

## > TARGETED THERAPIES IN CANCER: MYTH OR REALITY?

From empiricism to molecular targeted therapies

### Targeted therapies in cancer: myth or reality?

#### Synthesis of the scientific content of the congress

On opening the congress, **Umberto Rosa**, Chairman of Nerviano Medical Sciences, and **Umberto Veronesi**, Chairman of the European Institute of Oncology in Milan, will introduce the topics to be discussed during the two days dedicated to targeted therapies in cancer.

The first presentation dealing with historical and philosophical considerations of the development of anti-cancer drugs, will see the participation of the illustrious Italian scholars **Gilberto Corbellini** of the Section for the History of Medicine of the University of Rome 'La Sapienza', and **Giulio Giorello**, Philosophy of Science of the University of Milan. This part of the congress is dedicated to the evolution of research performed to identify compounds with anti-cancer activity and to the comprehension of the logical significance of the scientific content of the congress. A particularly "hot" issue will discuss the progression from an empiric to a "target-centric" or molecular approach, opening a new era in the field of one of the most ambitious medical challenges, the fight against cancer.

The second session, Small Molecules Targeting Cancer Cells, will open the working sessions of the congress.

**Doriano Fabbro** of the Novartis Institute for Biomedical Research, Basle (Switzerland), will present a lecture on drugs inhibiting an important class of enzymes, kinases, molecules of crucial importance for cell survival and growth and which are usually altered in the majority of cancers, thus representing a priority target for new generation "target-centric" drugs. Cancer research has focused largely on these enzymes in recent years, leading to important findings of clinical relevance. Fabbro states that "Drugs inhibiting kinase activity are capable of interacting with these enzymes at 4 different sites". The effects produced may vary depending on the binding site involved. Moreover, kinases may even undergo spontaneous modifications, becoming resistant to treatment. "New strategies to be applied in the production of second generation drugs are currently being investigated with the aim of minimising the possibility of these modifications taking place", continues the expert.

Among the kinases currently undergoing investigation, particular emphasis has been placed on molecules of the Aurora family and on cyclin-dependent kinases. "These enzymes are implicated in regulation of the cell cycle, or in the series of procedures undertaken by the cell in order to divide and proliferate", reports **Francesco Colotta**, vice-chairman of Nerviano Medical Sciences (NMS). New compounds discovered in the laboratories of NMS are capable of inhibiting these enzymes. Colotta continues "Subsequent to

displaying a proven anti-cancer efficacy in pre-clinical studies, the new compounds have been included in clinical trials. At the current time they have reached stages I and II of clinical development”.

Other kinases implicated in regulation of cell cycles affected by oncological diseases will be discussed by **Mohamad Raza (Raz) Dewji** of Pfizer, Sandwich (UK). “The CHK1 kinase regulating progression of cells during the final stage of the cell cycle is capable of reducing the efficacy of traditional anti-cancer drugs, the so-called cytotoxic agents used during chemotherapy”, explains the scientist. The latter occurs due to the fact that CHK1 facilitates repair of DNA damaged by anti-cancer drugs. Inhibition of CHK1 kinase activity allows cytotoxic drugs to explicate their action against cancer cells in a more efficient manner. This aim has been reached thanks to a new class of compounds, CHK1 inhibitors, currently under investigation. “Another drug undergoing development is orally active and targets another kinase, the hormone growth factor of hepatocytes (HGFR). HGFR is seen to be altered in numerous types of cancer, thus rendering it a promising oncological target”, maintains Dewji. The action of the new compound capable of inhibiting HGFR is two-fold: it destroys cancer cells directly and is capable of blocking the formation of blood vessels required for development of the tumor.

How to select the most appropriate molecular target from among the numerous kinases belonging to the same family (e.g. Aurora or Polo kinases) is the subject of the opening lecture presented by **Jurgen Moll** of Nerviano Medical Sciences, who will explain how molecular biology experiments are capable of providing correct indications to scientists. “By eliminating one kinase at a time from cancer cells we can ascertain which of these is the most important in promoting cancer proliferation”, says Moll. Once the key molecule destined to become the new therapeutic target has been identified, reactions leading to the selection of compounds are refined. The pharmacodynamic profile and therapeutic potentials of Aurora inhibitors currently undergoing development at NMS are illustrated. Furthermore, the efficacy of the latter in the treatment of chronic myeloid leukaemia (CML) is demonstrated.

**Robert A. Kramer** of the Biology Drug Discovery of Bristol-Myers Squibb, Princeton, NJ (USA) will provide confirmation of the clinical efficacy of kinase inhibitors. The most widely established founder of this class of drugs is imatinib (glivec) which has radically modified the treatment of chronic myeloid leukaemia (CML), followed by other molecules already used in clinical practice (erlotinib, sorafenib, sunitinib) capable of inhibiting simultaneously numerous kinases. The clinical success registered by this approach reveal the appropriateness of the choice of kinases as targets for anti-cancer drugs, ultimately leading to the achieving of the desired therapeutic outcomes. Kramer states “The kinase inhibitors currently used in clinical practice have recently seen the addition of dasatinib, registered for the treatment of patients with CML resistant to imatinib or who have displayed intolerance to the latter. Dasatinib is also indicated in treatment of a form of acute lymphoid leukaemia (Ph+)”. In the near future, in addition to first generation inhibitors, it is expected that second generation molecules with a higher selectivity for the specific kinases (several drugs already in

use inhibit more than one kinase) or with a lower probability of inducing resistance will be introduced.

The lecture illustrating the future of kinase inhibitors will close the section of the congress dedicated to new anti-cancer drugs, giving way to the session focusing on biological therapies (monoclonal antibodies and cellular approaches).

The formation of new blood vessels (angiogenesis) is of crucial importance for cancer growth. Accordingly, a wide area of research is involved in investigating factors promoting development of the vascular system which "feeds" the tumor. A key role to this regard is played by VEGF-A, growth factor of vascular endothelial cells. VEGF-A is therefore considered one of the most important molecular targets in the field of cancer angiogenesis. During the Congress in Milan **Napoleone Ferrara** of the Dept. of Molecular Oncology of Genentech, South San Francisco, CA (USA) will discuss the issue further. He will explain how the molecule, crucial in the development of tumors, is over-expressed in many forms of cancer and how the use of monoclonal antibodies (mAb) or of specific non-biological inhibitors may block activity of these molecules. "In this way, the vascularisation and growth of the cancer has been reduced in experimental models", comments Ferrara who presents clinical results obtained with bevacizumab, a recently developed anti-VEGF-A monoclonal antibody. In a stage III study performed on subjects with metastasized colorectal cancer, the use of this antibody in conjunction with chemotherapy has led to an increased survival rate respect to the use of chemotherapy alone. "Similar results, although only of a preliminary nature, have been obtained in breast and lung cancer" states Ferrara. Moreover, the anti-VEGF-A mAb may also be of clinical efficacy in the treatment of several eye diseases characterised by an excessive vascularization: proliferative retinopathies and macular degeneration. A further anti-VEGF-A mAb, ranibizumab, has recently been approved by the FDA for use in the treatment of macular degeneration.

Activation of the immune system in order to achieve recognition and destruction of cancer cells represents one of the main tasks of anti-cancer immunotherapy. This field has recently undergone considerable upheaval, leading to the making of important progress. Activation is not obtained merely through the use of monoclonal antibodies, but also by means of suitably stimulated cells (lymphocytes) in the immune system. Thus, the term "vaccine" is starting to cross the borders from infectious diseases into the field of oncology. **Malcolm Brenner** explains how vaccines active against cancer cells and capable of "educating" the T lymphocytes to recognise and destroy these cells, are developed. Dr Brenner, scientist at the Center for Cell and Gene Therapy (Baylor College of Medicine, The Methodist Hospital, Texas Children's Hospital), Houston, Texas (USA) illustrates the significant results obtained to date with this method for several cancers of the blood (EBV+ lymphomas) and solid tumors (nasopharyngeal cancer), even in the presence of relapse or drug resistance. The approach has proved promising to date although, for obvious reasons, is destined to be applied only in highly specialised university hospitals.

**Alessandro M. Gianni** of the Cancer Institute and University of Milan is involved in a different area of cell therapy. Here, cells normally present in

the organism (CD 34+) are used as vehicle to transport a molecule (TRAIL) capable of destroying cancer cells. TRAIL is inserted into CD34+ and subsequently expressed on the membrane by means of methods of molecular biology. "The contact between modified CD34+ and numerous types of cancer cells leads to the death of the latter" comments Gianni. Currently trials have reached the pre-clinical stage but support has been provided by the results of animal studies evidencing not only a decrease in volume of the tumor, but also a decrease in the number of blood vessels feeding the cancer. Indeed, endothelial cells present inside the blood vessels are sensitive to TRAIL activity as they express the receptor for this molecule.

The role of inflammation in cancer development is illustrated by **Alberto Mantovani** of the Humanitas Clinical Institute in Rozzano and the University of Milan, who explains how the presence of cells and chemical mediators determining the onset of inflammatory processes (macrophages, phages, cytokines such as TNF and IL-1 and chemokines such as CCL2) is often observed at cancer site, whilst a simultaneous remodelling of tissues and the development of new blood vessels is evidenced. "Proof of the involvement of inflammation in the growth of cancer cells is becoming increasingly evident" states Mantovani. Scientists and researchers are focusing increasingly on proteins known as chemokines that direct cells from the immune system (leucocytes) to the cancer site and intervene in processes of cancer progression.

The talk given by **Silvia Franceschi** of the Infection and Cancer Epidemiology Group, International Agency for Research on Cancer, focuses on the papillomavirus, HPV, virus suspected to induce the onset of numerous tumors of the uterine cervix. "The prevalence of these pathogens varies substantially between populations, although HPV infection remains to date the most widely diffused sexually transmitted disease in many areas of the world", underlines Franceschi. New data emerge from studies performed by Franceschi. "Infection by the papillomavirus is contracted early in the life of an individual and is strictly linked to the first sexual relationships", she confirms. Scientists agree that an adequate prophylaxis may affect both HPV positivity and the mechanisms leading to development of the tumor. During the presentation data pertaining to the efficacy of two types of vaccine differing as to viral strain (quadrivalent, HPV 6/11/16/18 e bivalent, HPV 16/18) and adjuvant, are presented, demonstrating the efficacy of both vaccines in preventing the onset of viral infection (protection > 90%) and correlated pre-cancerous lesions. "Anti-HPV vaccine may represent an effective tool for the prevention of cancer if used in mass immunisation campaigns among adolescents", maintains Dr Franceschi.

The section of the congress dedicated to clinical application of targeted therapies opens with a talk by **Manuel Hidalgo** of the Sidney Kimmel Comprehensive Cancer Center of the Johns Hopkins University, Baltimore, MD, (USA) who reviews the first clinical trials performed using targeted drugs. He states "Clinical trials carried out approximately ten years ago using inhibitors of the epidemic growth factor receptors, EGFR, demonstrated a series of findings which later proved to be of considerable relevance for the development of these molecules". Past studies led to the discovery of mutations capable of activating the receptor in the absence of

the growth factor and at the basis of the aberrant proliferation of cancer cells. It has moreover been observed that several of these mutations consisted in multiplication of the gene, giving rise to receptor formation. Hidalgo continues “The larger the number of copies made of the receptor gene, the greater the resistance of cancer cells to therapy”. A lesson that scientists have never forgotten. Furthermore, contrary to traditional cytotoxic drugs, it has been clearly underlined how the clinical development of a target-oriented drug must necessarily be subjected to the establishing of strict selection criteria for patients eligible for treatment.

**Jaap Verweij** of the Department of Medical Oncology, Erasmus University Medical Center, Rotterdam (The Netherlands) highlights how the use in clinical practice of one of the founders of kinase inhibitors, imatinib (glivec), has been extended to the treatment of a rare form of stomach cancer (GIST), following molecular analysis of the cells forming this cancer. The drug was first applied to block the growth of a blood tumor, chronic myeloid leukaemia, by inhibiting a molecule expressed by this cancer. Subsequently however, imatinib proved capable of blocking another two kinases responsible for mediating proliferation of the gastric cancer cells, on which it has since been tested with success. It has moreover been discovered that the outcome of treatment with imatinib in stomach cancer was limited by the presence of a specific alteration of one of these proteins (c-Kit) which accordingly came to represent a priority factor in the prognosis of treatment, also influencing drug dosage used. “The use of imatinib in this form of gastric cancer has become somewhat a paradigm in the field of targeted therapies” underlines Verweij. However, the picture is not always quite so clear. “In other types of cancer molecular alterations are less evident, thus complicating the scheduling of a specific therapeutic strategy” explains Dr Verweij.

The use of monoclonal antibodies has revolutionised the treatment of a specific form of blood cancer, non-Hodgkin lymphomas, illustrates **Bertrand Coiffier** from Lyon (France) in his talk. Rituximab, one of the first antibodies developed for this purpose, proved to be effective in the treatment of B cell lymphomas either when administered alone or in conjunction with chemotherapy. “The use of mAb in lymphomas is aimed at inducing cells in the immune system to react against cancer cells” Coiffier points out. The immuno-mediated activation determines an inhibition of proliferation and the death of cancer cells. Rituximab potentiates the efficacy of cytotoxic drugs, increasing survival and time free from relapse. The antibody has been proven effective in numerous forms of B cell lymphomas (DLBL, FL) whilst it showed scarce efficacy in the treatment of other types of T cell lymphomas. Rituximab has forged the way for the development of other monoclonal antibodies for use in the same field of application.

With regard to the molecular diagnosis of cancer, the Congress promises to reveal novel findings of particular clinical relevance and interest. “A new type of test, the Reverse Phase Microarray, has been developed, leading to the possibility of compiling a molecular identity card for the cancer of each single patient” states **Emanuel F. Petricoin** of the Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas

(VA, USA). The test, performed on an extremely small number of cancer cells obtained by means of biopsy, reveals molecular alterations present within the tumor. The results obtained will lead to the molecular characterisation of the tumor, thereby constituting a new means of classification no longer based on the morphologic features of the disease but rather on the biochemical characteristics of the cancer cells. Application of this test on a large scale would imply a considerable number of advantages: the cancer of each individual patient could be better defined and a molecular diagnosis performed for each single tumor. Moreover, novel findings would be made available to the field of basic research as support in the development of drugs better suited to the type of alterations present in the tumor, thus enabling the prescribing of adequate therapeutic options.