Author's response to reviews

Title: Identification of synthetic lethality of PRKDC in MYC-dependent human cancers by pooled shRNA screening

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Dr. Dafne Solera
Executive Editor
BMC Cancer

Dear Dr. Solera:

Attached please find our manuscript entitled “Identification of synthetic lethality of PRKDC in MYC-dependent human cancers by pooled shRNA screening” for publication in *BMC Cancer*.

MYC is one of the most frequently deregulated oncoproteins in human cancers. Due to the lack of a druggable domain, it has been challenging to develop small molecule inhibitors that target MYC itself, or disrupt MYC-mediated protein-protein or protein-DNA interactions.

In this manuscript, we decided to use a synthetic lethality approach to target the non-druggable MYC oncoprotein. To this end, we exploited a large-scale in-house kinome RNA interference lentiviral pool to investigate a large cohort of genes for loss-of-function effects in human MYC-deregulated cancers. We identified and confirmed PRKDC, a protein kinase with a major role in non-homologous end joining (NHEJ) DNA repair, as a novel synthetic lethal target in MYC-overexpressing cancer cells, suggesting differential MYC dependency between tumor and normal tissue. We demonstrated that knockdown of PRKDC expression in MYC-overexpressing cells led to a significant reduction of MYC dependent cell proliferation. Additionally, we observed that PRKDC can modulate MYC mRNA and protein expression levels. Furthermore, our data also reconfirmed that overexpression of MYC family proteins induces DNA double-strand breaks, which suggests that MYC-overexpressing cancer cells rely more on DNA repair machinery where PRKDC plays a vital role. Together, our findings indicate that PRKDC may be critical in MYC-driven oncogenesis, and supports PRKDC as a novel potential synthetic lethal target for MYC. We believe our findings will be of general interest to the broad *BMC Cancer* readership.

We would like to suggest Dr. Manuel Perucho (SBMRI; mperucho@sanfordburnham.org) as a potential Monitoring Editor, and Drs. Quinn L. Deveraux (Inhibrx, USA; quinn@inhibrx.com) and Kim C. Quon (Amgen, USA; kimq@amgen.com) as expert reviewers.

We hope that you will find our manuscript acceptable for publication in *BMC Cancer*; I appreciate and thank you for your time and attention.

Sincerely,

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