Meeting Report: The 11th International Conference on Differentiation Therapy and Innovative Therapeutics in Oncology

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Introduction

The International Conference on Differentiation Therapy group of clinicians and researchers has met for more than 20 years and the most recent meeting in 2005 was held in Shanghai, China (1). This group fostered the required networks to translate these novel strategies to clinical practice, as with retinoic acid (RA) differentiation therapy in acute promyelocytic leukemia (APL). The 11th International Conference on Differentiation Therapy and Innovative Therapeutics in Oncology was held between November 4 and November 8, 2006 in Versailles, France. The theme of this meeting was “Apoptosis, Differentiation, Signaling, Epigenetics, and Beyond...”. Approximately 350 scientists and clinicians from more than 30 different countries participated.

A major part of this year’s program was dedicated to transcriptional silencing with emphasis on epigenetics, having an important part in the diagnosis, prognostic assessment, and treatment of cancer. Another aspect was apoptosis, which determines treatment response. Understanding the molecular events regulating apoptosis in response to anticancer chemotherapies, and how cancer cells evade apoptotic death, provides novel opportunities to develop molecular-targeted therapies. Alterations in signaling pathways are involved in leukemogenesis both at the transcriptional level and downstream of membrane receptor activation. Integration of these pathways is necessary for optimal targeted approach. Other concepts were also discussed, such as cancer prevention and immunotherapy.

Apoptosis

Apoptosis of tumor cells allowed the development of inducing agents in cancer therapeutics. Seamus Martin (The Smurfit Institute, Dublin, Ireland) presented the different apoptotic and antiapoptotic molecules, identifying several novel granzyme B substrates. Raymond Warrell, Jr. (Genta Inc., Berkeley Heights, NJ) described the direct targeting of BCL-2 via an antisense oligonucleotide (Genasense), to enhance the effectiveness of standard anticancer therapy.

Arsenic trioxide (As2O3) induces apoptosis. In a workshop on apoptosis and signaling, Samuel Waxman (Mount Sinai School of Medicine, New York, NY) described proteins targeted by As2O3. Ruibao Ren (Mount Sinai, New York, NY) reported that As2O3 induces differentiation and apoptosis in vitro and reduces tumor load in vivo in some hematologic disorders. In APL and in chronic myelogenous leukemia (CML) cell lines, treatment with MEK1 inhibitors enhances the apoptosis induced by As2O3, according to Antonio Bonati (University Hospital of Parma, Parma, Emilia-Romagna, Italy). Trolox stimulates As2O3-mediated apoptosis in APL, CML, lymphoma, myeloma, and breast cancer cells as described by Wilson Miller, Jr. (McGill University, Montreal, Quebec, Canada). In a unique model of FIP1L1-platelet–derived growth factor receptor-positive cells, Carine Robert indicated that retinoids induce apoptosis and synergize with imatinib (INSERM U718, Paris, France). Catherine Brenner Jan (Université de Versailles, Versailles, France) described the implication of the adenine nucleotide translocator in cancer. Masahiro Kizaki (Keio University School of Medicine, Tokyo, Japan) reported that reactive oxygen species are mediators of apoptosis induced by a green tea polyphenol.

Differeniation

Pierre Chambron (Institut de Génétique et Biologie Moléculaire et Cellulaire, Illkirch, France) described molecular mechanisms through which both vitamin D3 and RA signaling pathways seem to be involved in the pathogenesis of atopic diseases. Thus, cytokine thymic stromal lymphopoietin, the expression of which is induced in mice upon keratinocyte-selective ablation of retinoid X receptors (RXRα and RXRβ), has a crucial role in initiating a systemic atopic dermatitis–like phenotype. Alan Rosmarin (Brown University, Providence, RI) presented the identification of a RA-dependent enhanceosome in myeloid cells. Cécile Rochette-Egly (Institut de Génétique et Biologie Moléculaire et Cellulaire) discussed the integration membrane and nuclear signaling pathways, stressing the importance of aberrant kinase activities in retinoid-based cancer therapy. Sylvie Mader (Université de Montréal, Montréal, Québec, Canada) revealed that the DR2 type of the retinoic acid response element was represented in the human genome. Sérénie Cathelin (INSERM U866, Dijon, France) presented proteomic analysis identifying proteins cleaved by caspasers during monopoiesis, Ruud Delwel (Erasmus University Medical Center, Rotterdam, the Netherlands) reported that EV1 interferes with erythropoiesis and that its overexpression is involved in myelodysplastic syndrome (MDS). Issai Kitabayashi (National Cancer Center Research Institute, Tokyo, Japan) described the role of MOZ [histone acetyltransferase involved in acute myelogenous leukemia (AML)] in the maintenance of hematopoietic stem cells after the generation of Moz-null mice, which died around E15.

In a session on erythropoietin, Catherine Lacombe (Institut Cochin, Paris, France) showed that the erythropoietin receptor is ubiquitinated and degraded by the proteasome. Pierre Fenaux (Hôpital Avicenne, Bobigny, France) summarized the improvements brought by erythropoietin therapy in MDS, and Paul Fisher (Columbia University, New York, NY) the follow-up in vitro

Note: The 11th International Conference on Differentiation Therapy and Innovative Therapeutics in Oncology was held from November 4–11, 2006, in Versailles, France. Requests for reprints: Christine Chomienne, INSERM U718, Institut Universitaire d’Hématologie, Université Paris 7, 75010 Paris, France. Phone: 33-1-42 49 42 54; Fax: 33-1-42 20 01 60. E-mail: christine.chomienne@ids.uhp-fr.fr.

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of a novel differentiation protein (da-7/IL-24) in metastatic melanoma.

In the workshop “Update of clinical trials in APL: where are we 20 years after”, Martin Tallman (Northwestern University Feinberg School of Medicine, Chicago, IL; North American APL Intergroup protocol), discussed the benefits of all-trans retinoic acid (ATRA) in induction and maintenance. Removing 1-β-d-arabinofuranosylcytosine, according to the Spanish PETHEMA (program for the study and treatment of malignant hemopathies), proved to be deleterious for high-risk patients in the randomized “Groupe Francophone des LAP” (Pierre Fenaux, Bobigny, France). The work of cooperative groups (Spanish PETHEMA, Italian GIMEMA, Francesco Lo Coco, Facoltà di Medicina e Chirurgia, Università di Roma, Lazio, Italy) suggest that combination of ATRA and chemotherapy for consolidation improves therapeutic results. Norio Asou (Kumamoto University Hospital, Kumamoto, Japan) presented a randomized study in newly discovered APL patients, showing no benefit for maintenance chemotherapy in PML/RARA-negative patients after consolidation. The PANDA group (M.S. Durranga-Sutton, Chile) showed how identical results might also be achieved in South America.

Arsenic trioxide is effective at inducing high rates of complete remission and molecular remission in patients with relapsed or refractory APL. Thus far, no deaths from As2O3-induced cardiac arrhythmia have been reported in 2,900 patients treated. J. Hu reported that As2O3 is effective in newly diagnosed and relapsed APL (Shanghai Institute of Hematology, Shanghai, China). Other drugs added in the APL regimens are the anti-CD33 antibody linked to a toxin [Myotarg as an additional targeted therapy (U.K., U.S., and Italian trials), and retinoids, Am80 (an RARα agonist; Japanese trials) or AS404 (China)]. Christopher Bunce (University of Birmingham, Birmingham, England, United Kingdom) described the results in AML patients with the combination of benzafibrate and medroxyprogesterone acetate.

In half of the “poor responders” of APL, maximal differentiation is achieved by ATRA combined with granulocyte colony-stimulating factor (Bruno Cassinat; INSERM U718, Hôpital Saint-Louis, Paris, France). Bob Gallagher (Montefiore-Einstein Cancer Center, New York, NY) identified target genes of the PML/RARα mutant. Ronan Quérité (Université de Montpellier, Montpellier, France) determined the pharmacogenomic profiles for ATRA sensitivity by comparing gene expression in ATRA “high” and “low” sensitive APL samples, and identified CYP26 as an ATRA target gene. Jian Guo (Shanghai Jiao-Tong University School of Medicine, Shanghai, China) reported that Rig-1 as a potent effector mediating RA-induced complete remission of APL. Hugues de Thé (Institut Universitaire d'Hématologie, Paris, France) described the role of cyclic AMP to reverse RA-resistance conferred by a point mutation in PML/RARα, and showed that translocation-induced dimerization transforms transcription factor into a dominant oncoprotein. Akhiro Tomita (Nagoya University, Nagoya, Japan) identified new molecular targets for differentiation therapies. Eric So (Institute of Cancer Research, London, England, United Kingdom) highlighted the pathologic significance of the RARα fusion RXRα-oligomeric complex and the potential use of the RXRα as a therapeutic target in APL.

**Signaling**

The combined altered pathways are of prognostic significance and provide the rationale for targeted therapies. Terry Rabbitts (MRC Laboratory of Molecular Biology, Cambridge, England, United Kingdom) developed two translocation mimics (Cre-loxP recombina-

**Epigenetics**

Carlo Croce (Ohio State University, Columbus, OH) described the combination of nonrandom chromosomal abnormalities and other types of genetic alterations or epigenetic events contributing to the down-regulation or overexpression of micro-RNAs. Abnormal expression of micro-RNAs affects cell cycle, survival, and differentiation programs. Selective targeting of these noncoding transcripts could provide novel therapeutic options for killing the malignant cells.

Frank Rauscher III (The Wistar Institute, Philadelphia, PA) described a new E3 ligase involved in sumoylation for genes silencing in mammalian cells. Stephen Baylin (Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD) discussed the relationship of DNA hypermethylation with other transcriptional silencing events. Robert Brown (University of Glasgow, Glasgow, Scotland, United Kingdom) reported that in ovarian cancer, methylation profiling of CpG islands could be used as a biomarker of acquired drug resistance. Christine Sers (Universitämedizin Charité, Berlin, Germany) analyzed the genes hypermethylated upon HRAS-mediated transformation in colon cancer cells. Audrey Cras (INSERM U718, Paris, France) identified an altered RARβ gene promoter signaling in thyroid cancer cells resistant to RA, whereas Sebastiano Battaglia (University of Birmingham, Birmingham, AL) showed epigenetic modifications linking prostate cancer progression to androgen resistance. Jean-Pierre Issa (M. D. Anderson Cancer Center, Houston, TX) discussed the therapies involving azacytidine, decitabine, and vorinostat in combination with biological response modifiers.
Peter Jones (USC/Norris Comprehensive Cancer Center, Los Angeles, CA) reported that the absence of nucleosomes in promoters with CpG islands is associated with gene silencing. Gene expression studies in mononuclear cells of AML patients included in a trial with the combination of HDACi and RA was presented by Christopher Bunce (University of Birmingham, Birmingham, England, United Kingdom) and Hervé Dombret (Hôpital Saint-Louis) who added theophyllin to this combination. Aurélie Baudet (Université de Montpellier) presented data on gene expression profiling, identifying patient response to the combination of HDCAi with vitamin D₃. Steven Gore (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD) described epigenetic modifications induced by DNMTi and HDACi in MDS, CMMI, and AML patients. Richard Momparler (Université de Montréal) correlated preclinical data with clinical response by using 5-AzacR. Feyruz Rassool (University of Maryland School of Medicine, Baltimore, MD) reported that some HDACi induced histone acetylation and DNA damage with apoptosis in leukemic cells. Leigh Ellis (Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia) presented the efficacy of HDACi in lymphoma murine models via apoptosis. Hervé Dombret (Hôpital Saint-Louis) reported that the use of Vidaza (5-azacytidine) maintains remission after intensive chemotherapy in high-risk patients (advanced MDS, elderly AML). Michael Lübbert (Freiburg University Medical Center, Freiburg, Baden-Württemberg, Germany) presented the use of low-dose Decitabine in older AML patients, whereas Christopher Bunce (University of Birmingham, Birmingham, England, United Kingdom) presented data from past and ongoing trials. Stanley Frankel (Merck Research Laboratories, North Wales, PA) discussed the antitumor activity of Zolinza (suberoylanilide hydroxamic acid).

And Beyond . . .

In the workshop "Targeting stem cells", Pier Giuseppe Pelicci (European Institute of Oncology, Milan, Italy) identified in leukemia animal models quiescent leukemic stem cells (LSC) and described their role in the maintenance of the leukemic clone. Florence Smadja-Joffe (INSERM U718, Paris, France) reported a novel therapeutic approach employing an activating monoclonal antibody for CD44. Rick Van Etten reported that AML-LSC (or CML-LCS in the European LeukemiaNet workshop) requires interaction with a niche to maintain their properties, providing a novel therapeutic strategy to eliminate quiescent AML-LSC. Keiya Ozawa (Jichi Medical University, Tochigi, Japan) used luciferase-engineered mesenchymal stem cells to assess their migration and tumor tropism as a means to target tumor cells. Yves Saint-Pierre (Université de Québec, Laval, Québec, Canada) showed the role of intercellular adhesion molecule-1 to induce the expression of genes involved in migration and homing of lymphoma cells.

In the workshop "Improving mAb therapy", Hervé Watier (Université de Tours, Tours, France) showed the importance of Fc-γ-RIIa in the efficacy of anti-CD20. Christian Berthou (Université de Brest, Brest, France) discussed the anti-B-cell antibody therapy. Sylvie Castaing (Hôpital de Versailles, Le Chesnay, France) described the effect of gentuzumab ozogamicin in CD33-positive adult AML in first recurrence. André Baruchel (Hôpital Saint-Louis) reviewed the efficacy of the combination of gentuzumab ozogamicin and cytarabine in childhood AML. Laurence Boumsell (Université Paris 12, Paris, France) presented monoclonal antibody therapies for solid tumors whereas Simon Benita (Pharmaceuticals Department, The Hebrew University of Jerusalem, Jerusalem, Israel) described improved efficiency via immunoeusions.

In the workshop "Targeted therapy for cancer prevention", Reuben Lotan (University of Texas, Houston, TX) indicated that N-(4-hydroxyphenyl) retinamide–induced apoptosis is triggered by reactive oxygen species increase. Ethan Dmitrovsky (Dartmouth Medical School, Hanover, NH) and Cedrik Haskovec (Institute of Hematology, Prague, Czech Republic) presented findings implicating cyclin D1 (novel antineoplastic target). Jeffrey Green (National Cancer Institute, Bethesda, MD) analyzed mouse models of human breast cancer and identified a unique gene expression signature predicting the aggressive behavior of several cancers. Paul Talalay (Johns Hopkins University, Baltimore, MD) discussed the prospects of combining electrophilic and oxidative stress, pathologic effects of inflammation, and radiation. Fabien Calvo (Hôpital Saint-Louis) reported a phase I trial combining low-dose interleukin 2 with IFNy 1101. A. Pellagatti (Leukaemia Research Fund, Oxford, England, United Kingdom) correlated the up-regulation of the SPARC gene with the pathogenesis of a MDS subgroup. R.A. Padua (INSERM U718, Paris, France) showed in an APL mouse model that DNA vaccination combined with ATRA results in a survival advantage with a significant increase in IFNy and an increase in anti-RARα antibody production, also observed in APL patients after maintenance with ATRA and chemotherapy (as reported by Marie Robin; INSERM U718, Paris, France), suggesting an antitumoral immune response enhanced to prevent relapses.

Conclusion

After ATRA in PML/RARα leukemias, the International Conference on Differentiation Therapy meetings continue to foster other targeted approaches with proof of principle data and drugs obtaining regulatory approval. Focus is also aimed at adapting combinational targeted therapies to multitargets or different patient subgroups. Combinations of targeted agents are being addressed to improve survival and reduce chemotherapy-related toxicity. Interactions between clinical groups such as between research laboratories and clinicians were the main feature of this meeting. The active presence of all speakers and participants made the interactions profitable for everyone, including nonactive members of the group.

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Reference

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