PD-L1 checkpoint blockade using a single-chain variable fragment targeting PD-L1 delivered by retroviral replicating vector (Toca 521) enhances anti-tumor effect in murine cancer models

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Novel Retroviral Replicating Vector (RRV) Platform:
Selective infection, spread and persistence in cancer cells

RRVs infect immune deficient cancer cells but not normal cells with intact immune systems

Cancer cell interferon pathway genetic defects reduce anti-retroviral resistance and Virus only infects replicating cells

Safety data in 127 patients supports selectivity of platform

Brain tumor with RRV stained brown (infected)

Normal brain cells not stained brown (uninfected)

Does not initially activate immune system, enabling viral spread

Non-lytic RRV budding from infected cell

Absence of vector insertion site clonality supports safety

Ostertag et al., 2012, Hogan et al., 2018
## Tocagen Pipeline

### Summary of Current Clinical Development Plan

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<tr>
<th>Candidate</th>
<th>Indication</th>
<th>Discovery</th>
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<th>Phase 1</th>
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<tr>
<td><strong>Toca 511 &amp; Toca FC</strong></td>
<td>Recurrent high grade glioma</td>
<td><strong>TOCA 5</strong></td>
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<td>2nd interim analysis projected 1H 2019 and final analysis by end-2019</td>
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<td>Advanced solid tumors (CRC, Melanoma, Pancreatic, Lung &amp; Breast)</td>
<td><strong>TOCA 6</strong></td>
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<td>Data updates anticipated 2018 and 2019</td>
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<td></td>
<td>Newly diagnosed high grade glioma</td>
<td><strong>TOCA 7</strong></td>
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<td><strong>Toca 521 (Anti-PD-L1)</strong></td>
<td>Oncology: Solid tumors</td>
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<td>Advancing into IND-enabling studies 2H 2018</td>
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</table>
Tumor Microenvironment in Glioblastoma

- Glioblastoma is a highly immunosuppressive tumor associated with extensive molecular heterogeneity
- Glioblastoma has few infiltrating T-cells with exhaustion phenotype and low number of somatic mutations (cold tumor)
- CheckMate-143: Nivolumab did not demonstrate an improved OS compared with bevacizumab in pts with recurrent GBM

*Modified from Lim et al., 2018*
Toca 521: A Next Generation Checkpoint Inhibitor

Rationale of RRV Expressing Single Chain Variable Fragment Targeting PD-L1 (scFv PD-L1)

- PD-1 and PD-L1 are both validated therapeutic targets in cancer patients
- scFvPD-L1 expression from RRV is as effective or better than α-PD1/L-1 mAb in several tumor models
- Potentially fewer toxicity vs mAb due to targeted nature of scFv PD-L1 production within the tumor
- Potential higher accessibility of the target within the tumor vs mAb
Toca 521 Encodes a New RRV Configuration Expressing Single Chain Variable Fragment Targeting PD-L1 (scFv PD-L1)

Used for *in vivo* studies

Used for *in vitro* characterization

**scFv**

**scFv-HF**

Signal peptide  
H = His tag  
F = Flag tag

Lin *et al.*, ASGCT 2018
Secreted scFv PD-L1 Expressed from Toca 521 Infected CT26 Tumor Cells Competes with PD-1 Binding to PD-L1
Secreted scFv PD-L1 Expressed from Toca 521 Infected Cells Binds Cell Surface PD-L1 of Cells Expressing the scFv PD-L1 as Well as Bystander Tumor Cells

* EMT6/RRV-scFv-PDL1; EMT6/RRV-GFP
Toca 521 Shows Anti-tumor Activity in GL261 Orthotopic Glioma Model with High Tumor Mutational Burden

IV infusion of immune CPI antibodies

Intratumoral delivery of scFv PD-L1 by RRV

Time course for α-PD-L1 treatment

Time course for α-PD-L1 treatment

Percent survival

Days post inoculation

Time course for α-PD-L1 treatment

Percent survival

Days post inoculation
Toca 521 Shows Anti-tumor Activity and Memory Response in Tu2449 Orthotopic Glioma Model with Low Tumor Mutational Burden

Time course for α-PD-1 treatment

![Graph showing percent survival and tumor burden over time post inoculation.](image)
scFv PD-L1 Level in Sera of Tumor-Bearing Mouse Models is Significantly Lower Than Sera of Human Patients Treated with Approved CPI Antibodies

* Anti-PD-1/L1 concentrations in human serum after 1 cycle i.v. infusion of 10mg/kg (Bevancio), 200 mg (Keytruda), 3 mg/kg (Opdivo) or 1200 mg (Tecentriq) Heery et al., 2017; Patnaik et al., 2015; Yamamoto et al., 2017; Stroh et al., 2017
Summary

• scFv PD-L1 expressed from Toca 521 infected cells competes with PD-1 for PD-L1 binding

• scFv PD-L1 expressed from Toca 521 infected cells binds to PD-L1 on the cell surface and is sufficient to achieve trans-binding activity on bystander tumor cells

• Toca 521 shows anti-tumor efficacy as a monotherapy in 2 orthotopic glioma models consisting of low and high tumor mutational burden

• Nominal levels of scFv PD-L1 in tumor-bearing mouse models may reduce systemic immune toxicities which could result in a favorable safety profile

• Toca 521 has a differentiated profile that may overcome some of the limitations with current check point inhibitors for the treatment of glioblastoma and other tumor types
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Douglas Jolly

Thank You!
I believe I belong on the acknowledgements.

Mainly, I was the first to suggest PD-L1 as our target for RRV.

I was also very interested in using the antibody, as there was human data on this approach.

I also contributed to the idea to replace the IRES with a small promotor and shrink it, to allow larger genes instead. 2A grew out of this emphasis.

Harry Gruber, 10/14/2018