

Inhibitor of RNA polymerase I shows promise as potential treatment for acute myeloid leukemia and multiple myeloma

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The investigational drug CX-5461, which blocks the protein RNA polymerase I (Pol I), prolonged survival in mouse models of highly aggressive acute myeloid leukemia (AML) and multiple myeloma, according to data presented at the American Association for Cancer Research special conference Hematologic Malignancies: Translating Discoveries to Novel Therapies, held Sept. 20-23.

"Some forms of AML and [multiple myeloma](#) are highly refractive to standard therapies," said Ross D. Hannan, PhD, head of the Oncogenic Signalling and Growth Control Program and a professor at the Peter MacCallum Cancer Centre, Melbourne, Australia. "There is an urgent need for new drugs that can treat patients with these cancers that have relapsed on standard therapy, which is why we chose to study the effects of CX-5461 in mouse models of these diseases.

"Our results show that CX-5461 was effective in preclinical models of MLL-AML and multiple myeloma refractory to standard therapy and that therapeutic efficacy was independent of p53 status," continued Hannan. "These results provide further rationale for the first-in-human phase I clinical trial that we initiated in July 2013 testing CX-5464 for patients with advanced hematological malignancies, including AML and multiple myeloma."

According to Hannan, Pol I levels are consistently found to be

upregulated in cancers, in particular hematologic malignancies, suggesting it might be a good therapeutic target. He and his colleagues found that CX-5461 significantly extended overall survival in a [mouse model](#) of highly aggressive AML, the MLL/ENL + Nras model. Median survival was 17 days for mice treated with vehicle with no drug, compared with 21 days for mice treated with the standard chemotherapy combination of cytarabine and doxorubicin and 36 days for mice treated with CX-5461.

In the V-kappa-MYC driven model of multiple myeloma, CX-5461 significantly prolonged overall survival: median survival was 103.5 days for mice receiving vehicle with no drug and 175 days for mice receiving CX-5461.

Pol I is a protein involved in a cellular process central to cell proliferation and survival; as such, it is referred to as a house-keeping protein. "We were excited to find that therapeutic doses of CX-5461 had little effect on normal cells in our experiments," said Hannan. "Prior to these studies, few people would have guessed that such a therapeutic window could be obtained by targeting a so-called house-keeping protein that is essential to all cells for survival."

Provided by American Association for Cancer Research

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