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Magnetic localization of magnetically-responsive nanoparticles to human ovarian carcinoma peritoneal xenografts

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Background: Peritoneal carcinomatosis is present in the majority of newly-diagnosed stage III-IV ovarian cancers. Following surgical debulking, treatment with taxane- and platinum-containing regimens is standard chemotherapy (CTX). Clinical trial results have demonstrated the advantage of intraperitoneal (i.p.) rather than i.v. CTX, as the i.p. route lead to improvements in lifespan of 16 months. We hypothesize that development of tumor-targeted CTX would lead to even greater therapeutic gain. Magnetically-responsive nanoparticles (MNPs) merit candidacy as drug carriers for such targeted CTX, using an external magnetic field to direct the MNPs to i.p. tumor foci where CTX could be released.
Materials, Methods, and Results: We first demonstrated the feasibility of magnetically vectoring MNPs within the mouse peritoneum. Silica-coated, magnetite-based ~15−20 nm MNPs were injected i.p. into mice at their midline; then a 5600 Gauss ~22 mm cylindrical magnet was placed on the side of the abdomens of the anesthetized mice for up to 2 hr. Coronal magnetic resonance (MR) images of the abdomens revealed that the MNP distribution became skewed toward the juxtaposed magnet, compared to images of control, non-vectored mice. Next, we attempted to direct MNPs to i.p.-implanted HEY human ovarian carcinoma xenografts, using either the cylindrical magnet or a pyramid-shaped magnet with its ~3 mm tip placed over the tumor injection site. Sagittal MR images indicated that while both magnets induced MNP movement to the tumor/peri-tumoral environment, the latter magnet achieved greater selectivity with less evidence for MNP accumulation toward the normal abdominal wall. Further, peritoneal magnetic localization could be achieved with either i.p. or i.v. administration of the MNPs.
Conclusions: MNPs can be magnetically directed to the tumor/peri-tumoral microenvironment in this ovarian xenograft model, a significant prelude to ongoing evaluation of the anti-tumor efficacy of CTX-loaded MNPs to treat carcinomatosis.

Drug design and synthesis

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Pharmacological profile of SB939, a novel, potent and orally active histone deacetylase inhibitor

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Histone deacetylases (HDAC) regulate a number of genes involved in cell proliferation and differentiation, cell cycle progression and the cell survival pathway and high expression of HDAC proteins is associated with tumorigenesis. Some small molecule HDAC inhibitors have been developed and shown to induce tumor cell cytostasis, differentiation and apoptosis in experimental models and efficacy in clinical trials in various hematological malignancies following intravenous administration. SB939 is a novel HDAC inhibitor with improved *in vivo* properties compared to other HDAC inhibitors currently in clinic trials, allowing oral dosing.
SB939 inhibits HDAC class I and II enzymes (Ki below or equal to 30 nM). In a similar concentration range, it significantly increases histone 3 (H3) and tubulin acetylation as well as enhances p21 expression. SB939 exerts potent anti-proliferative effects against a broad range of human tumor cell lines. Tumor cells are arrested at G_0/G_1 and/or G_2/M phase, followed by induction of apoptotic cell death.
In contrast to other compounds in clinical trials, SB939 has excellent pharmacokinetic properties. The oral anti-tumor activity of SB939 was studied in HCT116 tumor bearing nude mice. After daily oral administration for 14 days at 25, 50, 75 and 100 mg/kg, SB939 induced tumor growth inhibition (TGI) of 41%, 69%, 93% and 104%, respectively. SB939 was well tolerated in all experiments. SB939 increased the level of acetylation of histone H3 in the tumor tissue for up to 24 h at the 50 mg/kg dose, confirming its long lasting and potent target inhibition. Similar efficacy and tolerability have been observed in other tumor models.
These data demonstrate that SB939 is a potent and effective anti-tumor drug with potential as an oral therapy for a variety of human hematological and solid tumors.

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Characterization of novel Smac mimetics as highly potent and effective antagonists of X-linked inhibitor of apoptosis protein

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Background: X-linked inhibitor of apoptosis protein (XIAP) suppresses apoptosis in cells by binding to and inhibiting an initiator caspase-9 and effector caspases -3 and -7. XIAP represents a promising new molecular target for anticancer drug design. We have designed and synthesized a novel class of non-peptidic Smac mimetics that function as highly efficient antagonists of XIAP in cell-free assays and inducers of apoptosis in cancer cells.
Material and Methods: We present herein our detailed characterization of novel non-peptidic Smac mimetics that are highly antagonistic of XIAP activity as measured by biochemical and cell-free functional assays. We describe our initial evaluation of their activity in inhibition of cell growth and in induction of cell death in a panel of human cancer cell lines.
Results: In fluorescence-polarization-based binding assays our designed Smac mimetics bind to XIAP with low nanomolar affinity (IC_{50} values = 1–5 nM) that is 1000-times more potent than the Smac AVPI peptide. In cell-free functional assays, these Smac mimetics are highly effective in antagonizing XIAP as measured by the restoration of caspase-9, as well as caspase-3 and -7 activities, being 100-times more potent than the Smac AVPI peptide. We have further probed their mode of action in binding to XIAP through biochemical binding assays and gel filtration experiments using different XIAP constructs. These Smac mimetics are extremely potent cell growth inhibitors, achieving IC_{50} values less than 1 nM in a panel of human cancer cell lines, and inducing strong and rapid apoptosis at concentrations as low as 1 nM in cancer cells. Of significance, they show minimal toxicity to normal cells.
Conclusions: Our studies demonstrate that our Smac mimetics bind to XIAP with very high affinities and are extremely potent and effective antagonists of XIAP. In addition, they promote apoptosis in cancer cells with an outstanding selectivity over normal cells. Our results suggest that these potent Smac mimetics have promising therapeutic potential to be developed as a new class of anticancer agents.

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In vitro and in vivo evaluation of orally available potent and selective small-molecule antagonists of the MDM2-p53 interaction in multiple models of human cancer

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Introduction: Activation of p53 function using a non-peptidic small-molecule inhibitor of the MDM2-p53 interaction is currently being intensely pursued as a new and exciting therapeutic strategy for the treatment of human cancer. To date, no small-molecule inhibitor of the MDM2-p53 interaction has advanced into human clinical trials. Herein, we report extensive *in vitro* and *in vivo* evaluations of a class of ultra-potent, non-peptidic, small-molecule inhibitors of the MDM2-p53 interaction in multiple models of human cancer.
Results: **MI-63** (Ding et al. J Med Chem 2006; 49: 3432–3435) and its analogues were designed as a new class of potent and specific non-peptidic small-molecule inhibitors of the MDM2-p53 interaction. **MI-63** and its most potent analogues bind to MDM2 with K_i values of 1–3 nM in a competitive fluorescence-polarization-based binding assay, being 1000-times more potent than the natural p53 peptide and >10 times more potent than Nutlin-3. **MI-63** is highly effective in inhibition of cell growth, as determined by a water soluble tetrazolium (WST)-based assay, and in induction of cell death as measured by flow cytometric analysis in breast, prostate, lung, colon, melanoma, head-neck and osteosarcoma cancer cell lines with wild-type p53. Importantly, **MI-63** induces cell cycle arrest, but not cell death, in normal cells. Using the p53 wild-type/p53 knock-out isogenic HCT-116 colon cancer model and the p53 knock-down RKO colon cancer model by RNA interference, we have conclusively demonstrated that the growth inhibition, cell cycle arrest and apoptosis induced by **MI-63** and its potent analogues absolutely depends upon the presence of functional p53. Our mechanistic studies provide clear evidence that **MI-63** and its potent analogues have a mechanism of action highly consistent with targeting the MDM2-p53 interaction. Our *in vivo* studies demonstrate that **MI-63** and its potent analogues activate p53 in tumor tissues in multiple xenograft models of human cancer, consistent with their *in vitro* cellular mechanism of action.