Dr Minako Nagao: Tribute to an Extraordinary Cancer Researcher

To the Editor:
I had the pleasure and privilege to participate in a symposium held on May 15, 1998 at the National Cancer Center in Tokyo, in honor of the retirement of Dr Minako Nagao. Dr Nagao’s seminal contributions in cancer research have profoundly influenced the directions of research by colleagues around the world for a great many years. I would like to share with the readers of the journal a summary of the symposium, featuring talks by Dr Nagao and a few of the many individuals having past and present associations with this remarkable scientist. In doing so, I may note that all but two presentations at the symposium, mine and Dr Dashwood’s, were delivered in Japanese. Regrettably, my colleagues at the National Cancer Center Research Institute in Tokyo have managed to teach me only four essential words of the Japanese language — konnichiwa, sayonara, arigato and kampai! Therefore my summary of the symposium is limited to that which I was able to glean from the data slides of each presenter. While this was a great deal of fun, much of the significance will surely have escaped me. I hope my Japanese colleagues will forgive any misrepresentation of their work, and forgive the unavoidable omission of much that was presented verbally.

Sensei (Dr) Takashi Sugimura presented the opening address. He took the opportunity to review Dr Nagao’s many contributions over a 35 year history with the National Cancer Center Research Institute. Drs Nagao and Sugimura forged a strong collaborative interaction during this period, which led to major advances in many fields of cancer research. Highlights include: the discovery in 1965 that MNNG, the most potent mutagen then known, is a carcinogen in rodents; studies demonstrating poly(ADP)ribosylation in 1971; Dr Nagao’s classic 1978 paper in Annual Reviews in Genetics on environmental mutagens and carcinogens; and studies on heterocyclic amine carcinogenesis over the past two decades including her recent work on APC and beta-catenin gene mutations in heterocyclic amine-induced rat colon carcinogenesis. Dr Sugimura showed many historically interesting slides of Dr Nagao’s travels around the globe to scientific meetings in such places as Hawaii, Paris and Brussels. Judging from the laughter, Dr Sugimura presented his usual highly entertaining lecture, but my unfortunate lack of Japanese prevents me sharing his humor with the readers of the journal.

Dr Nagao followed with a historical overview of her work with the Institute, noting that she began her work at the time of the John F. Kennedy assassination. Within two years she had made seminal discoveries regarding the relationship between glandular stomach DNA alkylation, mutagenesis and carcinogenesis by MNNG and 4-NQO. Her work demonstrating mutagenicity and carcinogenicity of the food additive AF-2 was essential to the removal of this hazardous compound from the food supply in Japan. The 1978 Annual Reviews in Genetics paper emphasized that ‘nature’ is not benign, but produces many mutagens, such as the heterocyclic amines, mycotoxins, and bracken fern toxins, to which humans have adapted over the course of their evolutionary history. This is compared to human exposure to industrial chemicals over only the past 50 years or so. Following a presentation of her recent pioneering work relating heterocyclic amine mutagenesis and target organ carcinogenesis in the Big Blue Mouse model, Dr Nagao’s talk ended with the observation that about 3% of the mutations described in p53 from human cancers bears the PhiP mutational signature as an upper limit.

Professor Hikoya Hayatsu, one of the first scientists to consider the antimutagenesis approach to hazard reduction, discussed his early studies with his colleague Dr Negishi demonstrating suppression of heterocyclic amine mutagenesis by glutathione and hemin. Dr Nagao collaborated in this early work by supplying not only heterocyclic amines for study, but also by having trained Dr Negishi in her laboratory. Dr Hayatsu discovered in 1980 that hemin and protoporphyrin could form complexes with Trp-P2, and in 1989 reported that chlorophyllin could form a similar complex with Trp-P2. These findings provided a mechanistic basis for antimutagenesis by porphyrin-related compounds, and stimulated cancer chemoprevention studies with chlorophylls by a number of scientists around the world including Dr Dashwood and myself. Blue Cotton and Blue Rayon, which Dr Hayatsu initially developed for the isolation of heterocyclic amines, were used recently to detect Ames mutagens in the effluent of a dye factory on the Katsura River near Kyoto. This is a very interesting translation of cancer research into the environmental remediation arena. His presentation ended with a discussion of the use of these reagents to enhance sensitivity of DNA adduct detection by post-labeling protocols.

The next presentation (and the first in English) was by Dr Roderick Dashwood, discussing his work in Dr Nagao’s laboratory while on sabbatic leave from the University of Hawaii. His work has focused on apoptosis, rather than proliferation, as a major mechanism in colon carcinogenesis by PhiP and IQ. Dr Dashwood showed some quite beautiful immunohistochemical slides demonstrating alterations in the ratio of Bax (pro-apoptotic) and Bc12 (anti-apoptotic) expression during the initiation of aberrant foci and tumors in the rat by these heterocyclic amines, mycotoxins, and bracken fern toxins, to which humans have adapted over the course of their evolutionary history. This is compared to human exposure to industrial chemicals over only the past 50 years or so. Following a presentation of her recent pioneering work relating heterocyclic amine mutagenesis and target organ carcinogenesis in the Big Blue Mouse model, Dr Nagao’s talk ended with the observation that about 3% of the mutations described in p53 from human cancers bears the PhiP mutational signature as an upper limit.

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lates in the cytosol, dimerizes with other proteins, and translo­
cates to the nucleus to block apoptosis. Similarity of these
molecular events in the rat model to what is observed in human
colon tumor progression may be seen to provide supportive
evidence for a role of heterocyclic amines in the human disease.

Dr Okio Hino provided a discussion of ‘Well Deliberated
Cancer Research: Toward the 21st Century’. Part of his thesis was
toward a more relaxed approach to research. He noted the sense
of pressure based on the original idea that all talks at the
symposium, including his, might be delivered in English.
However, since his talk was in Japanese, he felt no pressure! Dr
Hino reviewed Alfred Knudson’s seminal work on the existence
of tumor suppressor genes in human cancer. His presentation
elicited continuous gales of laughter, the basis for which I regret
I am unable to communicate.

Dr Tomoyuki Shirai reviewed the history of heterocyclic amine
research, beginning with Widmark’s demonstration in 1939 that
mice fed broiled horse meat developed mammary tumors. PhiP,
the most prevalent dietary heterocyclic amine, elicits liver tumors
in female F344 rats, but colon and prostate tumors in the male.
Mechanisms for this gender difference were reviewed, and appear
to relate at least in part to differential target organ DNA adduction.
Thus males treated at 400 p.p.m. PhiP for 52 weeks were reported
to develop 70–80% incidence of tumors of the seminal vesicles,
ventral prostate, and anterior prostate, and to accumulate
PhiP-DNA adducts in the range of 4–10 adducts per 10<sup>7</sup> bases,
compared with only 0.57 per 10<sup>7</sup> bases in the liver. He then
reviewed studies on chemoprevention of PhiP carcinogenesis,
including Dr Dashwood’s work showing inhibition by chloro­
phyllin in the colon model and Dr Hirose’s work in 1995 showing
antioxidant-mediated reduction of DNA adducts, BrdU labeling,
and tumor multiplicity in a DMH initiation/PhiP promotion colon
model.

As the last speaker, I was pleased to discuss Dr Nagao’s
influence on my research in the past 10 years, and to present some
of the work from my laboratory on quantitative issues in cancer
chemoprevention research. Using the low cost, low background,
high sensitivity advantages of the rainbow trout model, Dr
Dashwood and other former associates in my lab have been able to
rigorously investigate the quantitative interrelationships be­
tween altered dose of carcinogen, altered dose of blocking agent,
altered target organ DNA adduction, and final tumor outcome.
The results revealed that, under some conditions but not all, DNA
adduct measurements can serve as quantitatively predictive
biomarkers of final tumor outcome in chemoprevention by
anticarcinogens that act as blocking agents. This work served as
the basis for our chlorophyllin intervention clinical trial now
nearing completion with a population of aflatoxin B, individuals
in Qidong, China. Comparison of such 10 000 trout tumor studies
with the less elaborate experimental designs typical of the more
costly rodent studies revealed: (1) that calculation of ‘% inhibition of tumor incidence’ can be a misleading measure of
anticarcinogen efficacy; and (2) that tumor chemoprevention
study designs should include at a minimum two carcinogen doses
at each anticarcinogen dose tested in order to assess the
carcinogen dose dependency of anticarcinogen efficacy.

The celebration honoring Dr Nagao’s extraordinary contribu­
tions to cancer research ended with a splendid banquet. I am sure
the readers of the journal will agree that Dr Nagao’s honors are
well deserved. Fortunately for the scientific community, it
appears that ‘retirement’ is only an illusion. Dr Nagao tells me
that she is now able to avoid her former administrative chores, and
I hear that she is working as hard as ever!

I am sincerely grateful to the Foundation for Promotion of
Cancer Research, whose generous financial support made it
possible for me to participate in this symposium.

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