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Defining the role of NRAS in melanoma maintenance

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Melanoma is the most rapidly increasing malignancy among young people in the U.S.

- The incidence of melanoma has increased by more than 600 percent over the last 30 years. (ACS statistics: www.cancer.org
- Melanoma is the leading cause of cancer death in women aged 25-29
- 5-year survival for advanced stages of the disease is < 20%

### Molecular Analysis of Human Melanoma

<table>
<thead>
<tr>
<th>Gene/Alteration</th>
<th>Familial/Sporadic</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRAS G12V (p.Glu12Asp)</td>
<td>S</td>
</tr>
<tr>
<td>p53</td>
<td>S</td>
</tr>
<tr>
<td>hTERT: PTEN</td>
<td>S</td>
</tr>
<tr>
<td>Trp53-12</td>
<td>S</td>
</tr>
<tr>
<td>NRAS</td>
<td>S</td>
</tr>
<tr>
<td>C-myc</td>
<td>S</td>
</tr>
<tr>
<td>R-RAS</td>
<td>S</td>
</tr>
<tr>
<td>MCR1 (stromal marker)</td>
<td>S</td>
</tr>
</tbody>
</table>

*Adapted from Castellano and Perentes: Melanoma Research 1999;9:431-432

### Initial Validation of Melanoma Associated Genes

Expression of RAS in SK-MEL cells and growth in soft agar. Cell lines from xenotransplanted SK-MEL cells that overexpress p21, p53, and C-myc and show loss of hTERT, PTEN, Trp53-12, and LOH were analyzed for growth in soft agar compared to wild-type SK-MEL cells. The results are shown in the figure.

### RAS/C/TV/A Melanoma Mouse Model System

TV-A helper virus

- A helper virus was used to deliver the RAS/C/TV/A virus to the mouse.

- The virus was injected into the mouse to express the RAS/C/TV/A gene.

- The expression of the gene was confirmed by observing the growth of the tumor in the mouse.

### Results and Conclusions

- Launch (2004) and 53.4% of TVNA mice were cured of tumors by Dox. CTV-A is a virus that can be used to cure melanoma tumors.

- Delivery of TVNA virus in TRE-NRAS-IRES-Cre mice developed melanoma that was highly significant (P<0.008). Demonstrating that the NRAS (p.Glu12Asp) gene targeted by TVNA is highly significant in the context of melanoma.

### Future Directions

- Preservation and evaluation of tumors to identify the mechanisms of resistance to either genetic or pharmacological manipulation of the MAPK pathway.

- Examination of resistant tumor samples to ensure expression of inhibited NRAS expression by both B-IRF and B-NIRF by Western blot analysis after established cell lines.

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