Targeting Telomerase to Induce Immune Responses in ccRCC

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**Telomerase is a hallmark of cancer**

- **Telomeres** are the protective caps at the chromosome ends
  - Progressively shorten with each cell replication
  - In tumor cells, telomeres enable cell growth and replication

- **Telomerase** is the enzyme responsible for maintaining telomere function
  - **Normal cells**: Absent or present in low levels
  - **Cancer cells**: Highly active (85-100% of cancer cells)

- Telomere function is critical for maintaining cancer cells

- The ability to disrupt telomere function via telomerase would be an almost universal anti-cancer approach.
**Accelerated Anti-tumor Effects of Telomerase-dependent Telomere-altering Compounds**

**Imetelstat**
- Inhibition of telomerase activity
- Tumors with longer telomeres require a longer treatment duration relative to tumors with shorter telomeres
- Increased toxicities

**6-thio-2’-deoxyguanosine (6-thio-dG)**
- Telomere “uncapping” in telomerase expressing cells
- Reduces the lag period irrespective of initial telomere length

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*Cancer Discovery 5(1) 1-12, 2015*
Cancer Cells are Almost Universally Sensitive to 6-thio-dG

6-thio-dG cause replication stress and programmed cell death (apoptosis) in cancer cells.

Mender et al, Cancer cell, 2020
• 6-thio-dG is preferentially recognized by telomerase over other polymerases and results in telomere damage in cells that express telomerase leading to an increase in micronuclei formation and cytosolic dsDNA that is released from tumor cells and taken up by dendritic cells.

• 6-thio-dG activates T cells through dendritic cells in MC38 model

Mender et al, Cancer cell, 2020
6TdTG induces systemic anti-tumor immunity and immune memory

Mender et al., Cancer cell, 2020

*naïve mice
Efficacy of 6TdG in metastatic Small cell lung cancer model

- 3 days: 6-thio-dG treatment (3mg/kg)
- 4 weeks: Tumor growth
- 4 weeks: Liver weights comparison

 Liver weights

- vehicle
- 6-thio-DG

p<0.0001

Tumor

Liver

6-thio-dG treated

Untreated

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Efficacy of 6TdT in Small cell lung cancer metastatic model

**Day 0**
- Lung cancer cells

**Day 17**
- 6-thio-dG Treatment (IP, 3 mg/kg)
- Dose 1

**Day 18**
- Dose 2

**Day 19**
- Dose 3

**Day 25**
- Sacrifice

**Tumor cells**

- **gH2AX**
  - Control
  - 6-TdG

- **Apoptosis**
  - Control
  - 6-TdG

**Cleaved Caspase-3**

- Control
- 6-TdG

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Efficacy of 6TdG in Small cell lung cancer metastatic model

Day 0                               Day 17    Day 18    Day 19           Day 25

IV Injection of RP Cells

Dose 1 Dose 2 Dose 3

6-thio-dG Treatment (IP, 3 mg/kg) Sacrifice

100

40

Percent

75

30

50

20

25

0

CD8

NK

Hepa.

B cells

Hepa.

CD8

TCF7+

TCF1

Immune cells

IV Injection of RP Cells

Cont Treat

Cluster

0 1 2 3 4 5 6 7 8 9 10 11 12

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6Tthio-dG treatment of Human SCLC in immunologically humanized mice

100cGy IR

NSG-SGM3-HLA-A2

10^5 human CD34+

Subcutaneous tumor implantation

6TdG PD-L1

No-reconstitution Human CD34+ reconstituted

H69 in NSG mice

Human CD34+ reconstituted

H69 in NSG mice
Based on preclinical work 6Tdg (THIO) is being clinically tested in lung cancers

Work leading
Shay lab
Fu lab, Shay lab, Akbay lab

The trial will test the hypothesis that lower doses of THIO administered prior to Libtayo treatment would enhance and prolong responses in subjects with advanced NSCLC who did not respond or progressed after first-line treatment with a checkpoint inhibitor.
Telomerase activity is observed in ccRCC but not in adjacent normal tissues

Trap assay based activity

<table>
<thead>
<tr>
<th></th>
<th>Telomerase activity (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Case number</td>
</tr>
<tr>
<td>Sex (Age: years mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23 (59.9 ± 12.7)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (62.1 ± 7.6)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Normal tissue adjacent</td>
<td></td>
</tr>
<tr>
<td>to the cancer</td>
<td>30</td>
</tr>
</tbody>
</table>

Fujioka Int J Urology, 2001
Noureen et al, Nat Comm, 2021

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Future directions

RENCA in vivo

To determine the leading to T cell activation after 6Tdg treatment in RCC
Determine role of cGAS/STING pathway activation in tumor/DCs or alternatives

Evaluate efficacy of 6Tdg and immune checkpoint blockade in RCC
Sequential treatment with 6Tdg and PD-1/CTLA4 antibodies or other treatments.
(Renca, alternative models - Hakimi et al,)
Humanized models (Patient samples from Brugaloras et al)
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