Cancer Chemother Pharmacol (1999) 43(Suppl): S1–S2 

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# Preface

Following in the tradition established by the late Dr Kiyoji Kimura, the 14th annual Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium focused on an area of clinical oncology that is both innovative and fundamental to the goal of developing useful therapies for the treatment of cancer. The theme for the meeting was "The Challenge of Cancer Metastasis," a broad area which enabled both basic researchers and clinicians to participate and which encouraged a free exchange of ideas and information among specialists in various fields of oncology. We believe that this meeting also furthered another goal of this symposium series, that of facilitating contacts and progress in research and clinical practice.

Most, if not all cancers are believed to develop in stages controlled by genetic and environmental factors. However, the critical points in this progression and the triggers and controlling factors for metastasis are not well understood. Thus much basic research is focused on determining how the processes of tumorigenesis and metastasis are controlled. This in turn has implications for drug development and clinical practice. Designing drugs that target specific stages in the process of tumorigenesis could allow the progression to cancer to be halted; designing better delivery systems, schedules, and ways of targeting existing drugs to tumors could improve the efficacy of drugs that may currently be used suboptimally. With this in mind, the program of the 14th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium incorporated various presentations to provide attendees with an overview of some techniques currently used to control metastasis and basic research which may produce exciting new therapies.

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In his Keynote Address, Dr Douglas Hanahan, Department of Biochemistry and Biophysics, Hormone Research Institute, University of California San Francisco, San Francisco, CA, USA, described his laboratory's use of mouse models to define critical parameters of tumorigenesis. One of these models, in which simian virus 40 Tag oncoprotein expression is induced in insulin-producing pancreatic β cells, has provided evidence of a clear system of progression: hyperplastic islets arise and a cell subset initiates angiogenesis and subsequent neovascularization; and a subset of the angiogenic islets forms progressive stages of solid tumor, including encapsulated tumors and a carcinoma stage that invades and metastasizes.

In a second model, human papillomavirus type 16 oncogene expression is targeted to basal keratinocytes, producing spontaneous squamous cell tumors of the head and neck via a multistage pathway. Female mice also develop cervical cancer with chronic estrogen treatment. Angiogenesis is activated early, at the hyperplastic stage, and upregulated in the dysplastic stages and carcinoma.

Using these models, Dr Hanahan and colleagues have investigated and compared the effect of various angiogenesis inhibitors on tumor progression. Endostatin, angiostatin, AGM1470, and BB94 have all been shown to reduce tumor burden and induce tumor cell apoptosis. This supports the concept that disrupting the tumor vasculature causes apoptosis rather than necrosis, although the angiogenic switch leading to vascularization may differ between tissues.

This supplement comprises many of the papers presented at subsequent sessions of the symposium. One highlight was the Kimura Memorial Lecture, given by Dr Isaiah J. Fidler, Department of Cell Biology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. Dr Fidler described critical features of tumors and metastases that have a role in the resistance of metastases to chemotherapy, including tumor cell heterogeneity, genetic instability in metastases leading to heterogeneity despite a clonal origin, and

interactions between metastatic cells and homeostatic mechanisms which they usurp. The latter is particularly important in the design of new therapies because the organ microenvironment can influence not only whether metastases form, but also how they respond to chemotherapy. This has opened the door to developing therapies that influence the microenvironment rather than killing tumor cells directly.

Other topics covered included preclinical studies of cancer metastasis, a session which indicated the complex interactions of factors controlling where and if tumors metastasize and models for studying these interactions; matrix metalloproteinase (MMP) and its inhibitors, in which the basic science of MMPs and their role in metastasis were reviewed and the activity of marimastat described; mechanisms of angiogenesis and antiangiogenetic drugs, which provided an overview of some of the factors involved in angiogenesis and the antitumor effect of drugs such as thalidomide and TNP-470; gene therapy strategies for tumor metastasis; and clinical evaluation of antimetastatic agents, a session which included a presentation by Dr Michael A. Friedman, Acting Commissioner of Food and Drugs, US Food and Drug Administration, Rockville, MD, USA, on regulatory issues and how they affect novel anticancer therapies. In addition to these sessions, a variety of clinical techniques such as radiosurgery for brain metastases, hepatic infusion therapy, and intraperitoneal chemotherapy were described.

We hope that the Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium is living up to the vision of its founder, and that researchers and clinicians worldwide will find much of interest in the papers included in this supplement. We believe that these papers reflect the cooperation between basic researchers, who continue to make findings critical to our understanding of disease processes in cancer, pharmaceutical companies, which use this improved understanding to develop new drugs, and the clinicians who evaluate those drugs.