Thermally triggered theranostics for pancreatic cancer


Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Copyright 2016 The Author.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
Conclusion: Our study shows that miR-625-3p induces oxaliplatin resistance by abrogating MAP2K6-p38 regulated apoptosis and cell cycle control networks, and corroborates the predictive power of miR-625-3p. This has significant clinical potential as the expression level of miR-625-3p, possibly combined with the expression level of MAP2K6, has the potential to serve as a predictive biomarker. Since ~20% of metastatic CRC patients have high miR-625-3p expression, the number of patients potentially benefiting from the use of miR-625-3p/MAP2K6 is substantial.

No conflict of interest.

586 The unique binding mode of NTRC 0066-0, a novel inhibitor of the spindle checkpoint kinase TTK (Mps1), leads to long target residence time and potently anti-tumor activity

G. Zaman1, J. Ultdelahag2, J. De Man2, N. Willemsen-Seegers2, J.G. Sterrenburg2, J. De Wit1, J. De Roos1, M. Prinsen3, R. Bijlsma4,5.
1Netherlands Translational Research Center B.V., Biology, Oss, Netherlands, 2Netherlands Translational Research Center B.V., Chemistry, Oss, Netherlands

Introduction: An abnormal number of chromosomes, or ‘aneuploidy’, is a common feature of solid human tumors and a predictor of poor prognosis in breast, lung, brain and colorectal cancer. Aneuploidy is caused by malfunctioning of the Spindle Assembly Checkpoint (SAC), a surveillance mechanism that ensures the fidelity of chromosome segregation. The protein kinase TTK (commonly referred to as Mps1) is a component of the SAC. Inhibition of TTK gene expression by RNA interference and inhibition of TTK kinase activity by small molecule kinase inhibitors causes chromosome missegregation and cancer cell death.

Materials and Methods: A novel class of compounds was identified that potently inhibits TTK enzyme activity and cancer cell line proliferation [1]. Its crystal structure, binding kinetics and cellular potency of NTRC 0066-0 were compared to that of other TTK inhibitors such as Mps1-IN-2, AZD-3146, Mps-BAY2b, Bay 1161909 as well as analogs from the NTRC 0066-0 series. This suggests that the unique binding mode of NTRC 0066-0 results in long target residence time which is most likely due to its strong anti-tumor activity. In subsequent mouse xenograft models of human cancer cell lines, NTRC 0066-0 inhibited tumor growth as a single agent after oral administration at 20 mg per kg.

Conclusions: NTRC 0066-0 is a novel TTK inhibitor with outstanding in vitro properties and potent anti-tumor activity in mouse xenograft models. Our data suggest that long target residence time corresponds with potent cellular activity for TTK inhibitors.

Reference(s)

No conflict of interest.