proceedings

MDPI

Extended Abstract

Targeting Neuronal Transcription Factor BRN2 in Neuroendocrine Tumors †

Ravi Munuganti, Daksh Thaper, Sahil Kumar, Soojin Kim, Olena Sivak and Amina Zoubeidi *

Department of Urologic Sciences, Vancouver Prostate Centre, University of British Columbia, Vancouver, BC V6H3Z6, Canada

* Correspondence: azoubeidi@prostatecentre.com

† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 30 August 2019

Keywords: neuroendocrine cancer; computer-aided drug discovery; hit-to-lead optimization

No targeted therapies exist against aggressive neuroendocrine tumors; hence, these patients are limited to platinum-based chemotherapy that has not advanced in over three decades. These treatments are merely palliative, and patients generally die within one year. Recently, our group identified the neural transcription factor BRN2 as a major clinically relevant driver of neuroendocrine prostate cancer (NEPC), suggesting targeting BRN2 is a promising strategy to prevent neuroendocrine differentiation or treat NEPC. Moreover, further analysis uncovered that BRN2 expression plays a critical role in other neuroendocrine cancers, such as small-cell lung cancer (SCLC) and Ewing sarcoma (ES). Hence, using the integrated power of a computational drug discovery platform and biological testing, we identified first-in-field inhibitors for BRN2.

First, a homology model of BRN2 protein was generated to perform virtual screening. Based on computational predictions, promising hits were purchased and tested using a series of experiments. Cpd18, a lead BRN2 inhibitor, exhibited profound inhibition of BRN2 in transcriptional assay. Direct binding of Cpd18 to the BRN2 protein was determined by BLI assay. Furthermore, Cpd18 reduced the expression of the neuroendocrine genes SOX2 and NCAM1. Importantly, Cpd18 displayed anti-proliferative activity specifically in the patient-derived $BRN2^{hi}$ NCI-H660 and $42D^{ENZR}$ cells while displaying no effect on $BRN2^{low}$ CRPC cells. Moreover, Cpd18 also affected the growth of $BRN2^{hi}$ SCLC and ES cells, selectively. Since Cpd18 showed a promising activity profile, it was subjected to further structure-based lead optimization to enhance the potency and pharmacokinetic properties. Consequently, one of the derivatives Cpd18-94 demonstrated 2 μM anti-proliferative activity with an hour of stability in human liver microsomes and reduced the growth of NCI-H660 NEPC tumors significantly in xenograft models.

We anticipate that the developed drug prototypes will lay a foundation for the development of small-molecule therapies capable of combating highly aggressive and lethal form of neuroendocrine tumors.