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Development of aptamer based HIV-1 entry inhibitor prophylactic drugs

Grace London
CSIR, Biosciences
Emerging Health Technologies Platform
Pretoria, South Africa

2nd International Conference and Exhibition on Pathology
Properties of Aptamers

➤ Aptamers are nucleic acids with properties of antibodies

➤ Generated by simple in vitro process called SELEX

➤ High affinity and specificity

➤ Small in size and fold in 3-D structure (e.g., RNA aptamers)

➤ Resistant to nucleases and chemically stable

➤ Low toxicity and non-immunogenic

Joubert et al., 2010
Applications of aptamers

- Marro et al., 2005
- Rotherham et al., 2012
- Rusconi et al., 2004

Green et al., 2001

Aptamers as diagnostics

Aptamers as therapeutics

High-throughput screening

Target validation

Aptamer

Anti-gp120 aptamers as HIV-1 entry inhibitors

Apt 1 bind gp120 trimer

Apt 2 bind recombinant gp120

Apt = aptamer

Khati et al., 2003; Cohen et al., 2008
HIV-1 entry and inhibitors

Outline of the study

1. Evaluate efficacy of anti-gp120 aptamer against HIV-1 subtype C
2. Test toxicity
3. Map “aptatope’s” on HIV-1 gp120
4. Test synergy with other entry inhibitors
Aptamers inhibit entry of HIV-1 subtype C Env pseudoviruses

<table>
<thead>
<tr>
<th>Env clone</th>
<th>Stages of disease</th>
<th>Geographic location</th>
<th>Apt 1</th>
<th>Apt 2</th>
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</table>

- **Apt 1** = inhibited 84% viruses
- **Mean IC<sub>50</sub>** 6.6 ± 8.1 nM
- **Apt 2** = inhibited 79% viruses
- **Mean IC<sub>50</sub>** 0.4 ± 0.3 nM

50 nM = No inhibition
NT = Not titred
* viruses using CXCR4 coreceptor

<table>
<thead>
<tr>
<th>% viruses neutralized</th>
<th>Mean IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>84%</td>
<td>6.6 ± 8.1</td>
</tr>
<tr>
<td>79%</td>
<td>0.4 ± 0.3</td>
</tr>
</tbody>
</table>

0.1-5 nM
5-25 nM
25-50 nM
>50 nM
Aptamers inhibit entry of HIV-1 subtype C PBMC

PMBC = 80 ± 11.8 nM

Mufhandu, H et al., J. Virol. (2012), 86(9), pp. 4989
Aptamers inhibit entry of HIV-1 subtype C in Macrophages

Mean IC$_{80}$ in MDM = 23 ± 10.4 nM

Aptamers exhibit no cytotoxicity

TZM-bl MTS based-assay

PBMC MTS based-assay

% Cell Viability

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Aptamers interact with conserved residues on gp120

Aptamers bind to amino acids within the coreceptor (CoRbs) CCR5 binding site

Mufhandu, H et al., J. Virol. (2012), 86(9), pp. 4989
Synergy of aptamers with HIV-1 entry inhibitors

Synergism: CI = 0.3 – 0.9
Antagonism: CI = >1
Anti-gp120 RNA aptamers are efficacious against HIV-1 subtype C isolates (concentrations in nanomolar).

- They interact with conserved residues on gp120, delay virus resistance.
- Not toxic in different cell types.
- Synergy with other entry inhibitors, combination therapy with other drugs.
- Anti-gp120 aptamers can be developed as entry inhibitor drugs.
Acknowledgements

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• IAVI
• NIH AIDS Reagents

Funding

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