First Symposium of Novel Molecular Targets for Cancer Therapy

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This symposium was convened in Buenos Aires, Argentina (October 5-6, 2000) to foster dissemination of new knowledge in the field of new drug development, with an emphasis on innovative cancer therapies. The organizers, *Adrian M. Senderowicz* and *Antonio Giordano*, assembled a team of experts in a wide spectrum of related fields: signal transduction, angiogenesis, invasion and metastases, gene therapy, apoptosis, immune modulation, and cell cycle control. The meeting was held under the auspices of three U.S. institutions: the National Cancer Institute (NCI), the National Institute for Dental and Craniofacial Research (NIDCR), and the Sbarro Institute for Cancer Research and Molecular Medicine. This meeting provided a unique opportunity for about 500 local clinicians, researchers, and medical students to interact with distinguished investigators from the U.S. and Europe. The fact that five out of 19 speakers had obtained their degrees in Argentina further stimulated the interest of the audience and strongly motivated many medical students to participate in the meeting.

The topics were organized in broad areas, such as modulation of signal transduction pathways, angiogenesis, invasion and metastases, gene therapy, apoptosis, and immunotherapy. Clinical applications of these novel therapies for specific tumor types were discussed on the last day of the symposium.

Dr. Senderowicz (NIDCR, National Institutes of Health [NIH]) opened the symposium with the statement that after many years of development in cancer treatments, patients with advanced solid tumors still have a very poor prognosis. He also emphasized that the lack of significant advances in the treatment of solid tumors in the last few decades was due to the lack of basic knowledge of carcinogenesis; this is reflected in the limited number of targets for cancer therapy developed in the last century (i.e., tubulin, DNA, protein synthesis). He then outlined new approaches/targets that academia and industry are testing in the clinic. Furthermore, he described how the new research tools and technologies, including DNA microarray and proteomics, may impact the diagnosis, prognosis and treatment of cancer therapy.

Dr. Silvio Gutkind (NIDCR, NIH) presented a comprehensive review of signal transduction pathways, with special emphasis on mitogen-activated protein kinase family and the nuclear factor kB. An in-depth description of receptor-activated interaction with *ras* and *src* oncogenes, and the multiple phosphorylation cascades modulating c-*jun* expression quickly followed a historical perspective, starting with the observations of *P. Rous* in 1911 on chicken tumorigenesis. An interesting finding highlighted by *Dr. Gutkind* was the fact that the Kaposi's sarcoma Herpesvirus encodes a G protein-coupled receptor with cell-transforming capabilities. This receptor, when activated, upregulates the transcription of vascular endothelial growth factor (VEGF), a growth factor that is thought to play an important role in the pathogenesis of this highly angiogenic tumor.

Dr. Dirk Mendel (Sugen Inc.; South San Francisco, CA) showed preclinical and early clinical data on two tyrosine-kinase inhibitors (TKI), SU 5416, and the antiangiogenic drug SU 6668. SU 5416, a drug that was shown to inhibit

receptor-dependent tyrosine-kinase by competing with ATP binding, entered clinical trials in 1997. In a phase I trial with 69 patients, a complete response was observed in a patient with basal cell carcinoma, along with partial responses in Kaposi's sarcoma and non-small cell lung cancer. The drug is generally well-tolerated. Combination trials with standard cytotoxic drugs are under way (i.e., with 5-fluorouracil [5-FU] and leucovorin in colon cancer patients).

The second antiangiogenic agent SU 6668 inhibits a wide range of receptor-dependent tyrosine kinases (platelet-derived growth factor receptors [PDGF-R], fibroblast growth factor-receptor [FGF-R], VEGF-R, among others). Since angiogenesis requires, among other mechanisms, an array of receptor-dependent tyrosine kinase activation processes leading to cell proliferation, migration, and adhesion, SU 6668 appears to be suitably targeted. Further clinical trials with both agents are needed to determine the exact therapeutic potential in cancer therapy.

A mutated form of the oncogene K-*ras* has been detected in clinical specimens in most pancreatic cancers, and in 50% and 30% of colon and lung cancer, respectively. It has been shown that the ras-encoded oncogenic protein, *p21ras*, exhibits GTPase activity. However, *p21ras* needs to be farnesylated and attached to cell membranes to be active. Farnesylation takes place at the C terminus of *p21ras*, where a CAAX (Cys-aliphatic-aliphatic-X aminoacid) recognition motif is found. The farnesylation step is thus a very attractive modulation target, and several pharmaceutical companies have launched efforts to design and develop an effective farnesyltransferase inhibitor (FTI). *Dr. Helgi Van de Velde* (Janssen Pharmaceuticals; Beerse, Belgium) presented the results of the first FTI tested in clinical trials, R115777, an orally active drug. Several treatment schedules have been evaluated in phase I trials, including a "daily-times-five" and continuous (chronic) oral treatment. Combination phase I trials with the antimetabolite gemcitabine have been completed, and phase III trials are planned. R115777 has a terminal half-life of 24 hours, thus reaching steady-state levels within a few days. At a dose of 300 mg oral twice a day (bid), reversible bone marrow suppression (mainly neutropenia) was noted in phase I trials. Fatigue, peripheral neuropathy, and skin rash were also reported. Nausea, vomiting, and diarrhea have been mild. Ataxia and confusion were dose-limiting at a level of 1,200 mg bid. Partial responses have been observed in non-small cell lung cancer and prostate cancer. Furthermore, nine responses were noted in a small group of patients with refractory leukemia. Interestingly enough, *Dr. Van de Velde* summarized the recent knowledge that it is possible that FTIs may owe their antitumor effects to mechanisms unrelated to FT inhibition: first, there are inconsistencies in the in vitro correlation between inhibition of FT and antitumor effect. Second, the kinetics of reversion of H-ras transformation by FTIs (evident within 18 hours of drug exposure) are different from what would be expected: the time to depletion of processed H-ras exhibits a half-life of 24 hours. In addition, K ras and N ras can also be modified post-translationally by another enzyme, geranyl-geranyl protein transferase. Furthermore, other CAAX-containing proteins involved in signal transduction, cytoskeleton organization, and mitosis are also farnesylated (i.e., RhoB and E GTPases, CENP-E, and others), suggesting that other targets beyond ras may be modulated by FTIs. The final discordant point is the lack of ras mutation in the nine responding patients with refractory leukemia. Although this is still an unresolved question, this novel class of compounds may have great potential in cancer therapy. Future clinical trials and assessment of pharmacodynamic endpoints may help to clarify this issue.

The cell cycle machinery stands as an exciting new field of discovery for drug development. *Dr. Senderowicz* summarized the experience with two small molecule cyclin-dependent kinase inhibitors in clinical trials, flavopiridol and UCN-01. Flavopiridol is a flavonoid that binds to the ATP-binding site of most cdks. Another interesting feature of flavopiridol is the depletion of cyclin D1 mRNA and the induction of apoptosis in several human cancer cell lines. Moreover, flavopiridol also inhibits the VEGF-mediated cellular response to hypoxia. Recently, flavopiridol was demonstrated to inhibit P-TEFb (positive transcription elongation factor b, also known as cdk9), responsible for the elongation process in transcription, a step necessary for HIV replication. Thus, these recent results provided the rationale for clinical trials of flavopiridol in cancer and HIV-dependent neoplasms. The initial phase I trial of flavopiridol was conducted at the NCI using a continuous intravenous infusion schedule. Secretory diarrhea was the dose-limiting toxicity, with a maximal tolerated dose (MTD) of 50 mg/m^2/day over a 72-hour continuous infusion every two weeks. However, the use of aggressive antidiarrheal prophylaxis with high-dose loperamide allowed the investigators to define a new MTD of 78 mg/m^2/day. Partial responses were observed in one patient with metastatic renal carcinoma, and minor responses in colorectal cancer, renal, non-Hodgkin's lymphoma and prostate cancer. An i.v. bolus (1 hour infusion) schedule was also evaluated in another phase I trial at the NCI, reaching an MTD of 37.5 m/m^2/day for five consecutive days every three weeks. Neutropenia, fatigue, nausea, and vomiting were noted. Flavopiridol is currently being studied in combination trials, with radiation therapy, and standard cytotoxics including either paclitaxel or cisplatin, since there is preclinical evidence of schedule-dependent synergism with these cytotoxic agents.

UCN-01 is a staurosporine analogue that inhibits protein kinase C, modulates cdks, and induces apoptosis. Another

interesting feature of this agent is the abrogation of checkpoints upon DNA damage. Normally, cells would stop cycling after suffering DNA damage. Under these circumstances, a prolonged G_2 phase would be needed to allow the damage to be repaired. Since UCN-01 abrogates the G_2/M checkpoint, exposure to this drug after DNA damage causes inappropriate accelerated mitosis and apoptosis. The abrogation of UCN-01 can be explained by the inhibition chk1, a protein kinase important for the G_2 checkpoint control. The first clinical trial of UCN-01 was conducted at the NCI. An interesting feature in this trial was the dramatic species-specific difference in pharmacokinetics (PK) parameters observed. While preclinical models had suggested a relatively short plasma half-life, PK parameters obtained in this trial revealed a prolonged half-life (more than 600 hours), approximately 100 times longer than in preclinical models. Very avid drug binding to human serum alpha1-acid glycoprotein was considered to be responsible for this clinical finding. Since the initial drug schedule for phase I called for dosing every 2 weeks, this would have subjected patients to the possibility of undue drug accumulation and, quite likely, severe toxicity. Thus, the information obtained by "real-time pharmacokinetics information" allowed the investigators to amend the protocol after only nine patients treated with the initial schedule. A further 38 patients were treated with a modified protocol (administration every 4 weeks), with no evidence of drug accumulation or drug-related fatalities. Myalgia, symptomatic hyperglycemia, lactic acidosis, nausea/vomiting, and pulmonary hypoxemia were the main toxicities. No myelosuppression was observed. A partial response in a patient with metastatic melanoma and evidence of stable disease for more than three years in a patient with anaplastic lymphoma was observed in this trial. Trials with shorter infusions and combination with cisplatin and gemcitabine are ongoing.

Dr. Manuel Hidalgo (University of Texas; San Antonio, TX) described the signaling pathways involving mTOR (mammalian target of rapamycin) kinase and the rational to modulated mTOR for cancer therapy. Rapamycin is a natural product with preclinical immunosuppressive and antitumoral activities. Rapamycin binds to the immunophilin FKBP-12 (an FK506-binding protein) and the rapamycin-immunophilin complex then inhibits mTOR leading to modulation of translation. Because rapamycin has poor solubility and stability, novel derivatives were synthesized to improve its pharmaceutical profile. The investigational drug CCI779 is a macrocyclic lactone analogue of Rapamycin. A phase I trial of CCI779 on a daily-times-five schedule every 2 weeks reached an MTD of 19 mg/m^2/day × 5 days. Skin toxicity, specifically rash and folliculitis was prominent, as has been the case with many other drugs targeting signal transduction pathways. Moderate hypertriglyceridemia, grade 3 thrombocytopenia,

and hypocalcemia were noted. Interestingly, no clinical evidence of immune suppression was observed. Drug metabolism is cytochrome P450-3 A4-dependent, and the drug is excreted in the urine. Significant interactions with anticonvulsant drugs were expected. Thus, a separate phase I trial is under way in patients with gliomas receiving CCI 779 and anticonvulsants to answer this question. Antitumor activity was observed in patients with renal cell carcinoma. Clinical trials exploring CCI779 in phase II trials in patients with renal cell carcinoma and combinations of CCI779 with either 5-FU or gemcitabine are also under way.

Dr. Claudio Conti (MD Anderson Cancer Center; Houston, TX) presented results with transgenic animal models for the development of novel therapeutic strategies for cancer treatment. *Dr. Conti* gave an overview of classic animal models such as rodent carcinogenesis and immunocompromised mice. The former have been used to investigate chemical carcinogenesis, and more recently to design cancer prevention strategies. Xenotransplants in nude mice have been widely used as a strategy to understand the in vivo behavior of tumor cell lines, and assess chemosensitivity to different agents. The speaker acknowledged the deep changes in this field of research brought about by genetically modified animals. New technologies have allowed researchers to introduce oncogenes or delete tumor-suppressor genes in these animals. Moreover, normal mouse genes can be replaced with mutated genes such as those frequently found in human tumors. These new, genetically modified animal models are now playing a key role in the preclinical development of novel therapeutic strategies. Thousands of new genes have been recently cloned. Their biological function is not yet fully elucidated, however. Characterizing these genes will in part involve both in vivo and in vitro models. Genetically modified mice will probably clarify some of the metabolic pathways related to newly discovered therapeutic targets. Besides their contribution in dissecting target metabolic pathways, new animal models have allowed in vivo drug testing against these cellular functions in a setting genetically modified to reproduce molecular changes usually found in human cancers. *Dr. Conti* selected two specific examples: the use of transgenic and knockout animals (those carrying a specific deletion of a key gene) related to cell cycle control or angiogenesis. For example, animal models showed that the cyclin D1 and cdk4 genes could be deleted with minimal effects on normal cells, but with a profound impact on tumor cells. This differential effect makes these molecules ideal candidates for development of novel therapeutic strategies. Two additional mouse models related to angiogenesis were described, with either overexpression or ablation of the VEGF gene.

Dr. Edward Sausville (NCI, NIH; Bethesda, MD) was the keynote speaker of the meeting. He discussed current

approaches for the design and development of antiangiogenic molecules. An initial classification in either angiotoxic or angioregulatory molecules was proposed. The angiotoxic class represents compounds that do not specifically target the endothelial cell; thus, this class of compounds has antiproliferative effects on endothelial cells besides the antiproliferative effects on tumor cells. Examples of this class include "classic" chemotherapeutic agents, fumagillin analogues (TNP-470), combretastatin, 2-methoxiestradiol, and phage-selected arginine-glycine-aspartic acid peptides. We can assess antitumor effects of this class of compounds by the classical cytotoxic paradigm that we have been using in the clinic for the last 30 years. Of note, this class of compounds showed synergistic preclinical effects when combined with other standard chemotherapies. In contrast, the angioregulatory class of antiangiogenic compounds consists of small molecules whose mechanism of action uniquely relates to endothelial cell function: we can subclassify this class in direct endothelial cell effectors such as cytokines (interferon γ, anti-VEGF, anti-VEGF-R), receptor-mediated (SU5416, SU101), fragments (angiostatin, endostatin, vasostatin, and thrombospondin); and indirect effectors such as those directed against stroma (halofuginone), copolymers conjugate with doxorubicin agents (PK1), and oxygen modulators (HIF1α modulators, INOS modulators, and nitrates). As expected, most angioregulatory molecules behave in a cytostatic fashion; thus, a significant challenge for the antiangiogenic field is to advance these molecules in the clinic despite lack of shrinkage of tumors. The necessity to measure surrogate markers for antitumor activity was discussed: noninvasive studies, such as positron emission tomography scanning, magnetic resonance imaging, etc., that can measure tumor blood flow, tumor metabolism, etc. Invasive surrogate markers include biopsies of normal/tumor tissues to measure microvessel density, proliferation/apoptosis of tumor and endothelial cells, production of angiogenesis-associated factors (matrix metalloproteinase expression and activity), and detection of endothelial cell receptors/antigens. Most surrogate markers should be prospectively validated to have utility in the clinic. The many challenges in the antiangiogenic therapies could be summarized: A) how to select best patient populations for these trials (i.e. established metastatic tumors versus adjuvant/preventive strategies); B) what is the best dose; C) how to assess antitumor activity, and D) validation of surrogate markers in prospective trials. Despite the many challenges described, this novel class of compounds may have an important role in the future therapy of cancer.

Dr. Scott H. Kaufmann (Mayo Clinic; Rochester, MN) provided an extensive review of the apoptotic machinery and its role in carcinogenesis and response to cytotoxic therapy. He described that most of the morphological and biochemical changes observed in apoptotic cells can be traced to the activation of a family of intracellular proteases called caspases—aspartate-directed sulfhydryl proteases, synthesized as zymogens and activated by proteolytic cleavage. Two major pathways of caspase activation were presented. One pathway starts with binding of an extracellular ligand to one of the cell-surface death receptors (i.e., Fas/CD95 or the tumor necrosis factor-α receptor). The death receptor pathway is modulated by molecules that regulate receptor oligomerization and by c-FLIP, a molecule that inhibits recruitment and activation of procaspase-8. The other caspase activation pathway starts with release of cytochrome c and other transmembrane proteins from mitochondria. Once released, cytochrome c binds to the cytoplasmic scaffolding protein Apaf-1 (apoptotic protease activating factor-1), which allows Apaf-1 to activate procaspase-9. Once activated, either caspase-8 or caspase-9 can activate the "downstream" or "effector" caspases-3, -6, and -7, which are responsible for most of the cleavages observed in apoptotic cells. Activation of the mitochondrial pathway is modulated by antiapoptotic Bcl-2 family members, outer mitochondrial membrane proteins that inhibit cytochrome c release. Caspase activation also appears to be regulated by IAPs (inhibitor of apoptosis proteins), which selectively bind to and inhibit caspases and their precursors. Apoptotic pathways are extensively targeted during carcinogenesis; both death receptor and mitochondrial pathways are downregulated in carcinogenesis. Most commonly utilized antineoplastic agents induce apoptosis in susceptible cell types. Current models suggest that most anticancer agents, including topoisomerase poisons, DNA damaging agents, and spindle poisons, induce apoptosis by causing mitochondrial release of cytochrome c. The mechanism by which these agents trigger cytochrome c release remains to be elucidated. Surprisingly, fluoropyrimidines induce p53-dependent apoptosis in colon cancer cells by inducing Fas ligand. These results have potentially important implications for current understanding of mechanisms of resistance to various anticancer agents.

Dr. Pier Paolo Claudio (Jefferson Medical College; Philadelphia, PA) presented an overview of the Rb tumor-suppressor family, pRb, p107, and pRb2/p130. All three Rb-family members localize primarily to the nuclear compartment of the cell and have strong structural homology. Like pRb, ectopic expression of p107 and pRb2/p130 is able to suppress the growth of the osteosarcoma cell line SAOS-2 (Rb minus). Despite structural identities between these proteins, they exhibit unique growth-suppressive properties that are cell-type specific, suggesting that although these pocket proteins may complement each other, they are not fully redundant. Recent immunohistochemical studies of the Rb family of proteins in different cancers show the tightest inverse association between the histological grading

in the most aggressive tumor types and pRb2/p130. Identification of Rb2/p130 mutations in cancer opens possible implications on guiding and designing standard as well as novel therapeutic regimes such as targeted viral and nonviral gene transfers. The retinoblastoma-related gene product pRb2/p130, a new tumor-suppressor gene cloned in 1993, is emerging as one of the candidate markers and targets for a gene therapeutic approach. In fact, different mechanisms of Rb2/p130 inactivation have been detected in various cancer histotypes so far, and viral-mediated gene therapy replacement approaches have been developed.

Dr. Roberto Bitton (Elea Laboratories; Buenos Aires, Argentina) presented an overview of current clinical developments of cancer vaccines, with special emphasis on ganglioside-based vaccines. These complex sialylated glycosphingolipids containing one or more negatively charged sialic acid residues are expressed on cell surface membranes of most mammalian cells. Depending on the type of sugar molecule, they can be classified in different subtypes (i.e., GM1, GM2, GM3, GD2, GD3). Aberrant glycosylation is a common phenomenon associated with oncogenic transformation: either incomplete synthesis with precursor accumulation or neosynthesis of aberrant structures will result in the high density of certain glycolipids on tumor cell surfaces. A central issue at stake is which ganglioside to select as target antigen: some of the more traditional approaches focused on GM2, or GD2. *Dr. Bitton's* group focused on two antigens: GM3, a ubiquitous antigen, overexpressed in several epithelial tumor types, and Neu-Glycolyl-GM3, a vaccination with gangliosides which has some limitations because it requires the antigen to be bound to a carrier and administered with an adjuvant to produce a good immune response. The gangliosides also have to undergo a complex and expensive process of purification. Another alternative is to use anti-idiotype (Ab2) antibodies as vaccines instead of using the purified antigen. *Jerne's* theory postulates that an Ab2 can mimic the antigenic structures recognized by immunoglobulins. The use of antibodies as vaccines is supported by the regulatory mechanisms of the immune responses which involve the recognition of idiotypes in the immunoglobulins and the T-lymphocytes, so that an antibody (Ab1) carrier of an idiotype directed against a tumoral epitope can generate antibodies (Ab2) against its own idiotype, which imitates the very tumoral epitope. In turn, these idiotypes directed against their own idiotype can generate a third antibody called "anti-anti-idiotype" (Ab3) directed against the tumoral epitope. The 1E10 vaccine, an anti-idiotype vaccine designed to mimic the N-Glycolyl GM3 gangliosides and generate a specific immune response against the human "N-Glycolylated" gangliosides, is being tested in phase I clinical trials.

Clinical applications of new concepts and knowledge derived from the bench do not always flow easily. *Dr. Manuel Alvarez* (Catholic University; Santiago de Chile, Chile) gave a general overview of the bridge between basic and clinical oncology research. He presented in detail the rationale to modulate the gene product of the multidrug protein gene for cancer therapy. Also, he outlined areas where faster progress was being made (such as monoclonal antibody [mAb]-based therapy, and combination strategies with both new and old drugs).

Dr. Hernán Cortés-Funes (Madrid, Spain) summarized the current status of clinical trials with antitumor compounds from marine origin. An interesting development is the recent recognition that some of these compounds are active against novel cellular targets. Of note, Ecteinascidine 743 (ET-743) has some preliminary activity against refractory soft-tissue sarcomas. Trials in this disease and combination with other cytotoxics are ongoing. Another interesting compound described by *Dr. Cortés-Funes* is aplidine. Aplidine is a marine depsipeptide that showed downmodulation of VEGF in tumor cell lines. Phase I trials with this compound are ongoing.

Dr. Cortés-Funes also gave an overview of new treatment options for breast cancer, with a focus on antibody targeting to the Her-2/neu family of receptors. He described in detail the combination trials of trastuzumab with standard cytotoxics. Moreover, he gave a broad overview of the phase I/II clinical experience with several epidermal growth factor-receptor (EGF-R) inhibitors, such as the chimeric anti-EGF-R mAb IMC-C225, and the tyrosine kinase inhibitors ZD1839, CP-358, among others.

Dr. Senderowicz discussed the poor outcome of patients with refractory squamous cell carcinoma of the head and neck (SCCHN) neoplasms and the urgent need to develop new drugs for the treatment of this disease. Three novel targets were discussed: angiogenesis, EGF-R, and Rb pathway. More than 90% of patients with SCCHN have overexpression of EGF-R. SCCHN patients with high EGF-R and/or transforming growth factor alpha (one of the ligands for EGF-R) have poorer prognosis than patients with low expression of either protein. Thus, modulation of EGF-R activity may have a therapeutic role in this disease. Several trials with EGF-R (small molecule, antibodies, etc.) are being developed. Moreover, SCCHN patients with high VEGF expression have poorer prognosis than low VEGF expressors. Efforts to modulate angiogenesis in this patient population are ongoing. Finally, approximately 91% of patients with SCCHN have aberrations in the Rb pathway, most likely due to hyperactivation of cdks. Thus, cdk modulators may have a role in this disease as well. Preclinical and clinical studies with cdk modulators (flavopiridol and UCN-01) were described in detail.

Dr. William Figg (NCI, NIH) discussed the rationale and importance of invasion and metastasis processes as targets for cancer therapy. He presented the NCI phase I trial with Col-3, a novel matrix metalloproteinase inhibitor. Moreover, *Dr. Figg* summarized the extensive NCI experience of more than a decade of clinical trials in prostate cancer. Investigational drug trials with suramin were presented in perspective, along with more recent results with thalidomide, flavopiridol, and other compounds.

Although we have achieved significant scientific advances in the solid tumor research arena, the success obtained with hematopoietic malignancies is clearly unsurpassed. *Dr. Preti* (M.D. Anderson Cancer Center) reviewed impressive progress in the treatment of hematologic malignancies, the development of novel purine analogues, mAbs (rituximab and gemtuzumab), and the recent, exciting results with STI 571, an orally active drug specifically designed for treatment of bcr/abl-positive chronic myeloid leukemia (CML). Initially he described the basic molecular and biochemical pathogenesis of CML and later presented the results of clinical trials with the bcr/abl-specific TKI, STI 571. The fusion gene *bcr/abl* is the result of the well-known translocation associated with CML. *Bcr/abl* encodes three proteins, one of which exhibits TK activity (p210). A number of TKIs have been studied, including the natural product, genistein, and the synthetic tyrphostins and STI 571, among others. STI 571 is an orally active, phenylamino-pyrimidine compound which competes for ATP at the catalytic site of the bcr/abl kinase, thus inhibiting kinase activity. STI 571 effectively kills bcr/abl-positive cells. Early clinical trials with the drug showed that patients with chronic phase CML refractory who received doses ≥300 mg orally daily have 100% of complete clinical responses and a 35%-45% cytogenetic response rate (no detectable genetic abnormality in blood or bone marrow), achieving a normal white blood cell count within a month.

Nausea, abdominal cramps, arthralgia, and periorbital edema are some of the reported adverse events.

In addition to the above-mentioned topics, *Dr. Chris Takimoto* (University of Texas) presented a carefully balanced evaluation of new treatment options in colorectal cancer. Furthermore, *Dr. George Yoo* (Wayne State University; Detroit, MI) presented a historical perspective and a summary of current clinical approaches to gene therapy of cancer, particularly in SCHHN cancer. Moreover, *Dr. Leonard M. Neckers* (NCI, NIH) discussed antitumor effects of geldanamycin, an ansamycin that modulates the chaperone heat shock protein 90 (hsp90).

Dr. Senderowicz closed the meeting with an optimistic view that with the understanding of the molecular and biochemical pathogenesis of human cancer we may be able to uncover pathways necessary for the development of human malignancies. These novel pathways may serve as novel targets for cancer therapy. Moreover, in the last 5 years, efforts from industry, government and academia demonstrated that it was possible to modulate these novel targets in patients by the discovery of novel molecules, antibodies and with the use of gene therapy in cancer therapeutics. The main challenges in drug development of the 21st century are to determine if these novel modalities are more useful than traditional ones, to determine if those novel therapeutic modalities can modulate pathways in patients' samples, and to create novel methodologies to assess response/activity with these agents.

Based on the excitement provided by the interaction between speakers, organizers, investigators, and students, the second Novel Molecular Targets for Cancer Therapy is planned to occur in Buenos Aires, Argentina, October 4-5, 2001. Based on the enthusiasm observed in all participants, the organizers are planning to host this meeting every two years, starting in 2001.