Nitric Oxide Lung Cancer Active Vaccination

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**DISCLOSURES – Prof. Ido Wolf**

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship(s)</th>
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<tbody>
<tr>
<td>MSD</td>
<td>Honorarium, research support, lectures</td>
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<td>Roche</td>
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Metastases are responsible for ~90% of all cancer-related deaths.

Anti-tumor immunity may destroy metastases and prevent new metastatic growth.
Endogenous Nitric Oxide (NO) at Physiologic Concentrations

- Endogenous NO at physiologic concentrations has been shown to activate innate and adaptive responses of the immune system against tumors.¹
- Endogenous NO affects the immune system by multiple pathways, including selective enhancement of Type 1 T-cell differentiation and induction of CD4+CD25+ Treg cells.²
- Interaction of endogenous NO with O₂ or O₂⁻ in situ results in reactive oxygen species formation, resulting in nitrosative and oxidative chemical stressors on cells.³,⁴
- Exogenous, high-concentration (>10,000 ppm), local delivery of gaseous NO may cause tumor cell death, resulting in release of tumor-specific antigens.

Exogenous High-Concentration NO (>10,000 ppm)

- Here we present a novel treatment paradigm that involves *in situ* tumor destruction with high-concentration gaseous NO.
- Our research group has developed an innovative NO-based tumor ablation method, in which high-concentration NO gas is delivered locally to solid tumors.
- To our understanding, this is the first time a concept of injecting gas to a tissue, and specifically high-concentration NO gas to tumors, is reported.
Background
Gaseous NO stimulates apparent immune response against murine CT26 colon cancer *in vivo*

Assay Scheme

<table>
<thead>
<tr>
<th>~Day -10</th>
<th>Day 0</th>
<th>Up to Day +14</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT26 Tumor Induction</td>
<td>Nitric Oxide Treatment</td>
<td>Contralateral Tumor Challenge</td>
<td>Assessment of Challenge Tumor</td>
</tr>
</tbody>
</table>

Data presented at the American Association for Cancer Research (AACR) June 22, 2020
**Background**

Gaseous NO stimulates apparent immune response against murine CT26 colon cancer *in vivo*

- *In vivo* results showed that all treated colon tumor-bearing mice were resistant to a second (“challenge”) CT26 cancer cell inoculation

* P-value (Chi-square) < 0.05

Data presented at the American Association for Cancer Research (AACR) June 22, 2020
Hypothesis

- **Endogenous** NO at physiologic concentrations has a known role in increasing immune response.
- **Exogenous** high-concentration gaseous NO administered directly to a solid tumor may result in local cell death resulting in systemic exposure to tumor antigens
- Tumor antigens may trigger a systemic immune response, thereby creating a memory immune bank that will recognize and attack subsequent primary tumor regrowth as well as distal metastases.
NO Blocks Lung Cancer Cell Proliferation *In Vitro*

Exposure of LLC1 cells to NO

**Time 0**
- Exposure of LLC1 cells to NO

**Time 24 hr**
- Cell viability: XTT assay

<table>
<thead>
<tr>
<th>Time</th>
<th>Air</th>
<th>10,000 ppm NO</th>
<th>20,000 ppm NO</th>
</tr>
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<tbody>
<tr>
<td>10 sec</td>
<td>*</td>
<td>*</td>
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</tr>
<tr>
<td>1 min</td>
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<tr>
<td>9 min</td>
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* P-value (T-test) <0.05
Most Lung Cancer Cells are at Late Apoptosis after Exposure to NO

**Time 0**
Exposure of LLC1 cells to NO

**Time 24 hr**
Cell viability: Annexin V-PI assay

- **Air, 3 min**
  - Early apoptosis
  - Late apoptosis

- **20,000 ppm NO, 3 min**
  - Early apoptosis
  - Late apoptosis

- **50,000 ppm NO, 3 min**
  - Early apoptosis
  - Late apoptosis
Gaseous Nitric Oxide Vaccinates Against Lung Cancer *In Vivo*

**Assay Scheme**

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<td>Tumor Induction</td>
<td>NO Treatment</td>
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</table>
Gaseous Nitric Oxide Vaccinates Against Lung Cancer *In Vivo*

- **Naïve (n=3)**
- **50,000 ppm NO (n=2)**

<table>
<thead>
<tr>
<th>% challenge tumor take</th>
<th>Day 5</th>
<th>Day 9</th>
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<tbody>
<tr>
<td>0%</td>
<td></td>
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<tr>
<td>20%</td>
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* P-value (chi-square) <0.05

**Treatment:** 50,000 ppm NO for 10 minutes
Conclusions

• Gaseous NO treatment results in dose- and time-dependent inhibition of lung cancer cell proliferation and reduced viability in vitro.

• Treatment of primary LLC1 lung tumors in mice with gaseous NO at a dose of 50,000 ppm for 10 minutes results in no uptake of a challenge tumor implanted up to 14 days later.

• No unanticipated mortality or signs indicating distress were noted in the animals.

• These preliminary data suggest that our innovative gaseous NO-based treatment may treat lung tumors locally and their distant metastases systemically, potentially via stimulation of an anti-tumor immune response.