# Stopping and starting cancer cell cycle weakens and defeats multiple myeloma

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Weill Cornell Medical College researchers have devised an innovative boxer-like strategy, based on the serial use of two anti-cancer drugs, to deliver a one-two punch to first weaken the defenses of multiple myeloma and then deliver the final knock-out punch to win the fight.

The study, published online by the journal *Blood*, is the first to show that precise timing of therapies that target a cancer cell's cycle — the life phases leading to its division and replication — disables key survival genes, resulting in cell death. The drug that delivers the weakening jab at the cell cycle is the experimental agent PD 0332991, which allows bortezomib, a proteasome inhibitor already approved for use in myeloma and lymphoma, to land the final defeating blow at lower than normal doses.

While this is potentially good news for patients with multiple myeloma, a cancer of blood plasma cells that is currently incurable, the study suggests that using this therapeutic strategy could also work for other tumor types, says the study's senior investigator, Dr. Selina Chen-Kiang, professor of Pathology and Laboratory Medicine and of Microbiology and Immunology at Weill Cornell Medical College.

"Because robust functioning of the cell cycle is crucial to cancer growth and survival, this mechanism-based strategy could theoretically be used against many kinds of cancers," she says.

"Based on the genetics of a patient's tumor, we could pair PD 0332991

with the right cytotoxic partner drug to both inhibit cancer cell division and sensitize the cells for that knock-out punch," says Dr. Chen-Kiang. "We are very excited about the promise of this approach."

In fact, physicians at Weill Cornell have opened two new human clinical trials, one in multiple myeloma and one in mantle cell lymphoma, based on the findings of this study in a mouse model as well as on a previous phase I clinical trial led by Weill Cornell investigators that tested PD 0332991 in patients with mantle cell lymphoma.

## Playing Havoc with the Cancer Cell Cycle

Dr. Chen-Kiang and her laboratory colleagues have long studied genes and proteins that control the cell cycle and cell suicide (apoptosis) in cancer. Cancer is fundamentally a disease of uncontrolled cell proliferation, where cells are able to continuously divide. In contrast, cell division in a healthy individual is regulated by the cell cycle, an orderly sequence of programmed gene expression in which the cell is driven through various checkpoints by a highly regulated network of proteins.

Cyclin-dependent kinases (CDKs) are molecules that power the progression of the cell cycle through its four phases. For example, CDK4 and CDK6 help move cells through the first G1 "gap" phase to later phases where the cell splits in two. In many cancers, these two enzymes are over-expressed, ensuring continual growth. Therefore, targeting CDK4 and CDK6 to shut them down has long been a goal of cancer drug discovery, but clinical success, so far, has been disappointing because of lack of effectiveness as well as drug toxicity, says Dr. Chen-Kiang.

PD 0332991, a small molecule synthesized by Pfizer, is different because it is exceptionally selective for CDK4 and CDK6, she says. The drug initially did not receive much attention because it is also reversible,

meaning that it needs to be used continuously to inhibit CDK4 and CDK6; withdrawing it would reactivate these enzymes, stimulating growth.

But Dr. Chen-Kiang had been searching for a drug that she could use for her selective cell cycle-based therapy — the idea being that playing havoc with a cancer cell's cycle would fatally weaken it when more traditional anti-cancer drugs are used sequentially.

"Given that the gene expression program is coupled to the cell cycle, we hypothesize that inhibition of CDK4/CDK6 maintains gene expression programmed for early G1, while preventing the expression of genes scheduled for other cell cycle phases," she explains. "And because metabolic needs in tumor cells differ from normal cells, this prolonged arrest in G1 would create an imbalance in gene expression that preferentially sensitizes tumor cells to cytotoxic drugs, allowing for low-dosage treatments."

"Because PD 0332991 is also reversible, we further hypothesize that release from G1 by removal of the inhibitor would synchronize the cell cycles, but may not synchronize gene expression schedules," Dr. Chen-Kiang adds. "This tension between cell cycle synchronization and differential gene expression synchronization further weakens the tumor cells during their progression, as does the heightened metabolic load and demand for energy to replicate DNA."

## Loss of Survival Protein

This is exactly what the researchers found. By using PD 0332991 several times to induce a prolonged arrest of G1, and then a release from that arrest, the cells were sensitized to killing by bortezomib. They found this to be the case in laboratory studies of primary myeloma tumor cells and in mice, which were left with healthy bone marrow cells.

"We found bortezomib, even when used in a low dose, was significantly more effective when the cancer cells were sensitized by our strategy," says the study's first author, Dr. Xiangao Huang, assistant research professor of Pathology and Laboratory Medicine at Weill Cornell Medical College.

In exploring the underpinning mechanism, the researchers discovered that prolonged arrest in G1 markedly enhances cell suicide, induced by bortezomib. They discovered that during this phase, the cell loses a protein called IRF4, an essential survival factor for myeloma cells, and gains several pro-apoptotic proteins.

"These findings demonstrate for the first time that key survival and apoptotic genes are regulated by the cell cycle in cancer cells, and suggest new molecular targets for intervention," Dr. Chen-Kiang says.

"This work represents the seamless integration of basic biological research on the cell cycle and direct medical application in clinical trials," she adds. "Both the tools available to us, and our unique location at NewYork-Presbyterian/Weill Cornell Medical Center, allow us to move biological research forward while rapidly translating our findings to therapy."

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