Intracellular Targeting of the Oncogenic MUC1-C Protein with a Novel GO-203 Nanoparticle Formulation

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Abstract

Purpose: The MUC1-C oncoprotein is an intracellular target that is druggable with cell-penetrating peptide inhibitors. However, development of pepidyl drugs for treating cancer has been a challenge because of unfavorable pharmacokinetic parameters and limited cell-penetrating capabilities.

Experimental Design: Encapsulation of the MUC1-C inhibitor GO-203 in novel polymeric nanoparticles was studied for effects on intracellular targeting of MUC1-C signaling and function.

Results: Our results show that loading GO-203 into tetrablock polyalactic acid (PLA)-polyethylene glycol (PEG)-polypolypropylene glycol (PPG)-PEG copolymers is achievable and, notably, is enhanced by increasing PEG chain length. In addition, we found that release of GO-203 from these nanoparticles is controllable over at least 7 days. GO-203/nanoparticle treatment of MUC1-C–positive breast and lung cancer cells in vitro was more active with less frequent dosing than that achieved with nonencapsulated GO-203. Moreover, treatment with GO-203/nanoparticles blocked MUC1-C homodimerization, consistent with on-target effects. GO-203/nanoparticle treatment was also effective in downregulating TIGAR, disrupting redox balance, and inhibiting the self-renewal capacity of cancer cells. Significantly, weekly administration of GO-203/nanoparticles to mice bearing syngeneic or xenograft tumors was associated with regressions that were comparable with those found when dosing on a daily basis with GO-203.

Conclusions: These findings thus define an effective approach for (i) sustained administration of GO-203 in polymeric PLA-(PEG-PPG-PEG) nanoparticles to target MUC1-C in cancer cells and (ii) the potential delivery of other anticancer peptide drugs.

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Introduction

The mucin 1 (MUC1) heterodimeric protein is aberrantly overexpressed by breast, lung, and other types of carcinomas and has been recognized as an attractive cancer target (1, 2). Studies on the oncogenic function of MUC1 were advanced by the demonstration that MUC1 consists of two subunits (1). The transmembrane MUC1-C subunit interacts with receptor tyrosine kinases, such as EGFR and HER2, at the cell membrane and contributes to activation of their downstream signaling pathways (3–5). The MUC1-C cytoplasmic domain interacts with the WNT pathway effector, β-catenin, and promotes the activation of WNT target genes in a nuclear complex with TCF7L2/TCF4 (5–7). MUC1-C also interacts with additional transcription factors, including NF-κB and STAT3, in the regulation of gene expression (8). The involvement of MUC1-C with effectors that have been linked to transformation (5) and the demonstration that MUC1-C drives self-renewal of cancer cells (8–10) have provided support for the development of agents that block MUC1-C function. In this respect, the MUC1-C cytoplasmic domain contains a CQC motif that is necessary and sufficient for MUC1-C homodimerization (5). In addition, mutation of the CQC motif to AQA blocks the capacity of MUC1-C to interact with diverse effectors and function as an oncoprotein (11). Based on these observations, a novel class of cell-penetrating peptides was developed to bind to the CQC motif and thereby block MUC1-C homodimerization and signaling (12, 13). The MUC1-C–targeted peptides induce death of MUC1-expressing cancer cells in vitro and inhibit growth of established tumor xenografts in mice (12, 14, 15). As shown for other small therapeutic peptides (16), the MUC1-C inhibitor peptides exhibited short circulating half-lives and thus required daily administration for sustained inhibition of tumor growth in mouse models (12, 14, 15). These findings provided the basis for phase I evaluation of the lead MUC1-C inhibitor peptide, designated GO-203, in patients with refractory solid tumors.

Cell-penetrating anticancer peptides are emerging as promising agents to target intracellular proteins that are otherwise undruggable with small-molecule inhibitors. For example, peptide drugs are under preclinical development to target proteins devoid of ATP-binding pockets, such as survivin (17), β-catenin (18), HDM2 (19), STAT3 (20), E2F (21), and...
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Tumor spheres

Cells were harvested with gentle trypsinization, washed, and resuspended in MammoCult Human Medium ( Stem Cell Technologies). Single cells were confirmed under a microscope, counted, seeded in 6-well ultralow attachment culture plates (Corning Costar), and cultured for 5 days. Tumor spheres of $\geq 100 \ \mu m$ were visualized and scored using a Nikon inverted TE2000 microscope. Sphere-forming efficiency (SFE) was calculated by dividing the number of tumor spheres by the number of suspended cells.

Assessment of antitumor activity

Mouse Ehrlich breast tumor cells were injected s.c. in the hind limb of syngeneic Balb/c mice (17–22 g). Mice bearing tumors (~40 mm$^3$) were divided into groups of 10 mice each and treated i.p. (i) each day with vehicle control or 15 mg/kg GO-203 for 21 days, or (ii) once each week with 10, 15, or 20 mg/kg GO-203/nanoparticles for 3 weeks. Four- to 6-week-old Balb/c nu/nu mice were injected subcutaneously with $5 \times 10^6$ ZR-75-1 cells in the flank. Mice with established ZR-75-1 tumors (90–120 mm$^3$) were randomized into groups of 6 mice each and treated i.p. (i) each day with vehicle control or 18 mg/kg GO-203 for 21 days, or (ii) once each week with vehicle control or 20 mg/kg GO-203/nanoparticles for 3 weeks. Tumors were measured every other day with calipers, and tumor volumes were calculated using the formula $(A \times B^2) \times 0.5$, where $A$ and $B$ are the longest and shortest tumor diameters, respectively. Statistical analysis of tumor volumes was performed by one-way ANOVA and the Dunnett test using Origin 8.0 (Origin Lab).

Results

Encapsulation of GO-203 into nanoparticles

Polymeric nanoparticles are being increasingly used for the delivery of small molecules (24, 31, 32); however, the experience with encapsulation of peptidyl drugs into nanoparticles is presently limited and will probably be dictated by the characteristics of the specific peptides under investigation. The present studies have focused on encapsulation of the MUC1-C inhibitor GO-203 peptide into tetrablock polymeric nanoparticles comprised of copolymers of PLA modified with polyethylene glycol (PEG)-polypropylene glycol (PPG) (PEG-PPG-PEG)$^{12,3K}$ (25). GO-203 is an all D-amino acid peptide that consists of a poly-R transduction domain linked to a CQCRRKN motif that binds to the MUC1-C cytoplasmic tail and blocks MUC1-C homodimerization (refs. 13, 15; Fig. 1A). Encapsulation of GO-203 into the core of the nanoparticles was increased by PEG modification (Supplementary Table S1). Thus, the encapsulation efficiency of GO-203 in PLA-PEG$_{4000}$ nanoparticles was higher than that obtained with PLA-PEG$_{600}$ nanoparticles (Supplementary Table S1). We also found that increases in PEG chain length improved the GO-203 encapsulation efficiency (Supplementary Table S1). We next studied the kinetics of GO-203 release from PLA-(PEG-PPG-PEG)$_{12,3K}$ nanoparticles. At pH 7.4, the percentage release per day of the encapsulated GO-203 decreased from approximately 15% on day 1 to approximately 4% on day 5, and then slowly declined over the next 55 days (Fig. 1B). In terms of cumulative release, over 50% of the encapsulated GO-203 was released by day 7 (Fig. 1C). These findings collectively provided support for prolonged kinetics of GO-203 release at physiologic pH. Accordingly, subsequent studies were performed with GO-203 encapsulated in PLA-(PEG-PPG-PEG)$_{12,3K}$ nanoparticles (GO-203/nanoparticles).

Treatment with GO-203/nanoparticles decreases survival of breast cancer cells

GO-203 is effective in inducing death of MUC1-expressing breast and other types of cancer cells (3, 15, 33, 34). To determine whether encapsulated GO-203 is also effective in inhibiting cell viability, we first treated ZR-75-1 breast cancer cells with 7.5 μmol/L GO-203/nanoparticles. In these studies, a single exposure to GO-203/nanoparticles on day 0 was associated with loss of survival as detected on day 3 (Fig. 2A, left). By contrast,
treatment with empty nanoparticles had little if any effect on cell viability (Fig. 2A, left). Similar results were obtained when MDA-MB-468 breast cancer cells were treated once with 7.5 μmol/L GO-203/nanoparticles or empty nanoparticles and analyzed on day 3 (Fig. 2A, right), confirming that GO-203 is active when delivered from nanoparticles. Moreover, treatment once with 7.5 μmol/L GO-203/nanoparticles was more effective than exposure to 2.5 μmol/L GO-203 (nonencapsulated) each day for 3 days (Fig. 2A, right). Based on these results, we explored the effects of GO-203/nanoparticles and nonencapsulated GO-203 at different doses and schedules. In this way, we compared treatment of ZR-75-1 cells with 2.5 μmol/L GO-203/nanoparticles or 2.5 μmol/L GO-203 on days 0 and 3 (Fig. 2B, left). Analysis of the cells on day 7 showed that the GO-203/nanoparticles are more effective than GO-203 (Fig. 2B, left). Treatment of MDA-MB-468 cells with 5 μmol/L GO-203/nanoparticles or GO-203 on days 0 and 3 further demonstrated that loss of survival was greater with GO-203/nanoparticles, as compared with GO-203, treatment (Fig. 2B, right).

To extend this analysis, BT-20 breast cancer cells were treated on day 0 with 7.5 or 10 μmol/L GO-203/nanoparticles or equal amounts of empty nanoparticles (Fig. 2C). As an additional control, cells were treated with nanoparticles containing a peptide (CP-2) that consists of poly-R linked to AQARRKN (Fig. 1A), which is inactive in binding to the MUC1-C cytoplasmic domain and ineffective in killing MUC1-expressing cells (3, 15, 33, 34). As analyzed on day 3, treatment with GO-203/nanoparticles was associated with a significant loss of survival as compared with that obtained with empty nanoparticles, which had little if any effect (data not shown) or with CP-2/nanoparticles (Fig. 2C). Moreover, treatment with 2.5 or 3.3 μmol/L unencapsulated GO-203 on days 0, 1, and 2 was clearly less effective than exposure to the same amounts of GO-203 in nanoparticles that was administered once (Fig. 2C). In contrast with these results, a similar study performed on MUC1-negative HCT116 cells demonstrated no significant difference in survival upon treatment with GO-203/nanoparticles, CP-2/nanoparticles, or unencapsulated GO-203 (Fig. 2D). These findings indicated that GO-203–induced loss of cell viability is more effective when delivered in nanoparticles and is selective for MUC1-positive cells.

GO-203/nanoparticles disrupt MUC1-C homodimerization and disrupt redox balance in breast cancer cells

Targeting MUC1-C with unencapsulated GO-203 induces death of carcinoma cells by blocking MUC1-C homodimerization and thereby disrupting redox balance (13, 15). To determine whether delivery of GO-203 in nanoparticles induces similar effects, we first treated ZR-75-1 cells with GO-203/nanoparticles and monitored effects on MUC1-C homodimerization. As found with nonencapsulated GO-203 (13), treatment with GO-203/nanoparticles was associated with inhibition of MUC1-C homodimer formation (Fig. 3A), indicating that delivery of GO-203 in nanoparticles to these carcinoma cells results in MUC1-C targeting. MUC1-C promotes expression of the p53-inducible regulator of glycolysis and apoptosis (TIGAR; ref. 35), which shunts glucose-6-phosphate into the pentose phosphate pathway (PPP; ref. 36). Consistent with targeting MUC1-C, we found that treatment of ZR-75-1 cells with GO-203/nanoparticles is associated with suppression of TIGAR levels (Fig. 3B). Moreover, addition of the antioxidant N-acetylcysteine (NAC) blocked GO-203/nanoparticle-induced TIGAR suppression (Fig. 3B), in concert with a ROS-mediated mechanism. TIGAR promotes the production of NAPDH and GSH by the PPP (36). In this way, targeting MUC1-C with GO-203/nanoparticles was also associated with marked decreases in NAPDH (Fig. 3C, left) and GSH (Fig. 3C, right).
levels. Moreover, and consistent with these results, we found that treatment with GO-203/nanoparticles, but not CP-2/nanoparticles, results in induction of phospho-p38 (Fig. 3D), which is activated in response to disruption of redox balance (37).

GO-203/nanoparticles are effective against non–small cell lung cancer cells

Non–small cell lung cancer (NSCLC) cells are also sensitive to GO-203 treatment (15). Accordingly, we asked if NSCLC cells respond similarly to GO-203/nanoparticles. Indeed, GO-203/nanoparticle treatment of H1975 NSCLC cells, which harbor the EGFR(L858R/T790M) mutations, was associated with loss of viability (Fig. 4A, left). Other studies performed with H460/KRAS(Q61H) NSCLC cells further demonstrated that GO-203/nanoparticles are active in the setting of mutant KRAS expression (Fig. 4A, right). By contrast, exposure of H1975 and H460 NSCLC cells to empty nanoparticles was associated with substantially lower levels of cell death that were not significantly different from those obtained for ZR-75-1 and MDA-MB-468 breast cancer cells (Fig. 2A, left and right). As shown for breast cancer cells, we also found that treatment of H1975 cells with GO-203/nanoparticles is associated with disruption of MUC1-C homodimers (Fig. 4B, left). Moreover, GO-203 treatment resulted in downregulation of TIGAR (Fig. 4B, right) and decreases in NADPH (Fig. 4C, left) and GSH (Fig. 4C, right) levels. Treatment of H1975 cells with GO-203/nanoparticles was also associated with activation of p-p38 (Fig. 4D), confirming that delivery of GO-203 in nanoparticles is effective in disrupting redox balance.

GO-203/nanoparticles inhibit breast and lung cancer cell self-renewal

Disruption of redox balance inhibits the capacity of cancer cells to undergo self-renewal (38). Accordingly, we first investigated the effects of GO-203/nanoparticles on clonogenic survival of ZR-75-1 cells. Treatment with the GO-203/nanoparticles, but not the empty nanoparticles, was highly effective in inhibiting colony formation (Fig. 5A, left). Similar results were obtained with GO-203/nanoparticle treatment of MDA-MB-468 (Fig. 5A, middle) and MCF-7 (Fig. 5A, right) cells, indicating that GO-203/nanoparticle exposure is sufficient to inhibit clonogenic survival of breast cancer cells. The formation of spheres under nonadherent conditions and in the absence of serum selects for the growth of self-renewing cancer stem–like cells (CSC) that survive anoikis (39, 40). Therefore, to determine if the GO-203/nanoparticles are active against self-renewing populations, MDA-MB-468 cells were treated with GO-203/nanoparticles or CP-2/nanoparticles for 48 hours and then grown in mammosphere medium in the absence of nanoparticles. As expected from previous studies (9), the control MDA-MB-468 cells formed mammospheres (Fig. 5B). Moreover, treatment with GO-203/nanoparticles, but not CP-2/nanoparticles, was highly effective in inhibiting mammosphere formation and decreasing SFE (Fig. 5B). GO-203/nanoparticles also inhibited MCF-7 mammosphere formation (Fig. 5C). The results were consistent with those obtained for breast cancer cells, and confirm previous reports by our group and others that GO-203 treatment results in an increase in NADPH and GSH levels (37). In the mammosphere assay, the decrease in SFE could represent the inhibition of tumorigenic cells, which are highly sensitive to GO-203/nanoparticles, or to the inhibition of CSC renewal. In a previous report, we showed that GO-203 treatment downregulates TIGAR and increases NADPH and GSH in breast cancer cells, and these effects are also observed in mammosphere cultures (37). It is possible that the increase in NADPH and GSH and the decrease in TIGAR could be sufficient to block CSC self-renewal, but further experiments are required to determine the mechanism of action of GO-203 in inhibiting mammosphere formation.
supporting the activity of GO-203/nanoparticles against self-renewing breast cancer cells.

In investigating the effects of GO-203/nanoparticles against clonogenic NSCLC cell populations, we found that GO-203/nanoparticles completely inhibited H1975 (Supplementary Fig. S1A) and H460 (Supplementary Fig. S1B) colony formation. Moreover, GO-203/nanoparticle treatment blocked growth of H1975 (Supplementary Fig. S1C) and H460 (Supplementary Fig. S1D) cells as spheres, indicating that encapsulation of GO-203 in nanoparticles is effective in inhibiting self-renewal of NSCLC cells.

GO-203/nanoparticles inhibit tumor growth

To investigate whether GO-203/nanoparticles are effective in inhibiting growth of human tumor xenografts in nude mice, we first performed studies in Balb/c mice bearing established subcutaneous syngeneic Muc1-positive Ehrlich breast tumors. In this model and consistent with previous studies of human tumor xenograft models (15), treatment with nonencapsulated GO-203 was associated with inhibition of Ehrlich tumor growth (Fig. 6A). Based on the kinetics of GO-203 release from the nanoparticles over 7 days (Fig. 1C), we treated the Ehrlich tumor–bearing mice i.p. once a week for 3 weeks with doses of 10, 15, or 20 mg/kg GO-203/nanoparticles (Fig. 6B). As compared with the control mice, treatment with 10 mg/kg GO-203/nanoparticles was associated with partial slowing of Ehrlich tumor growth (Fig. 6B). By contrast, i.p. dosing of 15 and 20 mg/kg GO-203/nanoparticles resulted in complete inhibition of Ehrlich tumor growth, supporting a dose–response effect (Fig. 6B). In previous studies of nude mice bearing subcutaneous NSCLC xenografts, treatment with nonencapsulated 30 mg/kg GO-203 i.p. daily for 21 days was associated with complete regressions (15). In the present work, i.p. administration of GO-203 each day at a dose of 15 mg/kg was also effective in the treatment of ZR-75-1 xenografts (Fig. 6C). Notable findings in these experiments were that treatment with GO-203 on a weekly or twice-weekly schedule had little, if any, effect on ZR-75-1 tumor growth, indicating that frequent (daily) dosing is necessary for activity (data not shown). By comparison, weekly treatment of ZR-75-1 xenografts with GO-203/nanoparticles at a dose of 20 mg/kg was highly effective in inducing tumor regressions (Fig. 6D). Significantly, there was no overt evidence of toxicity, such as weight loss, associated with GO-203/nanoparticle administration. These findings thus support the notion that delivery of GO-203 in nanoparticles requires less frequent administration and lower total doses than that needed for equivalent antitumor activity when treating with nonencapsulated GO-203.

Discussion

The oncogenic MUC1-C protein is aberrantly expressed in carcinomas of the breast, lung, and other epithelia (1, 5). In addition, recent evidence has supported a role for MUC1-C in promoting the epithelial–mesenchymal transition and other characteristics of CSCs (8, 9). These findings have collectively provided the rationale for developing therapeutic approaches that target MUC1-C function. The present studies have identified a novel strategy for targeting MUC1-C in carcinoma cells by
intracellular delivery of the peptidyl MUC1-C inhibitor, GO-203, in polymeric nanoparticles. Cell-penetrating peptides have emerged as promising therapeutics because of their potential for targeting intracellular proteins that lack hydrophobic pockets and thereby are often undruggable with small molecules. Moreover, peptidyl drugs have the potential for inhibiting intracellular proteins with greater specificity and less off-target toxicity than small molecules (41, 42). Nonetheless, the development of peptidyl drugs can be hampered by poor pharmacologic properties, such as short circulating half-lives, that require frequent administration (16). Therapeutic peptides can also be limited by extracellular degradation and inefficient cell-penetrating capabilities. Accordingly, the present work first investigated whether GO-203 could indeed be loaded into nanoparticles.

There is presently limited information about the optimal conditions for encapsulating peptides into polymeric nanoparticles, and the copolymers used will likely vary depending on the peptidyl drug itself. The approach we used in the present work was based upon a recent experience in which we encapsulated the anticancer peptide NuBCP-9 into tetrablock PLA-(PEG-PPG-PEG)_{12.5K} copolymers (25). The PLA-PEG copolymer is a bilayer structure with a PLA hydrophobic core and a PEG hydrophilic shell interacting with the aqueous medium. The importance of the tetrablock structure is that conjugation of PEG-PPG-PEG with PLA extends the hydrophobic core and thereby has the capacity for increasing peptide uptake and sustaining its release (25). The PLA-PEG-PPG-PEG formulation was thus selected based on the findings demonstrating that (i) peptide encapsulation is greater than that obtained with PLA, and (ii) peptide release is more sustained compared with that found for the PLA-PEG nanoparticles (25). Indeed, as compared with PLA-based nanoparticles, we found that loading of GO-203 is increased with PLA-PEG-PPG-PEG nanoparticles. We also found that approximately 50% of the GO-203 encapsulated into PLA-PEG-PPG-PEG nanoparticles is released over 7 days at physiologic pH, which appeared to be favorable kinetics when considering that an objective of delivering GO-203 in nanoparticles to cancer cells would be prolonged intracellular exposure of endogenous MUC1-C to this agent.

Nonencapsulated GO-203 is effective in inducing death of MUC1-positive carcinoma cells in vitro when low micromolar concentrations are added each day to the medium over 4 to 6 days (15). Importantly, the present studies show that encapsulation of GO-203 in nanoparticles is also effective in killing breast and lung cancer cells, indicating that loading of GO-203 into nanoparticles is not associated with loss of activity. Indeed, we found that treatment with the GO-203/nanoparticles is even more effective than that obtained with nonencapsulated GO-203 at equivalent doses. Moreover, delivery of GO-203 in nanoparticles required
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of cancer cells to 7.5 µmol/L GO-203/nanoparticles was far more active in inducing cell death than treatment with 2.5 µmol/L GO-203 each day for 3 days (Fig. 3E). GO-203 blocks MUC1-C homodimerization by targeting the MUC1-C CQC motif (13). As confirmation that GO-203 functions similarly when loaded into nanoparticles, we found that treatment with GO-203/nanoparticles also inhibits the formation of MUC1-C homodimers, supporting similar effects on MUC1-C targeting. Studies in malignant hematopoietic cells that express MUC1-C have demonstrated that GO-203 treatment downregulates TIGAR and thereby induces redox imbalance by decreasing NADPH and GSH levels (35, 43). The present results extend these observations to breast and lung cancer cells by demonstrating that treatment with GO-203 and GO-203/nanoparticles also suppresses TIGAR expression in association with decreases in NADPH and GSH. The GO-203–induced signals responsible for TIGAR downregulation in carcinoma cells will require further study; however, these observations further indicate that GO-203/nanoparticles induce loss of self-renewal in association with disruption of redox balance. In concert with this notion, GO-203/nanoparticles were highly effective in inhibiting clonogenic survival and tumor sphere formation of breast and lung cancer cells. Taken together, these findings indicate that encapsulation of GO-203 in nanoparticles is an effective approach for the delivery of GO-203 to cancer cells and that GO-203/nanoparticles function similarly to GO-203 in terms of inhibiting MUC1-C homodimerization and downstream signaling pathways.

However, the experience with nanoparticle delivery of anticancer peptides remains limited. The present results demonstrate that loading of GO-203 into polymeric nanoparticles markedly improves the delivery of GO-203 as an anticancer agent in vivo. In this way, the anticancer activity of nonencapsulated GO-203 requires daily administration to sustain tumor exposure, consistent with a short circulating half-life in mice (15). By comparison, administration of GO-203/nanoparticles once weekly was sufficient to confer a similar level of antitumor activity to that achieved with daily delivery of GO-203. The marked enhancement of antitumor activity found with GO-203/nanoparticles could be attributed in part to the EPR effect. In addition, uptake of GO-203/nanoparticles by tumor cells and the sustained release of GO-203, as observed over 7 days at physiologic pH, likely also contribute to more prolonged effects on intracellular targeting of MUC1-C function. These findings with GO-203/nanoparticles are in concert with the recent demonstration that in vivo anticancer activity of the NuBCP-9 peptide is markedly increased by delivery in polymeric nanoparticles, suggesting that this nanoparticle approach may be broadly applicable for other peptides that target intracellular effectors. Polymeric nanoparticles have been widely studied, and certain formulations have been found to be nontoxic and biodegradable (24, 31). For example, with degradation of PLA from the PLA-PEG-PPG-PEG nanoparticles (~12.5 kDa) is a nontoxic polymer that is an FDA-approved biomaterial for clinical use (44). With regard to polymeric nanoparticles already in the clinic, Genexol-PM is a paclitaxel-loaded biodegradable polymeric nanoparticle for the treatment of patients with solid tumors (24). These ongoing
clinical trials with polymeric nanoparticles and the present results thus provide support for the further development of GO-203/nanoparticles as a potential therapeutic agent. In this respect, a phase I trial of nonencapsulated GO-203 administered on a daily basis has been completed, and a MTD has been defined for phase II trials. Our findings here thus lend credence to the notion that GO-203 could be delivered in additional phase II studies on a less frequent schedule and at potentially lower total doses by encapsulation in polymeric nanoparticles.

Disclosure of Potential Conflicts of Interest

D. Kufe is an employee of, has ownership interest (including patents) in, and is a consultant/advisory board member for Genus Oncology. No potential conflicts of interest were disclosed by the other authors.

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