Using Proton MRSI to Predict Response of Vorinostat Treatment in Recurrent GBM


Epigenetic Mechanisms in Biology

• Acetylation: Histone acetylation tends to open up chromatin structure. Accordingly, histone acetyltransferases (HATs) tend to be transcriptional activators whereas histone deacetylases (HDACs) tend to be repressors. Many HAT genes are altered in some way in a variety of cancers. For instance, the p300-HAT gene is mutated in a number of gastrointestinal tumours. On the other hand, alteration of HDAC genes in cancer seems to be far less common. However, despite this low incidence of genetic mutation in cancer, HDAC inhibitors are performing well in the clinic as anti-cancer drugs.

• Methylation: All lysine methyltransferases that target histone N-terminal tails contain a so-called SET domain. Transgenic mice devoid of these enzymes are very susceptible to cancer, especially B cell lymphomas.

• Phosphorylation: H3S10 and H3S28 are phosphorylated at mitosis - a crucial part of the cell cycle; misregulation here is often associated with cancers. Indeed, the Aurora kinases that perform this H3 phosphorylation are implicated in cancer.

Histone Deacetylase Inhibitors

Epigenetic Drug

How does vorinostat work?

- By stopping HDAC activity

Role of HDAC Inhibitors in Tumor Control

• Redifferentiation
• Activation of tumor suppressor genes

Established HDAC Inhibitors

Zn\(^{2+}\) chelating strength
SAHA restores normal brain tissue-like metabolism

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Cho</th>
<th>NAA</th>
<th>Cr</th>
<th>Ins</th>
<th>Lac</th>
<th>Ala</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated controls (N=8)</td>
<td>1.69±0.87</td>
<td>9.34±0.69</td>
<td>10.25±0.7</td>
<td>6.36±0.72</td>
<td>1.89±0.75</td>
<td>9.24±1.16</td>
</tr>
<tr>
<td>SAHA treated</td>
<td>2.36±0.85</td>
<td>3.16±0.87**</td>
<td>5.84±0.86**</td>
<td>5.16±0.84**</td>
<td>3.24±0.56**</td>
<td>1.36±0.16</td>
</tr>
</tbody>
</table>

SAHA restores normal brain tissue-like metabolism.

Clinical Study Design

**Definition:** A treatment arm consists of patients with recurrent glioblastoma. B treatment arm consists of patients under treatment for newly diagnosed glioblastoma.


2DCSI (recurrent GBM): responder

**Definition:** A treatment arm consists of patients with recurrent glioblastoma. B treatment arm consists of patients under treatment for newly diagnosed glioblastoma.


Spectroscopic Restoration Index (SRI)

NAA, Cr and MI increased around the rim of the tumor by 10%, 20%, and 30%, respectively, suggesting early cellular redifferentiation, and Lac and Cho decreased by 5% and 55%, respectively, at day 7.

SRI (day 7) = 0.15 + 0.25 + 0.35 + 0.05 + 0.55 = 1.35
SRI (9 weeks) = 2.2

Spectroscopic Restoration Index (SRI)

SRI (day 7) = -0.2
SRI (9 weeks) = -0.1
### Summary of First Six Cases

Table 1. SRI (Spectroscopic Restoration Index), IDS-SR, and NAA/Cho at day 7 compared to day 0 are listed for 6 patients who enrolled into our Quick Trial of SAHA+TMZ. PT# is our patient number registry. Those patients who completed our study were all listed here.

<table>
<thead>
<tr>
<th>Metabolic Responders</th>
<th>Metabolic non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT#</td>
<td>SRI</td>
</tr>
<tr>
<td>002</td>
<td>1.14</td>
</tr>
<tr>
<td>007</td>
<td>1.40</td>
</tr>
<tr>
<td>008</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Two sample t-test was used to compare metabolic responders and metabolic non-responders. The test showed that there was highly significant difference between the two groups (p<0.001).

### Problem with Pseudoprogression

Sample IMRT treatment plan from Eclipse targeting the tumor volume generated from the Cho/NAA map of a GBM patient.

Sample Biopsy plan from Stealth Navigation System targeting the site with high Cho/NAA of a GBM patient.

### Conclusions and Future Directions

- MRSI has the potential to allow test drug delivery to determine if a tumor will or will not be sensitive to its effect
- MRSI can be used to minimize research study size and invasiveness
- Quantitative MRSI will allow tumor grading, and ongoing determination of prognosis in gliomas