colorectal carcinomatosis, 144 months for PMP associated with a 10-yr overall survival of 80%) associated with low perioperative morbidity and mortality rates. We have registered an overall major morbidity rate of 15%, decreased to 6.7% considering only the last two years associated with no perioperative death. Since January 2013 in our Institution we have performed more than 100 surgical cytoreductions, which 65 for ovarian carcinomatosis. The mainstay of treatment is the attempt to achieve complete surgical cytoreduction, identified as the most significant prognostic factor: in this regard we perform a high number of primary or interval debulking surgeries with no macroscopic residual disease (CC-0) in a substantial number of patients. In cooperation with medical oncology, considering that the follow-up is too short, the results in terms of long-term outcome are still being processed. We can assert that during the last two years we registered a major complications rate of 2-3% with no postoperative deaths. All the HIPEC procedures (45 cases) were carried out intraoperatively with an original “semi-closed” technique. During the last years we have redefined our patient selection policy and sought to restrict indications to patients with less advanced or less aggressive disease: the selection process for CRS and HIPEC is critical and prognostic factors are required to identify patients who may most benefit from these treatments. The standardization of the surgical technique borrowed from experience in the treatment of peritoneal carcinomatosis allows us to obtain good long-term results with limited costs and mean hospital stay time.

Conclusions and perspectives:
In order to perform a more careful selection of patients, we are investigating the practice of second look (technique) to identify patients that early presenting an higher risk of relapse; for that purpose we are, also, testing the use of the liquid biopsy for the detection of circulating DNA. We are also investigating the possibility of performing laparoscopic HIPEC on selected patients. Moreover, in order to evaluate achieved results, we intend to participate, subject to approval by the ethics committee, in randomized controlled trials for the treatment of peritoneal carcinomatosis of colonic and ovarian origin by cytoreductive surgery and HIPEC.

Biographical Sketch:
Michele De Simone has always been interested in research of new technologies in Surgical Oncology. (Anti-cancer Res. 2001 May-Jun;21(3C):2243-8.) He focused his experience in the field of primary and metastatic tumors taking an active part in many clinical research projects. (Rev Recent Clin Trials. 2007 Jan;2(1):43-8.) He developed research experience in treatment of peritoneal carcinomatosis (J Clin Oncol. 2004 Aug 15;22(16):3284-92). He has authored more than 150 papers published in peer-reviewed Journals.

Selected references


New strategies for breast cancer local-regional control

Re-definition of local-regional breast cancer treatment according to the risk of relapse

Team
Franziska Kubatzki, Furio Maggiorotto, Alessandra Magistris, Francesco Marocco, Stefania Renditore, Alessandro Rivolin, Paola Sgandurra, Salvatore Carlucci

Research topic:
Strategies for breast cancer loco-regional control

Background:
The prevention and early detection of local-regional relapses requires a better understanding of the complex relationship between the primary tumor and its metastatic dissemination. For optimal breast cancer care new advancements in surgery and radiotherapy must be integrated in to the complex and rapidly evolving armamentarium of targeted systemic therapies.

Research achievements:
The influence of several treatment-related (accelerated partial radiotherapy, width of surgical margins, endocrine therapy with aromatase inhibitors), tumor-related (lobular histology, miR148b expression) and host-related parameters (body mass index, polymorphisms at the CYP19A1 locus) on the likelihood of breast cancer relapse have been examined. The available data and the new hypotheses on the relationship between loco-regional control and survival have been reviewed from a breast surgeon’s standpoint.

Conclusions and perspectives:
The current understanding of breast cancer natural history points towards the existence of a complex interplay between loco-regional and systemic processes. Loco-regional recurrences are associated with decreased overall survival and this may be related to a complex relationship between circulating tumor cells, re-seeding of the primary tumor site and several metabolic effects linked to the act of surgery. A re-definition of local-regional breast cancer treatment according to the risk of relapse based on improved bio-molecular characterization of the tumor is required to tailor the adoption of diagnostic tools, loco-regional and systemic treatments.

Biographical Sketch:
In 1987 and 1988, he was employed in the laboratories of the Wistar Institute and Children Hospital of Philadelphia, U.S.A., where he acquired the basics of Molecular Biology and was involved in research projects on hyperphenylalaninemia and pterin metabolism (J Inher Metab Dis 1989; 12: 162)

After graduation, he was actively involved in the clinical and research activities at the Dept. of Gynecological Oncology, University of Turin, Italy, where he specialized in 1997. Over these years, he co-authored several papers on the prognostic significance of the family of kallikreins in breast and ovarian cancer (Cancer Res 1995; 55:2104-2110).

In 1995 – 1996 he attended as clinical research fellow the Royal Marsden and University College Hospital of London, UK, where he conducted clinical trails on innovative endocrine therapies for breast cancer (Br J Cancer 1999; 79: 311-5), and developed a personal interest is the clinical issues related to hereditary breast and ovarian cancer (Eur J Cancer 1998 ; 34 : 966-967).

From 1999 to 2009 he was appointed attending Gynaecologist at the Mauriziano Hospital of Turin and at the Institute of Candiolo. During these years he focused his research activity on the adjuvant (Ann Oncol 2006; 17: 1631–1636) and surgical (J Clin Oncol. 2009; 27:5547-51) therapy of breast cancer. In 2010 he was appointed Director of the Division of Gynaecological Oncology at the Institute of Candiolo.

His current research interests are devoted to tailoring loco-regional breast cancer treatments (Eur J Cancer. 2012;48:2311-8) and minimizing their side effects (Ann Surg Oncol. 2012 Nov;19:3755-61). He has also consolidated his expertise in pelvic surgery, with a particular interest in molecularly-based and innovative treatments of ovarian cancer. In his career, he has performed more than 4500 breast and pelvic surgeries and has authored more than 90 papers published in international peer-reviewed journals, as well as book chapters and national guidelines.

Selected references


Applications of Computer Assisted Diagnosis (CAD) in Radiology

The diagnostic imaging, improved by CAD systems, allows tumor diagnosis to be brought forward to an early asymptomatic phase.

Research topic:
Computer Aided Diagnosis (CAD) applications in Radiology

Background:
High resolution images of the human body are generally obtained by Computed Tomography (CT) or Magnetic Resonance (MR) imaging. CT Colonography is an example of such detailed imaging in which data from a CT scanner are processed by dedicated software to obtain a 3D representation of the colon from inside the intestinal lumen in a similar way to a conventional endoscope view. On the other side, MR imaging has shown promise in localizing cancers, because of its intrinsic high soft-tissue resolution, and combining two or more image modalities can improve the sensitivity of MR tests. However the more variables are introduced the more difficult it is to integrate all available information into one reliable final report, even for an experienced reader.

To deal with these complex problems, computer aided diagnosis systems (CAD) have been introduced to help radiologists in diagnosing disease.

Research achievements:

- The research group has developed a CAD able to produce quantitative maps of the prostate, providing malignancy probability information with useful data that might be difficult to assess visually from MR scans. Regarding the CAD colon, diagnostic performance of CT colonography in individuals at increased risk of colorectal cancer was investigated, and further studies are being conducted using the innovative dual energy technology, to generate so-called virtual non-contrast images. Finally, within the CAD-breast project, we have implemented a fully automatic method for detecting blood vessels in dynamic contrast-enhanced breast MR images. The method could be used to reduce labeling of vascular voxels as parenchymal lesions in the CAD breast, and it could also be used to evaluate the pathological response after neoadjuvant chemotherapy.

Conclusions and perspectives:
Recently, our group has published the results obtained using the CAD system for CT colonography screening. In these studies it has been demonstrated that, at the 6-mm threshold, sensitivity of unassisted reading (79.6%) increased significantly with the use of both second-reader CAD (86.0%) and a double-reading paradigm in which a first-reader CAD is followed by a fast 2-dimensional review (89.2%). Besides, the latter required less reading time than that for second-reader CAD (118 seconds) and was 59 seconds longer than unassisted reading. Conversely, the CAD prostate is still in a preliminary development phase. However, preliminary results obtained on a cohort of 33 patients reported a sensitivity of 94%, with a median number of FP per patient equal to 1, and 2 in the peripheral and central zone, respectively. Finally, regarding the breast project, we obtained promising results in detecting most vessels identified by an expert radiologist. Improving CAD performance will stimulate diffusion of such systems in clinical workflows, helping radiologists in detecting cancer, in particular when diagnosis is time consuming and requires deep expertise. A new branch of research is now focusing on the role of CAD in supporting prostatic MR-guided biopsy, and in estimating tumor aggressiveness by integrating the Gleason Score with imaging, in order to better stratify patients and personalize treatments.

Biographical Sketch:
Dr. Regge is the Director of the Radiology Unit at the IRCCS in Candiolo and he supervises a multidisciplinary team, which investigates advanced medical imaging technologies. The group seeks to enhance cancer diagnosis by means of Computer Aided Diagnosis (CAD) systems. His major scientific accomplishments are: (i) He is internationally recognized for his contributions to the CT-colonography field, being involved in clinical trials and coordinating the largest European multicentre study (JAMA;301:2453-61). This study, together with the ACRIN-6664, lead to the introduction of CT-colonography into the guidelines of the American Cancer Society as a screening test for colorectal cancer. (ii) He is PI of the first large world mass screening trial with CT-colonography conducted in Piemonte and in the province of Verona (http://clinicaltrials.gov/show/NCT01739608) (iii) He is active in the development and clinical validation of CAD systems for diagnosis of colorectal, breast and prostate cancer (Invest Radiol;49(3):173-82). (iv) He has given important contributions to the field of multiparametric-MRI, which helped change the diagnostic pipeline of prostate cancer(J Urol;192(1):60-6). He is the author of more than 100 peer-reviewed publications and more than 300 scientific contributions in national and international congresses, and he has been moderator or invited speaker at more than 250 conferences worldwide. Dr. Regge has been PI of several supported research projects, and he is part of the faculty of the European School of Radiology, founding Member and president elect of the ESOI, board Member and Secretary of the European Society of EuSoMII and President of the Italian Chapter of Imaging Informatics.

Selected references

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“Personalized” radiation-therapy based on genetic, biological, and “theragnostic” parameters

Adapting radiotherapy treatment to the modern concept of “personalized medicine” (“Precision radiotherapy”)

Team
Gaetano Belli, Gabriella Cattari, Marco Gatti, Gabriele Petrilli, Antonia Salatino, Antonella Suma,
Domenico Gabriele

Research topic:
“Personalized” Radiation-therapy based on genetic, biological, statistical and “theragnostic” parameters.

Background:
The improved IMRT techniques (Intensity Modulated Radiation Therapy) allow the use of high doses, perfectly “sculpted” on the areas that are going to be treated. A further improvement of radiation treatment is provided by “daily image control” based on the IGRT technique (Image Guided Radiotherapy). Genomic information and “theragnostic” data allow the defining models to optimize the use of radiotherapy, in order to personalize treatment.

Research achievements:
(i) We have proved - in collaboration with the cancer stem cell laboratory - that ionizing radiation (IR) leads to the expression of an oncogene (Met) involved in invasion and metastasis control; this data contributes to the ‘vexata questio’ debate about the possible radiotherapy side effects on metastasis sprouting. (ii) We performed a feasibility study on large fields, using Tomotherapy. (iii) A controlled clinical trial on IMRT-IGRT treatment protocols for head and neck tumors and recurrences, and three studies on prostate cancers are in progress. (iv) We are contributing to an international multicenter randomized phase III clinical trial on locally advanced rectal cancer. (v) We are leading the european project “Computational Horizons in Cancer” to create a predictive nomogram of prognosis.

Conclusions and perspectives:
We plan (i) to evaluate the possible impact of genetics and molecular biology data on radiotherapy of Glioblastoma Multiforme (GBM). The preclinical research will be implemented by “xenopatients” (immunocompromised mice transplanted with GBM of single patients, see above); (ii) to develop personalized radiotherapy treatment of pancreas cancer, of clivus cordoma, of pleural mesothelioma and of gynecological tumors; (iii) to implement treatment protocols by microwaves and radiofrequencies and by radiochemo-hyperthermia. This information will be the basis for personalized treatment by Tomotherapy, performing ‘Adaptive Radiotherapy’ treatment.

Biographical Sketch:

Selected references
Research topic:
Providing Personalized Medicine with Nuclear Molecular Imaging in Cancer Patients - PET/CT in early evaluation of cancer treatment response and targeting resistance to molecular therapies.

Background:
Early differentiation between responders and non-responders is a very important issue for the management of cancer patients. Wide evidence exists that FDG-PET can predict outcomes for many tumor types very soon after conventional systemic chemotherapy is started. In particular, compared with cytotoxic chemotherapy, many novel targeted therapies result in disease stabilization rather than tumor shrinkage. The activity of these novel agents might, therefore, be better reflected by changes in molecular features of the tumor rather than reduction in size or volume. Recent prospective studies show that a change in tumor glucose activity (measured with FDG PET standard uptake value-SUV) is a significantly more accurate parameter than a change in size in assessing histopathological response to neoadjuvant therapy in patients with GIST and high grade soft tissue sarcoma.

Research achievements:
The PET imaging facility has been qualified by CoreLab Partners, Inc. for the submission of Nuclear Medicine and PET images of the patients who are enrolled in the CAUY922A2109 study. The aim of this study is to evaluate the efficacy of AUY922 in combination with Trastuzumab in patients with locally advanced or metastatic HER2-positive breast cancer that has progressed after or during at least one Trastuzumab-containing regimen.

Conclusions and perspectives:
Research goals will be to assess the value of metabolic imaging with PET in predicting response to therapy, targeting resistance to molecular therapies, improving personalized therapy and prognosis.

Selected references


Varetto T, Durval C. Continuing Medical Education Committee and UEMS-EACCME. European Journal of Nuclear Medicine, 2013, 40:470-4

Biographical Sketch:
Teresio Varetto has more than 25 years’ experience in all diagnostic and therapeutic activities in Nuclear Medicine. During his career he has been a pioneer in the introduction of new diagnostic radiopharmaceutical methodologies in Cardiology (J Am Coll Cardiol, 22 (1993), pp. 1804–1808 – Q J Nucl Med Mol Imaging. 2005 Jun;49(2):171-91) and in Oncology (Eur J Nucl Med Mol Imaging 2005 Aug; 19:32(8):937-42). Since 1998 he is Professor at Turin University Postgraduate Specialization School in Nuclear Medicine and Postgraduate Specialization School in Hospital Pharmacology. As Senior Expert in Nuclear Medicine at International Atomic Energy Agency he accomplished Technical Cooperation Expert Missions in several African Countries collaborating in the creation and dissemination of Nuclear Medicine Units and giving lectures and counseling at the local University Hospitals.

As chairman of the Continuing Medical Education Committee of the UEMS European Board of Nuclear Medicine he is in charge of accreditation of International educational activities. (Eur J Nucl Med Mol Imaging 2013 Feb; 40(3):470-4; Eur J Nucl Med Mol Imaging 2014 Jan;41(1):191-6; Eur J Nucl Med Mol Imaging 2014 Nov 31;41(11):2169-73). Member of the Executive Board of the Italian Association of Nuclear Medicine and Molecular Imaging since 2000, he is Chairperson for CME in Nuclear Medicine at the National level. Since 2008 as Director of the Nuclear Medicine Department at the Candiolo Institute for Cancer Research he has been involved in research projects aimed at providing personalized medicine to cancer patients as the use of PET/CT in early evaluation of cancer treatment response and targeting resistance to molecular therapies.
Personalized therapies in Medical Oncology
A new avenue of cancer therapy

Team
Marco Fizzotti, Lucia Garetto, Cinzia Ortega, Veronica Prati, Delia Rota Scalabrini, Giorgio Valabrega, Fiorella Ruatta, Celeste Cagnazzo, Caterina Aversa, Rosa La Face, Sofia Genta, Rossella Martinello, Gloria Mittica, Sonia Capellero, Luca Crotto, Marta Fenoglio

Research topic:
Implementation of clinical trials based on the identification of specific molecular targets on tumor cells.

Background:
Target therapy represents the new avenue of cancer therapy. Although important results have been obtained with some tumors, on the whole the expected results have not been obtained. In most cases, even when tumor progression is blocked by targeting a specific molecular alteration, resistance to treatment will eventually develop. To understand the reason for drug resistance a continuous interaction between the clinic and the laboratory is needed. The analysis of the evolution of tumor genotype and phenotype during treatment is the only way to improve our capacity to treat tumors.

Research achievements:
Our units have been focusing mainly on the treatment of sarcomas, breast and digestive tract carcinomas, becoming a referral centre for these diseases. The breast unit recently became autonomous. The secondary projects (see below), dealing with the single diseases, will detail the results obtained. These results derive from a continuous interaction between the laboratory (both the unit’s lab and the other labs of the Institute) and the clinic. This made possible the implementation of clinical trials designed and conducted on the basis of hypotheses generated at the bench and translated to the bedside.

Conclusions and perspectives:
To continue our effort at designing clinical trials based on a thorough analysis of the tumor and of its interaction with the host. The secondary projects will detail the ongoing projects coordinated by our Unit. Moreover, strict cooperation is ongoing with the other leading clinical oncological institutions in Italy and in Europe.

Biographical Sketch:
Massimo Aglietta started his scientific career working in preclinical models of human tumors with the aim of developing rational chemotherapeutic schedules based on tumor cell kinetics (Cancer Res, 39:2727-32, 1979). A logical background has been the characterization of the growth pattern of normal and neoplastic hemopoietic progenitor cells (Cancer Res, 40:2507-11, 1980; Blood, 67:789-95, 1986). These preclinical studies led to the development of phase I/II clinical protocols that contributed to a rational scheduling of hemopoietic growth factors to allow dose dense chemotherapy regimens in solid tumors (J Clin Invest, 83:551-7, 1989; Blood, 82:2054-61, 1993; Cancer, 72:2970-3, 1993; Eur J Cancer 31: 46-9, 1995). This background was also behind the phase II protocols that explored the potential of stem cell transplantation outside hemopoietic malignancies like colon cancer and sarcomas (J Clin Oncol, 15:2150-6, 2002; Blood, 107: 3795-803, 2006; Nature Clin Practice Oncol (Review), 5: 256-267, 2008).


Selected references:


Clinical Services

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The head of the department of clinical services participates in the strategic planning process and contributes, with the formulation of proposals and opinions, to hospital management. He directs health services and is responsible for hygiene and prevention (hospital infection control and environmental hygiene).

The clinical service office monitors the appropriateness of admissions, the hospital stay lengths, the average weight of the so called ‘case mix’ and supervises the waiting list. He coordinates with the Operation Department the proper use of spaces and the timely flow of goods and services. The clinical service office:

(i) is in charge of the control of the fulfillement of results obtained within the assigned objectives; (ii) coordinates the facilities of the hospital including the provision of appropriate protocols; (iii) defines strategies and guidelines for extraordinary and/or urgent intervention; (iv) advises on building planning regarding further hospital expansion; (v) Supervises the ‘conventional’ agreements and the related relations with the University.

Antonino Sottile, M.D.
Direttore Operativo
and Laboratory Medicine
E-mail: antonio.sottile@ircc.it  ·  Phone +39.011.9933038

This Unit is mainly devoted to patient diagnosis and treatment. Nevertheless, a strong effort is made in performing analysis supporting clinical trials as well as translational research. The laboratory is also engaged in its own research activity aimed at developing and testing novel diagnostic procedures. A special emphasis is placed on the analysis of prostate cancer markers.

Felicino De Bernardi, M.D.
Cancer Pain
E-mail: felicino.debernardi@ircc.it  ·  Phone +39.011.9933018

Cancer pain significantly affects the physical, psychological and emotional components and quality of life of the individual. Our goal is the optimisation of pain relief through a patient-centred approach with particular attention to quality of life, personalized care and application of the newest drugs and treatments.

Michele Stasi, M.D.
Medical Physics
E-mail: michele.stasi@ircc.it  ·  Phone. +39.011.9933708

“Safe” dose escalation with Tomotherapy: from advanced segmentation to adaptive dose
Tumor segmentation based on multi-modal imaging, sophisticated patient specific Quality Assurance and treatment options such as Helical Tomotherapy, IMRT, IGRT, and adaptive radiotherapy.

Giovanni Galatola, M.D.
Gastroenterology
E-mail: giovanni.galatola@ircc.it  ·  Phone +39.011.9933410

The Gastroenterology Unit at IRCC is a dedicated provider of a wide range of diagnostic and therapeutic endoscopic procedures for the upper and lower gastrointestinal tracts, and is involved in the clinical care of patients with chronic viral hepatitis and those with gastrointestinal disorders in the medical oncology setting.

Alessandro Bonzano, M.D.
Cardiology
E-mail: alessandro.bonzano@ircc.it  ·  Phone +39.011.993.3888

The Cardiology Unit at the IRCCS is engaged in the prevention, diagnosis and treatment of cardiotoxicity caused by old chemotherapy drugs (anthracyclines, 5-fluorouracil) and new agents (trastuzumab). Doppler echocardiography and biomarkers as troponin are used to identify early damage of the heart during chemotherapy. A growing experience in the field of Cardioncology has lead to tailored treatment for cancer patients with cardiovascular complications.

Franca Goffredo, M.D.
Pharmacy
E-mail: franca.goffredo@ircc.it  ·  Phone +39.011.9933261

The Pharmacy Unit manages drug/medication related activities and issues for all IRCCS wards (drug lifecycle). Some of these activities include supplying, storage, distribution, drug information, therapeutic policy/formulary. Preparation of chemotherapy and supportive care medications for in and out patients, together with investigational drug management and research support (including regulatory issues) are the main and distinguishing activities, which are enhanced by integrated IT and automation. The staff is an active partner of the University in the pharmacy education and training programmes.

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Eighty-three | Educational Activities

The scientific and professional advanced teaching is based on lectures and practical courses. These last from one to three days and are aimed at newly graduated MD or PhD, as well as to Physicians, as refresher courses.

(a) Courses.
(b) Seminars and Workshops. (i) “Lezioni Magistrali”: one in basic research and one on clinical research, each held by eminent scientists. (ii) Formal seminars: throughout the year, divided among basic and clinical research, held by external invited speakers. (iii) Progress reports held by members of the Institute, once a week for 48 weeks of the year. (iv) International Workshops, on either basic or clinical research. These workshops are usually organized within the framework program of the European Molecular Biology Organization (EMBO) and of the European Society for Medical Oncology (ESMO).
(c) Research Doctorates aimed at the training of basic and clinical research.
(d) Master in Molecular Oncology.
(e) Post-doctoral programs.

2014 Courses
The Institute offers four different PhD programs.

(a) PhD in Molecular Medicine (Cell Sciences and Technology): a four-year course (under the auspices of the University of Torino) open to young graduates in Medicine, Biological Sciences, Biotechnology, Chemistry, and Pharmacology. It is aimed at training for basic and translational research in biomedical sciences.

(b) PhD in Complex Systems and Post Genomic Biology: a three-year course (under the auspices of the University of Torino) aimed at training graduates in the fields at the interface of medicine, life sciences, mathematics and physics.

(c) PhD Program in Biomedical Sciences and Oncology: a four-year course (under the auspices of the University of Torino) open to graduates in Medicine, and Biological Sciences and mainly aimed at training clinical researchers.

(d) PhD in Oncological Sciences: a three-year course (under the auspices of the Catholic University of Milano-Roma) aimed at exceptionally talented graduate students to be trained in cutting-edge oncological research at the highest level.

Graduate students are provided with an individual tailored guidance program and required to rotate through a number of laboratories to learn different research techniques collaborating with world-class scientists. Career counselors help students to investigate job types, develop curriculum vitae and resumes, and refine interview skills. After completing the PhD program students are encouraged to participate in internship opportunities in both basic or clinical research, technology transfer, science policy, and management.

All programs are open to Italian and foreign students. Fellowships are provided on a competitive basis.

Post-doctoral Programs
The Institute offers specialized post-doctoral programs for researchers interested in investigating concrete problems in the field of Molecular Oncology.

(a) IRCC International Cancer Research Training Program
This scheme employs scientists from all nationalities to improve scientific exchange between the Institute’s researchers and colleagues who have matured qualifying experience in foreign institutions. The research field is at the interface between molecular biology and medicine, referring in particular to today’s problems in molecular oncology.

(b) Marie Curie European Training Center
The European Commission has recognized IRCC as a qualified center for training young researchers in the experimental medical science field. Within the framework of the program, IRCC employs in rotation graduate students from member states for periods varying from six months to two years in the research laboratories.

2014 Seminars
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Molecular Oncology Master
The Institute, under an agreement with the University of Torino, also offers a two-year Master in Molecular Oncology aimed at providing clinical oncologists, surgical oncologists, radiologists, radiotherapists, and pathologists with up-to-date knowledge of cancer biology and genetics as well as of the novel diagnostic and therapeutic (e.g. precision medicine) approaches that arose from latest molecular and genomic information.
The ‘Xenopatients’ Platform for Experimental Oncology.
Andrea Bertotti, M.D., PhD
Assistant Professor
University of Torino Medical School
E-mail: andrea.bertotti@ircc.it
Phone. +39.011.9933242

Immortalized cancer cells exhibit a genetic drift, a biological compliance and phenotypic features different from original cancers in patients. Another drawback of the use of continuous cell lines is that the catalogue of currently available models is inevitably finite, and possibly poor for some tumour subtypes. Therefore, experiments with cell lines cannot recapitulate the wide heterogeneity of human malignancy that occurs among individuals on a population basis. One way to tackle this issue is to perform population-based in vivo studies by using large series of human cancer specimens directly transplanted into mice. This setting can be exploited as a bridgehead to unravel the genetic and biological complexity of cancer, as a prelude for the identification of novel therapeutic targets and unanticipated pharmacological approaches. XPERo provides researchers with a collection of liver metastases from colorectal cancer that have been systematically transplanted in immunocompromised mice to obtain stable tumor lines (xenopatients), which are available for any kind of in vivo/ex vivo study. This resource builds on three main cornerstones: (i) The viable biobank of colorectal cancer liver metastases. An institutional effort has led to the collection and implantation of more than 500 samples of metastatic colorectal carcinoma. This resource allows us to select the appropriate candidates among more than 300 experimental models, based on clinical, biological, genetic or gene expression traits. This, in turn, is instrumental for achieving the appropriate statistical power for any kind of translational study, even if focused on relatively small tumour subpopulations. (ii) The ‘Xenopatients’ experimental platform for in vivo drug screening. We have implemented a dedicated experimental pipeline that required the recruitment of ad-hoc personnel and the development of a specific workflow. The possibility to exploit trained staff and to apply robust standard operating procedures (SOPs) to experimental work confers high added value to research projects, in terms of both cost effectiveness and efficiency of the resources used. (iii) The Laboratory Assistant Suite package for data management and analysis. We have developed a web-based bioinformatics platform that assists biomedical researchers in multiple activities, which range from tracking data generation and SOPs execution to the management of multidimensional molecular profiles and complex data integration (The Laboratory Assistant Suite or LAS, http://devircc.polito.it/wordpress/). This kind of informatics support provides invaluable benefit by optimising quality and reproducibility of the experiments and by accelerating data mining and analysis.

The Oncogenomics Center (OGC)
Genetic alterations in tumors are predictors of response or resistance to targeted therapies, and their identification is mandatory for molecular diagnosis and therapeutic decisions. Technological advances in experimental and informatics methodologies over the past 10 years have made possible the characterization of cancer genomes. OGC is the supportive infrastructure for all genomic studies, including transcriptional, mutational and gene copy number analyses of cells, tissues and liquid biopsies. Dedicated personnel and instrumentation are devoted to provide services for qRT-PCR studies, Sanger and Next Generation Sequencing experiments, Gene Expression Array analyses and BEAMing tests.

The Bioinformatics Center (BIC)
Modern research in cancer biology implies the collection of extensive data from experimental models concerning specific genetic lesions that drive cancer initiation and progression. Such data will include, for example, large sets of expression transcript profiling, comparative genomic hybridization profiling, whole genome sequencing, immunohistochemical data, and morphologic data that will be peculiar to each specific tumor. Thus, a bioinformatics platform for integrated data tracking and normalization is critical to the successful realization of this endeavor. BIC comprises a web-based bioinformatics platform (Laboratory Assistant Suite, LAS; http://devircc.polito.it/wordpress/) that assists biomedical researchers in multiple activities, which range from tracking data generation and execution of standard operating procedures (SOPs) to management of multidimensional molecular profiles and complex data analysis and integration, by managing multiple independent databases that are linked together in an interconnected network (‘oncogrid’).

The Oncology Imaging Center (OIC)
Basic research in discioprtics such as cell biology, molecular genetics and developmental biology has provided invaluable insights into the regulatory circuits that govern cancer onset and progression. Within this context, we postulate that imaging studies in cell topics and tissues will parallel genomic analyses and in vivo experimentation, constituting an integrative platform for rapid testing of emerging research directions. OIC technologies include comprehensive microscopic imaging systems, such as confocal microscopes, live-cell devices for real-time monitoring of cellular behaviors, and high-throughput platforms for functional screening.

The Flow Cytometry Center (FLOCC)
Increasing evidence shows that tumors are structured in a hierarchical form, with a majority of cells undergoing aberrant differentiation but retaining a proliferative capacity limited over time, and a tiny fraction of cancer stem cells (CSCs) or cancer-initiating cells (CICs) that are able to self-renew and continuously regenerate or add to the tumor. FLOCC enables researchers to take advantage of state-of-the-art FACS (fluorescence-activated cell sorter) technologies and dedicated personnel with highly specialized technical skills in order to tackle these issues, by allowing analysis and prospective isolation of individual cancer cells within highly heterogeneous populations. series of human cancer specimens directly transplanted into mice (‘xenopatients’).

Team
Piero Alberto, Paola Bernabei, Jadwiga Biela, Michela Buscarino, Daniela Cantarella, Dario Caponi, Giorgio Corti, Giorgia Migliardi, Francesca Cottino, Alessandro Fiori, Emanuele Geda, Stefania Giove, Alberto Grand, Barbara Martinoglio, Laura Palmas, Roberta Porporato, Natalia Santoro, Solange Tienga.
Grant Office and Research Administration

The Scientific Director's Office supervises, coordinates and manages the basic, translational and clinical scientific research in the Institute. To this end, the Grant Office provides the scientific support for Institute research activities and acts as a liaison between researchers and funding agencies. The Grant Office assists researchers in identifying appropriate research funding opportunities, centralizing all information on major national and international, private or public, agencies, foundations, and institutions that support research. Whenever a call for a research grant is issued, it is advertised throughout the Institute by e-mail. The Grant Office provides assistance to researchers in the preparation of applications, in the drawing up of the budget - together with the administrative office of the Institute -, in completing the application forms and interpreting the regulations of the granting agencies, assuring compliance with the sponsors' policies and requirements. In case of successful outcome of the proposals, the Grant Office helps in preparing reports, consortium agreements with collaborating institutions, and renewal forms.

Electronic Data Processing Unit

The EDP unit develops and maintains the Master Database, a unique tool, developed in-house, which tracks the funds, human resources and research publication output, of the Research units at the Institute. The EDP unit runs the Candiolo Cancer Institute public web site and the Intranet. The unit also provides IT support to the Research departments and to the Institute's meetings and conferences. The unit prepares the annual Scientific Report.


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