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Meeting Report

Lost in translation: bridging the gap between cancer research and effective therapies

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Successful translation of the exciting results achieved in the understanding of the tumor pathobiology at the patient's bedside is probably the biggest challenge ahead in cancer research. Therefore, one of the main goals of the SIC Meeting was to 'bridge the gap between cancer research and effective therapies'. The entire program was ideally comprised between the opening lecture on *p53* by Karen Vousden (Glasgow, Scotland, UK) and the closing lecture on *Cancer stem cells* by Pier Giuseppe Pelicci (Milan, Italy), going through the traditional Giorgio Prodi lecture given by Marco Pierotti (Milan, Italy), who presented an overview of the progresses achieved in cancer research in the past 35 years.

The meeting kicked off with a talk by Margaret Foti, Chief Executive Officer of the American Association for Cancer Research, who lectured on the vital role of research in the conquest of cancer.

The p53 Family of Proteins

The double-edged functions of p53 (and its transcriptional targets, TIGAR and HK2) in the metabolic response of normal and transformed cells to different levels of oxidative stress were highlighted by Karen Vousden. She provided insights into how drugs that interfere with MDM2/MDMX (by either inhibiting interaction with wt p53 or blocking E3 ligase activity) may be useful to either treat tumors that harbor wt p53 or protect normal tissues from G2/M-acting DNA-damaging agents, but also warned against the risk of possible tumor-promoting effects that such agents may have by stabilizing mutant p53 that is expressed at low levels in normal/premalignant tissues. Gerry Melino (Rome, Italy) stressed the importance of p73 and p63 isoforms in the regulation of genes involved in different pathways: p73 in neural development and p63 in epidermal formation. The validation of TAp73 and TAp63 as tumor suppressors may offer novel and intriguing therapeutic approaches to enhance the chemosensitivity of tumor cells harboring mutated or inactivated p53.

Cancer Stem Cells

Ruggero De Maria (Rome, Italy) highlighted the plasticity of cancer stem cells that, in the glioblastoma model, give rise not only to the tumor cell population but also to the tumor-associated vasculature. Reverse phase-based high-throughput proteomic analysis has led to the identification of polo-like kinase and Chk1 as therapeutically relevant, potentially 'druggable', pathways operating in colon and lung cancer stem cells, respectively.

Mammary stem cells divide according to opposite modalities (predominantly asymmetric *versus* predominantly symmetric divisions) in normal and cancer context, respectively. This was highlighted in the presentation of Pier Paolo Di Fiore (Milan, Italy) and in the enthusiastic closing lecture given by Pier Giuseppe Pelicci. In addition to the functions highlighted above, p53 appears to have a pivotal role in maintaining an 'asymmetric' modality of stem cell division; conversely, the endocytic protein Numb, through modulation of Notch receptor signaling on one end and of p53 expression on the other, profoundly influences the replicative fate of mammary stem cells, while the cell cycle inhibitor p21 exerts similar functions in leukemic stem cells, maintaining their capability of dividing symmetrically, thereby expanding the leukemic stem cell pool. These findings may have therapeutic relevance, as Di Fiore and Pelicci showed that stabilization of p53 expression and function through MDM2 inhibition by nutlin restores a predominantly asymmetric division modality and leads to decreased cancer stem cell numbers both *in vitro* and *in vivo*. Robert Clarke (Manchester, UK) showed that breast cancer stem cells are responsible for resistance to radio/chemotherapy and tumor recurrence and that inhibition of Notch signaling by gamma-secretase inhibition sensitized breast cancer stem cells to the cytotoxic effects of conventional chemotherapy. He also highlighted the fact that signaling through Notch-4 is insensitive to gamma-secretase inhibition and is potentially a more relevant therapeutic target in breast cancer stem cells *in vitro* and *in vivo*.

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Epigenetic Alterations in Cancer

An intense and productive discussion on the role of different miRNAs in regulating cancer processes was engaged by Reuven Agami (Amsterdam, The Netherlands), showing the interaction between miRNA and regulatory RNA-binding proteins in carcinogenesis. Pumilio-1, a ubiquitously expressed RNA-binding protein, is upregulated in response to growth factor stimulation and is able to interact with the p27-3′ UTR. Its role is carried out by p27 inhibitors: miR-221 and miR-222. Carlo Maria Croce (Columbus, OH, USA) argued about the function of the miRNA in the downregulation of oncogene expression, some of them being both oncogenes and oncosuppressor genes depending on the pathway of action. He described results on the downregulation of miR-15a–miR-16-1 expression in patients with chronic lymphocytic leukemia. Stefano Piccolo (Padua, Italy) expanded the role of miRNAs to metastasis control. Findings demonstrating that miR-103/7 targeting dicer, a key component of the miRNA processing machinery, causes an epithelial-to-mesenchymal transition, promotes the invasive behavior of tumor cell, induces metastasis and correlates with metastasis-free survival in breast cancer patients, have been reported. Finally, Hendrix Stunnenberg (Nijmegen, The Netherlands), using the acute myeloid leukemia model, explained how next-generation sequencing and the Chip-Seq approach permit the integration of genome-wide identification, histone status study, transcriptome and DNA methylation evidence, and identification of transcription factor binding sites to better understand protein functionality.

Cancer Modeling

Natalie Cook (Cambridge, UK), by using a genetically engineered mouse model (driven by KRAS mutations) that recapitulates the development of the human ductal pancreatic cancer, showed how inhibition of the Hedgehog signaling pathway induces a transient increase in tumor vascularization and perfusion, thereby creating a 'window of opportunities' to more efficiently administer chemotherapy and leading to increased chemotherapy delivery and more efficient tumor responses. Giulia Piaggio (Rome, Italy) studied NF-Y-dependent transcription in living animals and developed a new tool based on NF-Y-responsive luciferase reporters that is useful to visualize cell proliferation *in vivo* and to facilitate investigations of the involvement of proliferation in disease pathogenesis.

Molecular Mechanisms of Senescence and Cell Death

Nadia Zaffaroni (Milan, Italy) reviewed current approaches aimed at interfering with the expression and/or function of telomerase, including the use of antisense oligonucleotides acting as template antagonists. She also described recent data on the use of competitive inhibition of the telomerase's catalytic activity by small molecules able to induce and stabilize selected G-quadruplex arrangements. The increasingly crucial role of host response was discussed by Guido Kroemer (Villejuif, France), who proposed an elegant 'key-lock model' in which the 'key' is represented by changes in the composition of the cell surface and in the release of soluble immunogenic signals, and the 'lock' by dendritic cells. He postulated that the immune system is crucial for the long-term success of anti-cancer therapies and that this immune response is dictated by immunogenic tumor cell death.

Microenvironment and Tumor Progression

Mario Paolo Colombo (Milan, Italy) addressed the relevance of macrophage-derived osteonectin in the assembly of tumor stroma and collagen fibers, as well as in providing chemotactic signals. Mast cells are also specifically enriched and degranulated in prostate adenocarcinoma and are involved in prostate cancer development, suggesting that the identification of liasons connecting mast cells and matricellular proteins in cancer could represent the key toward their effective targeting.

The parallelism between neural and cancer development was also highlighted. In particular, Federico Bussolino (Turin, Italy) argued about the role of neurexins/neuroligins in embryonic vascular development, blood vessels remodeling, extracellular matrix formation and VEGF-A gradient formation. The efficacy of semaphorin 3A in limiting endothelial cell functions, pancreatic carcinoma progression and vascular morphology was presented. Along similar lines, Angelo Vacca (Bari, Italy) presented data providing evidence that, in multiple myeloma (MM), exposure of bone marrow macrophages to zoledronic acid and bortezomib, alone and/or in combination, impacts their angiogenic and vasculogenic properties, suggesting that bone marrow macrophages may be considered as a target of both drugs in MM patients. Michael Andreeff (Houston, TX, USA) argued in favor of the role of multipotent mesenchymal stromal progenitor/stem cells in leukemia to form an essential component of the hemopoietic stem cell niche and convey drug resistance. Andreff proposed that the disruption of the SDF-1alpha/CXCR4 axis with CXCR4 inhibitors represents a novel strategy of sensitizing leukemic cells by targeting their protective bone marrow 'hypoxic' microenvironment.

Therapeutic Targeting of Signal Transduction Pathways

Massimo Aglietta (Turin, Italy) presented data about new therapeutic targets in osteosarcoma and, in particular, dissected the *in vitro* and *in vivo* molecular mechanism of sorafenib action. He showed that, in addition to blocking RAF kinase and the VEGFR-2/PDGFR-beta signaling cascade, sorafenib also abrogates MAPK and Ezrin phosphorylation and Mcl-1 expression. Controversial findings about the role of mutations affecting crucial signaling pathways and the responsiveness to EGFR-targeting agents, derived from clinical trials as well as from basic and translational studies, were highlighted by Federica Di Nicolantonio (Turin, Italy) and Fortunato Ciardiello (Naples, Italy). They discussed about the possible mechanisms of intrinsic and acquired resistance to EGFR inhibitors, and the relevance of several biomarkers, such as KRAS and BRAF, as potential predictors of clinical activity of EGFR inhibitors in metastatic colorectal cancer. Ciardiello also presented interesting data about the *in vitro* and *in vivo* antitumor efficacy of the MEK inhibitor, AS703026,

in models of lung adenocarcinoma. Non-canonical signaling pathways possibly representing novel therapeutic targets for cancer therapy were also discussed. Elisabetta Dejana (Milan, Italy) focused on the role of the Wnt/beta-catenin pathway in vascular stabilization. Endothelial-specific stabilization of Wnt/beta-catenin signaling alters early vascular development in the embryo and determines a phenotype resembling that induced by upregulation of Notch signaling. The established link between Wnt and Notch signaling in vascular development suggested that early and sustained beta-catenin signaling prevents correct endothelial cell differentiation, altering vascular remodeling and arteriovenous specification. Focusing on the Hedgehog pathway, Alberto Gulino (Rome, Italy) revealed a novel model in which acetylation of glioma-associated oncogene (Gli) proteins, effectors of the Hedgehog pathway, functions as an unexpected key transcriptional checkpoint. The HDAC-mediated deacetylation of Gli1 and Gli2 proteins promotes transcriptional activation and sustains a positive autoregulatory loop through Hedgehog-induced upregulation of HDAC1.

Development of New Anticancer Agents: The Pharma Industry Perspective

The importance of translational cancer research was the focus of the joint session with the Italian Association of Medical Oncology. Tom Lillie (Uxbridge, UK) confirmed the utility of KRAS as a predictive biomarker and reported on the development of Panitumumab, an EGFR-specific monoclonal antibody. Anti-EGFR therapies in patients with KRAS wild-type tumors can optimize the benefits while avoiding toxicity in patients with KRAS mutant tumors. Yury Rukazenkov (Macclesfield, UK) focused on the development of Gefitinib, the first tyrosine kinase inhibitor of EGFR, describing the major clinical trials in patients with NSCLC and the relevance of mutations in the activation of EGFR. The relevance of KRAS and BRAF, in addition to ERBB2, PIK3CA and PTEN status, in the sensitivity to BKM120, a PI3K inhibitor that entered the phase I clinical trials, was also underlined by Malte Peters (Basel, Switzerland), who discussed about the development of PI3K and double PI3K/mTOR inhibitors, alone or in combination with other pathway inhibitors. Jorge Gallo (Milan, Italy) described the early development of the small molecule, PF-03758309, acting as an inhibitor of p21-activated kinase. The antitumor and apoptotic activity of PF-03758309 in several tumor models allowed it to enter phase I clinical trials in patients with advanced solid tumors. Finally, in her talk, Francesca Russo (Sesto Fiorentino, Italy) reported on the obstacles encountered during Premetrexed development and how clinical research has led to the development of folate pretreatment and vitamin supplementation as an effective way to reduce drug toxicity, thus increasing the feasibility of a treatment that has proven effective for NSCLC and malignant pleural mesothelioma patients. All these speakers stressed the importance of epidemiological data and biological characterization of tumors and novel imaging techniques in selection of patients who have greater chances to respond. Although a fully personalized cancer treatment is still unrealistic for most therapeutic regimens, for some new agents directed on specific targets the biological and pharmacological data are becoming essential to select the most suitable therapy for different patient populations.

Closing Remarks

Progress is ongoing in laboratory and clinical research at an unprecedented pace and, as we gain more knowledge and have more therapeutic options to offer to our patients suffering from cancer, we face new challenges. The biggest one is probably to develop truly translational approaches that will speed up the process of turning exciting discoveries into more effective therapies. To enable this, we will need to develop a common language and to make every effort to fill in currently existing 'gap' between basic and clinical cancer research. As highlighted above, the SIC Meeting was a first step toward the achievement of such an ambitious goal; judging on the bases of the outstanding level of the numerous abstracts selected for either oral or poster presentations and of the extensive effort that all participants made to look at cancer science and therapy in a truly multidisciplinary way, we believe that the two extremes of the roman Sant'Angelo bridge, the symbol chosen for the Meeting, now really look closer to each other. It is therefore with renewed enthusiasm that we will go back to our benches and patients and work even harder to better understand cancer biology and develop more effective therapies.

We look forward to the next Annual Meeting in Turin, October 2011.

Conflict of Interest

The authors declare no conflict of interest.

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