Developing a selective cancer chemotherapy by small molecule-based targeting of PCNA protein

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Keywords: PCNA, transcription replication conflict, selective cancer chemotherapy

Proliferating cell nuclear antigen (PCNA) is critical to DNA replication and repair processes and it is also a proliferation biomarker in a variety of human tumours. A unique cancer-associated isoform of the protein, caPCNA, has been previously identified [1], allowing for rational-based drug discovery studies to develop leads with the potential for selective therapeutic targeting of cancer cells. Several strategies have been employed to develop agents targeting caPCNA, including peptide and small molecule-based inhibitors e.g. [2, 3], but the success in developing therapeutically tractable compounds has been limited so far.

Here, we present the crystal structures and corresponding biochemical characterizations of our novel small molecule-based caPCNA inhibitors, which bind into the PIP-box binding pocket of PCNA. One of our lead compounds is now an investigational new drug that we observed selectively kills cancer cells, and it appears to induce replication stress, apoptosis and increase cancer cell sensitivity to genotoxic agents, while these effects are not observed in non-malignant cell controls. This caPCNA inhibitor is orally administrable, metabolic stable and it suppresses tumour growth as a monotherapy or as a combination treatment, and it has entered clinical trials in the United States. PCNA plays a critical role in temporarily dislodging RNA polymerase II from transcription replication conflict sites, to enable the replication fork to proceed. Thus, structure-based drug discovery approaches to target transcription replication conflict resolution machinery, such as PCNA protein, may open a novel therapeutic avenue for exploiting this cancer-selective vulnerability.


This research was supported by grants from the Department of Defense (W81XWH-11-1-0786), National Institutes of Health/National Cancer Institute (R01 CA121289), St Baldrick’s Foundation (www.stbaldricks.org, accessed on 6 October 2021), the Alex Lemonade Stand Foundation (Rich Award), Tobacco-Related Disease Research Program (TRDRP-T31IP626), Melanoma Research Foundation (MRF-717178), and the ANNA Fund (www.annafund.com, accessed on 6 October 2021) to L.H.M. as well as the the Department of Defense CDMRP Breast Cancer Research Program to R.J.H. (W81XWH-19-1-0326) and to J.J.P.P. (W81XWH-19-1-0327).