The Marine Natural Product Mimic MHP88 Shows Anticancer Activity and has the Potential to Cause Immunogenic Cell Death

Background
The marine natural product mimic MHP88 is a novel synthetic molecule based on unique structures found in molecules from an arctic marine bryozoan (1, 2). Initial studies showed that MHP88 kills cancer cells efficiently, but is not hemolytic. In this study, we look closer at the mode of death induced by MHP88 in oral cancer (HSC-3) and lymphoma (Ramos) cell lines. Immunogenic cell death (ICD) is a mode of death that can be induced by some anticancer molecules and is characterized by the release and expression of certain damage-associated molecular patterns (DAMPs), which have immune stimulating effects. Specifically, the release of high mobility group box 1 (HMGB1) and ATP, as well as the translocation of calreticulin from the ER lumen to the outside of the cell membrane, constitute the major hallmarks of ICD (3). In vivo, ICD induced in cancer cells has a vaccination effect, protecting the host from future challenge with the same cancer cells. Animal studies on the molecule LTX-401, which has similar properties as MHP88, have successfully demonstrated this effect (4).

Hypothesis
MHP88 can induce immunogenic cell death

Screening of Anticancer Activity
Table 1 A cell death MTS assay was employed to determine the concentration of MHP88 needed to inhibit the growth of a panel of cell lines by 50% upon 4 hours of stimulation (IC50).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cell Line</th>
<th>IC50 (μM)</th>
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<tbody>
<tr>
<td>MHP88</td>
<td>Ramos</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>HSC-3</td>
<td>2.50</td>
</tr>
<tr>
<td></td>
<td>GL261</td>
<td>4.13</td>
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<tr>
<td></td>
<td>HEPG2</td>
<td>11.04</td>
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Figure 1 Scanning electron microscopy image of HSC-3 cells treated with MHP88 at the concentration corresponding to 1IC50 show major ultrastructural changes, particularly on the cell membrane, after only one hour.

MHP88 Induces Necrosis in Cancer Cells

Figure 2 Flow cytometric analyses were used to determine the mode of death induced by MHP88. Ramos and HSC-3 cells were treated with MHP88 in concentrations corresponding to 1IC50 and 2IC50. MHP88 for up to 4 hours. Phenomenon scoring was applied to measure apoptosis. Ramos and HSC-3 cells were seeded at 1x10^5 cells in 6-well plates and treated with MHP88 at various concentrations. Both apoptosis and necrosis were used as apoptosis controls for Ramos and HSC-3 cells, respectively. Both assays indicate that MHP88 induces necrosis.

Conclusion
Our studies indicate that the mode of death induced in cancer cells by MHP88 is of immunogenic nature and therefore might be able to turn cold tumors hot. This indicates that MHP88, as well as other marine natural product mimics, have the potential to be used as therapeutic agents in the future.

References