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Novel approach scores first success against elusive cancer gene

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Dana-Farber Cancer Institute scientists have successfully disrupted the function of a cancer gene involved in the formation of most human tumors by tampering with the gene's "on" switch and growth signals, rather than targeting the gene itself. The results, achieved in multiple myeloma cells, offer a promising strategy for treating not only myeloma but also many other cancer types driven by the gene MYC, the study authors say. Their findings are being published by the journal *Cell* on its website Sept. 1 and in its Sept. 16 print edition.

"Cancer is a disease of disregulation of growth genes in a cell, and MYC is a master regulator of these genes," says James E. Bradner, MD, of Dana-Farber, one of the study's senior authors. Previous attempts to shut down MYC by inhibiting it directly with drug molecules have been notably unsuccessful. "In this study, our idea was to switch MYC off, interfering with its ability to activate the cell-growth program."

They did so with a small molecule called JQ1, developed by Dana-Farber's Jun Qi, PhD, a co-author of the new study and namesake of JQ1. In multiple myeloma, MYC is hyperactive – constantly ordering cells to grow and divide – because it is in the wrong position in the cells' chromosomes. Instead of its normal, quiet neighborhood, MYC finds itself adjacent to a gene known as the immunoglobulin gene. This busy gene is switched on by bits of DNA known as immunoglobulin enhancers, which normally prompt the cell to begin producing disease-fighting antibodies. In myeloma, the immunoglobulin enhancers act on the out-of-place MYC gene like an impatient finger at a doorbell,

repeatedly activating it.

Researchers found that the enhancers are loaded with a "bromodomain" protein called BRD4, which, they demonstrate, is used to switch on MYC. Conveniently, it is targeted by JQ1. When investigators added JQ1 to laboratory samples of myeloma cells, the bromodomain proteins fell off the enhancers and the enhancers abruptly stopped working. The result: a shutdown of MYC and a slowdown of cancer cell division.

"In a sense, the JQ1 molecule cuts the cable that activates MYC and also connects MYC to the cell-growth genes," Bradner says. "The signal is interrupted and growth abruptly stops."

When investigators administered JQ1 to laboratory mice harboring myeloma cells, the disease receded and the animals lived longer than those that had not been treated. The study authors emphasize that JQ1 is a protytpe drug and cannot be used immediately to treat myeloma or other cancers. Its success in the current study illuminates the promise of JQ1-based therapies that target bromodomain proteins in cancers dependent on MYC for their growth.

"Together, our findings show that BRD4 has an important role in maintaining MYC activity in myeloma and other blood-related malignancies," says the study's senior author, Constantine Mitsiades, MD, of Dana-Farber. "They also point to the potential usefulness of drug-like bromodomain inhibitors as novel therapies against these diseases."

Provided by Dana-Farber Cancer Institute