

## Drug Fights Multiple Myeloma by Putting "Brakes" on Cell Proliferation, Weill Cornell Team Reports

Highly Targeted Agent Stops the Cancer in Animal Model and May Fight Other Tumor Types

NEW YORK (Aug. 1, 2006) -- An experimental drug targeted to a cancer-causing mechanism within the cell may be a powerful weapon against deadly multiple myeloma.

So concludes a team of researchers at the Weill Medical College of Cornell University in New York City. They report their findings in the Aug. 1 issue of *Cancer Research*.

Animal studies using human myeloma cell lines show that the experimental agent -- called PD 0332991, an orally active, small molecule -- inhibits specific enzymes and proteins that dysregulate the cell's division and expansion.

"Previous work in our lab showed that when these kinase enzymes -- Cdk4 or Cdk6 -- inappropriately match up with regulatory proteins called cyclin D1 or D2, you get the uncontrolled proliferation of cells that is a hallmark of myeloma relapse," explains senior researcher Dr. Selina Chen-Kiang, professor of pathology and laboratory medicine, and professor of microbiology and immunology at Weill Cornell Medical College. That groundbreaking work was published last December in *Cancer Research*.

Either combination -- Cdk4/cyclin D1 or Cdk6/cyclin D2 -- is like "adding gas to an engine," she explains. "Now, what we've found is a pharmacologic 'brake' that stops the myeloma motor, cold."

And because these enzyme-cyclin pairings can help trigger the proliferation of cancer cells in general, inhibitors like PD 0332991 might prove useful in treating a wide range of tumors.

"Our work is really opening up a whole new target for drug development -- not just for multiple myeloma, but potentially for all cancers," says study lead researcher Dr. Linda Baughn, a Leukemia and Lymphoma Society Fellow at Weill Cornell.

Multiple myeloma, found deep within the bone marrow, originates in cells called B lymphocytes. It is the second most common blood cancer, with more than 15,000 Americans diagnosed with the disease each year. Multiple myeloma is invariably fatal, with an average life expectancy after diagnosis of just three years.

"There are drugs that are geared to getting people into remission, but they ultimately fail because there are still cancer cells that have the potential for self-renewal -- they'll rise again and start dividing," Dr. Chen-Kiang explains.

Her lab's discovery last year of just how relapse occurs was a real breakthrough. The "sequel," Dr. Chen-Kiang says, was to find an agent that could stop it.

"We knew what we were looking for: a pill whose active agent was a molecule small enough that it could get deep inside the myeloma cell," adds co-lead researcher Dr. Maurizio Di Liberto, assistant research professor of pathology and laboratory medicine at Weill Cornell. "The drug also had to be highly targeted -- it had to stop the proliferation of myeloma cells without harming normal cells," he said. Luckily, researchers at the drug giant Pfizer, Inc., had already been busy developing just such an agent -- PD 0332991.

"We first observed PD 0332991's ability to rapidly stop patients' myeloma cells from dividing in tissue culture," Dr. Chen-Kiang explains.

Together with Dr. Malcolm Moore at the Memorial Sloan-Kettering Cancer Center, Dr. Chen-Kiang's team next injected human multiple myeloma cell lines into mice.

"PD 0332991 effectively prevented the growth of myeloma tumors in these mice," she says. "What's more, the drug appeared to inhibit Cdk4 and Cdk6 in a way that was proportional to the proliferating state of the cell."

In other words, the harder the Cdk4 and Cdk6 tried to "rev up" the myeloma engine, the stronger PD 0332991 put on the brakes.

The Weill Cornell team also went one step further.

"We noted that PD 0332991, by itself, does not induce apoptosis -- the death of existing cancer cells," Dr. Chen-Kiang explains. "So we wondered if combining it with other agents might help."

To find out, her team coupled the Pfizer compound with a steroid called dexamethasone -- long used by doctors to help slow multiple myeloma.

"Using these two drugs together seemed to have a synergistic effect. We observed markedly enhanced killing of myeloma cells, even though we used one-tenth the dose of dexamethasone that's usually delivered to patients," Dr. Chen-Kiang reports.

"Steroids are notorious for their side effects, so being able to dramatically reduce the dose would be of great benefit to patients," she says.

The researchers are hopeful that combining PD 0332991 with other chemotherapies will be equally or more effective. Early data suggest that this approach will bring equally impressive results.

The advent of a mechanism-specific agent that stops multiple myeloma in its tracks is both unique and exciting, the research team says.

"It's controlling the disease by controlling the mechanism of myeloma cells' division," Dr. Baughn explains. "We've never had anything like this before."

The implications for cancer research in general may be even more exciting, Dr. Chen-Kiang adds.

"Scientists have known for a long time that Cdk4 and Cdk6 play key roles in the proliferation of nearly all cancer cell types, but until now we haven't found an agent that specifically targets only those two enzymes," she says.

"We're confident that if this works in myeloma, it should work in a wide range of other tumors, too," she says.

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Co-researchers included Dr. Ruben Niesvizky, Dr. Hearn J. Cho, Ms. Tracey Louie, Ms. Rachel Gottschalk and Dr. Scott Ely -- all of the Weill Medical College of Cornell University, New York City; Dr. Kaida Wu and Dr. Malcolm A.S. Moore of Memorial Sloan-Kettering Cancer Center, New York City; and Dr. Peter Toogood of Pfizer Global Research and Development, Ann Arbor, Mich.

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