Advanced Breast Cancer Research Course
For Senior Oncologists

18TH – 22ND MAY, 2009
EUROPEAN INSTITUTE OF ONCOLOGY (IEO)
IFOM-IEO CAMPUS
Milan, Italy

With unrestricted educational grant of GSK Oncology

WELCOME

Welcome to the European Institute of Oncology (IEO) in Milan. Professor Umberto Veronesi started building this Comprehensive (European) Cancer Institute 15 years ago, after his retiral from the National Cancer Institute, also in Milan. While there, he had been the surgeon and inspiration behind the first ever randomized trial of lumpectomy versus mastectomy, the 20 year follow up of which was published in the New England of Medicine in 2004. He also developed CMF adjuvant chemotherapy in breast cancer with Gianni Bonnadonna, who also in turn created ABVD for Hodgkin's disease.

Fifteen years ago the site of the IEO hospital was a farm, and now it houses the fastest growing cancer institute in Europe, seeing 35000 new patients last year, operating on almost 12000 of them, and in particular treating almost 4000 women with breast cancer!

The driving force behind the growth of IEO has been breast cancer research in the lab and in the clinic. This innovative course will invite you to share in the various aspects of that research, and to understand how the translational process actually works here at IEO.

You will meet basic scientists and hear what makes them excited about cancer, applied scientists (doctors who work in the lab, and scientists who work in the clinic), and doctors who deliver what I believe is the highest standard of breast cancer care in Europe. The emphasis is on giving you in depth understanding of what happens in the lab, and why, and where it might illuminate the work of the breast cancer doctor. It is a first (Phase 1!) study for us, and you are the guinea pigs. I promise no toxicity, however, and I predict much enjoyment.

A VERY SPECIAL THANKS TO

Glaxo Smith Kline Oncology

ORGANIZATION

SCIENTIFIC & ORGANIZING COMMITTEE

Prof. J. Gordon McVie
European Institute of Oncology
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SCIENTIFIC PROGRAM

SUNDAY, MAY 17, 2009

Arrival of the participants and accommodation at the Grand Visconti Palace Hotel.

20.30 Buffet dinner at the hotel

MONDAY, MAY 18, 2009

08.30 Transfer from the hotel to IFOM-IEO Campus by private bus

IFOM-IEO Campus

09.00 Welcome Address:
"Breast Cancer: Past, Present, Future"
Umberto Veronesi

Hormone receptors
(Saverio Minucci)

09.30 Practical lab course
"Epigenetic Therapy Approaches"
Saverio Minucci

12.00 Plenary lecture
"Targetting Hormone Receptors"
Gordon McVie

13.00 Lunch

14.00 Practical lab course
"Epigenetic Therapy Approaches"
Saverio Minucci

17.00 Plenary lecture
"Lessons in Drug Development"
Silvia Marsoni

18.00 Transfer to the hotel by private bus

20.00 Transfer to the restaurant

20.30 Welcome dinner at the Restaurant "El Brellin"

SCIENTIFIC PROGRAM

TUESDAY, MAY 19, 2009

08.30 Transfer from the hotel to IFOM-IEO Campus by private bus

IFOM-IEO Campus

Stem cells (Giuliana Pelicci and Giuseppe Testa)

09.00 "Embryonic and Neural Stem Cells: Concepts and Applications"
Giuseppe Testa

12.00 Plenary Lecture
"Normal Mammary Stem Cells and their Relevance to Breast Cancer"
Salvatore Pece

13.00 Lunch

14.00 Practical lab course
"Glioma stem cells: how can we target them?"
Giuliana Pelicci

Cell division – part I (Andrea Musacchio)

17.00 Plenary lecture
"The Molecular Bases of Cell Division"
Andrea Musacchio

18.30 Transfer to the hotel by private bus

20.30 Informal and buffet dinner at the hotel

SCIENTIFIC PROGRAM

WEDNESDAY, MAY 20, 2009

08.30 Transfer from the hotel to IFOM-IEO Campus by private bus

IFOM-IEO Campus

Cell division – part II (Andrea Musacchio)

09.00 Plenary Lecture
"Inhibiting Cell Division"
Andrea Musacchio

10.30 Coffee break

11.00 Transfer to IEO by private bus

IEO

12.00 Lunch

Kinases (Giuseppe Viale)

13.00 Practical lab course
"FISH and Immuno Techniques in the Path Lab"
Giuseppe Viale

16.00 Plenary lecture
"Biomarkers in Breast Cancer"
Giancarlo Pruneri

17.00 Transfer to the hotel by private bus

20.30 Informal and buffet dinner at the hotel

SCIENTIFIC PROGRAM

THURSDAY, MAY 21, 2009

08.30 Transfer to the IEO by private bus

IEO

Angiogenesis (Francesco Bertolini and Giuseppe Petralia)

09.00 Practical lab courses
module A "Endothelial Cell Culture and Evaluation by Flow Cytometry"
Ines Martin-Padura
module B "Imaging of Angiogenesis"
Giuseppe Petralia

12.00 Plenary lecture
"Circulating Endothelial Cells"
Francesco Bertolini

13.00 Lunch

14.00 Practical lab courses
module A "Imaging of Angiogenesis"
Giuseppe Petralia
module B "Endothelial Cell Culture and Evaluation by Flow Cytometry"
Ines Martin-Padura

17.00 Plenary lecture
"Prediction of Antiangiogenesis in the Clinic"
Giuseppe Curigliano

Stem cells (Pier Giuseppe Pelicci)

18.00 Plenary lecture
"Breast Cancer Stem Cells"
Pier Giuseppe Pelicci

19.00 Transfer to the hotel by private bus

20.30 Transfer to the restaurant by private bus

21.00 Valedictory Dinner at the Restaurant "Taverna Visconti"

SCIENTIFIC PROGRAM

FRIDAY, MAY 22, 2009

08.30 Transfer to the IEO by private bus

IEO

Circulating tumor cells (Maria Teresa Sandri and Franco Nole')

09.00 "Different Methods for CTC Detection"
Maria Teresa Sandri

10.00 Practical lab course
"CTC Analysis"
Maria Teresa Sandri

12.00 Plenary lecture
"Future Applications of CTC Research"
Franco Nole'

12.30 Closing address
"Care for Women with Breast Cancer – 2009"
Aaron Goldhirsch

13.00 Lunch

14.00 End of the course and departure to the home countries

MAY 18, 2009 - LECTURES

MAY 18, 2009 - LECTURES

Breast Cancer: Past, Present and Future

Umberto Veronesi, MD
Scientific Director
Istituto Europeo di Oncologia, Milan - Italy

In the last ten years a number of revolutions have occurred in our understanding of the biology of breast carcinoma and have deeply influenced our approaches to the disease in terms of prevention, detection and treatment.
The genetic studies have identified subgroups at high risk of developing the disease creating the premises for programs of targeted chemoprevention. 2) Endocrine modulators and other active principles like retinoids have shown to be effective in reducing breast cancer incidence in specific subgroups of patients. 3) New developments in imaging procedures have made possible the detection of very early carcinomas greatly increasing the curability rates. 4) The analysis of the genetic profile of the cancer cells will be fundamental for prognostic evaluation and to assess the likelihood of response to medical treatments. 5) More and more non palpable tumors will be identified and destructed. Radio guided techniques to remove those occult lesions are now available. 6) Mastectomy is abandoned in favor of breast conservative treatments. 7) Thank to the Sentinel Node Biopsy procedure, the dissection of regional lymph nodes will be limited to patients with positive nodes. 8) Radiotherapy fields are being progressively reduced and partial breast irradiation is becoming a realistic perspective for the future. 9) Systemic treatments will be decided mainly according to the prediction of response to specific endocrine or chemical drugs. 10) New types of drugs built to meet specific biomolecular targets, expressed by mutated genes, are appearing as a result of the postgenomic research. 11) The cancer “stem cells” concept will open new roads in treatment. 12) TNM classification is being deeply modified. All these new facts are at the root of dramatic changes in paradigms for prevention, detection and treatment of breast cancer. The main shift refers to the progressive awareness of the importance of quality of life, which is changing the traditional approach based on the “maximum tolerated treatment” to the “minimum effective treatment”. This new trend has led to limited surgery (instead of mutilating operations), more targeted radiotherapy (instead of large field involving the regional nodes), less aggressive chemotherapy (instead of the high dose approach). This new trend will motivate more women to participate in early detection programmes, which in turn will lead to the reduction of mortality rates.

MAY 18, 2009 - LECTURES

Approaches to epigenetic therapies

Coordinator: Saverio Minucci, M.D. (IFOM-IEO Campus, University of Milan)
LECTURERS, CO-ORGANIZERS:
Ciro Mercurio, Ph.D. (Genextra-IFOM-IEO Campus)
Roberto Boggio, Ph.D. (Genextra-IFOM-IEO Campus)
Matias Soncini, Ph.D. (IFOM-IEO Campus)

General structure of the 1 day course:
We will have two theoretical lectures, to provide the biological bases of normal epigenetic mechanisms, their alterations in cancer, and the rationale for their targeting by drugs. We will provide examples of development and characterization of drugs targeting epigenetic enzymes, with an emphasis on the potential clinical relevance of these studies.
We will then show practically (visiting the laboratories of the Campus) a few examples of the assays described in the lectures, trying primarily to convey the sense of the experimental systems in "real life".
Finally, we will have an open discussion where we will try to wrap-up the links between the preclinical work discussed and performed in the laboratory, and the clinical practice.

Abstract
Definition of epigenetics
In biology, the term epigenetics refers to changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence, hence the name epi- (Greek: over; above) -genetics. The Greek prefix epi- in epigenetics implies features that are "on top of" or "in addition to" genetics; thus epigenetic traits exist on top of or in addition to the traditional molecular basis for inheritance.
These phenotypic changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations. However, there is no change in the underlying DNA sequence of the organism; instead, non-genetic factors cause the organism's genes to behave (or "express themselves") differently. The best example of epigenetic changes in eukaryotic biology is the process of cellular differentiation. During morphogenesis, totipotent stem cells become the various pluripotent cell lines of the embryo which in turn become fully differentiated cells. In other words, a single

fertilized egg cell - the zygote - changes into the many cell types including neurons, muscle cells, epithelium, blood vessels et cetera as it continues to divide. It does so by activating some genes while inhibiting others.

The similarity of the word to “genetics” has generated many parallel usages. The “epigenome” is a parallel to the word “genome,” and refers to the overall epigenetic state of a cell. The phrase “genetic code” has also been adapted—the “epigenetic code” has been used to describe the set of epigenetic features that create different phenotypes in different cells.

Molecular basis of epigenetics

There are several layers of regulation of gene expression. One way that genes are regulated is through the remodeling of chromatin. Chromatin is the complex of DNA and the histone proteins with which it associates. Histone proteins are little spheres that DNA wraps around. If the way that DNA is wrapped around the histones changes, gene expression can change as well. Chromatin remodeling is accomplished through several distincly different mechanisms:

1. The first way is post translational modification of the amino acids that make up histone proteins. Histone proteins are made up of long chains of amino acids. If the amino acids that are in the chain are changed, the shape of the histone sphere might be modified. DNA is not completely unwound during replication. It is possible, then, that the modified histones may be carried into each new copy of the DNA. Once there, these histones may act as templates, initiating the surrounding new histones to be shaped in the new manner. By altering the shape of the histones around it, these modified histones would ensure that a differentiated cell would stay differentiated, and not convert back into being a stem cell.

2. The second way is the addition of methyl groups to the DNA, at CpG sites, to convert cytosine to 5-methylcytosine. Cytosine is the nucleotide that our cells can “read.” Our cells cannot “read” methylcytosine. If DNA is conceived as an instruction manual again, changing cytosine to methylcytosine would be like changing the font on a Word document to “wingdings.” The contention would be that since the cell can no longer “read” the gene, the gene is turned off.

Although modifications occur throughout the histone sequence, the unstructured termini of histones (called histone tails) are particularly highly modified. These modifications include acetylation, methylation, ubiquitylation, phosphorylation and sumoylation. Acetylation is the most highly studied of these modifications. For example, acetylation of the K14 and K9 lysines of the tail of histone H3 by histone acetyltransferase enzymes (HATs) is generally correlated with transcriptional

competence.One mode of thinking is that this tendency of acetylation to be associated with “active” transcription is biophysical in nature. Because it normally has a positively charged nitrogen at its end, lysine can bind the negatively charged phosphates of the DNA backbone and prevent them from repelling each other. The acetylation event converts the positively charged amine group on the side chain into a neutral amide linkage. This removes the positive charge, causing the DNA to repel itself. When this occurs, other transcriptional factors can bind to the DNA, thus opening it up and exposing it to enzymes like RNA polymerase so transcription of the gene can occur.

It should be emphasized that differing histone modifications are likely to function in differing ways; acetylation at one position is likely to function differently than acetylation at another position. Also, multiple modifications may occur at the same time, and these modifications may work together to change the behavior of the nucleosome. The idea that multiple dynamic modifications regulate gene transcription in a systematic and reproducible way is called the histone code.

Because DNA methylation and chromatin remodeling play such a central role in many types of epigenic inheritance, the word “epigenetics” is sometimes used as a synonym for these processes. However, this can be misleading. Chromatin remodeling is not always inherited, and not all epigenetic inheritance involves chromatin remodeling.

Epigenetic research uses a wide range of molecular biologic techniques to further our understanding of epigenetic phenomena, including chromatin immunoprecipitation (together with its large-scale variants ChIP-on-chip and ChIP-seq), fluorescent in situ hybridization, methylation-sensitive restriction enzymes, DNA adenine methyltransferase identification (DamID) and bisulfite sequencing. Furthermore, the use of bioinformatic methods is playing an increasing role (computational epigenetics).

Cancer and epigenetic therapies

In 2008, the National Institutes of Health announced that $190 million had been earmarked for epigenetics research over the next five years. In announcing the funding, government officials noted that epigenetics has the potential to explain mechanisms of aging, human development, and the origins of cancer, heart disease, mental illness, as well as several other conditions. Some investigators think epigenetics may ultimately turn out to have a greater role in disease than genetics.

Cancer cells show global changes in chromatin structure, that lead to alterations in gene expression and other nuclear functions. Interestingly, unlike genetic lesions, those alterations are potentially reversible, making it feasible to target the epigenome to therapeutic ends.

In cancer cells, aberrant DNA methylation plays an important role in cancer initiation

and progression by suppressing transcription of genes essential for the control of normal cell growth and differentiation. Widespread alterations in histone acetylation patterns have been identified as common chromatin aberrations during tumorigenesis. In a few cases, these alterations have been linked to aberrant enzymatic activity of histone acetylases and deacetylases (HATs and HDACs, respectively). Altered expression and improper recruitment of HDAC containing complexes has been described in different malignancies. These changes occur early, and accumulate as cancer progresses: indeed, specific histone modifications can be used to predict cancer recurrence.

References

** Wikipedia, Epigenetics.*

** Joshua Lederberg,The Meaning of Epigenetics, The Scientist 15(18):6, Sep. 17, 2001.*

** B. D. Strahl and C. D. Allis (2000) The language of covalent histone modifications. Nature 403, 41-45.*

Attached: PDF files of relevant reviews.

MAY 18, 2009 - LECTURES

Targetting Hormone Receptors

J. Gordon McVie
European Institute of Oncology, Milan, Italy

This talk will concentrate on clinical/lab interactions in the development of receptor dictated treatment of breast cancer. And it starts with a history lesson! The whole concept of hormonal manipulation in the management of breast cancer started in 1896, in Glasgow, Scotland (the city of my birth), when Sir George Beatson, professor of surgery and farmer, published his observations. Much of the subsequent development of the concept was also led by surgeons like Veronesi, Fisher and Baum, and the lab only began to make an impact with tamoxifen, and subsequent aromatase inhibitors four decades ago. Trastuzamab and then Lapitinib are latecomers, and look like hopeful designer drugs, but they aren't "one drug cures all" developments, and they have yet to be shown to improve overall survival rates.

Some scepticism (my personal perception) will be presented, claiming that too much credence and certainly over much hype has been given by Research Funders, including Charities, Governments and Pharma, to targeted therapy as the Holy Grail. Which are the blockbuster designers still surviving longer term scrutiny? What is plan B if targeted approaches fail to cure more patients? What is plan C if plan B doesn't work either?

So the answers of each of these are disputable, but it is our intention in the course to concentrate on uncertain areas, to provoke discussion, and to destroy complacency!

My answer to the first question is that, after imatinib, the track record of targeted therapy is disappointing, and the main evidence is the fall in numbers of such drugs being approved by FDA over each of the last three years.

Plan B should never have been scrapped, as it yielded some superb drugs. Temozolomide is a good example of chemistry led discovery, rather than target led drugs, and it became a blockbuster (over $1bn sales) in November 2008. And Plan C will be discussed extensively in this course, namely isolation and characterization of cancer stem cells, which in our hypothesis are the source of drug resistance.

MAY 19, 2009 - LECTURES

MAY 19, 2009 - LECTURES

Embryonic and Neural Stem Cells: Concepts and Applications

Giuseppe Testa, MD, PhD, MA

The regulation of stem cell function intersects three fundamental questions of modern biology with remarkable applied potential, the physiology of lineage acquisition, its derangement in cancer and its manipulation for regenerative applications.
Over the past decade, the methylation of histones on lysine tails (HLM) has emerged as a central mechanism in the programming of genomes that underlies the establishment and maintenance of differentiated cell states. The connection between HLM and developmental fate became apparent with the realization that Ezh2, a member of the Polycomb group (PcG) of proteins first discovered in the fly as stable repressors of Hox genes, catalyzes the trimethylation of histone H3 on lysine 27 (H3K27me3) while Trx (and its mammalian homologs of the Mll family), identified in the fly as a stable activator of Hox genes, catalyzes the trimethylation of histone H3 on lysine 4 (H3K4me3). With the evidence that correlated various stages of cell differentiation with different H3K27me3 and H3K4me3 profiles, until recently the prevailing view held that histone methylation was irreversible and that this very irreversibility underlied lineage identity. Over the last three years the identification of several histone demethylases (HDMs) revealed that HLM can be instead highly dynamic, suggesting that it is the entire process of lineage acquisition that requires the regulated addition and removal of methyl marks.
Consistent with the role of PcG in lineage choices, alterations in H3K27me3 are emerging as early events in the cascade of epigenetic aberrations of cancer, particularly the hypermethylation of CpG promoters that is an important mechanism of tumor suppressor inactivation. Convergent lines of evidence indicate that CpG hypermethylation in cancer cells is the result of an instructive process through which altered developmental programs determine aberrant hypermethylation at multiple loci. The recent observation that most epithelial cancers share a core transcriptional signature with ES cells corroborates this model and suggests that epigenetic expression programs that orchestrate development in normal cells are hijacked in cancer cells as the main template for cancer DNA methylation. Yet, despite the growing evidence that correlates H3K27 and H3K4 methylation states to differentiation states, we still do not understand how this epigenetic system contributes to the maintenance of differentiated states and to the lineage derangements that characterize tumors.
This session will summarize the current models in the epigenesis of stem cell function, with a special focus on the advances in gene engineering that are enabling to probe the role of epigenetic regulation in physiologically and physiopathologically meaningful contexts.

Identification of markers and study of the mechanisms supporting the tumorigenic potential of cancer stem cells derived from glioblastoma.

Brescia P, Ortensi B, Osti D, Richichi C, Pelicci G.
Department of Experimental Oncology, European Institute of Oncology, Milan, Italy.

Glioblastoma multiforme (GBM) (WHO grade IV) is the most aggressive among the brain tumors of adults. GBM has the propensity to infiltrate throughout the brain (making complete surgical resection impossible), its cellular composition is heterogeneous and it is largely resistant to radiation and chemotherapy. It has been demonstrated that the bulk of malignant cells in GBM is generated by rare fractions of self-renewing, multipotent tumor initiating cells named cancer stem cells (CSCs) or tumor-initiating cells or tumor propagating cells (TPCs) (Singh S.K. et al., 2004; Galli R. et al., 2004).
The identification of tumoral neural stem cells provides a powerful tool to investigate the tumorigenic process in the central nervous system and to develop therapies targeted to these cells. Up to date, there are no specific markers that might be used as a tool to distinguish a normal stem cell from a cancer stem cell as well as stem cells from progenitors.
CD133 has been used so far as a cell surface marker of adult stem cells after the discovery of its expression by haematopoietic progenitors (Yin A.H. et al., 1997). The notion that CD133 might be a reliable cancer stem cell marker in brain tumors is currently under revision. It has been in fact recently reported from different authors (Beier D. et al., 2007) that also CD133- negative cells were tumorigenic in intrathecally injected nude mice. It has been recently demonstrated that in a mouse model of medulloblastoma the CD133+ cells were not able to form neurospheres and to propagate the tumor while CD133- expressing cells conversely were able to do so. This last subpopulation expressed indeed a different marker, the CD15 (Read T.A. et al., 2009), whose expression it is still unknown in CSCs derived from GBMs. We comply with the notion that specific genetic and molecular analysis of tumoral neural stem cells will ameliorate the understanding of the mechanisms of brain tumor growth. Therefore, looking for new, viable markers to be able to distinguish a normal stem cell from a cancer stem cell as well as stem cells from progenitors in order to identify tumor-inducing cells as a new target to fight cancer, has a high therapeutic significance.

MAY 19, 2009 - LECTURES

Molecular basis and inhibition of cell division

Andrea Musacchio
Department of Experimental Oncology, European Institute of Oncology, Milan, Italy

Protein kinases are enzymes that covalently modify their protein substrates with a phosphate moiety derived from ATP. Protein kinases represent one of the largest protein families in the human genomes, and they are involved in most, if not all, physiological processes taking place in our cells. In my lectures, I will concentrate on the role of protein kinases in the cell division cycle. The process of cell division is essential to the propagation of life. Discrete, consecutive steps define its layout. First, the genome is replicated in the mother cell, and is then equally parted in the daughter cells in a process named mitosis. The clock that runs the cell division process is based on the cyclical activation and inactivation of kinases. These, in turn, regulate "cascades" of other kinases that exercise control over different processes, such as the process of chromosome attachment to the mitotic spindle.

Kinases have long been identified as possible targets for pharmacological inhibition. The ATP-binding site of kinases is a deep pocket at the interface between two domains of the kinase and is ideally suited to host small organic molecules that displace ATP and prevent catalytic activity. Furthermore, the presence of small architectural differences in the residues lining the active site of kinases has been exploited to design specific and selective inhibitors.

Some kinases are directly deregulated in cancer. Examples of kinases that deliver more catalytic activity than is required for normal physiology are v-Src, Bcr-Abl, and certain mutants of the Epidermal growth factor receptor (EGFR). These kinases represent ideal direct targets for cancer therapy. In other cases, kinases are involved in fundamental cellular pathways that even cancer cells need to execute with a high degree of accuracy. The process of mitosis, for instance, has been recently identified as a possible target for cancer therapy, as cancer cells usually tend to divide more often than normal cells in a tissue.

In my lectures, I will explore the mechanism of action of protein kinases, the mechanism of inhibition, and will explain how resistance to pharmacological inhibition arises and how it could be exploited for target identification.

MAY 20, 2009 - LECTURES

MAY 20, 2009 - LECTURES

Biomarkers in Breast Cancer

Giancarlo Pruneri
European Institute of Oncology, Milan, Italy

The complex combination of a variety of traditional histopathological parameters and more recently recognized phenotypical and genotypical biomarkers allows to stratify breast cancer patients in groups with different clinical behaviour and response to specific therapies, in an effort to tailor the therapeutic strategy more and more properly. The main predictive and prognostic parameters for breast cancer patients are recognized by the San Gallen Consensus Conference, and include the traditional histological parameters of tumor size histological grade and axillary status, but also the estrogen (ER) and progesterone (PgR) receptor status, the Her-2 gene status and the Ki-67 labeling index. Breast cancer patients are roughly divided in three clinical categories, endocrine-sensitive, endocrine resistant and uncertain, on the basis of the recognition of ER and/or PgR expression in formalin-fixed and paraffin-embedded samples. Unfortunately, the discordance rate among different laboratories in assessing ER and PgR immunoreactivity still approaches 15%, leading to an unacceptably high percentage of incorrect and potentially harmful treatments. A similar scenario concerns the assessment of the Her-2 status, which may be performed by using alternatively immunohistochemistry or fluorescence in situ hybridization: different randomized studies have reported that the discordant rate of Her-2 assessment is approximately 30%. The DNA microarray technique allowed to create a new molecular classification of breast cancer and to recognize different risk categories. These data are very promising and deserve to be confirmed in randomized clinical trials, which are currently ongoing.

MAY 21, 2009 - LECTURES

MAY 21, 2009 - LECTURES

Imaging of Angiogenesis

Giuseppe Petralia
European Institute of Oncology, Milan, Italy

The connection of tumours with vascular growth and angiogenesis provides a number of targets of interest in oncology. Non-invasive assessment via imaging is a growing area for radiology.

We will review the techniques of positron emission tomography, ultrasound, computed tomography and magnetic resonance imaging. The application of these techniques is commonly referred to as perfusion imaging, though the resulting maps and measurements provide insight into a number of properties that are relevant to the characterisation of angiogenesis.

PET – A number of radio-isotopes are available for providing quantitative measures of perfusion and metabolic consumption of oxygen. A particularly important feature is the potential for labels to be tailored to specific antigens and some metabolic pathways. The cost and radiation exposure of PET studies however count against widespread use in large numbers of patients.

Ultrasound – Conventionally used for soft-tissue imaging and measurement of macrovessel blood flow, the recent development of blood-pool contrast agents has provided a technique reminiscent of microsphere perfusion which can be monitored non-invasively.

CT – Has been increasingly used in recent years due to the wide availability of CT scanners, the easy standardization of protocols and the relatively simple post-processing reliant on the direct relation between voxel concentration of contrast agent and X-ray attenuation. Currently the dominant method in trials.

MR – Provides the means to assess a wide range of tissue characteristics, including vascular density, flow, permeability, cellularity and hypoxia. The flexibility, however, makes interpretation difficult and in general multiple properties must be examined, adding to the complexity of studies. Lack of standardization is a significant limitation to the use of MR in a clinical setting.

It must be remembered that angiogenesis is neither a homogenous process in space, nor in time. At best, imaging can provide snapshots of this process at specific time points. Understanding the progression of disease and treatment response on the basis of such snapshots must be pursued with care.

Circulating endothelial cells (CECs) and progenitors (CEPs) for prediction of response in patients with breast cancer who receive chemotherapy and anti-angiogenic drugs: Different predictive potentials according to drug dose and schedule.

P Mancuso, A Calleri, J Quarna, P Antoniotti, G Curigliano, F Nolè, R Torrisi, M Colleoni, A Goldhirsch, F Bertolini

The addition of anti-angiogenic drugs to chemotherapy has led to improved survival in randomized trials involving colorectal, lung and breast cancer patients. However, this survival advantage was short, and was probably due to a larger benefit in a selected (but yet unrecognized) patient population rather than in the entire treated population. We investigated the kinetics and the predictive potential of CECs and CEPs in 4 phase II studies in which patients with advanced or locally advanced breast cancer received metronomic chemotherapy alone, metronomic chemotherapy plus the anti-VEGF antibody bevacizumab or regular-dose chemotherapy plus bevacizumab. CECs and CEPs were measured with a novel flow cytometry procedure including nuclear acid staining (Syto16 and 7AAD) able to investigate CEC/CEP viability and to discriminate between nucleated CECs/CEPs, CEC-derived fragments and platelets (Mancuso et al, Clin Cancer Res, in press). Compared with healthy controls, CECs (CD45-, CD31+, CD146+) and CEPs (either CD45-, CD133+ or CD45-, CD34+, VEGFR2+) were increased in patients with cancer, and in particular in patients with advanced breast cancer, where CEC count was found to be one log higher compared to controls. In patients receiving oral metronomic chemotherapy alone (either cyclophosphamide (CTX) plus methotrexate, in one study enrolling 104 patients, or vinorelbine alone, in another study enrolling 35 patients), therapy was associated with a decrease in viable CECs, and an increase in apoptotic CECs. In patients receiving CTX plus methotrexate, an increase in apoptotic CECs after two months of therapy was associated with improved survival (p=0.005). In another study enrolling patients with advanced breast cancer receiving metronomic capecitabine plus CTX plus bevacizumab (n=46), higher baseline CEC counts correlated with an improved response (p=0.02), clinical benefit (p=0.01) and progression-free survival (p=0.04). In a fourth study were 36 locally advanced patients received regular-dose chemotherapy (capecitabine plus vinorelbine), plus endocrine therapy (letrozole) plus bevacizumab before surgery, baseline CEP count was positively associated with a clinical response (p=0.02). Taken together, our studies indicate that assessment of CECs might be an estimation tool for prediction of response in patients with advanced breast cancer receiving metronomic chemotherapy alone or in association with bevacizumab. On the other hand, CEPs might be more promising for predicting response in patients receiving regular-dose chemotherapy plus anti-angiogenic drugs.

MAY 21, 2009 - LECTURES

Prediction of antioangiogenesis in the clinic

Giuseppe Curigliano, MD, PhD
Department of Medicine, Division of Medical Oncology, European Institute of Oncology, Milan, Italy

Anti-angiogenic therapies are increasingly used for cancer patients. However, their clinical development is currently hampered by the lack of markers able to predict who, among cancer patients, will benefit from these new drugs, how long these drugs should be administered and at what dosage. Antiangiogenic approach in cancer could be improved if reliable surrogate markers of drug biological activity were available. Our group developed clinical and experimental models to answer several crucial questions: circulating endothelial cells (CECs) and circulating endothelial progenitors (CEPs) measurements should be considered surrogate markers of anti-angiogenic drug activity? Can gene array analysis of breast cancer tissues provide a molecular signature of responsiveness to antiangiogenic therapy? We have found a crucial role for CEPs in the chemosensitizing effect of anti-angiogenic drugs. These data explain the efficacy of combined anti-angiogenic and cytotoxic therapies in breast cancer, and underline the need for an anti-angiogenic support in patients receiving some types of cytotoxic drugs. We have validated at the molecular, ultrastructural, intra- and inter-laboratory level a novel flow cytometry procedure for the enumeration of CECs and CEPs. We're running several clinical studies in which we defined a predictive role of CECs and CEPs in breast cancer cancer patients receiving anti-angiogenic therapies.

Breast Cancer Stem Cells

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Recent findings support the concept that cells with the properties of stem cells (SC) are integral to the development and perpetuation of several forms of human cancer, and that eradication of cancer stem cells (CSC) may be essential to achieve cancer cure. However, direct proof of these concepts is still lacking, mainly due the scarcity of appropriate model systems. We are characterizing the biological differences between normal and transformed SCs. SCs are defined by their abilities to generate more SCs ('self-renewal') and to produce cells that differentiate. One mechanism by which SCs accomplish these two tasks is asymmetric cell division, whereby each SC divides to generate one daughter with SC fate and one that differentiates. SCs, however, possess the ability to expand in number, as it occurs during development and in adulthood after injury or disease. This increase is not accounted by asymmetric divisions, in which only one daughter cell maintains SC identity. Recent findings in C.elegans and Drosophila indicate that SCs can also generate daughter cells that are destined to acquire the same fate (symmetric cell division). On the other hand, SC quiescence is critical to maintain tissue homeostasis after injury. We will present our recent findings showing increased symmetric divisions of CSCs in breast tumors (due to inactivation of the p53 tumor suppressor) and dependency of leukemia development on quiescent leukemia SCs (due to transcriptional up-regulation of the cell cycle inhibitor p21 by leukemia-associated fusion proteins). Our findings suggest that that asymmetric divisions of stem cells function as a mechanism of tumor suppression, that SC quiescence is critical to the maintenance of the transformed clone and that symmetric divisions of SCs permits its geometric expansion.

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Different methods for CTC detection

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CTCs are cells shed into the circulation from the tumor. The first description of the presence of tumor cells in the peripheral circulation dates the 19th century. A fraction of these cells probably derive from the primary tumor, and this may be considered as one of the initial step of the metastatic cascade, whereas another fraction may originate from metastatic lesions.
Their detection has been considered to be of great importance in oncology, and in the last decades numerous efforts have been made to develop reliable assays enabling the detection of CTC in peripheral blood. However the development of such assays was not so easy: first of all CTC in the blood are a quite rare event, and secondly, we do not have very specific CTC markers.
Many methods use enrichment procedure to overcome the low number of CTC possibly present in the blood, and the technologies used are fundamentally 2:
- the nucleic acid based methods, especially RT PCR for mRNA expression of different markers, which are not specific for CTC but may be expressed also by normal cells. This poses the problem of the sensitivity and of the correct threshold for these methods. Moreover the enumeration is not feasible
- assays using an “immunological” approach, therefore using immunolabelling of the cells which can then be detected and counted for example with a cell sorter.
We have implemented a recently introduced semi-automated standardized method, in which an immunomagnetic enrichment of the sample is followed by the identification of CTC, defined as cells positive for a nuclear staining, the DAPI staining, positive for CK 81 18 and 19 and lacking CD 45 expression.
Apart form enumeration, it is now possible to separate CTC and to characterize them: this represents an interesting and challenging area of research, and possible future application include the study of genetic alteration, phenotypic characterization or, for example, monitoring of patients treated with different drugs to examine tumor cells modification.

Future applications of Circulating Tumor Cells research

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Disseminated malignancy is the main cause of cancer-related deaths and, therefore, the main therapeutic and investigational challenge today. Metastases, occurring at the time of diagnosis or as a recurrence of a previously diagnosed cancer, are responsible for 90% of cancer-related deaths. Given that 1 cm3 of tissue may contain as many as 109 cells, a malignant growth can easily reach 1010 or 1011 cells before it is clinically detectable.

A number of sequential steps involving host-tumor interactions are required before a metastatic colony at a distant organ site develops. The first step involves cancer cells of the primary tumor breaching the basement membrane and reaching the peripheral circulation either directly or indirectly through the lymphatics. It has been estimated from model systems that approximately 1x 106 CTCs per gram of tumor tissue is released into the circulation daily. Once in the circulation CTCs can then arrest at a distant vascular bed, invade organ interstitium and parenchyma, and then proliferate to establish a metastatic colony.

However, a significant number of the CTCs are apoptotic. This coupled with the fact that not all CTCs have the same metastatic potential, a phenomenon explained by tumor heterogeneity, results in less than 0.1% of CTCs being ultimately successful in settling in secondary organs and establishing metastases. Research is currently focused at specifically identifying these CTC subsets and characterizing them at the molecular level to ultimately provide a tool that would allow tailoring treatment on an individual basis.

Methods of detection of CTC

Several methods have been used to detect CTCs in patients with breast cancer. Methods using polymerase chain reaction (PCR) techniques detect CTCs through the use of nucleic acid analysis. The major limitations of PCR-based assays include inability to quantify tumor cells, low sensitivity and specificity, and contamination of samples, all of which contribute to their inability to be used as functional assays.

One way to increase specificity is to use quantitative reverse transcriptase-PCR based assays that is able to increase the discrimination between mRNA expression in normal cells and CTC. The use of RNA based PCR methods also has the advantage over DNA-based PCR methods of detecting primarily viable cells. Overall, however, PCR

based assays are not commonly used in the detection of CTCs in patients with breast cancer. A more widely used method, with higher sensitivity and specificity, for the detection of CTCs is a cell enrichment method based on immunomagnetic separation technology. This technique involves the use antibodies directed against epithelial cells, linked to small magnetic beads, that enable target selection of tumor cells using a powerful magnet. The isolated cells can then undergo downstream reverse transcriptase PCR, flow cytometry, or immunohistochemical (IHC) analysis. Combining the principle of immunomagnetic separation, to isolate epithelial tumor cells, and subsequent counting of cells with immunofluorescent analysis of cytokeratin expression the CellSearch system (Veridex, LLC, Warren, NJ) was developed and approved by the US Federal Drug Administration.

There is a growing body of literature to suggest, that CTC might provide useful clinical information either in newly diagnosed patients or in those being monitored for recurrence or during treatment of metastatic disease.

CTC in patients with operable, early-stage breast cancer.

Adjuvant systemic therapy, including antiestrogen and anti-HER treatments and chemotherapy, have clearly resulted in remarkable decreases in breast cancer mortality. These treatments, however, are not without substantial toxicity, inconvenience, and cost. Therefore, it would be preferable to avoid treating those patients unlikely to benefit, either because their prognosis is so good that they simply do not need it, or their tumor is so unlikely to respond to a specific therapy that it will not do them any good. CTCs are currently being investigated for both their prognostic and predictive utility. Studies have suggested that CTC can be found in up to 40% of patients with newly diagnosed breast cancer when assayed by RT-PCR and in about 10% using CellSearch.

The presence of CTCs seems to be associated with a poorer prognosis at diagnosis regardless of nodal status or whether patients receive adjuvant systemic therapy, moreover, recent reports have suggested that increasing CTC results “during” or “residual CTCs after adjuvant treatment” may predict that the ongoing or prior therapy is ineffective. These results are consistent with findings by other investigators regarding bone marrow micrometastases. Presently, it is not clear how CTC levels might be used to make clinical decisions in the adjuvant setting, considering that each of these studies has been conducted within patient cohorts in which therapy was not prospectively dictated, and no study has used CTC results to direct therapy compared with a group of patients treated using standard prognostic and predictive criteria. Given the overall survival benefit of adjuvant chemotherapy, use of a tumor marker,

such as CTC, to make clinical decisions must be considered very carefully.

CTC in patients with metastatic breast cancer.

Although an occasional patient with metastatic breast cancer seems to be cured, most are destined to ultimately die of their disease. Nonetheless, a number of new therapies has been introduced for patients in this setting, resulting in modest prolongation of survival and substantial improvements in palliation. Thus, the goal of therapy for most patients with metastatic breast cancer is to choose the therapy with the highest likelihood of response and the lowest possibility of toxicity, thus balancing symptoms of the cancer with side effects of treatment. Indeed, a wide array of strategies and agents are now available to treat these patients, including antiestrogen therapies, chemotherapies, and other biological therapies. Once a palliative treatment regimen is selected for a patient with metastatic breast cancer, it is generally continued until either undue toxicity or evidence of progression. Current methods of determining progression include history, physical examination, serologic testing, and radiographic evaluation. Nonspecific serologic examinations, such as enzymes derived from bone (e.g., alkaline phosphatase) and liver (e.g., alkaline phosphatase and serum glutamate oxalate transferase) lack both sufficient sensitivity and specificity to be very helpful in this setting. The American Society of Clinical Oncology Tumor Marker Guideline Panel has recommended that assays for MUC-1 proteins (CA15-3 and CA27.29) and for carcinoembryonic antigen may be helpful in monitoring selected patients with metastatic breast cancer.

Elevated CTCs are found in 50% to 75% of patients with metastatic breast cancer by using either RT-PCR or immunomagnetic/fluorescence approaches. In prospective, clinical trials involving women with measurable, progressive metastatic disease who were about to start a new therapy, elevated CTC at any time point, using CellSearch, were associated with a high likelihood of a very short time to progression . In these trials, 50% - 60% of these patients had elevated CTC before starting a new treatment, and their prognosis was worse than those without elevated CTC. Patients with persistently elevated CTCs during chemotherapy, had a worse prognosis than patients who did not, and patients with elevated levels of CTCs before to start the treatment but with < 5 CTCs /7.5 ml of blood after the first cycle of chemotherapy, had a favorable prognosis, similar to those women without CTC at baseline, suggesting a therapeutic response . Likewise, elevated CTCs at later time points were also associate with rapid subsequent progression and Residual CTC at first follow-up was an indication of a very high likelihood of rapid progression. It is possible that changing therapy at this time point might be more beneficial than maintaining an apparently futile

treatment regimen. If these data are validated, CTC levels may ultimately represent a more objective and accurate determination of disease status than classic clinical and/or radiological assessment and as such, when elevated, may indicate the need to change therapy.

Future Directions

Simple enumeration of CTCs is just the tip of the iceberg with regard to the enormous biological and clinical contributions these assays may provide. Technology to detect and characterize CTCs is advancing rapidly and with current techniques, it is possible to perform gene expression profiling from CTCs. Several investigators have reported secondary phenotyping and genotyping of immunomagnetically detected cells for a variety of tumor associated markers, including HER2, IGFR1, BCL-2, measures of apoptosis, telomerase, Notch1, UUPAR and, in prostate cancer, even gene expression profiling. No trials have been reported describing how these assays might be used to direct clinical care, but their potential is provocative and exciting. . This enables studies that should allow deeper insights into the mechanisms allowing CTCs to form manifest metastasis. For example, it seems that, for breast cancer, only a small proportion of tumor cells, so-called 'cancer stem cells', have the capacity for self-renewal and unlimited growth. In view of the resistance of DTCs and CTCs to chemotherapy it is possible that some of these cells have stem-cell properties. Identifying these 'metastatic stem cells' will be the one of the challenges for future research.

Another aspect of clinical importance is the identification of therapeutic targets such as HER-2/neu on CTCs. HER-2 can be detected on CTCs with cytogenetic, immunocytochemical, and PCR methods. There are several possible implications of these findings. For example, it has been reported that nearly one-third of patients whose primary tumors were reportedly negative for HER-2 had CTCs with amplified HER-2 (as determined by FISH). Given the extraordinary impact of trastuzumab (Herceptin), a humanized monoclonal antibody directed against HER-2, in both the metastatic and adjuvant settings, monitoring CTCs for HER-2 could have an enormous influence on the application of this therapy. In addition, the presence of HER-2-positive CTCs seems to be associated with an impaired prognosis.

In conclusion, detection of CTCs in the peripheral blood of patients with breast cancer provides not only prognostic information but also provides a marker for monitoring efficacy of systemic treatment. Although studies have focused more on the use of CTCs in the metastatic CTCs appears to also be clinically relevant in patients with early stage breast cancer. To better understand the biology of CTC we need well-designed and well-conducted perspective trials.

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*Care for Women with Breast Cancer - 2009

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Adjuvant treatments for patients with breast cancer were developed during more than half a century mainly through randomized clinical trials. Different views about how to interpret their results led to an heterogeneous offer of treatment programs to similar groups of patients. One should always bear in mind that an adjuvant treatment offered to an individual patient cannot be checked for efficacy. Demonstration of benefit from an adjuvant therapy is exclusively possible within the context of clinical trials. Therefore, issues related to biological features of the disease and their clinical relevance for treatment choice on one hand, and social and public health considerations on the other should influence the way specific treatments are tailored for individual patients, but also the way trials are planned and conducted. Trials of the future should be designed to allow the best chance of response to novel treatments, based upon biological features of disease as well as on personal characteristics of the patient. In the past the Worldwide Overview was used to validate the efficacy of various therapies in the adjuvant setting, homogenizing the magnitude of effects of treatments in several similar clinical trials. A conference, like the one held in St. Gallen, was needed to provide an expert consensus on interpretation of data from the Overview and from individual trials, to guide women and their doctors in the selection of appropriate treatments. Menopausal status, age of the patients as well as classification of tumors according to their endocrine responsiveness (endocrine responsive, endocrine non-responsive and tumors of incomplete endocrine responsiveness) and according to responsiveness to trastuzumab were the first steps for proper treatment selection. Additional information based on several other markers is currently leading to a refinement of classification of tumors for a better selection of patients to new therapeutic trials. It is recognized that some of the patients with endocrine responsive disease might not get a sufficient benefit from endocrine therapies alone. Some of the patients with «triple negative» disease might require a different type of adjuvant cytotoxic therapy which includes primarily DNA-damaging agents rather than anthracyclines or taxanes. Finally, several new biomarkers might be necessary for a best choice of several biological compounds which are currently entering various phases of clinical testing in this setting.

**Partially presented at the 15th World Congress on Breast Diseases, Shanghai, China, October 23-26, 2008*

INVITED SPEAKERS

Francesco Bertolini	European Institute of Oncology - Milan, Italy
Giuseppe Curigliano	European Institute of Oncology - Milan, Italy
Aaron Goldhirsch	European Institute of Oncology - Milan, Italy
Silvia Marsoni	SENDO Foundation -Milan, Italy
Gordon McVie	European Institute of Oncology - Milan, Italy
Saverio Minucci	European Institute of Oncology c/o IFOM-IEO Campus - Milan, Italy
Andrea Musacchio	European Institute of Oncology c/o IFOM-IEO Campus - Milan, Italy
Franco Nole'	European Institute of Oncology - Milan, Italy
Ines Martin-Padura	European Institute of Oncology - Milan, Italy
Salvatore Pece	European Institute of Oncology c/o IFOM-IEO Campus - Milan, Italy
Giuliana Pelicci	European Institute of Oncology c/o IFOM-IEO Campus - Milan, Italy
Pier Giuseppe Pelicci	European Institute of Oncology c/o IFOM-IEO Campus - Milan, Italy
Giuseppe Petralia	European Institute of Oncology - Milan, Italy
Giancarlo Pruneri	European Institute of Oncology - Milan, Italy
Maria Teresa Sandri	European Institute of Oncology - Milan, Italy
Giuseppe Testa	European Institute of Oncology c/o IFOM-IEO Campus - Milan, Italy
Umberto Veronesi	European Institute of Oncology - Milan, Italy
Giuseppe Viale	European Institute of Oncology - Milan, Italy

ECM AND CME

La Commissione Nazionale per la Formazione Continua ha accreditato quale attività di formazione continua l'evento formativo "Advanced Breast Cancer Research Course " assegnando all'evento stesso N. 32 (trentadue) Crediti Formativi E.C.M.

The Accreditation Council of Oncology in Europe (ACOE) has appraised and approved the **"Advanced Breast Cancer Research Course"**. ACOE accreditation acknowledges the quality of the scientific programme and its educational value.
The Accreditation Council is a multidisciplinary body of full time specialists practising in the field of oncology and all recognised for their experience in education and expertise in their field.
The **"Advanced Breast Cancer Research Course"** is designated for a maximum of 27 educational hours.

INFORMATION ABOUT THE INSTITUTIONS

IEO – European Institute of Oncology

The **European Institute of Oncology** was established to implement an innovative model for health and advanced research in the international oncology field. Conceived by **Umberto Veronesi** and inaugurated in May 1994, the Institute became a r**esearch hospital and treatment centre** (**IRCCS** or "Istituto di Ricovero e Cura a Carattere Scientifico") through the Ministerial Decree issued in January 1996.
The European Institute of Oncology adopts the **non-profit** private-law organisation model and provides services through agreements with Italy's **National Health Service**. In keeping with the standards of the most advanced international oncology centres, the Institute fully integrates different activities involved in the fight against cancer: prevention and diagnosis, health education and training, research and treatment.

For further details please visit www.ieo.it

IFOM-IEO CAMPUS
The IFOM-IEO Campus is a new biomedical research centre, created by the joint efforts of the **FIRC Institute of Molecular Oncology Foundation** (IFOM) and the Department of Experimental Oncology of the **European Institute of Oncology** (IEO), which have expanded and integrated their research activities on a common campus. The IFOM-IEO Campus is located in Milan, the heart of the commercial/industrial north of Italy, where it benefits from numerous interactions with other scientific and medical organizations in the area (see participants below). The Campus is also home to the Ph.D programs of the European School of Molecular Medicine (SEMM), which it is running in collaboration with the University of Milan, the University of Naples "Federico II" and the Italian Institute of Technology (IIT) in Genoa.

For further details please visit www.ifom-ieo-campus.it

INFORMATION ABOUT THE INSTITUTIONS

SEMM FOUNDATION

SEMM (European School of Molecular Medicine) is a private foundation for higher education in biomedicine that is promoted by three Government Ministries: the Ministry of Health, the one of University and Research, and the Treasury.
The school has two sites (Milan and Naples) and the training activities are held at biomedical centers of excellence: **IFOM-IEO campus** in Milan, **CEINGE** and **TIGEM** in Naples. SEMM promotes training and research within emerging sectors of biomedicine, such as genomics, molecular medicine, nanotechnologies and bioethics. SEMM operates within centres of excellence and promotes the integration of basic research and clinical practice. SEMM collaborates with Italian Universities to create its training programmes.

For further details please visit www.semm.it

IMPORTANT ADDRESSES

Course venues

IFOM-IEO Campus
Via Adamello, 16
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Phone +39-02.574303200
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www.ifom-ieo-campus.it

European Institute of Oncology (IEO)
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Organizing Secretariat

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Phone +39.02.4804951
Fax +39.02.43911650 -
+39.02.43316070
Email: congress(at)cq-travel.com

Hotel of the course

Grand Visconti Palace Hotel
(4 star sup.)
Viale Isonzo, 14
20135 Milan, Italy
Phone +39.02.540 341
Fax +39.02.540 69 523
Email: info(at)grandviscontipalace.com

TOURISTIC INFORMATION ABOUT MILAN

Public transportation in Milan

Taxi

tel. 02/8585 - 02/4040 - 02/6969 - 02/4000

ATM

In Milan all the public transportation is managed by ATM. Some tickets are available at the registration desk of the conference. www.atm-mi.it

Utilities

Tourist Offices

A.P.T., Azienda di Promozione Turistica del Milanese, Via Marconi, 1
Ph. +39.02.725241 – email: apt@netitalia.it
I.A.T, Informazione e Accoglienza Turistica, Via Marconi, 1
Ph. +39.02.72524300?
Stazione Centrale, Departure Gallery - Ph. +39.02.72524360/370
TCI, Touring Club Italiano, C.so Italia, 10 – Ph. +39.02.5359971 –
email: info-touring@touringclub.it

Health

Free first aid services are available to all EU citizens who have a special form (E111) issued by the health authority of their own home country. For non-EU citizens we suggest to open a special insurance for the duration of the trip in order to avoid the cost of possible medical treatments.
Medicines can be bought at the pharmacy ("Farmacia"). They are identified by a red or green cross. For some medicines (antibiotics, etc.) a doctor's prescription is needed. They are opened from 8.00 am to 12.30 pm and from 3.00 pm to 7.00 pm.

Bank

Banks in Milan are opened Mondays-Fridays from 8.30 am to 1.30 pm and from 3.00 pm to 4.00 pm (opening times may vary from bank to bank).

TOURISTIC INFORMATION ABOUT MILAN

City Sightseeing

Servizio Autostradale A city sightseeing tour by bus and by walking. Departure from Piazza del Duomo at h. 9.30 a.m. The tickets are available at the APT office or in the major hotels in Milan. For info: +39.02.72524300

Tourist Tram, Ciao Milano.The Azienda Trasporti Municipali (ATM) organizes city sightseeing tours by antique tram. Departures from Piazza Castello. Tickets sold on the tram itself. For info: +39.02.72002584

Living in Milan

If you have some free time during your stay in Milan, we suggest you to visit the following website:
www.turismo.comune.milano.it
www.milanoinfo.eu
www.provincia.milano.it
www.ciaomilano.it

Useful Numbers in Milan

Police: 113
Carabinieri: 112
Fire Brigade: 115
Local Police: 02/77271
First Aid: 118
Medical Assistance: (available at nights and public holidays) 02/34567
Antipoison Center: 02/66101029
Oculistic First Aid: 02/63632239 (h. 8.00 am - 12.00 am)
02/63632864 (h. 12.00 am - 8.00 am)
Odontoiatric First Aid: 02/57992514

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