“Towards an HIV Cure”
Global Scientific Strategy

1st Stakeholders Consultation Meeting
28 September 2011, Canberra.

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Definitions

• The definition of a "functional HIV cure" means:- undetectable viremia without ART; - no disease progression; - no CD4 loss; - lack of HIV transmission

• Eradication/Cure: complete eradication of HIV infected cells from the body
# Cure Vs Functional Eradication

<table>
<thead>
<tr>
<th>Cure</th>
<th>Functional Cure/Remission</th>
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<tbody>
<tr>
<td><strong>Infectious Diseases model</strong></td>
<td><strong>Cancer model</strong></td>
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<tr>
<td>Elimination of all HIV-infected cells</td>
<td>Long term health in absence of HAART</td>
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<tr>
<td>HIV RNA &lt; 1 copy/ml</td>
<td>HIV RNA &lt; 50 copies/ml</td>
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<tr>
<td>Sterilising cure (Eradication)</td>
<td>Functional cure</td>
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Barriers to cure

- Latently infected T-cells
- Residual viral replication
- Anatomical reservoirs
Current Strategies aimed at eradication/functional cure

• Identification of reservoirs;
  – establishment
  – regulation
  – persistence
Strategies for cure

• Starting ART very early before reservoirs are fully established
• Eliminate residual virus replication by HAART intensification
• Eliminate latently infected cells
• Maintaining latency to keep proviral DNA permanently silenced
• Make cells “resistant” to HIV
• Enhance HIV-specific immunity
Eliminating viral replication: treatment intensification

Eliminate latently infected T-cells: activate latent HIV

Activated CD4+ T-cell

Resting CD4+ T-cell

HAART
Licensed drugs that activate latently infected cells

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<tr>
<th>Histone deacetylase inhibitors</th>
<th>Vorinostat</th>
<th>Yes</th>
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<tr>
<td></td>
<td>Romidepsin</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Panabinostat</td>
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<td></td>
<td>Entinostat</td>
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<td></td>
<td>Belinostat</td>
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<tr>
<td></td>
<td>Givinostat</td>
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<tr>
<td></td>
<td>Others (9)</td>
<td></td>
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<tr>
<th>Methylation inhibitor</th>
<th>5-azacytidine</th>
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<tr>
<th>Cytokine</th>
<th>Interleukin-7</th>
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<tr>
<th>Anti-alcoholic</th>
<th>Disulfiram</th>
<th>Yes</th>
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* Total number of trials listed on [http://clinicaltrials.gov](http://clinicaltrials.gov) (July 2011)

Make cells “resistant” to HIV: gene therapy

Scientific challenges

- Multiple barriers to eradication meaning a **combination approach** will be likely.

- Better **in vitro** and **animal models** to evaluate new strategies, alone and in combination.

- **Drug development** to increase specificity for latently infected cells and/or enhanced tissue delivery.

- Better understanding of the **immune system** in controlling low level viral replication.
Clinical and implementation challenges

• **Universal access** to cART must remain a top priority

• PLWHA on cART are **doing well** so low threshold for toxicities related to an intervention

• Clinical **endpoints** for successful “eradication” unclear. When will a treatment interruption be OK?

• Multiple **unknowns with gene therapy**: uncertain safety of delivery vectors and zinc finger nucleases