Impact of Vorinostat Treatment of Non-Hodgkin’s Lymphoma on HIV-1 Latent Reservoir

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HIV Cure Strategies

- Major barrier to HIV cure is a latent reservoir of replication competent HIV in resting CD4+ T cells that persists despite ART

- “Shock and Kill” Strategy
VOR in Cancer and HIV Cure

- Vorinostat (VOR) is a HDAC inhibitor that is approved for cancer treatment.
- Identified as a potential latency reversing agent (LRA).
- Prior clinical studies looking at impact of VOR on HIV persistence:
  - Increase of cell-associated HIV RNA.
  - Did not report on changes in replication competent HIV in resting CD4 T cells measured by viral outgrowth.
  - VOR is perturbing the latent reservoir.

Archin et al. (2012) Nature
Elliott et al. (2012) PLOS Pathogen
AMC 075: VOR for HIV Lymphoma Phase II, 90 participants

- Chemotherapy (R-EPOCH) with randomization +/- VOR
- VOR: 300 mg orally, day 1-5 of each 21 day cycle, for 6 cycles

Baseline  Cycle 1  Cycle 2  Cycle 3  Cycle 4  Cycle 5  Cycle 6  Visit 7 (270 d.)  Visit 12 (360 d.)

Pre-Rx  Measure Latent reservoir

Post-Rx  Measure Latent reservoir

- Latent reservoir was measured in a subset of patients whose HIV was suppressed at baseline and remained suppressed throughout study on ART
Quantitative Viral Outgrowth Assay

- Quantitative Viral Outgrowth Assay (QVOA)

Resting CD4+ T cells from patients on ART

Activation & Amplification

1x10^6 2x10^5 4x10^4 8x10^3 1.6x10^3 3.2x10^2

p24 Positive

p24 Negative

Day 14 supernatant p24 antigen detected by ELISA

- For statistics, a mixed effects Bayesian model

Impact of chemotherapy and VOR on CD4 counts

No significant change
HIV LR Measurements (n = 14)

VOR Treatment Effect

<table>
<thead>
<tr>
<th></th>
<th>Fold-change Median Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-patient average</td>
<td>1.08 (0.21, 5.13)</td>
</tr>
</tbody>
</table>
Individual treatment effect

Chemotherapy Arm

Fold-change median estimate

Chemotherapy Participants

031017 061025 081038 012047 022049 060071 061074

0.001

0.01

0.1

1

10

100
Conclusions

• In a randomized trial of VOR plus chemotherapy, there were no significant changes detected in the HIV LR by qVOA in 14 patients
  – By group (fold-change 1.08) or by individual (fold-change range 0.48-2.70)

• Limitations:
  – Large confidence intervals with qVOA
  – Small N to date (anticipating 6 additional patients)
  – Did not looked specifically for a “shock” or HIV reactivation effect
  – Patients with malignancies receiving chemotherapy may not have effective CTL responses to eliminate latently infected cells even if HIV is reactivated

• Consistent with a recent new study by Archin/Margolis of 5 patients who received VOR 3 days per week x 8 weeks, no change in reservoir by qVOA measurements

Archin et al. (2017) JID
Future Directions

• Need for more effective “kill” strategies
Acknowledgements

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## Probability of VOR Effect

<table>
<thead>
<tr>
<th>Participant</th>
<th>Fold-change Median Estimate (95% CI)</th>
<th>Probability that VOR increased IUPM</th>
<th>“p-value”</th>
</tr>
</thead>
<tbody>
<tr>
<td>152009</td>
<td>0.85 (0.16, 4.72)</td>
<td>41%</td>
<td>0.82</td>
</tr>
<tr>
<td>061053</td>
<td>0.95 (0.13, 6.67)</td>
<td>47.7%</td>
<td>0.954</td>
</tr>
<tr>
<td>081054</td>
<td>2.20 (0.38, 14.96)</td>
<td>81.5%</td>
<td>0.37</td>
</tr>
<tr>
<td>132070</td>
<td>1.51 (0.23, 11.32)</td>
<td>71.6%</td>
<td>0.57</td>
</tr>
<tr>
<td>152085</td>
<td>0.48 (0.01, 3.56)</td>
<td>24.5%</td>
<td>0.49</td>
</tr>
<tr>
<td>241088</td>
<td>0.62 (0.07, 3.81)</td>
<td>27.5%</td>
<td>0.55</td>
</tr>
<tr>
<td>132091</td>
<td>2.70 (0.45, 23.28)</td>
<td>86%</td>
<td>0.28</td>
</tr>
</tbody>
</table>
How to measure treatment effect while controlling for temporal change?

Method: Mixed effects Bayesian model coded in Stan

Baseline IUPM for each participant (fixed effect)

Temporal fold-change in IUPM (random effect, applies to both arms)

Treatment fold-change in IUPM (random effect, applies to treatment arm only)

“Effective IUPM” in well

Poisson likelihood that a well is positive / negative

# cells in well (known)

Method adapted from Rosenbloom, Deng, ..., Busch, Bacchetti (in prep)