Enhanced drug delivery to brain tumors with a new paclitaxel-peptide conjugate

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ABSTRACT

In vitro experiments:
- Human tumor cell lines:
  - NCI-H460 (human lung carcinoma)
  - U-87 MG (human glioblastoma)
- Determination of the IC50 and GI50 of ANG1005 and paclitaxel using MTS and BrdU assays, respectively

In vivo experiments:
- Pharmacokinetic study of ANG1005 in healthy Nude rats:
  - Determination of Cmax and AUC for IV bolus injection and IV infusion of ANG1005
  - Evaluation of intracranial tumor volume by MRI
- Antitumor efficacy study in tumor bearing Nude rats:
  - Implantation of catheters in the femoral vein of rats
  - Single treatment with ANG1005: IP bolus injection at 5 mg/kg, single IV bolus injection at 11.25 mg/kg and single 4-hour IV infusion at 15, 20, 25 and 30 mg/kg
  - Collection of blood for plasma concentration determination
  - Determination of ANG1005 levels in plasma using HPLC/MS
- Antitumor efficacy study in tumor bearing Nude rats:
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  - Collection of blood for plasma concentration determination
  - Determination of ANG1005 levels in plasma using HPLC/MS
- Evaluation of intracranial tumor volume by MRI

RESULTS

IC50 AND GI50 DETERMINATIONS

<table>
<thead>
<tr>
<th>Peptide</th>
<th>IC50 (nM)</th>
<th>GI50 (nM)</th>
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<tr>
<td>ANG1005</td>
<td>13 ± 9</td>
<td>14 ± 11</td>
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<tr>
<td>Paclitaxel</td>
<td>12 ± 3</td>
<td>12 ± 3</td>
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ANG1005 and paclitaxel exhibited equivalent cytotoxic activity against the NCI-H460 human lung adenocarcinoma cell line and against the U-87MG human glioblastoma cell line.

CONCLUSIONS

ANG1005 was as potent as paclitaxel to inhibit the in vitro growth of NCI-H460 and U-87 MG human tumor cell lines. Biodistribution studies showed that the maximal plasma concentrations were about 1,000-fold higher than the in vitro concentration required to induce a 50% cell death. Despite toxicity, preliminary antitumor efficacy studies revealed an early intracranial tumor growth inhibition after the treatments with ANG1005. These results need to be confirmed in further studies. ANG1005 is currently under evaluation in phase I studies in patients with brain cancer.