DNA-dependent protein kinase inhibitors as drug candidates for the treatment of cancer

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Abstract
Cancer presents a difficult challenge for oncologists, as there are few therapies that specifically target disease cells. Existing treatment strategies rely heavily on physical and chemical agents that nonspecifically affect DNA metabolism. To improve the effectiveness of these treatments, we have identified a new class of protein kinase inhibitor that targets a major DNA repair pathway. A representative of this class, 1-(2-hydroxy-4-morpholin-4-yl-phenyl)-ethanone, inhibits the DNA-dependent protein kinase (DNA-PK) and differs significantly from previously studied DNA-PK inhibitors both structurally and functionally. DNA-PK participates in the cellular response to and repair of chromosomal DNA double-strand breaks (DSBs). These new selective inhibitors recapitulate the phenotype of DNA-PK defective cell lines including those from SCID mice. These compounds directly inhibit the repair of DNA DSBs and consequently enhance the cytotoxicity of physical and chemical agents that induce DSBs but not other DNA lesions. In contrast to previously studied DNA-PK inhibitors, these compounds appear benign, exhibiting no toxic effects in the absence of DSB-inducing treatments. Most importantly, 1-(2-hydroxy-4-morpholin-4-yl-phenyl)-ethanone synergistically enhances radiation-induced tumor control in a mouse-human xenograft assay. These studies validate DNA-PK as a cancer drug target and suggest a new approach for enhancing the effects of existing cancer therapies. (Mol Cancer Ther. 2003;2(12):1257–1264)

Introduction
Many cancer therapeutics target and disrupt DNA function through adduct formation or by causing single- and double-chain scissions. We speculated that tumor cells could be made more sensitive to a specific DNA damaging agent if the cellular pathway responsible for the repair of that lesion could be inhibited. As a test of this hypothesis, we asked whether selective inhibitors of DNA-dependent protein kinase (DNA-PK) could enhance the toxic effect of chemical and physical agents that induce DNA double-strand breaks (DSBs).

DNA-PK participates in DNA DSB repair (DSBR) by activating the nonhomologous end-joining pathway (1, 2). DNA-PK is a trimeric protein complex composed of a protein kinase, a DNA-PK catalytic subunit, and a DNA damage acting the nonhomologous end-joining pathway (1, 2). DNA-PK participates in DNA DSB repair (DSBR) by activating the nonhomologous end-joining pathway (1, 2).

Materials and Methods

Cell Lines
Cells were purchased from the American Type Culture Collection (Manassas, VA) and grown as recommended. Culture reagents were from Life Technologies, Inc. (Gaithersburg, MD).

Kinase Assays
HeLa cell purified (24) DNA-PK was assayed by measuring phosphorylation of a p53 peptide substrate (EPPLSQEAFADLWKWR). Reaction cocktails contained 25-mM HEPES-KOH (pH 7.5), 10-mM MgCl2, 0.5-mM DTT, 50-μM ATP, 0.01-mCi/ml [γ-32P]ATP, 10-μg/ml linear plasmid DNA, 200-μM p53 peptide substrate, 0.2-μg DNA-PK (purified from HeLa S3 cells), and test compound.
Reactions were performed at 25°C and terminated after 10 min by spotting onto phosphocellulose paper, and radio-labeled phosphorylated peptide substrate was measured. Purified lipid kinases were assayed (25) by measuring incorporation of phosphate from $[^{32}P]ATP$ into phosphoryositides (Sigma Chemical Co., St. Louis, MO).

### Colony Forming Assay

HCT116 cells were incubated with 100–µM IC60211 or IC86621 and treated with increasing amounts of γ-radiation ($^{137}$Cs Mark I irradiator, J. L. Shepherd & Associates, San Fernando, CA) up to 1600 rad. Alternatively, cells were treated with etoposide (Sigma) up to 10 μM and/or IC86621 up to 100 μM for 24 h when drugs were removed and cells were incubated in fresh media without drugs. After ~1 week, colonies (greater than about 50–100 cells) were fixed, stained with crystal violet, and scored.

### Cell Proliferation Assay

Human tumor cell lines were incubated with DNA-PK inhibitor compounds at varying concentrations and treated with γ-radiation up to 800 rad. Cells were grown for 4 days and then pulsed with $[^3H]$-thymidine for 12–18 h. Cells were harvested and cellular radioactivity was determined. From these data, the effective concentration to achieve 2-fold sensitization (EC$_{TFS}$) was calculated as the drug concentration that enhanced radiation-induced cell killing 2-fold at the LD$_{90}$.

### DNA DSBR Assay

Confluent cultured cells (MDA-MB231, MO59K, and MO59J) were treated with DNA-PK inhibitor compounds or saline for 1 h before chromosomal DNA isolation. Cells then received (a) no treatment, (b) 25 Gy γ-radiation, (c) 25 GY and incubated at 37°C for 2 h, or (d) 25 GY and incubated with DNA-PK inhibitor compound at 37°C for 2 h. Cells were harvested in ice-cold D-PBS, concentrated, and added to warm 2% clean-cut agarose (Bio-Rad, Richmond, CA). Agarose embedded cell slurrries were proteinase K treated at 50°C overnight. Deproteinized agarose plugs were cast in 1% low melt agarose gels (Bio-Rad) and DNA was fractionated by pulsed field gel electrophoresis. Chromosomal DNA was visualized with SYBR Gold (Molecular Probes, Eugene, OR) and quantified with the Storm 860 (Molecular Dynamics, Sunnyvale, CA).

### DNA Damage-Induced Replication Protein A Phosphorylation

HCT116 were serum starved (0.5% fetal bovine serum) for 24 h and treated with 2 mM hydroxyurea (Sigma) for 18 h. Synchronized cells were treated with 16–µM camptothecin (Sigma) for 2 h with or without varying amounts of IC86621. Cells were lysed in the presence of protease inhibitors, fractionated by SDS-PAGE, and transferred to Immobilon (Millipore, Bedford, MA). Protein filters were probed with anti-replication protein A (RPA; Tom J. Kelly, Johns Hopkins University, Baltimore, MD) and anti-β-actin (Oncogene Science, San Diego, CA) followed by HRP-GaM (Bio-Rad). Immunobots were visualized with enhanced chemiluminescence (Pierce Chemical Co., Rockford, IL). Protein band intensity was quantified using the Storm 860 densitometer (Molecular Dynamics).

### Xenograft Assay

BALB/c nude mice (Taconic, Germantown, NY) grafted on the right hindquarter with HCT116 cells were divided into three groups and treated 4qd × 2 (days 1 and 3) when tumors reached a mass of ~50 mg. Treatment groups consisted of 10 animals each received (a) 4 × 0.1 ml s.c. injections of formulation vehicle ( cremophor EL:PBS, 1:3) over 4 h, (b) a single localized dose of 150-rad γ-radiation including multiple vehicle-only mock treatments, or (c) a single localized dose of 150-rad γ-radiation 30 min after s.c. administration of phospho-IC86621 (0.1 ml) at 400 mg/kg followed by three more hourly injections at this dose. Total radiation and drug doses given for the two treatments were 300 rad and 3200 mg/kg, respectively. Animals were handled and maintained in strict compliance with federal guidelines. Tumor mass was determined by the empirically derived formula for HCT116 tumor growth ($l \times w^2$)/3.3. Mice were euthanized when a tumor burden of >1000 mg was reached (~5% of body weight). Log cell kill was determined by the formula log$_{10}$ (cell kill) = ($T - C$)/3.3 $T_d$ (26).

### Results

#### Identification of Novel Kinase Inhibitors

Compounds inhibiting the DNA-PK-dependent phosphorylation of a p53 peptide substrate were identified from the ICOS Corporation (Bothell, WA) small molecule library. The initial library hit was IC60211 (2-hydroxy-4-morpholin-4-yl-benzaldehyde), an arylmorpholine with an IC$_{50}$ of 400 nM. Optimization of this moderately potent kinase inhibitor resulted in many DNA-PK selective inhibitors that maintained the arylmorpholine substructure (Table 1). Most of our studies used IC86621, a methyl ketone derivative of IC60211. Although IC86621 was not our most active compound, it was a convenient, easily synthesized, and chemically stable representative of this inhibitor class. This compound was also more amenable to in vivo studies described below. Because IC86621 was structurally very simple, we were surprised to find that this compound had activity neither against a panel of distantly related protein kinases, including cyclin-dependent kinase 2, Rous sarcoma tyrosine kinase, aurora-related kinase 2, protein kinase A, protein kinase C, checkpoint protein kinase 1, and casein kinase 1, nor against the closely related protein kinases, including ataxia telangiectasia mutant protein kinase, ataxia telangiectasia mutant/Rad3-related kinase, and FKBP12/rapamycin-associated protein kinase (at up to 100 μM; data not shown; 27–29). IC86621 and related compounds do have activity against the closely related phosphatidylinositol-3-kinases (Table 1). However, IC86621 and IC486154 are selective with respect to phosphatidylinositol 3-kinase catalytic subunit (p110) α, γ, and δ but are equipotent with p110β. The more highly evolved morpholino-flavonoid, IC87361, is 50-fold more selective for DNA-PK than for p110β. Despite the crossover into the lipid kinase family, none of these compounds were cytotoxic at concentrations of <50 μM as determined by measuring trypan blue dye uptake and $[^3H]$-thymidine incorporation (data not shown).
DNA-PK Inhibitors Recapitulate the SCID Phenotype

To support continued drug development of these lead compounds, it was necessary to demonstrate proof of concept at the cellular level. We first asked whether these compounds sensitized cells to DSB-inducing agents. IC60211 and IC86621 both enhance radiation-induced cell killing (Fig. 1A). At a fixed drug concentration, IC86621 is more potent than IC60211, reflecting its lower IC50 (see above). Radiation-induced cell killing was enhanced 4-fold by coincubation with IC86621 at the LD90. Radiation enhancement was also measured by comparing terminal survival slopes using the metric D0 (radiation dose required to reduce survival 1/e; 30). IC86621 reduces D0 3-fold from 150 to 50 rad. This is in good agreement with D0 values published for cells cultured from SCID mice. BALB/3T3 fibroblasts were found to be 2.9-fold more resistant than SCID fibroblasts (257 vs. 89 rad; 7). In a similar experiment, granulocyte/macrophage-colony forming unit from wild-type mice were 2.4-fold more resistant than the comparable cells from SCID mice (155 vs. 65 rad; 5). Cells cultured in the presence of up to 50-μM IC86621 showed no decrease in cell viability. At drug levels greater than 200 μM, IC86621 cell growth rate was retarded but cells remained viable during 2 weeks of continuous culture in the presence of drug (data not shown). This effect was reversible as a normal growth rate was reestablished when drug was removed from the culture medium.

Table 1. Activity of representative DNA-PK inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>IC50 (nm)a</th>
<th>IR sensitization</th>
<th>DNA DSBR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DNA-PK p110α</td>
<td>p110β</td>
<td>p110γ</td>
<td>EC50 (μM)b</td>
</tr>
<tr>
<td>IC86621</td>
<td>120</td>
<td>1400</td>
<td>135</td>
<td>880</td>
</tr>
<tr>
<td>IC486154</td>
<td>44</td>
<td>890</td>
<td>42</td>
<td>490</td>
</tr>
<tr>
<td>IC87102</td>
<td>35</td>
<td>2700</td>
<td>400</td>
<td>1800</td>
</tr>
<tr>
<td>IC87361</td>
<td>34</td>
<td>3800</td>
<td>1700</td>
<td>2800</td>
</tr>
<tr>
<td>Wortmannin</td>
<td>150</td>
<td>38</td>
<td>45</td>
<td>14</td>
</tr>
<tr>
<td>LYS94002</td>
<td>360</td>
<td>1000</td>
<td>920</td>
<td>600</td>
</tr>
</tbody>
</table>

aLipid kinase activity was determined by averaging the results of two independent assays.
bIonizing radiation sensitivity was determined by averaging the results from at least three cell proliferation assays.
cInhibition of DNA DSBR was determined from the average of two dose response curves.

IC86621 Specifically Affects the Cellular Metabolism of DNA DSBs

We tested a broad panel of chemotherapy drugs to see if IC86621 enhanced cell killing with any of these agents. IC86621 did not enhance tumor cell killing by vinblastine, doxorubicin, paclitaxel, cisplatin, cyclophosphamide, 5-fluorouracil, cytosine arabinoside, 6-mercaptopurine, methotrexate, or camptothecin (data not shown). However, IC86621 significantly enhanced the cellular toxicity of etoposide and bleomycin, two agents that induce DSBs (31–33). We examined drug-dependent potentiation of etoposide-induced cell killing in more detail (Fig. 1B). We found that at 100-μM IC86621 etoposide-induced tumor cell toxicity was enhanced 15-fold. Therefore, only repair of DNA DSBs but not single-strand breaks, alkylation, or other DNA adducts was blocked by these selective DNA-PK inhibitors. Furthermore, these inhibitors failed to enhance cell killing by the non-DNA damaging agents, paclitaxel and vinblastine.

We confirmed the mechanism by which our DNA-PK inhibitors enhanced cell killing by directly examining the effect on chromosomal DNA DSBR (Fig. 2, A and B). Three different arylmorpholines, IC86621, IC486154, and IC87102, and wortmannin blocked religation of radiation-induced chromosomal DNA DSBs in a dose-dependent manner. We also examined chromosomal DNA DSBR in the DNA-PK normal and defective cell lines MO59K and MO59J,
respectively (Fig. 2C). We corroborated previous observations that DNA DSBR is severely crippled in MO59J but not MO59K cells, suggesting that this DNA repair reaction is DNA-PK dependent (34). These data directly demonstrate that our selective DNA-PK inhibitors enhance radiation-induced tumor cell killing as a consequence of disrupting DNA DSBR. We tested over 35 inhibitor compounds for inhibition of DNA DSBR and found a similar strong correlation among DNA-PK inhibitory activity, radiation sensitivity, and chromosomal DNA DSBR activity (data not shown).

The EC50 values for these inhibitor compounds are significantly greater than their IC50 values (Table 1). This property is not uncommon among protein kinase inhibitors and may be due to several factors including cellular penetration and competition with endogenous ATP levels. DNA-PK is a highly abundant cellular protein that likely acts stoichiometrically in the end-joining process. Consequently, it may be necessary to inhibit a very large fraction of the total cellular protein pool to observe a significant effect. Therefore, we find the discrepancy between IC50 and EC50 values to be consistent with our understanding of DNA-PK function.

We also asked whether IC86621 could block intracellular DNA-PK-dependent protein phosphorylation. Campotothecin treatment of S-phase-arrested cells induces a DNA-PK-dependent phosphorylation of the RPA (35). We corroborated and extended this observation by demonstrating that IC86621 inhibited RPA phosphorylation under these conditions in a dose-dependent manner (Fig. 3). Moreover, the drug concentration required to achieve this effect was similar to that required to inhibit chromosomal DNA DSBR. Our observations support the hypothesis that blocking DNA-PK activity inhibits DNA DSBR and enhances the cellular toxicity of DNA DSB-inducing treatments.

**DNA-PK Inhibitors Enhance Radiation-Induced Tumor Control**

Our expectation was that these inhibitors would block DNA DSBR independent of cell type. Human tumor cells of varied origin and genetic background were screened for drug-dependent radiation sensitivity. We found that all cell lines tested exhibited similar sensitivity to IC86621 ranging from 1.5- to 4.2-fold (Table 2). We do not believe these differences to be significant but rather that all cell lines are likely to be sensitive to this approach. We therefore selected the HCT116 cell line for xenograft testing as this cell line grows rapidly in culture, is easily engrafted into nude mice, and has a moderately rapid and reproducible tumor doubling time as a xenograft.

To demonstrate in vivo proof of concept, we chose to examine drug-dependent potentiation of radiation-induced tumor cell killing instead of etoposide- or bleomycin-induced tumor cell killing because of the ease of radiation administration and for pharmacokinetic simplicity. With radiation as the DSB-inducing agent, we had only to control IC86621 drug levels. Furthermore, we did not have potential concerns regarding drug-drug interactions that might alter compound metabolism and elimination. Detailed cellular studies characterizing IC86621-dependent radiation-induced cell killing indicated that maximal activity was observed when cells were exposed to 50-μM drug for 10 h following radiation (data not shown). However, because of solubility limitations and rapid clearance of IC86621 from plasma, we were unable to maintain these levels in mice. We partially overcame these obstacles by administration of a phosphorylated prodrug of IC86621. Addition of phosphate to the free phenolic group greatly increased solubility, which permitted us to maintain drug levels of >50 μM for 4 h. Following administration of phospho-IC86621, we found only parent compound in plasma as the phosphoester bond is very labile in vivo.

Although 4-h drug exposure was less than our cell-based efficacy studies suggested, we were keen to test our hypothesis with this dosing strategy.

Nude mice engrafted with HCT116 human colon carcinoma cells were divided into three treatment arms
when tumors reached a mass of \sim 50 \text{ mg}. Because drug availability was limiting, we were unable to include a drug-only treatment group. However, previous xenograft studies with this compound indicated that drug treatment without radiation exerted no effect on tumor growth rate consistent with our observations from cellular studies. To optimally use available drug, we performed two cycles of drug and radiation treatments on days 1 and 3. We found that IC86621 exerted a profound enhancement of radiation-induced tumor control (Fig. 4A). Whereas radiation treatment (300 rad) extended the median time of tumor growth to 1000 mg from 25 to 29 days, drug combined with these two radiation treatments extended the median time to 45 days. This represents a 4-fold increase (4 \text{ vs.} 16 \text{ days}) in the effectiveness of radiation under these conditions. The delay in tumor growth rate also translated into a 4-fold survival benefit (10\% \text{ vs.} 40\%) at 45 days and a 2-fold survival enhancement when the experiment was concluded on day 55 (Fig. 4B). Similar results were also observed in a second experiment and in xenografts using

![Figure 2.](image-url)  
**Figure 2.** DNA-PK inhibitors block the repair of chromosomal DNA DSBs induced by ionizing radiation. A, fractionation of chromosomal DNA from MDA-MB231 cells by pulsed field gel electrophoresis. Following ionizing radiation, cells were allowed to repair damage for 2 hrs with or without increasing amounts of IC86621. DNA extracts were analyzed in duplicate. B, graphical representation of data. DNA damage index, the ratio of broken DNA to intact DNA. C, fractionation of chromosomal DNA from MO59K and MO59J cell lines. Top and bottom DNA staining band, intact, undamaged chromosomes and broken, damaged chromosomes, respectively.

![Figure 3.](image-url)  
**Figure 3.** IC86621 blocks intracellular DNA-PK-dependent phosphorylation of RPA following DNA damage. HCT116 cells synchronized in S-phase were treated with camptothecin to induce DNA DSBs and increasing amounts of IC86621. The average of two experiments is reported.
tumors engrafted from the human breast carcinoma cell line, MDA-MB231 (data not shown). These data demonstrate that chemical inhibition of DNA-PK enhances radiation-induced tumor control.

Discussion

DNA-PK represents a new target for cancer drug development. As a target for radiation enhancement, this approach differs significantly from previous attempts to develop radiation sensitizers (36). In contrast to oximimetic and bioreductive radiosensitizers that have failed clinically, these DNA-PK inhibitors appear benign and possess no inherent antitumor or cytotoxic activity. This attractive property suggests that combining enhancer drug with radiation or chemical DNA DSB-inducing chemotherapy will not add confounding toxicities to a clinical treatment strategy. The synergistic radiation enhancement we observe is unprecedented for a drug with no activity as a single agent.

The activity of these inhibitors is consistent with observations previously reported for DNA-PK defective cell lines (5, 7). We find that these inhibitors enhance the toxicity of chemical and physical agents that induce DNA DSBs but not other DNA lesions. Interestingly, the DNA-PK inhibitors do not enhance the cytotoxicity of camptothecin in culture. Camptothecin induces DNA single-strand breaks that are converted to DSBs during DNA replication in S phase (37). Replication-induced DNA DSBs appear to be repaired predominately by homologous recombination and to a lesser extent by the DNA-PK-dependent nonhomologous end-joining pathway (38). Cell cycle responses to camptothecin appear unaffected in MO59J cells, suggesting that signaling by DNA-PK may play an important albeit noncritical role in camptothecin-induced DNA damage (39). Although DNA-PK-dependent phosphorylation of DNA metabolic proteins is activated by camptothecin (34, 40), our observations support the hypothesis that the repair of DNA DSBs generated at replication forks is mediated by a DNA-PK-independent pathway, perhaps involving homologous recombination.

Table 2. Drug-induced radiation enhancement is cell type independent

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Cell type</th>
<th>Radiation enhancement</th>
</tr>
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<tbody>
<tr>
<td>HCT116</td>
<td>Human colon carcinoma</td>
<td>2.9</td>
</tr>
<tr>
<td>SW620</td>
<td>Human colon adenocarcinoma</td>
<td>2.4</td>
</tr>
<tr>
<td>HL60</td>
<td>Human promyelocytic leukemia</td>
<td>4.2</td>
</tr>
<tr>
<td>MOLT4</td>
<td>Human lymphoblast</td>
<td>2.1</td>
</tr>
<tr>
<td>H322</td>
<td>Human bronchoalveolar carcinoma</td>
<td>1.6</td>
</tr>
<tr>
<td>SKOV-3</td>
<td>Human ovary adenocarcinoma</td>
<td>1.9</td>
</tr>
<tr>
<td>OVCAR-3</td>
<td>Human ovary adenocarcinoma</td>
<td>2.4</td>
</tr>
<tr>
<td>PC-3</td>
<td>Human prostate adenocarcinoma</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Radiation enhancement is the ratio of the LD90 radiation dose (without drug) to the LD90 radiation dose (100-μM IC86621) from proliferation assay (averaged from two experiments).

We find that maximal radiation enhanced tumor cell killing is 2–4-fold in vitro. Similar enhancement was observed in the xenograft assay when measured by either tumor growth delay or survival (time to 1000 mg). Estimating the degree of tumor cell killing (26) in vivo from the data presented in Fig. 4A, we calculated log kill to be 1.8. This translates to tumor cell killing of 65-fold. This significant tumor activity was achieved despite reaching only 40% of our target drug exposure level. Because the dosing regimen can be optimized further and radiation treatments can be increased to more closely simulate a clinical treatment course, we believe that radiation-induced tumor control beyond what we have
demonstrated is possible. Furthermore, our observations suggest that this approach has potential for the treatment of a large number of cancers where radiation therapy is indicated.

The arylmorpholines that we report are a new serine-threonine protein kinase inhibitor class. Although similar in structure to chromones (11), such as LY294002, the arylmorpholines have several important differences. An indispensable feature of this class is the juxtaposition of H-bond donor-acceptor pair similar to those found in other serine-threonine protein kinase inhibitors but not the chromones. In addition, the relationship between the H-bond donor-acceptor pair and the morpholine moiety is important. IC87361 is itself a chromone; however, the relative position of morpholine on the flavonoid substructure is reversed relative to LY294002. Finally, we find that morpholine is absolutely required to maintain kinase inhibitory activity. These structurally simple molecules provide a great potential to evolve a drug with appropriate pharmacological properties of a clinical drug candidate.

Among the arsenal of cancer therapies are many DNA damaging agents. Unfortunately, the efficacy of this cancer drug class, including radiation, is limited as both tumor and normal cells are sensitive to their killing effect. We speculated that the therapeutic index of a relatively nonselective DNA damaging agent might be enhanced if it could be combined with a treatment that specifically blocked the cellular repair pathway for that lesion. As a first test of this hypothesis, we have demonstrated that a DNA-PK small molecule inhibitor enhances radiation-induced tumor control in a mouse-human xenograft model of cancer. In future studies, we will address the issue of therapeutic index by testing whether drug enhances radiation-induced toxicity. Our hypothesis is that tumor cells rely on DNA repair mechanisms to a greater extent than normal cells and when faced with this combination treatment will experience a greater degree of cell death.

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