“INNOVATIVE THERAPEUTIC CANCER VACCINES IN CUBA: AN UPDATE”

Luis E. Fernández
Vaccine Division
CIM
Estimated and Projected World Cancer Incidence by Selected Types of Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Lung</th>
<th>Breast</th>
<th>Colon</th>
<th>Stomach</th>
<th>Liver</th>
<th>Prostate</th>
<th>Cervical</th>
<th>Esophageal</th>
<th>Lymphoma</th>
<th>Pancreatic</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>1,352</td>
<td>1,200</td>
<td>1,025</td>
<td>935</td>
<td>627</td>
<td>680</td>
<td>492</td>
<td>463</td>
<td>364</td>
<td>233</td>
<td>160</td>
</tr>
<tr>
<td>2020</td>
<td>1,700</td>
<td>1,400</td>
<td>1,300</td>
<td>1,150</td>
<td>680</td>
<td>1,280</td>
<td>530</td>
<td>480</td>
<td>380</td>
<td>264</td>
<td>177</td>
</tr>
</tbody>
</table>

Percent Change (2005-2020)

- 1.5%
- 1.0%
- 1.6%
- 1.4%
- 0.5%
- 4.3%
- 0.5%
- 0.2%
- 0.3%
- 0.8%
- 0.7%

Estimated and Projected World Cancer Mortality by Selected Types of Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Lung</th>
<th>Breast</th>
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</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>1,180</td>
<td>410</td>
<td>529</td>
<td>700</td>
<td>598</td>
<td>222</td>
<td>274</td>
<td>386</td>
<td>195</td>
<td>227</td>
<td>41</td>
</tr>
<tr>
<td>2020</td>
<td>1,100</td>
<td>400</td>
<td>620</td>
<td>730</td>
<td>632</td>
<td>245</td>
<td>190</td>
<td>395</td>
<td>200</td>
<td>243</td>
<td>43</td>
</tr>
</tbody>
</table>

Percent Change (2005-2020)

- 0.5%
- 0.2%
- 1.1%
- 0.3%
- 0.4%
- 0.7%
- 2.4%
- 0.2%
- 0.2%
- 0.5%
- 0.3%

Source: US Census Bureau, NCI, WHO

New Cases of Cancer (2006) and Mortality (2008) in Cuba (greatest frequency types)

<table>
<thead>
<tr>
<th>Localization</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>4,378</td>
<td>5,051</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>2,527</td>
<td>2,509</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2,496</td>
<td>1,357</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1,683</td>
<td>1,869</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1,271</td>
<td>457</td>
</tr>
</tbody>
</table>

Source: National Cancer Registry and Department of Statistics. Cuban Health Ministry
The first cancer vaccine is now available for patients

FDA Approves Prostate Cancer Treatment
NBC Nightly News (4/29, story 3, 2:00, Williams) reported that "the FDA has approved" Provenge (sipuleucel-T), "a vaccine for prostate cancer."
Cuban Biotechnology in Cancer Vaccines
NSCLC: The EGF-P64 Vaccine

EGF Vaccine

Anti-EGF Ab blocks the EGF/EGFR binding

Inhibition of proliferation
**NSCLC: The EGF-P64 Vaccine**

**Randomized POC Phase II CT in 80 NSCLC patients**

Survival Functions

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>6.47</td>
</tr>
<tr>
<td>Control</td>
<td>5.33</td>
</tr>
</tbody>
</table>

Currently ongoing a Phase III pivotal trial in 579 NSCLC patients

**ITT (OS) Younger than 60 (OS)**

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<th>Median (months)</th>
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<td>Control</td>
<td>5.33</td>
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</table>
An Unique Target: N-Glycolylated Mono Sialyl Lactosyl Ceramide

- Initially reported by us in human breast tumours in the early nineties
- Also expressed in other types of cancers: NSCLC, Colon, Stomach, Ovarian, Melanomas etc
- Almost absent in human normal tissues
- A potent immunosuppressor, mainly for CD4+ T cells
- Available from horse erythrocytes and fully synthetic

Vaccine formulation: 1E10 mAb in Al(OH)₃
NSCLC: Racotumomab (1E10) Idiotypic Vaccine

Randomized POC Phase II CT in 174 NSCLC patients

Interim analysis at 81 events

Starting a Multinational Phase III pivotal trial in 1 084 NSCLC patients
Very Small Sized Proteoliposomes: the Common Fact

GM3

OMVs Neisseria meningitidis

VSSP

Size: 24.7 ± 1.1 nm
Zeta potential: -25.5 ± 2.54 mV

Estévez F. et al., Vaccine 1999;18:190-7
Very Small Sized Proteoliposomes: the Common Fact

- IFN-γ+ Tumor-free CD8+ T cells
- IFA/SIINFEKL DC/IFN-γ+ Tumor-free CD8+ T cells
- VSSP/SIINFEKL
- DC

# IFN-γ+/10^5 CD8+ T cells

- Tumor-free
- EG.7 Tumor

- ICS FACS
  IFN-γ/CD8/CD45.2
Breast Cancer: The GlycovaxGM3 Vaccine

Randomized POC Phase II CT in 79 MBC patients

Survival Analysis for Non Visceral Patients (ITT, n = 50/79)

<table>
<thead>
<tr>
<th>OS</th>
<th>GlycoVaxGM3</th>
<th>Control</th>
<th>Log Rank</th>
<th>Breslow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 23</td>
<td>N = 27</td>
<td>(p)</td>
<td>(p)</td>
</tr>
<tr>
<td>Median</td>
<td>26,17</td>
<td>12,17</td>
<td>0,269</td>
<td>0,049</td>
</tr>
</tbody>
</table>

Currently ongoing two Phase III pivotal trials, one in 776 MBC patients, other in 512 stage IIa, III patients
**Clinical Update**

- 5 patients with normalized prostate gland
- 1 patient with grade I prostate gland

**POC Phase II study starting in 2010**
CIGB 228: HPV E7 peptide for HLA-A*02 restriction in VSSP, SC injection

Phase I Clinical trial

- 7 patients with High Grade Cervical Dysplasia / HPV 16/ HLA-A*02, 4 doses of the vaccine
- End points: safety, colposcopy and histopathologic analysis, immunogenicity

- The vaccine was safe and well tolerated
- High-grade cervical dysplasias were resolved in 57% of patients
- Partial responses were obtained in 29% of patients
- Complete and partial responses observed in 86% of cases

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Colposcopy</th>
<th>Histology</th>
<th>Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>CR</td>
<td>CR</td>
<td>+++</td>
</tr>
<tr>
<td>02</td>
<td>SD</td>
<td>SD</td>
<td>++</td>
</tr>
<tr>
<td>03</td>
<td>PR</td>
<td>PR</td>
<td>++</td>
</tr>
<tr>
<td>04</td>
<td>CR</td>
<td>CR</td>
<td>+++</td>
</tr>
<tr>
<td>05</td>
<td>CR</td>
<td>CR</td>
<td>++</td>
</tr>
<tr>
<td>06</td>
<td>CR</td>
<td>CR</td>
<td>+++</td>
</tr>
<tr>
<td>07</td>
<td>SD</td>
<td>SD</td>
<td>+</td>
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Concluding Remarks

• Eight innovative therapeutic cancer vaccines are in development in Cuba as a consequence of the existence of the Cuban Biotech System

• Vaccine candidates are focused in the more frequent types of cancer affecting people in Cuba

• VSSP vaccine technology is the common fact present in the majority of these projects
Thanks for your attention!