Next-Generation CDK2/9 Inhibitors and Anaphase Catastrophe in Lung Cancer

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Abstract

Background: The first generation CDK2/7/9 inhibitor seliciclib (CYC202) causes multipolar anaphase and apoptosis in lung cancer cells with supernumerary centrosomes (known as anaphase catastrophe). We investigated a new and potent CDK2/9 inhibitor, CCT68127 (Cyclacel).

Methods: CCT68127 was studied in lung cancer cells (three murine and five human) and control murine pulmonary epithelial and human immortalized bronchial epithelial cells. Robotic CCT68127 cell-based proliferation screens were used. Cells undergoing multipolar anaphase and inhibited centrosome clustering were scored. Reverse phase protein arrays (RPPAs) assessed CCT68127 effects on signaling pathways. The function of PEA15, a growth regulator highlighted by RPPAs, was analyzed. Syngeneic murine lung cancer xenografts (n = 4/group) determined CCT68127 effects on tumorigenicity and circulating tumor cell levels. All statistical tests were two-sided.

Results: CCT68127 inhibited growth up to 88.5% (SD = 6.4%, P < .003) at 1 μM, induced apoptosis up to 42.6% (SD = 5.5%, P < .001) at 2 μM, and caused G1 or G2/M arrest in lung cancer cells with minimal effects on control cells (growth inhibition at 1 μM: 10.6%, SD = 3.6%, P = .32; apoptosis at 2 μM: 8.2%, SD = 1.0%, P = .22). A robotic screen found that lung cancer cells with KRAS mutation were particularly sensitive to CCT68127 (P = .02 for IC50). CCT68127 inhibited supernumerary centrosome clustering and caused anaphase catastrophe by 14.1% (SD = 3.6%, P < .009 at 1 μM). CCT68127 reduced PEA15 phosphorylation by 70% (SD = 3.0%, P = .003). The gain of PEA15 expression antagonized and its loss enhanced CCT68127-mediated growth inhibition. CCT68127 reduced lung cancer growth in vivo (P < .001) and circulating tumor cells (P = .004). Findings were confirmed with another CDK2/9 inhibitor, CYC065.

Conclusions: Next-generation CDK2/9 inhibition elicits marked antineoplastic effects in lung cancer via anaphase catastrophe and reduced PEA15 phosphorylation.

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Lung cancer is the most common cause of cancer-related mortality (1–3). Despite current treatments, the five-year survival rate of lung cancer is only approximately 17% (1–3). Innovative ways to treat or prevent lung cancer are needed.

Cyclin-dependent kinases (CDKs) form complexes with their cyclin partners; these complexes regulate cell cycle progression (4,5). CDK2 and its partner, cyclin E, promote DNA duplication and orchestrate the G1 to S cell cycle transition by phosphorylating retinoblastoma protein (6). The CDK2-cyclin E complex is deregulated in pulmonary dysplasia and cancer (7). Cyclin E overexpression is associated with unfavorable clinical outcome (8). Consistent with a role for cyclin E in lung carcinogenesis, engineered mouse models targeting cyclin E expression in the lung caused lung cancer formation that recapitulated human lung cancer features, including chromosomal instability (9,10).

Aneuploidy and chromosomal instability are hallmarks of cancer, and neoplastic cells often have supernumerary centrosomes (11). We previously reported that CDK2 inhibition by selticlib (Cycacel) treatment altered clustering of supernumerary centrosomes and induced multipolar anaphases and apoptosis in lung cancer cells (12,13). This was called anaphase catastrophe (12,13). Fates of selticlib-treated lung cancer cells were determined by live cell imaging that revealed that these cells succumbed to apoptosis after induced anaphase catastrophe (14). This study found that engaging anaphase catastrophe was a way to combat lung and other genetically unstable cancer cells with supernumerary centrosomes, sparing normal cells without supernumerary centrosomes. This could be exploited in the cancer clinic using an optimal CDK2 antagonist.

The centrosome protein CP110 is phosphorylated by CDK2 and was identified as a key mediator of CDK2 inhibitor-dependent anaphase catastrophe (14). We reported that KRAS mutant as compared with wild-type lung cancers expressed substantially lower CP110 levels that enhanced anaphase catastrophe levels after CDK2 inhibition (14,15). KRAS mutant lung cancer cells were particularly responsive to the first-generation CDK2/7/9 inhibitor selticlib (12). The next-generation CDK2/9 inhibitor CCT68127 (Cycacel) is more specific and selective than prior CDK2/9 inhibitors. The CCT68127 purine backbone modification augmented stability and CDK2/9 inhibition relative to selticlib (15). CCT68127 has antiproliferative activity against ovarian and colon cancer cells (16).

In the current study, the aneuploidyastic activity of CCT68127 was explored in murine and human lung cancers. Our hypothesis was that this next-generation CDK2/9 inhibitor would elicit marked aneuploidyastic activity in lung cancer by triggering anaphase catastrophe. Effects on proliferation, apoptosis, cell cycle distribution, anaphase catastrophe, in vivo tumorigenicity, and circulating tumor cells were determined. Downstream activity of CCT68127 on cell signaling pathways was interrogated by reverse phase protein arrays (RPPAs). Translational relevance was determined using lung cancer tissue arrays, robotic screens, and The Cancer Genome Atlas (TCGA).

**Methods**

**Chemicals and Cell Culture**

CCT68127, CYC065, and selticlib were from Cyclacel (Dundee, UK). Trametinib was purchased from Selleck Chemicals (Houston, TX). Murine lung cancer cell lines ED1, LKR13, and 393P were from lung cancers of wild-type cyclin E, Kras^{A146/146}, and Kras^{A146/146}; p53^{H1297X} transgenic mice, respectively, and were authenticated as described (9,10,17–19). Human lung cancer cell lines H522, H1703, A549, Hop62, and H2122 as well as murine C10 pulmonary epithelial and human Beas-2B immortalized bronchial epithelial cells were purchased and authenticated by American Type Culture Collection (Manassas, VA). Cells were cultured in RPMI 1640 media with 10% fetal bovine serum at 37 °C with 5% CO₂ in a humidified incubator.

**In Vitro Assays**

Proliferation assays, apoptosis assays, cell cycle analyses, washout assays, drug combination analyses, multipolar anaphase assays, and expression plasmids/siRNA experiments are described in detail in the Supplementary Methods (available online).

**Reverse Phase Protein Arrays**

Cell lysates were arrayed on nitrocellulose-coated slides and stained with 218 unique antibodies and analyzed, as before (20–22).

**Immunoblot Analyses and Real-Time Reverse Transcription Polymerase Chain Reaction Assays**

Details are in the Supplementary Methods (available online).

**Immunohistochemistry**

Lung cancer arrays containing 235 surgically resected non-small cell lung cancers (NSCLCs) were previously described (14). Correlative studies were approved by the MD Anderson Cancer Center Institutional Review Board, and informed consent was obtained from all the patients. Lung cancer arrays were probed with a PEA15 antibody (AB 135694; Abcam, Cambridge, MA; 1:100) using a Leica BOND-MAX automated stainer (Leica Microsystems, Wetzlar, Germany) and detected using Leica Bond Polymer Refine Detection reagent. Antibody specificity was confirmed using a blocking peptide. Immunohistochemical scoring was by a pathologist unaware of clinical data.

**In Vivo Experiments**

KRAS mutant murine lung cancer 393P cells (19) were infected with luciferase lentivirus (Cellomics Technology, Halethorpe, MD) and selected with puromycin. 393P (1 x 10⁸) stable transfectants were injected subcutaneously into six- to eight-week-old male immunocompetent 129S2/SVPasCrl mice (Charles River Laboratories, Wilmington, MA). Mice with palpable tumors were treated with 50 mg/kg of CCT68127 or vehicle (DMSO/water/HCl) daily for three weeks (five days on and two days off) by oral gavage following an Institutional Animal Care and Use–approved protocol (n = 4 per group). Body weights and tumor volumes were measured with tumor volume (V) calculated as \( V = \frac{\text{length} \times \text{width}^2}{2} \). Bioluminescence imaging was by D-Luciferin (Gold Biotechnology, Olivette, MO) and IVIS Lumina (Xenogen, Alameda, CA) and Living Imaging software (Xenogen) under 2% isoflurane. Mice were euthanized, and tumors were excised and weighed. Circulating tumor cells were measured as before (23).

**Statistical Analysis**

For each in vitro experiment, cells were plated in triplicates and treated independently. The averages of the triplicates were calculated to represent the value of that experiment. Then, the
entire experiment was repeated at least two more times for a total of three experiments. The data points shown displayed were based on the biomarker values from three independent experiments (n = 3). Analysis of variance was applied to compare the biomarker measure among different cell lines or among different drug concentrations. Differences between two groups were assessed by Student’s t test or Mann-Whitney U test. To control the overall type I error rate in addressing the multiple comparisons, Tukey’s method was used for all pairwise comparisons across cell lines or experimental conditions. Dunnett’s method was applied for comparing the result of different concentrations with the control (vehicle) group, as well as comparing PEA15-targeting siRNA effects with control siRNA. Tumor growth in vivo was analyzed using the mixed model analysis. Kaplan-Meier survivals were by the log-rank test. Statistical analyses were with SPSS Statistics software (version 23, SPSS, Chicago, IL) and GraphPad Prism software (version 6, GraphPad Software, San Diego, CA). All statistical tests were two-sided, and a P of less than .05 was considered statistically significant.

Results

CCT68127 Effects

The design of CDK2/9 inhibitor CCT68127 was based on the purine template of the prior CDK2/7/9 inhibitor, seliciclib (Figure 1A) (16). CCT68127 has enhanced potency and selectivity for CDK2 and CDK9 compared with seliciclib (16). To compare CCT68127 and seliciclib activities, cell proliferation response curves for drug concentrations vs vehicle controls were examined in genetically defined murine lung cancer cell lines (ED1 and LKR13). Dose- and time-dependent growth suppression was observed, and as expected CCT68127 effects were more potent than seliciclib (IC_{50} of CCT68127 was < 1 μM, while the IC_{50} of seliciclib was > 25 μM) (Figure 1B). Murine lung cancer cells with mutant KRAS (LKR13 and 393P) appeared more responsive to CCT68127 than were ED1 lung cancer cells with wild-type KRAS (IC_{50} of CCT68127 was 11.1 μM in ED1 and 3.6 μM in LKR13, 44.6% ± 5.8% in 393P, and 33.0% ± 1.0% in ED1 cells at 1 μM; 90.0% ± 1.6% in LKR13, 92.8% ± 1.5% in 393P, and 69.8% ± 2.4%
in ED1 cells at 2 μM (Figure 1C). In contrast, minimal growth inhibition was observed in C10 murine immortalized pulmonary epithelial (C10) and lung cancer (ED1, LKR13, and 393P) cells. Apoptosis induction after seliciclib treatment is shown for murine lung cancer cells.

CCT68127 treatment effects were next examined in human lung cancer cells. Human lung cancer cells with mutant KRAS (H522 and H1703) (growth inhibition \( P < .001 \)) were less sensitive to CCT68127 treatment (growth inhibition \( P = .02 \) and \( P = .04 \) for IC\(_{50}\) and IC\(_{70}\)) (Figure 1E; Supplementary Table 1, available online).

When CDK1, CDK2, or CDK9 was transfected individually, only CDK2 expression antagonized CCT68127 effects in the lung cancer cells (Figure 1F; Supplementary Figure 1A, available online). Additionally, phosphorylation of RNA polymerase II, a target of CDK9, was not affected by CCT68127 (Figure 1G; Supplementary Figure 1B, available online). In combination with trametinib, a MEK inhibitor, CCT68127 showed synergistic or at least additive effects based on the MacSynergy II method (Supplementary Figure 2, available online).

### Apoptosis and Cell Cycle Arrest by CCT68127

Apoptosis and cell cycle arrest induction after CCT68127 treatments of lung cancer cells were examined in a dose-dependent manner. Treatment effects occurred at much lower concentrations than with seliciclib (apoptosis \( \pm SD 20.3\% \pm 3.9\% \)) with \( P < .001 \) in ED1, 16.8\% ± 3.1\% with \( P < .001 \) in LKR13, and 18.2\% ± 1.5\% with \( P < .001 \) in 393P cells at 2 μM of CCT68127; while 13.9\% ± 3.1\% with \( P = .12 \) in ED1, 9.1\% ± 2.0\% with \( P = .40 \) in LKR13,
Anaphase Catastrophe by CCT68127

CCT68127 washout experiments were performed to learn if anti-neoplastic effects were reversible. Growth inhibition by CCT68127 treatment of lung cancer cells was only partially reversed after drug washout (P < .001) (Figure 3A). One possible engaged mechanism was induced anaphase catastrophe. To determine this, multipolar anaphases after CCT68127 or vehicle treatments were measured. CCT68127 readily caused multipolarity and anaphase catastrophe in both murine and human lung cancer cells, but not in bipolar control cells (C10 and Beas2B) (multipolar anaphase ± SD = 13.6% ± 3.7% with P = .001 in ED1, 10.7% ± 1.0% with P < .001 in LKR13, 13.7% ± 1.7% with P = .008 in A549, and 14.1% ± 3.6% with P = .009 in Hop62 cells; while 0.4% ± 0.1% with P = .52 in C10 and 0.5% ± 0.2% with P = .55 in Beas2B cells at 1 μM (Figure 3B). Additionally, CCT68127 was found to inhibit clustering of supernumerary centrosomes (P < .001) (Supplementary Figure 3, A and B, available online) without affecting the incidence of supernumerary centrosomes (Supplementary Figure 3C, available online). Notably, when these cells were engineered with gain of expression of the centrosome protein CP110, a mediator of anaphase catastrophe after CDK2 antagonism (14,15), CCT68127 treatment effects were antagonized (P = .02 in Ed1 and P = .04 in Hop62 cells at 0.5 μM (Figure 3C).
**PEA15 and CCT68127 Effects**

To uncover mechanisms engaged in CDK2/9 antagonism, CCT68127 treatment effects in lung cancer cells were comprehensively interrogated using RPPA. Expression profiles of 218 key growth-regulatory proteins were studied after 6, 24, and 48 hours of CCT68127 treatment relative to vehicle treatments of murine (ED1 and LKR13) and human (H522 and Hop62) lung cancer cells (Supplementary Figure 4, available online). Attention focused on the cluster of proteins that showed marked repression after CCT68127 treatment (Figure 4A). Among these proteins, the multifunctional growth regulator PEA15 was highlighted. Levels of Ser116 phosphorylated PEA15 were reduced in all examined lung cancer cells by up to 70.0% (SD = 6.9%) with a P value of .003, while its total expression was unaffected (Figures 4A and B). This finding was independently confirmed by immunoblot analysis (Supplementary Figure 5, available online). When these cells were engineered with gain of PEA15 expression, growth inhibition by CCT68127 was antagonized (P = .007 in ED1, P = .04 in LKR13, and P = .005 in Hop62 cells at 0.5 μM (Figure 4C), indicating the involvement of PEA15 in mediating CCT68127 antineoplastic effects.

**Effect of PEA15 Knockdown in Lung Cancer Cells**

Direct effects of regulating PEA15 expression in lung cancer cells were examined using siRNAs targeting PEA15. Independent knockdown of PEA15 by two different siRNAs was confirmed by real-time polymerase chain reaction (PCR) and immunoblot assays in both murine and human lung cancer cells (Figure 5A). PEA15 knockdown repressed lung cancer cell growth by up to 35.4% (SD = 6.9%) with P = .03 (Figure 5B), which was reversed by restoring PEA15 expression (Figure 5C). PEA15 knockdown increased growth inhibition after CCT68127 treatment of lung cancer cells (Figure 5D).

**PEA15 Expression in Lung Cancers**

PEA15 mRNA expression profiles in lung cancers were examined using TCGA data. Analyses revealed that PEA15 expression was statistically significantly lower in lung adenocarcinomas (ADs; P < .001) and lung squamous cell carcinomas (SCCs; P < .001) compared with normal lung tissues (Figure 6A). TCGA data established that PEA15 mRNA expression was reduced in...
the majority of different malignant vs normal tissues, including those of lung origin (Supplementary Figure 6, available online). PEA15 protein expression was investigated in 235 human lung cancers (142 ADs and 93 SCCs) by immunohistochemical analysis. Antibody specificity for PEA15 detection was confirmed using a blocking peptide (Supplementary Figure 7A, available online). Representative lung cancer PEA15 immunohistochemical expression was lower in lung cancers vs adjacent normal lung tissues, including those of lung origin (Supplementary Figure 6, available online).

Restored PEA15 expression after PEA15 knockdown in lung cancer cells. Error bars represent the standard deviation. The P values were computed using t test with multiple comparison adjustment by Dunnett’s method. All statistical tests were two-sided.

In Vivo CCT68127 Effects

In vivo CCT68127 effects on lung cancer growth were examined using a syngeneic murine lung cancer xenograft model. The 393P KRAS mutant murine lung cancer cell line was engineered to stably express luciferase. Cells were subcutaneously injected into immunocompetent syngeneic mice, which were subsequently treated with vehicle or 50 mg/kg of CCT68127 by oral gavage once daily for three weeks.

Tumor growth was analyzed using the mixed model analysis. Both the time effect and time by treatment interaction of tumor growth were statistically significant (P < 0.001), indicating that the tumor growth rate of the CCT68127-treated group was reduced as compared with the vehicle-treated control group (Figure 7A). There was no appreciable body weight loss, indicating that this agent was well tolerated at this dosage (data not shown). Excised tumors after completion of treatment were smaller in CCT68127-treated than in vehicle-treated mice (P < 0.001) (Figure 7A). Tumor burden was independently monitored via bioluminescent imaging. Representative images of vehicle vs CCT68127, consistent with results from tumor volume measurements (Figure 7A). Circulating tumor cells were measured using a method that we reported (23). Compared with vehicle-
Antineoplastic Activity of Second CDK2/9 Inhibitor

To independently determine the translational relevance of these findings, antineoplastic activities of a clinical lead CDK2/9 inhibitor, CYC065, were evaluated. Substantial growth suppression and apoptosis followed CYC065 treatment of murine (ED1 and LKR13) and human (HS22 and Hop62) lung cancer cells (IC_{50} ± SD = 0.45 ± 0.10 μM in ED1, 0.41 ± 0.06 μM in LKR13, 0.76 ± 0.03 μM in HS22, and 0.37 ± 0.09 μM in Hop62 cells; apoptosis ± SD = 22.1% ± 6.3% with P = .002 in ED1, 10.7% ± 2.2% with P = .005 in LKR13, 17.9% ± 2.1% with P = .02 in HS22, and 14.5% ± 2.6% with P = .004 in Hop62 cells at 1 μM) (Figure 8, A and B). CYC065 readily induced anaphase catastrophe (multipolar anaphase ± SD = 19.3% ± 1.9% with P = .005 in ED1 and 63.6% ± 4.5% with P < .001 in Hop62 cells at 0.5 μM) (Figure 8C).

Discussion

This study reports that the next-generation CDK2/9 inhibitor CCT68127 has potent antineoplastic activity against both murine and human lung cancers and that its activity is more pronounced than the first-generation CDK2/7/9 inhibitor seliciclib. Antineoplastic effects of CCT68127 were antagonized by the engineered gain of CDK2, but not CDK1 or CDK9 expression, indicating that CCT68127 treatment effects were largely due to CDK2 inhibition, as is consistent with a prior report (16) showing that CCT68127 treatment effects were antagonized by the engineered gain of CDK2, but not CDK1 or CDK9 expression, indicating that CCT68127 treatment effects were largely due to CDK2 inhibition, as is consistent with a prior report (16) showing that CCT68127 has highly selective inhibition against CDK2 as compared with other CDKs. Furthermore, a high-throughput screen using 75 human lung cancer cell lines revealed KRAS mutant lung cancer cells are more responsive to CCT68127 than were KRAS wild-type lung cancer cells. This has translational relevance because KRAS mutant lung cancers are an unmet medical need (24).

Interestingly, a synthetic lethal interaction between KRAS oncogenes and CDK4 is reported (25). The activity of CDK inhibitors in KRAS mutant lung cancers in the clinic will be worth exploring in future work. Another promising strategy to consider in KRAS mutant lung cancer is combination therapy (26).
Of note, CCT68127 had synergistic or at least additive effects when combined with trametinib treatment in lung cancer cells. CDK4/6 inhibition was recently found to have antineoplastic activity in KRAS mutant lung cancer when combined with trametinib (27).

CCT68127 readily induced anaphase catastrophe, as did seliciclib and dinaciclib treatment, as we previously reported (12,28). Anaphase catastrophe occurs when cells with more than two centrosomes are prevented from appropriately clustering supernumerary centrosomes at cell mitosis, sparing normal bipolar cells that do not have supernumerary centrosomes (12,13). In the current study, anaphase catastrophe was not appreciably induced in control bipolar immortalized cells. Likewise, growth inhibition and apoptosis induction by CCT68127 treatment were also minimally observed in these studied cells. It is hypothesized that CCT68127 treatment preferentially affects chromosomally unstable tumor cells with supernumerary centrosomes and thereby spares normal bipolar cells and tissues from anaphase catastrophe or toxicity.

Comprehensive analysis of expressed protein changes by RPPA uncovered PEA15 phosphorylation at Ser116 as substantially reduced after CCT68127 treatment. Based on the reported consensus amino acid sequence of CDK substrates (29–31) and our bioinformatic analysis of the amino acid sequence of PEA15 using GPS 2.1 software (32), PEA15 was not highlighted as a direct CDK substrate (data not shown). Yet gain of PEA15 expression reduced growth inhibition despite low-dose CCT68127 treatment. Given this, PEA15 likely played at least an indirect role in exerting observed CCT68127 effects.

PEA15 regulates diverse cellular processes, and both tumor-suppressive and oncogenic activities are reported in different cancers (33–37). In the current study, PEA15 knockdown inhibited lung cancer cell growth, implicating it as an oncogenic species in this setting. It is notable that immunohistochemical analysis revealed that PEA15 expression was statistically significantly lower in lung cancers than in normal lung tissues. Also, reduced PEA15 expression was associated with advanced lung cancer stage and an unfavorable overall survival, indicating a
potential tumor-suppressive role for PEA15. This dual nature of PEA15 is thought to depend on its phosphorylation state (33,38,39). When unphosphorylated, PEA15 binds ERK1/2 and is sequestered in the cytoplasm, preventing translocation into the nucleus (39–41). In contrast, PEA15 phosphorylation can release ERK1/2 into the nucleus (33,39,40). Upon phosphorylation, PEA15 binds Fas-associated death domain protein, inhibiting apoptosis (33). Changes in the phosphorylation state can turn PEA15 from a tumor suppressor to an oncogene (33,38,39,41). Future work should determine the precise role of PEA15 in lung cancer biology.

Substantial CCT68127 in vivo antineoplastic effects against lung cancer were uncovered. Using a xenograft of KRAS mutant murine lung cancer, modeling a clinical unmet need, CCT68127 exerted marked reduction of tumorigenicity as well as circulating tumor cells without conferring appreciable toxicity in mice at the displayed dosage. These data provide a strong rationale for clinical testing of a potent CDK2/9 inhibitor in lung cancer patients whose tumors harbor KRAS mutations. Because circulating tumor cells can predict metastasis (42), CCT68127-mediated reduction of circulating tumor cells implicates a role for this agent in preventing lung cancer metastasis.

The current study does have some limitations. For instance, when mice were treated with higher CCT68127 dosages (75 mg/kg or 100 mg/kg), they did not tolerate those dosages. Such toxicity might limit clinical efficacy of CCT68127. It is notable that a different next-generation CDK2/9 inhibitor (CYC065) was also examined in this study. This agent may exhibit greater efficacy along with reduced toxicity in the clinic than CCT68127. In this regard, this agent was particularly potent in inducing anaphase catastrophe. Future work should include testing of CYC065 in the cancer clinic.

In summary, the CDK2/9 inhibitor CCT68127 exerts prominent antitumor activity against lung cancer through mechanisms engaging anaphase catastrophe and reduced PEA15 phosphorylation. Clinical relevance of CCT68127 mechanisms of action was confirmed by studies of the related clinical CDK2/9 inhibitor CYC065. Further clinical investigation of an optimal CDK2/9 inhibitor is warranted, especially in lung cancer cases with KRAS mutation.

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Notes

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