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11 July 2012 | News | By BioSpectrum Bureau

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Singapore: Cylene Pharmaceuticals' research collaborators at the Peter MacCallum Cancer Centre (Peter Mac) in Melbourne, Australia, have established, for the first time, that RNA Polymerase I (Pol I) activity is essential for cancer cell survival and that its inhibition selectively activates p53 to kill tumors. Published in *Cancer Cell*, the findings show that Cylene's Pol I inhibitor, CX-5461, selectively destroys cancer by activating p53 in malignant but not in normal cells.

The researchers repeated these studies with in vivo models of blood cancers and demonstrated that the drug removed malignant cells from the bloodstream, while allowing normal healthy blood cells to grow, thus differentiating CX-5461 from genotoxic treatments. Targeting cancer's dependence upon Pol I to trigger cancer-specific activation of p53 signifies an entirely new approach to cancer therapy.

"The Pol I program represents the total package. Dr Ross Hannan, associate professor and group leader at Peter Mac's Growth Regulation Laboratory, performed elegant studies to validate Pol I as a cancer target, Cylene created CX-5461 as the first selective small molecule inhibitor of Pol I, and together we showed that this approach potently kills malignant cells through activation of p53," said Dr William G. Rice, president and CEO of Cylene Pharmaceuticals. "Building on our mechanistic understanding of CX-5461, we have identified specific genetic markers to select patient populations with the most sensitive solid tumor or hematological cancers."

"The combination of cancer's reliance on Pol I, the impressive preclinical activity of CX-5461, the development of clear predictive and prognostic biomarkers and the novelty of the therapeutic strategy is compelling," continued Dr. Rice. "As such, a First-in-Human clinical trial with CX-5461 is planned in collaboration with our colleagues at Peter Mac later this year."

The Cancer Cell publication highlighted a number of potential competitive advantages of CX-5461. An unanticipated finding was that malignant cells are considerably more dependent upon maintenance of high levels of Pol I activity than previously believed, and even modest inhibition of Pol I triggers cancer cell death. These results suggest that selective activation of a surveillance pathway to activate p53, using Pol I inhibitors such as CX-5641, is likely to be therapeutically useful in the treatment of a wide range of tumors. In addition, as a cancer-specific inducer of p53, CX-5461 was shown to be 300 times

more potent than currently studied non-genotoxic p53 activators with alternate mechanisms.