Dual-Targeting: PSMA

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Disclosure

• NHB is an Inventor on patents related to this presentation and assigned to Cornell University

• NHB is a paid advisor and shareholder of Convergent Therapeutics, Inc, the company to which this IP has been licensed for further development.
Tumor Therapy with Targeted Atomic Nanogenerators

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A single, high linear energy transfer alpha particle can kill a target cell. We have developed methods to target molecular-sized generators of alpha-emitting radionuclides to the inside of cancer cells using actinium-225 coupled to internalizing monoclonal antibodies. In vitro, these constructs specifically killed leukemia, lymphoma, breast, ovarian, neuroblastoma, and prostate cancer cells at becquerel (picocurie) levels. Injection of single doses of the constructs at kilobecquerel (nanocurie) levels into mice bearing solid prostate carcinoma or disseminated human lymphoma induced tumor regression and prolonged survival, without toxicity, in a substantial fraction of animals. Nanogenerators targeting a wide variety of cancers may be possible.

Alpha particles are high-energy, high linear energy transfer helium nuclei capable of strong, yet selective, cytotoxicity (1). A single atom emitting an alpha particle can kill a target cell (2). Monoclonal antibodies conjugated to alpha

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particle-emitting radionuclides (213Bi and 211At) are starting to show promise in radioimmunotherapy (3, 4). The conjugates [213Bi]-HuM195 (2) and [213Bi]J591 (5, 6) have been used in preclinical models of leukemia and prostate cancer, respectively, and in a phase I human clinical trial, [213Bi]HuM195 was active against leukemia, with no significant toxicity (3). Astatine-211–labeled antibodies to tenascin (anti-tenascin) have been used clinically to treat malignant gliomas in humans (4) in a phase I trial. For clinical use of 211Bi, we developed a therapeutic dose-level 225Ac211Bi generator device, approximately 1 cm by 6 cm in size,
PSMA-617-Ac\textsuperscript{225} exceptional response
PSMA-617-Ac\textsuperscript{225} exceptional response...

**Salivary gland toxicity**

**High renal exposure**

Haberkorn. Heidelberg
PSMA mAb J591 Bio-distribution

- Vascular system
- Liver
- Large bowel
J591-Ac$^{225}$ Single Ascending Dose Phase 1

Baseline Demographics (n=32)$^\dagger$

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>69.5 (52-89)</td>
</tr>
<tr>
<td>PSA, median (range)</td>
<td>149.1 (4.8-7168)</td>
</tr>
<tr>
<td>CALGB (Halabi) Prognostic Group, n (%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>High</td>
<td>23 (71.9%)</td>
</tr>
<tr>
<td>Sites of metastases, n (%)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>31 (96.9%)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>28 (87.5%)</td>
</tr>
<tr>
<td>Liver</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>Lung</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>Prior therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 2 potent AR inhibitors</td>
<td>25 (78.1%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>20 (62.5%)</td>
</tr>
<tr>
<td>Radium-223</td>
<td>9 (28.1%)</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>12 (37.5%)</td>
</tr>
<tr>
<td>PSMA-RL-Lu$^{177}$</td>
<td>14 (43.8%)</td>
</tr>
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</table>

Cohort Treatment Dose n

<table>
<thead>
<tr>
<th>Cohort</th>
<th>KBq/Kg</th>
<th>$\mu$Ci/Kg</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>13.3</td>
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<td>2</td>
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<td>1.08</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>53.3</td>
<td>1.44</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>66.7</td>
<td>1.80</td>
<td>6*</td>
</tr>
<tr>
<td>6</td>
<td>80.0</td>
<td>2.16</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>93.3</td>
<td>2.52</td>
<td>16</td>
</tr>
</tbody>
</table>

$^\dagger$One pt enrolled in both dose-escalation and expansion

Dose Escalation Results:

- 1 of 6 in Cohort 6 (80 KBq/Kg) had DLT (Gr 4 anemia and Gr 4 thrombocytopenia)
- 0 of 6 in Cohort 7 had DLT
- MTD not reached
- RP2D = 93.3 KBq/Kg

Tagawa et al. ASCO 2021
**PSA Response**

- 69% experienced any PSA decline
- 44% with >50% PSA decline

**Design:**

- 32 patients; NO PSMA imaging pre-selection used
- One dose only; 7 escalating dose levels
- Heavily Pre-treated patients (eg, ARi, chemo)
- 44% relapsed/refractory to prior PSMA-617-Lu$^{177}$
- 28% relapsed/refractory to prior Ra$^{223}$

**Results:**

- Well-tolerated
- **PSA$_{50}$ response = 14/32 (44%)**
- 1 DLT (platelets), MTD not reached
- 12 grade 1 xerostomia, 7 had prior 617-Lu$^{177}$
- Multi-dose trial underway

Tagawa et al. ASCO 2021
Multiple ascending dose J591-Ac\textsuperscript{225}  
Phase 1b / 2a

**Key Inclusion:**
- Progressive mCRPC
- Post ARSI
- Post taxane (or ineligible, refuse)

**Objectives:**
- Safety
- PSA50

**Secondary:**
- Radiographic Response Rate

- Short, dose-condensed course: J591-Ac\textsuperscript{225} Day 1 & 15  
  N=25

- J591-Ac\textsuperscript{225} 4 x 6-week cycles  
  N=25

- Expansion at RP2D

ClinicalTrials.gov Identifier: NCT04506567
Both PSMA Small Molecule Ligand (SML) and J591 can bind PSMA/tumor simultaneously and additively.
PSMA SML and J591 Bio-distributions and AE profiles are non-overlapping
Weill-Cornell’s differentiated approach

WCM recognized potential benefit of dual-targeting with Ab + RL (small molecule ligands)

- Both Ab and RL converge on the cancer
- No overlapping toxicity on normal tissue
- Each agent can carry a different payload

Others focus on EITHER RLs OR Abs

Substantially better anti-tumor efficacy with NO added side effects
PSMA RL plus J591=> SYNERGISTIC uptake
Antibody + RL targeting
Delivers SYNERGISTIC dose to tumor
Animal therapy study:
Synergy of alpha / beta RNT
Three Layers of Benefit from dual-targeted approach

1. Convergent Targeting => *additive dose to tumor* without increased toxicity

2. Ab improves uptake and retention of RL by tumor
   • Resulting dose to tumor is greater than sum of the parts

3. Addition of $\alpha$ to $\beta$ radionuclide therapy:
   • Provides the additional potency & precision of $\alpha$
   • Solves the limitations of RL-$\beta$ treatment of small volume lesions

Benefit of Ac$^{225}$ plus Lu$^{177}$ combination
One RNT compensates for the other

The smaller the lesion, the more poorly it retains SML RNT
This is exacerbated as Lu$^{177}$ delivers radiation outside the tumor margin of small volume lesions
Shorter range and more powerful effect of Ac$^{225}$ overcomes this problem


<table>
<thead>
<tr>
<th>Sphere diameter (µm)</th>
<th>90Y</th>
<th>177Lu</th>
<th>111In</th>
<th>161Tb</th>
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<tr>
<td>10,000</td>
<td>563</td>
<td>140</td>
<td>33.2</td>
<td>190</td>
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<tr>
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<td>96.3</td>
<td>25.7</td>
<td>135</td>
</tr>
<tr>
<td>500</td>
<td>39.2</td>
<td>69.2</td>
<td>19.4</td>
<td>104</td>
</tr>
<tr>
<td>200</td>
<td>15.8</td>
<td>38.6</td>
<td>11.2</td>
<td>72.3</td>
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<tr>
<td>100</td>
<td>7.93</td>
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<td>50</td>
<td>3.92</td>
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<td>7.15</td>
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<td>20</td>
<td>1.56</td>
<td>6.11</td>
<td>5.95</td>
<td>25.4</td>
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<tr>
<td>10</td>
<td>0.77</td>
<td>3.62</td>
<td>4.96</td>
<td>17.7</td>
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</tbody>
</table>
Benefit of adding α to β radionuclide therapy
RL-Lu$^{177}$ undertreats small volume lesions

“The results of multi-modality imaging can be summarised as demonstrating remarkable responses in nodal and visceral disease, but a pattern of ultimate progression in new sites of osseous disease or marrow infiltration. We postulate that $^{177}$Lu is less effective in targeting microscopic deposits of marrow disease” (pg 832)

Hofman MS* et al. Lancet Oncol. 2018 19:825-833

“25% of patients showed new LM [Lymph Node mets] despite response of existing lesions.”


“…three patients had a partial response, whilst four patients exhibited progressive disease due to new lesions.”


“After an initial response, patients predominantly progressed, with new focal or diffuse areas of involvement in the bone…”

Dual $\alpha$ (Ac$^{225}$) + $\beta$ (Lu$^{177}$) radionuclide therapy
Provides potency & precision of $\alpha$
Combining $\alpha + \beta$ particles extends “curability range”

Phase I/II study of $^{225}$Ac-J591 plus $^{177}$Lu-PSMA-I&T for progressive metastatic Castration-Resistant Prostate Cancer

In progress

ClinicalTrials.gov Identifier: NCT04886986