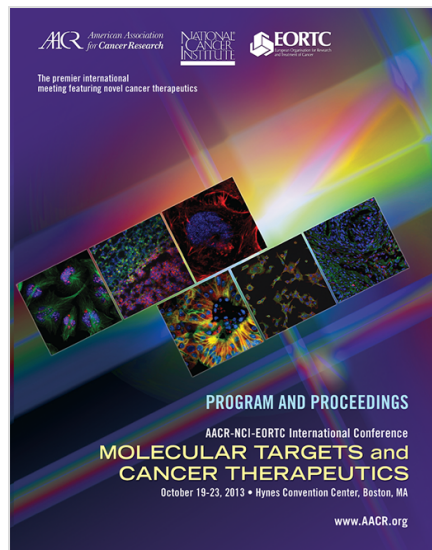




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Abstract

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Abstract B96: Design, synthesis and biological evaluation of a novel allosteric inhibitor of HSET that damages cancer cells with supernumerary centrosomes. **FREE**

Ciorsdaidh A. Watts; Frances M. Richards; Andreas Bender; Peter J. Bond; Oliver Korb; Oliver Kern; Michelle Riddick; Paul Owen; Rebecca M. Myers; Jordan Raff; Fanni Gergely; Duncan I. Jodrell; Steven V. Ley



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Abstract

Almost a century ago Theodor Boveri suggested that tumor cells differ from normal cells in their high incidence of centrosome amplification. However, only recently have new therapeutic strategies been explored in an attempt to exploit these differences and the role of kinesins in mitosis. Intense interest in the field has led to development of KSP and CENP-E inhibitors that have been tested clinically as treatments for human cancer. Success has been limited because both motor proteins are essential to normal mitosis and inhibition leads to mitotic arrest and associated neutropenia toxicity in normal cells. In contrast HSET is essential for survival of cancer cells with centrosome amplification and has been shown to be dispensable in normal cells. Hence, HSET inhibition offers a unique opportunity to selectively damage malignant cells with supernumerary centrosomes without affecting normal cells. In keeping with these findings we report discovery of a novel allosteric inhibitor of HSET, CW069, that does not disrupt division in normal human fibroblast cells, or in MCF-7 cells with normal centrosome numbers. In fact, CW069 induces multipolar mitosis exclusively in cancer cells with extra centrosomes, causing apoptosis via catastrophic aneuploidy.

The increased multipolar mitoses induced in N1E-115 cells by inhibitor CW069 recapitulates the phenotype described here, and by others, for siRNA depletion of HSET. The inhibitor also reduces cell growth and centrosome clustering in cancer cells with a lower incidence of centrosome amplification, including BT549 and MDA-MB-231 breast cancer cells. This is consistent with recent reports that depletion of HSET in DNA damage repair deficient cells may be lethal even to cancer cells with low-level centrosome amplification. Taken together, these data indicate that CW069 inhibition of HSET is not restricted to use in N1E-115 cells with high centrosome amplification, and could be broadly applicable to a range of human cancers. What is more, CW069 does not decrease the clonogenic capacity of primary adult human bone marrow cells, suggesting that it would not cause neutropenia toxicity in normal cells.

It is anticipated that HSET inhibition could have a greater therapeutic margin than KSP or CENP-E inhibition, and, to the best of our knowledge we have described the first allosteric inhibitor of HSET that reduces centrosome clustering but does not induce the mitotic phenotypes associated with inhibition of KSP or CENP-E. This selectivity for HSET is consistent with our computational model, which indicates that the HSET loop 5 displays dynamic conformational selection for CW069 that cannot be achieved by closely related KSP.

In summary, CW069 not only represents a substantial advance toward new cancer therapeutics, but also offers researchers a unique tool to unveil the full details of HSET function in mitosis.

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