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# Inhibition of ribosome biogenesis as a strategy to treat cancer

Thursday 16 May 2013, 1pm

**Associate Professor Rick Pearson**, Division of Cancer Research, Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia.

**Slatyer Seminar Room**, Building no. 46, Linnaeus Rd, ANU



**BIOGRAPHY:** A/Professor Richard Pearson was appointed as the Head of the Cancer Signalling Laboratory at the Peter MacCallum Cancer Centre in 1995 after 3 years as a Human Frontiers of Science Fellow at the Friedrich Miescher Institute in Basel Switzerland. He is also Co-Head of the Oncogenic Signalling and Growth Control Program at Peter Mac, is an NHMRC Senior Research Fellow and Principal Fellow in the Department of Biochemistry and Molecular Biology at the University of Melbourne. A major focus of his research is to understand the molecular basis of the regulation of ribosome biogenesis, protein synthesis and cell growth and to use this knowledge to address how deregulation of these processes contributes to malignant transformation. A/Prof Pearson currently receives project grant support from both NHMRC and Prostate Cancer Foundation of Australia and was awarded an NHMRC Program Grant with Prof Grant McArthur, A/Prof Ross Hannan and Prof Rod Hicks to understand the

mechanisms by which oncogenic signaling can be targeted to treat cancer, starting in 2014. He has co-authored 85 peer reviewed articles with an average citation rate per publication of 90. He has served on NHMRC Grant Review Panels from 2006-08 and on the NHMRC Assigners Academy in 2012 and 2013.

**ABSTRACT:** The dysregulation of ribosome biogenesis invariably occurs in cancer cells. However, a critical, unresolved question has been whether the accelerated ribosome is required for malignancy. Here we show that the PI3K/AKT pathway, deregulated in a high proportion of human tumours, is a critical regulator of ribosome biogenesis. Active AKT is sufficient to drive ribosome biogenesis and cooperates with c-MYC to drive this process, identifying the AKT/MYC network as a master controller of cell growth. Consistent with this concept, PI3K/AKT activity is required for maximal activation of rRNA synthesis and tumour formation in the  $E\mu$ -Myc mouse model of Burkitt's lymphoma. To test whether cancers characterized by unrestrained cellular growth are vulnerable to therapeutic strategies that target ribosome biogenesis, we used a novel selective inhibitor of Pol I transcription (CX-5461) to show that Pol I can be targeted in vivo to treat tumors in mouse models of lymphoma and leukemia through the activation of p53-dependent apoptosis. Strikingly, PI3K/AKT pathway inhibitors suppress rRNA synthesis independent of p53 and cooperate with CX-5461 in killing  $E\mu$ -Myc lymphomas providing a clear rationale for combining these agents in future clinical trials.

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