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Extended Abstract

Drugging the Undruggable: Inhibiting MYCN Signalling †

Jessica K. Holien [1,*], Michael W. Parker [1,2], Belamy B. Cheung [3,4,5] and Glenn M. Marshall [3,4,6]

1 St Vincent's Institute of Medical Research, Victoria 3065, Australia; mparker@svi.edu.au
2 Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville, Victoria 3010, Australia
3 Children's Cancer Institute Australia for Medical Research, Lowy Cancer Research Centre, UNSW Sydney, Kensington, NSW 2052, Australia; bcheung@ccia.org.au (B.C.); glenn.marshall@health.nsw.gov.au (G.M.)
4 School of Women's & Children's Health, UNSW Sydney, Randwick NSW 2031, Australia
5 School of Life Sciences and Technology, Tongji University, Shanghai 200092, China
6 Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW 2031, Australia
* Correspondence: jholien@svi.edu.au; Tel.: +61-9231-2633
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Neuroblastoma is the most common solid malignancy in early childhood, and advanced disease accounts for a disproportionately high mortality when compared with other child cancer types. The *MYCN* oncogene is amplified and overexpressed in 25% of patients with this embryonal childhood cancer. However, the design of MYC inhibitors has been hampered by the lack of globular functional MYC domains or deep protein 'pockets' for drug design. Moreover, MYC inhibitors carry a heightened potential for side-effects due to the dependency of most normal cells on transient MYC expression at entry into the cell cycle.

Enhanced MYCN protein stability is a key component of MYCN oncogenesis and is maintained by multiple feedforward expression loops involving MYCN transactivation target genes, regulated by multiple protein–protein and protein–DNA interactions. Therefore, using a combination of in silico, biochemical, in vitro, and in vivo studies, our multidisciplinary team has developed a program which has characterised protein–protein interactions responsible for MYCN protein stability in Neuroblastoma.

Furthermore, using structure-based drug design methods, we have designed potent and selective small molecules against these protein–protein interactions, which are active in our Neuroblastoma animal models. Here, I present an early stage drug discovery example of this approach.