Orally bioavailable macrocyclics that target Cyclins A and B RXL motifs cause tumor regression in xenograft models and in vitro show activity across multiple cancer types

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BACKGROUND

Cyclin A and B are key regulators of cell growth and division that exhibit distinct phase-dependent tissue distribution (Cyclin A), Cyclin A/Cyclin B and Cyclin A/RXL to regulate progression through the cell cycle. Cyclin A exhibits a highly conserved "A" motif in Cyclin B is divided into the "B"- and "C"-components (Cyclin B1 and B2), which exhibit distinct phase-dependent tissue distribution (Cyclin B1). In early Cyclin B is divided into the "B"- and "C"-components (Cyclin B1 and B2), which exhibit distinct phase-dependent tissue distribution (Cyclin B1). In early mitosis, Cyclin A expression is increased, while Cyclin B expression is decreased. Cyclin A is required for G1/S transition, while Cyclin B is required for G2/M transition. In late mitosis, Cyclin A expression is decreased, while Cyclin B expression is increased. Cyclin A is required for G2/M transition, while Cyclin B is required for G1/S transition.

While CDK inhibitors are approved for clinical use, attempts to target posttranslational modifications of these components have met with limited success, such as CDK4. We have not advanced beyond early research investigation.

Inhibition of valosin leading to Cyclin A in vivo has postulated to be synthetically lethal.

Using structure-guided design we have developed cell-permeable macrocyclic compounds that inhibit Cyclin A and B RXL. The compound is a highly conserved "A" motif and exhibits measurable tissue distribution (Cyclin B1). In early mitosis, Cyclin A expression is increased, while Cyclin B expression is decreased. Cyclin A is required for G1/S transition, while Cyclin B is required for G2/M transition. In late mitosis, Cyclin A expression is decreased, while Cyclin B expression is increased. Cyclin A is required for G2/M transition, while Cyclin B is required for G1/S transition.

RESULTS

Table 1. Biochemical potency and cellular activity of Cyclin A/B RXL inhibitors

Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM)</th>
<th>IC50 (% inhibition)</th>
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<tr>
<td>Cyclin A</td>
<td>100</td>
<td>0.05</td>
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<tr>
<td>Cyclin B</td>
<td>100</td>
<td>0.05</td>
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Compound A: IC50: 100 nM, IC50: 0.05

Figure 1. Cyclin A/B RXL inhibitors induce DNA damage, G2/M phase arrest, mitotic abnormalities and apoptosis

Figure 2. Cyclin A/B RXL inhibitors reduce the number of mitotic cells and reduce genomic and nuclear damage.

Figure 3. Cyclin A/B RXL inhibitors reduce the number of mitotic cells and reduce genomic and nuclear damage.

Figure 4. Activity against both Cyclin A and B is required to induce accumulation of G2/M phase markers and apoptosis

Figure 5. Cell lines from multiple indications exhibit sub-micromolar sensitivity to Cyclin A/B RXL inhibitors

Figure 6. Sensitivity of SCLC cell lines to Cyclin A/B RXL inhibitors correlates with RB alteration and increased DTI target gene expression

Figure 7. Cyclin A/B RXL inhibitors, exemplified by Compound A, exhibit no significant inhibition of kinase activity

CONCLUSIONS

Macroscopic Cyclin A/B RXL inhibitors have been optimized for oral bioavailability and show single agent tumor regression in SCLC and ovarian xenograft models.

In efficacious doses, Cyclin A/B RXL inhibitors are well tolerated with no neuropsychia, decrease in body weight, or markers of liver and kidney damage observed.

Cyclin A/B RXL inhibitors bind to Cyclin A/CDK2 and Cyclin B/CDK1 complexes with nonselective biophysical potency and disrupt Cyclin A and B RXL B-dependent interactions in cells. Consistent with a synthetic lethal mechanism, Cyclin A/B RXL inhibitors selectively block cancer cells in the G2/M phase and induce apoptosis.

Cyclin A/B RXL inhibitors show activity in cell lines from broad cancer indications and sensitivity correlates with increased expression of DTI target genes.

Selective inhibition of Cyclins offers a mechanistically distinct mode of action from strategies that inhibit cyclin kinase inhibitors. Given their compelling mechanism, we are progressing development of these macrocyclic Cyclin A/B RXL inhibitors to the clinic.

References