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Thermally triggered theranostics for pancreatic cancer

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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.

585 Gli1/DNA interaction is a druggable target for Hedgehog-dependent tumors

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Background: Hedgehog (Hh) pathway is essential for tissue development and stemness, and when deregulated leads to tumorigenesis. Although many Hedgehog-driven human cancers involve upstream pathway activation (i.e. either loss-of-function of the receptor Ptch1 or gain-of-function mutations of the transmembrane transducer Smo), Smo-independent hyperactivation of the downstream Gli transcription factor is responsible for the development of several tumors and resistance to therapy. This raises the need to identify novel Gli1 inhibitors, a challenging issue mostly due to the lack of information on the structural requirements of Gli1/DNA interaction.

Material and Methods: Molecular characterization of Gli1/DNA binding was performed by a mix of computational and experimental structure-based *in vitro* studies. Molecular dynamics simulations were carried out to identify the residues in Gli1 zinc-finger involved in DNA binding. The data obtained were then used to set up the docking-based virtual screening of a natural products library available in house, with the aim to discover pharmacological agents able to interfere with Gli1/DNA interaction. The molecules identified as potential Gli1 inhibitors were investigated for their functional activity through a Gli-dependent luciferase reporter screening assay. The most active was tested for its effectiveness to counteract Hh-dependent tumor growth by medulloblastoma and basal cell carcinoma allograft model from Ptch+/- mice and orthotopic medulloblastoma xenograft.

Results: We identified a small molecule, Glabrescione B (GlaB), an isoflavone naturally found in the seeds of *Derris glabrescens* (Leguminosae), able to impair Gli1/DNA binding as revealed by Chip and EMSA assays. In agreement with these molecular results, GlaB revealed great antitumor efficacy. Indeed, we observed that GlaB strongly inhibited the growth of Hedgehog-dependent tumor cells *in vitro* and *in vivo* as well as the self-renewal ability and clonogenicity of tumor-derived stem cells.

Conclusions: Our study highlighted the relevance of structural details of Gli1/DNA interaction as a promising tool to discover small molecules able to inhibit Hh pathway by directly targeting Gli1. Here we identified GlaB as a potent and specific Gli1 inhibitor able to interfere with Gli1/DNA binding, resulting in the inhibition of Hh-dependent tumor cells and cancer stem cells growth, thus becoming a profitable pre-clinical candidate.

No conflict of interest.

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

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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.

Material and Method: A novel class of compounds was identified that potently inhibits TTK enzyme activity and cancer cell line proliferation [1]. Its binding mode and that of reference inhibitors was characterized by protein crystallography. Binding kinetics and target residence time were determined by surface plasmon resonance. Anti-proliferative activity was measured on a broad panel of cancer cell lines [2,3].

Results and Discussion: The clinical candidate, NTRC 0066-0, inhibits TTK with subnanomolar potency (IC50) in a kinase enzyme assay and is more than 200 times selective over 276 kinases examined, including mitotic and cell

cycle dependent kinases (CDKs). X-ray structures of the TTK kinase domain in complex with NTRC 0066-0 and analogs indicate that this class of compounds induces a large conformational shift in the glycine-rich loop, invoking an inactive kinase conformation. In surface plasmon resonance experiments, NTRC 0066-0 exhibited slow dissociation kinetics, resulting in a long target residence time. Parallel surface plasmon resonance experiments confirmed the exquisite selectivity of NTRC 0066-0 for TTK over Aurora and Polo-like kinases. NTRC 0066-0 inhibited the proliferation of a wide variety of human cancer cell lines in the same potency range as marketed cytotoxic agents. The 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 contributes 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)

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Conflict of interest: Ownership: I am a shareholder of Netherlands Translational Research Center B.V. (NTRC). Board of Directors: I am a managing director of Netherlands Translational Research Center B.V. (NTRC). Other Substantive Relationships: I am a co-founder of Netherlands Translational Research Center B.V. (NTRC).

587 Thermally triggered theranostics for pancreatic cancer

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Background: Pancreatic cancer is the 4th most aggressive cancer in the western world with less than 34% of patients surviving past 5 years. Lack of specific symptoms results in delayed diagnosis. Theranostics are new platforms, which offer simultaneous diagnosis and therapy resulting in a decrease in treatment time. Here treatments are conjugated onto diagnostics by stimuli responsive binding allowing for controlled drug release resulting in a rapid and localised clinical effect. Hybrid nanoparticles are composed of an iron oxide core surrounded by a rigid gold shell. These particles undergo manipulation due to inherent magnetism of the core whilst laser irradiation of their gold shell results in localised heating due to surface plasmon resonance. Hence, they can be utilised as diagnostics using MRI and laser irradiation can be used as a trigger for drug release.

Methods: Proof of concept studies have been carried out using a novel bisnaphthalamido (BNIP) based drug series. BNIPs are a series of novel compounds, which have exhibited exciting potential as chemotherapy agents. HNPs were fabricated and characterised using PCS, TEM, MRI, SQUID and zeta potential measurement. Drug conjugation and release was quantified using reverse phase HPLC. Cellular response and cytotoxicity assays were carried out using trypan blue exclusion, MTT assay and atomic force microscopy.

Results and Discussion: In our studies, we designed hybrid nanoparticles (50 nm) capable of drug loading onto their surface (3:1:0.25, Drug:Fe:Au). By exploiting the gold surface-to-drug interaction of a range of novel Bisnaphthalamido based agents a system with heat triggered drug release was produced. *In vitro* studies of these formulations showed the novel formulations possess a 10-fold lower IC50 value when compared with the free drug after only 24 h. These cytotoxicity studies combined with cellular uptake studies showed the formulations to be significantly more effective compared with gemcitabine. *In vivo* trials have commenced to further elucidate their viability for use as theranostics.

Conclusion: These data highlight the potential of HNPs as dual imaging agents and contrast agents for pancreatic cancer therapy.

No conflict of interest.