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Elucidating cannabinoids’ effects on Ewing’s sarcoma tumor vasculature

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Ewing’s sarcoma (ES) is the second most common pediatric bone cancer. With patients having a 5-year survival rate of 30%, alternative treatments must be developed. Certain cannabinoids have been shown to induce apoptosis and inhibit angiogenesis in ES cells/tumors. We are specifically observing naturally occurring cannabidiol (CBD) and ajulemic acid (AJA), a synthetic cannabinoid. AJA is structurally similar to tetrahydrocannabinol (THC), the active compound in marijuana. However, AJA and CBD do not produce any psychoactive effects, making them viable treatments for children.

### Background

Ewing’s sarcoma (ES) is the second most common pediatric bone cancer. With patients having a 5-year survival rate of 30%, alternative treatments must be developed. Certain cannabinoids have been shown to induce apoptosis and inhibit angiogenesis in ES cells/tumors. We are specifically observing naturally occurring cannabidiol (CBD) and ajulemic acid (AJA), a synthetic cannabinoid. AJA is structurally similar to tetrahydrocannabinol (THC), the active compound in marijuana. However, AJA and CBD do not produce any psychoactive effects, making them viable treatments for children.

### Abstract

To elucidate the mechanism by which AJA affects Ewing’s Sarcoma cellular pathways, we conducted an angiogenic array to observe AJA’s effects on fifty-five different angiogenic proteins. The angiogenic array showed potential upregulation of TIMP-1, an angiogenic inhibitor, but similar results have yet to be replicated in subsequent ELISA’s. Solid tumors commonly have high vascular densities and increased interstitial fluid pressures (IFP), which reduce the efficacy of treatments by inhibiting the absorption of therapeutic drugs. To determine the effects of AJA and CBD on IFP, and thus on vasculature in vivo, we measured IFP levels in mouse xenograft ES tumors. AJA and CBD both produced significant decreases in IFP within thirty minutes of injection, affirming their potential as legitimate cancer treatments.

### Experiments & Results

**Angiogenic Array:** quantifying the effect of AJA on 55 various angiogenic proteins via antibody binding and chemiluminescence

**Results/Conclusion:** TIMP-1, a matrix metalloproteinase inhibitor, was dramatically up-regulated upon treatment with AJA. TIMP-1 inhibits ECM degradation, making it anti-angiogenic.

**Future Studies**

- Synergistic administration of cannabinoids and chemotherapy drugs
- Investigating cannabinoids’ effects on angiogenic protein receptors
- Replicate spheroid invasion assay with ES cells

### Experiments (Cont.)

**TIMP-1 ELISA’s:** quantifying effect of AJA on TIMP-1 in vitro

**Results/Conclusion:** AIA had no consistent effect on TIMP-1

**Measuring Tumor Interstitial Fluid Pressure in vivo:** monitoring TIFP in mouse xenograft ES tumors over 30mins. after administration of AJA and CBD (0.025mg/g)

**Change in TIFP over 30mins.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Change in TIFP</th>
</tr>
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<tbody>
<tr>
<td>Unt.</td>
<td>+7%</td>
</tr>
<tr>
<td>10μM AJA</td>
<td>-27%</td>
</tr>
<tr>
<td>20μM AJA</td>
<td>-41%</td>
</tr>
</tbody>
</table>

**Results/Conclusion:** Mice treated with AJA and CBD displayed remarkable decreases in TIFP.

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