Disruption of the Rbm38-eIF4E Complex with a Synthetic Peptide Pep8 Increases p53 Expression
Christopher A. Lucchesi1, Jin Zhang1, Buyong Ma2, Mingyi Chen3, and Xinbin Chen1

Abstract
Rbm38 is a p53 target and an RNA-binding protein known to suppress p53 translation by preventing eukaryotic translation initiation factor 4E (eIF4E) from binding to p53 mRNA. In this study, we show that synthetic peptides corresponding to the binding interface between Rbm38 and eIF4E, including an 8 amino acid peptide (Pep8) derived from Rbm38, are effective in relieving Rbm38-mediated repression of p53. Molecular simulations showed that Ser-6 in Pep8 forms a hydrogen bond with Asp-202 in eIF4E. Substitution of Ser-6 with Lys, but not with Asp, enhanced the ability of Pep8 to inhibit the Rbm38-eIF4E complex. Importantly, Pep8 alone or together with a low dose of doxorubicin potently induced p53 expression and suppressed colony and tumor sphere formation and xenograft tumors in Rbm38- and p53-dependent manners. Together, we conclude that modulating the Rbm38-eIF4E complex may be explored as a therapeutic strategy for cancers that carry wild-type p53.

Significance: Disruption of the Rbm38-eIF4E complex via synthetic peptides induces wild-type p53 expression, suppresses tumor growth and progression, and may serve as a novel cancer therapeutic strategy.

Introduction
As a focal regulatory component of RNA metabolism, RNA-binding proteins (RBPs) modulate all facets of RNA biogenesis, including RNA surveillance and maturation, subcellular localization and nucleocytoplasmic transport, translation, and degradation (1). Given the fact that RBPs control RNA metabolism, defects in the function of RBPs can have far-reaching implications, such as neurodegenerative disorders, muscular atrophy, and numerous cancers (1, 2). RBPs are also shown to form complex integrated networks, which differentially regulate both oncogenes and tumor suppressors, and thus, can have opposing effects on tumorigenesis (3, 4).

The p53 gene is one of the most important and well-studied tumor suppressors. Inactivation of p53 occurs in more than 50% of human cancers and is a hallmark of tumor progression (5, 6). Functionally, p53 predominantly acts as a transcription factor that can be activated by multiple stimuli, including DNA damage, hypoxia, and oncogene activation (6–8). Activated p53 can stimulate multiple antiproliferative mechanisms by modulating expression of genes involved in cell-cycle arrest, cellular senescence, and apoptosis (9). Because of compromised p53 activity in a vast amount of human cancers, regaining wild-type function of p53 is being explored as a therapeutic approach.

RNA-binding motif protein 38 (Rbm38), also known as RNPC1, is an RBP that contains one RNA recognition motif with sequence homology to nucleolin and HuR (10). The Rbm38 gene resides on chromosome 20q13, which has been shown to be frequently amplified in multiple cancers (11–14). Rbm38 functions by positively regulating the mRNA stability of p21, p73, and HuR, whereas it negatively regulates the mRNA stability of p63 and MDM2 (10, 15–19). Furthermore, elevated levels of Rbm38 are correlated with poor prognosis in patients with breast cancer (20, 21) and are associated with malignant transformation of colorectal adenoma to carcinoma (22, 23). Our group discovered that Rbm38 suppresses p53 mRNA translation by directly interacting with eukaryotic translation initiation factor 4E (eIF4E) on p53 mRNA (24). Consistently, Rbm38-deficient mice are prone to premature aging and early onset of multiple tumors in a p53-dependent manner (25). Of interest, phosphorylation of Rbm38 at serine 195 by glycogen synthase kinase-3 (GSK3) inhibits its interaction with eIF4E, switching Rbm38 from a suppressor to an activator of p53 mRNA translation (26). Further, Rbm24, a homologous family member, also interacts with eIF4E, leading to decreased p53 translation (27). As a key component of the eIF4E complex, eIF4E binds to the 5’ mRNA cap, which is known to be the rate-limiting step in mRNA translation (28, 29). Therefore, removing Rbm38 translational inhibition to enhance p53 expression may prove to be an effective therapeutic option for cancers that often carry wild-type p53.

Materials and Methods
Human cell lines
RKO and MCF7 cells were cultured at 37°C in DMEM (Invitrogen) supplemented with 10% FBS (HyClone) in a humidified incubator with 5% CO2. Cell lines RKO (CRL-2577) and MCF7 (HTB-22) were obtained from the ATCC between 2007 and 2016 and used below passage 25 or within 2 months after thawing.
Cells were tested negative for mycoplasma after thawing and used within 2 months. Because all cell lines from the ATCC have been thoroughly tested and authenticated, we did not authenticate the cell lines used in this study.

**Mice**

Six-week-old athymic nude mice from Charles Rivers were ordered and used to generate xenograft tumors. Mice were maintained in accordance with NIH animal guidelines following protocols approved by UC Davis Institutional Animal Care and Use Committee. Sample size and power analysis was determined based on the work by Hather and colleagues (30).

**Plasmids and cell line generation**

Generation of Rbm38-null and p53-null cells lines was achieved by using CRISPR-Cas9, pSpCas9(BB)-2A-Puro vector expressing guide RNAs (Rbm38: 5'-TTT TCT CCA TCA GGG CAC GT 3'; p53 guide #1: 5' -CCA TTG TTC AAT ATC GTC CG, p53 guide #2: 5'-TCC ATT GTG TGG CAC GGC AA). The cells were selected with puromycin, and each individual clone was confirmed by Western blot analysis. GST-Rbm38 and His-eIF4E expression plasmids were generated as previously described (26). pTXB1-eIF4E plasmid was generated by amplifying eIF4E using His-eIF4E expression plasmid as template. The ampiclon was then cloned into pTXB1 via NdeI and SapI. The primers used to amplify expression plasmids were generated as previously described (26).

**Peptide synthesis and delivery**

Western blotting

Western blot procedures were as previously described (31). Briefly, membranes were blocked in PBS containing 5% milk for 1 hour at 20°C. Primary antibodies in PBS containing 3% milk were incubated at 4°C rocking overnight. The following morning membranes were washed 3x with PBS followed by the addition of secondary antibody in PBS containing 3% milk at 20°C for 2 hours. Membranes were then washed 3x with PBS. All Western blot figures are representative data of at least two independent replicates. Band intensities were calculated using ImageJ (32).

**RNA-chromatin immunoprecipitation**

RKO cells were seeded at 2 × 10^6 cells per plate in four 10-cm plates. The next day, two plates were treated with 1.5 μmol/L Pen-Ctrl and two plates with 1.5 μmol/L Pen-Pep8 for 2 hours. RNA-chromatin immunoprecipitation (ChIP) was performed as previously described (33).

**35S-metabolic labeling**

Metabolic labeling of newly synthesized protein was performed as previously described (34). Briefly, RKO cells were treated with Pen-Ctrl or Pen-Pep8 (5 μmol/L) for 18 hours. Next, the cells were incubated for 1 hour in methionine-free DMEM before being labeled with 100 μCi/ml 35S for 30 minutes. The amount of 35S incorporation was measured by TCA precipitation and scintillation counting. Equal amounts of 3H-labeled lysates (3.7 × 10^6 cpm) were incubated with 1.0 μg anti-p53 antibody and Protein G agarose beads (25 μL bed volume). The immunocomplexes were resolved on an 8% SDS-PAGE gel and subjected to autoradiography.

**Competition pull-down assays**

Peptide bound to TentaGel beads bound to peptides were incubated with cold PBS with 1% BSA for 1 hour rotating at 4°C. Beads were washed 5x with PBS and incubated overnight at 4°C with equal amounts of purified eIF4E in PBS containing 0.1% BSA and 0.1% Triton X-100. The following day beads were washed 5x with PBS containing 0.1% Triton X-100 before being eluted with 1× SDS-lysis buffer and subjected to Western blot analysis. For GST-Rbm38 competitive pull-down assays, pGEX-4T3-Rbm38 plasmid was transformed into BL21 (DE3)-competent Escherichia coli. One liter culture was grown at 37°C until OD600 = 0.6–0.8 and then induced with a final concentration of 0.1 mmol/L IPTG for 4 hours. Bacteria were spun down, and the pellet was placed in –80°C overnight. Pellets were lysed, sonicated, and centrifuged in 20 mL lysis buffer with 1% Triton X-100, 1 mmol/L DTT, and protease inhibitor cocktail. Lysates were then incubated with GST beads rocking at 4°C for 2 hours. Beads were washed 3x with lysis buffer. After brief centrifugation, lysates were carefully removed. Beads were then resuspended in lysis buffer with 0.1% Triton X-100 to make a 50% bead slurry. Note that 100 μL bead slurry was incubated in 650 μl lysis buffer, 5 μmol/L peptide (Ctrl, Pep8, Pep8S-D, Pep8S-K), and 5 μmol/L purified eIF4E in a 1.5 mL tube. Samples were rocked overnight, washed 3x with lysis buffer, and eluted with 60 μL 1x SDS-loading buffer before Western blot analysis.

**Colonization formation**

Colonization formation assays were performed as previously described (35). Briefly, 1,000 cells were plated in 6-well plates. The following day peptides and/or doxorubicin were added to the media. Following 3-day incubation, the media were replaced with fresh complete DMEM. Cells were grown until colonies were visible. Cells were fixed using (7:1) methanol: acetic acid followed by crystal violet staining.

**Tumor spheres formation**

MCF7 cells were cultured in MammoCult (Stemcell) media as per the manufacturer's guidelines. Twenty thousand cells per well were seeded in 6-well ultralow adherent plates. The following day the cells were treated with 5 μmol/L Pen-Ctrl or Pen-Pep8 for 20 minutes followed by vehicle or 6.25 ng/mL doxorubicin for 7 days. After 7 days, tumor spheres larger than 50 μm were counted.

**Xenograft tumor generation**

Female 6-week-old athymic nude mice were injected using a 24-gauge needle with 1 × 10^6 RKO cells in 0.2 mL of serum-free RPMI 1640 mixed with Matrigel at a 1:1 ratio (100 μL of cells mixed with 100 μL of Matrigel, BD Biosciences) subcutaneously into the right flank of each nude mouse. Mice were randomly separated into Pen-Ctrl or Pen-Pep8 with or without doxorubicin-treated groups. After the xenograft tumors reached a volume larger than 100 mm^3, mice were intratumorally injected with 5 μmol/L Pen-Ctrl or Pen-Pep8 (50 μL injection) every other day for 14 days. For the doxorubicin-treated groups, mice received two doses.
Based on these findings, several peptides were synthesized, including Pep8 derived from Rbm38/Rbm24 and Pep23 derived from eIF4E (Supplementary Table S1). To test their ability to modulate the interaction between Rbm38 and eIF4E, competitive pull-down assays were performed. We showed that the Rbm38-eIF4E complex was diminished by Pep23 or Pep8 compared with the control peptide (Fig. 1B, compare lane 1 with 2–3).

Next, replica exchange molecular dynamics simulations (REMSD) were performed and identified a potential binding pocket for Pep8 in eIF4E (Fig. 1C). The model predicted that Tyr-3/Ser-6/Ala-8 in Pep8 form hydrogen bonds with Thr-203/Asp-202/Thr-205 in eIF4E, respectively (Fig. 1D). Because Ser-6 in Pep8 makes a key interaction with Asp-202 in eIF4E, we theorized that Pep8S-D (Ser-6 to Asp-6) would abolish the affinity of Pep8 to eIF4E. To test this control (11-aa nonspecific peptide), Pep8, and Pep8S-D were conjugated to TentaGel beads and examined for their abilities to pull down purified eIF4E. We showed that only Pep8 was able to pull down eIF4E, suggesting that Ser-6 is necessary for the binding to eIF4E (Fig. 1E).

We further demonstrated that Pep8S-K, but not Pep8S-D, was able to reduce the Rbm38-eIF4E complex, we tested their ability to modulate p53 expression in vivo. We found that Pep8S-K was more potent than Pep8 to increase p53 expression (2.3 vs. 1.8 folds of induction; Fig. 2C), consistent with their ability to moderate the Rbm38-eIF4E complex (Fig. 1F).

Next, we sought to determine whether these peptides increase p53 expression in an Rbm38-dependent manner. To that end, Rbm38- and p53-null RKO and MCF7 cells were generated. As expected, Rbm38 was not detectable in Rbm38-null cells, whereas p53 was not detectable in p53-null cells (Supplementary Fig. S2D and S2E). In addition, the level of p53 was increased in Rbm38-null RKO and MCF7 cells, consistent with our previous observations (24). Demonstrating that Pep8 functions through an Rbm38-dependent manner, we showed that Pep8 was capable of increasing p53 expression in wild-type, but not in Rbm38-null RKO or MCF7 cells (Fig. 2D and E, compare lanes 1 and 2 with lanes 3 and 4, respectively; Supplementary Fig. S2D and S2E). In addition, MDM2 and p21, both of which are known p53 targets, were upregulated upon treatment with Pen-Pep8 in wild-type, but not in Rbm38- and p53-null cells (Fig. 2D and E, compare lanes 1 and 2, 3 and 4, and 5 and 6, respectively). Further, we demonstrated that both MDM2 and p21 mRNA were increased following Pep8 treatment in wild-type, but not in Rbm38- and p53-null RKO cells (Supplementary Fig. S2F).

Previously, we found that Rbm38 prevents eIF4E from binding to p53 mRNA, RNA-ChIP assays were performed. We found that Pen-Pep8 increased the association of eIF4E with p53 mRNA as compared with Pen-Ctrl (Fig. 2F, compare lanes 5 and 6). To further determine whether Pep8 modulation of the p53 mRNA, RNA-ChIP assays were performed. We found that Pen-Pep8 increased the association of eIF4E with p53 mRNA as compared with Pen-Ctrl (Fig. 2F, compare lanes 5 and 6). To further determine whether Pep8 modulation of the p53 mRNA, RNA-ChIP assays were performed. We found that Pen-Pep8 increased the association of eIF4E with p53 mRNA as compared with Pen-Ctrl (Fig. 2F, compare lanes 5 and 6). To further determine whether Pep8 modulation of the
Rbm38-eIF4E complex enhances p53 translation, de novo synthesis of p53 protein was examined in 35S-labeled cells. As shown in Fig. 2G, the amount of newly synthesized p53 was increased by Pep8 as compared with control. Collectively, these data suggest that Pep8 is capable of increasing p53 expression by modulating p53 mRNA translation.

Pep8 inhibits tumor cell growth in Rbm38- and p53-dependent manners

To determine if increased expression of p53 by Pep8 has a physiologic response, colony formation assays were performed. We showed that Pep8 caused a substantial decrease in colony formation in wild-type, but not in Rbm38-null RKO and MCF7 cells, suggesting that the effect of Pep8 is dependent on Rbm38 (Fig. 3A; Supplementary Fig. S3, left and middle plots). We also found that Pep8 had no effect on colony formation in p53-null RKO and MCF7 cells, supporting the idea that the effect of Pep8 on colony formation is p53-dependent (Fig. 3A; Supplementary Fig. S3, right plot).

Recently, tumor sphere assays were found to accurately represent the potential of a therapeutic compound in vivo (37). Thus, we measured the effect of Pep8 on tumor sphere formation and found that Pen-Pep8 significantly reduced the ability for MCF7 cells to form tumor spheres as compared with Pen-Ctrl (Fig. 3B).
and C). In addition, Pep8 had little if any effect on tumor sphere formation in Rbm38- and p53-null MCF7 cells (Fig. 3B and C). Together, these data suggest that Pep8 suppresses cell growth in Rbm38- and p53-dependent manners.

Pep8 sensitizes tumor cells to doxorubicin

It is widely accepted that DNA damage, including treatment with doxorubicin, induces p53 protein accumulation through multiple posttranslational modifications (38). In addition, our group has demonstrated that Rbm38 is capable of decreasing p53 expression even after doxorubicin treatment (24). Thus, we sought to address if Pep8 can cooperate with doxorubicin to increase p53 expression. We used 6.25 ng/mL of doxorubicin, a relatively low dose, as high doses lead to massive p53 induction, which would obliterate any changes in p53 by Pep8. To that end, RKO and MCF7 cells were first treated with Pen-Ctrl or Pen-Pep8
for 20 minutes followed by a low dose of doxorubicin (6.25 ng/mL) for 18 hours. Pen-Pep8 increased p53 expression in both RKO and MCF7 cells (Fig. 4A and B; compare lanes 1 and 2), where an additional increase in p53 was observed upon concurrent treatment of Pep8 and doxorubicin in both cell lines (Fig. 4A and B; compare lanes 3 and 4). Furthermore, p53 induction was enhanced by concomitant treatment of either Pen-Pep23 or Pen-Pep8 with etoposide, another topoisomerase II inhibitor (Supplementary Fig. S4).

To determine if Pep8 is capable of sensitizing cancer cells to low-dose doxorubicin, colony formation assays were performed. Wild-type RKO cells showed increased sensitivity to doxorubicin upon Pep8 treatment (Fig. 4C). Captivatingly, although Pep8 treatment alone had no effect on Rbm38- or p53-null RKO cells, Pep8 treatment sensitized both Rbm38- and p53-null RKO cells to doxorubicin treatment (Fig. 4D and E). These data suggest that other targets of Pep8 may cooperate with DNA damage to inhibit cell growth independent of Rbm38 and/or p53. Next, tumor sphere assays were performed with MCF7 cells and showed that Pen-Pep8, but not Pen-Ctrl, was able to cooperate with doxorubicin to suppress tumor sphere formation (Fig. 4F). Similarly to the observations by colony formation assays, Rbm38- and p53-null MCF7 cells were not sensitive to Pep8 alone, but sensitive to concurrent treatment with Pep8 and doxorubicin (Fig. 4G–I). Collectively, these data suggest that Pep8 together with a low dose of a chemotherapeutic agent has an additive effect on p53 expression and suppression of colony/tumor sphere formation primarily in a p53-dependent manner.

Pep8 increases cellular senescence in Rbm38- and p53-dependent manners

Because Pep8 was shown to increase p21 (Fig. 2D–E), a marker for cellular senescence, we hypothesized that Pep8 may cooperate with doxorubicin to modulate cellular senescence. First, we looked at induction of p21 in cells treated with Pep8 and doxorubicin. We found that in both MCF7 and RKO cells, p21 induction was further enhanced in Rbm38- and p53-dependent manners (Fig. 5A; Supplementary Fig. S5). Similarly, induction of p130, a senescence marker, was enhanced in cells treated with Pep8 and doxorubicin in Rbm38- and p53-dependent manners (Fig. 5A; Supplementary Fig. S5). Next, SA-β-gal staining was performed and showed that cellular senescence was significantly increased by Pen-Pep8 alone or in combination with doxorubicin in wild-type, but not in Rbm38-null or p53-null MCF7 cells. Tumor spheres (>50 μm) counted 1 week after peptide treatment. C, Quantification of tumor spheres from B. Values represent the mean ± SEM of three independent experiments (*, P = 0.0013).

Figure 3. Pep8 inhibits tumor cell growth in Rbm38- and p53-dependent manners. A, Pen-Pep8 (5 μmol/L) treatment decreases colony formation in wild-type, but not Rbm38- or p53-null RKO cells. B, Pen-Pep8 (5 μmol/L) treatment reduces MCF7 tumor sphere formation in wild-type, but not in Rbm38- or p53-null MCF7 cells. Tumor spheres (>50 μm) counted 1 week after peptide treatment. C, Quantification of tumor spheres from B. Values represent the mean ± SEM of three independent experiments (*, P = 0.0013).
of xenograft tissues for p53 demonstrated that Pen-Pep8 alone or with doxorubicin was capable of increasing p53 expression in tumor cells (Supplementary Fig. S6). These data are consistent with the results observed in cell lines (Fig. 4A and B), suggesting that Pen-Pep8 has the ability to decrease solid tumor growth by induction of p53 and sensitize tumors to doxorubicin treatment.
Discussion

Restoration of wild-type p53 has been explored and found to be an effective strategy to suppress tumor growth in animal models (39–41). Our group previously identified that Rbm38, an RBP and a p53 target, can inhibit p53 translation via interaction with eIF4E (24). Interestingly, phosphorylation of Rbm38 at Ser-195 abrogates its ability to interact with eIF4E, converting Rbm38 from a repressor to an activator of p53 translation (Fig. 7; ref. 26). With these data in hand, we aimed to test if peptide modulators of the Rbm38-eIF4E complex could increase p53 translation (Fig. 7) and, thus, would have a therapeutic application in treating tumors that harbor wild-type p53. We identified two peptides corresponding to the binding interface between Rbm38/Rbm24 and eIF4E. These peptides were capable of moderating the Rbm38-eIF4E complex, thereby abrogating the translational inhibition of...
p53 by Rbm38. Significantly, Pep8, an 8 amino acid peptide moderator, is a highly potent inducer of p53 translation, leading to decreased colony/tumor sphere formation and reduced xenograft tumor growth in nude mice. In addition, Pep8 substantially sensitizes cancer cells to doxorubicin. Collectively, these findings support the idea that rationally designed peptide moderators of the Rbm38-eIF4E complex may be explored as a therapeutic agent.
Figure 7.

Protein–protein interactions (PPI) are necessary for many cellular functions and can modulate complex biological activities, such as normal cellular homeostasis and pathogenesis of diseases, including cancer (39). The use of peptides to block PPIs comes with certain advantages, such as high potency, target specificity, and increased safety (42). Here, we tested and showed that rationally designed peptides, especially Pep8, can diminish the Rbm38-eIF4E complex, thereby restoring p53 expression. REMDS predict that Pep8 is docked in a pocket at the carboxyl-terminus of eIF4E, with Ser-6 in Pep8 forming a key hydrogen bond with Asp-202 in eIF4E (Figs. 1C and D). To test this model, we created single-point mutants of Pep8 that would either enhance or decrease the ability of Pep8 to form a hydrogen bond with Asp-202 in eIF4E. Indeed, Pep8S-D was found to be inert, likely due to the inability for Asp-6 in Pep8S-D to interact with Asp-202 in eIF4E (Figs. 1E and F, and 2C; Supplementary Fig. S1). In contrast, Pep8S-K, in which Lys-6 in Pep8S-K can potentially form a hydrogen bond with Asp-6 in Pep8S-D to interact with Asp-202 in eIF4E (Figs. 1E and F, and 2C; Supplementary Fig. S1). These data suggest that Pep8 may compete with Rbm38 for GSK3, a kinase known to phosphorylate Rbm38 at Ser-195 (26). Moreover, because Rbm38 interacts with Ago2 to regulate the stability of multiple transcripts, such as p21, Pep8 may in

Our results showed that Pep8 induces p53 expression, leading to increased cellular senescence and growth suppression in Rbm38- and p53-dependent manners (Figs. 3A–C and 5A–C; Supplementary Fig. S3). However, Pep8 is still capable of inducing growth suppression in Rbm38-null and p53-null RKO and MCF7 cells when combined with doxorubicin (Figs. 4D and E, 4G–I, and 5A–C). These data suggest that Pep8 may modulate other targets to sensitize cancer cells to doxorubicin independent of Rbm38/p53. Because Rbm24 can also regulate p53 through the dissociation of eIF4E from p53 mRNA, Pep8 is likely to modulate the Rbm24-eIF4E complex (27). In addition, Pep8 may compete with Rbm38 for GSK3, a kinase known to phosphorylate Rbm38 at Ser-195 (26). Moreover, because Rbm38 interacts with Ago2 to regulate the stability of multiple transcripts, such as p21, Pep8 may influence growth suppression via other Rbm38/Rbm24 targets (45). However, further investigations are needed.

A major hurdle to design an effective peptide for an intracellular target is how to deliver the peptide into the cell. Moreover, peptide delivery to tumors faces additional challenges. For example, peptides are known to have short circulating plasma half-life, induce systemic cytotoxities, accumulate in major organs, and lack tissue specificity (42, 46, 47). In this study, intratumoral injection was used to deliver Pen-Pep8 to xenograft tumors to circumvent these concerns. However, intratumoral injection has its own limitations, such as a diminished accessibility of targeted tumor tissues and decreased dissemination of the peptide throughout the tumor (46, 48). Thus, future studies are needed to devise an approach to deliver Pep8 systemically and specifically to tumor cells, such as conjugated antibody delivery and nanoparticle technologies.

Collectively, our findings here demonstrate that Pep8 can modulate the Rbm38-eIF4E complex, thereby increasing p53 expression. Although these findings are exciting, other questions are still yet to be addressed. For example, does Pep8 stabilize mutant p53, and is Pep8-induced cell sensitivity to doxorubicin a result of increased p53 expression or another yet to be determined mechanism? Further, does reduced doses of doxorubicin together with Pep8 relieve systemic toxicities but still have therapeutic benefits?
Disclosure of Potential Conflicts of Interest

M. Chen is a consultant/advisory board member for BMS Biomarkers and Diagnostics HCPC Advisory Board. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: C.A. Lucchesi, J. Zhang, B. Ma, X. Chen
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.A. Lucchesi, J. Zhang, B. Ma, M. Chen, X. Chen
Writing, review, and/or revision of the manuscript: C.A. Lucchesi, J. Zhang, B. Ma, M. Chen, X. Chen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.A. Lucchesi
Other (histopathology analysis): M. Chen
Other (performed experiments): C.A. Lucchesi, J. Zhang, B. Ma, and M. Chen

Acknowledgments

C.A. Lucchesi received T32 CA108459. X. Chen received NIH RO1 CA076069 and NIH RO1 CA195828. B. Ma was funded with federal funds from the Frederick National Laboratory for Cancer Research, NIH, under contract HHSN261200800001E. We thank the UC Davis Combinatorial Chemistry and Chemical Biology shared resource, which is funded by the UC Davis Comprehensive Cancer Center Support Grant (CCSG) awarded by the National Cancer Institute (NCI P30CA093373). We thank Shakur Mobhi for technical support and guidance with the project.

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Received July 18, 2018; revised November 5, 2018; accepted December 18, 2018; published first December 27, 2018.

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