Treatment of Vestibular Schwannoma Cells with ErbB Inhibitors

Matthew L. Bush, M.D.
The Ohio State University
Department of Otolaryngology – Head and Neck Surgery
Columbus, Ohio, USA
Presenter Disclosure

Co-authors:
Sarah S. Burns, MA
Janet L. Oblinger, Ph.D.
Sholpan Davletova, Ph.D.
Long-Sheng Chang, Ph.D.
Abraham Jacob, M.D.
D. Bradley Welling, M.D., Ph.D.

No relationships to disclose
No off-label drug/device treatment of patients
OSU IRB protocol: 1994H0241
A Need for Therapeutic Development
Introduction

• Vestibular schwannomas (VS) result from NF2 mutations that cause loss of tumor suppressor activity
• These mutations also result in altered transmembrane receptor tyrosine kinase (RTK) function
• ErbB RTK family linked Schwann cell proliferation and differentiation (Dong 1995, Levi 1995)
Introduction

• ErbB receptors are expressed in VS tumors (Brown 2008, Doherty 2008)
• The activity and mechanism of ErbB receptors in VS development and tumor progression is unknown.
• RTK represent potential therapeutic targets if proven to be essential for VS tumor growth.
Hypothesis

- Human vestibular schwannomas possess aberrant activation of ErbB family receptor tyrosine kinases (RTK) which renders them susceptible to growth suppression by RTK inhibitors.
B. VS

Nerve

#2 VS-VN RTK Intensity

- EGFR
- ErbB2
- ErbB3
- ErbB4
- Insulin R
- PDGFRb
### Ratio of Activated Receptors in VS–VN Pairs

<table>
<thead>
<tr>
<th>Tumor</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>1.02</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>ErbB2</td>
<td>6</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>ErbB3</td>
<td>12.8</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>ErbB4</td>
<td>1.5</td>
<td>2.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Cultured VS

HMS-97 Cell Line

Cultured Schwann Cells
<table>
<thead>
<tr>
<th>Tumor</th>
<th>Type</th>
<th>Size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NF2</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>Sporadic</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>Sporadic (Cystic)</td>
<td>2.1</td>
</tr>
<tr>
<td>4</td>
<td>Sporadic</td>
<td>2.2</td>
</tr>
<tr>
<td>5</td>
<td>Sporadic (Cystic)</td>
<td>2.3</td>
</tr>
</tbody>
</table>
2.5μM IC₅₀

5μM IC₅₀
C. Lapatinib Effects on VS

15µM IC₅₀

D. Lapatinib Effects on HMS

10µM IC₅₀
A

- EGFR
- ErbB2
- ErbB3
- ErbB4

Untreated Vestibular Schwannoma

B

- Untreated HMS-97

VS treated with Erlotinib 5μM for 24 hours

HMS-97 treated with Erlotinib 5μM for 24 hours
Conclusions

• Vestibular schwannomas express multiple ErbB receptors but show high expression and activation of ErbB3
• Erlotinib is a potent inhibitor of VS proliferation and decreases activation of multiple ErbB receptors
• Further investigation of ErbB signaling and drug-inhibition mechanisms is warranted
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