JAB-X1800: a potent immunostimulatory antibody-drug conjugate (iADC) targeting CD73

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Abstract #2923

Background
- STING is an important immune-oncological target that stimulates the production of type I interferon and downstream antitumor targets. Clinically, the systemic administration of STING agonist may be challenged by toxicity due to broad biodistribution. Therefore, targeting STING activation by immunostimulatory antibody-drug conjugate (iADC) which conjugates STING agonist to an antibody targeting tumor cells is warranted.
- We have developed a highly potent STING agonist JAB-27610 with favorable selectivity as an ADC payload.
- CD73 is an important immune checkpoint in adenovirus pathway, highly expressed in many types of cancers and undergoes internalization after binding to antibody. We have developed a CD73 antibody JAB-83102 which is in clinical development (NCT05174945).
- We have developed JAB-X1800, a first-in-class CD73-STING iADC by conjugating our own STING agonist to CD73 antibody. JAB-X1800 exhibits stability, target-specific internalization, potent antitumor activity and good tolerability in pre-clinical study.

JAB-X1800 induces anti-tumor cytokines and leads to potent killing of cancer cells

Table 1

<table>
<thead>
<tr>
<th>STING variant</th>
<th>HEX200 Parental</th>
<th>HEX200 STING agonist</th>
<th>Hex-200 STING agonist</th>
<th>Hex-200 STING agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hex-200</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
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<tr>
<td>Hex-200</td>
<td>2.4 ± 0.2</td>
<td>2.4 ± 0.2</td>
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<td>2.4 ± 0.2</td>
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<tr>
<td>Hex-200</td>
<td>2.9 ± 0.2</td>
<td>2.9 ± 0.2</td>
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CD73-dependent internalization of JAB-X1800 in cancer cells, but not in peripheral B and T cells

JAB-X1800 targets CD73+ cancer cells. MDA-MB-231/PBMCs co-culture treated with JAB-X1800 at concentration of 10000 nM induced a significant decrease in cell viability compared to the untreated control (Figure 6). Similarly, JAB-X1800 exhibited potent antitumor activity in vivo, as the tumor volume was significantly reduced in the treated group compared to the control group (Figure 7).

Conclusions
- JAB-X1800 shows potent antitumor activity with immune memory and good tolerability in vivo.
- JAB-X1800 is a first-in-class potent iADC by conjugating potent STING agonist to CD73 mAb (CD73-STING iADC).
- JAB-X1800 exhibits favorable plasma stability.
- JAB-X1800 shows target-specific internalization in CD73+ positive cancer cells and induces antitumor cytokines, leading to potent killing of cancer cells in tumor cells and PBMC co-cultures.
- JAB-X1800 exhibits CD73-dependent and potent antitumor activity with a single dose administration in multiple mouse models.
- JAB-X1800 induces higher CXCL10 protein expression in tumor, and limited systemic toxicity, suggesting an enhanced antitumor activity with low risk of cytokine storm.

Acknowledgment
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References
1. Prog Clin Biol Res. 2003 Dec;559:1-16 (Adv 3-4).