# Young Cooperative Oncology Group Spans Southeast Asia, Australia

Linda Wang

After years of working in the United States, John Eu-Li Wong, M.D., returned to Asia to head the Cancer Institute in Singapore. He was struck by how differently his Asian patients responded to certain cancer drugs compared with his Caucasian patients.

Dr. John Eu-Li Wong

"The breast cancer I was treating in New York for many years was somehow different from the breast cancer I was treating in Singapore," he recalled.

His Asian patients were experiencing more side effects from the same drugs that were well-tolerated by his patients in the United States. On the other hand, the Asian patients were not experiencing some side effects often seen in Caucasian patients.

Wong also noticed a lack of new drugs for cancers prevalent in Asia, such as liver, stomach, and nasopharyngeal cancer. "All the treatment advances were being made in cancers common in North America but very [few] advances [were being made] in cancers common in Asia," he said.

These concerns motivated Wong and a group of his colleagues to create the Cancer Therapeutics Research Group (CTRG), the first cooperative group to test cancer compounds simultaneously in Asians and Caucasians. The group also promises to bring new cancer drugs to Asia earlier through its clinical trials system.

In just 5 years, the CTRG has built up an impressive infrastructure, presented a number of studies at cancer meetings, and is about to publish its first peer-reviewed paper.

## A Unique Collaboration

Wong's earliest partner in the CTRG was his friend and colleague, James F. Bishop, M.D., director of the Sydney Cancer Center in Australia. Wong noted that Bishop's cooperation was crucial because, by bringing in patients from Australia, the CTRG could compare drug responses in Asians and Caucasians. With Bishop's support, Wong launched the CTRG in October 1997. The Chinese University of Hong Kong later joined the group in 1999.

Today, the CTRG includes the National University of Singapore, National University Hospital in Singapore, the University of Sydney in Australia, the Sydney Cancer Center, Johns Hopkins in Singapore, and the Chinese University of Hong Kong.

The CTRG hopes to include other Asian countries as well, but differences in each country's resources and emphasis on research could pose a challenge, said Benny Zee, Ph.D., director of the Comprehensive Cancer Trials Unit at the Chinese University of Hong Kong.

Zee, who is a partner in CTRG, pointed out that some countries do not have enough oncologists to sustain a major clinical trials effort, while other countries lack government support and adequate drug monitoring systems. Still other countries are politically unstable.

For the countries that do join, the CTRG must respect their regulations and system of patient care. "We have to deal with different partners and understand the needs of each partner," Zee said.

The CTRG owes much of its success to the Singapore government. The group's clinical trials are partially funded by the Singapore Economic Development Board and the Singapore National Science and Technology Board, and additional funding comes from individual institutions and pharmaceutical companies. The CTRG has partnerships with more than 30 drug companies, including AstraZeneca, Eli Lilly, and Merck Germany.

"The immediate benefit [for pharmaceutical companies] is that it opens up a whole new set of centers for us where we know we can get good high-quality clinical research done," said George Blackledge, M.D., Ph.D., medical director of oncology at AstraZeneca. "We clearly see Southeast Asia as an area of potential growth over the years ahead."

With Singapore, Hong Kong, and Australia, the CTRG still only represents a small proportion of the Asian population. China's abundant population and wide range of cancers could provide a wealth of insight into poorly understood cancers, said Alex Chang, M.D., director of oncology at Johns Hopkins in Singapore and a partner in CTRG.

Even with only three countries on board, the CTRG is making progress in cancer research. They have presented results from completed trials at recent American Society for Clinical Oncology meetings and seven new trials are about to open.

In 1999, they released results from a phase II trial on docetaxel and carboplatin in advanced non-small-cell lung cancer. In 2001, they presented results on a phase II study of thalidomide in unresectable liver cancer. This May, they described results from a phase I study of weekly paclitaxel, UFT, and leucovorin in patients with metastatic breast cancer. A study of cetuximab (C225) plus carboplatin in patients with recurrent or metastatic nasopharyngeal cancer is nearing completion. This phase II study is important because it addresses a cancer more common in Asia than in the United States or Western Europe, Zee said.

In addition, the group will publish results from a trial later this year that will reveal differences in metabolism of the drug docetaxel between Asian and Caucasian cancer patients.

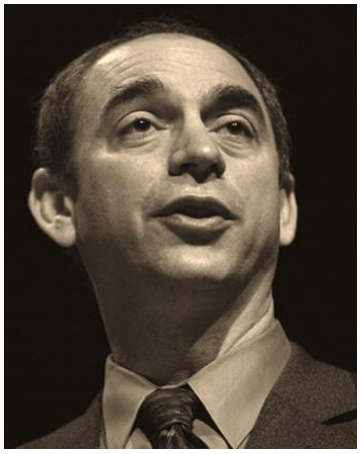
Despite their progress, Zee is quick to point out that the group is still working to fill out their infrastructure. "What we want to do is make sure everything works well and the machine of CTRG is well greased," said

Zee. The group is trying to attract more support staff, such as more clinical nurses, research nurses, and data managers.

"I think it's too early to count the success [of CTRG] in the Asian clinical trials arena, but the infrastructure itself is the most important start," said Zee. "If the infrastructure is there, the opportunities are unlimited."

## Identifying Racial Differences

One opportunity is to study why Asians and Caucasians differ in response to certain cancer drugs and to develop more effective drugs for Asians.



Dr. Mark Ratain

"Most drug development is done in western Europe and North America and so when you go to parts of the world that have a different environment or different genetics it's important to understand whether the recommendations are going to be valid," said Mark Ratain, M.D., who studies ethnic differences in drug metabolism at the University of Chicago.

By understanding these differences, physicians can recalibrate drug doses, explore different drug delivery systems, and be more vigilant about different side effects that may occur in the different ethnic groups.

The CTRG can also reexamine old drugs for new indications. Wong pointed out that the cancer drug amonafide, a topoisomerase II inhibitor, was tested by U.S. cooperative groups and shelved because it did not appear to have any effect.

Researchers later found that amonafide requires a chemical change called acetylation to become active, and most Caucasians are slow acetylators. Because many Asians are fast acetylators, the drug showed considerably more activity in this racial group.

The CTRG also hopes to conduct trials on new experimental agents, thereby bringing these drugs to Asia more quickly. "Drug development is becoming more global every day," said Ken Kobayashi, M.D., a senior investigator in the National Cancer Institute's Cancer Therapeutics Evaluation Program. "I think it's important for the NCI to recognize that and to develop closer collaborations with investigators and academic institutions in the Asia-Pacific region." The CTRG has accreditation from the NCI for drug development work in cancer, which allows the group to bid for clinical drug trials offered by NCI.

Current Clinical Trials of the Cancer Therapeutics Research Group

| Phase | Drug | Patients |
|---|---|---|
| II | C225 with carboplatin | Metastatic nasopharyngeal carcinoma |
| I/II | Weekly paclitaxel and ORZEL (UFT + leucovorin) | Metastatic breast cancer |
| I/II | Infusional gemcitabine in combination with carboplatin | Chemo-naïve advanced non-small cell lung cancer |
| II | 5-FU, folinic acid, gemcitabine, and cisplatin | Metastatic or recurrent colorectal carcinoma |
| II | Irinotecan, 5-FU, and folinic acid | Unresectable liver metastases from colorectal cancer |

As the *Journal* went to press, Kobayashi was preparing for a trip to Singapore to meet with CTRG members and discuss potential collaborations with the NCI's investigational drug program.

Two other avenues the CTRG wants to pursue are phase III clinical trials and studies on the molecular biology of racial differences in drug response. The CTRG is collaborating with the Genome Institute of Singapore on developing overlapping genetic studies between Asians and Caucasians, said Edison Liu, M.D., executive director of the Genome Institute of Singapore.

Ultimately, the goal of the CTRG is to bring people together to make a contribution to cancer research. “I think it’s important for people to know that Asian research groups can work together and do some serious research in cancer clinical trials,” said Zee.