BCL6 Inhibition Represses HIV Infection of CD4+ T Cells ex vivo
& Reduces Germinal Center Hyperplasia in Rhesus Macaque

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## Disclosure

<table>
<thead>
<tr>
<th>Relations that could be relevant for the meeting</th>
<th>Company names</th>
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<tr>
<td>Sponsorship or refund funds</td>
<td>• N/A</td>
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<td>Payment or other financial remuneration</td>
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BCL6 BTB-specific Inhibition Reduces Germinal Center Formation & Lowers Tfh CD4+ T Cells \textit{in vivo}


www.iasociety.org
BCL6 BTB-specific Inhibition via FX1 Treatment Represses HIV Infection & Reactivation ex vivo

BCL6 protein expression

Reduction of HIV infection (Tonsillar Tfh/non-Tfh)

Repression of HIV reactivation

Peripheral CD4+ T cells


www.iasociety.org
FX1 Treatment Reduces Tfh CD4+ T Cells, Tfh Precursor Cells & BCL6 Expression in the GC of Macaques with Lymphoid Hyperplasia

CD3 CD68 BCL6

Pre-treatment

Post-treatment

Resting (12 days)

FX1 injection

Biopsy sample collection

Bleeding

Normal

Hyperplasia

Hyperplasia +FX1

PD1

CXCR5

1.39

9.52

1.74

13.2

17.5

13.3
FX1 Treatment Lowers the Expression of Ki67 in the GC of Macaques with Lymphoid Hyperplasia
Summary

- The expression of BCL6 protein is associated with T cell activation & Tfh differentiation

- *Ex vivo* BCL6 BTB-specific inhibition
  - Reduce HIV infection of Tfh & non-Tfh CD4+ T cells
  - Repress HIV reactivation

- *In vivo* BCL6 BTB-specific inhibition
  - Repress GC reaction (Murine)
  - Reverse lymphoid hyperplasia (NHP)

- Immune modulation associated with BCL6 BTB-specific inhibitor treatment
  - Reduce the frequency of Tfh
  - Block Tfh differentiation
  - Lower T cell activation / proliferation

Could BCL6 BTB-specific inhibition provide a “Block and Tfh/GC Loss” Strategy?

Could BCL6 BTB-specific inhibition be used with to a “Shock & Kill” Strategy?
hetIL-15 treatment in SHIV+ macaques

Reduces viral transcription (SHIV infection)

Increases anti-SIV Gag CD8 responses

**Future Studies:** cycles of "Shock and Kill" to be followed by "Block and Tfh/GC Loss"

**Shock & Kill**

- Anti-SIV CD8 & NK response
- Non-Tfh reservoir
- Tfh CD4 T cell reservoir

**Block & Tfh/GC Loss**

- Germinal centers as sanctuary sites

**Conceptual Model for Tx cycle Effects**

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<th>Week 1</th>
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<td>21</td>
<td>hetIL-15 (ug/kg)</td>
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Day 1: 2, 3, 4, 5, 6, 7

M-Monday; Th-Thursday. ▲ hetIL-15 or PBS, S.Q.  ♦ AP4-287 (6.25 mg/kg) or vehicle, S.Q., twice daily

**Viral burden**

- ART + hetIL-15/BCL6i

**Time**

- hetIL-15
- BCL6i
Acknowledgements

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Histotechnology Core
Fangping CHEN
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James Hayden
Aubrey Leso

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Ronald S Veazey
Megan A Watkins
Xiaolei WANG
Cecily C. Midkiff
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Neil D Romberg
Carole Le Coz

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National Cancer Institute
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